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ANALYSIS *and* SIMULATION *of the* CARDIAC SYSTEM — ISCHEMIA

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Analysis and Simulation of the Cardiac System — Ischemia

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PREFACE

Today we celebrate the 4th birthday of a dream come true; a dream to bring together the diversified expertise in the various fields of science, engineering, and medicine so as to better serve humanity through better understanding of the cardiac system; a dream to combine the numerous interactive parameters and disciplines involved in the performance of the heart into a quantitative comprehensive framework. It is a dream based on the belief that science is not beset by cynicism and selfishness, but rather dominated by an international brotherhood of truth-seeking scientists who, by sharing the results of their individual efforts, reach out to make a better world for all.

This gathering of distinguished, outstanding scientists from all over the world is a living testimonial to the fact that scientific cooperation is indeed possible. Furthermore, it highlights the pleasure of joining hands in the pursuit of the wildest of all dreams: to decipher the secrets of life. We must never forget that our achievements are only limited by our own imagination!

The first Henry Goldberg (HG) workshop, held in Haifa in 1984, introduced the concept of the interaction of mechanics, electrical activation, perfusion, and metabolism, emphasizing imaging in the clinical environment. The second workshop, in 1985, discussed the same parameters with a slant towards the control aspects. The third HG workshop, held in the U.S. at Rutgers University in 1986, highlighted the transformation of the microscale activation phenomena to macroscale activity and performance, relating electrophysiology, energy metabolism, and cardiac mechanics.

Following the success of these workshops, the 4th Henry Goldberg workshop continues the effort to elucidate the interactions between the various parameters affecting cardiac performance, mainly in the ischemic heart. It aims to highlight the metabolic implications and contractile dynamics associated with impaired perfusion and disarrayed electrical phenomena and its relationship to the formation of arrhytmias in the ischemic muscle. Bringing together the leading experts and outstanding scientists in the various related disciplines will catalyze further personal interactions, stimulate new answers, and hopefully generate some new questions.

It is with great pleasure that I acknowledge here those who have made this meeting possible. First and foremost, our dear departed friends, who are not with us any more: Mrs. Pearl Milch, past Chairman of the Board of the ATS Women's Division, New York, whose endless love, dedication, and support put the wings on our dream; Mr. Michael Kennedy-Leigh of London, whose confidence, trust, and generous encouragement kept us moving towards the promised land, and Professor Henry Neufeld, of Tel Hashomer, whose clinical wisdom and human compassion sharpened the infinite outlines of our fantasies. Special thanks are due to Mr. Julius Silver and Ms. Dinny Winslow (Silver) of New York, for their personal support and continued friendship which inspired and shaped our goal and made it possible. Thanks are also due to the Women's Division Presidium, Miriam Leighton, Ramie Silbert, Rita Wallach, and the Executive Director Mrs. Flo Cohen, who encouraged us with their unshakable trust and provided the means to start the Heart System Research Center. Personal thanks go to a friend and collaborator, Professor Walter Welkowitz of Rutgers University, who was the first to learn of our wild dream and helped make it all possible; thanks also go to our colleagues in the Technion who kept us on an even keel, and to Mr. Jacob Sapir, Director of the Ministry of Science and Development, which sponsored the workshop. Finally, last, but by no means least, our warm hearted thanks to Mr. Henry Goldberg, a young man of 87, and his beautiful wife Violla, for their selfless generosity and kindness which made these Henry Goldberg Workshops significant milestones in cardiac research.

THE EDITORS

Samuel Sideman, D.Sc., Professor of Chemical Engineering and R. J. Matas/Winnipeg Professor of Biomedical Engineering, is chairman of the Department of Biomedical Engineering from 1980 and Head of the Cardiac System Research Center of the Technion-Israel Institute of Technology.

Born in Israel (1929), he received his B.Sc. (1953) and D.Sc. (1960) from the Technion and his M.Ch.E. (1955) from the Polytechnical Institute of Brooklyn. On the faculty of the Technion since 1957, he served as Dean of Faculty, Dean of Students, Chairman of Chemical Engineering, and Director of the Julius Silver Institute of Biomedical Engineering since 1980. Dr. Sideman has been Visiting Professor of Chemical Engineering at the University of Houston (1972 to 1973) and CCNY (1976 to 1977), a Distinguished Visiting Professor of Biomedical Engineering at Rutgers University, Piscataway, NJ (1985 to 1988), and a Visiting Professor of Surgery (Bioengineering) at Rutgers Medical School, New Brunswick, NJ.

His biomedical interests cover biological transport phenomena, blood and detoxification therapeutics, artificial blood, modeling of the energy-metabolism system, and simulation of the cardiac performance. Dr. Sideman has authored and co-authored over 250 scientific publications in journals and books and co-edited books on multiphase systems, hemoperfusion, and cardiac analysis and simulation. He is a member of a number of engineering and biomedical engineering societies, on the editorial board of some major scientific journals, and has recently been elected as Fellow of the American Institute of Chemical Engineering and Fellow of the New York Academy of Science.

Rafael Beyar, M.D., D.Sc., is a Senior Lecturer in the Department of Biomedical Engineering and is the Coordinator of the Cardiac Research Center at the Technion.

Born in Israel in 1952, he graduated from the Sackler Medical School in Tel Aviv University with a M.D. degree and obtained his D.Sc. degree in Biomedical Engineering from the Technion-Israel Institute of Technology in 1983. He has been active in initiating and coordinating the Heart System Research Center in the Julius Silver Institute at the Technion. A senior lecturer in the Technion since 1984, he spent 2 years (1985 to 1987) at the Division of Cardiology, Johns Hopkins University Hospital, Baltimore. His research interests include simulation of the cardiovascular system, resuscitation, circulatory assistance, and complex interactions between energetics perfusion and mechanics of the heart.

Dr. Beyar is a member of the American College of Cardiology, Biomedical Engineering Society (U.S.), Israel Society of Biomedical Engineering, Israel Medical Association, Israel Cardiology Association, Cardiovascular System Dynamic Society (U.S.), and the American Medical Association. He received the graduate studies Gutwirtz Award, the Kennedy Leigh Award for his D.Sc. thesis, and the Jolodan Research Award.

Dr. Beyar has authored and co-authored over 50 scientific publications in journals and books and is co-editor of 4 books on the analysis and simulation of the cardiac system.

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Dedicated to:
Julius Silver and Dinny Winslow (Silver), for putting us on the map of the Biomedical Sciences;
Henry and Viola Goldberg, for making this book possible;
and our families, for their quiet encouragement and love that made life more bearable.

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Cardiac Mechanics

Chapter 1

COMPUTER INTERACTIVE METHODS OF MEASURING REGIONAL LEFT VENTRICULAR DYSFUNCTION IN ISOLATED DISEASE OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY

M. S. Gotsman, S. Welber, D. Sapoznikov, M. Mosseri, and A. T. Weiss

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ABSTRACT

Temporal and spatial disturbances of left ventricular function were studied in the cineangiogram in 34 patients with isolated disease of the left anterior descending (LAD) coronary artery and compared with 12 normal subjects. Classical anterior wall infarction caused impaired contraction of the distal two thirds of the anterior wall, the apex, and the distal quarter of the inferior wall, with marked delay in contraction and relaxation of the border zones and hyperkinesis of the inferior wall. Left bundle branch block induced profound temporal delay particularly during relaxation.

Different methods of assessing spatial and temporal contraction defects were measured and compared. The dysfunction index, calculated as the area that the shortening fraction curve of the patient derived from 100 equiangular radii, fell below 1 SD of the normal population, was simple to measure, and gave good discrimination between different syndromes of left ventricular dysfunction.

When classical thrombolysis with intravenous streptokinase was used to achieve reperfusion (65 patients with a first anterior myocardial infarction and a patent infarct related coronary artery), the dysfunction index was an excellent method of assessing myocardial damage. The dysfunction index showed that infarct size was related to the time delay until streptokinase was administered (less than 2 h), the delay until reperfusion was achieved (an additional $1^1/_2$ h), and residual stenosis of more than 75% in the infarct-related coronary artery. Simple computer interactive methods can be used to assess regional ventricular dysfunction and infarct size.

I. INTRODUCTION

Five discrete pathological processes occur in primary atherosclerotic disease of the coronary arteries:

1. Gradual atheroma accretion due to the deposition of cholesterol in the arterial subintima[1]
2. Sudden and explosive plaque rupture due (a) to denudation of the endothelial cap of the atheromatous plaque — a random, stochastic process — or (b) plaque fissuring from intraluminal hemodynamic stresses or spasm of the residual muscular media and cracking of a nonresilient plaque[2,3]
3. Superadded thrombosis due to activation of the thrombotic cascade by the exposed underlying collagen, fibronectin, and von Willebrand factor[4]
4. Spontaneous fibrinolysis by activation of circulating plasminogen and the dynamic interaction between plasmin, fibrin, and $alpha_2$ antiplasmin[5]
5. Rethrombosis after spontaneous or therapeutic fibrinolysis[6,7]

Narrowing of the artery with reduction of blood flow causes rest- or effort-induced ischemia and angina pectoris. Total obstruction of the artery leads to irreversible myocyte necrosis within 50 min unless the ischemic region has an adequate collateral circulation.[8] This chapter will examine methods of measuring regional ventricular dysfunction, use the derived indices to classify different syndromes of isolated disease of the LAD coronary artery, and examine how the indices can be used to assess the functional effects of therapeutic thrombolysis with intravenous streptokinase.

II. PATIENTS AND METHODS

A. Patient Population

We studied 12 normal subjects and 34 patients with significant, isolated disease of the LAD coronary artery.[9] A total of 65 patients with a first anterior myocardial infarction and

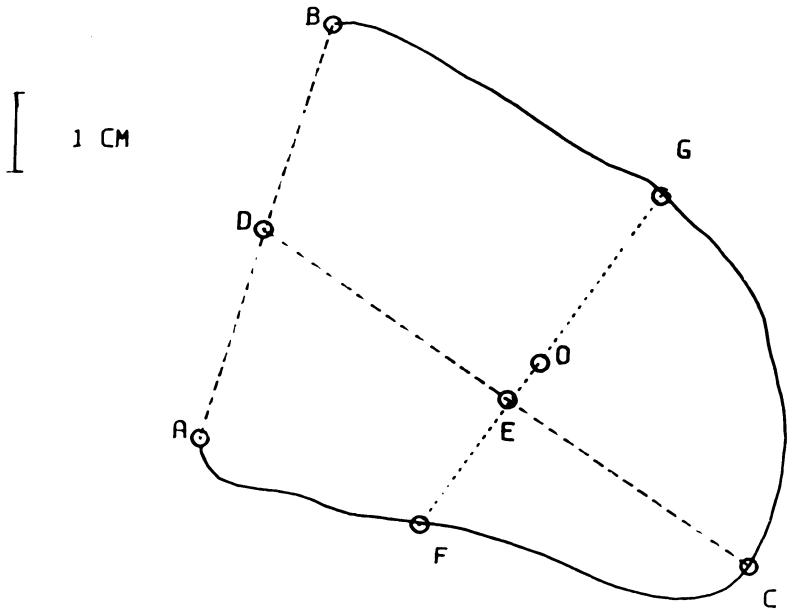


FIGURE 1. Method of defining the centroid of the left ventricle from the diastolic outline of the right anterior oblique cineangiogram (see text for details). (From Sapoznikov, D., Welber, S., Lotan, C., Mosseri, M., Shimoni, Y., and Gotsman, M. S., *Cardiology*, 74, 444, 1987. With permission.)

a patent infarct-related coronary artery were selected from a consecutive group of 200 patients who received intravenous thrombolysis. They were studied to assess the influence of different pathogenetic mechanisms on the size of the infarct.

B. Coronary Angiography

The coronary arteriogram was made using a high-magnification 4 $^{1}/_{2}$-in. General Electric® image intensifier and an overframing lens in four different projections, including the craniocaudal views, to obtain optimum definition of asymmetrical atherosclorotic disease. Narrowing was expressed as a percentage of the coronary artery in the view showing the maximum stenosis, although this may overestimate the degree of stenosis.

Left ventricular angiography was performed in the RAO position on a 9-in. image intensifier using a 40-ml high-pressure injection of 70% renographin. Ventricular function was studied in sinus rhythm and ectopic beats and two subsequent postectopic sinus beats were excluded. We examined the patients frame by frame (50 frames per second) and the largest and smallest frames were regarded as the end-systolic and end-diastolic frames, respectively.

The left ventricular cineangiograms were projected on a Tage Arno projector. The projected image of each frame was recorded on a Sanyo® video TV camera and stored on a Matrox QRGB-256 imaging system and QFG-01/8 frame grabber attached to a PDP® 11/34 computer.

The end-diastolic frame was used as a reference (Figure 1). The aortic mitral plane (annulus) was identified and each end was marked (points A and B). The apex was defined manually using a light cursor and a joy stick (point C). The computer found the midpoint of AB (point D) and joined it to point C. Point E was the midpoint of CD. A perpendicular to CD was drawn through E to intersect the ventricular circumference (point FG). The midpoint of FG (point O) was regarded as the center of the ventricle. The edge of the ventricle was then drawn manually on the TV screen using a light cursor and a joy stick. The computer then automatically drew 100 radii, emanating from center O so that each

segment subtended an identical angle at the center. The coordinates of the intersection of the 100 radii with the circumferential arc (AB) were recorded and stored.

The second frame of the cardiac cycle was projected and recorded and the ventricular outline was drawn by manual interaction with the computer using the light cursor and joy stick. The points of intersection of arc A_2, C_2, B_2 (frame 2), and the 100 radii were then recorded and stored. This process was then repeated for each frame throughout a complete cardiac cycle.

The distance between centimeter line marks on a grid were measured and entered into the computer and the dimension of each radius was calculated in absolute terms. The shortening of each radius in the particular beat was calculated by subtracting the radius of each frame from the end-diastolic radius.[9]

III. RESULTS

A. Frame-by-Frame Analysis

1. Normal Subjects

The pattern of ventricular contraction in normal subjects is shown in Figure 2. This shows symmetrical contraction of the left ventricle around the central point (Figure 2A), symmetrical synchronous contraction of each frame in a time length domain (Figure 2B), a central ridge of contraction in a three-dimensional space-time model (Figure 2C), and a central ridge on a contraction pattern contour map (Figure 2D).

2. Classical Anterior Myocardial Infarction with Total Obstruction of the Left Anterior Descending (LAD) Coronary Artery (17 Patients)

The contraction pattern shows supernormal contraction in the proximal inferior wall (radii 1 to 10); delayed outward motion (relaxation and filling) in the distal inferior wall (11 to 21); delayed contraction (inward motion) and relaxation (outward motion) in the peri-infarcted area (22 to 36); decreased contraction with dyskinesis and delayed outward wall motion (relaxation or filling) in the region of the infarct-distal inferior wall, apex, and distal two thirds of the anterior wall (37 to 71); normal function with delayed oscillation of the marginal zones (probably very marked delay in contraction) (72 to 88); and then delayed contraction and outward motion of the proximal anterior wall (89 to 100) (Figure 3).

3. Anterior Myocardial Infarction with Residual Coronary Reperfusion

These patients all had an anterior myocardial infarction clinically. In two the LAD coronary artery had recanalized spontaneously and in four intracoronary reperfusion of the LAD coronary artery with streptokinase had been undertaken 2 to 4 h after the onset of chest pain. These patients had similar findings to the patients with classical anterior myocardial infarction, and it was clear that spontaneous reperfusion or late thrombolysis had occurred too late to salvage significant myocardium.

4. Patients with Anterior Infarction and Left Bundle Branch Block (Two Patients)

These patients had large infarcts, but more asynchrony. They showed the signs of apical and anterior infarction, delayed contraction and outward motion of the base (anterior and inferior walls), possibly due to late conduction to the basal region, and then markedly delayed after-contractions with delayed contraction and relaxation in the infarcted and peri-infarcted areas (Figure 4). This was probably due to late activation and contraction of islands of residual viable myocardium in this area.

5. Anterior Subendocardial Infarction Followed by Return of the R Waves in the ECG (Two Patients)

These patients had total obstruction of the LAD coronary artery, but a good collateral

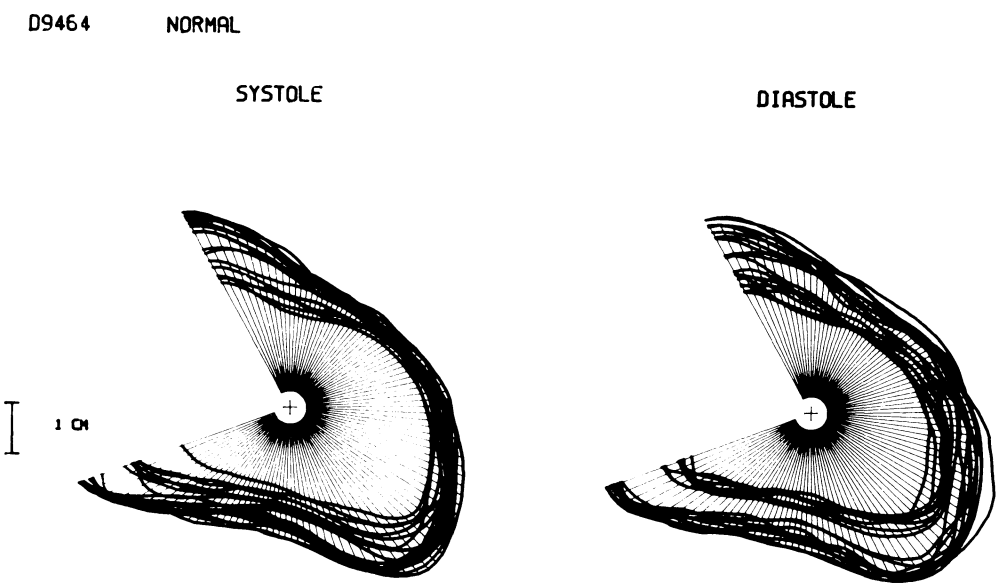


FIGURE 2. Normal left ventricle in the right anterior oblique position. (A) Superimposed frames in systole on the left and in diastole on the right showing equiangular radii radiating from the diastolic LV centroid. There is symmeterical contraction of the radii. (B) Individual pattern of contraction and relaxation of each of the 100 radii. Time is shown on the horizontal axis, and extent of shortening or contraction is shown on the vertical axis. Frame 1 shows the first radius of the inferior wall and 1 to 100 progresses anticlockwise to the proximal anterior wall. There is symmetrical, synchronous contraction of each radius. (C) Three-dimensional representation of the plane of contraction and relaxation of the ventricle. The contraction and relaxation pattern of 8 is shown on the X-Y-Z axes. This shows a central, synchronous ridge of contraction in a three-dimensional space time framework. (D) Plane of ventricular motion in C as a contour map. There is a central ridge of symmetrical contraction. (From Sapoznikov, D., Welber, S., Lotan, C., Mosseri, M., Shimoni, Y., and Gotsman, M. S., *Cardiology,* 74, 444, 1987. With permission.)

circulation. They had smaller infarcts, although the pattern was similar to the findings in anterior infarction with decreased movement and asynchrony.

6. Patients with Angina Pectoris and 50 to 95% Narrowing of the LAD Coronary Artery (Six Patients)

These patients had not experienced an infarct, but had anterior wall ischemia. In three there was normal left ventricular function with very slight asynchrony, while three showed hypokinesis and delayed contraction of the anterior wall.

B. Spatial Dysfunction is the Simplest Method of Discriminating Disturbances of Left Ventricular Function

Each patient was reassessed to quantitate the spatial and then the interrelated spatial and temporal abnormality of contraction. To assess the spatial abnormality only, the end-diastolic and end-systolic frames were compared and the degree of shortening of each of the 100 radii was calculated. The normal and 1 SD about the mean were then recorded on a graph and the patient's contraction curve was superimposed (Figure 5).

We calculated the number of radii and the area below and the mean defective shortening fraction of each radius (area/number of radii) (1) below the mean, (2) 20% below the mean, (3) 1 SD below the mean, and (4) below zero contraction to separate the different subgroups. Examination of the 12 different indices showed that the results were all statistically similar,

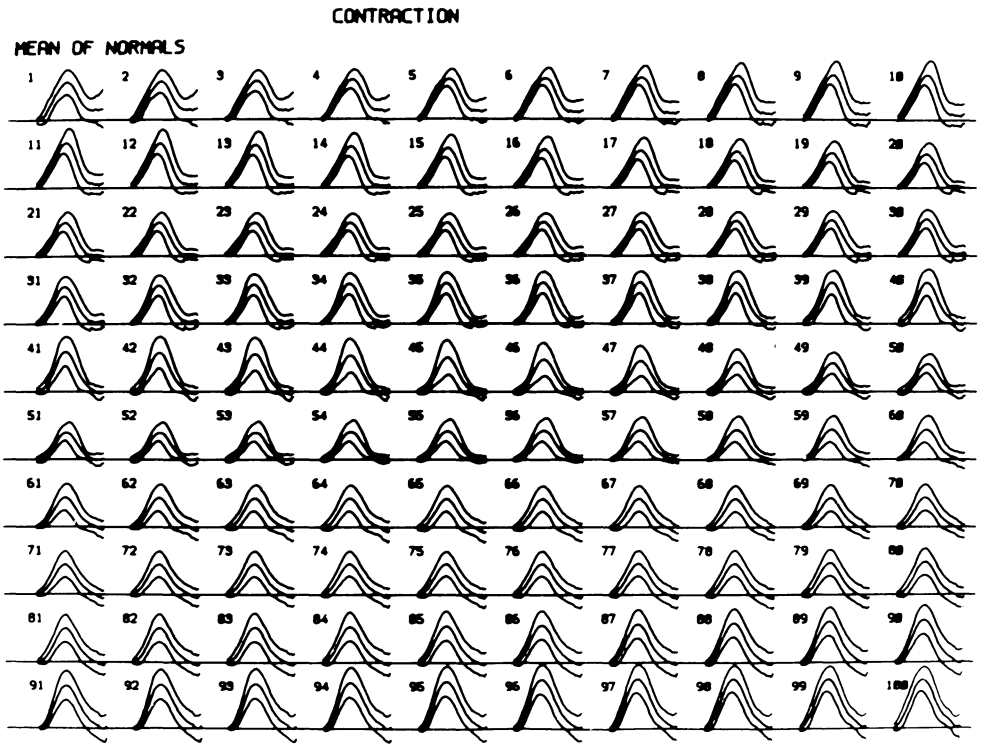


FIGURE 2B.

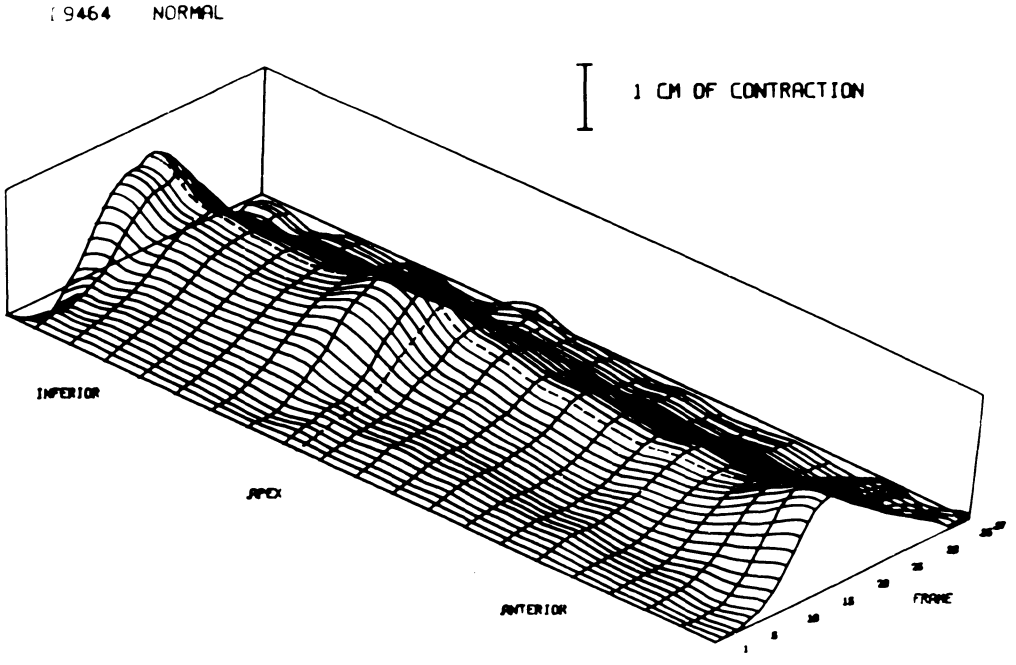


FIGURE 2C.

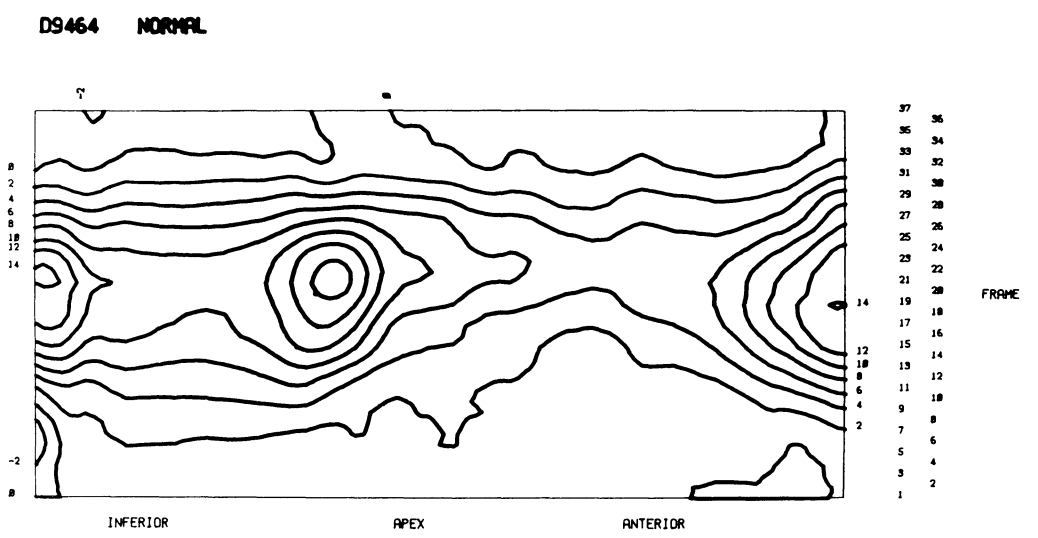


FIGURE 2D.

but the area of defective contraction below 1 SD had the greatest discriminating value and this we have defined as the dysfunction index.

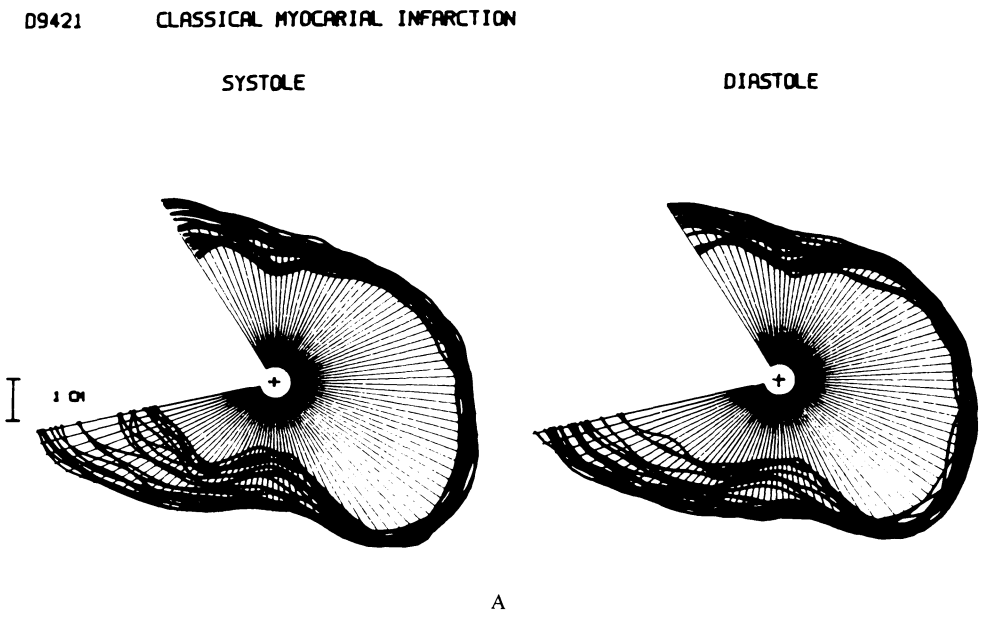
We also calculated the area under the systolic portion of each individual time-radial contraction curve to measure both spatial and temporal defects of contraction and expressed this as a percentage of normal (Figure 6). We then reconstructed the shortening fraction curve so that it would take into account both defective as well as delayed shortening. This did not improve the discriminating value when compared to the simple shortening fraction, and since this technique required frame-by-frame analysis, which is difficult and time consuming compared to measurement of two frames only, we felt that the simple dysfunction index was more suitable for clinical use.

C. The Dysfunction Index is a Sensitive Method of Assessing Left Ventricular Dysfunction

The dysfunction index was compared with left ventricular ejection fraction, left ventricular regional ejection fraction, and QRS score in 65 patients who underwent thrombolysis. There was an excellent correlation between the different measurements ($p < 0.01$). The statistical analysis is given in Table 1 and the comparison of dysfunction index and global ejection fraction is shown in Figure 7.

D. The Extent of Left Ventricular Dysfunction after Intravenous Thrombolytic Therapy is a Time-Dependent Process

We studied a sequential group of 200 patients who received intravenous streptokinase therapy and selected 65 patients with a first anterior myocardial infarction and patent infarct-related coronary artery. Table 2 and Figure 8 compare the different indices of left ventricular dysfunction to the time between the onset of chest pain and streptokinase administration. Dysfunction index, which expresses infarct size, increases progressively with time to streptokinase administration, and 2 h is the dividing line between large and small infarcts. All patients who received streptokinase more than 2 h after the onset of chest pain had large infarcts, whereas the two thirds given streptokinase in less than 2 h had small infarcts. Figure 9 shows the relationship between infarct size (dysfunction index) and the total duration of pain. It shows that 3 $^1/_2$ h is the critical time interval between small and large infarcts. This time interval — total pain duration — reflects the total duration of ischemia: it includes two



A

FIGURE 3. Pattern of contraction of the left ventricle in classic anterior wall myocardial infarction. (A) Superimposed frames in the RAO position, in systole on the left and in diastole on the right, showing equiangular radii radiating from the diastolic LV centroid. Diminished contraction and outward motion (relaxation and early filling) of the distal two thirds of the anterior wall, apex, and distal quarter of the inferior wall and left ventricle are shown with hyperfunction of the inferior wall. Asynchrony is not obvious. (B) Individual pattern of contraction and relaxation of each of the 100 radii. Time is shown on the horizontal axis and extent of shortening or contraction is shown on the vertical axis. Frame 1 shows the first radius of the inferior wall and 1 to 100 progresses anticlockwise to the proximal anterior wall. There is hypercontraction, with prolonged systole of the proximal inferior wall with slight retardation of relaxation (radii 1 to 10); normal contraction with sustained systolic contraction and delayed relaxation in the middle third of the inferior wall (11 to 21); delayed contraction and relaxation of the marginal zone (22 to 36); dyskinesis with delayed contraction of the infarcted zone (37 to 71); hypofunction with delayed contraction of the marginal zones (72 to 88); and normal function with delayed relaxation of the proximal anterior wall (89 to 100). (C) Three-dimensional representation of the plane of contraction and relaxation of the ventricle. The contraction and relaxation pattern of B is shown in the X-Y-Z axes. There is a steep zone of hypercontraction, with a peaked ridge, and then a distal but delayed slope of relaxation of the proximal inferior zone; then a delayed, more gradual slope of late relaxation of the marginal inferior zone, a steep cliff approaching an undulating plain with a depression, and late ridges of contraction in the infarcted area; and then delayed relaxation of the proximal anterior wall. The dotted line along the central ridge shows end-systole. (D) The plane of ventricular motion in C as a contour map. There is a steep ridge of hypercontraction at the left, falling to an undulating plain of noncontraction in the center with valleys of dyskinesis and hills of delayed contraction in the proximal anterior wall. The scale at the far right shows frame number. The numbers at the edge of the rectangle are the isocontour lines of equicontraction. (From Gotsman, M. S., Welber, S., Sapoznikov, D., Freiman, I., Rosenman, D., and Lotan, C., *Cardiology*, 73, 22, 1986. With permission.)

time epochs — from the onset of pain to the administration of the thrombolytic therapy and the time for the biochemical reaction of thrombolysis to achieve sufficient reperfusion to decrease or abolish chest pain.

Some of the patients treated early still had important infarcts. When we examined the residual stenosis in the infarct-related coronary artery, it was evident that residual stenosis of more than 75% was important in reducing blood flow, so that patients treated early who were left with residual stenosis (and an inadequate blood flow) developed a large infarct. In patients treated in under 2 h, residual stenosis of less than 75% in the infarct-related coronary artery was associated with a small infarct, whereas those with more severe stenosis had large infarcts. All patients treated later had large infarcts (Figure 10).

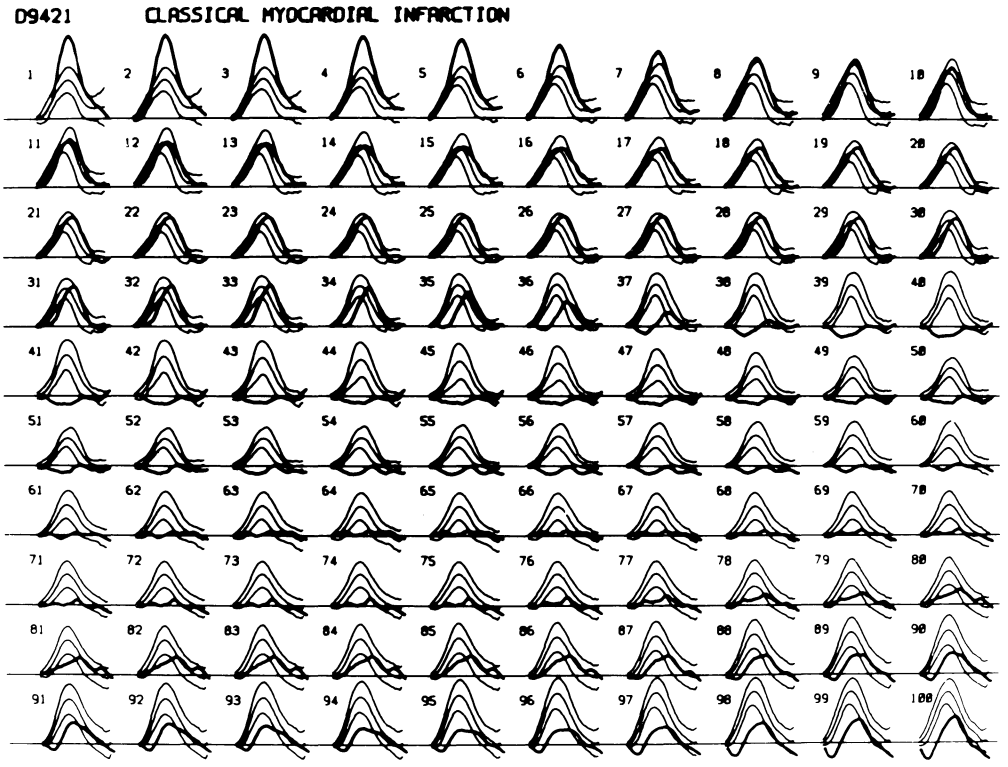


FIGURE 3B.

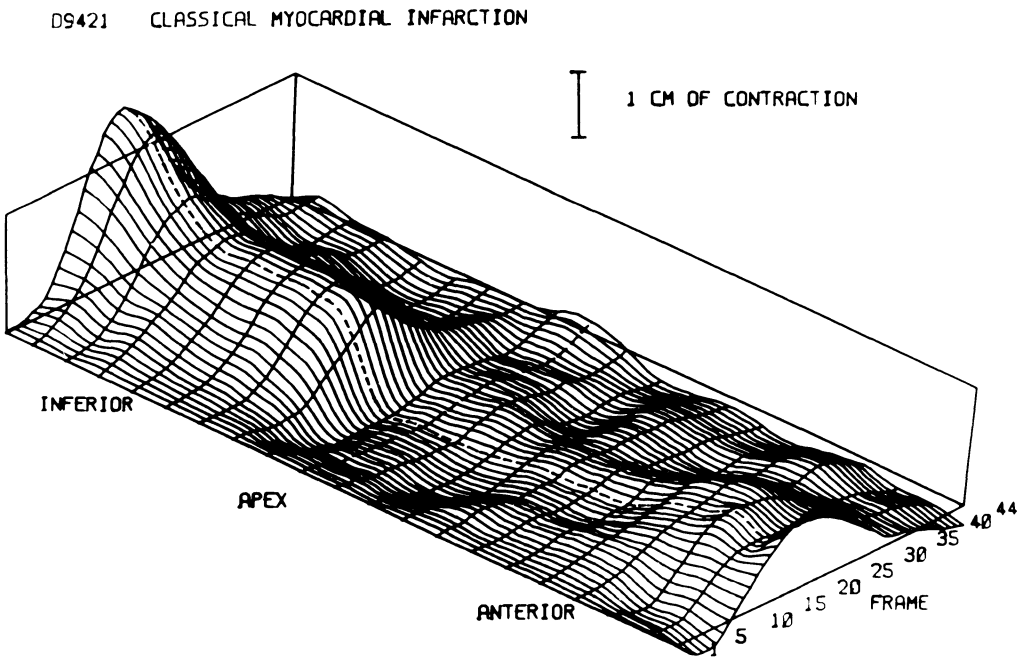


FIGURE 3C.

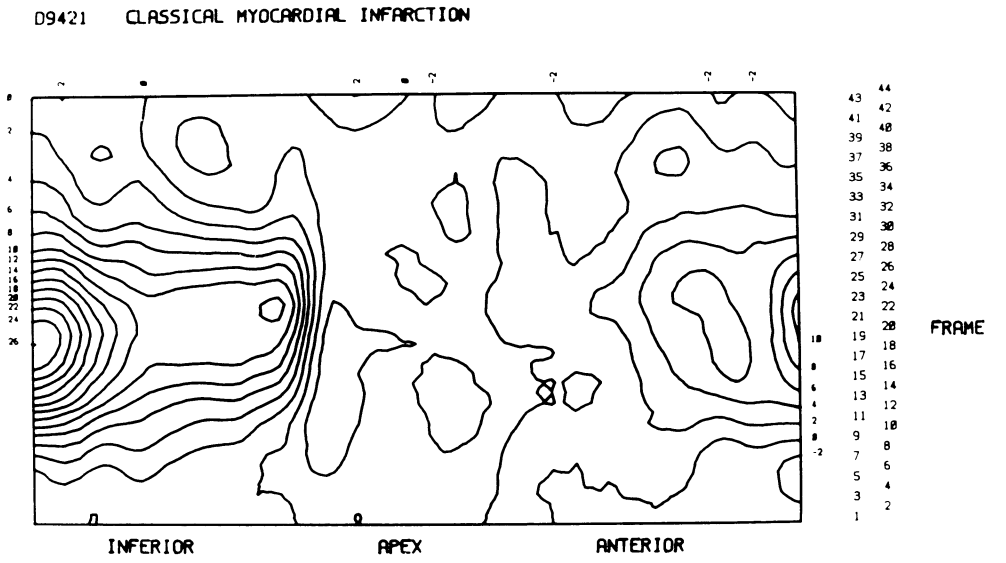


FIGURE 3D.

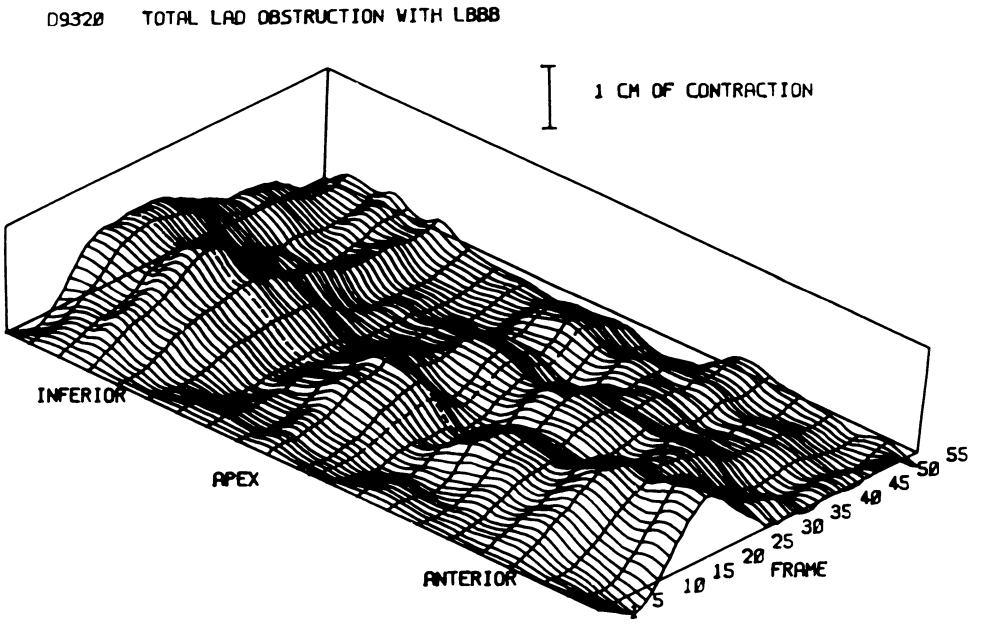
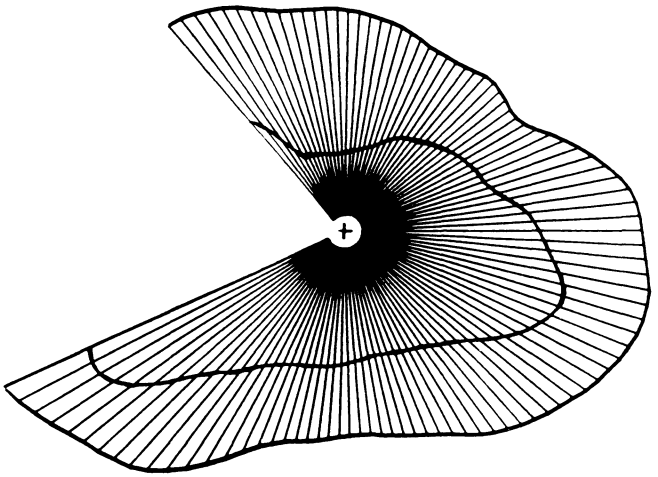


FIGURE 4. Total LAD coronary artery obstruction with anterior wall infarction and left bundle branch block. This shows the three-dimensional plane of contraction of the left ventricle. Central plane of the infarcted area with striking undulations in late systole and diastole, after contractions and delayed relaxation. (From Gotsman, M. S., Welber, S., Sapoznikov, D., Freiman, I., Rosenman, D., and Lotan, C., *Cardiology*, 73, 22, 1986. With permission.)



A

FIGURE 5. (A) Method of calculating the dysfunction index. The end-diastolic and end-systolic frames are superimposed after correcting the translation motion. Equiangular radii (100) are drawn from the center of the ventricle as shown, and the end-diastolic length and end-systolic length of each radius are measured. The shortening fraction of each radius is calculated as shortening fraction = end-diastolic length minus end-systolic length ÷ end-diastolic length. (B) Method of calculating the dysfunction index. The graph shows radius number on the horizontal axis and shortening fraction on the vertical axis. The mean and SD of the normal subjects are shown. The shortening fraction of the patient is superimposed. This shows a patient with a classical anterior myocardial infarction and the hatched area shows the dysfunction index which represents the size of the infarct and is the area of shortening fraction below 1 SD of the normal population.

IV. IMPLICATIONS OF THE STUDY

Coronary artery narrowing impairs myocardial blood flow and the effect depends on the local anatomy of the artery and its branches, the site of the lesion, the suddenness of narrowing or complete occlusion, and the extent and development of the collateral circulation and its physiological effectiveness.[10,11] Thus, there may be impaired flow to a region which causes ischemia, during stress or even at rest, or complete cessation of flow without adequately functioning collaterals, causing necrosis.

This study shows that ischemia or necrosis and fibrosis is associated with defective spatial contraction and also delayed contraction with asynchrony. Asynchrony is more marked in the presence of left bundle branch block. It confirmed our previous studies[12-19] and others made by Gibson,[20-23] Weyman,[24,25] and others.[26]

Acute myocardial infarction is associated with total obstruction of the LAD coronary artery, but spontaneous fibrinolysis may leave only a 95% narrowing of the artery.[4] In these patients, recanalization is too late to prevent myocardial infarction. Similar results were obtained in our intracoronary streptokinase patients, where treatment was given too late.

The use of intravenous streptokinase to lyse the offending thrombus has shown that in lesions of the LAD coronary artery, infarction is a time-dependent process and confirms numerous other studies in the literature.[27-31] A total ischemia time of 3 $^{1}/_{2}$ h (or 2 h from pain onset to the onset of treatment) is the critical time domain for myocardial salvage, but even if reperfusion is achieved early, residual stenosis of the infarct-related coronary prevents adequate reperfusion and is responsible for important infarction.[32,33] Contrast angiography with measurement of a computer interactive dysfunction index is a simple, reliable, and repeatable technique of assessing left ventricular dysfunction.

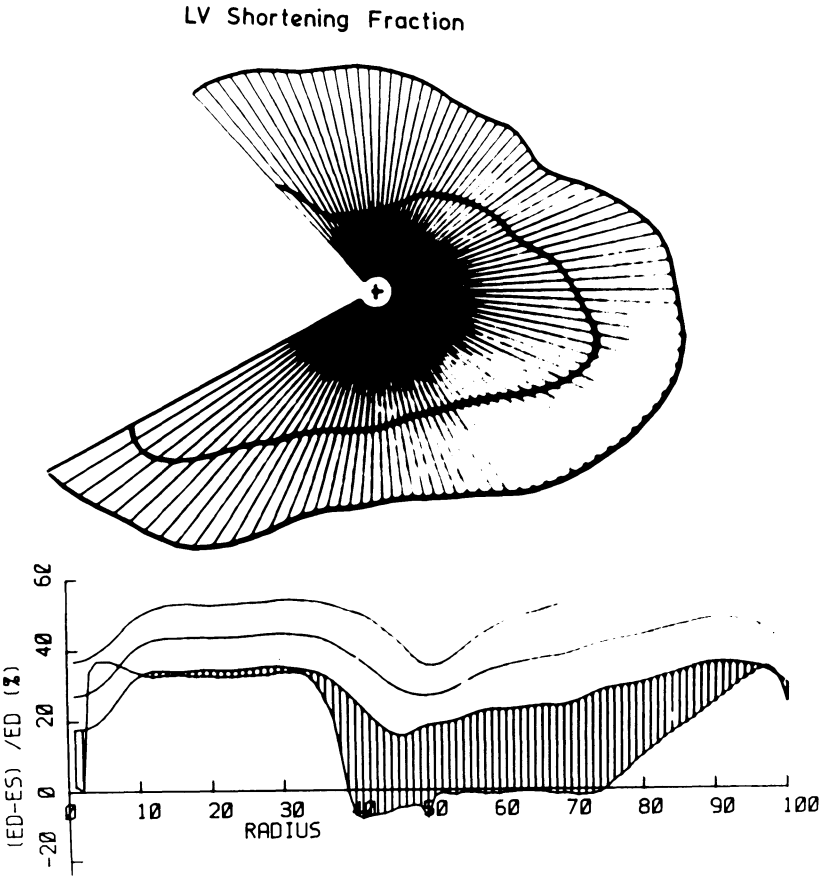


FIGURE 5B.

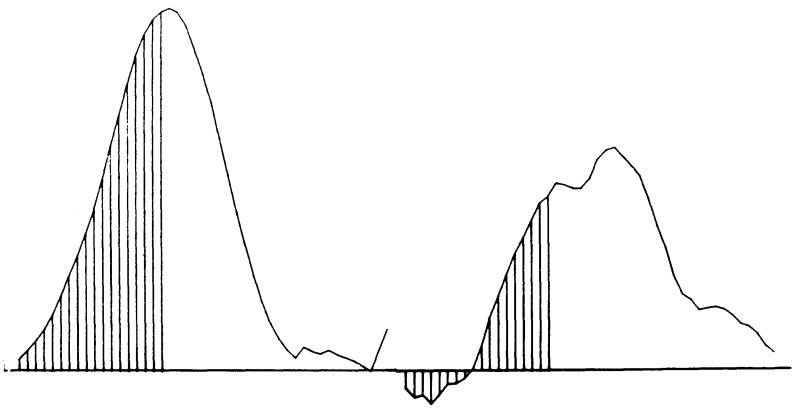


FIGURE 6. Method of measuring defective time-shortening integral taking into account the defective and delayed contraction. The curve on the left shows a radial contraction curve of a normal subject, and the curve on the right shows the contraction curve of a patient with decreased and delayed contraction. The shortening fraction ratio is the hatched area of the radial time contraction integral in the second curve divided by the hatched area in the first curve. (From Sapoznikov, D., Welber, S., Lotan, C., Mosseri, M., Shimoni, Y., and Gotsman, M. S., *Cardiology*, 74, 444, 1987. With permission.)

Table 1
CORRELATIONS WITH DYSFUNCTION INDEX[a]

	All patients			First anterior infarct			First inferior infarct		
	No.	R	*p*	No.	R	*p*	No.	R	*p*
GEF	166	0.87	<0.001	65	0.91	<0.001	68	0.79	<0.001
IRREF	165	0.76	<0.001	64	0.90	<0.001	68	0.68	<0.001
SCORE	151	0.46	<0.001	58	0.36	<0.01	62	0.20	NS

[a] GEF, global ejection fraction; IRREF, infarct-related regional ejection fraction; SCORE, QRS score;[34] No., number of patients; R, correlation coefficient; *p*, statistical significance (from linear regression analysis); NS, not significant.

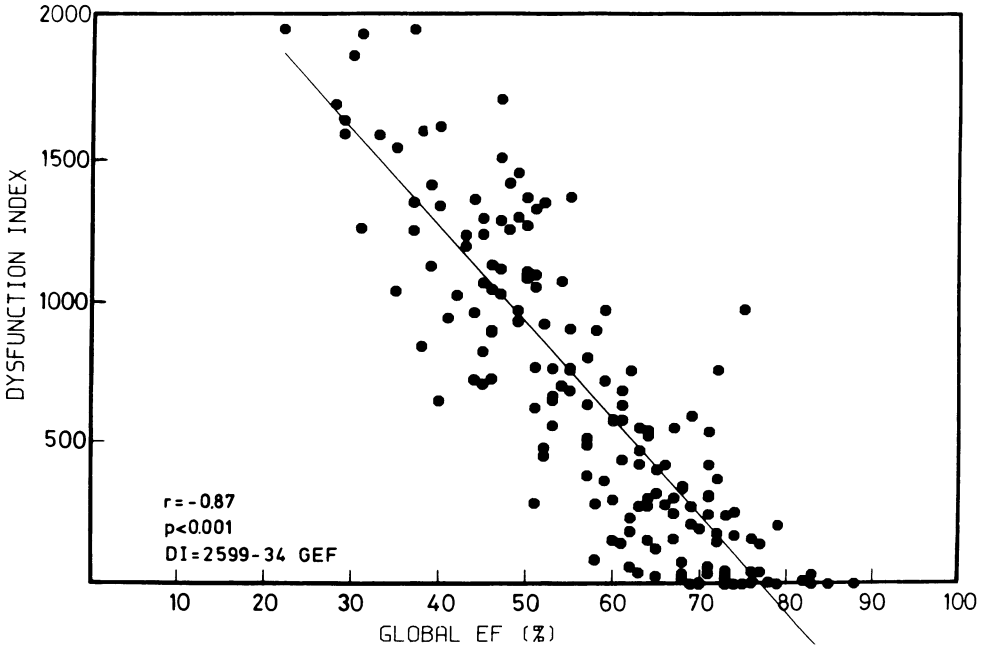


FIGURE 7. Comparison of dysfunction index with global ejection fraction in 171 patients after thrombolysis.

Table 2
INFLUENCE OF PAIN DURATION UNTIL STREPTOKINASE INFUSION ON INFARCT SIZE[a]

	First anterior infarction and patent artery			
Time to STK (h)	0—1	1—2	2—3	3—4
Number of patients	20	21	17	7
Age	55 ± 9	61 ± 10	60 ± 11	51 ± 15
QRS score	5.8 ± 3.1	6.7 ± 4.3	10.5 ± 5.0	8.1 ± 4.6
LVEF	59 ± 10	57 ± 15	48 ± 15	53 ± 8
IRREF	56 ± 20	49 ± 23	35 ± 21	48 ± 15
DI	604 ± 502	716 ± 584	1006 ± 504	815 ± 456
CPKr	1198 ± 900	2042 ± 1797	2592 ± 973	1399 ± 922

[a] STK, streptokinase; QRS score, EKG scoring; LVEF, left ventricular ejection fraction; IRREF, infarct-related regional ejection fraction; DI, dysfunction index; CPKr, cumulative CPK release.

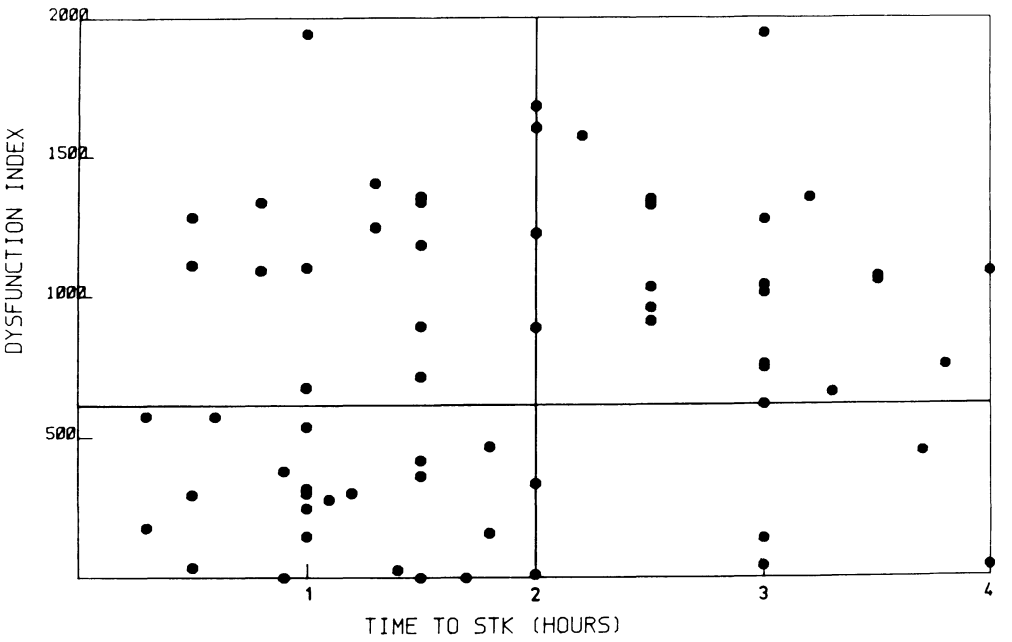


FIGURE 8. Comparison of dysfunction index with time from onset of pain to streptokinase administration. Two thirds of patients given streptokinase in less than 2 h have small infarcts, whereas nearly all those who received streptokinase after 2 h had large infarcts.

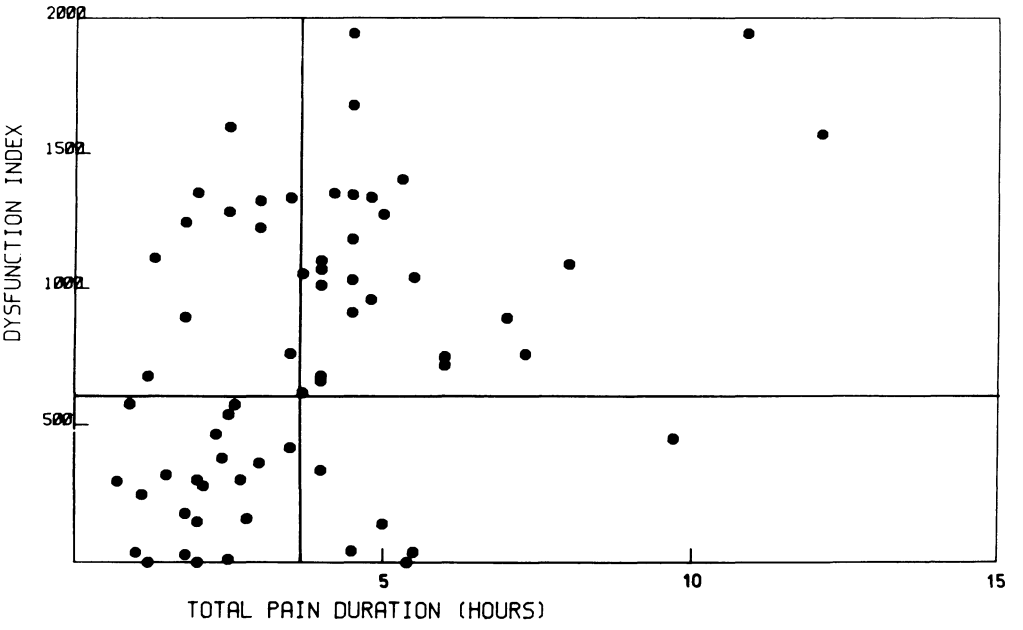


FIGURE 9. Comparison between dysfunction index and total duration of pain. The critical time interval between small and large infarcts is $3^1/_2$ h.

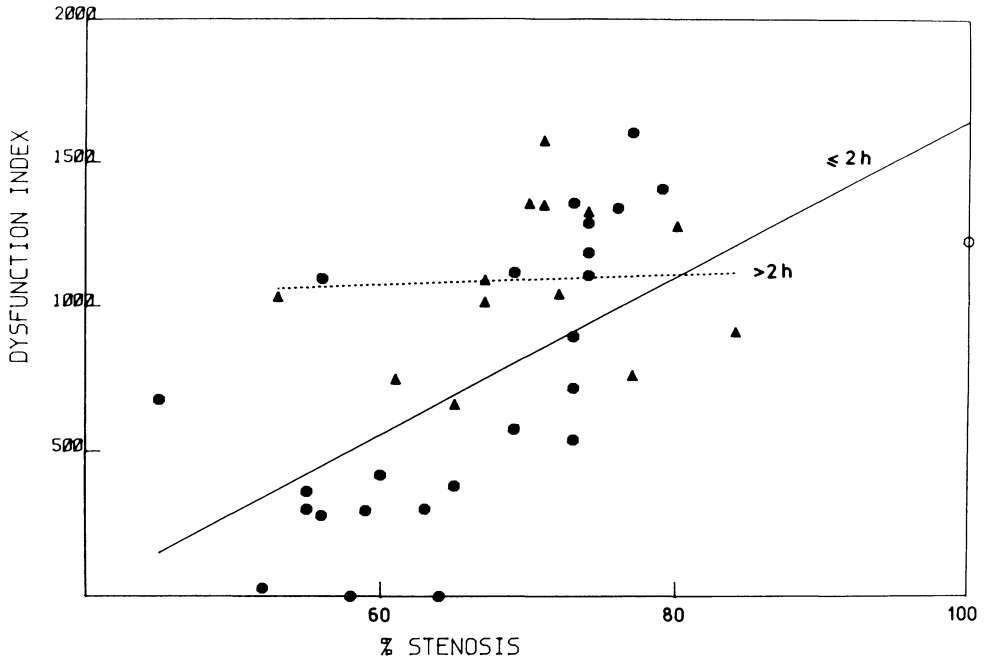


FIGURE 10. Relationship of infarct size to residual stenosis in the infarct-related coronary artery. Patients treated in under 2 h are represented as circles; the regression line as a solid line. Patients treated after 2 h are shown as triangles. In patients treated in less than 2 h, there is a simple linear relationship between infarct size and the degree of residual stenosis of the infarct related coronary artery. All the patients treated after 2 h had a large infarct. There is no relationship between the infarct size and the degree of residual stenosis in the infarct-related coronary artery.

V. DISCUSSION

Dr. Dinnar: I understand that you defined the center point in the fully dialated stage of the left ventricle. How stable is this point if you repeat the same procedure throughout the cycle? What is the deviation of the center as it moves through the cycle?

Dr. Gotsman: A lot depends upon how you measure this motion. If you measure it in centimeters it is very small. I believe it is in the order of about 0.25 cm between points of measurements.

Dr. Dinnar: Some of the pictures you have shown are at end-systole. The center would have moved significantly. Do you take the line at end-systole? Do you draw it between the center and the apex? How much does the new line shift from the center line at the end-diastole?

Dr. Gotsman: I cannot give you the exact numbers because it is very difficult to know what frame of reference one uses. We have looked at the repeatability of the technique and either between the same observer measured twice or between two observers, it is less than about 2%.

Dr. Beyar: You showed an interesting observation that when you put a patient on an intra-aortic balloon pump, you get an improvement in the regional function of the border zone. Is it due to the unloading of the function of the ventricle or is it due to an increase in coronary flow to the border zone?

Dr. Gotsman: I do not think that I can give you an exact answer to this question because these factors, both, are operative. I would think it is mainly due to the increased unloading. But whatever you are doing, you are decreasing oxygen consumption either in the infarced area or in the surrounding area. But we have seen that in some conditions the area does not improve. In other words, the muscle is dead and is functionless.

Dr. Sideman: How long does it take to do one of these invasive angiograms and to get the data?

Dr. Gotsman: We have a trained technician who outlines the angiogram. We take it from a projector, put it through a television camera. We have a frame grabber in the computer and we can analyze 30 frames quite quickly. The operator simply takes a joy stick around the edges. It takes an hour to record and analyze the data.

Dr. Beyar: Was the improvement immediate after the PTCA?

Dr. Gotsman: We made three measurements. The first one was immediately after thrombolysis, the second was some 3 months later when we found that the patient had residual stenosis. We then made a PTCA and the third catheterization was 3 months after the PTCA.

Dr. Sideman: Have you looked at the right ventricle?

Dr. Gotsman: We have looked at the right ventricle in these patients where nuclear angiograms in the right ventricle were needed and we found that all the patients with right coronary artery lesions have a low ejection fraction in the right ventricle, irrespective of the function of the left ventricle. In other words, for some reason, even if we open the artery early we do not prevent right ventricular infarction.

Dr. Sideman: The inferior infarction looked smaller than the anterior infarction. Is that because the damage is distributed? Is it smaller?

Dr. Gotsman: We have two separate issues here. The area of the left ventricle supplied by the right coronary artery is smaller, therefore the infarct is a smaller one than of the left coronary artery. This also means that you have less salvage in the right coronary artery. In inferior infarct there is a smaller area to salvage and many people have suggested that one should not be salvaging them at all because of the danger of giving thrombolytic therapy. On the other hand, many of the patients with inferior infarction have a large right ventricular infarct. This we seem to have prevented with our thrombolytic therapy. We have a group of patients whom we studied much later. The right ventricle does not appear to improve very much.

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Chapter 2

ELECTRICAL AND MECHANICAL MAPPING OF THE LEFT VENTRICULAR FREE WALL DURING NORMOXIA AND REGIONAL MYOCARDIAL ISCHEMIA — THE EFFECT OF ELECTRICAL STIMULATION

Robert S. Reneman, Maurits A. Allessie, Theo Arts, Cornelis H. Augustijn, Henny M. Leerssen, and Frits W. Prinzen

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I. INTRODUCTION

Although left ventricular pump function is assumed to be rather effective under normoxic circumstances, relatively little is known about the degree of synchronization of contraction of the various areas of the left ventricle. Especially when the heart is electrically stimulated from different sites in the right or left ventricle, nonsynchronous electrical activation of the left ventricle and, hence, inhomogeneities in myocardial contraction may be anticipated. During myocardial ischemia, detailed information about the functional interaction between healthy and diseased tissue is lacking. The functional interaction between normoxic and ischemic tissue can be adequately investigated only when the electrical activation of the left ventricle, which is likely to be disturbed under these circumstances, is considered.

To be able to study the relation between the time sequence of electrical activation and myocardial contraction of the left ventricular free wall in detail, the use of methods to assess both electrical and mechanical activity simultaneously in various regions is required. In this chapter, the preliminary results of a study on this relation during normoxia and ischemia, using systems for mapping electrical activation[1] and myocardial contraction,[7] are reported.

II. EPICARDIAL MAPPING OF ELECTRICAL ACTIVATION OF THE LEFT VENTRICLE

To obtain a detailed map of the sequence of electrical activation, 192 extracellular recordings are made with the use of a brush applied to the epicardium of the left ventricle.[10] The brush consists of unipolar silver electrodes. Time-dependent potential distributions at the epicardial surface are made with a mapping system described in detail before.[1] A block diagram of all the essential components of the mapping system is depicted in Figure 1. The top part depicts the recording system and the bottom part shows how the data are played back for off-line analysis. For recording, 192 differential amplifiers with a filter setting of 2 to 400 Hz are used. The amplifiers are equipped with an autoranging facility that allows automatic setting of the amplification for each individual amplifier. This feature not only makes possible the operation of as many as 192 amplifiers, but also results in an optimal signal-to-noise ratio of the recorded electrograms. In the present study, a fixed amplification setting was used to obtain information about the amplitude of the signal. This was possible because the amplitude of the electrical signals recorded was rather similar. After amplification, the 192 signals are fed into three identical multiplexers (Kayser 1280-00) receiving 64 analogue inputs each. The electrograms are sampled with a sampling rate of 2000 samples per second and digitized with 8-bit resolution. After pulse-code modulation (Miller code) the outputs of the three multiplexers are recorded in 3 tracks of an analogue tape recorder (Ampex® PR 2230) running at 60 in./s. Except for the 64 analogue inputs, the multiplexers also receive 4 separate digital inputs. These extra channels are used to mix a digital time code (resolution 1 msec) with the analogue data. By this direct coupling of an accurate time reference with the recorded electrograms, possible errors, as caused by variations in speed of the tape recorder, are avoided. Additional tracks of the tape are used to record a conventional slow time code (Systron Donner®), one or two separate reference signals, and a voice log. The bottom part of Figure 1 shows two different ways for reproducing the stored information. For conventional readout, the data are demultiplexed (Kayser 1280-10) and displayed on an oscilloscope (Tektronix® 5103N) or a physiological recorder (Schwarzer). For computer analysis (PDP® 11/04 and 11/73), the information is directly transferred to a direct memory access interface (DR11B) and stored on disk. A DEC® VT 240 is used for system communication and graphic output. Software has been developed to search the electrograms for the intrinsic deflections and to plot the set of activation times as isochronic maps.

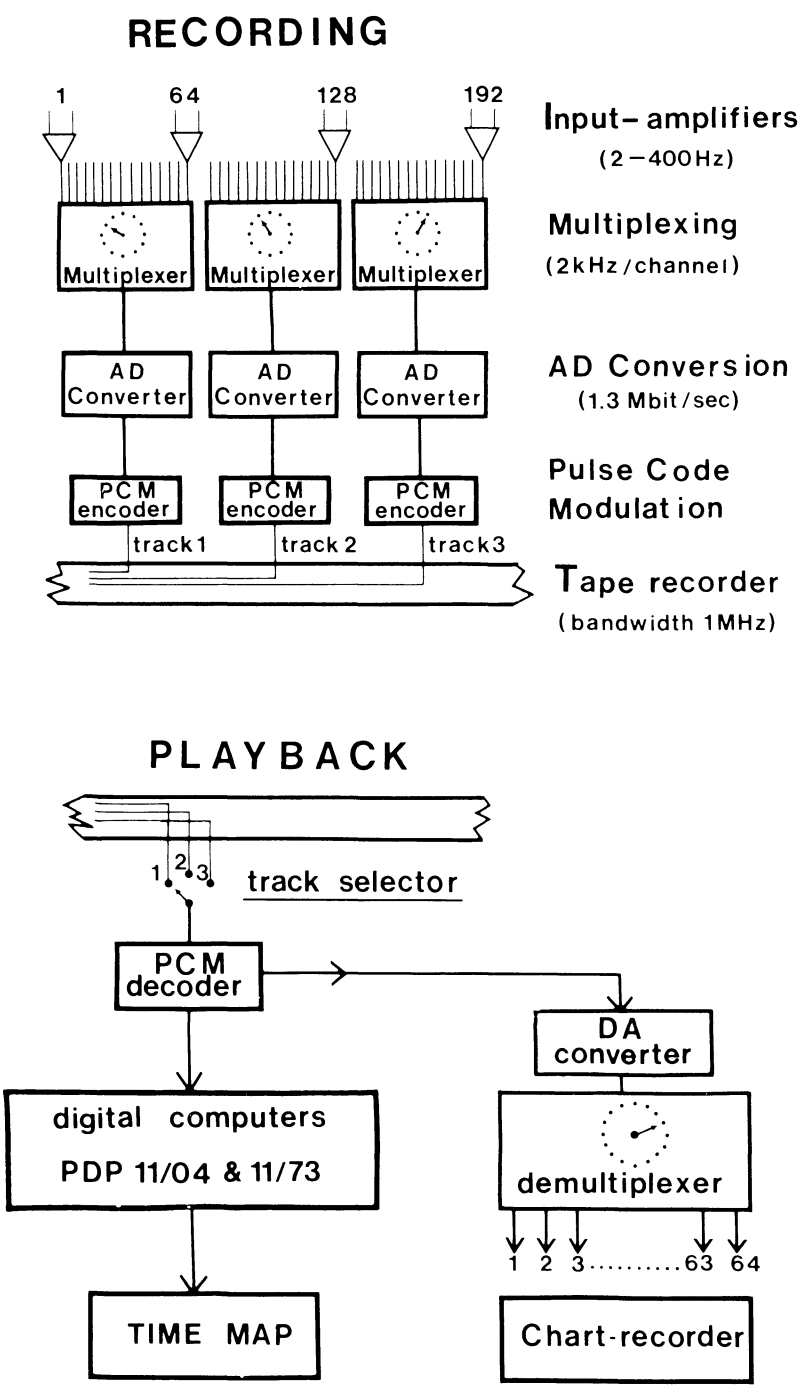

FIGURE 1. Block diagram of the system to map the time-dependent potential distributions at the epicardial surface of the left ventricle. (Top) Recording system; (bottom) two alternative ways for playback and off-line analysis.

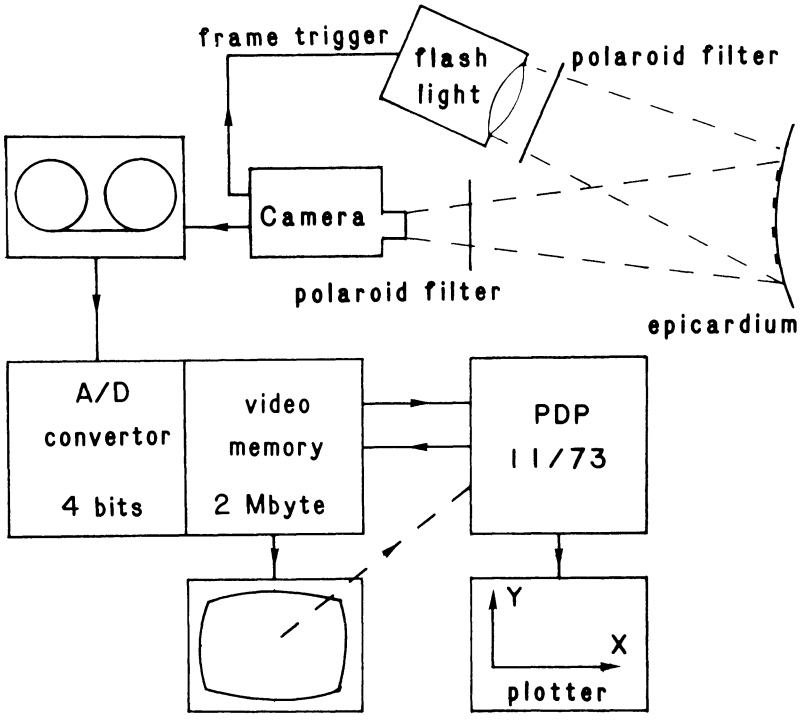

FIGURE 2. Block diagram of the recording and processing system for the measurement of epicardial deformation of the left ventricle, using video techniques. Visual inspection by the operator is indicated by a dashed arrow.

III. EPICARDIAL MAPPING OF MECHANICAL CONTRACTION OF THE LEFT VENTRICLE

Epicardial fiber shortening can be assessed[6] from the epicardial deformation parameters circumferential shortening, base-to-apex shortening, and shear deformation which is associated with torsion of the left ventricle around the base-to-apex axis.[2] These deformation parameters can be determined locally by assessing the mutual displacement of a triplet of markers. In the mapping system in use in our laboratories,[7] the motion of white markers (1.5 mm in diameter), attached to the epicardium with histoacryl glue at distances of 5 to 7 mm, is recorded by means of a video camera similar to methods used in gait analysis[8] or to measure strains in cat knee joint capsule.[3] The motion of the markers is recorded at a distance of 2.5 m through a mirror mounted above the heart at an angle of 45° and using a 200-mm teleobjective. One marker is made larger so that it can be used as a reference in all frames. A physiological signal (ECG or the left ventricular pressure or aortic flow tracing) is recorded on one of the audio channels for synchronization with the electrical data. A total of 40 to 60 markers is placed randomly on the surface of the anterior left ventricular wall covering an area of 10 to 15 cm^2. To avoid blurring, due to heart motion during the exposure time, the heart is illuminated by a xenon-flash light, triggered by the 50-Hz video frame pulse. The light beam is directed almost parallel to the camera axis. Unwanted strong reflections of the wet surface of the heart are eliminated by two perpendicularly oriented polaroid filters, one between the light source and the heart and the other between the heart and the camera. After storage on tape, marker positions and displacements are determined by off-line analysis of the video images in a highly automated way. A block diagram of the measuring setup and the data processing sequence is shown in Figure 2.

After the experiments, the analogue video data, as obtained from the video recorder, are digitized by a four-bit analogue-to-digital converter at a sample rate of 5 MHz. From each 20-ms frame, a segment of 256 × 256 pixels is stored in the Digital Video Memory designed and built in our laboratories. The 2-Mbyte memory of the Digital Video Memory allows the storage of 64 consecutive frames, representing 1280 ms video recording time. In the digitized video frames, the physiological signal is visible in the upper left corner. From the Digital Video Memory, the video data are transferred to a computer (PDP 11/73). Markers are distinguished from the background by applying a suitable grey-level threshold, and the pixels exceeding the threshold are displayed on a monitor. If necessary, the threshold is adjusted. A suitable threshold has been found to be about three times the standard deviation above the mean grey level of the image. Pixels exceeding the threshold and mutually bordering are grouped in subsets. A subset is recognized as a marker if the number of pixels in the subset exceeds a chosen minimal value. The position of the marker is calculated as the center of gravity of the subset, which is depicted as a black pixel in the original video image. After inspection of the resulting marker positions, the minimal number of pixels per subset can be adjusted by the operator. A special program has been developed to trace the markers from frame to frame.[7] To calculate fiber shortening in the epicardial fiber direction, this direction, as assessed in each experiment, is fed into the computer.

We limited ourselves to a two-dimensional analysis of epicardial deformation by using only one camera and assuming the epicardial surface to be perpendicular to the optical axis. This simplification is acceptable because of the long distance between the camera and the heart and the relatively small area under observation.[7] Occasionally, however, measurements near the margin of this area are inaccurate due to curvature effects.

IV. THE RELATION BETWEEN ELECTRICAL ACTIVATION AND FIBER SHORTENING AT THE EPICARDIUM IN THE OPEN-CHEST DOG

A. Experimental Setup and Procedure

The experiments were performed on mongrel dogs of either sex and unknown age, ranging in weight from 25 to 34 kg. The dogs were premedicated with Hypnorm (1 ml/kg^{-1} i.m.; 1 ml of Hypnorm contains 10 mg of fluanison and 0.2 mg of fentanyl base). Anesthesia was induced with pentobarbital sodium (10 mg/kg^{-1} i.v.) and, after endotracheal intubation, was maintained with O_2/NO_2 and a continuous infusion of pentobarbital sodium (2 mg/kg^{-1}/min^{-2}). Ventilation was kept constant with a positive pressure respirator (Pulmonat). The chest was opened through the left fifth intercostal space and the heart was suspended in a pericardial cradle. The ECG was derived from limb leads. Left ventricular and aortic pressure were measured with catheter-tip micromanometers (Millar). To assess the onset and end of the ejection period, phasic ascending aortic flow was measured with a sine-wave electromagnetic flowmeter (Skalar). Corrections were made for the position of the probe and the delay of the electronic circuit.[9] The white markers (40 to 60) were randomly attached to the epicardium of the anterior left ventricular free wall, including the area expected to become ischemic when narrowing the left anterior interventricular coronary artery (LAICA; see below). Bipolar platinum stimulation electrodes were placed on the right atrium, the right ventricular outflow tract, and the apex of the left ventricle. A polyethylene catheter was inserted into a small side branch of the LAICA for the measurement of blood pressure distal to the stenosis, which was induced by inflating a cuff placed on this artery just distal to the diagonal branch. The cuff was connected to a micrometer so that the cuff could be inflated carefully until the desired degree of stenosis was reached (mean poststenotic coronary artery pressure: approximately 4.0 kPa). This degree of stenosis was maintained throughout the experimental period using a servomotor pump controlled by the mean coronary artery pressure distal to the cuff.[4,5] In this way, electrical and mechanical maps could be made during

regional low-flow ischemia. The ECG and the hemodynamic variables, except for the mapping results, were recorded on an oscilloscope (Knott), a physiological recorder (Schwarzer), and a multichannel tape recorder together with the electrical signals.

After a recorded control period, the brush with 192 electrodes was placed on the left ventricular free wall and electrical activation was recorded during a series of sinus beats. Immediately thereafter the movement of the white markers was recorded during a series of sinus beats under identical hemodynamic circumstances, as far as left ventricular, aortic, and coronary artery pressure and ascending aortic blood flow are concerned. The sinus node area was frozen with a cryoprobe to lower heart rate and the heart was continuously paced from the right atrium at a rate of 100 beats per minute. Thereafter the heart was sequentially activated from each stimulation site. When stimulated from the various positions, electrical activation and movement of the markers on the left ventricle were recorded as during the sinus beats. Then part of the anterior left ventricular wall was made ischemic by inflating the cuff on the LAICA (see above), and electrical and mechanical mapping was performed at an interval of 1 min. The electrical and mechanical maps, as shown during myocardial ischemia, were recorded 150 min after induction of the LAICA stenosis. The electrical and mechanical maps were made off-line. Local deformation was determined by assessing the mutual motion of at least three markers. In the maps, strain ($\Delta l/l$) is presented, using end-diastolic epicardial fiber length as a reference. The start of the R wave of the ECG or the stimulation artifact was used as a reference (time = 0) when comparing the electrical and mechanical maps.

B. Results and Comments

In this preliminary report, electrical and mechanical maps, as obtained under identical experimental conditions during normoxia or ischemia, are shown. Electrical stimulation of the heart was limited to pacing from the right ventricular outflow tract and the left ventricular apex.

1. Normoxia

An example of epicardial activation during normal sinus rhythm is shown in Figure 3. In this example, epicardial breakthrough is seen near the apex and near the base on the side of the LAICA. The remainder of the anterior part of the left ventricular free wall is activated only slightly later (about 5 to 7 ms) in a rather homogeneous way. Epicardial fiber strain decreases (which means fiber shortening) during the isovolumic phase of contraction about simultaneously in all areas recorded during a sinus beat (Figure 3). The extent of fiber shortening is rather homogeneous over the anterior aspect of the left ventricular free wall. The epicardial fiber shortening in all areas of the anterior part of the left ventricular free wall during isovolumic contraction implies that the epicardial fibers in other regions of the left ventricle have to be stretched during this phase of the cardiac cycle. A possible candidate is the posterior wall of the left ventricle which is activated later during normal sinus rhythm. Except for the regions toward the left marginal branch, fiber shortening stops and relaxation starts at the end of the ejection phase. The mechanism responsible for the prolonged fiber shortening near the left marginal branch during the relaxation phase is incompletely understood.

When the heart is electrically stimulated from the right ventricular outflow tract, the epicardium of the anterior left ventricular wall is activated from the base near the LAICA to the apex in the vicinity of the left marginal branch, closely following the epicardial fiber direction (Figure 4). The delay between activation of the base and the apex is about 50 ms, an activation pattern less synchronous than that during a sinus beat. This less synchronous activation pattern is associated with a pattern of epicardial fiber shortening different from that observed during a sinus beat (Figure 4). Although epicardial fiber shortening starts

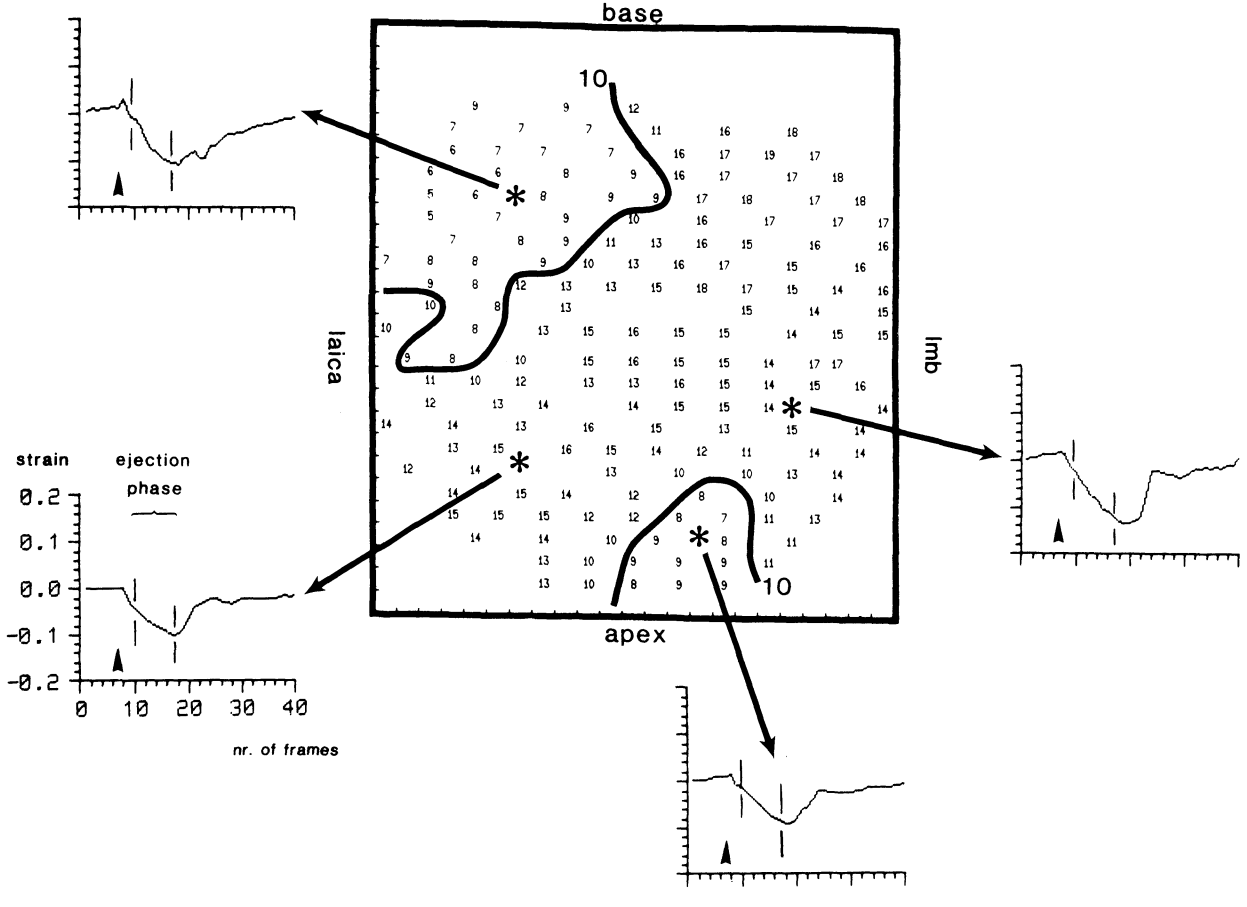

FIGURE 3. The time sequence of electrical activation and the pattern of fiber shortening (i.e., a decrease in strain) at the normoxic epicardium of the anterior left ventricular wall during a sinus beat. Each frame represents 20 ms. The arrowhead indicates the start of the R wave of the ECG; lacia, left interventricular coronary artery; lmb, left marginal branch.

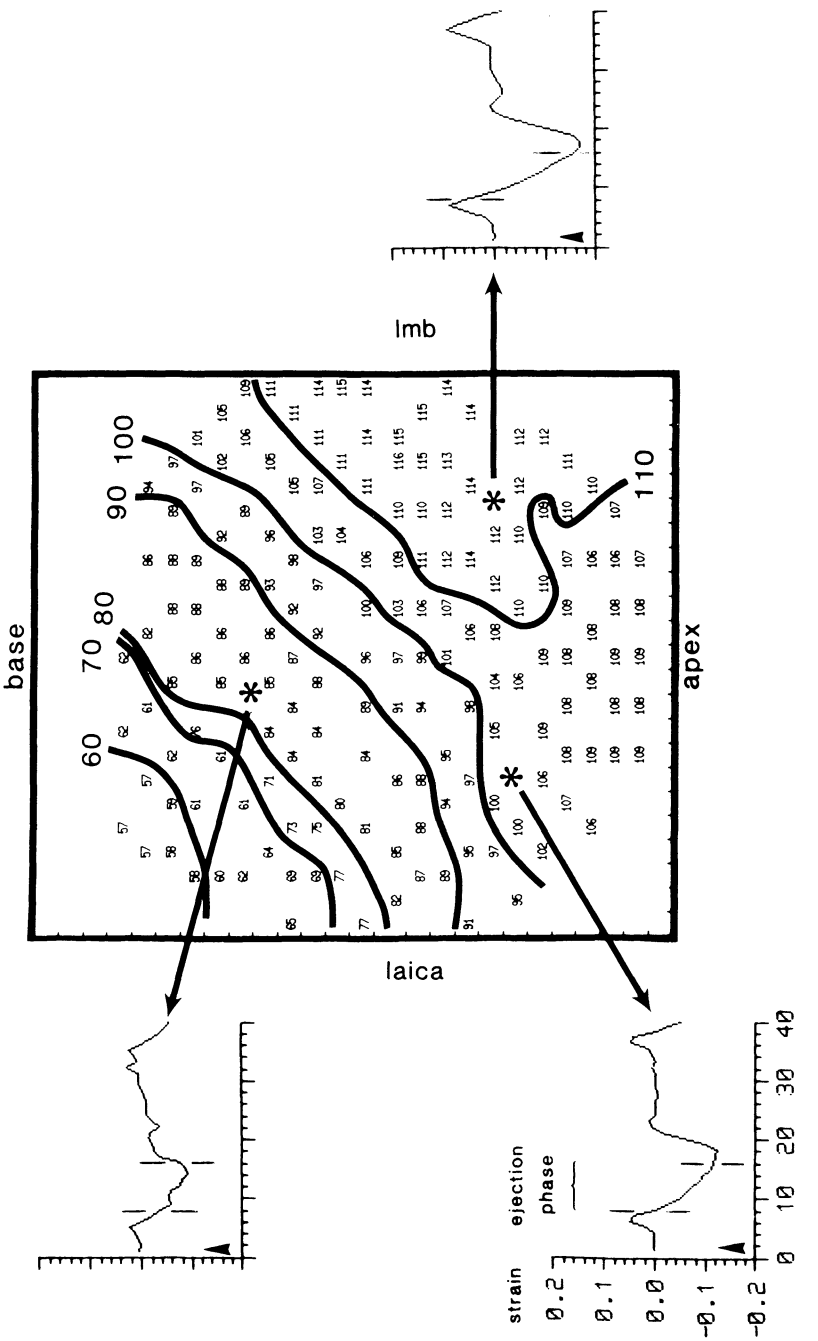

FIGURE 4. The time sequence of electrical activation and the pattern of fiber shortening (i.e., a decrease in strain) at the normoxic epicardium of the anterior left ventricular wall, when the heart is electrically stimulated from the right ventricular outflow tract. Each frame represents 20 ms. The arrowhead indicates the start of the stimulation artifact; laica, left interventricular coronary artery; lmb, left marginal branch.

during isovolumic contraction in most areas of the anterior left ventricular wall, the shortening is preceded by a short period of stretching, which is most pronounced in duration and extent toward the apex and the left marginal branch. The fibers in this area, which is activated relatively late, are stretched due to contraction of earlier activated parts of the left ventricle. The finding that the epicardial fibers of the anterior left ventricular wall stretch during the isovolumic phase can be explained by early contraction of the septum which under these circumstances is electrically activated before the anterior wall. At the anterior left ventricular wall, the extent of epicardial fiber shortening during the ejection phase is inhomogeneous; fiber shortening tends to be most pronounced in areas with the largest stretch in the isovolumic phase of contraction. This is in agreement with the fact that muscle contraction is more vigorous at a greater initial length.

When the heart is electrically stimulated at the left ventricular apex, the anterior left ventricular wall is activated from apex to base with a total delay of about 40 ms (Figure 5). Epicardial fiber shortening starts during the isovolumic phase in the areas near the apex and left marginal branch (Figure 5). Fiber shortening starts later in the other areas and is generally preceded by fiber stretching, which is most pronounced in the vicinity of the base and LAICA. When all fibers on the anterior left ventricular wall are mechanically activated, epicardial fiber shortening during ejection leveled off in the areas activated first. In these areas, a second phase of fiber shortening was seen during the relaxation period, indicating that in these regions fiber shortening could only continue when the vast majority of left ventricular mass had stopped to contract. During the relaxation phase, a secondary phase of fiber shortening was observed near the base and LAICA. This fiber shortening is incompletely understood, but seems to be a real phenomenon because it is associated with stretching near the apex.

2. Regional Myocardial Ischemia

The electrical and mechanical maps shown are made after 150 min of low-flow ischemia. When stimulated from the right ventricular outflow tract, the left ventricle is activated from the base near the LAICA toward the apex as during normoxia (Figure 6). In the ischemic area, however, the arrival of the activation wave at the apex is delayed by about 20 ms (total delay between base and apex of about 70 ms), as compared with the normoxic situation (Figures 4 and 6). A block area can be seen near the base between the LAICA and the middle of the anterior free wall. As during normoxia in the nonischemic areas, epicardial fiber shortening starts during the isovolumic phase of contraction and is preceded by a short, but less pronounced, period of stretching, especially in the regions near the apex and left marginal branch (Figure 6). Like during normoxia, epicardial fiber shortening during the ejection phase is most pronounced in these regions and in some of them even continues during the relaxation phase. In the central ischemic area, epicardial fibers are stretched during both the isovolumic phase and the ejection phase, occasionally followed by some shortening at the end of ejection and/or during relaxation (Figure 6). The prolonged stretching can be explained by muscle weakness in combination with the relatively late arrival of the electrical pulse.

When under identical circumstances the heart is stimulated from the left ventricular apex, the left ventricle is more homogeneously activated from apex to base with a delay of about 30 ms between these sites (Figure 7). In this situation, the area of conduction block is less pronounced, probably as a result of breakthrough of the activation wave from deeper layers of the left ventricle. As a consequence, the start of epicardial fiber shortening in the normoxic area is more homogeneous under these circumstances with only a slight delay between apex and base (Figure 7). Over the normoxic part of the left ventricle, epicardial fiber shortening during ejection is also rather homogeneously distributed, but in several areas, especially near the apex and left marginal branch, the shortening is less pronounced than when the

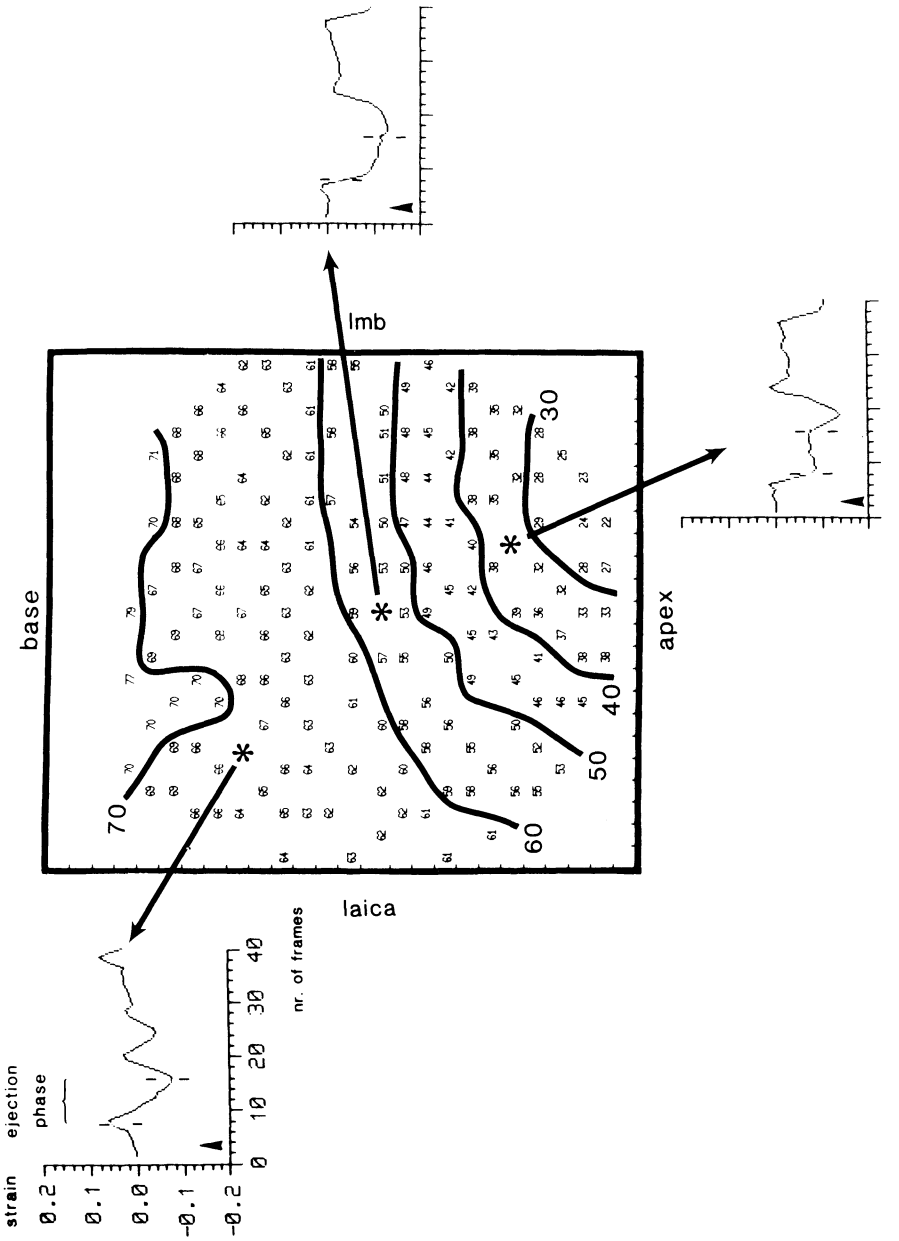

FIGURE 5. The time sequence of electrical activation and the pattern of fiber shortening (i.e., a decrease in strain) at the normoxic epicardium of the anterior left ventricular wall, when the heart is electrically stimulated from the left ventricular apex. Each frame represents 20 ms. The arrowhead indicates the start of the stimulation artifact; lacia, left interventricular coronary artery; lmb, left marginal branch.

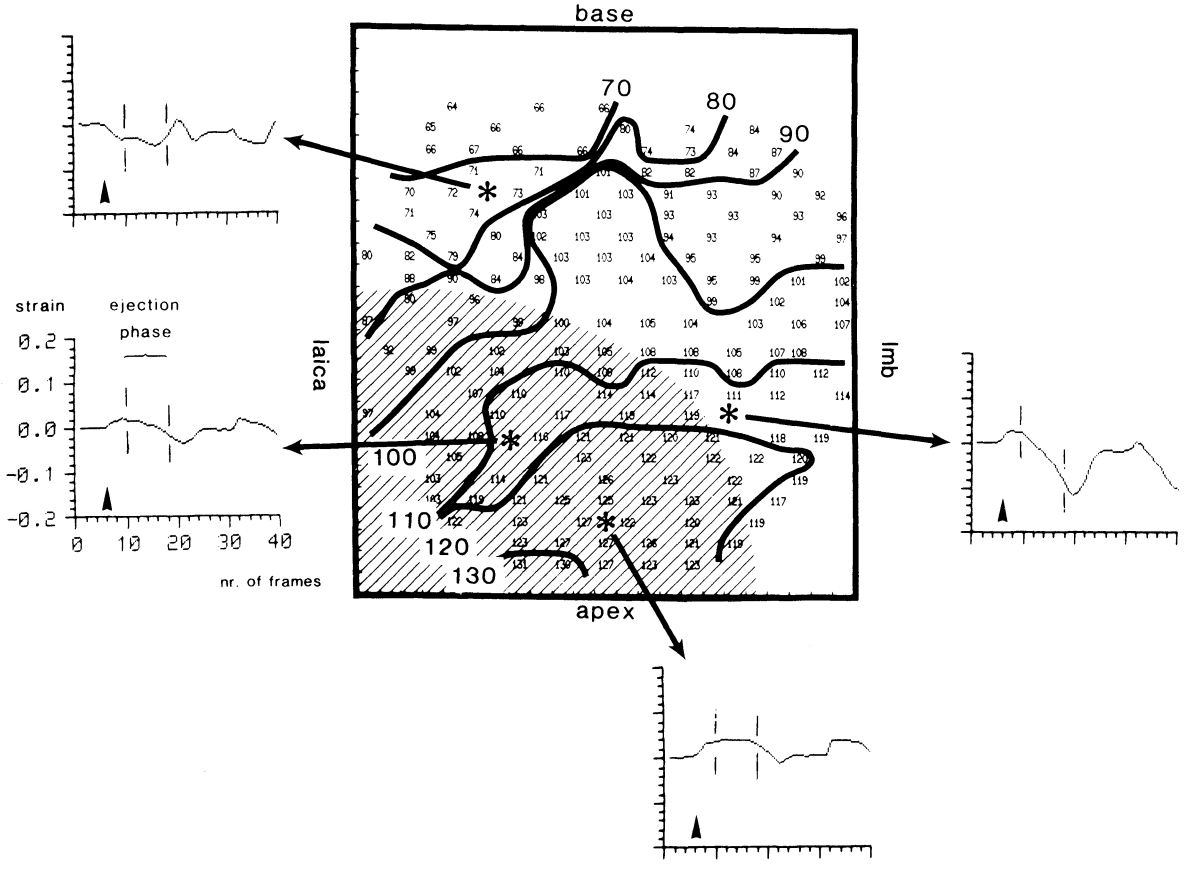

FIGURE 6. The time sequence of electrical activation and the pattern of fiber shortening (i.e., a decrease in strain) at the ischemic epicardium of the anterior left ventricular wall, when the heart is electrically stimulated from the right ventricular outflow tract. Each frame represents 20 ms. The arrowhead indicates the start of the stimulation artifact; lacia, left interventricular coronary artery; lmb, left marginal branch. The dashed area represents the region in which myocardial flow (assessed with radioactive microspheres; data not shown) dropped to less than 40% of the control value after stenosis of the laica.

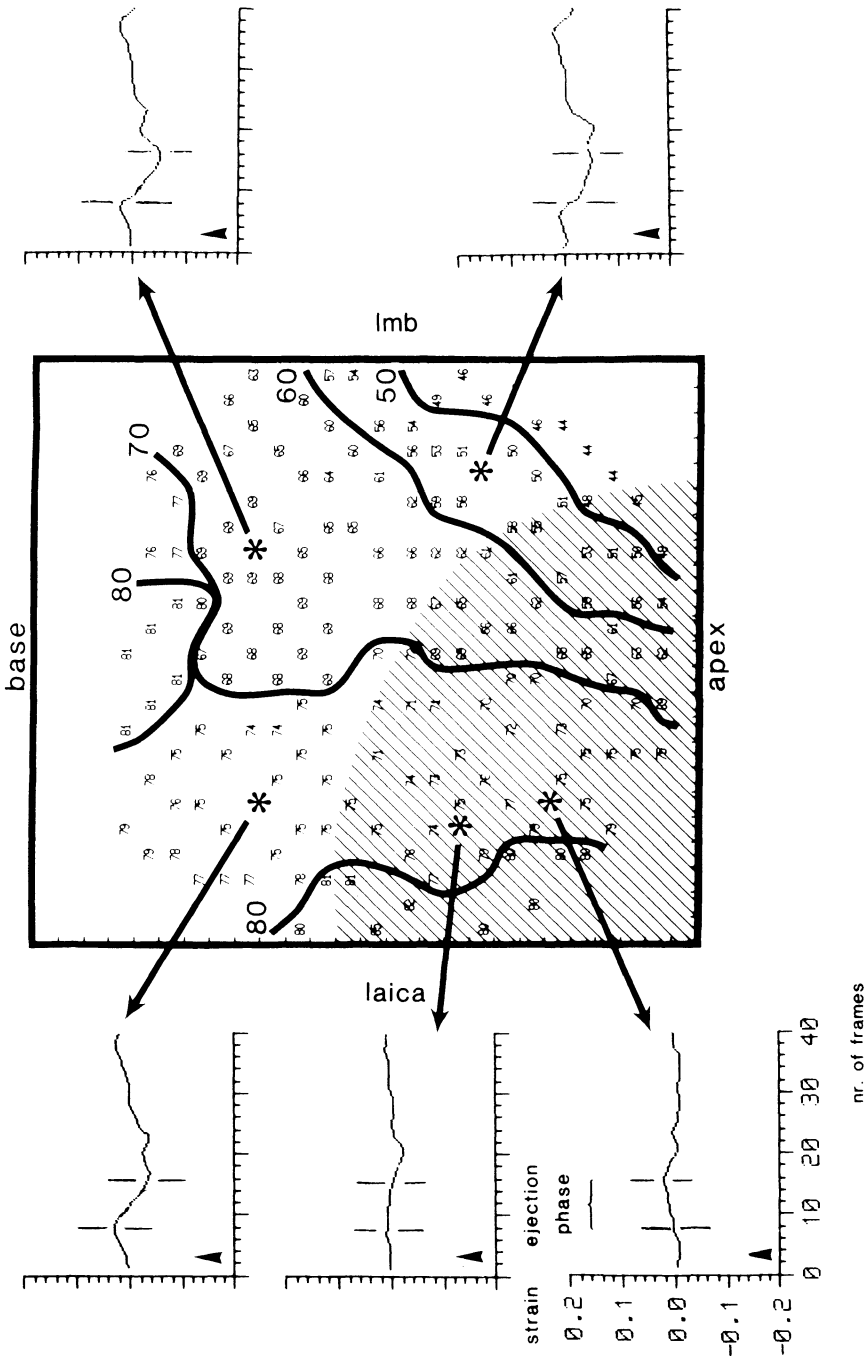

FIGURE 7. The time sequence of electrical activation and the pattern of fiber shortening (i.e., a decrease in strain) at the ischemic epicardium of the anterior left ventricular wall, when the heart is electrically stimulated from the left ventricular apex. Each frame represents 20 ms. The arrowhead indicates the start of the stimulation artifact; laica, left interventricular coronary artery; lmb, left marginal branch. The dashed area represents the region in which myocardial flow (assessed with radioactive microspheres; data not shown) dropped to less than 40% of the control value after stenosis of the laica.

heart is paced from the right ventricular outflow tract (see Figures 6 and 7). It is interesting to see that in these areas the epicardial fibers are barely stretched during the isovolumic phase. In the central ischemic area, epicardial fibers do not shorten or are stretched, but to a lesser extent than when the heart is stimulated from the right ventricular outflow tract, a situation in which electrical activation of the left ventricle is less synchronous. Whether the more homogeneous, but less vigorous, contractions in the normoxic areas and the limited stretching in the central ischemic region lead to a more efficient pump function of the left ventricle is subject to further investigations.

V. CONCLUSIONS

The opportunity to map both the time sequence of electrical activation and the pattern of fiber shortening at the epicardium of the anterior left ventricular wall makes it possible to study the relation between electrical and mechanical activation in detail under a variety of experimental circumstances. During a sinus beat, the anterior left ventricular wall is homogeneously activated (delay between the various areas about 10 ms), resulting in synchronous contraction of and about equal epicardial fiber shortening in the whole area under observation. When the heart is stimulated from the right ventricular outflow tract or the left ventricular apex, there is a significant delay (40 to 50 ms) in the electrical activation from base to apex and from apex to base, respectively. This results in a nonsynchronous start of epicardial fiber shortening. The fibers in areas which are activated late show an initial stretching before they contract. Regions in which stretching during isovolumic contraction is most pronounced generally show the largest epicardial fiber shortening during the ejection phase.

During regional myocardial ischemia, the arrival of the activation wave in the ischemic area near the apex is delayed by about 20 ms (total delay between base and apex of about 70 ms), as compared with the normoxic situation, when stimulated from the right ventricular outflow tract. When stimulated from the left ventricular apex, the delay of electrical activation between apex and base is only about 30 ms. In right ventricular outflow tract stimulation, the areas in the normoxic part of the left ventricle, which are activated last, show the same phenomenon as during normoxia, i.e., epicardial fiber stretching in the isovolumic phase and the most pronounced shortening during ejection. Under these circumstances, the epicardial fibers are stretched in the central ischemic area during both isovolumic contraction and ejection, occasionally followed by some shortening later during the cardiac cycle. When the regionally ischemic heart is stimulated from the left ventricular apex, the start and extent of epicardial fiber shortening in the normoxic part of the left ventricle is more homogeneous than when paced from the right ventricular outflow tract. However, in several regions, the degree of fiber shortening is less pronounced. In the central ischemic area, epicardial fibers do not shorten and are stretched only to a limited extent when stimulated from the left ventricular apex. It would be interesting to know whether a more homogeneous but weaker contraction in the normoxic areas, together with a limited stretching in the central ischemic region, would lead to a more efficient left ventricular pump function. This is subject to further investigations.

VI. DISCUSSION

Dr. Beyar: Am I right that the strains that you were showing were all in the principal fiber shortening direction?

Dr. Reneman: We have shown fiber shortening along the fiber direction of the epicardial fibers.

Dr. Kass: Dr. Waldman and some of us (with Dr. Hunter) have been looking in simultaneous layers. The epicardium seems to show the greatest disparity of principle shortening, either in the fiber direction or the anti-fiber direction. On the other hand, you might postulate that with some of differences in the pacing sites, or with ischemia, the relationship is essentially in the anti-fiber direction and this would show up also in the extent which shears would change, particularly when you alter the activation sequence, and also with ischemia.

Dr. Reneman: We have looked into that, but with another technique. We have done this with induction coils, looking at one area of the anterior left ventricular wall. You definitely have a difference in the behavior of endocardial and epicardial fiber shortening during myocardial ischemia. Immediately following the onset of ischemia, endocardial fiber shortening, as estimated from the epicardial deformation parameters, stops, whereupon, about 30 s later, shortening in the epicardial fibers ceases or diminishes, depending on the degree of ischemia. In the endocardial layers, the fiber shortening stopped without significant disorders in myocardial biochemistry. We believe that fiber shortening in the epicardial layers ceases due to changes in the loading condition. When endocardial contraction fails, the epicardial fibers cannot bear the whole load anymore, and then the epicardial fibers stretch so that they cannot contract anymore.

Dr. Sideman: The proposed analytical technique is exciting because it presents a potential to answer two important questions: first, what happens on the borders of an ischemic region and, second, but not least important, in the effect of variable conduction velocity in the ischemic region?

Dr. Reneman: Regarding your first question, we have mapped the border zone with this technique and determined myocardial blood flow in the same areas with the use of radioactive microsphere technique. We feel that there is a border zone, as far as contraction is concerned, which is sometimes smaller and sometimes larger than the border zone for flow. I do not know why. Your second question concerns the conduction velocity in the ischemic area. We have not done any measurements yet. The only thing I know is that across areas with 60% flow reduction or more, there is a delay, as far as the propagation of the activation wave is concerned, of 20 ms, as compared with the propagation across normoxic areas of the same size.

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