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REFERENCE FRAME FREE LEFT VENTRICULAR SHAPE, THE TANGENT ANGLE FUNCTION, AND CORONARY ARTERY DISEASE

City University of New York PH.D. 1983

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REFERENCE FRAME FREE LEFT VENTRICULAR SHAPE, THE TANGENT ANGLE FUNCTION, AND CORONARY ARTERY DISEASE

by

MARK L COHEN

A dissertation submitted to the Graduate Faculty in Biomedical Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Harry Smith, Jr.
Dr. Harry Smith Jr.
Chairman of Examining Committee

April 26, 1983
date

Dr. Terry Krulwich
Executive Officer

Dr. John Ambrose
Dr. Charles Peskin
Dr. Louis Teichholz
Dr. John Thornton

Supervisory Committee

The City University of New York

To Jane, whose love and support are a
continual source of joy and comfort

ABSTRACT

REFERENCE FRAME FREE LEFT VENTRICULAR SHAPE, THE TANGENT ANGLE FUNCTION, AND CORONARY ARTERY DISEASE

by

Mark L. Cohen

Supervising Professor: Dr. Harry Smith Jr.

The outline of the cavity of the left ventricle of the heart is visualized during cardiac catheterization. Despite the almost routine use of this technique, there is no consensus as to how the two-dimensional outline is to be analyzed. This is because all current methods attempt to measure wall motion: a measurement that, in its definition, requires the use of conceptually unverifiable assumptions about the motion of the heart.

In this dissertation, shape and shape change are presented as alternatives to wall motion. The tangent angle function is shown to be a measure of shape that involves no assumptions about the motion of the heart and that has interesting interpretations in the setting of coronary artery disease.

The tangent angle function was applied to the end diastolic and end systolic outlines of the hearts of patients who had isolated single vessel coronary artery disease, or no coronary artery disease. The tangent angle functions

were parameterized and, using discriminant analysis, combined into two canonical variables. These were shown to abstract end systolic dysfunction with compensation, and total systolic shape change. Using a jackknife, 70% of the patients were allocated to the correct coronary artery group using the shape-derived canonical variables. This was verified with an independent set of test data.

The reproducibility of this approach was assessed with an additional independent set of test data, and with a study of the variability in transferring the outlines from the catheterization films to the computer. Both these studies showed considerable variability with respect to the initial results, indicating that additional quality control and study of the patient population is necessary before the method can be used clinically.

It is concluded that shape and shape change are useful alternatives to wall motion in the study of the left ventricular outline. The combining of parameters of shape offers interesting insights into the response of the left ventricle to coronary artery disease. Extensions to other areas of application in clinical cardiology and to the methodology are discussed. The reliability of the data, and the possibility that the patient population and catheterization techniques did not remain standard, are identified as major limitations.

ACKNOWLEDGEMENTS

After writing so many pages in the quasi third-person-invisible scientific voice, it is a pleasure to write in the first person. Completing an MD-PhD program is a time of looking back and reflecting, as well as a time of looking ahead. Writing the acknowledgements of the PhD dissertation is a time of looking back.

My direction and development have been influenced by an uncountable number of people. Some have been heroes, some have been role models, and some have been "just friends" who cared about me and about whom I cared. I cannot remember the names of most of these people, but they are with me none the less. To them I owe thanks.

I thank Senta Frank and Lena Townsend, who have taken care of the administrative problems over the last few years, particularly considering my levels of anxiety when such problems arose. I thank Dr.'s Ambrose and Thornton for their reading of the dissertation and their comments. Dr. Krulwich, the director of the MD-PhD program, has been more than supportive of me as I followed an interdisciplinary program that involved three universities and almost involved a year in Israel. I do apologize for the gray hair. Dr. Smith has been a thesis chairman extraordinaire. He allowed me to pursue my interests, while preventing me from digging myself into holes that were deeper than eye level. Dr.'s Peskin and Teichholz, in addition to being indefatigable teachers, have been role models of interdisciplinary scientists. They have shown me that being a philosopher, a researcher, an educator, and, in the case of Dr. Teichholz, a clinician, can all be facets of one profession. I hope that what they have given to me I can one day pass along to my students.

I wish to acknowledge the contribution of Dr. Fred L. Bookstein. Although we have never met, his monograph The Measurement of Biological Shape and Shape Change (Springer, 1978) provided the start and much of the direction to this project.

Dr. Lou Wasserman has been a constant presence during my seven years at Mt. Sinai. Our Tuesday morning breakfasts were always a time to look forward to, and I will miss them in the years to come.

Parents, of course, are acknowledged last. Such is their lot in life. This is because there are no words to describe their roles in my life. I feel that life is a process of building bridges from one relationship to the next. My mother, father, Eric, and Toba are on the other side of the very first bridge.

Mark L. Cohen
New York, 1983

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CHAPTER 1: INTRODUCTION

> "The use of a definition of shape based on the properties of the cavity as a whole has certain advantages. It is not dependent on the position of the zero reference used for defining cavity outlines, and so is insensitive to overall movement of the ventricle in space. It does not require the definition of any fixed point on the perimeter such as the 'apex', which may be difficult in the presence of abnormal wall movement or aneurysm. It assumes no idealized cavity geometry and, being dimensionless, is unaffected by cavity size. Finally, it is not invalidated by local abnormalities of wall movement.
>
> In contrast, techniques based on the superimposition of an arbitrary grid depend on identification of the apex or are sensitive to overall movement of the heart in space. In general, these methods assess wall movement only at the point where the axis and cavity outline intersect one another. Localized abnormalities of wall movement might thus be missed altogether or may cause relative movement of the axes and the myocardium with the effect that different regions of the ventricle are studied at different times in the cardiac cycle." Gibson and Brown (58)

I. PHILOSOPHY

I.1 Clinical Left Ventriculography

Diagnostic tests in medicine have often been developed in rather haphazard ways. The questions concerning the use of the test and the interpretability of the results have often been deferred to the excitement that surrounds the realization of new information about the body and its function. Such has been the case with diagnostic cardiac catheterization.

Cardiac catheterization involves placing a catheter in

or near the heart, usually by threading it through a blood vessel, and using the catheter as an access to the central circulation. One can measure pressures and electrical activity. By injecting radio-opaque dye, the cavities enclosed by the chambers of the heart can be visualized with X-rays. If the tip of the catheter is placed into the ostia of the coronary arteries and the dye injected, the coronary circulation can be imaged. With the explosion of information about the heart that occurred with the advent of catheterization, it is no wonder that some of the detailed questions about exactly what was being measured by these techniques were not asked for some time. In particular, the questions of how to describe the information have lagged behind the acquisition and use of the information itself. This problem is particularly apparent in the case of the image of the left ventricular cavity.

The use of the image of the left ventricle in clinical decision making has resulted in the peculiar situation in which the data is being acquired in the routine diagnostic evaluation of patients without a consensus as to how the data should be used. The dynamic image is readily obtained; physiologic understanding and intuition dictate that the image contains useful information; yet there is no accepted method of measuring or describing the image. This lack of consensus undoubtedly has impeded the further understanding of the determinants of the shape of the left ventricle. In this dissertation, it is hoped that by first addressing the

general problems in the measurement of shape, the specific applications can be investigated in a rational way.

I.2 Hypothesis

The motivation for investigating a method of measuring the shape of the left ventricle of the heart comes from the premise that the shape contains information that is useful in the understanding of cardiac physiology and pathology. While the basic premise, in general, is easily inferred from the knowledge of cardiac physiology, the details of the relationship must be established by observation and experimentation. In order to conduct an experiment, a specific question must be asked. The exact question depends on the aspect of physiology that is to be examined. In the case of shape of the heart, the relationship of shape to coronary artery disease is a natural focus and the question,

> "To what degree can shape of the left ventricle discriminate among patients with coronary artery disease?",

is a natural question. This dissertation provides an approach to this question, and a partial answer.

This question is an allocation problem. Patients can be grouped on the basis of coronary artery status (the "accepted" way of grouping). Using the measure of shape of the heart (the "investigational" method), we try to reproduce the accepted grouping. The extent to which we succeed determines the accuracy of the investigational method for predicting the accepted. This approach contains some

implicit assumptions.

The first assumption is that it is appropriate to want the investigational method to reproduce the accepted. Rarely will this be exactly true. While the investigational and the accepted methods are usually chosen because they reflect common aspects of physiology, they generally do not reflect identical aspects. To the extent that they differ, one would expect the grouping of patients to differ.

The second assumption is that both the investigational and the accepted methods truly reflect the aspects of physiology they are assumed to. In grouping patients based on certain characteristics, other characteristics have been left out. This represents a simplification, and can be expected to decrease the correspondence between the groupings and the underlying physiologic theory. This simplification of the theory will distort the relationship between the two methods, because the relationship between each method and the common underlying theory has been distorted.

The third assumption is that the utility of the investigational method lies in its correspondence to the accepted. Because of the first two assumptions, this is a narrow point of view. The investigational method contains information different from the accepted. Since this information is not addressed in the original hypothesis, it is reflected in a lack of correspondence between the two methods. This is an inescapable part of the allocation strategy. One cannot transcend the accepted method without new

theory or new information. One can, however, try to understand why the differences in classification occurred.

The differences in classification reflect the reasons discussed. By examining the differences, one hopes to gain insight into both the investigational and the accepted methods. From this, the interaction of each method with the physiologic theory can be better understood and new approaches suggested.

Despite the limitations in the assumptions, the allocation approach is useful for studying a new methodology. It provides a framework from which other studies can be derived.

II. OVERVIEW OF THE DISSERTATION

The thesis of this dissertation is that the shape of the left ventricle of the heart bears a demonstrable relationship to the presence and location of a coronary artery stenosis.

In the dissertation the motivating problem and the approaches to a solution taken by others are discussed. A precise definition of shape is offered and a method of measuring shape that satisfies the properties dictated by the definition is described. A method of extracting parameters from the measure of shape is given, as is an interpretation of the parameters.

The next part of the dissertation is devoted to the allocation problem discussed earlier. A cohort of patients

is identified based on coronary artery anatomy and pathology (the accepted grouping). The shapes of the left ventricles are measured and parameters are extracted. The parameters serve as the investigational data types, and the allocation problem is addressed using discriminant analysis.

The last part of the dissertation is a discussion and an interpretation of the results. Limitations and extensions, as well as future work are discussed.

In order to facilitate reading, the relevant literature is reviewed in a separate chapter. The table of contents has deliberately been made detailed and hierarchical, and serves as an outline of the entire dissertation.

III. MOTIVATING PROBLEM: CORONARY ARTERY DISEASE AND SHAPE OF THE LEFT VENTRICLE

III.1 Coronary Artery Disease

Coronary artery disease is a pathological process in which the lumen of one or more of the coronary arteries becomes narrowed. As the disease progresses and the stenosis becomes more severe, the blood flow through the artery becomes impaired. When the flow of blood to a region of muscle is insufficient to meet the metabolic needs of the muscle, then impairment of myocardial contraction and pain (angina pectoris) result. If the blood flow is sufficiently curtailed, then irreversible damage to the muscle results.

The anatomy of the coronary circulation is fairly stylized and well described (1). Each section of muscle is sup-

plied with blood from a branch of a main artery. If the coronary artery is narrowed beyond a critical amount, then the flow of blood is assumed to be insufficient to meet the needs of the muscle all the time. If one could observe the muscle, there would be some amount of damage and impairment of the ability to generate force. The amount of narrowing deemed critical is not simply a function of blood flow, because the metabolic needs change with the physiologic demands placed on the muscle by the body: for example, blood flow may be adequate at rest, but insufficient during exercise. Therefore, the degree of stenosis that has been accepted as critical is based in part on the experience of cardiologists and pathologists, and represents observations on coronary artery narrowing and cardiac muscle damage and dysfunction (LITERATURE REVIEW IV).

In addition to blood from the main artery, blood is supplied from a highly variable collateral circulation that arises from the branches of other main arteries. In some individuals it can be shown that all of the blood supply to a region of muscle comes from the collaterals, while in others no collateral circulation can be demonstrated. In most cases the bulk of the blood supply appears to be from the main artery, and in most individuals the collateral circulation is not felt to be sufficient to totally support the needs of the muscle (2-5,145).

The model of coronary artery disease, in its most simplified version, states that each region of muscle is sup-

plied with blood from a single coronary artery, the distribution of all of which are known. If the artery is narrowed beyond a critical amount, then dysfunction of the muscle with some degree of irreversible damage will result. The patient experiences signs and symptoms referable to cardiac ischemia and dysfunction. While this model may seem overly simplified, it has demonstrated clinical utility, particularly as the justification for, and the basis of, coronary artery bypass surgery.

III.2 Diagnostic Cardiac Catheterization

The data used to study coronary artery disease and its effects on the heart come mainly from cardiac catheterization. Using the catheter that has been threaded through the blood vessels (either arteries or veins, depending on which side of the heart is to be investigated), access to the heart is achieved. While many different procedures and studies can be performed (some of which are discussed in LITERATURE REVIEW), the mainstay in evaluating coronary artery disease is the injection of radio-opaque dye into the coronary arteries and into the cavity of the left ventricle with the recording of fluoroscopic movies: the angiogram and the ventriculogram, respectively.

The angiogram provides pictures of the blood within the coronary arteries. Narrowings are visualized, and the degree of narrowing can be determined. In keeping with the coronary artery disease model, the number and locations of critical stenoses can be determined and the regions of

involved muscle demarcated.

The ventriculogram provides a film of the cavity of the left ventricle as the heart is beating. The shape and the movements of the walls are observed. These observations, via the disease model, can be correlated with the angiogram. Regions of muscle supplied with blood by a coronary artery with a critical stenosis should appear abnormal, while other regions should appear normal. This concept has recieved a significant amount of attention in the cardiac literature, and will be reviewed.

III.3 Left Ventricular Shape

The history of ventriculography and the specific approaches taken by others to left ventricular shape analysis are reviewed in LITERATURE REVIEW. The general problems are discussed here.

The disease model, although greatly simplified, is particularly compelling. It provides an explanation for a great deal of the observations made by angiography and ventriculography. In many cases the correlation between a coronary artery stenosis and an abnormal ventriculogram is obvious. The problems begin when attempts are made to measure the outline of the left ventricular cavity.

In quantitating the ventriculogram, investigators try to show that some areas of muscle (parts of the outline) contract normally, while other areas contract abnormally. Regions of the heart are defined. Measures of contraction are developed that usually involve the distances that these

regions move during systole. Two problems become immediately apparent.

The first problem is that there are no obviously delimited regions of the left ventricle. The cavity has an orientation, in that the valve openings are at one end, but there are no other unambiguously demarcated regions. This creates problems when one tries to talk about corresponding sections of muscle in different hearts, or even in different pictures of the same heart.

The second problem is that the heart is not rigidly fixed in the chest. During the cardiac cycle there is a clearly observed motion of the heart as a whole, in addition to local movement of regions of the ventricle. This becomes apparent when one tries to measure the movement of different parts of the heart. Implicit in the concept of movement is that it is movement with respect to something. If the entire heart itself is moving, then one would like to measure the local movements independent of the movement of the heart as a whole. However, it is not clear on what basis the components can be separated, and neither component can be ignored.

The two problems of identifying regions and of measuring movement have occupied the energies of those concerned with analyzing the ventriculogram. The problems are of sufficient magnitude that there is no consensus about how the ventriculogram should be analyzed. Many investigations do not address the problems at all, but rely on a subjective

interpretation. It is to these issues that a formal consideration of shape is relevant.

IV. SHAPE AND MEASUREMENT OF SHAPE

> "Informally, a shape is an outline-with-landmarks from which all information about position, scale, and orientation has been drained." Bookstein (7)
>
> "Informally ...a shape measurement... is a function embodying the outline from which all information about position, scale, and orientation has been removed." Bookstein (8)

IV.1 Shape

The single plane ventriculogram is a two dimensional outline that varies with time. By looking at the issues involved in measuring two dimensional outlines in general, some insight into a rational approach for measuring ventriculograms can be gained.

Shape is an intuitive concept that is well expressed by Bookstein in the first quote above. Shape is the aspect of an outline that is independent of size, orientation (rotation), and position in space. If an outline is uniformly scaled to be larger or smaller, it still has the same shape. If it is rotated in its two dimensional plane, it still has the same shape. If it is moved to another location in the plane, it still has the same shape. By necessity then, all information about shape is contained in the outline itself, independent of the coordinate system in which it is embedded.

A landmark is an unambiguously defined point on an out-

line. An example that embraces the intuitive concept of a landmark is a corner: a point at which the outline is continuous, but the first derivative has ceased to exist. Note that the definition of a landmark involves only the part of the outline in the immediate vicinity of the landmark (in the limit this vicinity shrinks to zero), and does not involve parts of the outline that are more distant. This has two implications. The first is that "constructed" points, such as the center of gravity, the point farthest from another point, or the point of maximum curvature, are not landmarks. The second is that the location of a landmark is not affected by any change to the outline that preserves shape. In other words, the outline can be rotated, scaled, and moved, and the landmarks, as well as the shape, do not change.

The fact that constructed points are not landmarks, but are a relationship derived from the shape of an outline, deserves comment. A landmark is a local phenomenon. If the shape of the outline is perturbed in a region distant to the landmark, the landmark is unaffected. A constructed point is not a local phenomenon. It <u>depends</u> on the shape of the outline for its definition, the extent of which depends on the specific construction. If the shape of the outline is changed distant to the constructed point then, unlike the landmark, the constructed point may change its location and relationship to the unchanged parts of the outline. The constructed point contains information about the outline.

The landmark only defines a property in its immediate (approaching infinitesimal) vicinity. This has important consequences when one constructs a measure of shape.

The definition of shape is a definition by exclusion. If a statement is to be made about the shape of an outline, then to be assured that shape alone is being addressed, it is necessary to determine that the statement does not change if the outline is moved, scaled, or rotated. This is not to imply that the location, size, and orientation of the outline in some coordinate system are not important attributes of the figure, but rather that they are not attributes of the shape of the figure. By conceptually distilling each attribute from an outline, the practical problems involved in the measurement of the attributes can be approached.

IV.2 Measurement of Shape

In searching for a measure of shape, some guiding principles are indicated.

The measure should reflect the definition of shape. This seems obvious. A measure of shape should not be influenced by the position, size, or orientation of the outline.

The measure should be unique. Each unique shape should correspond to one "value" of the measure, and each value should correspond to one shape. Value does not imply a single number; the result of measuring the shape of an outline may turn out to be as complicated as the outline itself. Whatever the result, it should have a one to one correspondence to the shape of the outline. If it doesn't, then two

outlines may have different shapes, but have the same measured shape, or two different values of the measure may correspond to one shape. This creates problems when the measure is used to distinguish one shape from another.

If the value of the measure is itself complicated, then it may be necessary to simplify it for a particular application, and thereby lose the one to one correspondence. It is important that this be a separate process, and that lack of uniqueness is not built into the measure itself.

The measure should not involve reference to specific points that are not landmarks. The differences between a landmark and a constructed point have been described. If a measure of shape is based on a constructed point, then changes in the shape of the outline have the potential to change the value of the measure of the outline in ways that are difficult to predict, because the location of the constructed point may change with the changes in the outline. One does not know if the changes in the value of the measure are a result of the changes in shape, the changes in the constructed point, or some combination of the two.

The measure should be interpretable. This is not an absolute criterion, but a desirable one. If the value of the measure can be understood conceptually, then its utility in applications will be more readily apparent.

These guiding principles are rigorous, and it is difficult to adhere completely to them in all applications. They do, however, represent the goals to which a measure of shape

should aspire, and any departures should be considered carefully. A discussion of the reference frame approach taken in the cardiology literature is instructive.

IV.3 Reference Frames

During the cardiac cycle, the heart undergoes changes in position, size, orientation, and shape. The exact magnitudes of the changes depend on the individual heart and its history. The disease model indicates that in different situations some of the changes are more important than others, and the methods of analysis of the left ventricular outline are designed to abstract the important changes by controlling for the unimportant ones. Virtually all the methods center on the concepts of regional wall motion and reference frame.

Regional wall motion is an appealing self-descriptive term. It means the motion of a part (region) of the ventricular wall over a portion of the cardiac cycle - usually the contraction phase. It describes what is often visually apparent: one region of the heart often moves in a different pattern from another. The patterns are often nicely explained by the coronary artery disease model. The concept of a reference frame is needed to measure the regional wall motion. Two points of view exist.

The external reference frame point of view states that the motion of the heart should be viewed with respect to the non-moving structures surrounding the heart (ribs, diaphragm, edges of the X-ray film). If these structures move

during the period of measurement, for instance the patient moves relative to the X-ray film, then they are realigned before any measurements of regional wall motion are made. The measurements are then made with no further adjustment: for example the distance an implanted intramyocardial metal marker moves during systole.

The internal reference frame point of view states that much of the observed movement is of the heart as a whole, and does not represent regional wall motion. Before the regional motion is measured, the images must be realigned according to a frame of reference that moves with the heart itself (an internal reference frame), in order to correct for the "artifactual" motion. Once this is done, regional motion is measured as movement with respect to this internal frame. Clearly the internal and the external reference frame approaches will not always lead to the same interpretations of the contraction of the heart.

A further complication arises in the definition of the wall motion once the images have been realigned. Almost all methods use constructed lines and points. The lines (reference lines) are typically defined in terms of other lines that connect anatomical landmarks or geometric features of the outlines (e.g., the center of gravity). Wall motion becomes the distance a point on the outline travels towards the reference point or line. The point on the outline is not a landmark, but is constructed from the reference lines. As with the reference frames, not all approaches are equiva-

lent, and there is no way to choose one approach over another.

The literature of methods to analyze wall motion is large and is reviewed in LITERATURE REVIEW. Almost all methods use a reference frame, and almost all concentrate on wall motion. All of the authors recognize that they are using a method that cannot be consistent all of the time.

In contrast to the reference frame methods, the discussion of shape suggests approaches that are internally consistent. In approaching the study of left ventricular outlines from the study of shape, we are recognizing that the outline is simultaneously undergoing deformations in shape, changes in size, changes in position, and rotations in the plane. It is not possible to "correct" for one aspect without influencing the others. It is not reasonable to ignore any aspect. Rather, by looking at shape, we are taking an approach that looks at an aspect of the dynamic outline that is by definition independent of the factors for which other approaches have tried to correct. It is not necessary to determine which reference frame is best: shape is independent of reference frame.

CHAPTER 2: THE TANGENT ANGLE AND THE CORONARY DISEASE STUDY

As has been discussed, the outline of the left ventricle as it is visualized during left ventriculography is of physiologic and clinical interest, and has recieved considerable attention in the cardiology literature. A limiting factor in research studies has been the absence of a single accepted method to analyze the outline. The reasons for this lack of consensus have been presented, and shape is proposed as an alternative to the existing reference frame methodology.

In this chapter, the tangent angle function is presented, and shown to be a measure of shape with properties that have useful interpretations when applied to the outline of the left ventricle. The study that has been done to investigate the value of shape in a clinical setting is also described.

Before discussing the tangent angle function, the characteristics of left ventricular outlines are mentioned.

I. LEFT VENTRICULAR OUTLINES

The outline of the left ventricle obtained from ventriculography is an irregular curve that approximates an ellipse. The edges are not always smooth due to invaginations of muscle; the degree of smoothness depends on the phase of contraction and the patient's underlying heart dis-

ease. At one "end" of the ellipse are the openings of the aortic and mitral valves. The points at which the fibrous tissue of the valves join the muscle of the ventricle are the only landmarks on the outline. Other anatomical features, such as the apex and the origins of the papillary muscles, are landmarks on the outlines of the hearts of some patients, but not on those of others. The part of the outline that is formed by the valve openings is not defined: the blood mixed with contrast agent is flowing through these openings and therefore, there is no visible anatomical structure connecting the landmarks that mark the openings. This will turn out to be a limiting factor in parameterizing the tangent angle function.

II. TANGENT ANGLE FUNCTION

The tangent angle function is a plot of the phase of the tangent vector (considered as a complex number) to the outline as a function of normalized arc length. A more visual, and equivalent, definition is a plot of the angle that the tangent to the outline makes with a fixed axis, as a function of normalized arc length. The Appendix gives a detailed symbolic definition. LITERATURE REVIEW V gives a discussion of other applications of the tangent angle function.

II.1 Construction

Arc length is defined as the distance along the outline from a landmark (starting point). For left ventricular

outlines, the starting point is the junction of the aortic valve with the anterior wall of the ventricle (the anterior aortic root point). Arc length is defined as positive in the clockwise direction. Because the outline across the valve openings is not defined, the outline ends at the junction of the mitral valve with the inferior ventricular wall (the mitral valve point).

To construct the tangent angle function, the following procedure is followed:

(1) The outline is placed on an X-Y coordinate plane. The orientation and location of the outline relative to the plane are arbitrary, but remain fixed.

(2) Beginning at the starting point (the anterior aortic root point) and proceeding clockwise until the ending point (the mitral valve point), tangents to the outline are constructed at each point of the outline (figure 1).

(3) At each of these points the following are recorded:

    (a) The arc length to the point from the start point.

    (b) The angle that the tangent line makes with the X axis.

(4) The angle is plotted as a function of arc length (figure 2).

(5) The arc length axis is rescaled to a total length of one (figure 3).

In the definition of the tangent angle function it is not necessary to have an ending point: if the outline were closed, then the function could be computed all the way

around back to the starting point (with this once-around distance taken to be unity). It is because of the valve openings that this cannot be done. In section III.3.1 of this chapter techniques appropriate to closed outlines are mentioned, and the possibility of artificially closing the outline is discussed.

II.2 Properties

The tangent angle function satisfies the requirements of a measure of shape (INTRODUCTION IV.2): independence from size, orientation, and position; uniqueness; absence of constructed points; and interpretability. Relevant proofs are in the Appendix.

Because arc length has been normalized, the function is independent of size. All outlines are scaled to have the same perimeter.

The function is independent of orientation in that if the outline is rotated with respect to the X-Y axis, the entire function shifts up or down. The zero of the function is determined by the arbitrary orientation of the outline and is therefore also arbitrary, but the structure of the function is not affected by rotations. Any parameters derived from the function that do not depend on the absolute zero of the function will likewise be independent of orientation. Deviation from the mean is an example of such a parameter.

The independence from position is clear. Arc lengths and the angles of the tangents are not affected by changing

the location of the outline in the plane.

Uniqueness except for absolute scale is a property of the tangent angle function. Each outline, scaled to unit perimeter, corresponds to one tangent angle function, and each function corresponds to one scale-normalized outline. Given a tangent angle function and the value for total arc length, it is possible to reconstruct the original outline exactly. Except for the absolute scale, no information has been lost in representing the outline by the function. The tangent angle function accomplishes a transformation of the original outline, not a reduction.

The lack of reference to constructed points is built into the definition of the function.

II.3 Curvature Interpretation

The interpretation of the tangent angle function is interesting. The derivative of the function is the curvature as a function of arc length of the original outline (9).

A property of curvature at a point is that it is equal to one over the radius of the circle that is just tangent to the outline at that point (10). If the outline is sharply curved then the circle that is just tangent will be small, have a small radius, and therefore have a large curvature (figure 4).

The tangent angle function is derived from tangents to the outline. The derivative of the tangent angle function is precisely the rate of change of the angles of these tan-

gents: the rate at which the tangents are rotating as one moves along the outline. If the curvature of the outline is large then the rate of rotation of the tangents is also large. This will be reflected in a tangent angle function that is moving upward rapidly - i.e. has a large derivative (figure 5).

If the curvature of the outline switches from positive to negative, the outline has switched from convex to concave. This will cause the tangent angle function to move downward (have a negative derivative, figure 6).

By inspecting the tangent angle function it is possible to get a sense for the shape of the original outline:

(1) If the function is increasing rapidly (large positive derivative) the outline has a large curvature - is sharply convex. This is the behavior near the apex of the heart (figure 5).

(2) If the function is decreasing (negative derivative), the outline is concave. This is seen in the "hyperkinetic" inferior wall at end systole of a heart with a large anterior wall aneurysm (figure 6).

(3) If the function if jagged, the outline is oscillating between convex and concave. This is seen in the "noise" of the muscle irregularities (figure 7).

(4) If the tangent angle function is a straight line, the original outline is a circle (figure 8). The derivative of this tangent angle function is the slope of the line, which therefore is also the curvature of the circle.

One over the curvature (slope) is the radius of the circle.

The interpretation of the tangent angle function lends insight into the types of outlines that will generate functions that are readily discernable. If the difference between two outlines is a result of small differences in curvature, such as between two similar ellipses, then the respective tangent angle functions will be very similar (figure 8). If the curvatures of two outlines differ markedly, the tangent angle functions will be very different. This is important in understanding the different applications in which the tangent angle function will be useful. The strengths and the limitations of the method are determined by the behavior of the function.

III. THE STUDY OF SHAPE IN SINGLE VESSEL CORONARY DISEASE

This section is an introduction to the study that was done to determine the ability of parameters derived from the tangent angle function to discriminate among a selected cohort of patients with coronary artery disease. The specific details of the study are given in METHODS, and specific literature is reviewed in LITERATURE REVIEW.

The general design of the study was as follows:

(1) All patients catheterized at our institution over a two year period were considered, and those with a critical stenosis of the left anterior descending coronary artery alone (LAD), of the right coronary artery alone (RIGHT),

and those with no critical stenoses (NORMAL) were the study population. Patients who were NORMAL but had suffered a myocardial infarction were excluded. Otherwise infarction was not a selection factor.

(2) The catheterization films of all included patients were viewed. The end diastolic and end systolic outlines from the thirty degree right anterior oblique projections of the left ventricles of the patients who had technically adequate sinus conducted beats that did not follow a premature contraction were traced onto paper and digitized into a computer.

(3) The tangent angle functions of each outline were computed and parameters derived that were true descriptors of shape.

(4) The parameters were used to construct the discriminant functions that maximally distinguished among the three groups of patients.

Each of these steps deserves comment (the tangent angle function was described in the previous section).

III.1 Patient Selection

Patients undergoing cardiac catheterization exhibit a wide spectrum of heart disease. By far the largest number are those suspected of having coronary artery disease and who are being evaluated for coronary artery bypass surgery. These typically are patients who are presenting with a chest pain syndrome and may have had a myocardial infarction. Most have undergone noninvasive testing as a part of the

pre-catheterization work-up. Other patients undergoing catheterization are those with valve disease, previous bypass surgery, congenital heart disease, conduction disturbances, intrinsic cardiac muscle disease (cardiomyopathy), and evaluation of the great vessels.

Patients included in the study were those with a critical stenosis of the left anterior descending coronary artery alone, the right coronary artery alone, or no critical stenosis in any coronary artery. In the simplified coronary artery disease model the left anterior descending coronary artery supplies blood to the anterior wall of the heart and the right coronary artery supplies blood to the inferior wall of the heart (INTRODUCTION III.1, reference 1) and these two walls form the borders of the outline of the ventricle when it is filmed in the thirty degree right anterior oblique projection. Therefore, as the disease model suggests, a stenosis in either of these arteries would be expected to affect the regions of muscle that are visualized using the ventriculogram. The normal group provided a population of control patients.

The degree of stenosis of a coronary artery is evaluated by filming the dye-filled artery in different projections and estimating the proportion of the diameter of the artery that has been narrowed. This estimation is done by a consensus agreement within a group of cardiology fellows and attending cardiologists. Each coronary artery is evaluated in this way and a report written that lists the locations

and magnitudes of all stenoses in each artery, as well as a description of any anatomical variations and collateral circulation.

The NORMAL patients were those with no critical stenoses and no demonstrable heart disease. However, because these patients were those whose signs and symptoms led them to be catheterized, it is doubtful that they were representative of a truly normal population. Unfortunately, catheterization is an invasive procedure with a level of morbidity and mortality (11-13). Catheterizing completely asymptomatic individuals is not justified.

III.2 Ventriculograms

The ventriculograms from all included patients were viewed. Decisions about rhythm, technical quality, and the border of the ventricular cavity were made.

Injection of the radio-opaque dye into the cavity of the left ventricle frequently induces premature ventricular contractions that usually cease with the completion of the injection. The heart beat that immediately follows the premature contractions is a potentiated beat and, like the irregular beats, may not be representative of the baseline cardiac function (14). While the irregular beats are thought to be so dependent upon the sequence of activation of the muscle that they cannot be analyzed, the potentiated beat has been studied as a measure of the maximum contractile function available, the cardiac reserve (LITERATURE REVIEW III.4.3). In this study, only the non-potentiated

regularly conducted beats were analyzed.

The technical quality of the outlines can vary considerably. In an effort to decrease the radiation exposure of the patient and to increase the resolution of the images, the field of exposure to the X-rays is not made as large as possible. Because of this, the entire outline is frequently not seen at one time. This is not a limitation for subjective methods of analysis because by panning the camera over the heart, the entire image is covered and the observer can form a mental image of the entire left ventricle. If a quantitative method that requires the entire outline is used, then either a composite image formed from different beats must be used, or the image must be discarded.

Another limiting technical aspect occurs when the cavity is not sufficiently opacified to determine the exact border of the endocardium. This happens most often when the premature contractions induced by the injection last until most of the dye has been washed out of the cavity by the incoming unopacified blood. The visual contrast between the unopacified muscle and the opacified cavity becomes lost, and the beat cannot be analyzed.

The majority of unanalyzable outlines are those with technically inadequate beats. The rest are due to obliteration of the cavity at end systole. This is felt to occur chiefly in patients with particular ventricular muscle disorders, and is a phenomenon in which the walls of the ventricle appose at end systole and there is no visible outline

(16-18). Patients with unanalyzable outlines were excluded from the study.

III.3 Parameterization

The tangent angle function is a transformation of an outline, and as such has as many data points as the outline from which it came. Since the function is a measure of shape it holds some interest in its basic form, but to be used in statistical applications it must be reduced to a smaller number of data points. This is the process of parameterization.

The approach to parameterization taken in this study involves approximating a set of data by a function whose mathematical form is known, and then using the values of the parameters of the approximation in place of the original data in any applications. For example, the raw data can be approximated by a single value such as the mean. In this case the approximating function and the parameter are the same. Another example is to use as the approximating function a straight line. The form of the approximating function is

$$Y = m X + b$$

and the parameters are m and b.

In parameterizing a set of data no function is the a priori "correct" function to use. The choice depends on the particular application. In general, it is desirable to know what is being discarded from the raw data by using the (simplified) function, and to have some interpretation of

the parameters of the function. Neither of these are necessary conditions, but they make a parameterization easier to understand and more attractive to use.

Several different approaches to parameterizing the tangent angle function were considered. Two were oriented towards considering the left ventricular outline as closed: i.e., the valve openings were included. One approach did not include the valve openings, but was an attempt to parameterize the entire tangent angle function in one approximation. The last approach, the piecewise approach, considered the left ventricular outline to be composed of an anterior and an inferior wall, split at the apex. Each approach had strengths and weaknesses. The final choice was not optimal in every sense, but was biased towards simplicity and ease of interpretation.

III.3.1 Closed (Periodic) Outlines

Although the parts of the left ventricular outline corresponding to the valve openings are not well defined, the points at which the valve tissue is connected to the myocardium are. The outline can be arbitrarily defined across the valve openings by connecting these points with straight lines, thereby giving an outline that has no undefined regions. If the outline is followed around, starting from a particular point, eventually the starting point will be reached again. In this sense, the outline is periodic (figure 1).

The first approach to parameterizing the periodic out-

line used the tangent vector (expressed as a complex number), rather than the tangent angle function. The tangent vector is used in the derivation of the tangent angle function. The derivation and demonstrations of the properties of the tangent vector are in the Appendix. The tangent vector is a complex valued function and if the outline is periodic, is itself periodic. When appropriately normalized, it has the same properties of independence from size, position, and orientation that the tangent angle function has, and is therefore also a measure of shape. Because the tangent vector is periodic, Fourier series suggests itself as a natural parameterization.

When expressed as a complex Fourier series, further interpretations of the tangent vector become clear. The magnitudes of the terms of the series are independent of the orientation of the outline. The magnitude of the first term ranges from zero to one, and is a measure of the amount that the outline deviates from a circle. If the outline is a circle, the magnitude of this term is one and all others are zero. As the outline deviates from a circle, the magnitude of the first term approaches zero. The series can be simplified by truncation, and a smoothed outline recovered. The truncated Fourier series provides the parameters for subsequent statistical analyses, and the smoothed outline corresponding to the truncated Fourier series provides a representation of the information that has been retained.

The second approach to the periodic outline was differ-

ent from the tangent vector approach in that it used the tangent angle function as it is presented in section II of this chapter, but with the outline including the valve regions (dotted region in figure 2). In words, the computation of the tangent angle function begins at the anterior aortic root point, proceeds clockwise to the mitral valve point, and then continues along the lines of the valve regions back to the anterior aortic root point, at which point it has covered one complete revolution, or two pi radians. In this sense, the function is periodic, although it is continually increasing. There is however, a point of view that makes the function truly periodic.

The tangent angle function of a circle is a straight line that rises two pi radians in one revolution, the same amount covered by any simple closed outline. If this line is subtracted from the tangent angle function, the function that remains represents the deviations of the outline from a circle, and is truly periodic. As with the tangent vector, Fourier series is suggested. The series is simplified and the outline smoothed by truncation, with the truncated series providing the parameters for the statistical applications. Also, as with the tangent vector, this is an attractive approach.

Both these approaches are limited for the same reason: the valve regions represent a large portion of the outline, and are arbitrary. Because the valve regions are not the portion of the outline involved with coronary artery and

myocardial pathology, and because they are not well defined, it was felt that to use a method of measuring shape in which the valve regions were integral was not appropriate. While both these methods may have applications to outlines that are truly periodic, they are not well suited to the analysis of left ventricular outlines.

III.3.2 Open (Non-Periodic) Outlines

With the outline and tangent angle function considered without the valve regions, as in sections I and II of this chapter, the methods oriented towards periodic functions are no longer suitable. The first approach was to parameterize the entire tangent angle function with a single approximating function.

Different classes of functions were examined for suitability of parameterizing the entire tangent angle function: polynomials, Fourier series, and Fourier series with the linear trend of the tangent angle function removed. None of these proved satisfactory because of the lack of interpretability of the parameterizations in terms of the coronary artery disease model.

As has been discussed, the disease model relies on the regional distribution of blood flow to the myocardium. In looking at the outline as having no orientation, "regional" has no meaning. Although it is possible to parameterize the entire tangent angle function using a function of sufficient order, the interpretation of the coefficients is not apparent. It was for this reason that the piecewise approach was

examined.

At its most basic level, the coronary artery disease model regards the anterior wall of the ventricle as being supplied with blood by the left anterior descending coronary artery and the inferior wall as being supplied by the right coronary artery. These walls, joined at the apex, form the outline of the left ventricle that is seen during thirty degree right anterior oblique ventriculography. For these reasons regarding the outline, and the tangent angle function, as being composed of these same walls is an attractive approach.

The piecewise parameterization divides the ventricle into the two walls at the apex (figure 9). Each piece of the tangent angle function (corresponding to a wall) is approximated by a polynomial function individually, and the coefficients of the polynomials constitute the shape parameters. Unlike the other approaches, the individual parameters are associated with a particular wall of the ventricle, providing for interpretation and association with the disease model.

The order of the polynomial ultimately used is a trade-off among the number of parameters, faithfulness of the parameterization in describing the intricacies of the data being parameterized, and the interpretability of the parameters. This is truly a trade-off. Unless the original data being parameterized are fairly simple, all of these concerns can not be met simultaneously. In parameterizing

the tangent angle functions of left ventricular outlines in the context of the coronary artery disease model, interpretability was felt to be the most important.

III.4 Discriminant Analysis

At this point in the analysis of left ventricular shape and coronary artery disease, a cohort of patients has been defined and the data on each patient (the outlines of the left ventricle at end diastole and end systole) reduced to a small set of parameters. A useful point of view is that each patient has been replaced by the parameters and the coronary artery group membership information. Discriminant analysis is the appropriate technique with which to address the allocation - discrimination problem that provides the thesis of this dissertation (INTRODUCTION I.2), and proceeds as follows (19,20).

Given a cohort of individuals, each of whom is represented by a set of parameters and membership in a group, discriminant analysis constructs variables (canonical variables), each of which is a linear combination of the parameters. The canonical variables maximally discriminate among the groups in the sense that the between group variability is maximized with respect to the within group variability (20). In other words, the means of the groups will be as far apart as possible with respect to the dispersion within the groups. This technique allows the parameters to be used in the allocation - discrimination problem without having to arbitrarily pick one parameter or one combination of parame-

ters. All parameters are combined in the construction of the canonical variables, and the particular combination is optimal.

The canonical variables are useful for evaluating the data from which they were derived. A plot of the individuals on the canonical variable axes allows a graphic representation of the degree of separation among the groups. As is the case with the coronary artery disease cohort, the basis for forming the original groups (location of critical stenoses) may not be perfect, and the plot can lend some insight into this allocation. The degree of homogeneity of the groups is apparent and individuals who seem to be very different from their group can be quickly identified.

Unknown individuals are allocated to one of the groups in a straightforward way. In addition to canonical variables, discriminant analysis generates discriminant functions: functions that allow the computation of the distance any individual is from the mean of a group, in normalized units. With these distances, the posterior probability that the unknown individual came from each group is easily determined (19). The individual is then allocated to the group that gives the highest probability of membership. This is the application most often used in medical diagnostics.

The specific canonical variables of this study are presented in RESULTS. Interpretations of the canonical variable coefficients turn out to be interesting, particularly in the context of the coronary artery disease model.

In this chapter the more general aspects of the tangent angle function and of the clinical study have been addressed. The specific literature is reviewed in the next chapter. The specific details of the study are presented in METHODS.

CHAPTER 3: LITERATURE REVIEW

> "In discussing the movements and functions of the heart and arteries, we should first consider what others have said on these matters, and what the common and traditional viewpoint is." William Harvey, 1628 (22)

The literature relevant to the thesis of this dissertation has been grouped as follows:

I. History.

II. Methods of describing shape in the clinical setting.

III. Applications of the ventriculogram.

IV. Coronary artery disease model.

V. Tangent angle function.

Sections I - III are concerned with the role of left ventricular shape in clinical cardiology and the approaches taken by others to measure shape. Section IV concerns the aspects of the coronary artery disease model used in the design of the study to examine the tangent angle function in the clinical setting. Section V is directed to the tangent angle function itself.

Because ventriculography is routinely performed during cardiac catheterization, virtually all publications concerned with catheterization make some reference to the ventriculogram. As a result, the literature of ventriculography is a significant percentage of the recent cardiology literature. Therefore, in section III the review has been limited to studies in which the primary focus was on the

ventriculogram. In section III.3, shape and coronary artery bypass, only illustrative studies are discussed.

Section I is particularly illuminating. The observations on the shape and movements of the heart, and the problems that have occupied the time and energy of so many researchers, are far from new.

I. HISTORY OF OBSERVATIONS ON SHAPE OF THE HEART

Angiographic methods of visualizing the endocardial surface of the heart were not used until the early 1950's. Before angiography, physiologists were limited initially to direct observation of the beating heart, and later to fluoroscopic shadows of the pericardial surface.

William Harvey, who is credited with the first correct interpretation of the expulsion of blood from the left ventricle during systole (21), also provided one of the earliest descriptions of the movement and shape of the heart:

> "...The heart is lifted, and rises up to the apex, so that it strikes the chest at that moment..." (23)
>
> "...It contracts all over, but particularly to the sides, so that it looks narrower and longer." (23)
>
> "...that the heart contracts in a continuous movement with the auricles, but also a peculiar sidewise turning toward the right ventricle as if it twists slightly on itself in performing its work." (24).

In 1891, Haycraft reported his observations on the contraction of the heart as viewed through the cardioscope - a lens covered with a rectangular grid that allowed him to

construct accurate sketches of the heart at various points in the cardiac cycle (26). Haycraft confirmed Harvey's observations:

> "...the long axes and also the front to back diameters diminish during systole and increase during diastole, so that in the latter condition the heart bulges towards the sternum and the apex descends away from the base."

In addition, Haycraft commented on the problem of separating motion of the heart as a whole from that of shape change:

> "In the ...(in situ)... case the organ is supported in nearly its natural position by the tissue and organs behind it, and it chiefly changes in volume, in the ...(open chest)... case the heart has fallen back into the chest and changes in volume, and in addition it shifts its position as a whole. We have therefore a complication here, which will have to be carefully unravelled."

In 1926, Chamberlain and Dock reported on the motion of the heart as photographed from a fluoroscopy screen (27). While much of their report was concerned with the technology involved in taking the photographs, they described the motion of the heart in one normal subject and in two patients with mitral valve disease. They concluded that in order to obtain useful films:

(1) One has to be able to accurately align successive frames in order to look at motion.

(2) There must be a film-synchronized electrocardiogram.

(3) During filming, the patient should maintain full inspiration.

(4) The heart motion is best measured with the aid of lines drawn on the film, perpendicular to the film border.

(5) A successful analysis will involve examining many points on the border of the heart.

Each of these principles is incorporated in all current methods of measuring left ventricular shape and shape change.

In 1951, Rushmer and Crystal (28) and Rushmer and Thal (29) reported on the image of the heart during cinefluorographic angiocardiography. These authors noted that during systole there was a marked decrease in the width of the ventricle relative to the change in length, again confirming the observations of Harvey some 320 years before. They then went further and made measurements of the area and geometry of the ventricle as a function of time over the cardiac cycle (29). In order to do this, they introduced a long axis and a perpendicular bisector to the long axis - a technique used in one form or another by most investigators of left ventricular shape since then.

II. METHODS OF DESCRIBING SHAPE FROM CINEANGIOGRAPHIC IMAGES

The methods of describing the ventriculogram can be divided into groups as being reference-frame based, reference-frame independent, and subjective. Of the reference-frame based methods, the internal reference frame has recieved the most attention. The reference-frame independent methods tend to be global measures and are not widely used. In the applications literature, the subjective method of ventriculogram analysis predominates.

II.1 Internal Reference Frame

As discussed in INTRODUCTION IV.3 (Reference Frames), the internal reference-frame methods arose from a desire to abstract the regional motion of the walls of the heart by "correcting" the observed motion of the walls for the "artifactual" motion of the heart as a whole. The methods differ in the way in which the reference frame is defined, and in the particular measurements taken (29-43). The prototype of these methods, and the first to introduce the concept of "hemiaxes", is the study of Herman et al, in 1967 (30).

In their study, Herman et al considered the midpoint of the aortic valve and the cardiac apex to be the "fixed" points that defined the long axis. Any motion of the long axis during the cardiac cycle was felt to be due to the rocking and rotation of the heart as a whole. Therefore, before any analysis, successive frames of the ventriculogram were aligned by superimposing the long axes and the midpoints of the aortic roots. In other words, the long axis and the aortic root midpoint constituted the frame of reference from which to view the contraction of the ventricle.

The constructed hemiaxes used by Herman et al were three perpendicular lines to the end diastolic long axis. They also constructed two lines through the center of, but at 45 degrees to, the long axis as the radial axes. They presented plots of the length of these axes as a function of time, and were able to show differences among patients with and without coronary artery disease. They also introduced

the now accepted nomenclature for the different contraction patterns. Most investigators who have studied a different method for analyzing wall motion have done so by varying one or more of the components of this prototype.

II.1.1 Long Axis Definition

The definition of the long axis was addressed by two groups (31,32). In one case the long axis started at the inferior aspect of the aortic root (31), and in the other it was defined as being the line from the apex that bisected the area of the left ventricle (32).

II.1.2 Method of Internal Alignment

The method of alignment of the end diastolic and end systolic images used by Herman et al was to rotate the images until the long axes were parallel, and then superimpose the aortic valve points. This alignment was varied in twelve studies in which the introduction of a new method of shape analysis was central to the investigation (32-43). Alignment of only the long axis, with no other superpostion was used in five studies (31,33,35-37); the midpoints of the long axes at end diastole and end systole were superimposed in two studies (34,43); the points of intersection of the long axes of the end diastolic and end systolic frames were considered to be superimposable in three (32,39,40); and the centers of gravity of the images were superimposed in two (38,41). In a single study, the center of gravity and the midpoint of the valve plane were used in a complicated realignment scheme (42).

II.1.3 Radii and Bisectors

Herman et al used lines perpendicular to the long axis and lines oriented radially from the midpoint of the long axis as the measures of wall motion. The number of hemiaxes was varied in eight studies: one hemiaxis was used in two (31,33), three or four hemiaxes in three (32,40,44), nine hemiaxes in one (35), fifty hemiaxes in one (36), and fifty four in one study (34). Radial axes were used in five studies, with the number of radial lines used being twelve (40), fifty four (37), seventy two (34), ninety (42), and one hundred twenty eight (41). Two studies did not use axes per se, but points on the perimeter (38,45). One study used radially oriented lines, but looked at the square root of the enclosed pie shaped areas (39), and one used the direction of motion of points on the outline itself to determine the location of the origin of the lines to be measured (43).

It should be emphasized that there is no basis for using one of these methods over another (INTRODUCTION IV.3). They are all based on the concept that part of the motion of the heart is artifactual and part is real, a concept that is conceptually unverifiable. In addition, constructed points and lines are integral parts of all the methods. The problems associated with these have been discussed.

II.2 External Reference Frame

The external reference-frame philosophy is to correct only for motion of the heart that is clearly that of the heart as a whole (e.g. movement of the patient with respect

to the X-ray camera, or movement of the heart caused by respiration). Because it involves fewer assumptions, this is a more conservative philosophy than that of the internal reference frame.

This approach was taken by Chaitman et al (46). They required that the diaphragm and two external markers on the patient's chest not move during the analysis. They compared their method, which involved no realignment, with two different methods that did involve realignment, and were able to find significant differences in some patients. Two points deserve comment.

The first point is that in this paper no method of quantitating the change in the outline from end diastole to end systole was offered. While the authors correctly pointed out that the measurement of wall motion depends on the particular internal reference frame used, they did not provide an alternative using the external reference frame.

The second point is that they did not address the problems that will arise in cases where there is in fact significant motion of the heart as a whole during the cardiac cycle. In a case report of massive pericardial effusion, Rizi et al reported marked motion of the heart as a whole (47). The motion was sufficiently dramatic that it could not have been due to regional contraction, but this motion would have been considered part of the contraction by the external reference approach. Since this dramatic motion must at some time have been significant, but less than dra-

matic, it is not sufficient to only use the external reference approach is cases other that this. A supporting conclusion was reached by Clayton et al in a vector analysis of a simple model of left ventricular contraction (48). The motion of the heart as a whole cannot be ignored.

II.3 Myocardial Markers

Some authors have studied left ventricular wall motion by identifying specific areas of myocardium with metal clips inserted either via catheters or at the time of open chest procedures (e.g. cardiac transplantation). In this way, they addressed the problem of determining which regions of the heart being measured at end diastole correspond to those being measured at end systole. These studies took place in dogs (49,50,56), and in man (51-55), and involved inserting the clips into the endocardial surface (49,56), midwall (53), epicardial surface (51,52,54), or both endocardial and epicardial surfaces (50). The last study allowed the measurement of wall thickness as well as of motion. One study, instead of metal clips, tracked the three-dimensional movement of the epicardial coronary artery bifurcations with interactive real time computer graphics (55).

While with these studies one has indeed identified a specific piece of muscle, a reference frame was still necessary to describe the motion of the clips. For example, Ingels et al (53), in addition to measuring the reference-frame free inter-clip distances, measured hemiaxis shortening of the clips: an internal reference frame. Carlson

(49) plotted the movements of the clips in space: an external reference frame.

Smulyan et al (57) did not use clips, but studied patients with left ventricular aneurysms in which the region of infarction was clearly demarcated from the surrounding viable regions. The points of demarcation served as a pair of markers that were connected by a straight line and, with the left ventricular silhouette, defined two regions - "normal" and "aneurysmal". The change in these areas with systole and with aneurysmectomy was studied - an internal reference frame type approach.

The lack of consensus concerning the optimal reference frame method of analysis of the ventriculogram is well illustrated by the number of papers devoted to the subject. Recognizing the problems inherent in the reference-frame approach, some groups have examined methods that do not use a reference frame. These can be divided into the global indices, approximations to curvature, and the completely subjective approach.

II.4 Global Indices of Shape

Global indices of shape reduce the entire outline, or a portion of the outline, to a single number. The shape parameter of Gibson et al (58) divided the cavity area by the squared perimeter and normalized the result to be unity for a circle. While there are relatively minor problems with this approach concerning the measurement of perimeter and the assumption of the closure of the outline at the aor-

tic and mitral valves, a major drawback is the built-in lack of uniqueness of the measure before any parameterization is attempted. Since it is based only on the total perimeter and the area enclosed, all local features of shape have been lost. Many outlines can have different shapes, but have the same value of the measure.

Masuda et al (59) looked at the area enclosed by each transverse slice obtained by a computerized axial tomographic (CAT) scan that was gaited to the electrocardiogram. This was a disguised external reference-frame method. The width and the orientation of the slices were determined relative to the X-ray source.

II.5 Approximations of Curvature

Two groups utilized curvature in their approach to left ventricular shape analysis. Hutchins et al (60) looked at autopsy specimens and, by hand, determined the radius of the circle that best approximated the walls of the ventricles. Greenbaum and Gibson (61) did not look at curvature per se, but rather whether each wall was convex always, concave always, or mixed. These are in fact reference-frame independent methods but, like the global parameter methods, both lose almost all local features of shape.

II.6 Subjective Methods

The subjective method of analyzing the ventriculogram is based on the experience and judgement of an observer. No measurements are taken, and usually no realignment is done. This approach recognizes the limitations of the quantitative

methods and the remarkable pattern recognition abilities of human brains, but suffers from a lack of standardization and reproducibility. This approach is the one most often used in the evaluation of individual patients. Two studies are representative.

Hamby et al studied patients who presented with "late systolic bulging of the left ventricular wall" (62). No definition or measurement of bulging was given. Patients either had bulging or they did not.

In a two dimensional echocardiography study, Horowitz et al looked at patients who had suffered an acute myocardial infarction (63). The ventricle was divided into segments, and each was graded by multiple observers as being hypokinetic (score of 1), or akinetic (score of 2). Total wall motion was the sum of the scores, averaged over observers. The definition of hypokinetic was "decreased relative motion" and of akinetic was "no motion".

These studies were similar in their lack of standardization and their subjective criteria of evaluation. The limitations involved in using measures such as these include bias, lack of reproducibility, low precision, and low resolution. These limitations are not sufficiently countered by the intuitiveness of the measure or by the ease of implementation.

II.7 Multiple Methods and Comparisons

With the large number of methods available to describe left ventricular wall motion, many authors used more that a

single approach. Of the papers already discussed, six reported the results of using two or more approaches to wall motion analysis, without specifically attempting to compare the methods (29,37,39,45,52,59). Because there is no standard for wall motion, there is no basis on which to evaluate the differences in the observations.

Studies that specifically attempt to determine the "most correct" method of analysis, rather than introduce a new method by comparing it to an existing one, have begun to appear more recently. These studies compared three methods (43,64), six methods (40,65), and nineteen methods (66) to each other. One study looked at three methods, but in relationship to a fourth (67). As with the studies that did not specifically compare results, there is no basis on which to evaluate these reports. No method of analysis is more correct than another. They differ only in the assumptions made and in the sources of bias.

III. SHAPE AND CLINICAL CARDIOLOGY

The shape and systolic change in shape of the left ventricle have long been of interest to clinicians and physiologists. Harvey commented on the apex beat (23) and on the appearance of the heart when an animal is near death (25). Miller and Matthews, in 1909, noted dilatation of the ventricle of a dog when the left coronary artery was ligated (68). Herrick, in an autopsy study in 1912 noted fibrosis and aneurysmal dilatation in the ventricles of patients with

occluded coronary arteries (69). Chamberlain and Dock introduced the early fluoroscopic cinematograph of Ruggles and Fletcher by studying a normal subject and two patients with mitral valve disease (27), and in 1935 Tennant and Wiggers performed the now classic experiment of accurately recording the contraction of the heart during the acute ischemia produced by clamping a coronary artery (70).

With the advent of contrast ventriculography and coronary angiography, the image of the left ventricle became an essential ingredient in most studies of cardiac function. While in many of these, left ventricular shape and wall motion analysis did not play a central role, in others they represented the primary focus of the study. For the purposes of review, the studies in which shape was central are divided into the following groups:

(1) Myocardial ischemia.

(2) Non-coronary, cardiac disease.

(3) Coronary artery bypass.

(4) Non surgical interventions on left ventricular function.

Within each group, different populations of patients were studied and different hypotheses tested. As a result, the studies differ in major ways and the influence of the method of shape analysis on the final conclusions is difficult to address. However, the role of left ventricular shape in clinical cardiology and in cardiac research, and the need for a standard technique of measuring shape, can be readily appreciated.

III.1 Myocardial Ischemia

III.1.1 Coronary Artery Disease

Herman et al continued their 1967 study with a now landmark paper in which patients were divided into those with normal and those with abnormal wall motion, based on subjective criteria (71). Several parameters were examined for correlation to this grouping, including the presence of a coronary artery lesion. All of the abnormal wall motion patients had coronary artery disease, but so did two thirds of the normal wall motion patients, showing that normal wall motion does not rule out coronary artery disease. This result was verified in three other studies (72-74). In these studies only patients with coronary artery disease were examined, and subjective interpretations of wall motion were made. Two studies reported more positive results, showing a correlation between the amount of coronary artery disease and regional wall motion (75), and between wall motion and the progression of coronary artery disease with time (76).

Two studies that looked at myocardial perfusion (as assessed by thallium perfusion scan) gave results intermediate to those that only looked at coronary artery disease (77,78). Wall motion was strongly correlated with perfusion, while the correlation with coronary artery disease was more variable.

Of these studies, only three used quantitative methods (75,76,78), with a different method used in each.

III.1.2 Single Vessel Disease

Single vessel coronary artery disease is of clinical and physiological interest because, from the coronary artery disease model, the ischemia is expected to affect only a discrete definable region of myocardium. The regions of myocardium subserved by undiseased coronary arteries should function normally, or even compensate for the affected regions with increased function.

Codini et al studied patients with occlusive disease of the right coronary artery who had undergone coronary artery bypass surgery (79). By a subjective analysis, 29% of the patients had a preoperative ventriculographic abnormality. A myocardial infarction had been suffered by 34%. While they did not report which of the patients had both a myocardial infarction and a contraction abnormality, from the percentages, some of the patients with myocardial infarctions had normal ventriculograms.

Brooks et al reviewed the catheterization records of patients who had a critical stenosis of only the left anterior descending coronary artery (80). The location of the stenosis was graded as being proximal, mid or distal. The ventriculogram was divided into five segments and wall motion was evaluated by a subjective technique. They found that the mean number of abnormally contracting segments increased as the coronary stenosis became more proximal, and was higher in the patients who had suffered an infarction. They did not report on the locations of the abnormal seg-

ments or on the correlation between abnormal segment location and myocardial infarction.

Kumpuris et al reported on the hemiaxis measured shortening velocity of portions of the left ventricular outline from the ventriculogram (an internal reference frame) in patients with isolated stenosis of the left anterior descending coronary artery or isolated stenosis of the right coronary artery (81). The location of the stenosis was graded as being proximal, mid or distal for the left anterior descending and proximal or distal for the right. The presence of a previous infarction was noted. Patients with no stenoses served as controls.

The results of this study were similar to those of Brooks et al, and were as predicted by the coronary artery disease model. If there was a stenosis and a myocardial infarction, the shortening velocity was decreased in the region subserved by the affected artery. If there was a stenosis of the left anterior descending coronary artery but no infarction, the severity of the contraction abnormality was more severe for the proximal versus the distal stenoses. In patients with stenoses of the right coronary artery but no infarction, there was no decrease in shortening velocity.

These three studies support the coronary artery disease model. Although each used a different method of ventriculographic analysis, including the use of a velocity by one, the results are similar. The location of a critical stenosis, particularly if there has also been a myocardial

infarction, can be related to the contraction pattern as it is assessed from the ventriculogram.

III.1.3 Myocardial Infarction

Virtually all studies of patients who are catheterized include a sub-population of patients who have had a myocardial infarction. Some studies have addressed the shape of the left ventricle in this sub-population exclusively.

Two groups studied patients during the acute phase of myocardial infarction (82,83). Both looked at hemiaxis shortening and "per cent abnormally contracting segments", and concluded that the ventriculogram correlated well with other measures of left ventricular function. In studying convalescent and healed post-infarction patients, Field et al (84) found that the extent of asynergy did not separate patients with heart failure from those without, because of the large variability in the measure of wall motion. Miller et al (85) found some correlation to other measures of ventricular function in patients post-infarction and Ideker et al (86) found that a hemiaxis measure of asynergy varied with the histologic presence of fibrosis in a pathology study.

III.1.4 Phases of the Cardiac Cycle

The majority of studies of the ventriculogram are based on analyzing the change in the left ventricle from end diastole to end systole - the contraction phase of the cardiac cycle. Some groups have looked at other parts of the cycle.

Left ventricular wall motion during isovolumic systole

was examined by two groups, both of whom found that expansion of the equatorial region of the ventricle was related to cardiac and coronary disease (87,88). Leighton et al found that one half way through systole, wall motion in many patients with coronary artery disease was significantly different from that of patients without coronary artery disease, but was often normal at end systole (89). When isovolumic relaxation was examined, one group concluded that early diastolic bulging (segmental early relaxation phenomenon) was a normal phenomenon (90), while others felt it to be indicative of cardiac disease (91,92).

The studies discussed have all been ones in which the focus of the investigation was left ventricular shape or wall motion in patients with myocardial ischemia. There is no standardization of analysis and in most cases there are studies with contradictory results. Because of the lack of standardization it is difficult to form a precise overall conclusion concerning the shape and motion of the heart in this clinical situation.

III.2 Non-Coronary Artery Cardiac Disease

Fewer studies of ventriculogram recorded left ventricular shape in the setting of non-coronary disease were found than in the setting of ischemia. These were concerned with valve, myocardial, and conduction tissue disease.

III.2.1 Valve Disease

Aortic valve disease was studied with the "eccentricity" index by two groups, both of whom found an abnormal

roundness of the ventricle in volume overload that was corrected by valve surgery (93,94). A third group studied regional wall motion using hemiaxes in patients with aortic and mitral regurgitation. When compared with a group of control patients, regional and global abnormalities were found (95).

III.2.2 Myocardial Disease

The eccentricity index was also used in studies of myocardial disease. In patients with idiopathic hypertrophic subaortic stenosis, the ventricle became less round than normal (96) and in primary myocardial disease it became more round (97). The latter study also showed some more localized disorders, but by subjective techniques. In a similar investigation, patients with Chagas' disease were grouped according to subjective wall motion and correlates to other parameters were found (98).

III.2.3 Conduction Tissue Disease

A single study looked at the wall motion of patients with left bundle branch block and concluded that ten of twelve had abnormal wall motion along at least one hemiaxis, while by qualitative methods only six of fifteen patients were abnormal (99). As with many other studies, since there are no standards of wall motion, a large group of controls were examined in order to establish the normal range of the method.

III.3 Coronary Artery Bypass

Coronary artery bypass (CAB) surgery is the focus of a

large percentage of the recent cardiology literature. Neither indications for, nor efficacy of, the procedure have been completely agreed upon, for reasons that are beyond the scope of this review. Uniform consensus, however, dictates that every patient who is considered for the procedure undergo a diagnostic catheterization, and the results of the catheterization provide a large part of the data upon which the decision to operate is made. In addition, many patients who are operated upon undergo follow-up catheterizations months and years after the bypass. These follow up procedures provide the data for the pre and the post CAB surgery ventricular function studies.

As with the other literature reviewed, the differences among studies are usually more numerous than just differences among the methods of analysis of left ventricular shape. Such factors as patient selection, CAB graft patency, and infarction status have prime importance in determining the results of any study. However, since CAB is designed to improve the function of specific regions of the myocardium, its effect on regional shape and wall motion is usually an important part of the results of the studies. In this context, it is particularly bothersome that there is no standardization or well accepted method of describing the shape of the left ventricle. A few representative studies differing in post CAB results and a few looking at predictive variables are illustrative.

III.3.1 Improvement with Bypass

Four uncontrolled studies in which left ventricular wall motion improved after CAB surgery are representative of positive studies. Chatterjee et al used subjective analysis and showed that abnormal wall motion before CAB improved to normal in five of six patients after CAB, while the sixth was normal before CAB and remained normal after CAB (100). This same group studied twenty nine patients before and after CAB using a hemiaxis description of wall motion with patients who were catheterized but not operated upon providing the normal values (101). Wall motion improved in the non-infarcted areas.

Wolf et al studied the thirty seven patients who agreed to a post CAB catheterization (102). Regions of the ventricle were classified as recieving blood supply from one of three groups: from a non-operated artery, from a bypassed artery whose graft was patent, or from a bypassed artery whose graft was closed. The regions were also subgrouped into pre-operative normal or sub-normal wall motion. Wall motion was measured with hemiaxis methods. The results were as the disease model predicted: abnormal wall motion improved if there was a patent graft, while wall motion deteriorated if the graft was occluded.

The study of Mintz et al was different from the others in that wall motion was assessed using surgically implanted epicardial markers and an internal reference frame alignment (103). Total wall motion was felt to have significantly

improved with CAB, due mostly to improvement in areas of previous infarction. These results should be interpreted with caution because of the use of epicardial markers and because of the improvement of performance in areas of the ventricle that would be expected to be mostly fibrous scar tissue.

III.3.2 Lack of Improvement with Bypass

Five studies are representative of those reporting negative or equivocal results of CAB. Bourassa et al reported that only one half of the regions subserved by patent grafts showed improved wall motion (104). Griffith et al reported that of the regions subserved by a patent graft, 22% improved and 35% actually deteriorated post operatively (105). Two studies reported results sufficiently pessimistic to conclude that CAB does not improve left ventricular function (106,107). It should be noted that although these studies reported results that may be representative of early experience with CAB and patient selection, the lack of standardization makes further inference difficult.

III.3.3 Prognostic Indices

Three studies are of interest because they used wall motion in the derivation of prognostic indices. Levine et al developed an "index of vascularity" and tried to show a correlation to the per cent change in hemiaxis shortening after CAB (108). The Collaborative Study in Coronary Artery Surgery (CASS) used a multivariate approach to predict CAB operative mortality. A subjectively derived measure of wall

motion was the fourth of six variables included in the stepwise discriminant analysis (109). Similar results were also reported from the CASS data elsewhere (110).

III.4 (Reversible) Intervention Ventriculography

The function of the heart can be transiently influenced by drugs, changes in the heart's rhythm and rate, and changes in cardiac demand. These reversible interventions (as opposed to the irreversible surgical interventions) have provided the material for studying the change in wall motion caused by a change in overall cardiac function. As with the other areas reviewed, the purpose here is to illustrate the areas of application of left ventricular wall motion analysis.

III.4.1 Nitroglycerin, Digitalis, and Epinephrine

Several studies have examined the effect of nitroglycerin on wall motion. Improvement of wall motion in regions of presumed ischemia following the administration of nitroglycerin was observed in four studies. Three used the location of a coronary artery stenosis (111,112,113), and one used radionuclide perfusion scanning (114), to determine the region of ischemia. One study looked at overall wall motion after nitroglycerin in patients with coronary artery disease (115), one showed that during catheterization the development of spontaneous angina pectoris produced wall motion changes that were reversed with nitroglycerin (116), and one looked at the degree of myocardial fibrosis as assessed by biopsy and the improvement of wall motion after nitroglyce-

rin administration (117).

Two studies examined the acute effect of intravenous digitalis-like drugs. In both, improvement of overall function was noted, as was improvement in one half to two thirds of the regional segments (118,119). In some cases, regional function deteriorated (119). These results were similar to those observed with the acute administration of epinephrine (120).

III.4.2 Propranolol and Nifedipine

Propranolol and nifedipine are both negative inotropic agents that, because of the different levels of circulatory control, have both positive and negative effects on heart function. In three studies of the acute effects of propranolol, regional left ventricular function deteriorated in one (121) and did not change in two (122,123). The single nifedipine study looked at implanted midwall marker motion and found that the effect depended on whether the drug was given intracoronary or intravenous (124). All four studies characterized wall motion differently.

III.4.3 Post-Extrasystolic Potentiation and Pacing

Post-extra systolic potentiation (PESP) is the technique of looking at the changes in ventricular function that are induced in the beat following a premature (extra) systole. These studies were similar to the drug studies and similar hypotheses were tested. With PESP regional wall motion improved (125), was correlated with recovery of cardiac function after CAB (126), and was felt to be artifactu-

ally increased due to improved contraction in other areas (127).

Pacing the heart by electrically stimulating the atria or the right ventricle increases oxygen consumption by the heart, and is expected to cause wall motion to deteriorate in regions that have a marginal blood (oxygen) supply. This hypothesis was confirmed (128-130) and correlated to an improvement in function at rest after CAB (131).

III.4.4 Combined Interventions

Several studies examined multiple interventions that were administered either simultaneously or sequentially. Two groups showed nitroglycerin to be similar to PESP, with no added benefit when the two were administered simultaneously (132,133). In one study nitroglycerin, PESP, and pacing were examined sequentially (134), while in a different study nitroglycerin was administered during pacing (135). The effect of atenolol (a propranolol-like drug) was compared to the effect of nitroglycerin in patients with and without coronary artery disease (136), and lastly isometric exercise was added to atrial pacing in an effort to significantly decrease left ventricular function (137). In all these studies a pre and a post intervention state was examined using different measures of left ventricular wall motion.

In this section the areas of clinical and physiologic research that involve analysis of the ventriculogram have been reviewed. The emphasis has been on illustrating the

diversity of conclusions and the complete lack of standardization of the method of analysis of the ventriculogram. The role of the ventriculogram in cardiology, and the need for a single method of analysis, is apparent.

IV. CORONARY ARTERY CRITICAL STENOSIS

The degree of coronary artery stenosis that is accepted as being critical is central to all investigations of the effects of coronary artery disease. Because of the complexity of the physiology involved in the dynamics of myocardial oxygen demand and supply, accepting a single value of stenosis as being critical will not be appropriate for all patients. However, despite the degree of simplification imposed, there is a general consensus among investigators that a narrowing of 50% of the diameter of a coronary artery (decreasing the luminal area to 25% of the unaffected areas) will compromise the blood flow to the subserved myocardium.

Three experimental studies in dogs and one in-vitro study directly measured the hemodynamics of different caliber artery stenoses. May et al applied an external clamp to the in-vivo iliac arteries of dogs (138). They noted a reduction in the resting pressure and flow distal to the stenosis when the diameter of the artery was reduced 55% (area of the arterial segment reduced 80%).

Feldman et al studied experimentally produced narrowings in in-vivo dog coronary arteries (139). They found that resting coronary blood flow was not decreased until the

arterial diameter was decreased 80% if the narrowing was short, but that blood flow was affected by 40% to 60% narrowings when the length of the stenosis was increased to ten millimeters. They also studied the increase in flow after the stenosis was released: the reactive hyperemic flow. In this high flow state, the 40% to 60% narrowings had an even more marked effect on coronary flow. This supports the idea that a narrowing of 50% of the diameter of a coronary artery may not be significant at rest, but can impinge on blood flow during the high flow requirements of hemodynamic stress. This was verified by the same group in a later study in which a short 60% diameter stenosis of a coronary artery was studied (140). This narrowing produced no compromise of flow at rest, but during the hyperemic increase in demand, flow was decreased and a pressure gradient was recorded across the stenosis.

Sabbah et al studied an in-vitro coronary artery preparation (141). They found that a short 50% decrease in the diameter of the artery caused a negligable decrease in flow under resting conditions. However, when three stenoses were imposed on the artery, flow decreased 20%, as compared to the 8% reduction observed with a single stenosis of equivalent length. Thus, multiple stenoses may be critical at rest, whereas a single one may not be.

Two studies were addressed to angiographic measurements of coronary artery stenoses in man. Rafflenbeul et al studied the relationship of coronary artery stenoses to the

presence of chest pain, collateral circulation, and regional wall motion (142). They found that the critical stenosis was around 50% of the diameter of the left anterior descending coronary artery, but less for the right coronary artery: as low as 40%. McMahon et al studied patients who had chest pain at rest and determined that the critical stenosis was a reduction of the diameter by 72% (143). This result was similar to the 80% reduction needed to decrease the resting flow that was observed by Feldman et al.

This group of studies indicates that during times of increased demand, a 50% reduction in the diameter of a coronary artery will impinge on the blood flow. This is the definition of a critical stenosis that is used by most clinical investigators (144).

V. THE TANGENT ANGLE FUNCTION

The literature of the tangent angle function seems to be confined chiefly to military applications. The images being examined in these studies (the silhouettes of tanks and aircraft mostly) are usually piecewise linear outlines that therefore have piecewise constant tangent angle functions. Parameterization and analysis of these functions is substantially different from that of the tangent angle functions of left ventricular outlines.

Fritzsche, in 1961, studied the transformation of hand written characters by the tangent angle function (146). He parameterized the functions by Fourier series, and con-

cluded:

"(1) Each character is representable by a unique mathematical expression.
(2) The recognition technique is independent of character size.
(3) The technique is independent of character orientation.
(4) The gross features of a character are identified by using only a limited number of terms of the mathematical expression."

He also noted that the technique was sensitive to irregularities or distortions of standard figures. This was probably because of the stylized nature of the images he was analyzing.

Raudseps, in 1965, studied the transformations of tank and aircraft outlines by the tangent angle function (147). Much of this work was concerned with the effect of the resolution of the raw data on the function. He also used Fourier series as the parameterization scheme and plotted different coefficients to obtain discrimination among the objects. Apparently, much of the work was motivated by computational constraints that are no longer relevant.

Zahn and Roskies studied the Fourier series of the tangent angle function and its derivative for different shapes (148). They examined the properties of the Fourier coefficients and showed that these were true measures of shape. They examined many symmetries of shape in relation to the Fourier coefficients.

Bookstein discussed the tangent angle function in his monograph reviewing the measurement of shape (6). Much of the discussion of shape presented earlier is present in this

book, and the properties of the tangent angle function presented in this study are expanded. Bookstein also offers other applications of shape measured by the tangent angle function, particularly to the analysis of the shapes of skull X-rays.

Wallace et al examined the tangent angle functions of several two-dimensional projections of aircraft (149). This was the only reference found that addressed the three-dimensional objects generating the two dimensional outlines. The approach taken to analyzing the three-dimensional objects was to construct feature vectors composed of information from the different two-dimensional projections. This study made extensive use of the piecewise linear nature of the objects being studied, an aspect not shared by left ventricular outlines.

Each of these studies presented a different application of the tangent angle function. Each considered only closed (periodic) outlines, and each used either Fourier series or information from curvature maxima as the shape descriptors. These investigations were of general relevance to the study of left ventricular outlines, but the specifics of the basic data being investigated limited the applicablility of the results.

CHAPTER 4: METHODS

I. CLINICAL MATERIAL

I.1 Clinical and Angiographic Criteria for Inclusion

The population considered for inclusion in the study consisted of those patients recorded as having undergone cardiac catheterization at the Mount Sinai Hospital between January 1, 1978 and December 31, 1979.

The catheterization procedure and interpretation of the results were carried out by one or more cardiology fellows and attending cardiologists. A patient report consisting of a short clinical history, physical findings, relevant laboratory data, catheterization results (hemodynamic, angiographic, ventriculographic, and the results of any pharmacologic or physiologic interventions), and any interpretations was the source of the clinical and angiographic data used to classify the patients for the study. The ventriculogram cine itself was used as the source of all ventriculographic data.

Based on the reports, patients falling into one of the following three groups met the clinical criteria for inclusion in the study:

(1) Significant stenosis (disease) of the left anterior descending coronary artery alone (LAD).

(2) Significant stenosis (disease) of the right coronary

artery alone (RIGHT).

(3) Chest pain syndrome, normal coronary arteries (NORMAL).

A significant stenosis was defined as blockage of at least 50% of the diameter of the main branch of the artery in at least one location (LITERATURE REVIEW IV).

Patients were excluded from the study on clinical grounds for any of the following conditions:

(1) A complete angiographic or ventriculographic study was not performed. This was often the case when a patient was referred for evaluation of a cardiac problem other than suspected coronary artery disease.

(2) Presence of valvular, congenital, or organic heart disease.

(3) Presence of any extra-cardiac thoracic vascular disease, e.g., pulmonary hypertension, pulmonary embolus, coarctation of the aorta.

(4) Coronary artery disease other than RIGHT or LAD.

(5) History of a thoracic surgical procedure.

(6) Non-sinus rhythm, e.g., atrial fibrillation or artificial pacing.

Patients with an isolated coronary artery stenosis were classified as LAD or RIGHT, as appropriate to the location of the lesion.

Patients were classified as NORMAL if, in addition to (1) through (6) above:

(7) There was no evidence of heart failure.

(8) There was no history or evidence of a previous myocar-

dial infarction.

(9) There was no conduction abnormality.

Therefore, patients satisfying the clinical and angiographic criteria for inclusion were either "normal" or had a critical stenosis of either the left anterior descending coronary artery alone, or of the right coronary artery alone, with no evidence for any other cardiac or thoracic abnormality. The patients with coronary artery disease may or may not have sustained a myocardial infarction.

I.2 Ventriculographic Criteria for Inclusion

The thirty degree right anterior oblique left ventriculograms of the patients satisfying the clinical and angiographic criteria for inclusion were projected on a TagArno 35XR viewer. Ventriculograms were viewed by a single observer who did not have knowledge of the patient's angiographic and clinical diagnoses; the angiograms were not viewed. Films were viewed in the order of the performance of the catheterizations (chronological order).

The end diastolic and end systolic frames from all heart beats that showed a clear left atrial systolic contribution to diastolic filling of the left ventricle (the "A wave": an indication of sinus conduction of the beat), that did not follow an extrasystole, and were of adequate technical quality were manually traced. The tracing outlined the contrast-endocardial border and, in the areas of papillary muscle, followed the endocardial border, not the papillary muscle outline. End diastole was defined as the last frame,

after atrial systole, before inward motion of the endocardium was observed. End systole was defined as either the last frame showing inward motion of the endocardium, or the last frame before the onset of closure of the aortic valve leaflets when they could be visualized. The junction of the mitral valve with the inferior endocardial surface (the mitral valve point) and the junction of the aortic root with the left ventricle (the anterior and inferior aortic root points) were marked.

Beats were judged to be of adequate technical quality if:

(1) There was sufficient opacification to ensure visualization of the entire endocardial border and the valve points. Note that this excluded beats showing "obliteration of the apex", in which the apical region of the outline was not visualized at end systole.

(2) The entire endocardial border and valve points were within the field of view of the cine camera.

(3) There was no evidence of intramyocardial injection of contrast agent.

In many cases, conditions (1) and (2) were not satisfied for only a small portion of the image. If it was possible to approximate this portion from either an adjacent frame or from another beat at the corresponding part in the heart cycle, then this was done and the approximated region was recorded as such.

II. NUMERICAL HANDLING OF IMAGES

II.1 Discretization of the Images

In order to manipulate the images numerically, it was necessary to convert the tracings to a series of (x,y) points stored in our computer. Using a Graf-Pen sonic digitizing pen that has a resolution of .1 mm (150), each outline traced from the cine was converted to a discretized image (set of discrete (x,y) points) and, with the mitral valve and aortic root points, stored on magnetic disk. Although not needed for the subsequent analyses, fiduciary alignment points from the film were also recorded.

The discretized image was generated from the cine tracing by starting at the anterior aortic root point and following the tracing with the digitizing pen to the inferior aortic root point. Every effort was made to cover the cine tracing at a uniform density of recorded points by moving the digitizing pen (which emits points at constant intervals of time) at a constant rate. The cine tracing was covered with a high density of points by moving the digitizing pen slowly. The mitral valve and aortic root points were defined by touching the appropriate point on the tracing from the cine and recording the pointer to the nearest (x,y) location in the set of discretized points.

If a section of the cine image had been approximated, then the borders of the approximated region were recorded in the same manner as were the valve points. All further anal-

ysis was done on the discretized images stored as the series of discrete (x,y) points.

II.2 Definition of the Apex

Although it involved the introduction of a constructed point, the interpretation of the shape of the cine images was facilitated by identifying regions of the outline as the anterior wall, the inferior wall, and the apical region (THE TANGENT ANGLE AND THE CORONARY DISEASE STUDY III.3.2). To do this, it was necessary to precisely define the limits of these regions on the outline. This was done in terms of an apex and a long axis.

Using the point on the outline farthest from the anterior aortic root point (ant-ARP) as the apex (151), the long axis was defined as the line connecting the apex to the midpoint of the line connecting the ant-ARP to the inferior aortic root point (inf-ARP, figure 10). A perpendicular to this line was drawn at a percentage of the total distance from the aortic root plane. This percentage was designated 1. The perpendicular intersected the outline at two points. The point closer to the ant-ARP was designated the anterior apical point (ant-AP). The point closer to the inf-ARP was the inferior apical point (inf-AP). The anterior wall was defined as the segment of the outline between the ant-ARP and the ant-AP, the inferior wall as the segment between the inf-AP and the mitral valve point. The apical region was the segment between the ant-AP and the inf-AP (figure 11). Emperically, 1 was chosen to be a value that gave wall defi-

nitions that conformed with observer's expectations of the location and bounds of the walls. Note that these limiting points do not exist as part of the cardiac anatomy, but are constructed points defined in terms of the parameter l. This particular algorithm for defining the limiting points was chosen because, by varying l, the influence of the location of the limiting points on the subsequent parameterization of the tangent angle function could be demonstrated.

III. DEFINITION OF THE TANGENT ANGLE FUNCTION AND ARC LENGTH

III.1 Tangent Angle Function

The derivation of the tangent angle function ($\theta(s)$) is presented in the Appendix. The computation of the tangent angle function was accomplished in a straightforward implementation using a double precision FORTRAN IV computer program (APPENDIX, reference 152).

III.2 Arc Length Computation

Computation of $\vartheta(s)$ from the discrete tracing involves the computation of the distance along the curve (arc length, s). When a curve is digitized using a digitizing pen that transmits (x,y) points periodically, small fluctuations of the digitizing pen about the curve being traced produce noise in the discretized curve. Arc length is equivalent to the distance travelled along the curve: the more irregular the curve, the longer the distance travelled. Although the noise is of low amplitude, it has a relatively high frequency. Because of this noise, the estimate of arc length

becomes inflated (153). Sampling the curve at points farther apart will give a better estimate of the true arc length, but at the expense of a decrease in the resolution of the digitized representation. A compromise is to sample the curve at points that are far enough apart to give a reasonable estimate of arc length, while close enough together to preserve detail.

The cine tracings were digitized at a slow rate (high density of points) to maximize accuracy and detail. The solution to the problem of arc length inflation was to determine a minimum sampling distance, and then reject points that were separated by less that this distance. The minimum sampling distance was determined by simulation.

III.2.1 Simulation of Digitizing

The total arc length of diastolic images for most magnifications was around 4000 Graf-Pen units (400 mm), with approximately 200 points in the discretized curve. The simulation of the digitizing process was constructed to represent the discretization of a straight line 4000 units in length, using 200 points.

Two hundred pseudo random numbers distributed uniformly on the interval (0,4000) were generated by the SAS function UNIFORM to represent the X values of a line lying on the X axis and covering the interval that runs from 0 to 4000 (154). Unequally spaced X's were chosen to represent the variable density of digitized points that arises in practice. These points represented the "true" line to be

traced.

Simulated digitized points were created by adding a pseudo random number to the X coordinate, and creating a pseudo-random Y coordinate. The number added to the X coordinate was normally distributed, with mean 0 and standard deviation 2. The Y coordinate was also normally distributed, with mean 0 and standard deviation 5. These numbers were generated by the SAS function NORMAL, and each pseudo random sequence was started with a different seed.

The standard deviation of the X component represented the experimentally determined precision in touching a single point with the Graf pen (METHODS VI.1 and RESULTS V.1). The standard deviation of the Y component was chosen to give a worse estimate of the noise than was expected to be encountered in practice. These points represented the "noisy" points that resulted from digitizing.

The total arc length of the line using the "noisy" points was computed for minimum sampling distances of 10, 20, 30, 40, 50, 60, and 70 Graf-pen units (1 through 7 mm), and compared to the "true" arc length. A minimum sampling distance that resulted in an inflation of arc length by less than five per cent was considered desirable, subject to the condition of preservation of detail.

IV. PIECEWISE PARAMETERIZATION

The goals of parameterizing the measure of left ventricular shape, the tangent angle function, are twofold. The

first goal is to decrease the amount of information in the function, making the measure more suitable for statistical applications. The second goal is to extract particular features from the measure that enhance the understanding and interpretability of the outlines from which the tangent angle functions were derived (THE TANGENT ANGLE AND THE CORONARY DISEASE STUDY III.3).

The piecewise parameterization is oriented to the coronary artery disease model. The outline of the left ventricle was considered to consist of three pieces: the anterior wall, the inferior wall, and the apical region (METHODS II.2). In the subsequent parameterization, each piece of the tangent angle function was considered separately.

The parameterizations considered were polynomials of order one through five for the anterior wall (piece) and for the inferior wall (piece). The apical region was not included. For any given parameterization (model), the General Linear Models procedure of the statistical package SAS was used to compute the least squares estimates of the coefficients of the model (154). Before the models were fit, arc length was normalized.

IV.1 Normalization of Arc Length

Once the left ventricular outline has been separated into pieces, each piece must be parameterized independent of the others: when each piece is considered, the arc length axis must pertain only to that piece. This was accomplished by a redefinition of the arc length axis for each piece.

The redefinition of the arc length axis was accomplished by scaling and translating the part of the axis that corresponded to each piece of the outline to cover the same portion of the redefined axis. In this way, the parameters from different pieces of the outline could be compared directly, without having to take into account their location on the arc length axis (figure 12). If this scaling and translation were not done, then the value of the coefficients of the polynomial models (the parameters) would be dependent upon the location and length of the particular wall segment on the arc length axis.

The arc length of each wall was scaled and translated to lie between -1 and 1 by the formula

$$s = -1 + 2(s'-si)/(sf-si)$$

where:
s' = raw arc length
s = scaled and translated arc length
si = arc length of the initial point of the wall (0 for the anterior wall, the arc length to the inf-AP for the inferior wall)
sf = arc length of the final point of the wall (the arc length to the ant-AP for the anterior wall, 1 for the inferior wall)

This transformation scaled the length of the wall segment to two, and then translated the first point of the segment to minus one. This interval was chosen as a convenient one that was symmetric about the origin.

IV.2 Polynomial Models

Using the scaled arc length (s), the least squares estimates of the coefficients for polynomial models of order one through five were obtained for each segment. For exam-

ple, for the third order model, the coefficient estimates were computed by least squares for the approximation

$$\theta(s) = b0 + b1(s) + b2(s^2) + b3(s^3)$$

for <u>each segment individually</u>. The coefficient for the linear term is b1, for the quadratic term b2, etc. The set of coefficient estimates (the b's) were the shape parameters for that outline. The shape parameters for the end diastolic and the end systolic outlines were the shape parameters for the entire beat. The apical region was not included in the shape parameterization although, if it was felt to be important, it could be. Note that given the b's, the arc lengths of each wall, and the apical region, the parameterization can be "inverted", and a smoothed heart shape recovered. If the apical region is not used, then the smoothed anterior and inferior walls can be recovered as individual segments. The degree of smoothing depends upon the order of the model: as the order increases, the degree of smoothing decreases.

V. DISCRIMINANT ANALYSIS

Using the slopes of the piecewise linear model (the curvatures of each wall) and the coronary artery group membership, discriminant analysis was carried out, and verified using an independent set of data. For patients with more than one technically adequate heart beat, the averages over beats of the curvatures of each wall were used. All computation was done using the discriminant analysis procedures

in the SAS and BMDP statistical packages (154,155).

V.1 Discriminant Method

Discriminant analysis determines the linear combinations of the parameters that maximizes the between group separation with respect to the pooled within group variability (20). These linear combinations are the canonical variables (THE TANGENT ANGLE AND THE CORONARY DISEASE STUDY III.4). The procedure implemented in BMDP takes a stepwise approach to the construction of the discriminant functions and the canonical variables. The procedure adds variables to the analysis until any choice for a variable to enter does not increase the separation among the groups by an amount specified before the procedure begins. Because there were relatively few parameters, liberal entry criteria were used to ensure that all parameters were included in the canonical variables. In the particular setting of three groups, only two independent canonical variables exist. These were used as coordinate axes upon which to plot the "location" of each patient, and thereby obtain a visual representation of the degree of separation among the groups. This was also done by the BMDP procedure.

Individual patients were classified, based only on shape, into one of the coronary artery groups using the calculations of the discriminant analyses. An individual was classified as belonging to the group that gave the largest posterior probability of belonging to that group. This is equivalent to allocating the individual to the group whose

mean he was closest to, in distance that has been normalized by the variances and covariances of the groups.

V.2 Jackknife

A jackknife approach was used to form the posterior probabilities that individuals belonged to each group, classify the individual patients, and estimate the percentage of patients in each coronary artery group that were classified correctly and incorrectly based on shape (the overall classification percentages). This approach was taken because the individuals initially used to test the overall classification percentages were the same individuals from whom the classification criteria were developed in the first place.

The jackknife works by computing the discriminant criteria as many times as there are individuals in the study (if there were 100 individuals, then the computation would be done 100 times, figure 13). At each iteration, one individual is left out of the computation of the discriminant criteria. These criteria are then applied to the deleted individual and the posterior probabilities of group membership are computed. The individual is allocated to the group with the largest posterior probability. In this way, classification of the individual is done using criteria that are independent of that individual. Although this approach does not give estimators of the overall classification percentages that are completely uncorrelated with the original data, Monte Carlo results indicate that the correlation is small (156).

V.3 Verification

The canonical variables and discriminant functions were computed using data from patients who were catheterized during 1978. The stability of the canonical variables was assessed using the jackknife classification matrices.

The validity of the canonical variables was tested using data from patients whose catheterizations were performed during 1979. These patients had their shape parameters computed, and were classified into coronary artery groups using only the discriminant functions determined from the 1978 data. Computation of the discriminant functions from the 1978 data, and classification of the 1979 data, were done using PROC DISCRIM in SAS by utilizing the TESTDATA option.

V.3.1 A Second Verification

The verification procedure was repeated by combining the patients from 1978 and 1979 into one set, forming the discriminant criteria from this set, and then applying these criteria to patients whose catheterizations were performed between January 1, 1980 and December 31, 1980.

VI. PRECISION, VARIABILITY, SENSITIVITY, AND REPRODUCIBILITY

VI.1 Precision of Digitizing

The precision of digitizing was measured as the variability of X and Y coordinates in repeated touching of single points. The X and Y coordinates were used separately to avoid the assumption that the precision in the vertical

direction was the same as that in the horizontal direction.

Ten points were each touched ten times with the Graf-Pen. The means and variances for the x and y coordinates for each point were computed, and then pooled to give overall variance estimates for each direction. This was done for 10 points lying on a horizontal line, on a vertical line, and on a circle with a radius of approximately 10 cm.

VI.2 Beat to Beat Variability Within Patients

The beat to beat variability within patients was measured as the variability in the curvatures of each wall of the outlines of the patients who had multiple technically adequate beats. Only walls that had no amount of approximation were used.

VI.3 Sensitivity of Curvature to the Apex

The piecewise linear model was computed for l (the parameter of the long axis - METHODS II.2) equal to .875, .9, .925, .95, .975, .98, and .99 for the outlines of end diastole and of end systole of patients from each clinical group. These values of l were within the range of reasonable choices for l (figure 14). The coefficient estimates were plotted to demonstrate the dependence of the curvatures on the value of l.

VI.4 Reproducibility

VI.4.1 Reproducibility of Digitizing

The error introduced by the digitizing process itself was measured as the variation in total arc length and curvature of the walls of the outline for a single image digi-

tized multiple times.

A single frame was traced ten times and the tangent angle curves constructed and parameterized by the piecewise linear model. The variation was computed for the slope of the linear model, total arc length of the image, and the arc length of each wall.

VI.4.2 Observer Reproducibility

Once an image has been digitized, the remainder of the analysis is automated, and is without any variability. Therefore, observer variability could be introduced only in the stages of the study prior to and including the digitizing of the images. These stages were:

(1) Determination of technically adequate films.

(2) Selection of the end diastolic and end systolic frames.

(3) Tracing the outlines from the film.

(4) Digitizing the film tracings into the computer.

With care, the systematic error introduced in digitizing a tracing into the computer is negligible, and in this analysis assumed to be zero. The random error in digitizing was ascertained as in Methods VI.4.1. The reproducibility of the selection of adequate films, of the definition of the timing of end diastole and end systole, and of tracing the image were ascertained as follows.

Twenty films were randomly chosen: ten with no technically adequate beats, and ten with one technically adequate beat each. Without knowledge of the initial judgement of adequacy, these twenty films were viewed by the original

observer and judged to be either adequate or inadequate. The degree to which the initial decisions agreed with those of the repeat viewings was the measure of reproducibility in determining technical adequacy.

The ten films judged adequate on the initial viewing were viewed again and, without knowledge of the initial decisions, the frame numbers of the end diastolic frame and the end systolic frame were recorded. The correspondence between the repeat and the initial frame numbers was the measure of reproducibility of determining the timing of end diastole and of end systole.

Ten films that each had two technically adequate beats were randomly selected and viewed a second time. For each film, and without knowledge of the initial tracing except for the frame numbers, the outlines of end diastole and end systole of each beat were traced. The same frames that were initially traced were traced this second time. These tracings provided the data for determining the reproducibility of tracing a specific image. The corresponding tracings were compared visually, and the variability of the curvatures of each wall were computed.

CHAPTER 5: RESULTS

I. CLINICAL MATERIAL

Catheterization records were available for 1371 adult patients for the period January 1, 1978 through December 31, 1979. Of these patients, 353 (26%) met the clinical criteria of a critical stenosis of the left anterior descending coronary artery alone, of the right coronary artery alone, or no critical stenosis of any coronary artery, and had no other cardiac or extracardiac abnormality severe enough to cause exclusion. Tables 1 and 2 list the numbers of patients in each category of the exclusions on clinical grounds.

Of the 353 patients who fulfilled the clinical requirements, 85 (24%) had ventriculograms of adequate technical quality with at least one sinus conducted heart beat that did not immediately follow a premature ventricular contraction. Table 3 lists the numbers of patients in each category of exclusion from this group. The 85 patients who fulfilled the clinical and technical requirements for inclusion constituted the study group.

Table 4 lists the number of acceptable beats per patient. Forty two percent had only one acceptable beat and 79%, the majority of patients, had either one or two acceptable beats. This was largely a result of the irregular

rhythm induced by the high pressure injection of dye. In many cases, by the time the heart had resumed a normal rhythm most of the dye had washed out of the ventricle, leaving only one or two beats with a sufficient amount of dye left for opacification.

II. NUMERICAL HANDLING OF THE IMAGES

II.1 Determination of the Apical Region

Although not necessary for the tangent angle transformation, the parameterization and interpretation of the transformation were facilitated by defining an apical region of the ventricle. The region was delimited on the outline itself, in terms of the single parameter l. Figure 14 shows the apical region, as a function of l, for different outlines. The perpendiculars to the long axis were drawn for values of l between .875 and .99. As the figure shows, the amount of arc length contained in the apical region was a function of the curvature of the outline in the neighborhood of the apex. If the curvature was large (a sharp apex), the apical region was short; if the curvature was close to zero (a broad apex) then the apical region was longer. This corresponds to one's intuition about the location of the apex: if the apical region is fairly flat then it is difficult to pick, with certainty, a small region as representing the apex. If the apical region is pointed, the choice is not so difficult.

From examining outlines such as those of figure 14, l

was chosen to be .975. In the worst case of figure 14, an aneurysm in the region of the apex, the choice of the apical region reflected the uncertainty in the location of the apex. If this heart were examined histologically, the entire region of the "true" apex would be seen to be involved by the scar. In these types of hearts, the concept of an apex becomes questionable.

II.2 Simulation of Digitizing

For the simulation of digitizing a straight line, table 5 gives the "true" arc length, the per cent inflation of arc length due to noise, and the number of points used in the computation of arc length for each imposed minimum interval. With a minimum interval of 20 Graf pen units (2 mm), arc length was inflated by only 2.6%, with 99 of the original 200 points retained. Each of the 101 points not included were within 20 units (the minimum sampling interval) of the last point included, and were skipped. Although skipping half the data points seems extreme, recall that only points closer than 2 millimeters to the previous point were not used, and therefore resolution was not degraded. Two millimeters to the previous point was chosen as the minimum sampling interval in all computation that involved arc length.

III. PIECEWISE PARAMETERIZATION

The piecewise approach involved splitting the outline at the apical region into anterior and inferior walls

(pieces). Each piece was then parameterized with successively higher order polynomials. Outlines with different shapes were parameterized by polynomials of degree one through five and the smoothed outlines that corresponded to the parameterizations were recovered. In this way, the amount of information that was lost (or gained) in choosing a particular order model was illustrated. Figure 15 shows the smoothed outlines that resulted from each order model for two images: one in which little was lost by using the low order model (figure 15a), and one in which a high order model was necessary to capture the original shape (figure 15b).

The degree to which the smoothed outlines (the inversions of the polynomial models) resembled the originals clearly improved as the order of the model increased in figure 15b. Examining the inversions shows that the second order model did not change the qualitative appearance of shape over the first order model. This was the case for all outlines examined. In figure 15b, the third order model was minimally better than the second, and seemed to have introduced an excessive curvature in the anterior wall. It was not until the fourth order model was used that any suitable approximation to the anterior wall was reached. The fifth and higher order models provided successively better degrees of approximation. This behavior was not uncommon for other complicated outlines.

As this example shows, a piecewise linear model gave

general information about the outline, but was not always adequate for accurately describing the outlines with more complicated shapes. The example also shows that to be assured of consistently achieving a high degree of representation, a high order model (at least fourth degree) was necessary. The decision to use the piecewise linear model involved a trade-off of the high degree of representation of the higher order model for the interpretability and small number or parameters of the linear model. Figure 16 shows two additional examples of the piecewise linear parameterization, and of the types of smoothing encountered.

IV. DISCRIMINATION - ALLOCATION

Using the tangent angle function and the piecewise linear model, the ventriculograms of each patient had now been reduced to four shape parameters. These four parameters per patient, the curvatures of each wall at end diastole and end systole, plus the coronary artery group identification, were the data used to investigate the discrimination - allocation problem. The patients whose catheterizations were during 1978 were used to form the canonical variables and the criteria for allocating patients to one of the three coronary artery groups. These patients were the learning set of patients. These criteria were then applied tc the patients whose catheterizations were during 1979, the test set of patients.

IV.1 The Learning Set

IV.1.1 Summary Statistics

The values of the four shape parameters within each coronary artery group are plotted in Figure 17. The parameters for the two diastolic walls did not show substantial differences among the groups. The parameters for the inferior walls however, showed clear differences among the means. Recalling that the parameters are equivalent to curvature, that positive curvature is a convex shape, and that negative curvature is a concave shape, provides an interpretation of the systolic parameters in terms of the coronary artery disease model.

The disease model states that the isolated left anterior descending coronary artery disease hearts (LAD) should have anterior wall dysfunction with the inferior wall compensating with increased function; hearts with isolated right coronary artery disease (RIGHT) should have inferior wall dysfunction with the anterior wall compensating with increased function. If a shape that is more convex than normal represents dysfunction, and one that is more concave than normal represents increased function, then the systolic anterior and inferior wall shape parameters, on the average, were consistent with the disease model.

Table 6 gives the means and variances, within each coronary artery group, for each of the shape parameters. While the dispersions within groups were not uniform, neither did they show overwhelming differences. The group with a rela-

tively extreme value of the variance was the inferior wall at end systole in the RIGHT hearts.

IV.1.2 Test of Normality

The normality of each parameter, within each coronary artery group, was tested with the Kolomogorov - Smirnov test (154,157). Although using this test on the twelve groups without adjusting the significance level may give some spurious significant results, it does give an idea as to the normality of the groups.

With a significance level, p, of .05, the only group for which normality would be rejected was the inferior wall at end diastole in the hearts with no coronary artery disease (NORMAL), for which the p value was .04. Because this value was unadjusted for running multiple tests, and because discriminant analysis is robust with respect to departures from normality, this was not felt to be a serious problem (160).

In addition to normality, linear discriminant analysis assumes that the covariance matrices for the three coronary artery groups can be pooled to form one covariance matrix. This assumption of homogeneity of covariance was tested with a statistic suggested by Kendall and Stuart (154,161). The result was that there was insufficient evidence to reject the null hypothesis of homogeneity of covariances (chi square = 119.5, degrees of freedom = 110, p = .25). Therefore, the covariance matrices were pooled in the discriminant analysis.

IV.1.3 One-Way Analyses of Variance

As an indication of the degree of difference among the groups in figure 17, one way analyses of variance were computed for each shape parameter to test the hypothesis of no difference among the coronary artery groups. Table 7 gives the results. The p values (unadjusted for computing four tests) indicated a significant difference, at the .05 level, among the groups for the systolic walls only.

The multiple range test of Duncan was computed for the four parameters with an unadjusted p value of .05 (154,158). Table 8 gives these results. As would be expected from figure 17, there was no difference among the groups on the inferior wall at end diastole. The LAD and the RIGHT disease groups differed on the other three variables. NORMAL and LAD differed on the anterior wall at end systole, while NORMAL and RIGHT differed on the inferior wall at end systole. The walls on which NORMAL differed from LAD and RIGHT were the walls subserved by the stenosed coronary artery for each group, in keeping with the coronary artery disease model.

Satisfyingly, and as shown in figure 17, not only was the relative order of the parameters preserved on each variable at end systole, with the mean values for LAD and for RIGHT bracketing the mean for NORMAL, but the rank order of the means was as the coronary artery disease model predicted: on the anterior wall parameter, the mean of LAD was largest, and on the inferior wall parameters, the mean of

RIGHT was largest.

IV.2 Determination of the Canonical Variables

The results of the stepwise discriminant analysis on the four shape parameters of the patients in the learning set are given in table 9. At each step, the following were noted (19):

(1) The variable entered into the analysis at that step, with the corresponding F-to-enter, and degrees of freedom. The F-to-enter is based on the decrease in the U statistic achieved by entering the variable into the canonical variables. While the F-to-enter cannot be used in a test of significance, it does provide a measure of the decrease in U.

(2) The U statistic that resulted when the variable at that step was entered, along with an approximate F, degrees of freedom, and p value. The U statistic is a measure of the degree of separation among the three coronary artery groups that has been achieved by the variables entered into the analysis up to the current step. The statistic ranges from zero to one, with smaller values indicating a larger amount of separation. The approximate F is derived from the U statistic under the null hypothesis of no separation among the groups.

The shape parameters with the largest F's-to-enter were the anterior and inferior walls at end systole. This might have been guessed from figure 17 and from table 7. The incremental increase in separation among the groups achieved

by including the diastolic parameters was much less, with the anterior wall at end diastole contributing the least. The U statistic of step four is for the final discrimination using all four parameters. The approximate F of step four is for the final discrimination, and is significant at $p < .05$.

IV.3 Canonical Variables

For three groups, there exist two canonical variables (20). Table 10 gives the eigenvalues and, of the total dispersion that is accounted for by the two variables, the percent accounted for by each. Table 11 gives the coefficients of the canonical variables. Figure 18 is a plot of the learning set on the canonical variables.

Canonical variable one (CV-1) accounted for 81% of the dispersion accounted for by the canonical variables; canonical variable two (CV-2) accounted for the remaining 19%. Thus, the bulk of the discrimination among the groups was being accounted for by the first variable. This is apparent in figure 18: the three groups are separated much more along the X axis (CV-1), than along the Y axis (CV-2).

The location of each patient in figure 18 was determined from the coefficients of the canonical variables: the value of each variable for a patient was simply the sum of the shape parameters for the patient, each multiplied by the appropriate coefficient in table 11, with a constant added to each variable to center the graph at the origin. The values of the two variables for each patient were then plot-

ted, with figure 18 resulting. Each patient was plotted with a line connecting that patient to the coronary artery group from which the patient came.

The separation of the three groups, when plotted on the canonical variables, is apparent. The LAD hearts plotted to the upper right, the RIGHT hearts plotted to the upper left, and the NORMAL hearts plotted to the lower center. There was overlap between each of the groups with coronary artery disease and the NORMAL group, but fairly little overlap between the two disease groups.

Because the coefficients of the canonical variables were determined to maximize the separation of the coronary artery groups, these coefficients are the "optimal" weights to use when combining shape parameters to obtain an overall shape score. The interpretation of the canonical variables comes from examining the relative weights of the coefficients. Because the shape parameters were all measured on a common scale, and had ranges of values that were similar, the coefficients of the canonical variables can be compared to each other directly. This would not have been the case if different units were used for different shape parameters.

Recall that the shape parameters are each the curvature of a wall of the simplified model of the heart at either end diastole or at end systole. A convex shape (a bulge) corresponds to a positive value of the parameter, a concave shape (an "inward bulge") has a negative value of the parameter. Each canonical variable coefficient is the size and the sign

of the multiplier assigned to each shape parameter in the determination of the overall value of the cancnical variable.

Specific examples from figure 18 are presented with the interpretations of the canonical variables. The classification of individual patients into a coronary artery group, based on heart shape, is presented after the interpretations of the canonical variables.

IV.3.1 Canonical Variable 1: Dysfunction with Compensation

Because the magnitudes of the systolic coefficients for CV-1 were much larger than for the diastolic coefficients, the interpretation of this canonical variable was in terms of the shape of the systolic outline only. CV-1 abstracted the phenomenon of dysfunction of one wall with compensatory increased function of the other wall. This behavior was predicted by the coronary artery disease model.

For end systole only, CV-1 one was (table 11):

CV-1 = 3.0(anterior curvature) - 3.1(inferior curvature)

A patient with a convex anterior wall at end systole, and a concave inferior wall at end systole will have a relatively large positive value for CV-1, and will be to the right on figure 18: the region with most of the patients with isolated left anterior descending coronary artery disease. A patient with a convex inferior wall at end systole and a concave anterior wall at end systole will have a relatively negative value for CV-1, and will plot to the left on figure 18: the region with the patients with isolated right coro-

nary artery disease. Intermediate values will fall in between: the region with most of the patients with no coronary artery disease.

Two heart shapes that plotted to the right of figure 18 and one that plotted to the left of figure 18 are shown in figure 19. The two hearts that plotted to the right (figures 19a and 19b) were from the LAD group, and showed qualitatively similar shapes. The degree of anterior wall dysfunction with inferior wall compensation was greater for the heart of figure 19a, which had a larger value for CV-1, than for the heart of figure 19b.

The third shape is of a heart with right coronary artery disease, inferior wall dysfunction, and anterior wall compensation (figure 19c). This heart had a large negative value on CV-1, and is the "opposite" of the other two.

With a convex shape accepted as representing dysfunction, and a concave shape as representing increased function, these results were predicted by the coronary artery disease model of left ventricular function.

IV.3.2 Canonical Variable 2: Shape Change

The magnitudes of all four canonical variable coefficients were approximately the same for CV-2, and all were involved in the interpretation of this variable. CV-2 abstracted the change in shape from diastole to systole, and helped to separate "normal" shape change from "abnormal" shape change.

CV-2 was (ant: anterior, inf: inferior, dia: diastole,

sys: systole, table 11):

CV-2 = -4.9(ant dia curvature) + 3.4(ant sys curvature) +
-4.8(inf dia curvature) + 3.0(inf sys curvature)

The first line above is (approximately) the negative of the change in shape from diastole to systole of the anterior wall; the second line above is (approximately) the negative of the change in shape from diastole to systole of the inferior wall. The magnitudes of the coefficients indicate that rather than a strict

-(diastolic curvature) + (systolic curvature)

expression of shape change for each wall, an expression in which the diastolic curvatures were weighted more than the systolic curvatures provided better separation of the coronary artery groups.

A heart in which both the anterior and inferior walls changed from convex (positive curvature) at end diastole towards concave (negative curvature) at end systole had values of CV-2 that were relatively negative: towards the bottom of figure 18. This was the region with the hearts that <u>did not</u> have coronary artery disease. A heart in which one wall remained convex during systole, while the other wall changed towards concave had a relatively positive value for CV-2: towards the top of figure 18. This was the region that had the hearts <u>with</u> coronary artery disease.

The heart shape with the most negative value on CV-2 is shown in figure 19d. Note that, as the interpretation of CV-2 indicated, both walls changed from convex towards con-

cave during systole. While the absolute change in the curvatures was not dramatic, the difference between this heart and those of figures 19a - 19c was that both walls had similar shape changes. In this sense, CV-2 abstracted the symmetry of the contraction.

The difference between the two hearts with left anterior descending coronary artery disease of figure 19 was also in the symmetry of contraction, but in this case in the relative symmetry. Figure 19b exhibited almost no change in the anterior wall curvature during systole but had a large decrease in the inferior wall curvature. The walls had dissimilar shape changes, and this gave a positive value for CV-2. Figure 19a, because of the marked concave region at end systole of the anterior wall near the aortic valve, had an overall decrease in curvature of the anterior wall during systole. Coupled with the decrease in curvature of the inferior wall, this provided for an overall contraction pattern that was more symmetric, and hence this heart had a negative value of CV-2.

As for CV-1, the behavior of these examples was also predicted by the coronary artery disease model. The separation of the disease groups on CV-2 was not as large as on CV-1. This was indicated by the percentage of the dispersion accounted for by each eigenvalue of the discriminant analysis.

IV.4 Discrimination - The Learning Set

The degree to which the discriminant analysis was

effective in discriminating among the three coronary groups was assessed by using the results of the analysis to classify the individuals in the learning set into one of the three coronary artery groups, based on shape alone. The information necessary to classify individuals, the classification functions, is given in table 12.

The classification functions are used to compute a constant times the Mahalanobis distance of an individual from each group mean. The Mahalanobis distance can be thought of as the distance of an individual from a group mean, in units normalized by the variances and covariances of the data. Using the Mahalanobis distances of an individual from each of the three groups, it is possible to compute the posterior probability that an individual belongs to one of the groups. The individual is then assigned to the group that gives the highest posterior probability of membership. The particular formulation of the classification functions in table 12 is such that a large posterior probability of group membership is equivalent to a large value of the classification function for that group (19).

The procedure for calculating the value of the classification functions from each group for each individual using table 12 is the same as that used to calculate the values of the canonical variables using table 11. The shape parameters for an individual are each multiplied by the appropriate coefficients in a column of table 12, the products are added together, and the constant at the bottom of the column

is added to the sum. This is done for each column, and the individual is allocated to the group whose column gives the largest value.

These calculations were done for each individual of the learning set, and the results tallied in table 13. Overall, 73% of the cases were classified correctly. The bulk of the misclassifications were between each of the coronary artery stenosis groups with NORMAL. Satisfyingly, there was little confusion between LAD and RIGHT. This was suggested in figure 18.

Table 13 would be expected to give results that were biased towards correct classifications. This is because the set of individuals classified in the table and the set of individuals used to generate the classification functions of table 12 were the same. It is therefore possible that the classification functions were "tuned" to this particular set of data. As discussed in METHODS V.2, the jackknife is a procedure that operates on the data set, and gives an almost unbiased estimate of the classification results that would have been be achieved with an independent set of data.

The jackknife classification results are presented in table 14. There was minimal change in the table, indicating that the degree of "tuning" was minimal. One additional heart was misclassified from LAD to NORMAL, and one additional NORMAL was misclassified as LAD. The classification of the RIGHT hearts did not change.

These results indicate what the four shape parameters,

combined into the classification functions of table 12, would achieve in a prospective study in which left ventricular shape was used to predict the location of a coronary artery stenosis (within the limited cohort of this study). About two thirds of those with LAD disease would be classified correctly. Of those classified as LAD, 14/18 (78%) would in fact have left anterior descending coronary artery disease; the other 4/18 (12%) would be patients without coronary artery disease who were misclassified. About three fourths of the patients with right coronary artery disease would be classified correctly. Of those classified as RIGHT, 10/14 (71%) would in fact have right coronary artery disease; of the other 4/14, 2/14 (14%) would be NORMAL, and 2/14 (14%) would be LAD.

When the results in table 14 were used to rule in or to rule out any coronary artery disease, table 15 resulted. The proportion of hearts with coronary artery disease that was picked up by shape (the sensitivity) was .74. The inverse, the proportion of abnormal shapes that had coronary artery disease (the positive predictive value) was .81. The proportion of NORMAL hearts that were classified as NORMAL by shape (the specificity) was .71. The inverse of this, the proportion of normal shapes that were classified as NORMAL (the negative predictive value) was .625. Thus, if the shape was abnormal there was an 81% chance that the coronary arteries were also abnormal. If the shape was normal, there was still a 37% chance that the coronary arteries were

abnormal.

IV.5 Allocation - The Test Set

The classification criteria developed from the learning set were applied to the hearts in the test set. This was a test of the criteria using a completely independent set of data: the learning set from which the classification criteria were developed contained only patients catheterized during 1978; the test set contained only patients catheterized during 1979. The results are presented in table 16.

The proportion of hearts in each cell of table 16 was almost exactly as predicted by the jackknifed classification, table 14. The proportion of hearts classified correctly ranged from 70% to 75%. The proportion of hearts with a coronary artery stenosis that were misclassified into the incorrect stenosis group was small; more of the incorrect classifications were between the stenosis groups and NORMAL. The number of individuals in each of the incorrect classification cells was small however, and the exact estimates of these percentages may not be reliable.

A plot of the individuals in the test set on the canonical variables determined from the learning set is shown in figure 20. Figure 21 shows a plot of the mean values of each coronary artery group of the learning set and of the test set on the canonical variables. In examining these two figures, several observations can be made.

As would have been guessed from table 16, the overall relationships of the coronary artery groups noted for the

learning set were preserved in the test set. The RIGHT group was above and to the left of NORMAL, and LAD was above and to the right of NORMAL. The major overlap among the groups was between each coronary artery disease group and NORMAL, and not between the two disease groups.

The mean value of LAD did not change substantially from 1978 to 1979. The 1979 mean value of NORMAL moved somewhat to the left, towards RIGHT. RIGHT in 1979 however, moved considerably to the right - towards NORMAL and towards LAD.

There are individuals in each group of figure 20 who were located a considerable distance from the mean of their group. Most prominent were the two extreme values on CV-1 from NORMAL.

Figure 22a shows the outlines of the heart without coronary artery disease whose shape had the extreme positive value for CV-1. Figure 22b shows the outlines of a nearby heart with LAD disease for comparison. These two ventriculograms were virtually indistinguishable. Their large positive values for CV-1 were due to the end systolic convex anterior and concave inferior walls, as described in section IV.3.1.

Figure 22(c) shows the heart without coronary artery disease whose shape plotted to the extreme negative on CV-1, with figure 22d showing a nearby heart with right coronary artery disease. As with figures 22a and 22b, these ventriculograms are very similar. Their end systolic concave anterior and convex inferior walls determined their values

of CV-1. In the outlines of figures 22a - 22d, the amount of convexity and concavity of the walls was not dramatic. Rather, it was the combination of concave and convex in the same image that gave the extreme values of CV-1.

Figure 22e shows the heart with RIGHT disease that was closest to the mean value of LAD. Although this patient was not reported as having suffered a myocardial infarction, it seems clear from figure 22e that there was severe basilar inferior wall dysfunction with compensation by the basilar anterior wall and the apical inferior wall. It is difficult to decide if the convex region of the anterior wall represents normal or dysfunctional myocardium.

This heart was classified into the LAD group. The reason is because of the apical region at end systole: the apical "half" of the end systolic outline resembled that of an outline with anterior wall dysfunction and inferior wall compensation. Because of this, the inferior wall had an overall curvature that was not representative of the basilar region, and the anterior wall also had an overall curvature that was not representative of the basilar region. Because the value of CV-1 is primarily in terms of end systole, this image had a relatively large value and therefore, plotted to the right. This heart had the overall curvatures that it did because only a single curvature was derived from each wall in the parameterization scheme. This is an example in which a single parameter per wall was not adequate.

IV.5.1 A Second Test Set

The clinical study was continued into 1980 using the same criteria that were applied to the patients from 1978 and 1979. The patients from 1978 and 1979 were combined to form the 1978-79 learning set, with the patients from 1980 forming the 1980 test set. The results of classifying the 1980 test set using the discriminant functions of the 1978-79 learning set were not consistent with those involving the 1978 and 1979 patients alone.

The results of performing the discriminant analysis on the 1978-79 learning set are shown in figure 23 and tables 17 and 18. These results were similar to those of the 1978 learning set and 1979 test set, as would be expected from the similarity between those two groups of patients. The plot of the 1978-79 learning set on the canonical variables determined from these 85 patients (figure 23) showed a similar distribution to the other canonical variable plots. This was reflected in the classification matrix (table 17) and the jackknifed classification matrix (table 18).

The results of allocating the 1980 test set using the 1978-79 learning set discriminant functions are shown in figures 24 and 25, and table 19. The plot of the mean values of the 1980 test set on the 1978-79 learning set canonical variables (figure 24) showed that while LAD did not change location substantially, RIGHT and NORMAL moved much closer together, and towards LAD. Figure 25, the plot of the 1980 test set on the 1978-79 learning set canonical

variables showed that the discrimination on CV-2 was entirely lost, and only a small amount of separation among the groups on CV-1 remained. These results were borne out in table 19, the classification matrix of the 1980 test set.

As a further exploration of the 1980 test set, the discriminant analysis was computed using these patients as the learning set. The canonical variable plot reduced to a histogram, because only the curvature of the inferior wall at end systole had any discriminating power (figure 26). The classification matrix (table 20) was stable under the jackknife (table 21), but reflected the small amount of separation of the coronary artery groups shown in figure 26. This implied that the relationship between the location of a coronary artery stenosis and the shape of the left ventricle that was so clearly demonstrated with the patients from 1978 and 1979, was not present in the group of patients catheterized during 1980.

V. PRECISION, VARIABILITY, SENSITIVITY, AND REPRODUCIBILITY

V.1 Discretization = Precision

Table 22 presents the variances of the estimates of X and Y coordinates of individual points lying on a line oriented approximately horizontally, approximately vertically, and on a circle of radius approximately 10 cm. The maximum variance was close to 10 Graf Pen units: 1 mm. The pooled standard deviations varied between 1.55 and 2.19 units (.1 to .2 mm). There does not appear to be any significant dif-

ferences between the variations of the X and the Y coordinates. Table 23 shows the results of digitizing a single outline ten times. The variation in arc length and curvature was minimal.

V.2 Beat to Beat Variability in b1 of the Linear Model

The within patient variances of b1 for each wall of the end diastolic and the end systolic outlines were computed for each patient with at least two beats. Walls that had an approximated part were excluded - in some cases this resulted in more beats for one wall than another for a patient with multiple beats. Table 24 lists the pooled estimates of the within patient variances for each wall.

The individual variances were all small, ranging from .000001 to .01. The pooled estimates of the variances were all of the order of less than .01. The coefficients of variation showed more variation, with a few values being very large, but this was a reflection of several of the mean values for b1 being very close to zero. Plots of the variance versus the mean, and of the standard deviation versus the mean showed no obvious pattern.

V.3 Sensitivity to the Apex

Figure 27 shows a plot of B1 of the linear model (curvature of the wall) versus l for two patients shown in figure 14 (METHODS II.2 gives the definition of l). As the plots show, there was often a trend (usually not linear) in b1 as the location of the apex changed. This was anticipated from figure 14. The magnitude of the trend depended

on the exact shape of the outline.

V.4 Walls with Approximated Sections

As discussed in METHODS II.1, it was often necessary to approximate sections of the film outlines when tracing, due to either ambiguity of part of the outline (inadequate opacification, marked trabeculation), or to part of the image being out of view of the camera. Also included as approximated sections were the cases in which the outline visible on the film was felt to be that of a papillary muscle, and the endocardial border was traced instead. The number of patients that would have been excluded from the study for technical reasons under each of the following strategies was determined.

(1) Any beat with any amount of approximation was discarded.

(2) Any wall with an approximated part was discarded. This differed from (1) in that the beat was used, but without the wall that had the approximated part. This meant that for a single patient with multiple beats, it was possible for the average values of the parameters to be based on different numbers of walls.

(3) Both (1) and (2) were repeated, but beats in which the approximated section traversed the papillary muscle origin were not discarded.

Table 25 shows the number of patients deleted from the 1978-79 learning set under each condition above. If the most rigorous stand were to be taken, and only outlines with no degree of approximation were accepted, then of the 85

patients studied, 33 (39%) would have been excluded from the study. If only the walls with the approximated parts were discarded, then 30 (35%) patients would have been excluded.

V.5 Reproducibility

The reproducibility of determining the technical acceptability of films, of determining the timing of the end diastolic and end systolic frames, and of tracing the outlines was large for picking the film and the frames, and less for tracing the outline.

The results of viewing ten acceptable and ten unacceptable films a second time and determining their acceptability are shown in table 26. One film judged acceptable at the first viewing was judged unacceptable at the second: at the second viewing the atrial contribution to diastolic filling of the ventricle was not appreciated, and the film was rejected as having an undefined rhythm. One film initially judged unacceptable was judged acceptable at the second viewing: the end systolic outline was felt to lack sufficient contrast for reliable tracing at the initial viewing, but not at the second.

The results of viewing ten films with one technically acceptable beat each, and determining the timing of end diastole and of end systole are shown in table 27. For two films, end diastole at the second viewing was judged to have occurred one frame earlier than it was judged to have occurred at the first viewing. For one film, end systole was judged to have occurred one frame later at the second view-

ing than at the first. For the other seven films, the decision as to the timing of end diastole and of end systole did not change from the first to the second viewings. Filming speeds in our catheterization laboratory were, at the minimum, thirty frames per second.

The reproducibility of tracing a particular outline involves two processes: determining the location of the valve points, and determining the location of the outline itself. Two examples of variability in the choice of valve points are shown in figure 28. Both involved the choice of the inferior aortic root point and of the mitral valve point.

In figure 28a, it is seen that at the first viewing a point closer to the mitral valve was chosen as representing the inferior aortic root point than was chosen at the second viewing. At the second viewing, this point was felt to have been an overlying part of the aortic root that was partially obscuring the true location of the leaflet. In figure 28b, the same problem occurred, but the overlying aortic root was appreciated at the first viewing.

Figure 28a shows a relatively minor difference in the choice of the location of the mitral valve point that occurred between the two viewings. Figure 28b however, shows a more substantial difference, with the mitral valve point having been chosen more apically at the second viewing than at the first. At the first viewing, the sharply convex region chosen as basal inferior wall myocardium was felt to

have the configuration it did because of the particular angle of projection of this part of the heart on the film. At the second viewing, partially because of the choice of the location of the aortic valve, this was felt to represent fibrous tissue of the mitral valve apparatus, and was therefore excluded.

Variability in the choice of the location of the outline is illustrated by figures 28a and 29. In figure 28a, the location of the apex was difficult to determine, resulting in a more sharply convex shape at the first viewing than at the second. Figure 29 shows an end systolic outline in which a substantial difference in the location of the inferior wall outline was noted. At the first viewing a much lighter region was noted at the apical inferior wall that was interpreted as dye trapped in myocardial trabeculations, and was therefore excluded from the cavity. At the second viewing this lighter area was felt to be part of the cavity that, either because of inadequate mixing of blood with dye or because of a peculiar angle of projection, appeared lighter than the rest of the cavity and was therefore included in the outline.

Because of the extreme differences in the two viewings, the ventriculogram of figure 29 was viewed by two experienced ventriculographers. Viewing only the right anterior oblique ventriculogram, neither was able to determine the reason for the inferior lighter region, and both were unable to determine with confidence which region should be included

with the outline. When the left anterior oblique projection was viewed, the apex was seen to contract well and a large inferior papillary muscle was appreciated. With this additional information, they together decided that the lighter region represented part of the ventricular cavity in which either the papillary muscle or increased contraction of the lateral wall were displacing blood and accounting for the differences in contrast. Neither however, was confident of the decision.

The magnitude of the variability in the two viewings was assessed with the two way analysis of variance shown in table 28. The beat to beat variability was used to estimate the inherent variability of tracing because of the systematic differences between viewings illustrated in figures 28 and 29. The analysis was computed for each wall at end diastole and at end systole separately. Table 29 gives the results. The only wall for which there was significance at the .05 level was the inferior wall at end systole. While this result indicated that, for the group as a whole, the variability in choosing the location of the outline was not much larger than the inherent beat to beat variability of a patient, figures 28 and 29 clearly show that the variability within an individual patient could be quite large.

CHAPTER 6: DISCUSSION

I. CLINICAL MATERIAL

Approximately 60% of the 1371 catheterizations performed during 1978 and 1979 were for suspected coronary artery disease. Forty three percent of these (one fourth of all patients catheterized) met the criteria for a critical stenosis of the left anterior descending coronary artery alone, of the right coronary artery alone, or no critical single vessel stenoses, and were included in the study. The number of patients with congenital abnormalities was very small (19/1371, 1.4%) because pediatric cases were not considered.

Of the 353 patients fulfilling the clinical criteria for inclusion, 85 (about one fourth) had analyzable ventriculograms. The largest number of exclusions were due to only premature contractions being opacified (46% of all exclusions). In most cases this was a result of the use of a single end hole catheter, in which the high pressure stream of dye was directed towards the ventricular wall, inducing the arrhythmia. Towards the end of the series, catheters with side holes and coiled catheters (pigtail catheters) were used more frequently, with a possible effect on the incidence of induced arrhythmia.

Twenty two percent of the exclusions were due to either

the entire end diastolic or end systolic outline not being within the field of view of the X ray camera. As previously discussed, there is a large priority given to reducing the radiation exposure of the patient and increasing the resolution of the image and therefore, the field of exposure is kept to a minimum. Because the subjective methods of interpretation used clinically do not require the entire outline to be visible at one time, this priority is appropriate. A possible contributing factor is that more difficulty with centering the image was likely to have been encountered with large ventricles than with small ones. Because the amount of dye injected to obtain the ventriculogram imposes a hemodynamic stress on the patient (162), it is rare that an inadequate study is repeated.

The possible biases in excluding patients have been alluded to. The effect of excluding patients who had a long period of an irregular rhythm with subsequent inadequate opacification is difficult to predict. Patients with large regions of infarcted myocardium may be less susceptible to arrhythmia because the jet of dye impinging on an infarcted area of muscle may not have the same irritable effect as when it impinges on viable muscle. On the other hand, patients with myocardial ischemia are more prone to arrhythmias, and may therefore be more sensitive to the high pressure stream of dye.

The other possible source of selection bias is in the framing of the ventricle prior to the injection. If in fact

large ventricles are selected against, then the included population will be biased towards less serious ventricular and therefore less serious coronary pathology. It is difficult to estimate the magnitudes of these biases. Filming, calibration, and injection techniques have been evolving in an uncontrolled manner in our catheterization laboratory, and much of the information necessary to study these effects is not available.

II. NUMERICAL HANDLING OF OUTLINES

II.1 Apex

The problems associated with using constructed points as pseudo-landmarks have been discussed at length, and in the development of this project considerable effort was expended in searching for a parameterization scheme that did not use any constructed points. It was with caution therefore that the decision was made to introduce an apex of the ventricle into the analysis, knowing that it was one such point. The benefits have outweighed the costs.

Based on visual criteria, the ventricle has a clear orientation, both in the chest and with respect to the valve openings. Without defining regions of the ventricle, it is not possible to refer to this orientation in describing the location of an abnormality. In analyzing the shape of the ventricle without acknowledging the general orientation, interpretations seem overly restricted.

The regions of the ventricle that are of interest are

the apex, the anterior wall, and the inferior wall. On a muscle fiber level there is an apex to the heart (163). The apex is not a ventriculographic landmark because it is not always a region of high curvature on the outline. Nearer, and with respect to the valve opening, the ventricle clearly has an anterior and an inferior wall. These walls are an essential part of the disease model.

The problem with making reference to the orientation of the ventricle lies not in determining regions of the ventricle with respect to the orientation, but rather in the exact definitions of the points that delineate the regions. Unfortunately, other than the valve points, the ventricle has no reliable landmarks. Therefore, any reference to location, by definition, will be constructed. The method used to split the ventricle at an apex took into account the visual component of the apex and the indeterminancy in the location of the point.

Locating the apex as the point on the outline farthest from the anterior aortic root point incorporated the visual component, in that this algorithm gives the point that most closely agrees with observer's assessment of the location of the apex (151). Choosing an apical region, rather than a point, incorporated the indeterminacy in locating the apex.

It is important to note that the subjective decisions involved in determining the apex were in the choice of the algorithm that determined the point, not in the choice of the point itself. This ensured that the same procedure was

applied to all patients in a reproducible way. In addition, in the particular approach taken in this investigation, the definition of the apical region was in terms of the single parameter 1. By doing this, the other subjective component of the apical region, the exact amount enclosed, could be demonstrated (figures 14 and 27).

The apical region is constructed: it is not a landmark. It was introduced in response to what seemed to be an unnecessary degree of restrictiveness in the analysis and the interpretation of shape otherwise. The method of defining the region was automated and therefore, all possible bias was incorporated in the choice of algorithm and the value of the single parameter, and was easily investigated. The cost of introducing this region was the cost associated with any constructed region: the pathology being investigated may have influenced the choice of the region, and thereby have influenced the analysis of the pathology. There are no guarantees that an unusual outline was not misanalyzed because of this.

II.2 Discretization: Resolution and Arc Length

There is no "true" degree of resolution or "true" arc length: both are a function of the magnification used in recording an image, and are related. Regardless of the device used to record the image, as resolution increases, arc length becomes inflated. As the resolution decreases, the arc length becomes more determinate (153). The decision to choose a minimum distance between points of two millime-

ters (20 Graf-pen units) was intended to err on the side of increased resolution. At this spacing, the estimated inflation of arc length was around 2.5%, and the degradation in resolution was not visually detectable. It probably would be possible to use a wider spacing between points and still obtain adequate resolution, but the marginal decrease in the inflation of arc length did not justify this.

The issue of noise in digitizing is a result of the particular methods used to transfer the outlines from the film to the computer: manual tracing onto paper, and then retracing with the Graf-pen. The tracing onto paper resulted in an outline that had relatively little noise. The hand held Graf-pen however, introduced a significant amount of noise in the form of a high frequency, low amplitude, "jitter" that was most pronounced when tracing slowly (a high density of points). This is not a deficiency in the Graf-pen, but was a result of its high resolution and high data acquisition rate. The problem could undoubtedly have been avoided altogether with a different method of transferring the outline to the computer (e.g. an optical scanner with a fixed resolution), but the solution implemented seems more than adequate.

III. TRANSFORMATION AND PARAMETERIZATION

The differences between the method of analysis of the ventriculogram taken in this investigation, and the methods in the cardiology literature, center on two steps of the

analysis:

(1) The transformation and the determination of the parts of the ventricle to include in the analysis.

(2) The method of extracting parameters from these parts.

The approach taken in this study to the first step was to transform the entire left ventricular outline, using the tangent angle function, to a form suitable for the extraction of parameters. In keeping with the coronary artery disease model, and the known landmarks of the ventricle, the valve regions were excluded and the outline was split into pieces at the apex. These aspects of the analyses were approached as separate decisions.

The approach to the second step was to parameterize the two pieces of the transformed outline separately. Each piece was used entirely in the computation of the parameters; in keeping with the decision about the locations of landmarks on the outline, no subdivision of the pieces was done. The parameters served as the features of the shape of the outlines and as the input to the subsequent discriminant analysis. The approach to these steps by the regional wall motion methods is different.

III.1 Tangent Angle Function

The discussion of the regional wall motion methods has centered on the use of a reference frame and the use of constructed points (INTRODUCTION IV.3, LITERATURE REVIEW II). The differences between a transformation of the outline and the use of hemi or radial axes deserves further comment.

The axes methods are based on the motion of a finite number of specific points on the outline. The resolution of these methods is limited to the number of axes drawn. The locations of the axes are not determined with consideration to a particular disease model, but are arbitrary (e.g. equal increments of the long axis). Some axes have no interpretation, such as those that involve the valve regions, and apical end diastolic axes that do not intersect the end systolic outline. If the outline is particularly noisy, then the specific point chosen for an axis may not be representative of the surrounding points, but the axes representation does not provide for a method of smoothing the outline.

Many of these problems arise because the axes methods attempt to transform, determine regions, parameterize, and extract features all at once. The tangent angle transformation, by contrast, is only a transformation. Each of the other steps is taken, and examined, separately. This approach has not been studied in the cardiology literature prior to this investigation, and may be in part responsible for the large number of methods tried, the lack of acceptance of a single method, and the persistence of a subjective method of analysis in many studies.

There are other approaches to transforming two dimensional outlines that may also have utility in the analysis of ventriculograms. There is no way to know if the tangent based methods are optimal. However, because of their interpretability and their satisfaction of the requirements of a

measure of shape, the behavior of the tangent based methods in response to different outlines is easily predicted and understood. This cannot be said for the methods currently used in clinical cardiology.

III.2 Parameterization

The differences between parameterizing the tangent angle function and the axes methods of analysis have been described. In the axes methods, the axes drawn are the parameters of the outline: the entire outline, or even a region of the outline, is not used in the determination of axes. In contrast, the parameterization of the tangent angle function was based on an entire section of the outline. The decision to not increase the resolution of the parameterization was made separate from the parameterization itself, and was dictated by the lack of landmarks on the outline and by the lack of interpretability of the higher order parameterizations. In the axes methods, because only single points are used, increasing the resolution is the same as increasing the number of parameters.

Parameterizing the outline by the piecewise linear model is equivalent to representing the image with the sections of two circles connected at the apex. Each circular arc is determined separately from the corresponding piece of the tangent angle function. The curvature of the circular arc is the slope of the linear model fit to the piece of the tangent angle function. The shape parameters of the outline are these curvatures.

The curvature of the arc has been determined from the entire section of the outline. There is only one arc, and therefore, one parameter, per wall. As figure 15 shows, if the curvature of the wall was approximately the same everywhere, then modeling the wall with an arc of a circle gave a good representation of the original outline. If the wall had convex and concave regions, then the representation, which was only a single arc, was not as good.

The higher order models gave more faithful representations of the pieces of the outlines. However, whereas the coefficient (parameter) of the linear model was easily understood as curvature, those of the higher order models were not so readily interpreted. In the higher order models, the terms of the models are added to each other and the representation of the original shape is by this sum. Therefore, it is difficult to know what one term from the sum means in the absence of the others.

The difference in the number of parameters is obvious. In the piecewise approach, the anterior and the inferior walls of the end diastolic and the end systolic outlines are modeled individually, giving four walls per beat. The number of parameters per beat therefore is four times the order of the model. The linear model has four parameters. The fourth order model needed to approximate the example in figure 15 has sixteen parameters. This has implications in the determination of the number of patients necessary to achieve stable estimates in the discriminant analysis.

IV. DISCRIMINANT ANALYSIS

In RESULTS sections IV.4 and IV.5, the application of the curvature parameters to the discrimination among patients with and without coronary artery stenoses was presented. Using a learning set of patients, discriminant functions were defined that were based only on the shape parameters. The discriminant functions were than applied to an independent test set of data, and patients were allocated to one of the three coronary artery groups. Approximately 70% of the test set was allocated correctly.

The canonical variables of the discriminant analysis were presented in RESULTS section IV.3. Canonical Variable 1 (CV-1) was interpreted as systolic dysfunction with compensation, and Canonical Variable 2 (CV-2) was interpreted as the shape change from end diastole to end systole. Using the canonical variables, the patients of the learning set and of the test set were plotted (figures 18 and 20). Individuals that were far from the mean values of their known group were identified (figures 19 and 22).

The differences between these results and those of the literature center on four areas:

(1) The transformation of the outlines.

(2) The parameterization of the transformation.

(3) The discriminant analysis approach to determining the optimal combinations of the parameters to distinguish among the coronary artery groups (the canonical vari-

ables).

(4) The use of the discriminant functions to allocate patients based on the probability of group membership.

Points (1) and (2) have been discussed. Points (3) and (4) will be discussed here.

IV.1 Canonical Variables

The reference frame based methods of left ventricular outline analysis have been discussed in detail. The various methods have been described (LITERATURE REVIEW II), as have the validity of the assumptions involved (INTRODUCTION IV.3). One aspect of the wall motion methods deserves further comment in relation to the canonical variables: the use of wall motion per se as the measure of the outline.

IV.1.1 Hemiaxes versus Canonical Variables

Whether hemiaxes, radial axes, or myocardial markers are used, all reference frame methods measure the axes with the following quantity (ED: end diastole, ES: end systole):

(ED axis length - ES axis length) / (ED axis length)

or equivalently,

1 - (ES axis length / ED axis length)

This is the proportion of the diastolic length of the measured axis that is accounted for by the systolic motion of the walls of the heart. The need for using proportional lengths is based on the accepted observation that there is a large variation among patients in the sizes of their hearts. This variation would contribute a considerable degree of artifact to any analysis based on the absolute lengths or

absolute length changes of the axes. It is not possible to consider the systolic and diastolic contributions of the shape analysis separate from each other: the proportional length change combination of the end diastolic and end systolic information is dictated by the size variations of hearts. Without any published investigation of the optimal way in which the measurements of the outline should be combined, all reference frame methods have used this particular proportional lengths combination. By contrast, the size invariance of the tangent angle function and of the curvature parameters allowed the weights of the eventual shape discriminators (the canonical variables) to be determined by the data, rather than a priori.

The interpretations of the weights of the canonical variables centered on the identification of pairs of weights of comparable magnitudes and related these pairs to systolic function (CV-1) and to shape change (CV-2). The actual use of the canonical variables however, used the weights as they were determined. Using these weights gave the optimal separation of the coronary artery groups. This separation was better than any that would have been achieved using any other linear combination of the shape parameters. This lack of dependence on an a priori combination of parameters is an advantage of both the size invariance of the tangent angle transformation, and of discriminant analysis.

IV.1.2 Interpretations of the Weights

The interpretation of CV-1 involved only the end sys-

tolic curvatures, and served to separate LAD from RIGHT (figure 18). By abstracting the phenomenon of systolic dysfunction of one wall with increased function of the other, CV-1 established a scale of measurement of systolic shape. The scale ran from RIGHT (negative values), through NORMAL, and up to LAD (positive values).

CV-2 involved the end diastolic outline and the end systolic outline, and abstracted the shape change from end diastole to end systole. On CV-2, LAD and RIGHT were separated from NORMAL: the scale ran from abnormal shape change (positive values) to normal shape change (negative values). A closer examination of the weights of CV-2 showed that the coronary artery disease hearts were undergoing asymmetric shape changes, while the NORMAL hearts had a more symmetric contraction.

Although CV-1 and CV-2 may seem to be abstracting similar aspects of heart function - contraction of one wall compared to the other - it is important to recall that the variables are statistically independent (19). The symmetry of contraction (CV-2) is not the same as the final end systolic shape (CV-1).

The simplified coronary artery disease model supports the interpretations of the canonical variables in the context of discriminating among hearts with isolated LAD disease, isolated RIGHT disease, or no coronary artery disease. The regions of cardiac muscle subserved by the two arteries form the borders of the left ventricle in the thirty degree

right anterior oblique projection. The dysfunctional section of muscle will have decreased wall tension by passively bulging and assuming a decreased radius of curvature (the Laplace relation, reference 14). In order to maintain the volume of blood ejected from the heart with each beat, the functional regions of muscle will contract to a greater than normal extent. CV-1 isolates which section of muscle has the increased curvature; CV-2 whether one side is contracting more than another.

The studies of left ventricular dysfunction using the hemiaxis methods support the interpretations of the canonical variables if the dyskinesis of one wall with hyperkinesis of the other is regarded as the analog of increased curvature of one wall with negative curvature of the other. It must be remembered that while the hemiaxis studies are supportive, the measurement of systolic function offered by the canonical variables cannot be made using hemiaxes. Because of the size problem discussed, one would not attempt to directly compare one end systolic outline to another using hemiaxes. Because of the proportional wall motion used by hemiaxes, separation of end diastole from end systole is not possible.

IV.2 Discrimination - Allocation

The thesis of this dissertation is that shape of the left ventricle of the heart bears a relationship to the location of a coronary artery stenosis, and that this relationship can be demonstrated using a reference frame free

measurement of shape. The classification matrices of tables 13, 14, and 16 substantiate the thesis. This result will be discussed in relation to the following areas:

(1) The limitations of the coronary artery disease model.

(2) The limitations of the piecewise linear parameterization.

(3) The similarities and differences between this result and the work done by others.

IV.2.1 Limitations of the Disease Model

The coronary artery disease model used in the design of this study was a simplified model. Hearts were grouped based only on the presence or absence of an isolated critical coronary artery stenosis, with the assumption that myocardial shape would follow the same grouping. The reasons for using a simple model were two fold. The first reason is that much of the data needed to define a more complete model were not available for the patients used in the study. The second reason is that the significance and interpretations of many of the elements of the more complete model are controversial, and were felt to be beyond the scope of this project.

The complete model of coronary artery disease makes the transition from a coronary artery stenosis to the adequacy of regional myocardial blood flow. This involves consideration of the location of the stenosis along the artery, the collateral circulation to the affected region of muscle, and the amount of blood flow to the region. The model would

also include a measure of the amount of damage sustained by the affected region of muscle. An explicit delineation of the affected region on the two dimensional ventriculogram is also involved.

Measurements of these quantities are available. The location of a stenosis can be recorded in relation to a more detailed depiction of the coronary artery tree. Collateral circulation can be visualized at the time of angiography. Blood flow and myocardial damage can be assessed using radionuclide techniques. Using this information, the affected region of the ventriculogram should be estimatable.

As mentioned however, each one of these methods is itself controversial. In this initial study of left ventricular shape, it was felt appropriate to not enter in these additional controversies.

Because of the limitations of the simplified model, the percentages of correct classifications in tables 13, 14, and 16 seem reasonable. With an extended model, these percentages would be expected to increase.

IV.2.2 Limitations of the Parameterization

The piecewise linear parameterization reduced each wall of the left ventricular outline to a single parameter. A total of only four parameters per patient were used to describe the dynamic shape of the left ventricle. This was a tremendous reduction of the shape to a few parameters. The reasons for not using a higher order model have been detailed, and involved the interpretability and number of

parameters of the model. Despite this tremendous reduction, the classification tables and plots of the patients on the canonical variables demonstrate that a significant amount of information about coronary artery disease has been abstracted by the parameters of shape.

It seems reasonable to assume that a parameterization scheme could be found that would provide a more faithful representation of the tangent angle functions of left ventricular outlines. In the context of the simplified disease model, it is not clear that the classification results of tables 13, 14, and 15 would be improved upon with a more detailed parameterization. However, with a more detailed coronary artery disease model, a more complete parameterization might prove fruitful.

IV.2.3 Relationship to Other Investigations

Use of the left ventricular outline to discriminate among patients with coronary artery disease has not been investigated prior to this study. In other investigations the outline is chiefly used as supportive data for other measures of cardiac function. Many different clinical groups of patients are usually examined, and the statistics of the outlines are not usually presented in sufficient detail to provide meaningful comparisons to the current study. One study however, looked at the outlines of patients with isolated single vessel coronary artery disease, and provides an interesting comparison to the discriminant results.

Kumpuris et al studied the right anterior oblique left ventricular outlines of patients with isolated left anterior descending coronary artery disease (LAD), isolated right coronary artery disease (RIGHT), or no coronary artery disease (NORMAL) (81). Their definition of a critical stenosis was narrowing of the artery diameter by 75% (versus the 50% used in the current study). Patients were classified as having a proximal, mid, or distal LAD stenosis, or as having a proximal or distal RIGHT stenosis. Patients were also classified as to the presence or absence of a myocardial infarction (MI). Thus, they examined their cohort of patients in terms of a more detailed coronary artery disease model than was used in the current study.

The measure of wall motion used was an internal reference frame, percent hemiaxis shortening velocity. Six axes total were used: three on the anterior wall and three on the inferior wall. While the use of a velocity has theoretical justification as a measure of contractility (15), it has not been used in other studies of wall motion.

The shortening velocity of each of the six hemiaxes of the LAD and RIGHT hearts were compared to the corresponding velocities of the NORMAL hearts. These comparisons were done for each of the sub-groups based on the location of stenosis, and the presence or absence of MI.

The results of this study were consistent with the coronary artery disease model: the anterior wall had depressed shortening velocity in the LAD group and the inferior wall

had depressed shortening velocity in the RIGHT group. The effect was more marked as the stenosis became more proximal, and if there was an MI (this was more apparent for LAD; in particular sub-groups the significance was variable). They did not observe an increase in the shortening velocity of the unaffected wall.

The points of comparison between this study and the current one are many. The use of hemiaxes versus curvatures has been discussed in detail. The use of a percent shortening velocity complicates the comparison of their results to those in the current study, but both are as predicted by the coronary artery disease model. Their subdivisions of LAD and RIGHT by location of stenosis and presence of MI was elegant, and provides a hint of the results that could be expected if the coronary artery disease model were extended in the current study. Their use of a more severe definition of a critical stenosis would be expected to increase the differences among the groups.

The principle point of comparison between Kumpuris et at and the current study lies in their use of multiple comparisons to NORMAL, as opposed to the construction of canonical variables. In Kumpuris et al, when comparing a coronary group to NORMAL, there was no way to compare the <u>vector</u> of hemiaxes that constituted the wall motion measures of each patient. Only the individual hemiaxes were examined. In their study, there was no result that was analogous to the interpretations of the canonical variables.

Most of these points have been discussed elsewhere in the dissertation. The differences in methodology and philosophy of analyzing outlines are major. It is satisfying to note that the results using the different methods are similar.

IV.3 Failure of the 1980 Test Set

The results and interpretations of the discriminant analyses of the data from 1978 and from 1979 were consistent between the two years, and with the coronary artery disease model. These results were not verified by the data from 1980: the discriminant functions computed from the 1978-79 learning set were unable to classify the 1980 test set with the degree of accuracy observed with the 1978 and 1979 data alone. In addition, when discriminant analysis was carried out with the 1980 data as the learning set, the shapes of the left ventricles were not able to discriminate among the coronary artery groups. The possible reasons for this inconsistency fall into three areas: patient selection for catheterization, angiographic and ventriculographic techniques, and tracing outlines from the films. In each area, it is necessary to postulate that a change occurred over time, and that this change accounted for the differences in the data over the three years.

IV.3.1 Patient Selection

A change in the population of patients being catheterized could account for the lack of a strong relationship between coronary artery disease and left ventricular shape

if, in the population, the degree of ventricular pathology decreased for a given coronary artery stenosis. If patients with less severe myocardial damage became more prevalent in the coronary artery disease groups, then these groups would begin to have left ventricular shapes that appeared more like each other, and more like the NORMAL group. A larger proportion of patients with coronary artery disease would have truly normal left ventricles, and shape would be unable to discriminate among the different locations of coronary artery stenoses. The most likely situation that would cause this change in the population would be the increasing use of increasingly sensitive non-invasive tests in the pre-catheterization diagnosis of coronary artery disease. Patients with minimal symptoms and minimal myocardial damage would be referred for catheterization, whereas in the past, without the more sensitive pre-catheterization tests, they might not have been. A contributing factor would be a decrease in the morbidity and mortality of catheterization over time, increasing the liklihood that this invasive procedure would be undertaken.

In order to substantiate this hypothesis, it would be necessary to document a change in the presenting signs and symptoms of the catheterized population over time. These would include changes in the cardiac history, including the history of myocardial infarction; the increasing use of non-invasive diagnostic procedures and the degree to which they contributed to the decision to catheterize; and a

change in the hemodynamic and angiographic variables other than shape of the ventricle. One might also expect a change in the proportion of patients with coronary artery disease, and in the degree of severity of the disease.

A related aspect of patient selection concerns the technical adequacy of the films. This has been discussed. As the catheterization techniques have improved, particularly as they relate to the induction of an irregular heart rhythm by the injection of the dye, it seems likely that fewer patients would be excluded from the study for this reason. This may have been offset however, by a change in the X-ray equipment to a smaller field of view, and thus an increase in the number of exclusions due to part of the outline not being visualized.

IV.3.2 Interpretation of Angiograms

A change over time in the definition of the percent stenoses would account for the change in the relationship between the stenoses and the left ventricular shape. Postulating this as the cause of the discrepancy between the 1978-79 data and the 1980 data however, is purely speculative. If a marginal stenosis that previously would have placed a patient in the NORMAL group would now place the patient in either the LAD or the RIGHT groups, then the proportion of hearts in these groups with normal or marginally abnormal shapes would increase. This would occur if the level of sophistication in the interpretation of the angiogram increased, and more coronary artery lesions were iden-

tified, or lesions were recognized as being more severe. For example, if a lesion of the right coronary artery was previously called a 40% stenosis, but was now called a 60% stenosis, the patient would shift from NORMAL to RIGHT. If the heart shapes were normal in these patients, the overlap among the groups would increase.

This effect could be documented by a blinded re-reading of a sample of the angiograms from the three years of the study. While the classification of severe stenoses might not have changed, it is conceivable that the classification of ambiguous lesions has changed over time.

IV.2.3 Intraobserver Bias

The study reported in this dissertation was performed by a single observer. The intraobserver variability in the different aspects of handling the films was presented. It was shown that the variability in choosing acceptable outlines was small, while that of tracing specific outlines was large. Because each ventriculogram was examined without knowledge of the corresponding angiogram, it is difficult to imagine a systematic bias at this level. Although the initial reading of the angiogram report could not be blinded, it involved only decisions about critical stenoses and the presence or absence of specific historical features and therefore, a systematic bias at this level does not seem likely either. The possibility of intraobserver bias could be examined with a second observer and the reexamination of a sample of the patient reports and ventriculograms.

V. REPRODUCIBILITY

V.1 Approximated Sections of Outlines

The proportion of outlines in which it was necessary to approximate a region was large. Of the 85 patients in the 1978 learning set and the 1979 test set with initially adequate films, 33 (39%) had some amount of approximation. Under the most stringent criteria for technical acceptability of an outline, these patients would have been discarded. With less stringent criteria, more patients would be included, particularly if the patient had multiple beats. This degree of exclusion on the basis of technical deficiency is not reported in other studies, and was an unexpected finding. The reasons for this relate to the technical requirements dictated by analyzing the entire outline.

As has been discussed, the subjective and hemiaxis methods do not require high quality images for analysis. If a small section of the outline is ambiguous, or the contrast of the cavity relative to the background is low, the data is still sufficient to categorize the image as normal or abnormal. The tangent angle function requires that the entire outline of the left ventricle be available, and therefore only very high quality ventriculograms can be used. This robustness with respect to the quality of the outlines is a strength of the subjective and hemiaxis methods. The clinical data is often fuzzy, and the catheterization cannot be repeated until the image is perfect. On the other hand,

these may be the reasons that obtaining the highest quality images is not the highest priority. It is possible that even with a change in priorities, the necessity of using only very high quality data will prove to be a serious limitation of outline based methods of left ventricular analysis.

The decision to accept some degree of contamination of the data seems reasonable. In most patients the amount approximated was small. In many patients, multiple beats were averaged, so the effect of the approximations would be expected to be small.

V.2 Beat to Beat Variability and Outline Identification

The beat to beat variability in the outlines and the observer variability in identifying and tracing the outlines was presented in RESULTS V.2 and V.5. It was shown that the beat to beat variability in the curvatures of the walls of the outlines was fairly small. The observer variability in identifying films with technically adequate beats was small, as was the variability in the identification of the film frames representing end diastole and end systole. The observer variability in the identification and tracing of outlines from specific frames however, was large.

V.2.1 Beat to Beat Variability

The beat to beat variability of the outlines was expected to be small. While some studies have indicated a myocardial depressant effect of the contrast agent, this effect develops over many beats (162). In this study, only

a small number of patients had ventriculograms with more than two technically adequate beats (RESULTS I). Any change in the outline that was manifested over many beats was unlikely to cause a dramatic change in the outline over two consecutive beats.

An additional reason for a relatively small beat to beat variability within a patient is that the outlines from consecutive beats were traced from the film during a single session. If a decision was made about the location of an ambiguous part of the outline, it was applied to all beats from that patient and therefore, this source of variability was not expressed. However, the variability in tracing an outline from the film, once the outline had been identified, was still present. Thus, the beat to beat variability represents the change in the outline from one beat to the next, plus the inherent variability in tracing a specific outline.

V.2.2 Observer Variability

The standards for technical adequacy of the films were set high in this study. Other studies have shown a substantial inter-observer variability in determining volume and wall motion from the ventriculogram (164,165), but did not provide the details of the source of the variability. The standards of this study arose from the judgement that if only high quality images were included, the variability in choosing the outline would not be large. This judgement proved reasonable in the choice of technical adequacy and in the timing of contraction events, but not in the determina-

tion of the location of the outline itself.

The high reproducibility of determining technical adequacy was expected because of the stringent requirements imposed. These requirements however, resulted in the exclusion of approximately 70% of the films considered (table 3). It is possible that with looser criteria, some of the films excluded would have been included: particularly among the 46% that did not have adequate opacification after a series of irregular beats. If a simultaneous electrocardiogram were available, then some of the films excluded because of an ambiguous rhythm might have been included with a sinus rhythm. The decision was made in the design of the study to err on the side of excluding films.

The high reproducibility in the determination of the timing of end diastole and end systole was also expected. These events were identified by a change in the direction of the motion of the outline: an event usually easily recognized. The most difficulty occurred with the timing of end systole when the aortic valve leaflets could not be identified, and thus were not available as timing markers. In some cases, a part of the outline appeared to be relaxing while other parts were still contracting. This phenomenon, which represents either asynchronous termination of systole or asynchronous onset of diastole, has been recognized by others (LITERATURE REVIEW III.1.4), and contributes to the difficulty in the precise definition of end systole. However, as table 27 showed, a single definition could be

applied consistently.

The poor degree of reproducibility in the location of the outline itself, illustrated by figures 28 and 29 was unexpected. Particularly with the example of figure 29, this was felt to represent true ambiguity in the definitions of the locations of the outline and landmarks. This ambiguity may prove to be the major limitation in the use of outline based methods of ventriculogram analysis.

The single plane right anterior oblique left ventriculogram is a projection of the dynamic three dimensional cardiac anatomy onto a single plane. The outline of the projection, the X-ray shadow that is seen on the film, is formed by the radio-opaque dye that is mixed with blood within the cavity of the ventricle. These two aspects of ventriculography have the potential for causing confusion about the location of the actual border of the heart.

The film from which figure 29 was traced had one inferior wall edge at end diastole, but two distinct outline edges in the inferior region at end systole: one slightly lighter than the other. As this heart moved through systole, the inner outline gradually became more distinct and dominant. The lighter outer region seemed to move, but not to clearly contract. The two edges of the outline seem to have resulted from contraction of walls in the direction of the X-ray beams: a movement that cannot be directly appreciated in a single plane. This type of behavior, in which the outline at one point of the cardiac cycle is formed by a

part of the wall of the ventricle that does not form the border at another part of the cycle, undoubtedly occurs in less dramatic cases than the one illustrated in figure 29.

The inner border of the heart is not smooth, but is formed of protruding muscle trabeculations. The amount of contrast agent that is contained within the infoldings of muscle between the trabeculations determines the contrast between the cavity of the ventricle and the background tissue. As the heart contracts and the trabeculations thicken, the amount of contrast agent at this border changes. If enough dye is lost at the border, the apparent border shifts. If dye is lost only at part of the ventricle, then only part of the border shifts. If some dye remains, the border remains, but with reduced contrast.

The decision rule used in this study was that trabeculations were <u>not</u> included as part of the left ventricular cavity. In the cases of a hypertrophied ventricle, or in the particular case of the papillary muscles, this rule was not difficult to follow. It does not seem reasonable however, that those apparent cases were the only ones. In cases where the border was visible, but at decreased contrast, there would undoubtedly be more variation in tracing. In cases where the extrusion of blood from the endocardial invaginations occurred just out of the plane of the film, the definition of the border could become even more difficult.

The definition of the valve points was also affected by

the dynamic anatomy of the ventriculogram. In figure 28, overlying aortic sinuses were pointed out as causing ambiguity in the definition of the aortic root points. In cases in which the sinuses were only lightly opacified or were heavily opacified, there would be no difficulty in identifying the valve, although in the second case a consistently incorrect decision would be made. The difficulty arises when the sinus is somewhat opacified, or becomes more opacified as the injection proceeds. The location of the valve may be clear at one time, but not another.

A similar problem existed in locating the mitral valve point. During diastole, the edge of the incoming, unopacified, stream of blood from the left atrium usually clearly delineated the edge of the valve annulus. However, as the contraction commenced, a portion of what appeared to be myocardium was often seen to be part of the valve apparatus: either because the region moved with the mitral valve and not the myocardium, or because a portion of the mitral valve not in the plane of the film became visible.

In defining the landmarks, an attempt was made to be consistent and have the points at end diastole correspond to the same points at end systole. With the characteristics noted above, variability in the definition of the landmarks was introduced.

A critical examination of the characteristics of the left ventricular outline has not been published; the subjective methods of analysis do not require a rigorous consider-

ation of the outline. Because of the high technical quality required in the design of this study, it seems that much of the variability in determining the location of the outline is inherent in the outline itself. Two approaches to this ambiguity suggest themselves.

The first approach is to use information from the left anterior oblique view in the recognition of the right anterior oblique border. Requiring that the same border be recognized in both views would help resolve the ambiguities caused by overlying and dynamic anatomical characteristics.

The second approach is to use the techniques of digital background subtraction and contrast enhancement such as those now being used in digital venous imaging (166). In this technique, the entire film is converted to digital form and the pre-injection film is electronically "subtracted" from the post-injection film. This would address the problems of decreased contrast at the border of the ventricle. It is of interest that Rushmer and Crystal suggested this, although using a completely manual approach, in 1951 (28).

The problems in identification of the border of the ventricle may limit the applications of outline based methods of ventriculogram analysis. Although analysis using the tangent angle function is completely automated and has few assumptions, its utility is limited if the basic data being analyzed is subject to question. The reproducibility of the outline must be improved, whether by consensus of multiple viewers, or by the techniques suggested above.

CHAPTER 7: CONCLUSIONS - FUTURE WORK

I. CONCLUSIONS

In this dissertation, the motivation for studying the left ventricles of patients with coronary artery disease was presented. The problems associated with using the reference-frame based methods of measuring left ventricular wall motion were discussed, and shape was offered as an alternative to these methods. The tangent angle function was shown to be a measure of shape that could be interpreted in terms of the coronary artery disease model, and a parameterization scheme was detailed that abstracted intuitive aspects of the shape of the left ventricle.

The next part of the dissertation was addressed to a study of left ventricular shape in patients with coronary artery disease. A cohort of patients was defined from the population of all patients undergoing catheterization. The shapes of the left ventricles of their hearts were measured and discriminant analysis was used to form the canonical variables that maximally discriminated among the groups. The two canonical variables were shown to have interpretations that fit nicely into the coronary artery disease model. Using the discriminant functions based only on the shape parameters, approximately 70% of the cohort could be allocated to the correct coronary artery group. This was

verified both within the cohort using a jackknife, and with an independent set of test data, although it could not be verified with a second set of test data.

The last part of the dissertation was addressed to the reproducibility of the steps involved in transferring the left ventricular outlines from the catheterization film to digital form in the computer. Determining the technical acceptability of the films and the timing of the systolic events was highly reproducible, as was the digitizing of specific outlines into the computer. The tracing of an outline from the film however, had significant variability.

I.1 The Tangent Angle Function

The tangent angle function, and through it the consideration of shape, provide a new point of view from which to examine left ventricular outlines. The logical inconsistencies of the reference-frame based methods have effectively demonstrated the need for such a point of view. It is interesting to note that using the tangent angle function, two outlines can be directly compared without introducing any relative alignment. This was not immediately obvious in the early work on the function, nor to those used to working with the reference-frame based methods.

The tangent angle function behaves like a derivative, responding dramatically to abrupt changes in the curvature of the outline and less dramatically to more gradual changes. As figure 9 showed, some outlines can be visually different, but have very similar tangent angle functions.

This is a potential limitation in the use of the function in left ventricular outline analysis: some of the features of the outlines that are appreciated by the observer are these slow changes.

I.2 Discriminant Analysis

The approach taken to the discrimination among patients with coronary artery disease was greatly simplified and straightforward. Patients were classified into one of three groups based on the presence or absence of an isolated critical coronary artery lesion. The ventriculograms were reduced to four parameters: one for the anterior wall and one for the inferior wall at end diastole and at end systole. These four parameters were then used to discriminate among the coronary artery groups. With this degree of simplification, it was not obvious that the degree of discrimination would be as high as it was.

The interpretations of the canonical variables in terms of the coronary artery disease model were particularly satisfying. Canonical Variable one was shown to represent end systolic dysfunction of one wall with increased function of the other wall. The variable provided a scale in which patients with inferior wall dysfunction (right coronary artery disease) had negative values, patients with anterior wall dysfunction (left anterior descending coronary artery disease) had positive values, and patients with no dysfunction (no coronary artery disease) were in between. End diastole contributed little to the value of this variable.

Canonical Variable two was interpreted as the shape change from end diastole to end systole. Patients in whom both walls changed from convex towards concave (no coronary artery disease) had negative values. Patients in whom one wall became increasingly convex during systole (dysfunction of the wall) had more positive values, regardless of the wall. Thus, Canonical Variable two provided a scale that ranged from normal (negative values) to abnormal (positive values). This variable incorporated both end diastole and end systole, but contributed only 20% of the separation among the three groups.

This was perhaps the central result of the dissertation. The shape parameters, the input to the discriminant analysis, were not based on any reference frame or model of left ventricular contraction. The coefficients of the canonical variables were those coefficients that maximized the separation of the three groups. Thus, the canonical variables did not depend on any unverifiable assumptions, and optimally discriminated among the three groups. This approach to the measurement of left ventricular dynamics has not been taken in the cardiology literature prior to this study.

This result must be interpreted with caution in light of its failure to be substantiated by a second set of test data. Although the second set of test data appeared to be inconsistent with the initial learning and test sets, it was gathered and analyzed according to the same procedures used

for the initial sets. Until the reason for this apparent inconsistency is found, the validity of the method of shape analysis and of the interpretations of the canonical variables must be questioned. If the reason for the apparent lack of consistency is related not to the methods, but to the patient population, then the utility of examining future patients using discriminant criteria based on historical data must be reexamined. Different investigations to determine the sources of the inconsistencies in the data were suggested in DISCUSSION IV.3.

I.3 Parameterization

The piecewise linear parameterization of the tangent angle function was attractive for two reasons. The first reason was that it provided a first order approximation to the shape of the heart. The heart was approximated with the sections of two circles connected at an apex. Although higher order shape was not captured, this first order approximation proved to be enlightening and useful.

The second reason was that the parameters were easily interpreted: both singly and in the weighted combinations of the canonical variables. This interpretability, and thus ease of association with the disease model, was not apparent with any of the other parameterizations examined.

The two limitations introduced by the parameterization involved the need to construct an apex, and the loss of higher order behavior. The apex was introduced to facilitate the parameterization. This meant accepting a con-

structed point in the definition of the walls of the outline, and therefore accepting the potential for unusual outlines to give unusual wall definitions. The definition of the apex was automated, and so observer bias was not a consideration, but a systematic bias in individual cases was possible. This bias was not observed, but this does not mean that it could not be observed in the future.

The first order parameterization of shape smoothed over all higher order behavior. This resulted in at least one case in which a patient was allocated to the incorrect coronary artery group because of the smoothing. This was an unavoidable consequence of using a highly simplified model. The performance of the simplified model was felt to be sufficient justification for this loss of higher order shape.

I.4 Outlines

The proportion of outlines that were technically acceptable for this investigation was around 25%. The majority of the exclusions were because of a lack of sinus beats that did not follow a premature contraction. The remainder of the exclusions were due to a lack of sufficient opacification of the ventricle and due to inadequate centering of the ventricle over the X-ray camera. This large proportion of exclusions was an important finding, and has implications for the use of outline based methods of ventricular analysis. It indicates that a technique of analysis such as the one investigated here would not be clinically useful in a general population because it could not be reliably applied

to every patient. In order for the subjective methods of analysis to be replaced by objective quantitative outline based techniques, the technical quality of the left ventriculograms will have to be improved.

The lack of reproducibility of determining the exact location of the outline also has important implications for analysis of the outlines. It is perhaps obvious: the data must be reproducible in order for the applications of the measure to have validity. The examples presented indicated that much of the variability in the outlines was due to ambiguity in the definition of the outline, not random error about a true outline. This indicates that a more sophisticated approach to the identification of the border of the ventricle is required to achieve the required degree of reproducibility.

II. FUTURE WORK

Each step in the development of the measure of the left ventricular outline and in the clinical study suggested further work to be done. The order in which the ideas are presented is suggested as a resonable sequence of investigation.

II.1 Outlines

The outline of the left ventricle is the basic data on which all studies are based: a reproducible method of determining the location of the outline must be found. As a first step, outlines could be viewed by multiple observers,

and disagreements resolved by consensus. If, as has been suggested in this study, there is no "true" outline, but rather an "accepted" outline, then this approach is reasonable. With this approach, incorporation of the left anterior oblique projection in the recognition of the right anterior oblique outline would be straightforward.

The next step in outline recognition would be to remove all observer input and completely automate the process. This would involve many aspects of pattern recognition, and would serve to remove all variability in the analysis.

II.2 Coronary Artery Disease Model

The coronary artery disease model used in this study was a simplification of the true anatomy and physiology. This model could be extended by using a more detailed description of the coronary artery pathology, such as the number and severity of stenoses in a single artery, and the amount of collateral circulation provided to the myocardium distal to the stenosis. This would be a first step towards using blood flow to the myocardium as the basic measure of pathology, and as a more accurate comparison to the shape of the left ventricle.

II.3 Discriminant Analysis

The discrimination among patients with coronary artery disease was based only on shape in order to study the reference-frame free measure of shape. This discrimination would be expected to improve if other measures of cardiac performance and history were included as well. Measures that have

been well studied, and are immediately accessible, are the ejection fraction and the presence or absence of a myocardial infarction. End diastolic and end systolic volumes would also be expected to improve the discrimination, but these require a calibration for image magnification that was not available for the early patients in this study. Other indices of left ventricular function are available, such as the rate of rise of left ventricular pressure and the rate of circumferential fiber shortening, and could also be included. Interpretation of the canonical variables for these mixtures of parameters would be challenging.

II.4 Parameterization

The parameterization scheme, while simple and interpretable, was not wholly satisfactory. The search for a scheme that did not involve an apex while also capturing more of the shape of the outlines could proceed in parallel to the other areas discussed.

The difficulty involved in using an apex in the analysis of shape is that it is not a landmark. However, the pathology being investigated, coronary artery disease (or more specifically myocardial ischemia), is regional. The problem is that the heart lacks the landmarks necessary to delimit the regions. The approaches to parameterizing the tangent angle function, or any other measure of left ventricular shape, will have to address this problem directly, and in a way that does not involve constructed points. Two approaches suggest themselves.

The first approach is to dispense with the piecewise modeling and look for parameterization schemes that address the shape of the entire outline. The tangent vector was one such approach, and could perhaps be exploited more than it was in this study. Another possibility would be to try template matching, with the degree of similarity between the outline and various templates of myocardial pathology providing the measures of shape.

The second approach is to search for landmarks on the ventricle. The coronary arteries themselves could provide the needed points. If the outline were to broken into sections based on blood flow and coronary artery perfusion, then one would have functional, rather than anatomical, landmarks. For example, rather than parameterizing the anterior wall, one would parameterize the section of the outline perfused by the left anterior descending coronary artery. This would be a closer step to the underlying patho-physiology on which the coronary artery disease model is based.

These ideas are speculative. The parameterization problem occupied the bulk of the time spent on this project: it will not be easily solved.

II.5 Further Applications

Further applications of the methodology presented in this dissertation involve extending the discriminant analysis, and studying other problems in cardiology.

The discriminant analysis is extended naturally by

including patients with other classes of coronary artery disease: two vessel disease, three vessel disease, and disease of the circumflex coronary artery. Most interesting would be those patients with two vessel disease involving the left anterior descending and the right coronary arteries. These patients might have dysfunction of both the anterior and inferior walls, appear "normal" to Canonical Variable one, but "abnormal" to Canonical Variable two. A similar situation might be expected with isolated circumflex coronary artery disease, in which the lateral wall of the heart is involved and the shape abnormality is out of the plane of the right anterior oblique ventriculogram. Of course with four clinical groups there would be three canonical variables, raising the possibility that another aspect of shape or shape change would make itself known.

The applications of shape to other problems in cardiology are those areas discussed in LITERATURE REVIEW. Perhaps most fruitful would be the pre and post intervention studies. In these studies, the patient serves as his own control: a natural area of application of a quantitative measure of shape.

II.6 Other Methods of Imaging the Heart

The tangent angle function is a technique for transforming an arbitrary two dimensional outline into a function that is suitable for parameterization. Nuclear cardiography and two dimensional echocardiography noninvasively provide outlines of the ventricle whose shape could be investigated.

The outlines obtained with these technologies have more noise associated with them than do the ventriculographic outlines; it is likely that visual border recognition would not be sufficient in the identification of the outlines. Therefore, the first step in investigating these outlines would have to be the development of an automated border detection algorithm.

The chief advantage to the noninvasively acquired outlines is that, because of the lack of morbidity, one can study large numbers of individuals multiple times. Particularly with echocardiography, serial studies and pre and post intervention studies can be done without confronting the ethical issues of performing catheterizations for investigational purposes. An additional advantage is that people felt to be truly "normal" could be studied - as contrasted with the catheterization group NORMAL that consisted of symptomatic patients with no demonstrable heart disease.

II.7 Other Methods of Measuring Shape

This investigation of the tangent angle function has brought one technique of shape measurement to bear on the analysis of left ventriculograms. There are many others (167). One that seems particularly intriguing is the medial axis, or skeleton, described by Blum (168).

The skeleton of a closed outline is the locus of points enclosed by the outline, each of whose minimum distance to the outline is not unique. Thus, the skeleton of a circle is a single point at the center (all other points within the

circle have a single minimum distance to the outline). The skeleton of a wiggly snake is a line along the midline. More complicated shapes generate more complicated skeletons, some of which have branches in addition to the main axis. The properties of this transformation are provided by Blum. It is a true measure of shape.

Abstraction of the skeleton of the outline of the left ventricle could prove illuminating. The skeleton would be a stick figure whose bends were a reflection of the symmetry of the outline. It is quite likely that certain shapes would generate branches from the central skeleton, and the presence or absence of branches could provide an additional measure. The skeleton has been investigated by others (169-175), but has not been applied to problems in cardiology.

The final area of further work to be mentioned is that of analyzing the full three dimensional shape of the left ventricular cavity. This image is not currently available clinically, but certainly will be in the future with the increasing use of tomographic imaging via X-rays (computerized axial tomography), magnetism (nuclear magnetic resonance), and isotopes (positron emission tomography). The three dimensional outline will certainly provide a much richer and more complete source of data for left ventricular analysis. Hopefully this will not be offset by the problems of regional reference and parameterization that will certainly arise.

APPENDIX

I. DERIVATION OF THE TANGENT VECTOR AND TANGENT ANGLE FUNCTION

(a) Consider the outline to lie in an arbitrarily oriented complex plane.

(b) Assume that the outline is sufficiently smooth that arc length is defined.

(c) Pick a starting point and an ending point on the outline. If the outline is closed (periodic) then these are the same point.

(d) Let s measure arc length from the starting point, in the clockwise direction.

(e) Scale the entire outline uniformly so that the total arc length from the starting point to the ending point is 1.

(f) Parameterize the curve in terms of arc length. i.e. let

$$z(s) = x(s) + i \cdot y(s) \qquad 0 \leq s \leq 1 \qquad (1)$$

represent the curve.

Differentiation of (1) gives

$$dz(s) = dx(s) + i \cdot dy(s) \qquad (2)$$

Since

$$|dz(s)|^2 = (dx)^2 + (dy)^2$$

$$|dz(s)|^2 = (ds)^2$$

$$\left|\frac{dz(s)}{ds}\right| = 1 \qquad (3)$$

And from (2)

$$\frac{dz(s)}{ds} = \frac{dx(s)}{ds} + i \cdot \frac{dy(s)}{ds} \qquad (4)$$

It follows that

$$\frac{dz(s)}{ds} = e^{i\theta(s)} \qquad 0 \leq s \leq 1 \qquad (5)$$

In other words, $\frac{dz(s)}{ds}$, the derivative of the outline with respect to arc length, is a complex number with magnitude 1.

$\frac{dz(s)}{ds}$ is the tangent vector. $\theta(s)$, the argument of the tangent vector, is the tangent angle function. For convenience, the tangent angle function used in the study was defined to be the negative of the argument of $\frac{dz(s)}{ds}$.

II. PROPERTIES

II.1 Size Invariance

Size invariance is implicit in the scaling of the images to unit arc length.

II.2 Position Invariance

Suppose that the outline is shifted with respect to the coordinate axes by a complex number c. Let

$$\hat{z}(s) = z(s) + c \qquad (6)$$

be the shifted outline. Then, the tangent vector of the shifted outline is

$$\frac{d\hat{z}(s)}{ds} = \frac{d}{ds}(z(s) + c)$$

$$= \frac{d}{ds}(z(s))$$

and is clearly unaffected by the shift.

II.3 Rotation Invariance

Let the outline be rotated with respect to the coordinate axes by an angle γ. Let

$$\hat{z}(s) = e^{i\gamma} z(s) \qquad (7)$$

be the rotated outline. The tangent vector of the rotated outline is

$$\frac{d\hat{z}(s)}{ds} = \frac{d}{ds}\left(e^{i\gamma}z(s)\right)$$

$$= e^{i\gamma}\frac{dz(s)}{ds} \qquad (8)$$

Substitution of (5) gives

$$\frac{d\hat{z}(s)}{ds} = e^{i(\vartheta(s)+\gamma)} \qquad (9)$$

Thus, the tangent vector has been multiplied by a complex constant with magnitude 1: a pure phase shift. The tangent angle function of the rotated outline is

$$\arg\left(\frac{d\hat{z}(s)}{ds}\right) = \vartheta(s) + \gamma \qquad (10)$$

This is the tangent angle function of the original function, with a constant added.

II.4 Tangent Angle Function of a Circle

A circle with unit perimeter is expressed in the complex plane as

$$z(s) = \frac{1}{2\pi}e^{i2\pi s} \qquad 0 \leq s \leq 1 \qquad (11)$$

The tangent vector is

$$\frac{dz(s)}{ds} = i\cdot e^{i2\pi s}$$

$$= e^{i(2\pi s + \pi/2)} \qquad (12)$$

A circle that has been phase shifted by $\frac{\pi}{2}$.

The tangent angle function of the circle is

$$\arg\left(\frac{dz}{ds}\right) = 2\pi s + \frac{\pi}{2} \qquad (13)$$

A straight line with slope 2π.

II.5 Fourier Series of the Tangent Vector

The Fourier series of the tangent vector is

$$\frac{dz(s)}{ds} = \sum_{k=-\infty}^{\infty} a_k \cdot e^{i2\pi ks}$$

a_k is obtained by the usual integral formula

$$a_k = \int_0^1 (\frac{dz}{ds}) e^{-i2\pi ks} ds$$

Substituting (5) for $\frac{dz}{ds}$ gives

$$a_k = \int_0^1 e^{i\theta(s)} \cdot e^{-i2\pi ks} ds \qquad k \text{ integer} \qquad (14)$$

II.5.1 Rotation Invariance of the Fourier Coefficients

Let $\hat{z}(s)$ be the outline rotated by $e^{i\gamma}$, as in (9). Let $\hat{a}_k$ be the Fourier coefficients of $\hat{z}(s)$. Then

$$\hat{a}_k = \int_0^1 (\frac{d\hat{z}}{ds}) e^{-i2\pi ks} ds$$

Substituting (9) gives

$$\hat{a}_k = \int_0^1 e^{i(\theta(s)+\gamma)} \cdot e^{-i2\pi ks} ds$$

$$\hat{a}_k = e^{i\gamma} \int_0^1 e^{i\theta(s)} \cdot e^{-i2\pi ks} ds$$

$$\hat{a}_k = e^{i\gamma} \cdot a_k \qquad (15)$$

and $\quad |\hat{a}_k|^2 = |a_k|^2$

II.5.2 Fourier Series of a Circle

The Fourier series of the tangent vector of a circle has only a_1 nonzero.

It is easily shown (see II.5.3) that for an arbitrary

function f(s) that is periodic on (0,1), and that has Fourier coefficients a_k, that

$$\sum_{k=-\infty}^{\infty} |a_k|^2 = \int_0^1 |f(s)|^2 ds \tag{16}$$

In the case of the tangent vector

$$f(s) = e^{i\vartheta(s)}$$

so

$$\sum_{k=-\infty}^{\infty} |a_k|^2 = 1 \tag{17}$$

The tangent vector of a circle is given by (12). Substituting into (14) gives

$$a_k = \int_0^1 e^{i(2\pi s+\pi/2)} e^{-i2\pi ks} ds$$

$$= e^{i\pi/2} \int_0^1 e^{i2\pi(1-k)s} ds \tag{18}$$

If k = 1, then

$$a_1 = e^{i\pi/2} \int_0^1 ds$$

$$a_1 = e^{i\pi/2} \tag{19}$$

and $|a_1| = 1$

If $k \neq 1$, it follows from (17) that

$$|a_k| = 0 \qquad k \neq 1 \tag{20}$$

In other words, only a_1 is $\neq 0$. All other coefficients are zero.

As the outline deviates from a circle, the a_k ($k \neq 1$) will become nonzero. From (17), a_1 will become less than 1.

In this sense then,

$$1 - |a_1|^2$$

measures the deviation of the outline from a circle.

II.5.3 Sum of Fourier Coefficient Magnitudes

The proof of (16) is as follows:

f(s) is periodic on (0,1), and has Fourier coefficients

$$a_k = \int_0^1 f(s) e^{-i2\pi ks} ds$$

Derive the magnitude of a_k:

$$|a_k|^2 = \{ \int_0^1 f(s) e^{-i2\pi ks} ds \} \{ \int_0^1 \overline{f(\xi)} \cdot e^{i2\pi k\xi} d\xi \} \quad (21)$$

The second term of (21) is the conjugate of the first term, with s replaced by the dummy argument ξ. Rearranging (21) gives

$$|a_k|^2 = \int_0^1 \int f(s) \overline{f(\xi)}\, e^{-i2\pi k(s-\xi)} ds\, d\xi$$

$$\sum_{k=-\infty}^{\infty} |a_k|^2 = \int_0^1 \int f(s) \overline{f(\xi)} \{ \sum_{k=-\infty}^{\infty} e^{-i2\pi k(s-\xi)} \} ds\, d\xi \quad (22)$$

The term of (22) in brackets is the Fourier series of the delta function

$$\delta(s-\xi) = \begin{cases} 1, & s=\xi \\ 0, & \text{otherwise} \end{cases} \quad (23)$$

Substituting (23) into (22) gives

$$\sum_{k=-\infty}^{\infty} |a_k|^2 = \int_0^1 \int f(s) \overline{f(\xi)} \delta(s-\xi)\, ds\, d\xi$$

The outer integral on ξ is zero everywhere except when $s = \xi$. Therefore,

$$\sum_{k=-\infty}^{\infty} |a_k|^2 = \int_0^1 f(s)\overline{f(s)}ds$$

$$= \int_0^1 |f(s)|^2 ds$$

as was to be proved.

III. Computation of the Tangent Angle Function

III.1 Formulation

Let the discretized curve be represented by the coordinate pairs

$$z_i = (x_i, y_i) \qquad i = 1,2,\ldots,n$$

where z_1 = the starting point (s=0)

and z_n = the ending point (s=1) (24)

Let the vectors that are the line segments that connect the consecutive points be written as

$$\Delta z_i = ((x_{i+1}-x_i), (y_{i+1}-y_i)) \qquad i = 1,2,\ldots,n-1$$

$$= (\Delta x_i, \Delta y_i) \qquad (25)$$

i.e., the Δz_i are labeled according to the initial point of the line segment. The angle that Δz_i makes with the X axis is

$$\tan(\theta_i) = \frac{\Delta y_i}{\Delta x_i}$$

$$\theta_i = \tan^{-1}\left(\frac{\Delta y_i}{\Delta x_i}\right) \quad i = 1,2,\ldots,n-1 \qquad (26)$$

The cumulative arc length to z_i is

$$s_i = \sum_{j=1}^{i-1} |\Delta z_j| \qquad i = 2,\ldots,n \qquad (27)$$

where s_1 equals zero.

The pairs of values (s_i,ϑ_i) are the values of the negative of the tangent angle function (the tangent angle function was defined as the negative of the angles to provide a function that increased in value as the curves moved in the positive direction). Note that with (26) and (27) defining s_i and ϑ_i, the function is continuous from the right: i.e., arc length is to the point z_i, but the angle is that of the vector from z_{i+1} to z_i. This means that θ_n is not defined.

If (26) is used to compute θ_i, the tangent angle function will jump by 2π when the branch cut of tan is crossed. The following computational procedure avoids this.

It is easily shown (176) that

$$\tan(\alpha-\beta) = \frac{\tan(\alpha)-\tan(\beta)}{1+\tan(\alpha)\tan(\beta)} \qquad (28)$$

let $\alpha=\theta_i$ and $\beta=\theta_{i-1}$, and take $\tan^{-1}$ of both sides of (28):

$$\vartheta_i-\vartheta_{i-1} = \tan^{-1}\left(\frac{\tan(\vartheta_i)-\tan(\theta_{i-1})}{1+\tan(\theta_i)\tan(\theta_{i-1})}\right) \quad i = 2,\ldots,n-1 \qquad (29)$$

Substitute (26) for $\tan(\theta)$ and manipulate the right hand side of (29):

$$\vartheta_i-\vartheta_{i-1} = \tan^{-1}\left(\frac{\frac{\Delta y_i}{\Delta x_i}-\frac{\Delta y_{i-1}}{\Delta x_{i-1}}}{1+\frac{\Delta y_i}{\Delta x_i}\cdot\frac{\Delta y_{i-1}}{\Delta x_{i-1}}}\right)$$

$$\theta_i = \theta_{i-1} + \tan^{-1}\left(\frac{\Delta x_{i-1}\Delta y_i - \Delta x_i \Delta y_{i-1}}{\Delta x_i \Delta x_{i-1} + \Delta y_i \Delta y_{i-1}}\right)$$

$$i=2,3,\ldots,n-1$$

$$\theta_1 = \tan^{-1}\left(\frac{\Delta y_1}{\Delta x_1}\right) \qquad (30)$$

If $\tan^{-1}$ is taken with attention to the appropriate quadrant of the argument (e.g., by the FORTRAN function ATAN2), then the branch cut will not be encountered as long as $|\theta_i - \theta_{i-1}| < \pi$.

III.2 FORTRAN Subroutine

The following FORTRAN subroutine computes the tangent angle function of an arbitrary curve, using the algorithm of section III.1. The routine assumes that the curve consists of N consecutive (x,y) pairs stored in the one dimensional array CV as x(1), y(1), x(2), y(2), ... ,x(N), y(N). With this formulation, the index of x(j) is CV(2*j-1), and the index of y(j) is CV(2*j). A one dimensional array of pointers into CV is passed to the subroutine in PTR. These pointers might be fiduciary points on the original curve for which the corresponding points in the tangent angle curve are desired. PTR(1) contains the number of pointers, and PTR(2) through PTR(n+1) contain the n pointers.

The tangent angle function is returned in the one dimensional array TS. TS(2*j-1) is the value of cumulative arc length to the jth point, and TS(2*j) is the cumulative tangent angle to infinitesimally past the jth point (this makes the tangent angle function continuous from the right).

The number of points in TS is returned in NT. The pointers into TS that correspond the the pointers passed in PTR are returned in the one dimensional array PTRT. PTRT(j) corresponds to PTR(j). PTRT(1) is not altered by the subroutine.

Because of the indeterminacy in the arc length of a noisy curve, only points of CV that are a distance TOL apart are included in the computation of TS. This means that in general, NT does not equal N, and PTRT(j) does not equal PTR(j).

The routine also assumes that the last point of CV is not the same as the first point. The last two points of TS are the values of the part of the tangent angle function that connects the last point of CV to the first point.

The computation is done in double precision (REAL*8), while the arguments are all in single precision. It is emphasized that arc length is defined as the arc length <u>to</u> the point, while the angle at that point is the <u>forward</u> pointing angle.

```
      SUBROUTINE TACOMP (CV,N,TS,NT,PTR,PTRT,TOL)
C
C DX(1) AND DY(1) HOLD THE DX AND DY TO THE CURRENT POINT
C DX(2) AND DY(2) HOLD THE DX AND DY FROM THE CURRENT POINT
C TO THE NEXT ONE.
C
C TOLD, ALD, AND TAD ARE THE *8 VALUES OF THE CORRESPONDING
C *4 VARIABLES TOL,TS(2*K-1),TS(2*K)
C
      REAL CV(1),TS(1),TOL
      REAL*8 DX(2),DY(2),TOLD,ALD,TAD
      INTEGER N,NT,INDX,PTR(1),PTRT(1)
C
C NT IS THE INDEX OF THE NEXT POINT IN TS
```

```
C INITIALLY SET NT TO 1 AND
C INITIALLY SET PTRT TO THE FIRST POINT
C
      NT=1
      DO 5 K=2,PTR(1)+1
       PTRT(K)=1
 5    CONTINUE
C
C I WILL BE THE INDEX INTO CV OF THE CURRENT POINT
C J WILL BE THE INDEX INTO CV OF THE NEXT POINT
C INCREMENT J UNTIL THE DISTANCE FROM POINT I TO POINT J
C IS >= TOL.  FOR THE FIRST POINT, I=1
C
      J=2
      TOLD=TOL
C
 10   DX(1)=DBLE(CV(2*J-1))-DBLE(CV(1))
      DY(1)=DBLE(CV(2*J))-DBLE(CV(2))
      IF (DX(1)**2+DY(1)**2 .GE. TOLD**2) GO TO 20
       J=J+1
       GO TO 10
 20   CONTINUE
C
C START WITH 0 ARC LENGTH AND FORWARD POINTING ANGLE
C (CONTINUOUS FROM THE RIGHT)
C SAVE THIS ANGLE IN TAD FOR THE COMPUTATION OF
C THE NEXT ANGLE
C
      ALD=0.
      TS(1)=0.
      TAD=DATAN2(DY(1),DX(1))
      TS(2)=TAD
C
C INCREMENT THE VALUES OF PTRT UNTIL J > PTR(K).
C I.E. UNTIL THE POINTER INTO CV HAS BEEN PASSED.
C
      DO 30 K=2,PTR(1)+1
       IF (J .LE. PTR(K)) PTRT(K)=2
 30   CONTINUE
C
C SAVE THE INDEX OF THE LAST POINT OF THE FIRST SEGMENT
C TO USE IN CLOSING THE CURVE
C
      INDX=J
C
C THIS IS THE MAIN LOOP.  NOTE THAT NT IS INCREMENTED
C BEFORE THE POINT IS FOUND.
C LOOP UNTIL J>N
C
C FIND THE 2ND POINT OF THE NEXT SEGMENT
C
 200  NT=NT+1
      I=J
```

```
      J=J+1
 210  IF (J .GT. N) GO TO 1000
       DX(2)=DBLE(CV(2*J-1))-DBLE(CV(2*I-1))
       DY(2)=DBLE(CV(2*J))-DBLE(CV(2*I))
       IF (DX(2)**2+DY(2)**2 .GE. TOLD**2) GO TO 220
        J=J+1
        GO TO 210
C
C FOUND THE END POINT, COMPUTE ARC LENGTH AND ANGLE,
C AND UPDATE DX AND DY
C
 220   ALD=DSQRT(DX(1)**2+DY(1)**2)+ALD
       TS(2*NT-1)=ALD
       TAD=TAD+DATAN2((DY(2)*DX(1)-DX(2)*DY(1)),
     X                (DX(1)*DX(2)+DY(1)*DY(2)))
       TS(2*NT)=TAD
      DX(1)=DX(2)
      DY(1)=DY(2)
C
C INCREMENT THE POINTERS UNTIL WE HIT OR PASS THE POINT
C IN CV.  THE POINTER IN PTRT WILL BE THE NEXT POINT IN TS.
C THIS IS THE POINT WHOSE ANGLE CORRESPONDS TO THE POINT
C IN CV
C
      DO 250 K=2,PTR(1)+1
       IF (J .LE. PTR(K)) PTRT(K)=NT+1
 250  CONTINUE
C
      GO TO 200
C
 1000 CONTINUE
C
C FINISHED CV. NOW ADD ON TS POINTS TO CLOSE CV
C
C THE NEXT SEGMENT IS FROM THE LAST TO THE FIRST POINT.
C COMPUTE THIS ANGLE. UPDATE THE LAST POINT OF TS.
C
      DX(2)=DBLE(CV(1))-DBLE(CV(2*I-1))
      DY(2)=DBLE(CV(2))-DBLE(CV(2*I))
      ALD=DSQRT(DX(1)**2+DY(1)**2)+ALD
      TS(2*NT-1)=ALD
      TAD=TAD+DATAN2((DY(2)*DX(1)-DX(2)*DY(1)),
     X               (DX(1)*DX(2)+DY(1)*DY(2)))
C
      TS(2*NT)=TAD
C
      NT=NT+1
      DX(1)=DX(2)
      DY(1)=DY(2)
C
C INDX IS THE 2ND POINT OF THE FIRST SEGMENT THAT DEFINED
C THE FIRST POINT OF TS
C
```

```
      DX(2)=DBLE(CV(2*INDX-1))-DBLE(CV(1))
      DY(2)=DBLE(CV(2*INDX))-DBLE(CV(2))
C
C ADD IN 2 EXTRA POINTS: (1) CONSTANT ANGLE ALONG THE LONG
C SEGMENT FROM THE LAST TO THE FIRST POINT OF CV, AND (2)
C THE JUMP IN ANGLE TO 2 PI + THE FIRST ANGLE, TO COMPLETE
C THE CURVE
C
      ALD=ALD+DSQRT(DX(1)**2+DY(1)**2)
      TS(2*NT-1)=ALD
      TS(2*NT)=TS(2*(NT-1))
C
C NOTE THAT THIS MEANS THAT THE LAST S OF TS IS
C SINGLE VALUED.
C
      NT=NT+1
      TS(2*NT-1)=TS(2*(NT-1)-1)
      TS(2*NT)=TAD+DATAN2((DY(2)*DX(1)-DX(2)*DY(1)),
     X                    (DX(1)*DX(2)+DY(1)*DY(2)))
C
C CHANGE SIGN OF ANGLES
C
      DO 300 I=1,NT
       TS(2*I)=-TS(2*I)
 300  CONTINUE
C
      RETURN
      END
```

TABLE 1 CLASSIFICATION OF CATHETERIZATION REPORTS

	Number	Per Cent
Valve Disease	304	22.17 %
Other CA Disease	451	32.90 %
Post CA Bypass Surgery	105	7.66 %
Normal, Previous Infarction	23	1.68 %
Other Condition	135	9.85 %
Fulfill Clinical Criteria	353	25.75 %
Total	1371	100 %

CA: Coronary Artery

TABLE 2 OTHER CONDITION LEADING TO EXCLUSION

	NUMBER
Complete Study not Performed	53
Extra-cardiac Abnormality	
Pericarditis	5
Pulmonary Embolus	2
Post Thoracic Surgery	4
Pulmonic Stenosis	1
Pulmonary Hypertension	2
Coarctation of the Aorta	1
Intra-Aortic Balloon Pump	15
Complications	3
Cardiac Abnormality	
Congenital Heart Disease	19
Cardiomyopathy	11
Conduction or Rhythm Disturbance	18
Left Atrial Myxoma	1
Total	135

TABLE 3 PATIENTS FULFILLING CLINICAL CRITERIA

	Number	Per Cent
No non post-PVC beats visualized	163	46.18 %
Entire outline not on film	78	22.10 %
Obliteration of apex	8	2.27 %
Film not available or lost	19	5.38 %
At least 1 non post-PVC of adequate quality	85	24.08 %
Total	353	100 %

PVC: Premature Ventricular Contraction

TABLE 4 NUMBER OF BEATS OF ADEQUATE QUALITY

Number of Beats	Number of Patients	Per Cent
1	36	42.35 %
2	31	36.47 %
3	12	14.12 %
4	4	4.71 %
5	2	2.35 %
Total	85	100 %

TABLE 5 SIMULATION OF DIGITIZING - ARC LENGTH INFLATION

Minimum Interval	# of Points	Distance Actual	Estimated	Difference	Percent
10	149	3962	4309.21	347.21	.0876
20	99	3946	4047.48	101.48	.0257
30	75	3946	3979.85	33.85	.0086
40	63	3921	3950.39	29.39	.0075
50	57	3946	3962.30	16.30	.0041
60	46	3946	3954.62	8.62	.0022
70	44	3962	3970.56	8.56	.0021

Note: The last actual point of the line corresponds to the last simulated point: this was not the same for each minimum interval.

TABLE 6 CURVATURE SUMMARY STATISTICS

Phase	Wall	Coronary Disease Group LAD	Normal	RIGHT	
DIA	ANT	.81	.79	.71	(Mean)
		.013	.014	.025	(Variance)
DIA	INF	.49	.57	.60	
		.075	.022	.042	
SYS	ANT	.44	.17	.01	
		.083	.037	.033	
SYS	INF	-.02	.03	.45	
		.054	.061	.128	
TOTAL	(N)	22	21	13	

The first line of each cell is the mean and and the second line the variance of the curvature of the indicated wall in the indicated sub-group.

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole
LAD, NORMAL, RIGHT, as in text.

TABLE 7 ONE-WAY ANOVA FOR EACH CURVATURE

Phase	Wall	F(2,53)	P
DIA	ANT	2.8	.07
	INF	1.3	.29
SYS	ANT	15.2	<.001
	INF	14.2	<.001

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole

TABLE 8 MULTIPLE RANGE TEST ON CURVATURES

Phase	Wall	Coronary Artery Group L	N	R
DIA	ANT	****		
			XXXX	
DIA	INF	*******		
SYS	ANT	*	XXXX	
SYS	INF	****		X

For each Phase-Wall group, coronary artery groups with the same symbol are not significantly different from each other.

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole
L: LAD N: NORMAL R: RIGHT as in text

TABLE 9 STEPWISE DISCRIMINANT ANALYSIS SUMMARY

Step	Curvature Entered Phase	Wall	F to Enter	DOF	U	Approx. F	DOF	
1	SYS	ANT	15.2	2,53	.64	15.2	2,53	
2	SYS	INF	12.5	2,52	.43	13.7	4,104	
3	DIA	INF	2.3	2,51	.40	10.1	6,102	
4	DIA	ANT	1.6	2,50	.37	8.1	8,100	*

* P < .001 for U of step 4.

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole

TABLE 10 EIGENVALUES OF THE DISCRIMINANT ANALYSIS

Variable	Eigenvalue	Proportion of Dispersion
CV-1	1.14	.81
CV-2	.26	.19
Total	1.40	1.00

CV-1, CV-2: as in text.

TABLE 11 CANONICAL VARIABLE COEFFICIENTS

Phase	Wall	Coefficient CV-1	CV-2
DIA	ANT	.35	-4.92
DIA	INF	.89	-4.78
SYS	ANT	3.04	3.37
SYS	INF	-3.11	2.99
CONSTANT		-1.15	5.31

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole

TABLE 12 CLASSIFICATION FUNCTIONS

Phase	Wall	Coronary Disease Group LAD	NORMAL	RIGHT
DIA	ANT	75.5	80.3	74.8
DIA	INF	37.3	41.4	35.1
SYS	ANT	-7.2	-13.6	-15.6
SYS	INF	-11.0	-11.2	-2.7
CONSTANT		-39.2	-43.4	-37.3

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole
LAD, NORMAL, RIGHT as in text.

TABLE 13 DISCRIMINATION: LEARNING SET

		Shape Group L	N	R	TOTAL
Coronary Group	L	15 (.68)	5 (.23)	2 (.09)	22 (1.00)
	N	3 (.14)	16 (.76)	2 (.10)	21 (1.00)
	R	0 (.00)	3 (.23)	10 (.77)	13 (1.00)
Total		18	24	14	56

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 14 DISCRIMINATION: LEARNING SET, JACKKNIFE RESULT

		Shape Group L	N	R	TOTAL
Coronary Group	L	14 (.64)	6 (.27)	2 (.09)	22 (1.00)
	N	4 (.19)	15 (.71)	2 (.10)	21 (1.00)
	R	0 (.00)	3 (.23)	10 (.77)	13 (1.00)
Total		18	24	14	56

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 15 NORMAL VS ABNORMAL BY SHAPE, THE LEARNING SET

		Shape Group		
		Normal	Abnormal	Total
Coronary Group	Normal	15	6	21
	Abnormal	9	26	35
	Total	24	32	56

Chi Square (1) = 11.2, P<.001

The following statistics refer to the ability of abnormal shape to predict abnormal coronary arteries.

Sensitivity = 26/35 = .74
Specificity = 15/21 = .71
Positive Predictive Value = 26/32 = .81
Negative Predictive Value = 15/24 = .63

TABLE 16 ALLOCATION OF THE TEST SET

		Shape Group			
		L	N	R	TOTAL
Coronary Group	L	9 (.75)	2 (.17)	1 (.08)	12 (1.00)
	N	1 (.14)	5 (.71)	1 (.14)	7 (1.00)
	R	1 (.10)	2 (.20)	7 (.70)	10 (1.00)
	Total	11	9	9	29

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 17 DISCRIMINATION: 1978-79 LEARNING SET

		Shape Group L	N	R	TOTAL
	L	24 (.71)	8 (.24)	2 (.06)	34 (1.00)
Coronary Group	N	4 (.14)	21 (.75)	3 (.11)	28 (1.00)
	R	1 (.04)	6 (.26)	16 (.70)	23 (1.00)
Total		29	35	21	85

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 18 DISCRIMINATION: 1978-79 LEARNING SET, JACKKNIFE

		Shape Group L	N	R	TOTAL
	L	21 (.62)	10 (.29)	3 (.09)	34 (1.00)
Coronary Group	N	5 (.18)	20 (.71)	3 (.11)	28 (1.00)
	R	2 (.09)	6 (.26)	15 (.65)	23 (1.00)
Total		28	36	21	85

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 19 ALLOCATION OF THE 1980 TEST SET

		Shape Group			
		L	N	R	TOTAL
Coronary Group	L	11 (.73)	4 (.27)	0 (.00)	15 (1.00)
	N	9 (.65)	2 (.14)	3 (.21)	14 (1.00)
	R	5 (.45)	3 (.27)	3 (.27)	11 (1.00)
	Total	25	9	6	40

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 20 DISCRIMINATION: 1980 LEARNING SET

		Shape Group			
		L	N	R	TOTAL
Coronary Group	L	7 (.47)	6 (.40)	2 (.13)	15 (1.00)
	N	6 (.43)	3 (.21)	5 (.36)	14 (1.00)
	R	3 (.27)	1 (.09)	7 (.64)	11 (1.00)
	Total	16	10	14	40

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 21 DISCRIMINATION: 1980 LEARNING SET, JACKKNIFE

		Shape Group L	N	R	TOTAL
	L	7 (.47)	6 (.40)	2 (.13)	15 (1.00)
Coronary Group	N	6 (.43)	2 (.14)	6 (.43)	14 (1.00)
	R	3 (.27)	1 (.09)	7 (.64)	11 (1.00)
Total		16	9	15	40

Numbers in parentheses are the proportion of each coronary group classified into the shape group.

L: LAD N: NORMAL R: RIGHT as in text

TABLE 22 PRECISION OF DIGITIZING

	Horizontal Line X	Horizontal Line Y	Vertical Line X	Vertical Line Y	Circle X	Circle Y
Point 1	1.33	9.78	1.72	0.00	1.00	4.44
Point 2	3.00	7.11	3.89	1.78	1.78	4.44
Point 3	3.78	1.78	3.39	5.33	3.11	3.56
Point 4	7.78	5.33	1.33	5.33	1.78	5.33
Point 5	6.44	2.67	3.33	10.67	2.67	3.11
Point 6	7.56	5.33	4.17	1.78	4.00	2.22
Point 7	2.11	3.56	1.61	4.44	1.11	1.78
Point 8	3.11	5.33	3.00	3.56	4.28	5.33
Point 9	4.89	3.56	2.72	2.67	2.61	3.56
Point 10	2.00	3.56	2.44	5.33	1.67	4.44
Standard Deviation	2.05	2.19	1.66	2.02	1.55	1.96

Each entry is the variance of the coordinate, in Graf-pen units, based on ten replications (1 unit = .1 millimeter).

TABLE 23 VARIATION IN DIGITIZING A SINGLE OUTLINE

		Mean	Variance	
Arc Length	Total	3148	92.1	dof: 9
	Anterior	1589	92.5	
	Inferior	1454	69.4	
Curvature	Anterior	-.02	.0003	
	Inferior	.06	.0001	

Units are Graf-Pen units. 10 units = 1 millimeter.

TABLE 24 POOLED ESTIMATE OF BEAT TO BEAT VARIANCES

PHASE	WALL	ESTIMATE	DF
DIA	ANT	.0024	46
DIA	INF	.0028	65
SYS	ANT	.0043	69
SYS	INF	.0088	55

ANT: Anterior INF: Inferior
DIA: Diastole SYS: Systole

TABLE 25 APPROXIMATED SEGMENTS

Part Approximated	Wall or Beat Deleted	Patients Deleted Number	Per Cent
Any Part	Beat	33	39 %
Any Part	Wall	30	35 %
Any Part Except PM	Beat	26	31 %
Any Part Except PM	Wall	23	27 %

PM: Papillary Muscle Segment
Note: Per cent deleted is per cent of the 1978-79 learning set.

TABLE 26 DETERMINATION OF TECHNICAL ADEQUACY

		Second Viewing Acceptable	Unacceptable	Total
Initial Viewing	Acceptable	9	1	10
	Unacceptable	1	9	10
	Total	10	10	20

The large numbers on the diagonals indicate that the judgements of adequacy did not change from the first viewing to the second.
McNemar's test, with the correction for continuity (159), gives Chi Squared = .50, $.25 < p < .5$, for the null hypothesis of no difference between viewings.

TABLE 27 DETERMINATION OF SYSTOLIC TIMING

ID	Difference End Diastole	End Systole
9187	0	-1
9250	1	0
9413	1	0

Diastolic Frames: $t(9) = 1.5$ $.1 < p < .2$
Systolic Frames: $t(9) = -1.0$ $.2 < p < .5$

Listed are the films in which the repeat determinations of the timing of end diastole and of end systole showed a difference. Response is the difference in frame numbers between viewing 1 and viewing 2.

TABLE 28 REPRODUCIBILITY OF TRACING: DESIGN

	ID 1	ID 2	...	ID 10
Viewing 1	Beat 1	Beat 1	...	Beat 1
	Beat 2	Beat 2	...	Beat 2
Viewing 2	Beat 1	Beat 1	...	Beat 2
	Beat 2	Beat 2	...	Beat 2

ANOVA TABLE

Source	Mean Square	dof	Expected Mean Square
ID	MS(ID)	9	$s^2(E) + 2s^2(ID*V) + 4s^2(ID)$
Viewing	MS(V)	1	$s^2(E) + 2s^2(ID*V) + 20s^2(V)$
ID * Viewing	MS(ID*V)	9	$s^2(E) + 2s^2(ID*V)$
Error	MS(E)	20	$s^2(E)$

Note: ID and Viewing are random effects.

TABLE 29 REPRODUCIBILITY OF TRACING: RESULT

PHASE	WALL	MS(E)	MS(ID*V)	MS(V)	F	P
DIA	ANT	.002	.003	.013	4.8	.05 < p <.1
DIA	INF	.002	.007	.031	4.7	.05 < p <.1
SYS	ANT	.003	.010	.010	.9	
SYS	INF	.007	.004	.035	8.2	.01 < p < .025

Note: F = MS(V)/MS(ID*V)

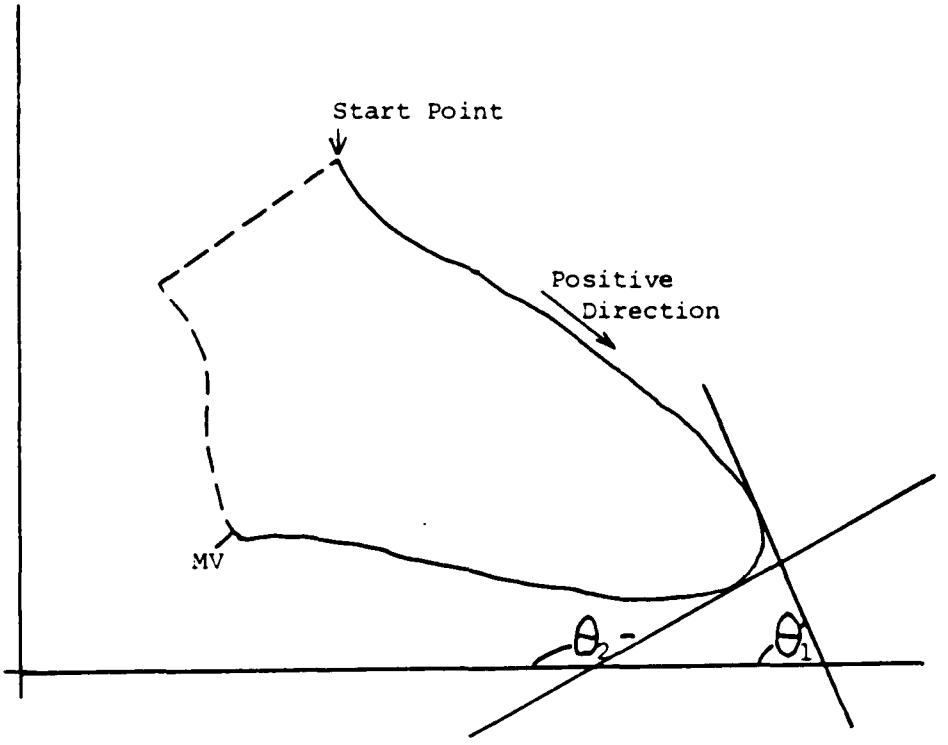


FIGURE 1
Outline of the left ventricle, arbitrarily oriented on an X-Y plane.

Dotted lines are the valve region.
MV: mitral valve point

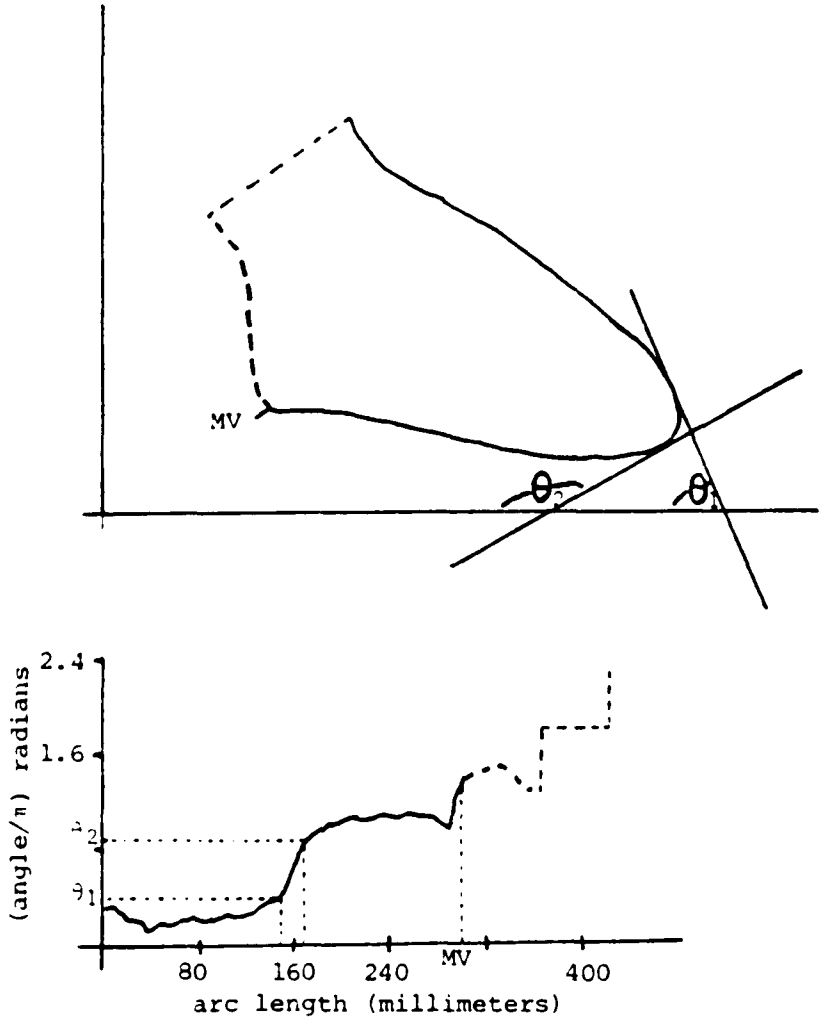


FIGURE 2
Tangent Angle Function.

Note that ϑ_1 and ϑ_2 are on either side of the apical region.

Dashed: valve region
MV: mitral valve point

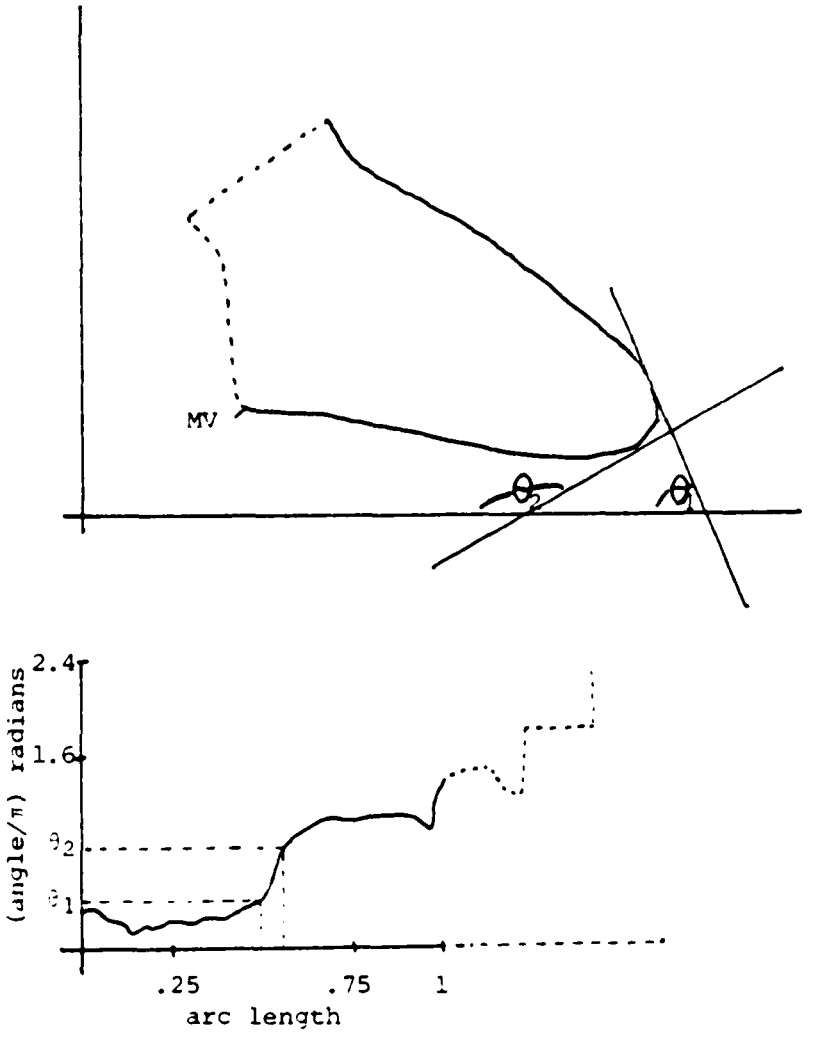


FIGURE 3
Tangent angle function with arc length rescaled.
The distance to the mitral valve point is unity.

Dashed: valve region
MV: mitral valve point

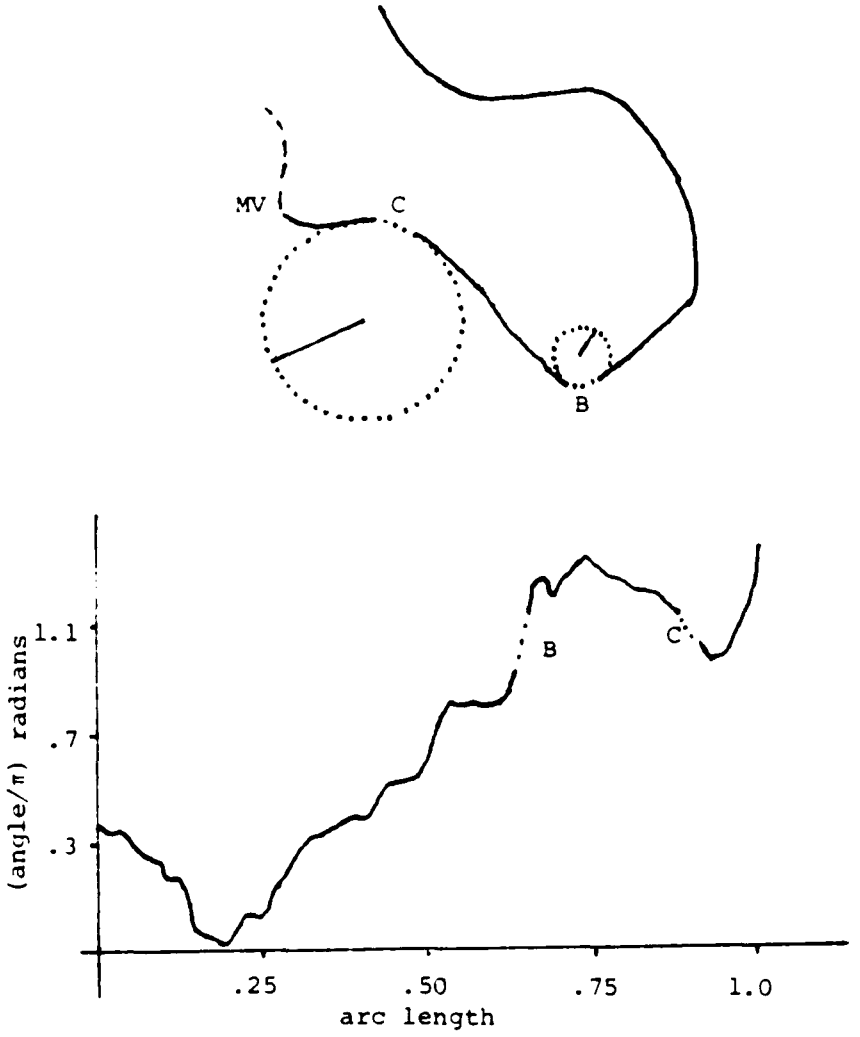


FIGURE 4
Curvatures. Corresponding regions are indicated. (1/radius) of each circle equals the derivative of the tangent angle function at that point.

Region C has negative curvature.

MV: mitral valve point

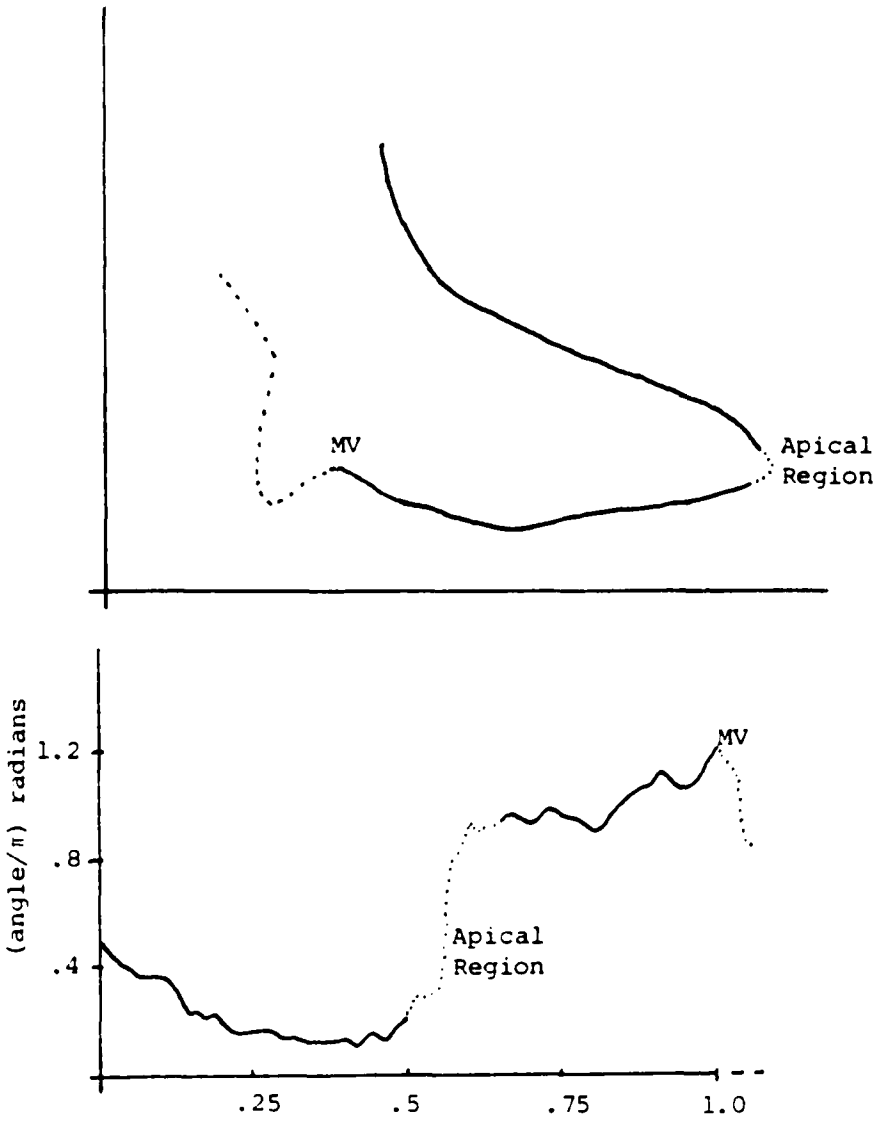


FIGURE 5
Tangent angle function:
Positive curvature at the apex

MV: mitral valve point

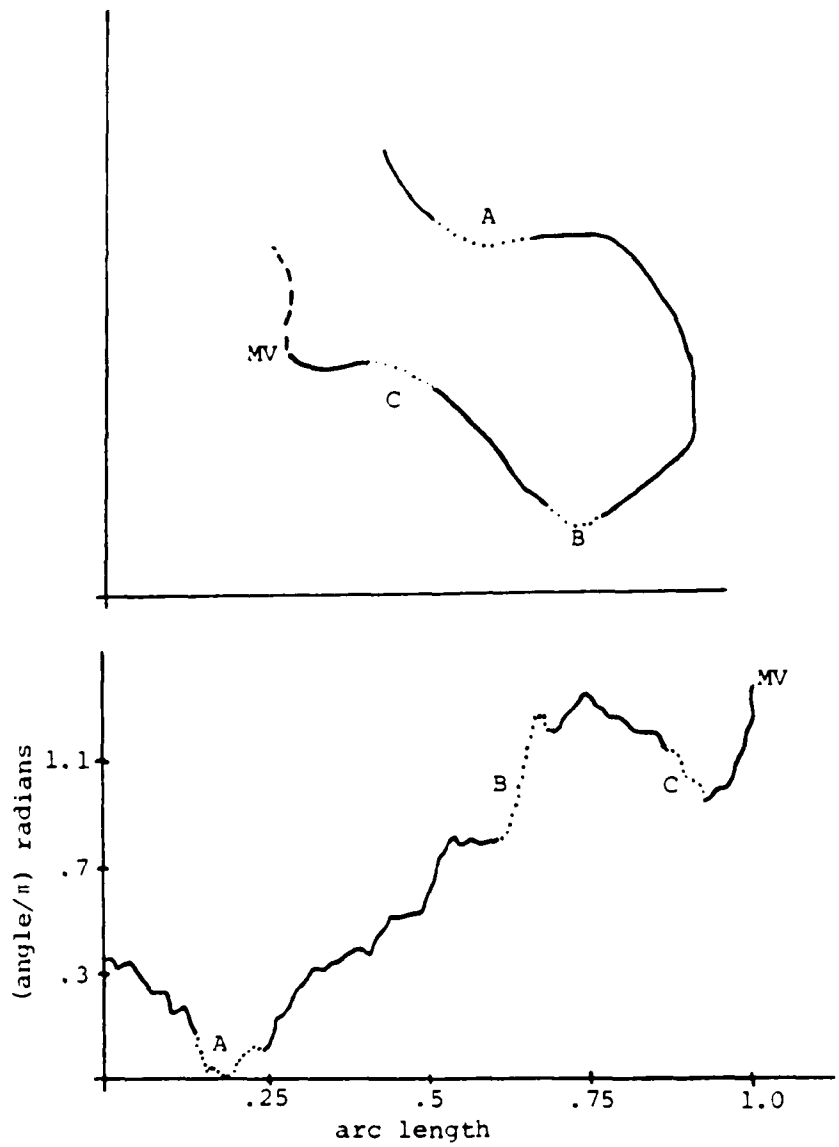


FIGURE 6

Tangent angle function:
Negative curvature

Note negative and positive regions.
Corresponding regions are indicated.

MV: mitral valve point

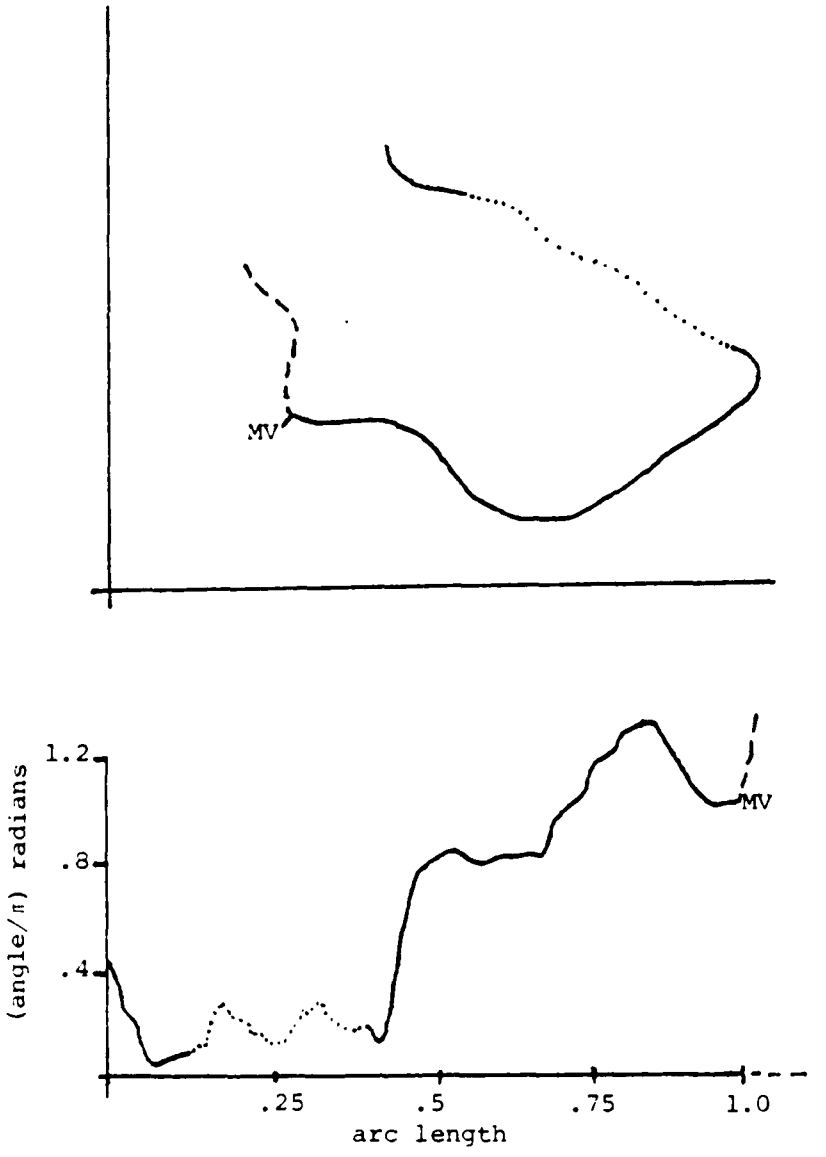


FIGURE 7
Tangent angle function: oscillating curve.
Dotted segments of the outline and the tangent angle function correspond.

MV: mitral valve point

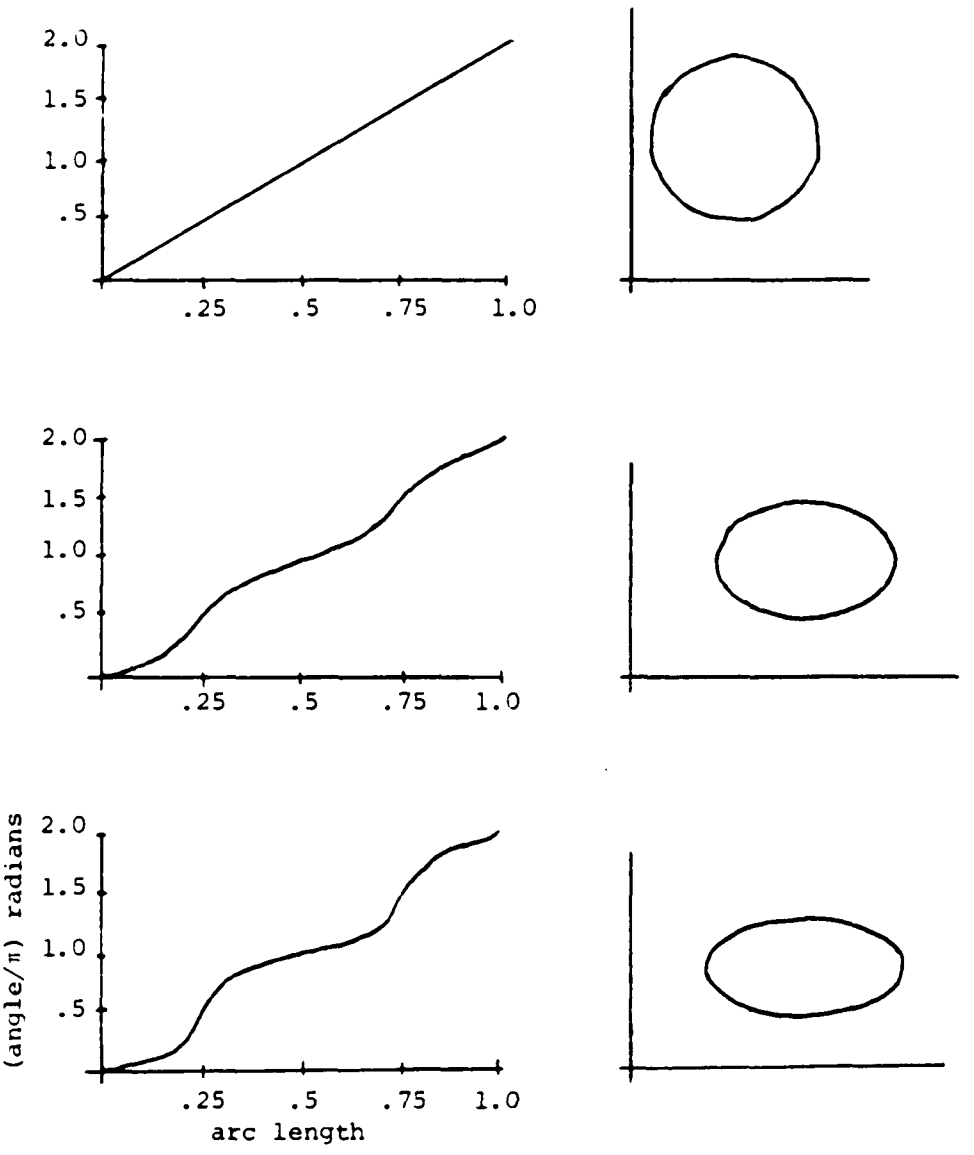


FIGURE 8
Tangent angle functions of circle and ellipses.

Note: The tangent angle function of the circle is a straight line.

The similarity of the tangent angle functions of the two ellipses.

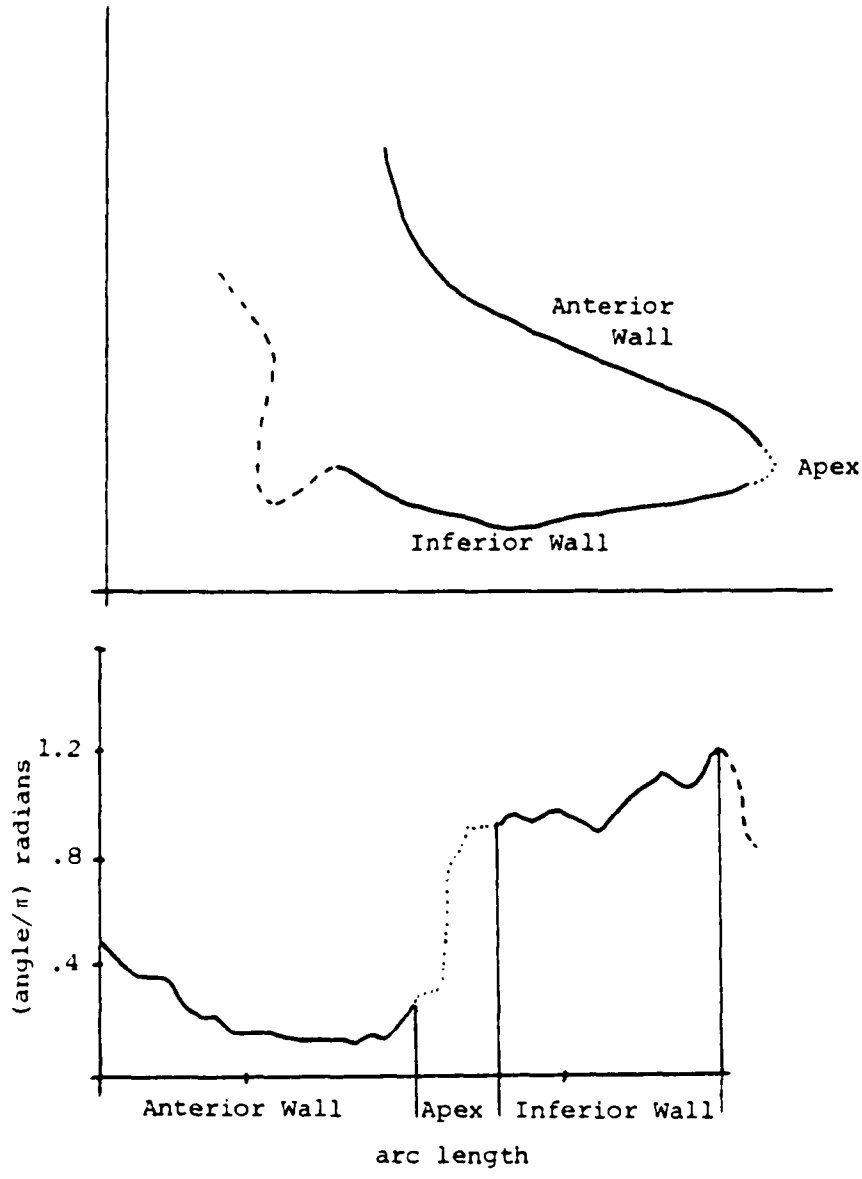


FIGURE 9
Piecewise separation of the tangent angle function at the apex.

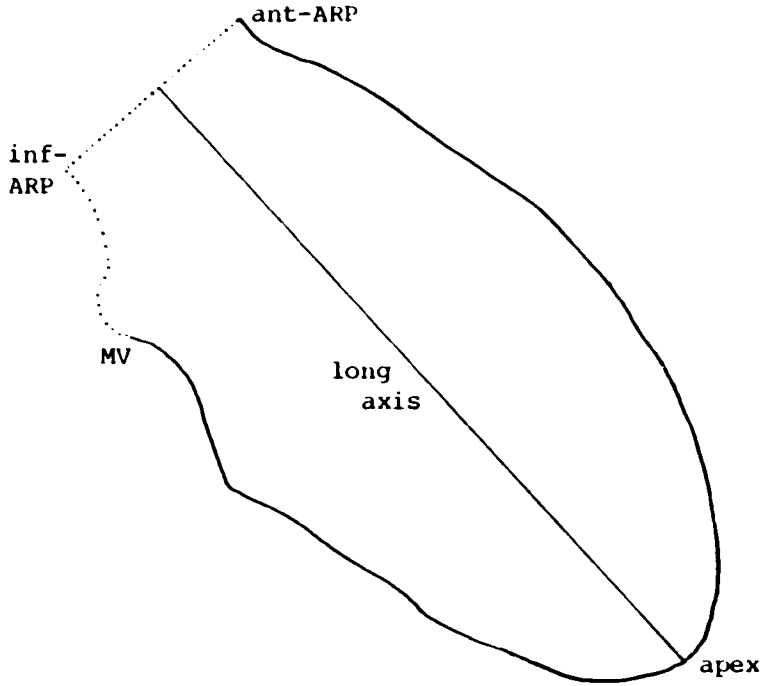


FIGURE 10
Apex Definition

The apex is the point farthest from the ant-ARP.

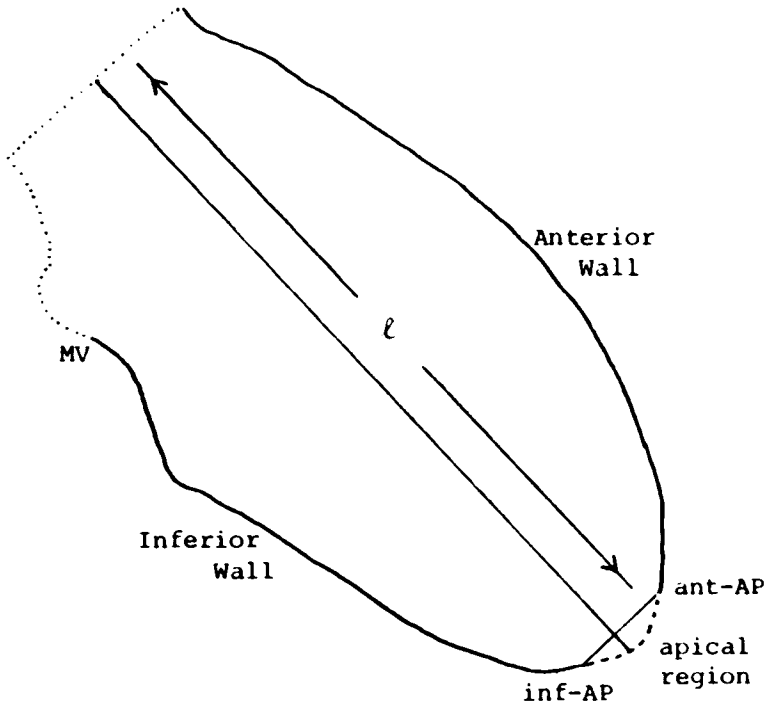


FIGURE 11
Apical Region Definition, illustrating ℓ

inf: inferior ant: anterior
ARP: aortic root point
AP: apical point
MV: mitral valve point

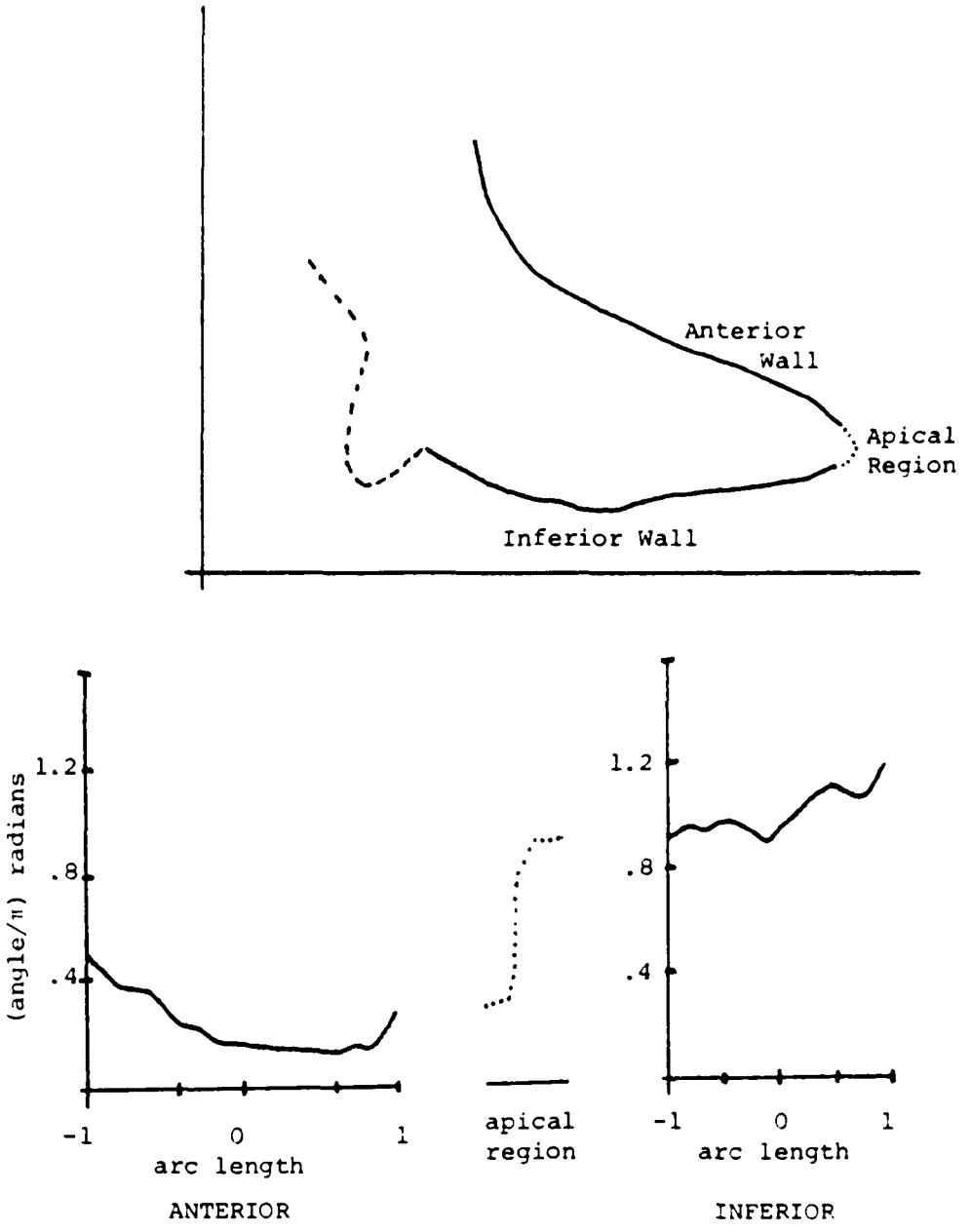
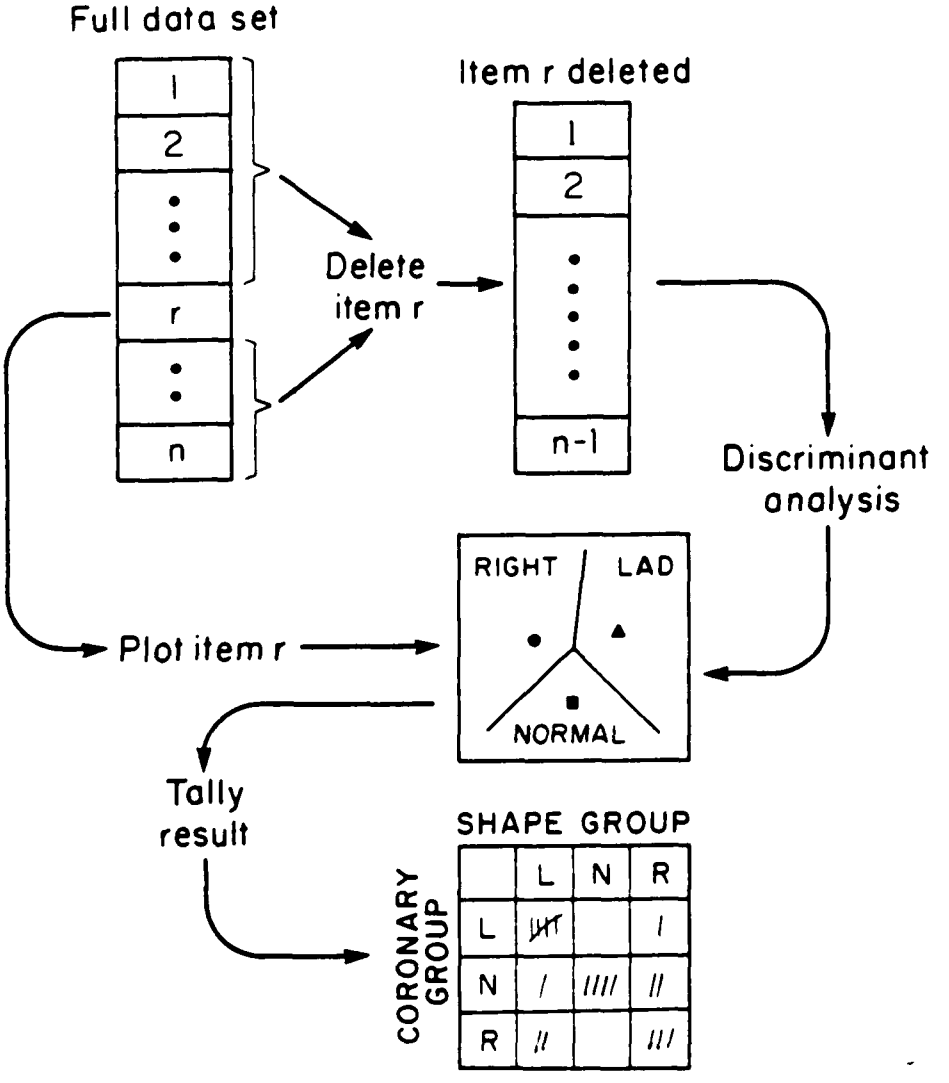


FIGURE 12
Rescaling of arc length axes. The walls of the outline that correspond to each piece of the tangent angle function are indicated.

FIGURE 13

JACKKNIFE



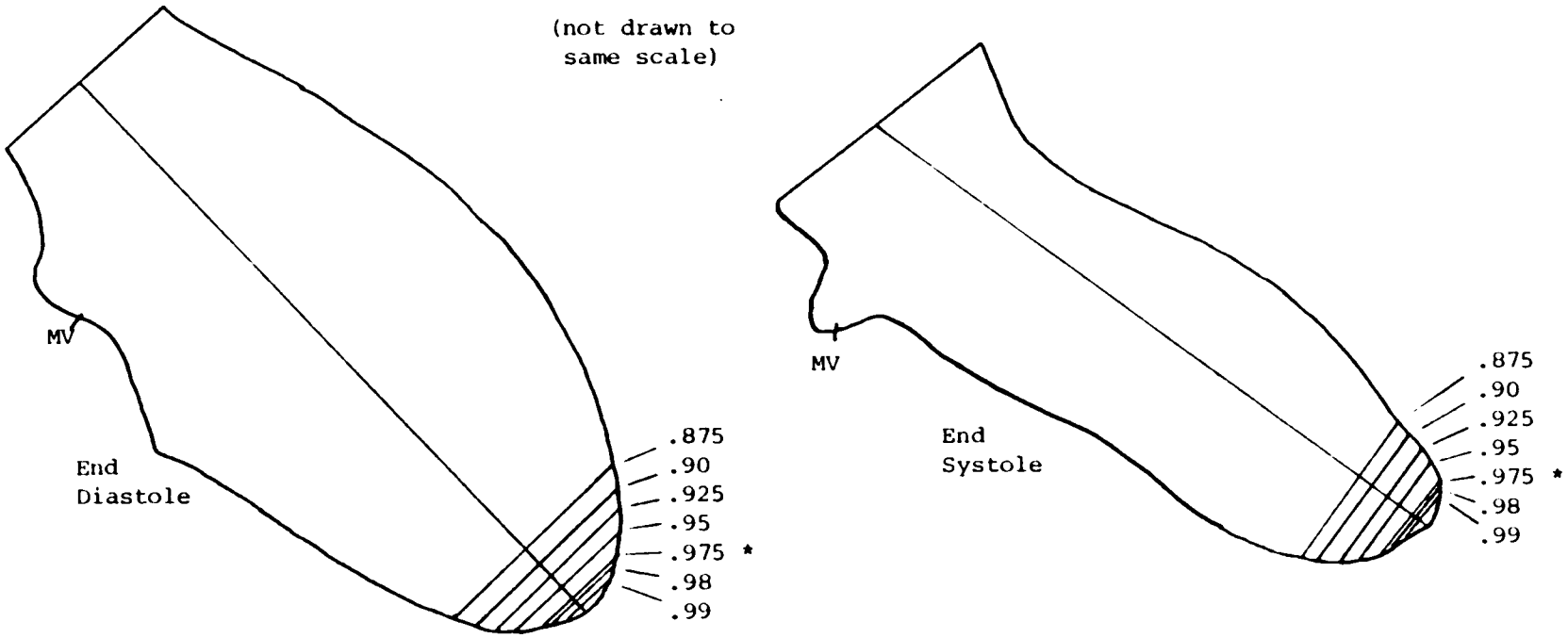


FIGURE 14a
Definition of the Apical Region.
ID 8786
Note the curvature of the apical region.

Numbers are the percent distance of the long axes.
MV: Mitral Valve Point

Bisectors are not exactly parallel because the outline is composed of discrete points.

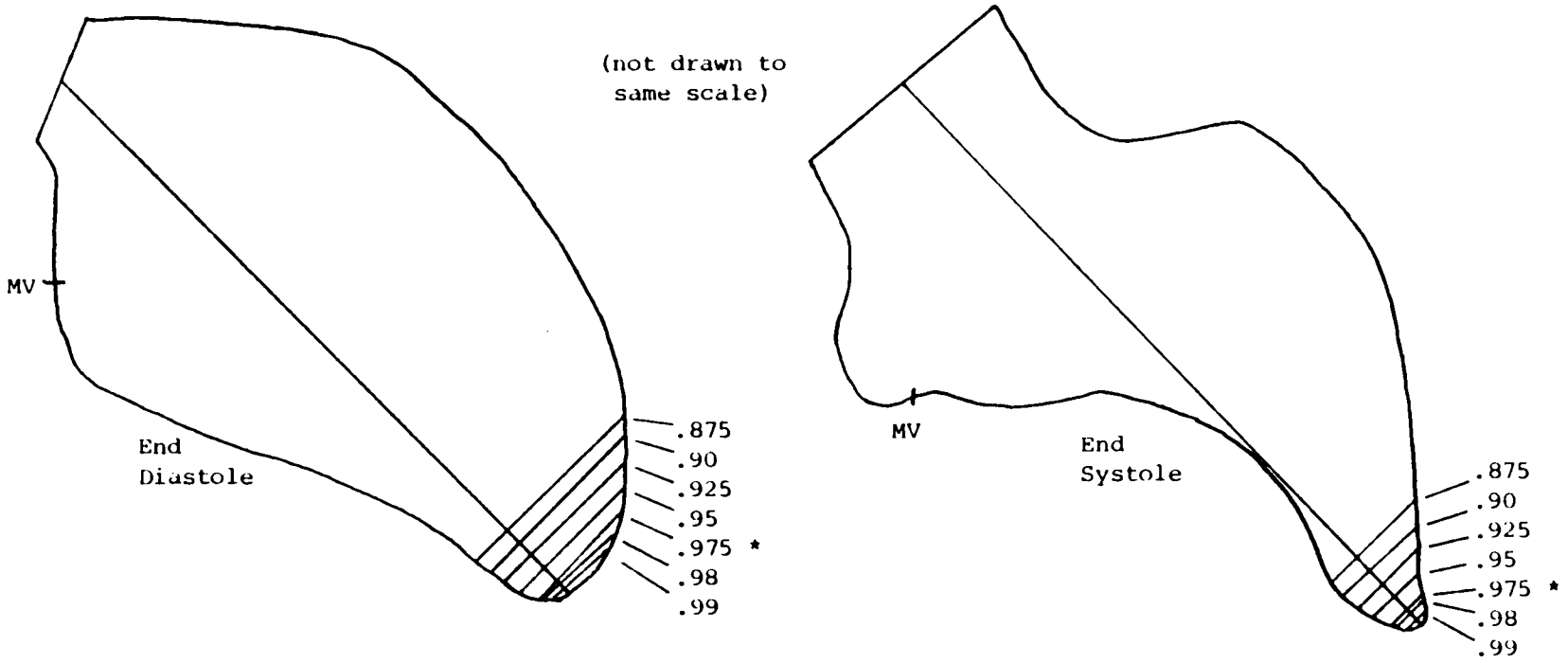


FIGURE 14b
Definition of the Apical Region.
ID 9037
Note the differences in the curvatures of the apical regions at end diastole and end systole.

Numbers are the percent distance of the long axes.
MV: Mitral Valve Point

Bisectors are not exactly parallel because the outline is composed of discrete points.

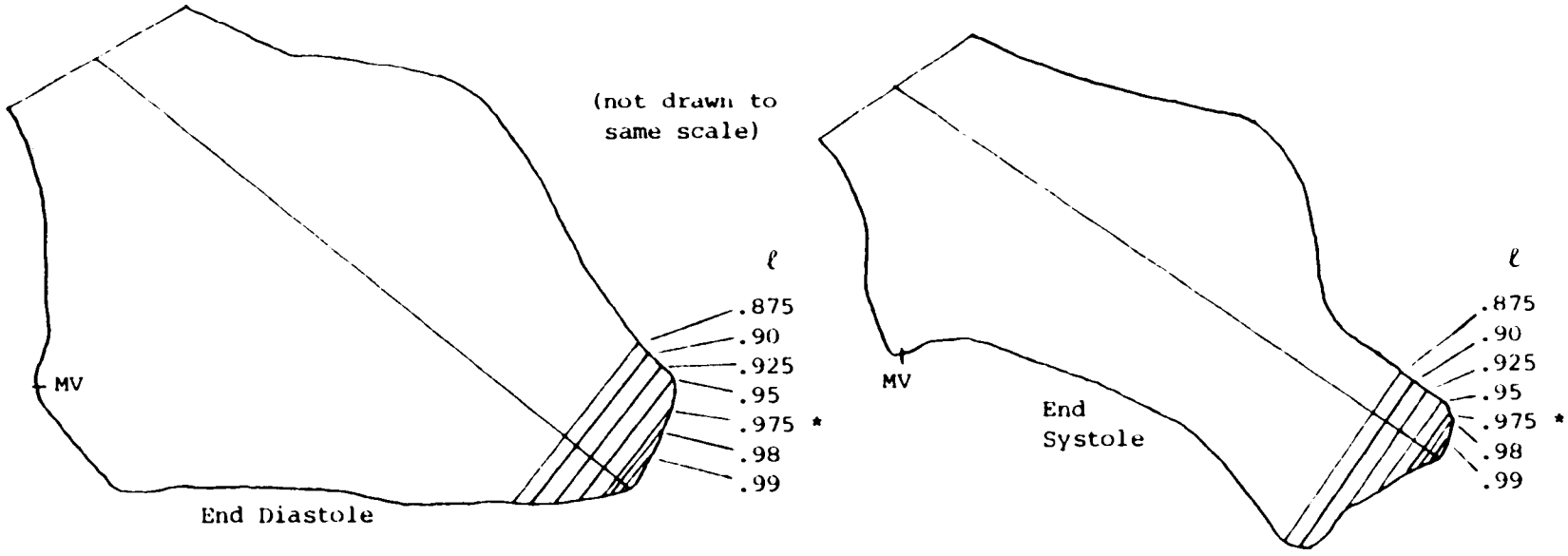


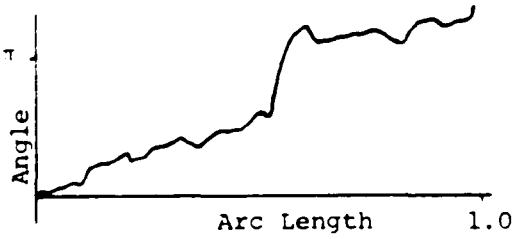
FIGURE 14c
Definition of the Apical Region.
ID 10025
Note the dependence of the apical region on ℓ.

Numbers are the percent distance of the long axes (ℓ).
MV: Mitral Valve Point

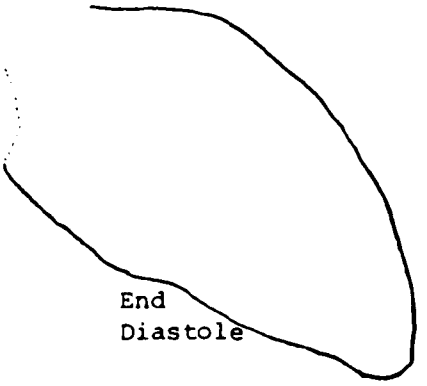
Bisectors are not exactly parallel because the outline is composed of discrete points.

TANGENT ANGLE FUNCTIONS

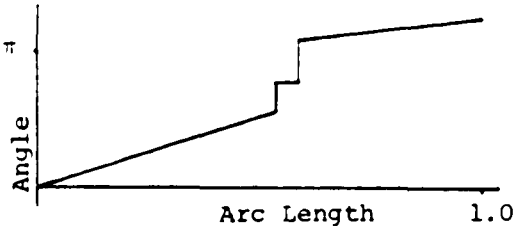
CORRESPONDING OUTLINES



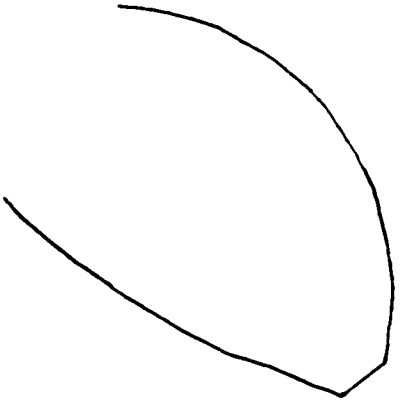
$Y = \theta(s)$



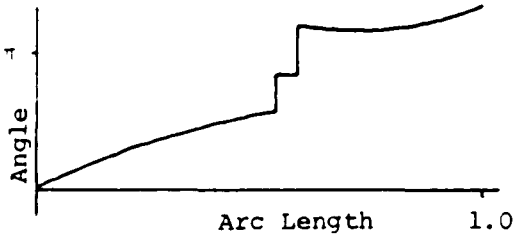
RAW IMAGE



$\hat{Y} = b_0 + b_1 s$



Note that the image corresponding to this model is a reasonable approximation to the raw image.



$\hat{Y} = b_0 + b_1 s + b_2 s^2$

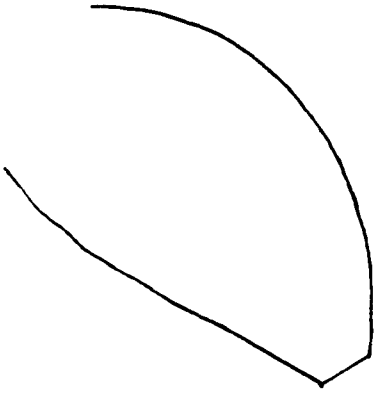
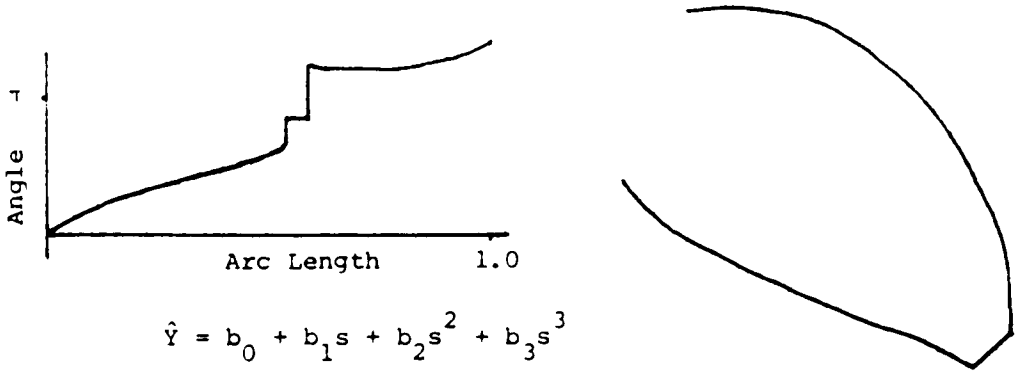
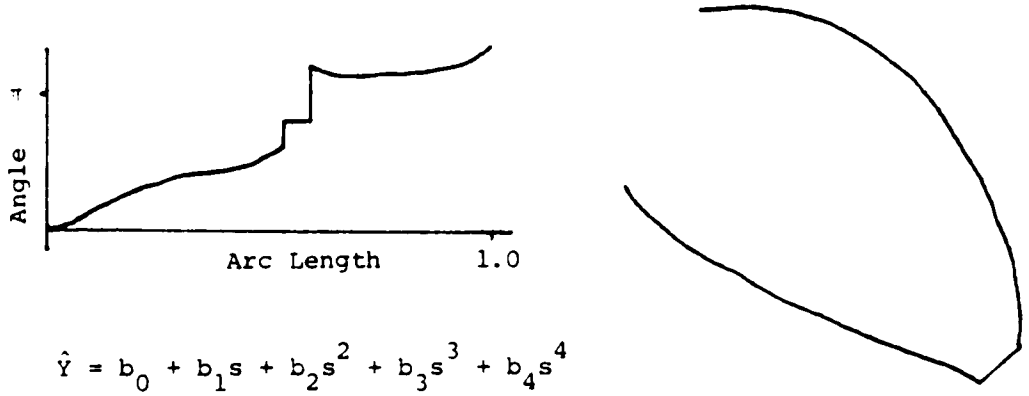


FIGURE 15a

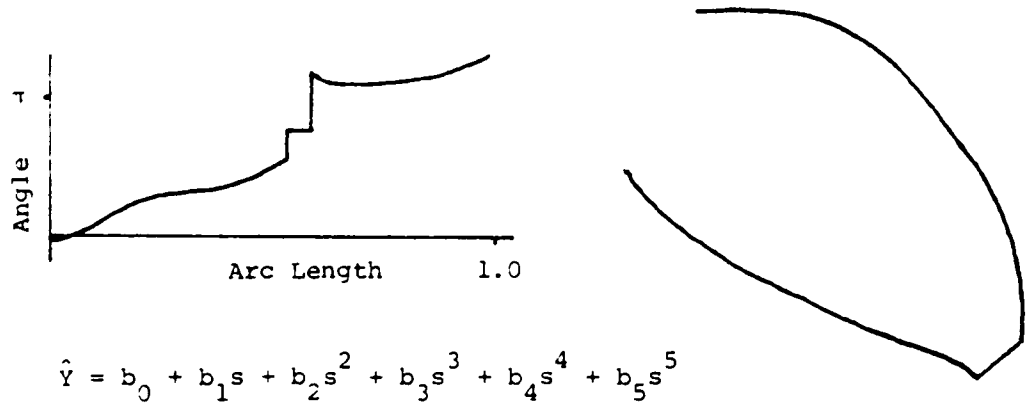
Piecewise Polynomial Parameterizations



$$\hat{Y} = b_0 + b_1 s + b_2 s^2 + b_3 s^3$$



$$\hat{Y} = b_0 + b_1 s + b_2 s^2 + b_3 s^3 + b_4 s^4$$

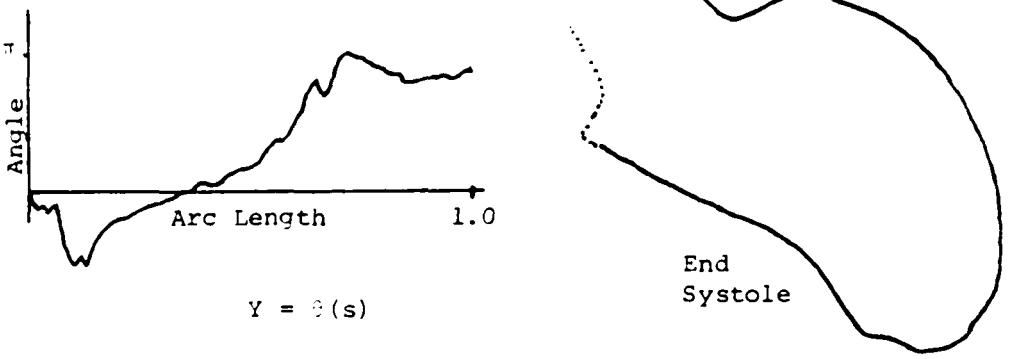


$$\hat{Y} = b_0 + b_1 s + b_2 s^2 + b_3 s^3 + b_4 s^4 + b_5 s^5$$

FIGURE 15a (cont.)

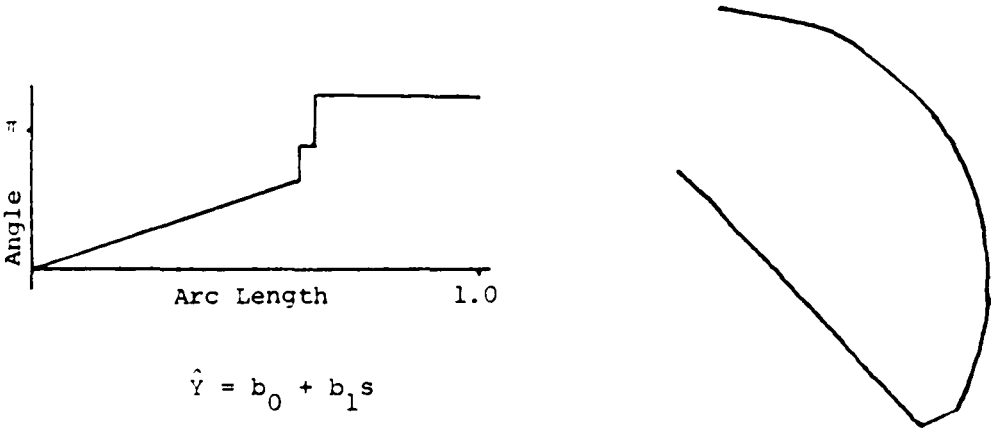
TANGENT ANGLE FUNCTIONS

CORRESPONDING OUTLINES



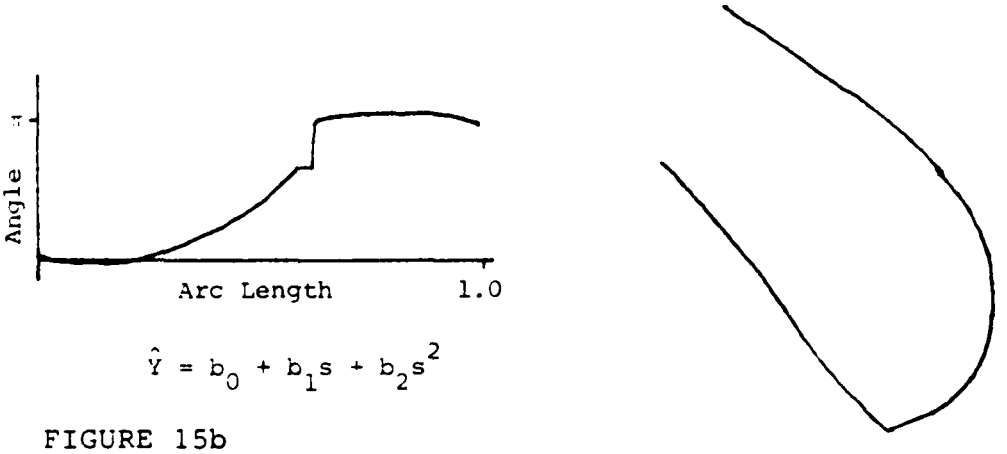
$Y = \theta(s)$

RAW IMAGE



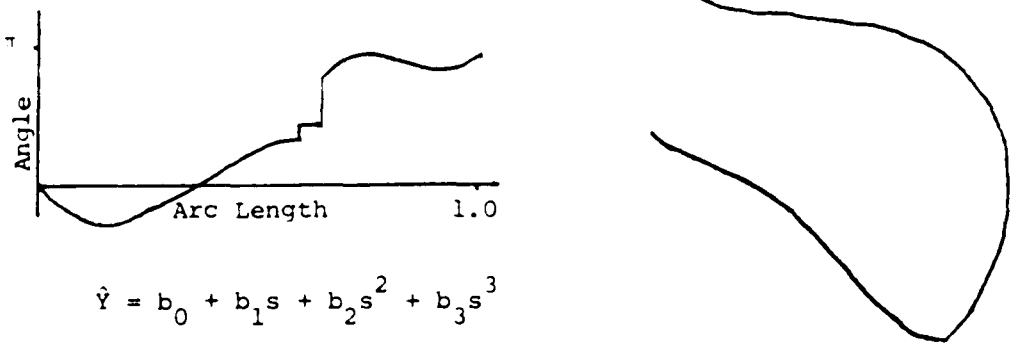
$\hat{Y} = b_0 + b_1 s$

Note the lack of reproduction of the anterior wall.



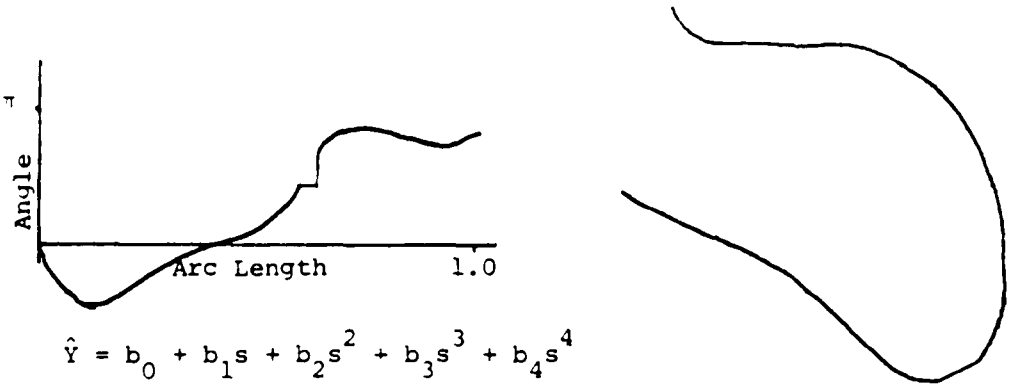
$\hat{Y} = b_0 + b_1 s + b_2 s^2$

FIGURE 15b
Piecewise Polynomial Parameterizations



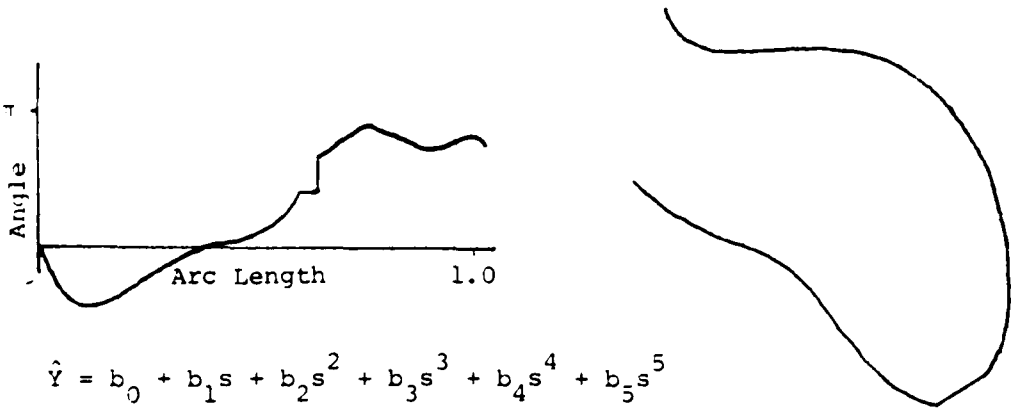
$$\hat{Y} = b_0 + b_1 s + b_2 s^2 + b_3 s^3$$

Note the artifactual anterior wall bulge



$$\hat{Y} = b_0 + b_1 s + b_2 s^2 + b_3 s^3 + b_4 s^4$$

This order parameterization was necessary to capture the anterior wall shape.



$$\hat{Y} = b_0 + b_1 s + b_2 s^2 + b_3 s^3 + b_4 s^4 + b_5 s^5$$

FIGURE 15b (cont.)

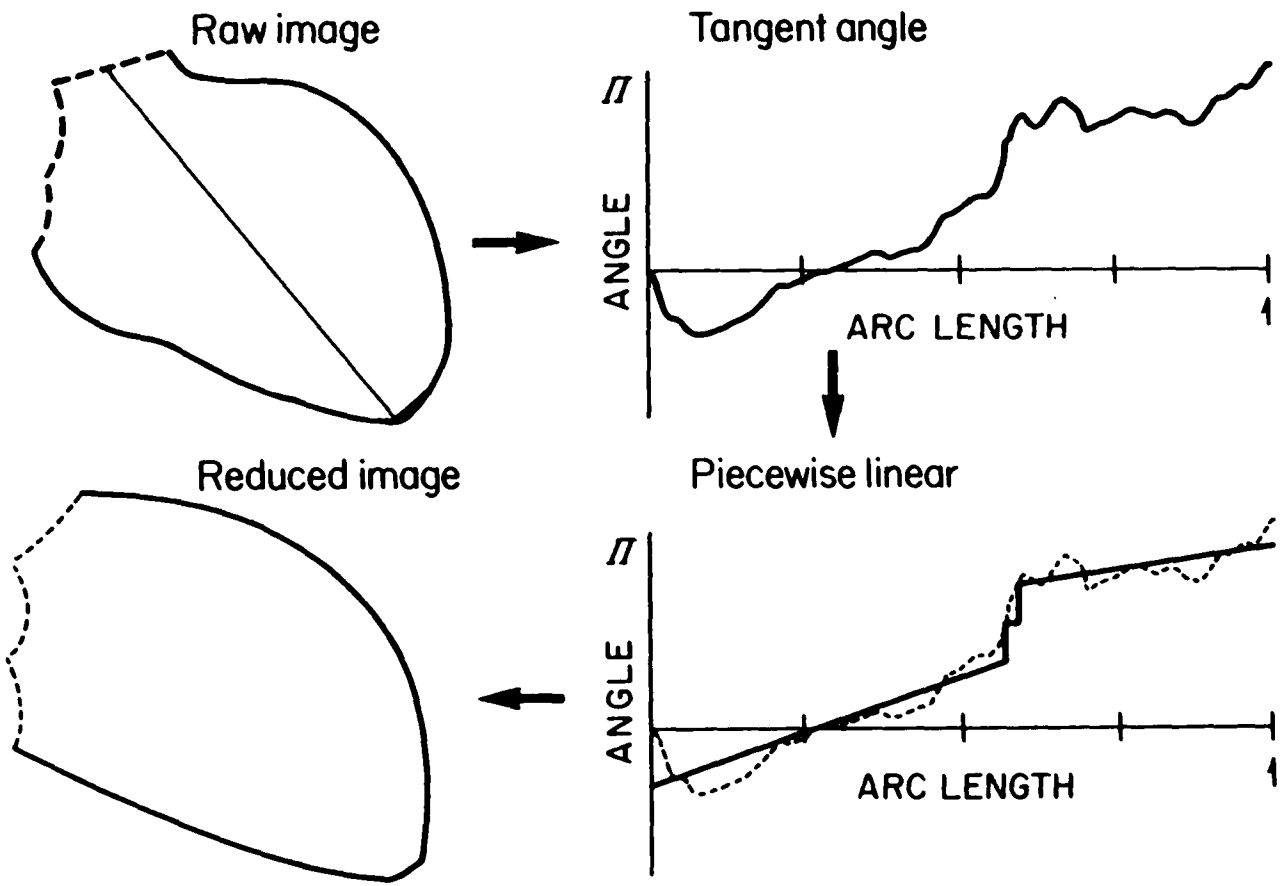


FIGURE 16b
Piecewise Linear Parameterization

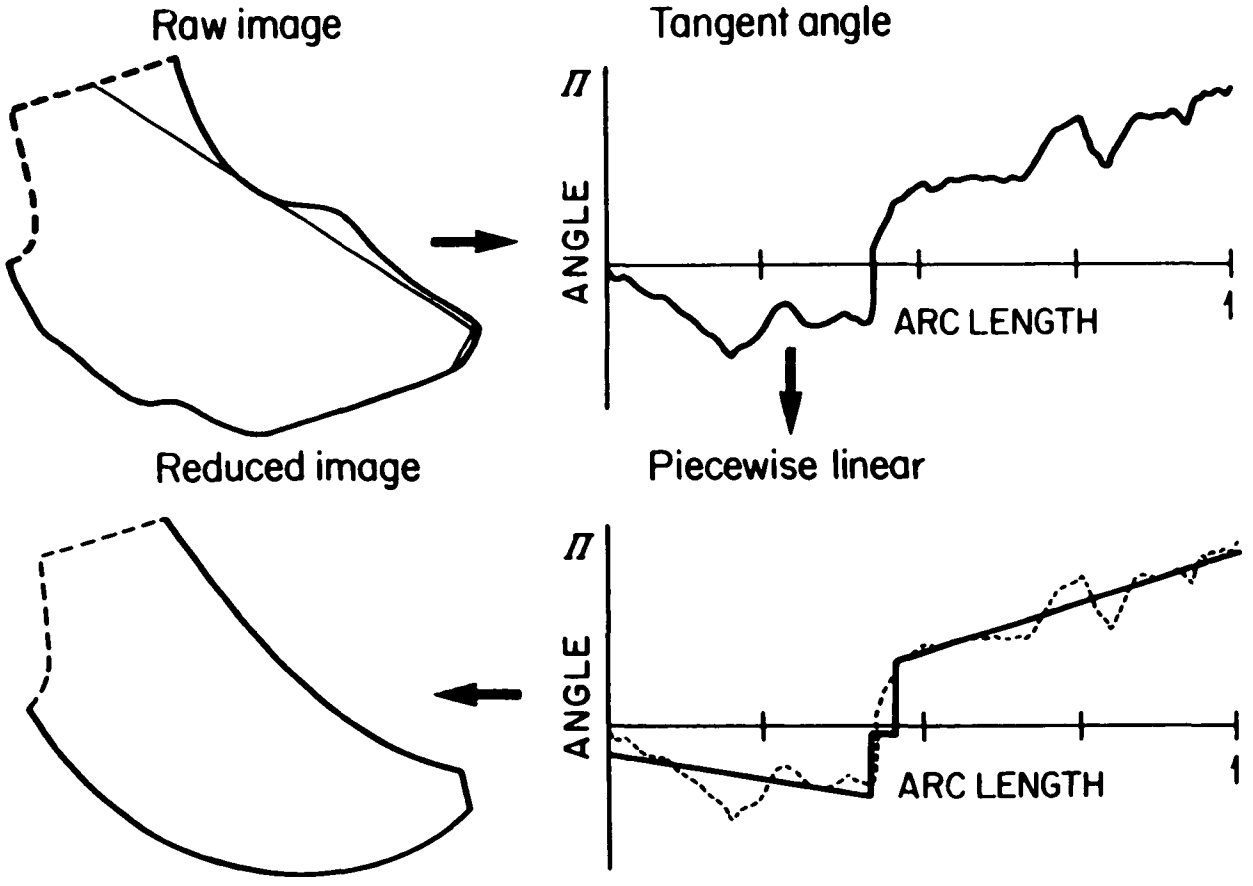
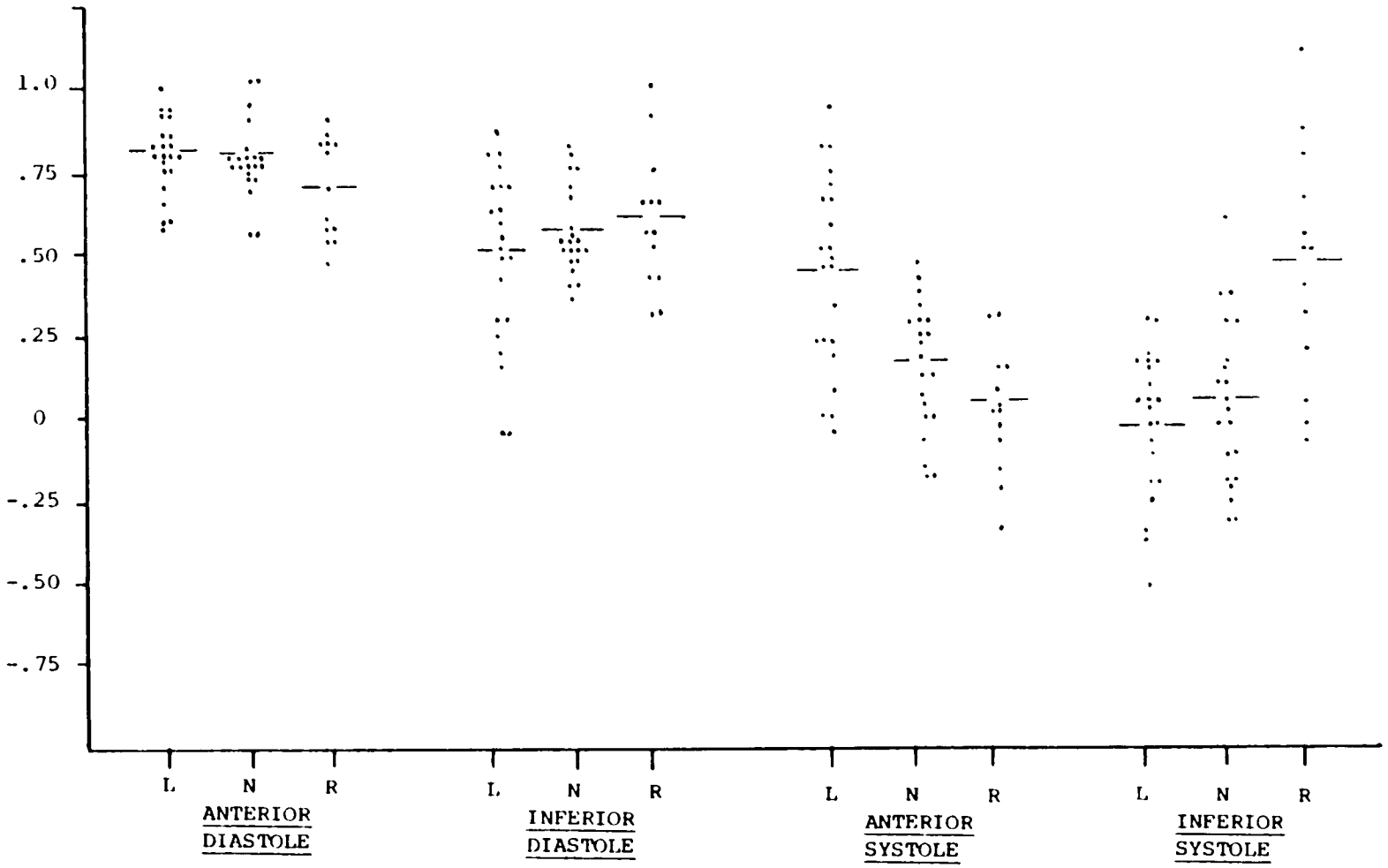


FIGURE 16b
Piecewise Linear Parameterization.
Note the anterior wall smoothing.



Curvatures of the Learning Data Set.

FIGURE 17

Horizontal Bar: Mean of Group
L: LAD, N: NORMAL, R: RIGHT, as in Text

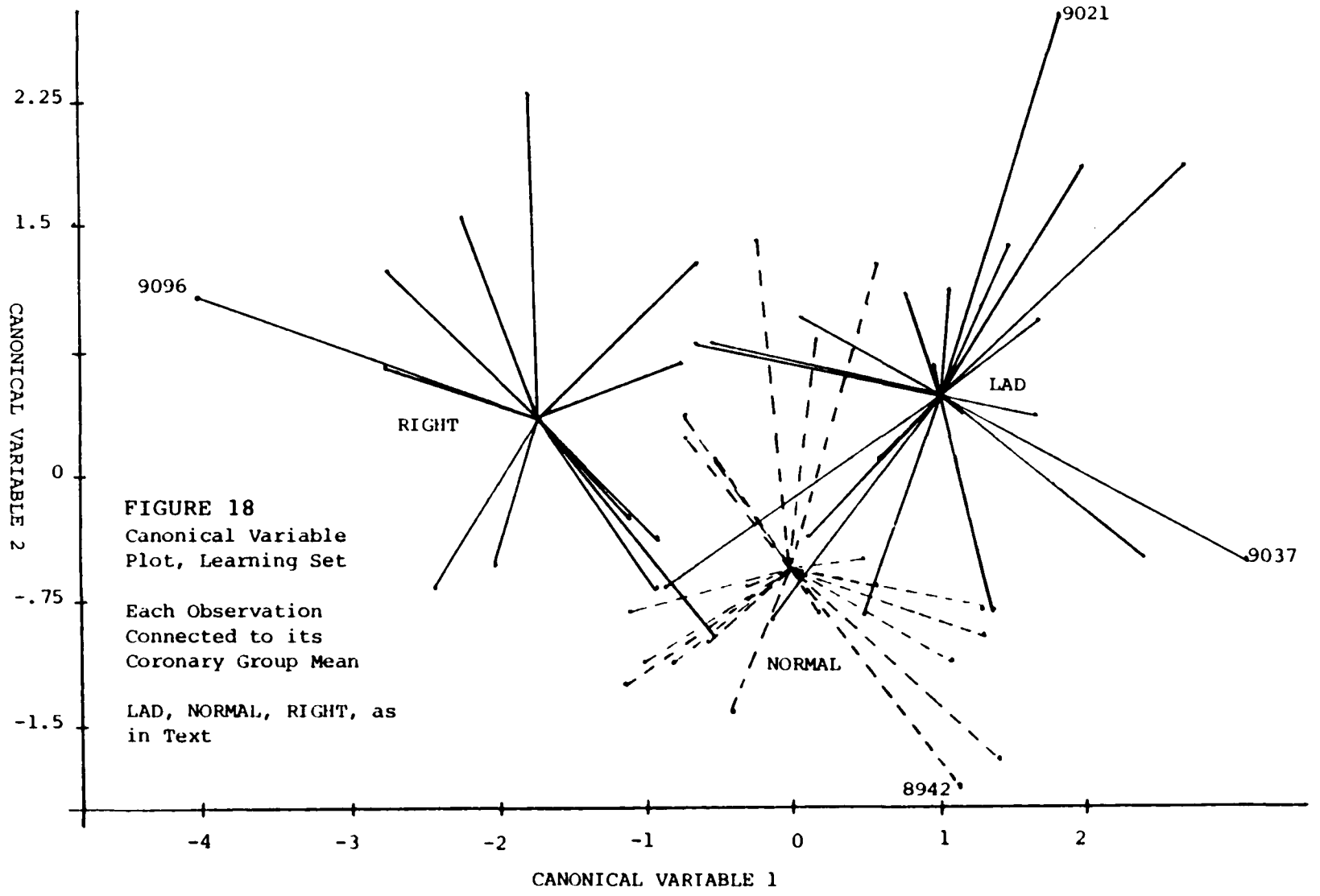


FIGURE 18
Canonical Variable
Plot, Learning Set

Each Observation
Connected to its
Coronary Group Mean

LAD, NORMAL, RIGHT, as
in Text

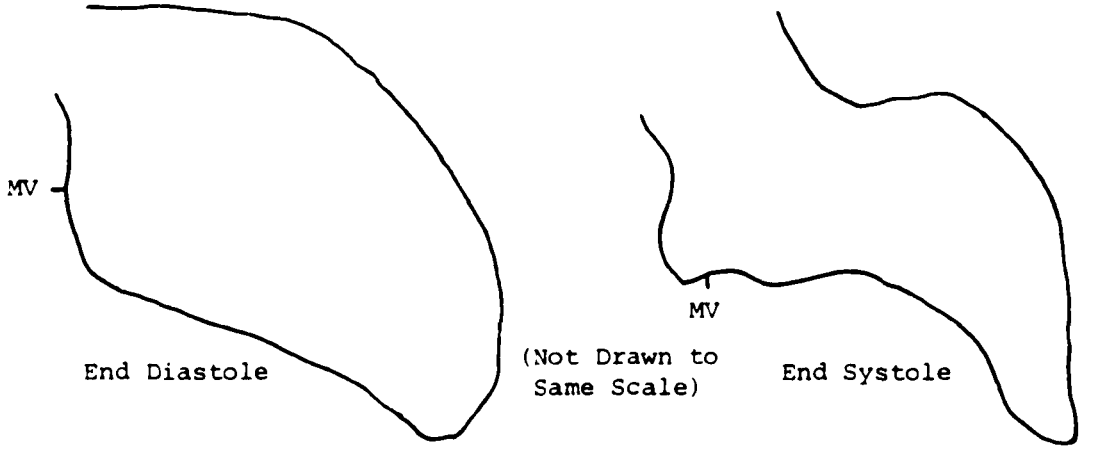


FIGURE 19a
ID 9037 from the learning set.
Anterior wall dysfunction with inferior wall compensation.

MV: Mitral Valve Point

CURVATURES

Diastole	Anterior	.94
	Inferior	.31
Systole	Anterior	.59
	Inferior	-.58

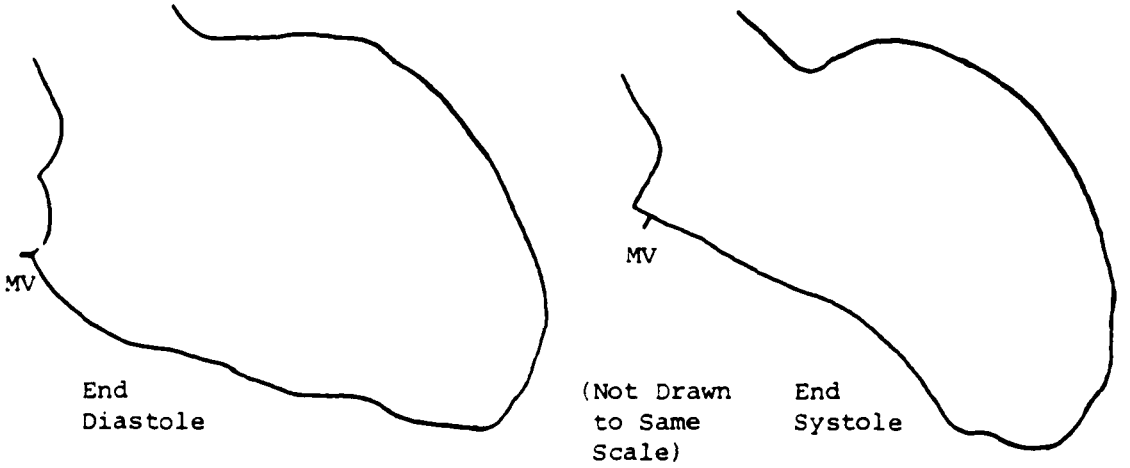


FIGURE 19b
ID 9021 from the learning set.
Anterior wall dysfunction with inferior wall compensation.

MV: Mitral Valve Point

CURVATURES

Diastole	Anterior	.83
	Inferior	.30
Systole	Anterior	.85
	Inferior	.04

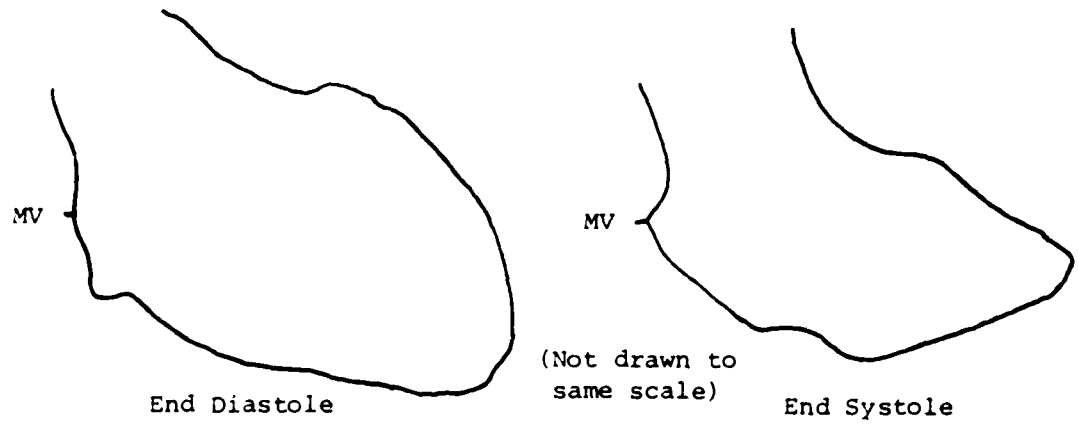


FIGURE 19c

ID 9096 from the Learning Set. Inferior wall dysfunction with anterior wall compensation.

MV: Mitral Valve Point

CURVATURES

Diastole	Anterior	.55
	Inferior	.65
Systole	Anterior	-.31
	Inferior	.88

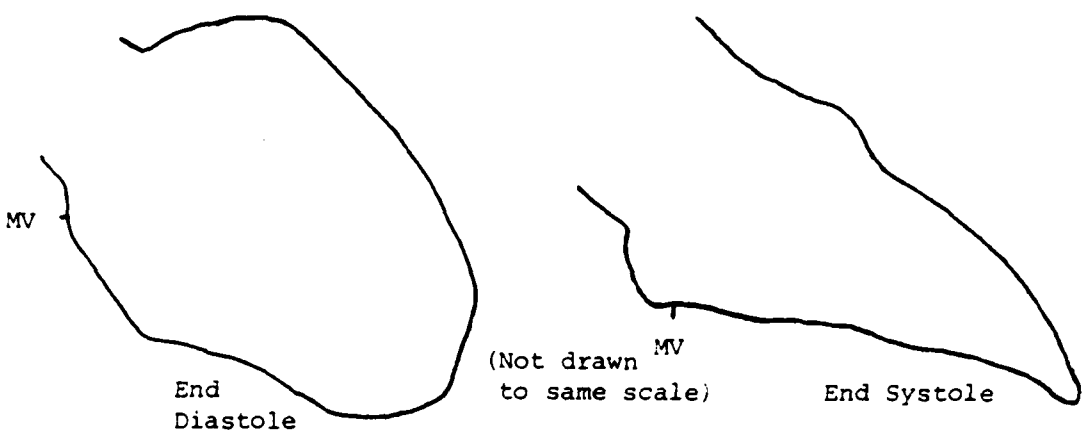


FIGURE 19d

ID 8942 from the Learning Set. Symmetrical contraction.

MV: Mitral Valve Point

CURVATURES

Diastole	Anterior	1.0
	Inferior	.56
Systole	Anterior	.29
	Inferior	-.18

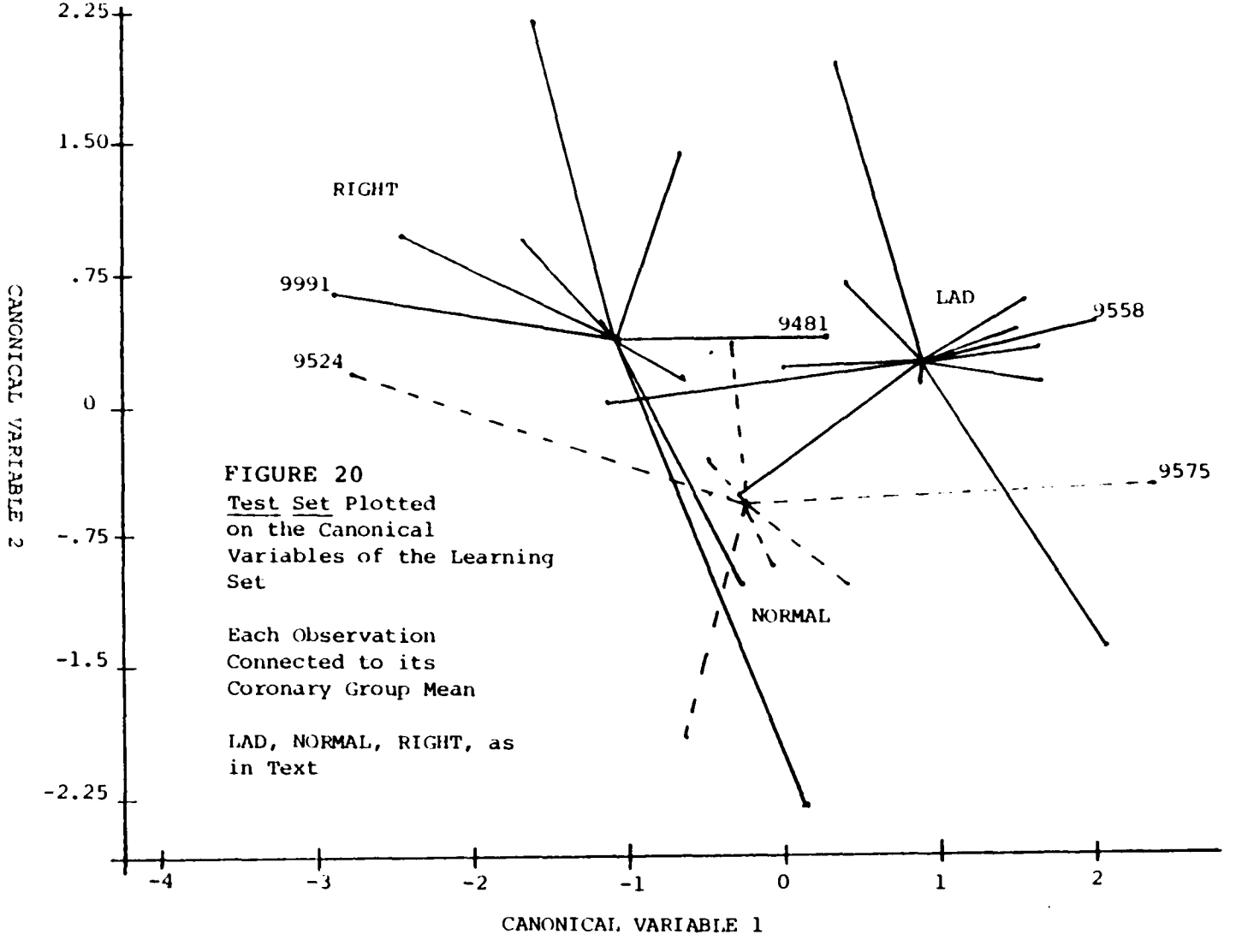


FIGURE 20
Test Set Plotted on the Canonical Variables of the Learning Set

Each Observation Connected to its Coronary Group Mean

LAD, NORMAL, RIGHT, as in Text

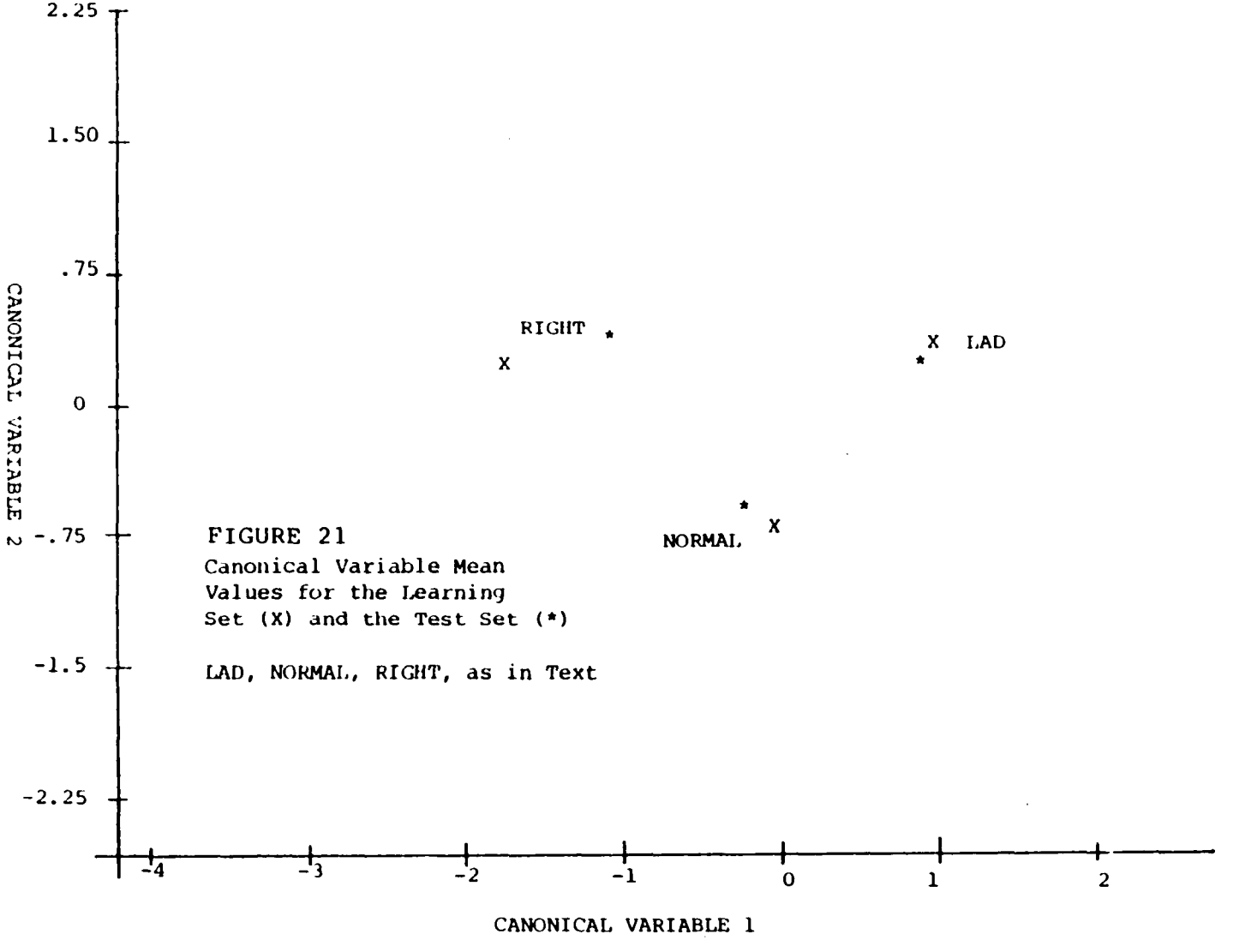


FIGURE 21
Canonical Variable Mean Values for the Learning Set (X) and the Test Set (*)

LAD, NORMAL, RIGHT, as in Text

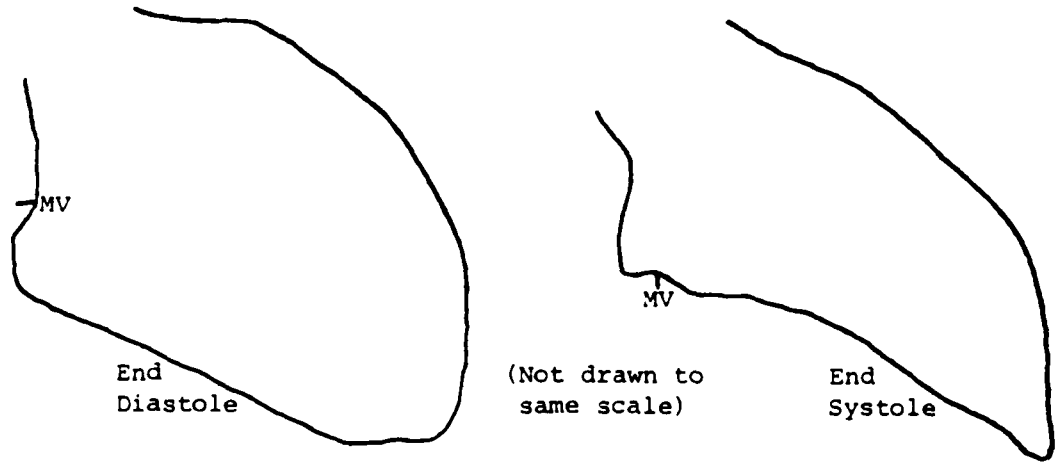


FIGURE 22a
ID 9575 from the Test Set.
Outlier from NORMAL.

MV: Mitral Valve Point
NORMAL: as in text

CURVATURES

Diastole	Anterior	.93
	Inferior	.52
Systole	Anterior	.65
	Inferior	-.23

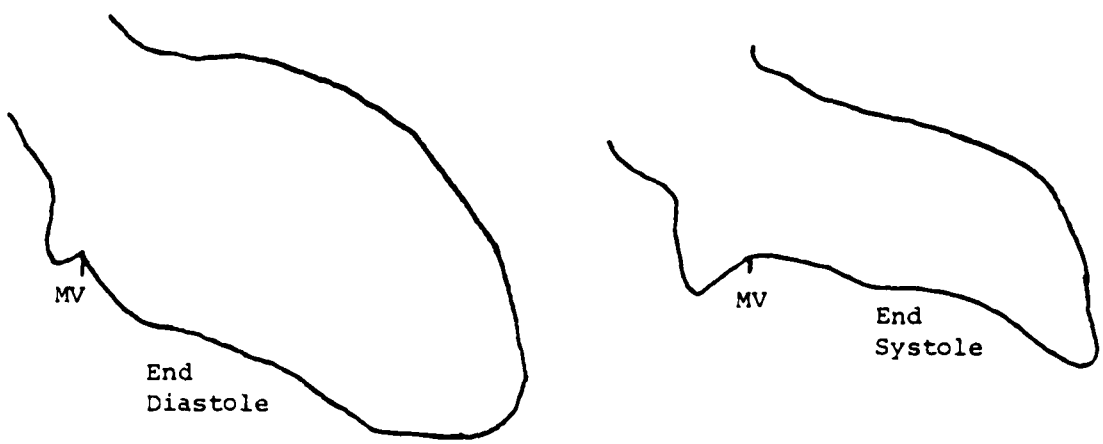


FIGURE 22b
ID 9558 from the Test Set.
LAD, to compare with 9575 above.

MV: Mitral Valve Point
LAD: as in text

CURVATURES

Diastole	Anterior	.72
	Inferior	.38
Systole	Anterior	.48
	Inferior	-.35

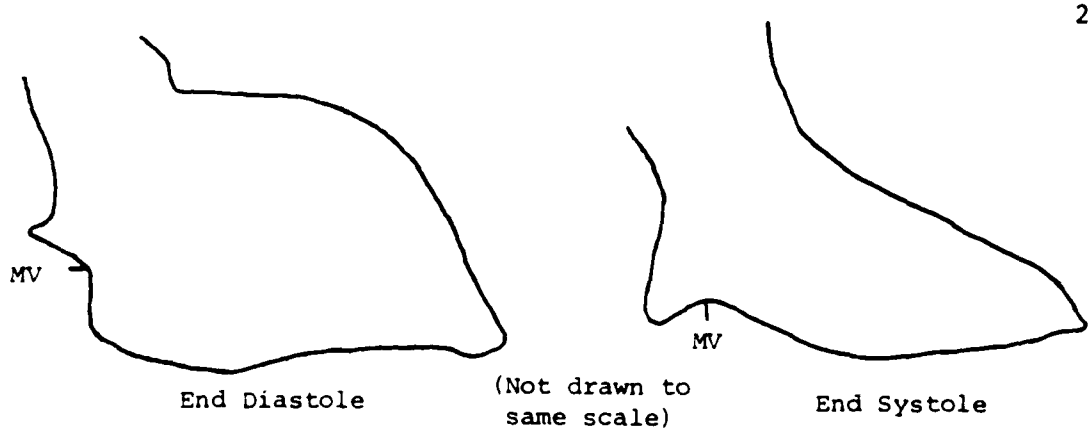


FIGURE 22c

ID 9524 from the Test Set.
Outlier from NORMAL.

MV: Mitral Valve Point
NORMAL: as in text.

CURVATURES

Diastole	Anterior	.41
	Inferior	.64
Systole	Anterior	-.35
	Inferior	.39

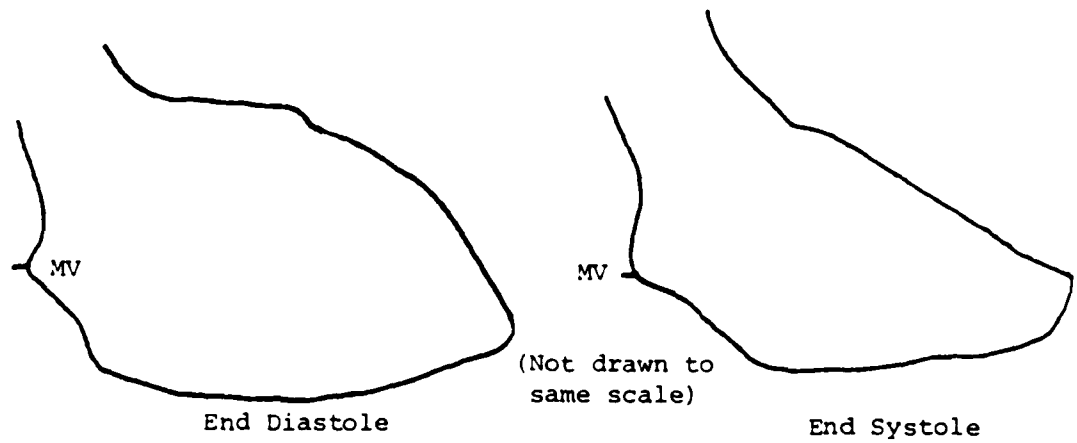


FIGURE 22d

ID 9991 from the Test Set.
RIGHT for comparison with
9524 above.

MV: Mitral Valve Point
RIGHT: as in text

CURVATURES

Diastole	Anterior	.37
	Inferior	.76
Systole	Anterior	-.25
	Inferior	.55

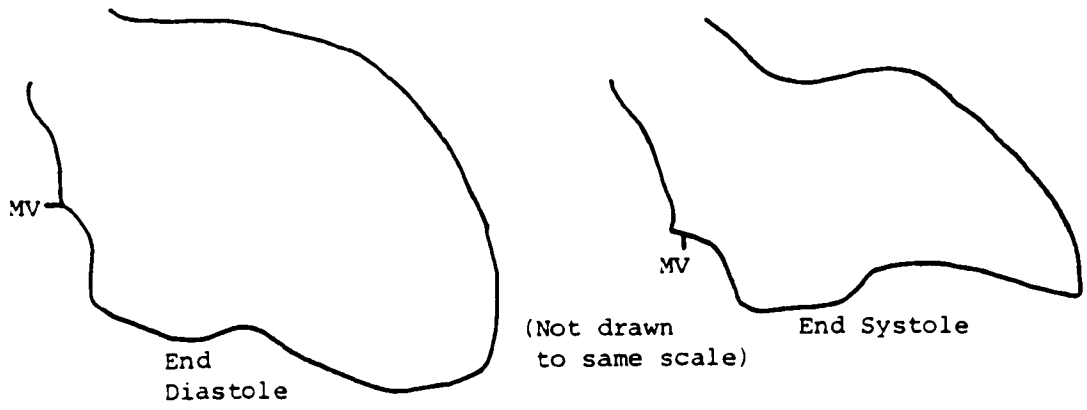


FIGURE 22e
ID 9481 from the Test Set.
RIGHT misclassified as LAD.

MV: Mitral Valve Point
LAD, RIGHT, as in text

CURVATURES

Diastole	Anterior	.86
	Inferior	.64
Systole	Anterior	.48
	Inferior	.28

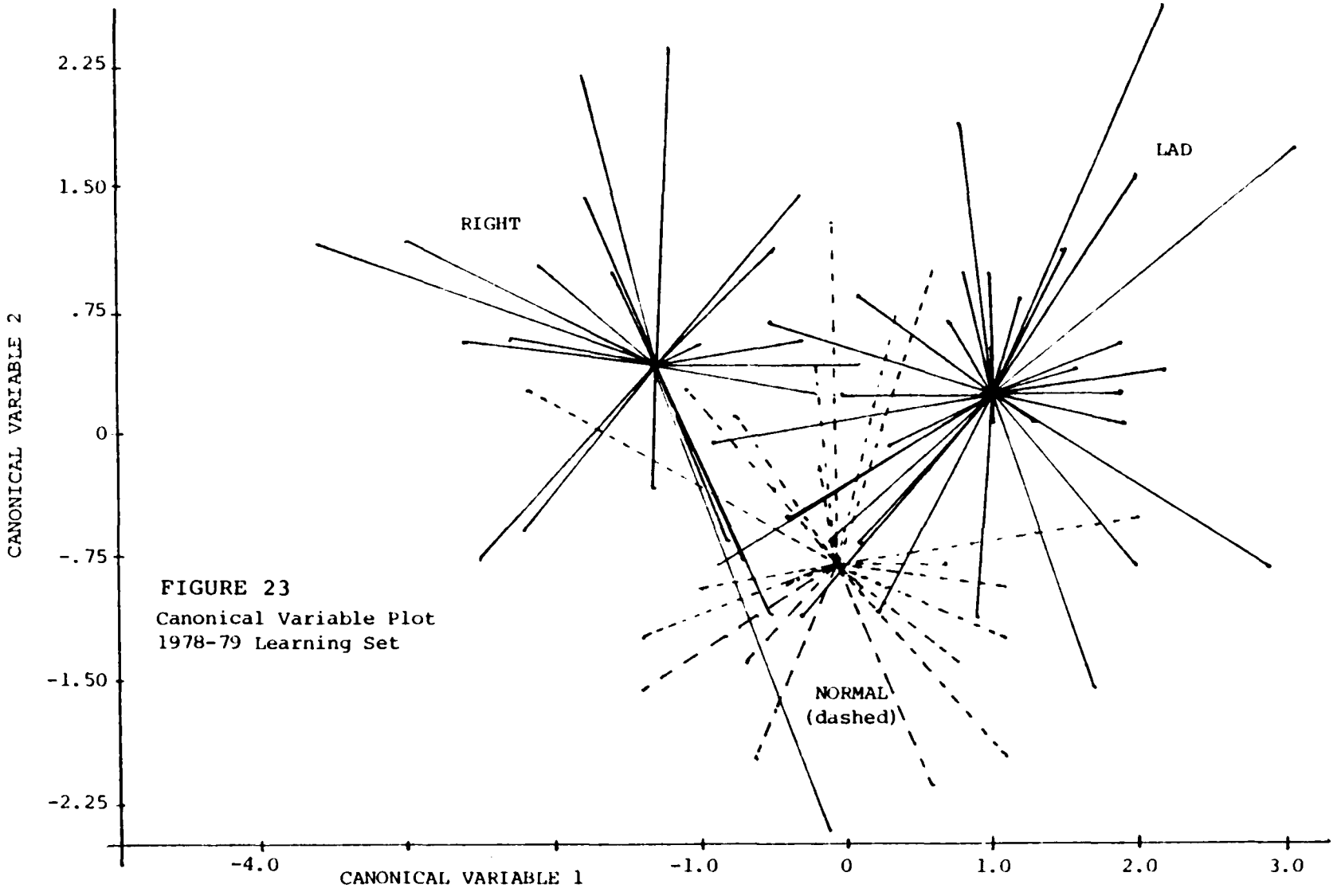


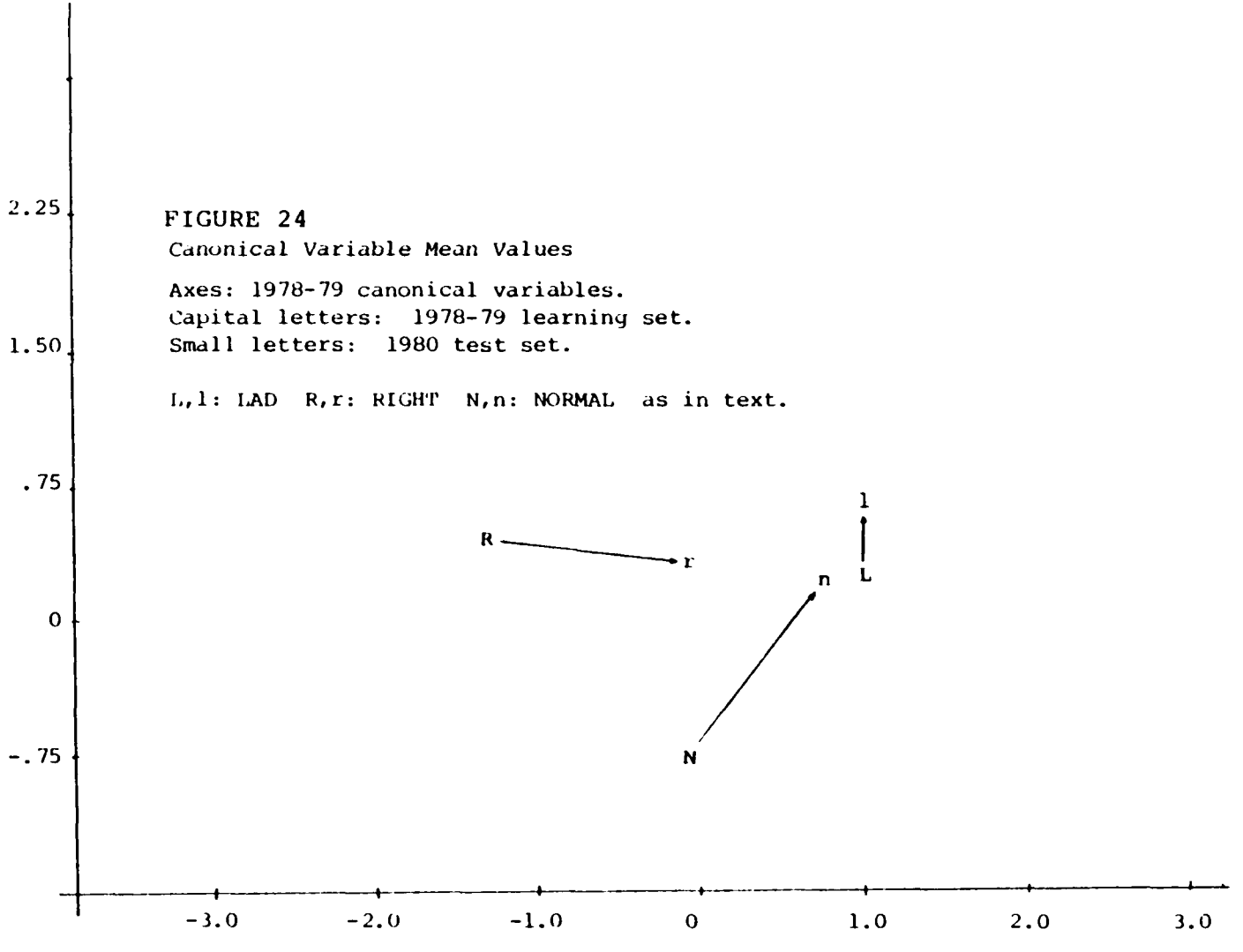
FIGURE 23
Canonical Variable Plot
1978-79 Learning Set

FIGURE 24

Canonical Variable Mean Values

Axes: 1978-79 canonical variables.
Capital letters: 1978-79 learning set.
Small letters: 1980 test set.

L,l: LAD R,r: RIGHT N,n: NORMAL as in text.



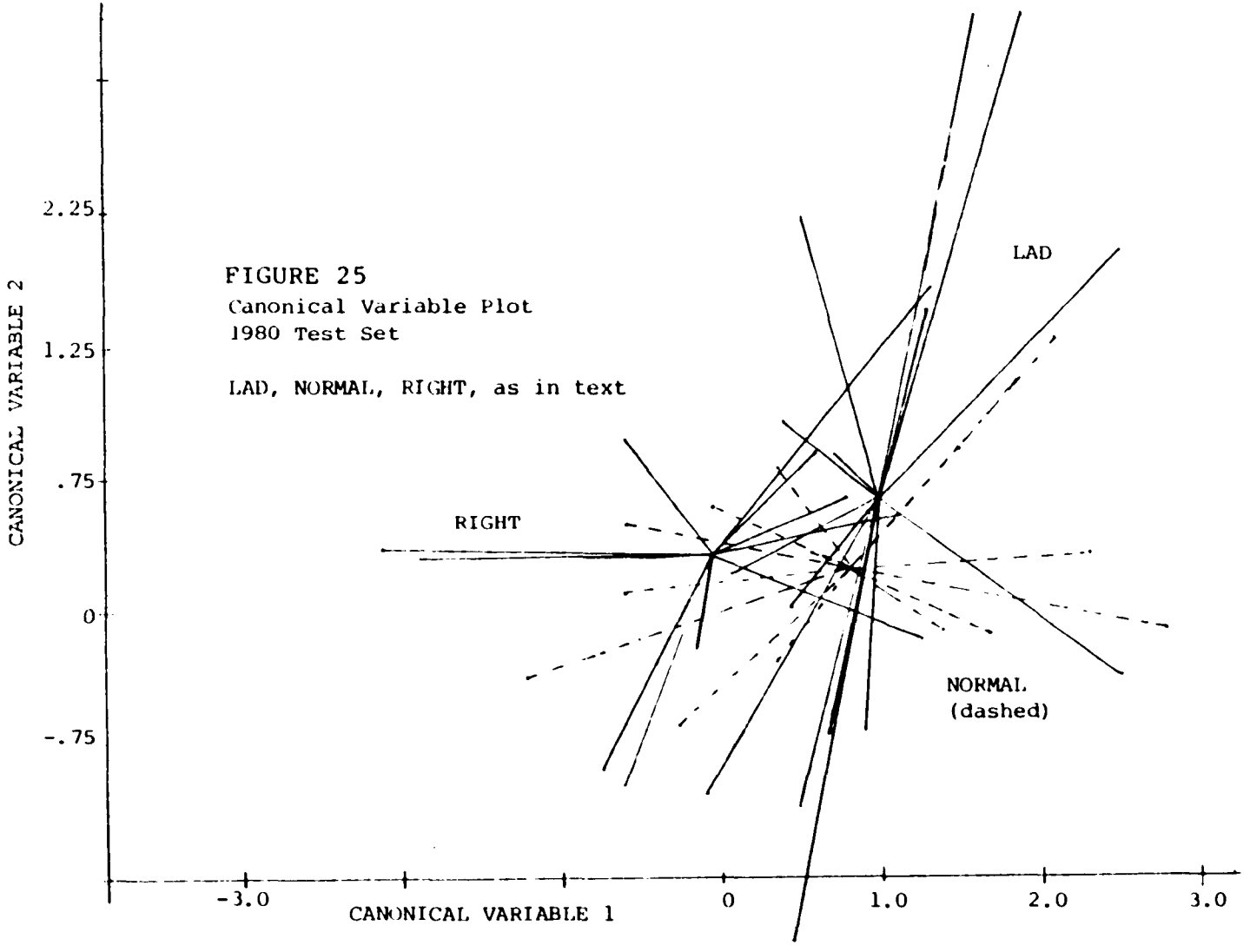


FIGURE 25
Canonical Variable Plot
1980 Test Set
LAD, NORMAL, RIGHT, as in text
LAD
RIGHT
NORMAL
(dashed)
CANONICAL VARIABLE 2
2.25
1.25
.75
0
-.75
-3.0
0
1.0
2.0
3.0
CANONICAL VARIABLE 1

FIGURE 26
"Canonical Variable" plot of 1980 learning set.

Only the inferior wall at end systole had any discriminating power.

L: LAD, N: NORMAL, R: RIGHT, as in text.

Each observation indicated by a letter.
Vertical bars: group means.

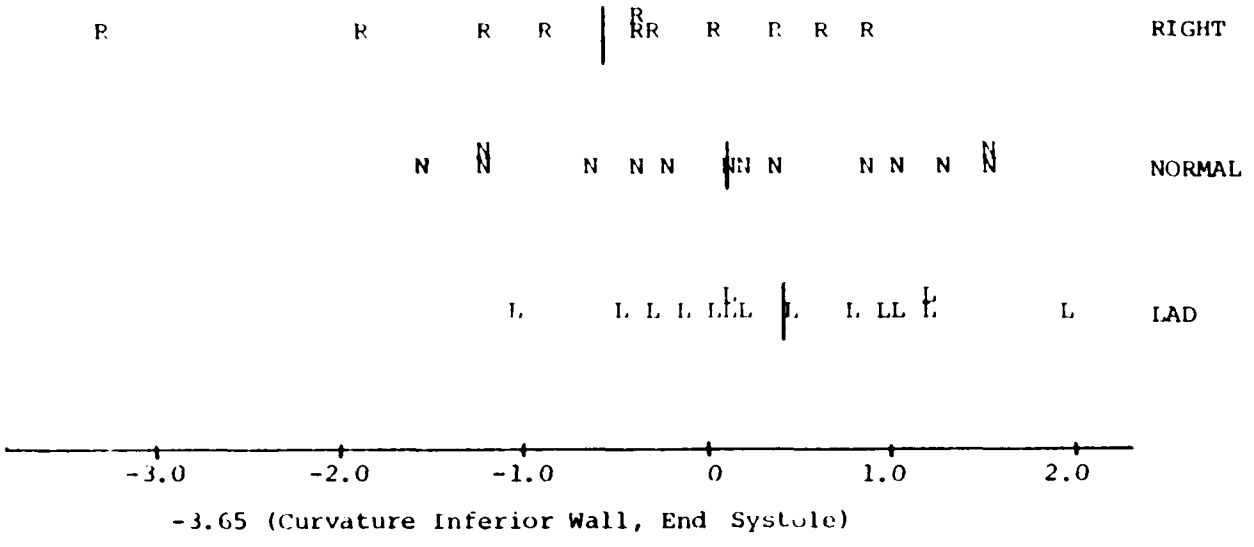
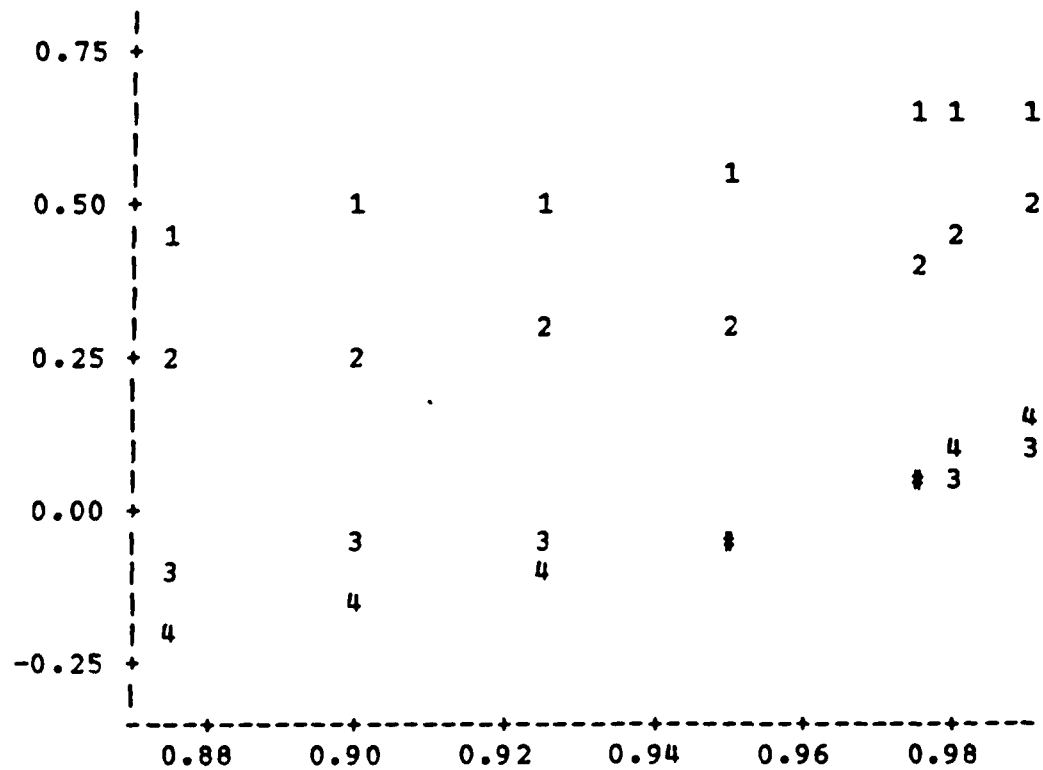
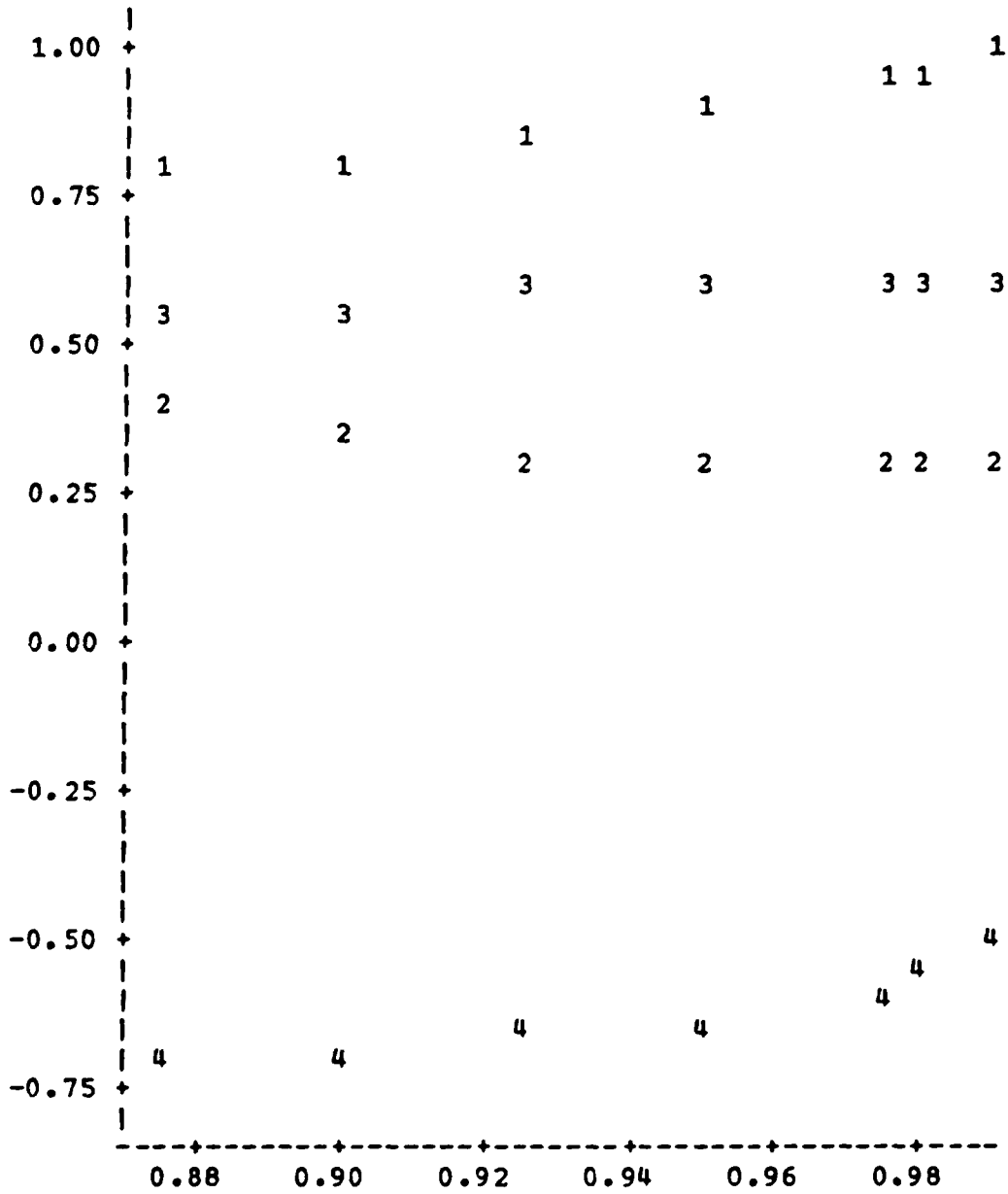


FIGURE 27 PLOT OF B1 VERSUS L



ID: 8786 Symbols 1: Anterior Diastole 2: Inferior Diastole
3: Anterior Systole 4: Inferior Systole

FIGURE 27b PLOT OF B1 VERSUS L



ID: 9037 Symbols 1: Anterior Diastole 2: Inferior Diastole
3: Anterior Systole 4: Inferior Systole

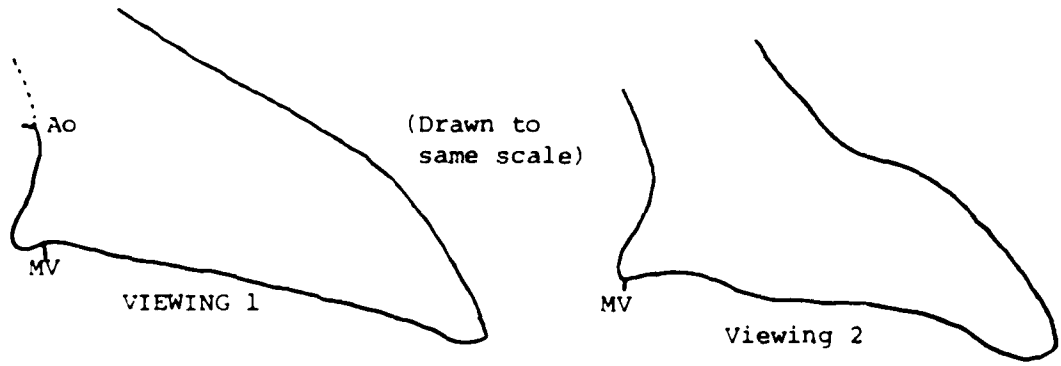


FIGURE 28a
End Systolic Outlines

Note MV, Ao, Apex.

MV: Mitral Valve Point
Ao: Aortic Root Point

		CURVATURES	
	VIEWING	1	2
Systole	Anterior	.34	.07
	Inferior	-.07	-.19

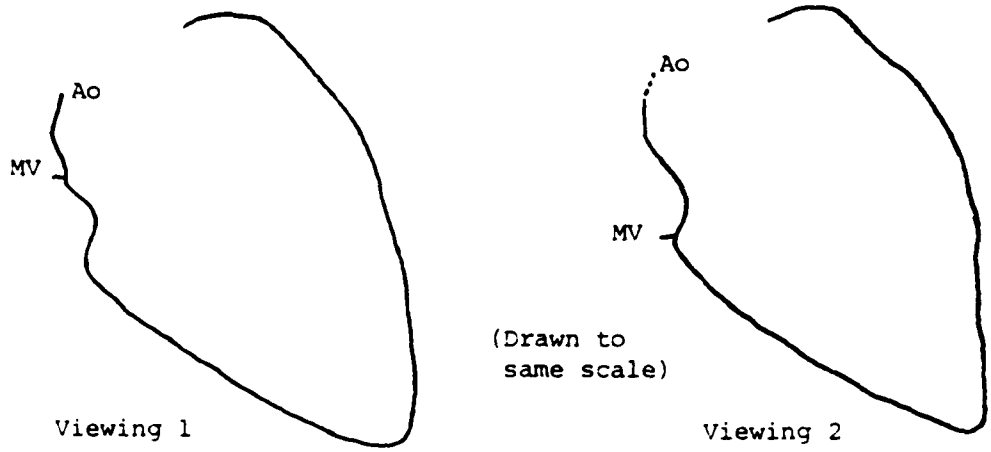


FIGURE 28b
End Diastolic Outlines

Note MV, Ao

MV: Mitral Valve Point
Ao: Aortic Root Point

		CURVATURES	
	VIEWING	1	2
Diastole	Anterior	.82	.84
	Inferior	.45	.31

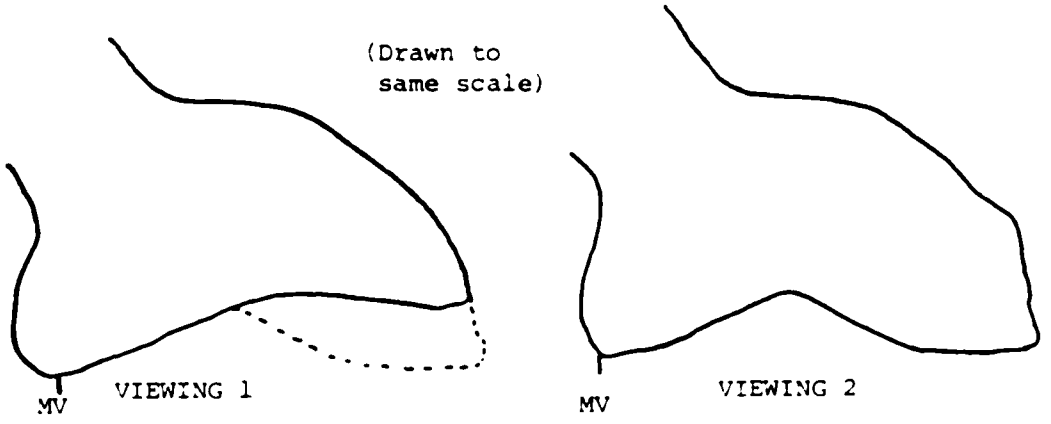


FIGURE 29

Note inferior wall. Dotted line of viewing 1 is the inferior wall of viewing 2. The enclosed region was much lighter on the film.

MV: Mitral Valve Point

		CURVATURES	
	VIEWING	1	2
Systole	Anterior	.32	.33
	Inferior	-.21	-.30

BIBLIOGRAPHY

1. James TN. Anatomy of the Coronary Arteries. New York: Paul B Hoeber Inc. Medical Division of Harper Brothers

2. Helfant RH, Kemp HG, Gorlin R. Coronary atherosclerosis, coronary collaterals, and their relation to cardiac function. Ann Intern Med 1970;73:189

3. Carroll RJ, Verani MS, Falsetti HL. The effect of collateral circulation on segmental left ventricular contraction. Circulation 1974;50:709

4. Schwarz F, Flameng W, Ensslen R, Sesto M, Thormann J. Effect of coronary collaterals on left ventricular function at rest and during stress. Am Heart J 1978;95:570

5. Cohn PF, Maddox DE, Holman BL, See JR. Effect of coronary collateral vessels on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 1980;46:359

6. Bookstein FL. The Measurement of Biological Shape and Shape Change. New York: Springer-Verlag, 1978

7. ibid., 8

8. ibid., 9

9. Stoker JJ. Differential Geometry. New York: Wiley-Interscience, 1969:21-23

10. ibid., 29-31

11. Cabin HS, Roberts WC. Fatal cardiac arrest during cardiac catheterization for angina pectoris: analysis of 10 necropsy patients. Am J Cardiol 1981;48:1

12. Kennedy JW. Complications associated with cardiac catheterization and angiography. Cathet Cardiovasc Diagn 1982;8:5

13. Davis K, Kennedy JW, Kemp HG, Judkins MP, Gosselin AJ, Killip T. Complications of coronary arteriography from the Collaborative Study of Coronary Artery Surgery (CASS). Circulation 1979;59:1105

14. Braunwald E, Ross J, Sonnenblick EH. Mechanisms of Contraction of the Normal and Failing Heart, second edition. Boston: Little, Brown and Company, 1976:92-131

15. ibid., 131-165

16. St. John Sutton MG, Tajik AJ, Smith HC, Ritman EL. Angina in idiopathic hypertophic subaortic stenosis. Circulation 1980;61:561

17. Sobrino JA, Lanchas CH, del Rio A, Mate I, Carrillo A, Imizcoz MA, Sobrino N. Left ventricular cavity obliteration: hemodynamic behavior of the postextrasystolic beat. Am Heart J 1980;99:319

18. Grose R, Maskin C, Spindola-Franco H, Yipintsoi T. Production of left ventricular cavitary obliteration in normal man. Circulation 1981;64:448

19. Jennrich RI. Stepwise Discriminant Analysis. In: Enslein K, Ralston A, Wilf HS, eds. Statistical Methods for Digital Computers. New York: John Wiley and Sons, 1977:75-95

20. Kendall M. Multivariate Analysis. London: Charles Griffin and Company Ltd., 1975:145-170

21. Harvey W. Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus. translation by Leake CD. Illinois: Charles C Thomas, 1941

22. ibid., 7

23. ibid., 29

24. ibid., 48

25. ibid., 28

26. Haycraft JB. The movements of the heart within the chest cavity and the cardiogram. J Physiol 1891;12:438

27. Chamberlain WE, Dock W. The study of the heart action with the roentgen cinematograph. Radiology 1926;7:185

28. Rushmer RF, Crystal DK. Changes in configuration of the ventricular chambers during the cardiac cycle. Circulation 1951;4:211

29. Rushmer RF, Thal N. The mechanics of ventricular contraction: a cinefluorographic study. Circulation 1951;4:219

30. Herman MV, Heinle RA, Klein MD, Gorlin R. Localized disorders in myocardial contraction: asynergy and its role in congestive heart failure. N Engl J Med 1967;277:222

31. Lynch PR, Bove AA. Geometry of the left ventricle as studied by a high-speed cineradiographic technique. Fed Proc 1969;28:1330

32. Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. Circulation 1974;50:121

33. Bove AA. Radiographic evaluation of dynamic geometry of the left ventricle. J Appl Physiol 1971;31:227

34. Harris LD, Clayton PD, Marshall HW, Warner HR. A technique for the detection of asynergistic motion in the left ventricle. Comput Biomed Res 1974;7:380

35. Stewart DK, Dodge HT, Frimer M. Quantitative analysis of regional myocardial performance in coronary artery disease. In: Harrison DC, Sandler H, Miller HA, eds. Cardiovascular Imaging and Image Processing. California: The Society of Photo-optical Instrumentation Engineers, 1975:217-224

36. Bove AA, Kreulen TH, Spann JF. Computer analysis of left ventricular dynamic geometry in man. Am J Cardiol 1978;41:1239

37. Clayton PD, Bulawa WF, Klausner SC, Urie PM, Marshall HW, Warner HR. The characteristic sequence for the onset of contraction in the normal human left ventricle. Circulation 1979;59:671

38. Tzivoni D, Diamond G, Pichler M, Stankus K, Vas R, Forrester J. Analysis of regional ischemic left ventricular dysfunction by quantitative cineangiography. Circulation 1979;60:1278

39. Warren SE, Bhargava V, Vieweg WVR, Dennish GW, Alpert JS, Hagan AD. Semiautomated method for evaluation of left ventricular regional wall motion in coronary artery disease. Am J Cardiol 1980;46:832

40. Slack JD, Landon JK, Cole JS, Hanley HG. Biplane regional wall motion analysis: optimal method for identification of left ventricular akinesis/dyskinesis with quantitative cineangiography in man. Comput Biol Med 1981;11:21

41. Fujita M, Sasayama S, Kawai C, Eiho S, Kuwahara M. Automatic processing of cineventriculograms for analysis of regional myocardial function. Circulation 1981;63:1065

42. Rickards A, Seabra-Gomes R, Thurston P. The assessment of regional abnormalities of the left ventricle by angiography. Europ J Cardiol 1977;5:167

43. Goodyer AVN, Langou RA. The multicentric character of normal left ventricular wall motion. Implications for the evaluation of regional wall motion abnormalities by contrast angiography. Cathet Cardiovasc Diagn 1982;8:225

44. Sniderman AD, Marpole D, Fallen EL. Regional contraction patterns in the normal and ischemic left ventricle in man. Am J Cardiol 1973;31:484

45. Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. Br Heart J 1976;38:1010

46. Chaitman BR, Bristow JD, Rahimtoola SH. Left ventricular wall motion assessed by using fixed external reference systems. Circulation 1973;48:1043

47. Rizi HR, Kline RC, Thrall JH, Besozzi MC, Lee IP, Keyes JW, Pitt B. Pericardial effusion swinging heart phenomenon by dynamic radionuclide ventriculography. Am Heart J 1981;101:347

48. Clayton PD, Jeppson GM, Klausner SC. Should a fixed external reference system be used to analyze left ventricular wall motion?. Circulation 1982;65:1518

49. Carlsson E. Experimental studies of ventricular mechanics in dogs using the tantalum-labeled heart. Fed Proc 1969;28:1324

50. Mitchell JH, Wildenthal K, Mullins CB. Geometrical studies of the left ventricle utilizing biplane cinefluorography. Fed Proc 1969;28:1334

51. Harrison DC, Goldblatt A, Braunwald E, Glick G, Mason DT. Studies on cardiac dimensions in intact, unanesthetized man. Circ Res 1963;13:448

52. McDonald IG. The shape and movements of the human left ventricle during systole: a study by cineangiography and by cineradiography of epicardial markers. Am J Cardiol 1970;26:221

53. Ingels NB, Daughters GT, Stinson EB, Alderman EL. Measurement of midwall myocardial dynamics in intact man by radiography of surgically implanted markers. Circulation 1975;52:859

54. Brower RW, ten Katen HJ, Meester GT. Direct method for determining regional myocardial shortening after bypass surgery from radiopaque markers in man. Am J Cardiol 1978;41:1222

55. MacKay SA, Potel MJ, Rubin JM. Graphics methods for tracking three-dimensional heart wall motion. Comput Biomed Res 1982;15:455

56. Walley KR, Grover M, Raff GL, Benge JW, Hannaford B, Glantz SA. Left ventricular dynamic geometry in the intact and open chest dog. Circ Res 1982;50:573

57. Smulyan H, Eich RH, Johnson LW, Parker FB, Potts JL, Tracy GP. An evaluation of the results of left ventricular aneurysmectomy: use of a simplified method for analysis of the left ventriculogram. Am Heart J 1978;96:596

58. Gibson DG, Brown DJ. Continuous assessment of left ventricular shape in man. Br Heart J 1975;37:904

59. Masuda Y, Yoshida H, Morooka N, et al. ECG synchronized computed tomography in clinical evaluation of total and regional cardiac motion: comparison of postmyocardial infarction to normal hearts by rapid sequential imaging. Am Heart J 1981;103:230

60. Hutchins GM, Bulkley BH, Moore GW, Piasio MA, Lohr FT. Shape of the human cardiac ventricles. Am J Cardiol 1978;41:646

61. Greenbaum RA, Gibson DG. Regional non-uniformity of left ventricular wall movement in man. Br Heart J 1981;45:29

62. Hamby RI, Aintablian A, Tabrah F, Reddy K, Wisoff G. Late systolic bulging of left ventricle in patients with angina pectoris: a form of asynchronous contraction. Chest 1974;65:169

63. Horowitz RS, Morganroth J. Immediate detection of early high-risk patients with acute myocardial infarction using two-dimensional echocardiographic evaluation of left ventricular regional wall motion abnormalities. Am Heart J 1982;103:814

64. Gelberg HJ, Brundage BH, Glantz S, Parmley WW. Quantitative left ventricular wall motion analysis: a comparison of area, chord and radial methods. Circulation 1979;59:991

65. Ingels NB, Daughters GT, Stinson EB, Alderman EL. Evaluation of methods for quantitating left ventricular segmental wall motion in man using myocardial markers as a standard. Circulation 1980;61:966

66. Karsch KR, Lamm U, Blanke H, Rentrop KP. Comparison of nineteen quantitative models for assessment of localized left ventricular wall motion abnormalities. Clin Cardiol 1980;3:123

67. Bhargava V, Warren S, Vieweg WVR, Shabetai R. Quantitation of left ventricular wall motion in normal subjects: comparison of various methods. Cathet Cardiovasc Diagn 1980;6:7

68. Miller JL, Matthews SA. Effect on the heart of experimental obstruction of the left coronary artery. Arch Intern Med 1909;3:476

69. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. JAMA 1912;59:2015

70. Tennant R, Wiggers CJ. The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935;112:351

71. Herman MV, Gorlin R. Implications of left ventricular asynergy. Am J Cardiol 1969;23:538

72. Vieweg WVR, Alpert JS, Johnson AD, Dennish GW, Nelson DP, Warren SE, Hagan AD. Distribution and severity of left ventricular wall motion abnormalities according to age and coronary arterial pattern in 500 patients with coronary artery disease and angina pectoris. Am Heart J 1980;99:707

73. Bjork L, Cullhed I, Hallen A. Cineangiocardiographic studies of the left ventricle in patients with angina pectoris. Circulation 1967;36:868

74. Hamilton GW, Murray JA, Kennedy JW. Quantitative angiocardiography in ischemic heart disease: the spectrum of abnormal left ventricular function and the role of abnormally contracting segments. Circulation 1972;45:1065

75. Cosby RS, See JR, Giddings JA, Talbot JC, Ishikawa K, Buggs HC, Mayo M. Left ventricular dyskinesia in infarction and angina. Am J Med 1975;59:13

76. Markis JE, Joffee CD, Roberts BH, Ransil BJ, Cohn PF, Herman MV, Gorlin R. Evolution of left ventricular dysfunction in coronary artery disease: serial cineangiographic studies without surgery. Circulation 1980;62:141

77. Bodenheimer MM, Banka VS, Fooshee C, Hermann GA, Helfant RH. Relationship between regional myocardial perfusion and the presence, severity and reversibility of asynergy in patients with coronary heart disease. Circulation 1978;58:789

78. Massie BM, Botvinick EH, Brundage BH, Greenberg B, Shames D, Gelberg H. Relationship of regional myocardial perfusion to segmental wall motion: a physiologic basis for understanding the presence and reversibility of asynergy. Circulation 1978;58:1154

79. Codini MA, Hassan PW, Hauser RG, Goldin MD, Messer JV. Occlusive disease confined to the right coronary artery: clinical features, surgical treatment and long-term follow-up in 124 patients. Am J Cardiol 1979;43:1103

80. Brooks N, Cattell M, Jennings K, Balcon R, Honey M, Layton C. Isolated disease of left anterior descending coronary artery: angiographic and clinical study of 218 patients. Br Heart J 1982;47:71

81. Kumpuris AG, Quinones MA, Kanon D, Miller RR. Isolated stenosis of left anterior descending or right coronary atery: relation between site of stenosis and ventricular dysfunction and theraputic implications. Am J Cardiol 1980;46:13

82. Rigaud M, Rocha P, Boschat J, Farcot JC, Bardet J, Bourdarias JP. Regional left ventricular function assessed by contrast angiography in acute myocardial infarction. Circulation 1979;60:130

83. Bertrand ME, Rousseau MF, Lablanche JM, Carre AG, Lekieffre JP. Cineangiographic assessment of left ventricular function in the acute phase of transmural myocardial infarction. Am J Cardiol 1979;43:472

84. Field BJ, Russell RO, Dowling JT, Rackley CE. Regional left ventricular performance in the year following myocardial infarction. Circulation 1972;46:679

85. Miller RR, Olson HG, Vismara LA, Bogren HG, Amsterdam EA, Mason DT. Pump dysfunction after myocardial infarction: importance of location, extent and pattern of abnormal left ventricular segmental contraction. Am J Cardiol 1976;37:340

86. Ideker RE, Behar VS, Wagner GS, Starr JW, Starmer CF, Lee KL, Hackel DB. Evaluation of asynergy as an indicator of myocardial fibrosis. Circulation 1978;57:715

87. Karliner JS, Bouchard RJ, Gault JH. Dimensional changes of the human left ventricle prior to acrtic valve opening: a cineangiographic study in patients with and without left heart disease. Circulation 1971;44:312

88. Gibson DG, Doran JH, Traill TA, Brown DJ. Abnormal left ventricular wall movement during early systole in patients with anginal pectoris. Br Heart J 1978;40:758

89. Leighton RF, Pollack MEM, Welch TG. Abnormal left ventricular wall motion at mid-ejection in patients with coronary heart disease. Circulation 1975;52:238

90. Altieri PI, Wilt SM, Leighton RF. Left ventricular wall motion during the isovolumic relaxation period. Circulation 1973;48:499

91. Ruttley MS, Adams DF, Cohn PF, Abrams HL. Shape and volume changes during "isovolumetric relaxation" in normal and asynergic ventricles. Circulation 1974;50:306

92. Wilson CS, Krueger S, Forker AD, Weaver WF. Correlation between segmental early relaxation of the left ventricular wall and coronary occlusive disease. Am Heart J 1975;89:474

93. Fischl SJ, Gorlin R, Herman MV. Cardiac shape and function in aortic valve disease: physiologic and clinical implications. Am J Cardiol 1977;39:170

94. Herreman F, Ameur A, de Vernejoul F, Bourgin JH, Gueret P, Guerin F, Degeorges M. Pre- and postoperative hemodynamic and cineangiocardiographic assessment of left ventricular function in patients with aortic regurgitation. Am Heart J 1979;98:63

95. Osbakken MD, Bove AA, Spann JF. Left ventricular regional wall motion and velocity of shortening in chronic mitral and aortic regurgitation. Am J Cardiol 1981;47:1005

96. Klein MD, Lane FJ, Gorlin R. Effect of left ventricular size and shape upon the hemodynamics of subaortic stenosis. Am J Cardiol 1965;15:773

97. Kreulen TH, Gorlin R, Herman MV. Ventriculographic patterns and hemodynamics in primary myocardial disease. Circulation 1973;47:299

98. Carrasco HA, Barboza JS, Inglessis G, Fuenmayor A, Molina C. Left ventricular cineangiography in Chagas' disease: detection of early myocardial damage. Am Heart J 1982;104:595

99. Williams RS, Behar VS, Peter RH. Left bundle branch block: angiographic segmental wall motion abnormalities. Am J Cardiol 1979;44:1046

100. Chatterjee K, Swan HJC, Parmley WW, Sustaita H, Marcus H, Matloff J. Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous-vein bypass. N Engl J Med 1972;286:1117

101. Chatterjee K, Swan HJC, Parmley WW, Sustaita H, Marcus HS, Matloff J. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease: with and without previous myocardial infarction. Circulation 1973;47:276

102. Wolf NM, Kreulen TH, Bove AA, et al. Left ventricular function following coronary bypass surgery. Circulation 1978;58:63

103. Mintz LJ, Ingels NB, Daughters GT, Stinson EB, Alderman EL. Sequential studies of left ventricular function and wall motion after coronary arterial bypass surgery. Am J Cardiol 1980;45:210

104. Bourassa MG, Lesperance J, Campeau L, Saltiel J. Fate of left ventricular contraction following aortocoronary venous grafts: early and late postoperative modifications. Circulation 1972;46:724

105. Griffith LSC, Achuff SC, Conti R, Humphries JO, Brawley RK, Gott VL, Ross RS. Changes in intrinsic coronary circulation and segmental ventricular motion after saphenous-vein coronary bypass graft surgery. N Engl J Med 1973;288:589

106. Hammermeister KE, Kennedy JW, Hamilton GW, Stewart DK, Gould KL, Lipscomb K, Murray JA. Aortocoronary saphenous-vein bypass: failure of successful grafting to improve resting left ventricular function in chronic angina. N Engl J Med 1974;290:186

107. Shepherd RL, Itscoitz SB, Glancy DL, et al. Deterioration of myocardial function following aorto-coronary bypass operation. Circulation 1974;49:467

108. Levine JA, Bechtel DJ, Cohn PF, Herman MV, Gorlin R, Cohn LH, Collins JJ. Ventricular function before and after direct revascularization surgery: a proposal for an index of vascularization to correlate angiographic and ventriculographic findings. Circulation 1975;51:1071

109. Kennedy JW, Kaiser GC, Fisher LD, et al. Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery (CASS). J Thorac Cardiovasc Surg 1980;80:876

110. Chaitman BR, Rogers WJ, Davis K, et al. Operative risk factors in patients with left main coronary-artery disease. N Engl J Med 1980;303:953

111. Banka VS, Bodenheimer MM, Helfant RH. Determinants of reversible asynergy: effect of pathologic Q waves, coronary collaterals, and anatomic location. Circulation 1974;50:714

112. Leighton RF, Rich JM, Pollack ME, Altieri PI. Clinical applications of a quantitative analysis of regional left ventricular wall motion. In: Harrison DC, Sandler H, Miller HA, eds. Cardiovascular Imaging and Image Processing. California: The Society of Photo-optical Instrumentation Engineers 1975:203-208

113. Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banka VS. Nitroglycerin to unmask reversible asynergy: correlation with post coronary bypass ventriculography. Circulation 1974;50:108

114. McEwan MP, Berman ND, Morch JE, Feiglin DH, McLaughlin PR. Effect of intravenous and intracoronary nitroglycerin on left ventricular wall motion and perfusion in patients with coronary artery disease. Am J Cardiol 1981;47:102

115. McAnulty JH, Hattenhauer MT, Rosch J, Kloster FE, Rahimtoola H. Improvement in left ventricular wall motion following nitroglycerin. Circulation 1975;51:140

116. Sharma B, Hodges M, Asinger RW, Goodwin JF, Francis GS. Left ventricular function during spontaneous angina pectoris: effect of sublingual nitroglycerin. Am J Cardiol 1980;46:34

117. Bodenheimer MM, Banka VS, Hermann GA, Trout RG, Pasdar H, Helfant RH. Reversible asynergy: histopathologic and electrographic correlations in patients with coronary artery disease. Circulation 1976;53:792

118. Ferlinz J, DelVicario M, Aronow WS. Effects of rapid digitalization on total and regional myocardial performance in patients with coronary artery disease. Am Heart J 1978;96:337

119. Kleiman JH, Alderman EL, Goldman RH, Ingels NB, Daughters GT, Stinson EB. Effects of digitalis on normal and abnormal left ventricular segmental dynamics. Am J Cardiol 1979;43:1001

120. Horn HR, Teichholz LE, Cohn PF, Herman MV, Gorlin R. Augmentation of left ventricular contraction pattern in coronary artery disease by an inotropic catecholamine: the epinephrine ventriculogram. Circulation 1974;49:1063

121. Helfant RH, Herman MV, Gorlin R. Abnormalities of left ventricular contraction induced by beta adrenergic blockade. Circulation 1971;43:641

122. Shubrooks SJ, Zir LM, Dinsmore RE, Harthorne JW. Left ventricular wall motion response to intravenous propranolol. Circulation 1975;52:124

123. Coltart DJ, Alderman EL, Robison SC, Harrison DC. Effect of propranolol on left ventricular function, segmental wall motion, and diastolic pressure-volume relation in man. Br Heart J 1975;37:357

124. Serruys PW, Brower RW, ten Katen HJ, Bom AH, Hugenholtz PG. Regional wall motion from radiopaque markers after intravenous and intracoronary injections of nifedipine. Circulation 1981;63:584

125. Dyke SH, Cohn PF, Gorlin R, Sonnenblick E. Detection of residual myocardial function in coronary artery disease using post-extra systolic potentiation. Circulation 1974;50:694

126. Popio KA, Gorlin R, Bechtel D, Levine JA. Postextrasystolic potentiation as a predictor of potential myocardial viability: preoperative analyses compared with studies after coronary bypass surgery. Am J Cardiol 1977;39:944

127. Slack JD, Landon JK, Cole JS, Hanley HG, O'Connor W. Limitations of post-extrasystolic potentiation in assessing regional myocardial viability in man. Cathet Cardiovasc Diagn 1980;6:373

128. Dwyer EM. Left ventricular pressure-volume alterations and regional disorders of contraction during myocardial ischemia induced by atrial pacing. Circulation 1970;42:1111

129. Pasternac A, Gorlin R, Sonnenblick EH, Haft JI, Kemp HG. Abnormalities of ventricular motion induced by atrial pacing in coronary artery disease. Circulation 1972;45:1195

130. Stone D, Dymond D, Elliott AT, Britton KE, Spurrell RAJ, Banim SO. Use of first-pass radionuclide ventriculography in assessment of wall motion abnormalities induced by incremental atrial pacing in patients with coronary artery disease. Br Heart J 1980;43:369

131. Sesto M, Schwarz F. Regional myocardial function at rest and after rapid ventricular pacing in patients after myocardial revascularization by coronary bypass graft or by collateral vessels. Am J Cardiol 1979;43:920

132. Klausner SC, Ratshin RA, Tyberg JV, Lappin HA, Chatterjee K, Parmley WW. The similarity of changes in segmental contraction patterns induced by postextrasystolic potentiation and nitroglycerin. Circulation 1976;54:615

133. Banka VS, Bodenheimer MM, Shah R, Helfant RH. Intervention ventriculography: comparative value of nitroglycerin, post-extrasystolic potentiation and nitroglycerin plus post-extrasystolic potentiation. Circulation 1976;53:632

134. Schwarz F, Ensslen R, Thormann J, Sesto M. Effects of nitroglycerin, postextrasystolic potentiation, and pacing-induced ischaemia on wall motion in patients with ischaemic heart disease. Br Heart J 1977;39:44

135. Dove JT, Shah PM, Schreiner BF. Effects of nitroglycerin on left ventricular wall motion in coronary artery disease. Circulation 1974;49:682

136. Amende I, Simon R, Hood WP, Lichtlen PR. The effects of the beta-blocker atenolol and nitroglycerin on left ventricular function and geometry in man. Circulation 1979;60:836

137. Krayenbuehl HP, Schoenbeck M, Rutishauser W, Wirz P. Abnormal segmental contraction velocity in coronary artery disease produced by isometric exercise and atrial pacing. Am J Cardiol 1975;35:785

138. May AG, DeWeese JA, Rob CG. Hemodynamic effects of arterial stenosis. Surgery 1963;53:513

139. Feldman RL, Nichols WW, Pepine CJ, Conti CR. Hemodynamic significance of the length of a coronary arterial narrowing. Am J Cardiol 1978;41:865

140. Conti CR, Pepine CJ, Feldman RL, Curry RC, Christie LG, Nichols WW. Angiographic definition of critical coronary artery stenosis. Adv Cardiol 1979;26:100

141. Sabbah HN, Stein PD. Hemodynamics of multiple versus single 50 percent coronary arterial stenoses. Am J Cardiol 1982;50:276

142. Rafflenbeul W, Urthaler F, Lichtlen P, James TN. Quantitative difference in "critical" stenosis between right and left coronary artery in man. Circulation 1980;62:1188

143. McMahon MM, Brown BG, Cukingnan R, Rolett EL, Bolson E, Frimer M, Dodge HT. Quantitative coronary angiography: measurement of the "critical" stenosis in patients with unstable angina and single-vessel disease without collaterals. Ciculation 1979;60:106

144. Hurst JW, King SB, Walter PF, Friesinger GC, Edwards JE. Atherosclerotic coronary heart disease: angina pectois, myocardial infarction, and other manifestations of myocardial ischemia. In: Hurst JW, ed. The Heart, arteries and veins. New York: McGraw-Hill Book Company, 1982:1009-1149

145. ibid., Kirk ES, Jennings RB. Pathophysiology of myocardial ischemia. 976-1008

146. Fritzsche DL. A systematic method for character recognition. Document AD 268 360. National Technical Information Service. Springfield Va. 22161

147. Raudseps JG. Some aspects of the tangent-angle vs. arc length representation of contours. Document AD 462 877. National Technical Information Service. Springfield Va. 22161

148. Zahn CT, Roskies RZ. Fourier descriptors for plane closed curves. IEEE Trans Comput 1972;c-21:269

149. Wallace TP, Mitchell OR, Fukunaga K. Three-dimensional shape analysis using local shape descriptors. IEEE Trans Pattern Anal and Machine Intell 1981;PAMI-3:310

150. Graf/Pen Model GP-3 Operator's Manual. Science Accessories Corporation. Southport Connecticut 06490

151. Brower RW. Evaluation of pattern recognition rules for the apex of the heart. Cathet Cardiovasc Diagn 1980;6:145

152. PDP-11 FORTRAN Language Reference Manual. Digital Equipment Corporation. Massachusets: 1974

153. Mandelbrot BB. Fractals: Form, Chance, and Dimension. San Francisco: WH Freeman and Company

154. Statistical Analysis System, release 79.5. SAS Institute Inc, Cary, North Carolina 27511

155. BMDP Biomedical Computer Programs P-Series, 1979. Department of Biomathematics, University of California, Los Angeles California 90024.

156. Lachenbruch PA, Mickey MR. Estimation of error rates in discriminant analysis. Technometrics 1968;10:1

157. Zar JH. Biostatistical Analysis. New Jersey: Prentice Hall Inc, 1974:41-58

158. ibid., 151-162

159. ibid., 127

160. Lachenbruch PA. Discriminant Analysis. Biometrics 1979;35:69

161. Kendall MG, Stuart A. The Advanced Theory of Statistics, volume 3. New York: Hafner Publishing Company, 1961

162. Fischer HW, Thomson KR. Contrast media in coronary arteriography: a review. Invest Radiol 1978;13:450

163. Warwick R, Williams PL, eds. Gray's Anatomy, 35th British edition. Philadelphia: WB Saunders Company, 1973:599-615

164. Cohn PF, Levine JA, Bergeron GA, Gorlin R. Reproducibility of the angiographic left ventricular ejection fraction in patients with coronary artery disease. Am Heart J 1974;88:713

165. Wexler LF, Lesperance J, Ryan T, et al. Interobserver variability in interpreting contrast left ventriculograms (CASS). Cathet Cardiovasc Diagn 1982;8:341

166. Vas R, Diamond GA, Forrester JS, et al. Computer-enhanced digital angiography: correlation of clinical assessment of left ventricular ejection fraction and regional wall motion. Am Heart J 1982;104:732

167. Pavlidis T. Algorithms for shape analysis of contours and waveforms. IEEE Trans Pattern Anal and Machine Intell 1980;PAMI-2:301

168. Blum H. Biological shape and visual science (part 1). J Theoret Biol 1973;38:205

169. Calabi L, Hartnett WE. Shape recognition, prairie fires, convex deficiencies and skeletons. Am Mathem Monthly 1968;75:335

170. Montanari U. A method for obtaining skeletons using a quasi-euclidean distance. J Assoc Comput Machinery 1968;15:600

171. Montanari U. Continuous skeletons from digitized images. J Assoc Comput Machinery 1969;16:534

172. Levi G, Montanari U. A grey-weighted skeleton. Informat and Control 1970;17:62

173. de Souza PV, Houghton P. Computer location of medial axes. Comput and Biomed Research 1977;10:333

174. Weber RL, Blum H. Angular invariants in developing human mandibles. Science 1979;206:689

175. Lee DT. Medial axis transformation of a planar shape. IEEE Trans Pattern Anal and Machine Intell 1982;PAMI-4:363

176. Selby SM, ed. Standard Mathematical Tables, 21st edition. Cleveland: The Chemical Rubber Company, 1973;230