COMPUTER ANALYSIS OF CARDIAC CATHETERIZATION DATA

PROEFSCHRIFT

DOOR

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To my shipmates

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CONTENTS

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CHAPTER I

AN OVERVIEW AND SUMMARY OF THIS THESIS

The aim of the thesis is to describe the design, the development and the first six years of application of a computer based cardiac catheterization system currently in daily use at the Thoraxcenter of the University Hospital in Rotterdam, The Netherlands.

Over the past three decades cardiac catheterization has become an increasingly sophisticated and complex procedure, which currently is considered as an indispensable step in the procedures leading to cardiac surgery. Given the need for accuracy, the need for automation has become evident. The steps along which this development took place, form the substance of the various chapters of this work.

In chapter II the available literature has been reviewed and condensed in three parts: first, a selective description of the most relevant publications which existed prior to the design and development of the system; a second section in which all relevant previous publications from the Rotterdam group are enumerated but not further discussed, and a final listing of all the most important sources of reference that were utilized in one form or another in the entire text of this work.

A detailed description of the system appeared in print in the peer-review literature in 1975. It forms the culmination of many years of work and details all the components in the design of hardware and software. Also it analyses the day-by-day operation of the entire system and provides some early insight in the experience accrued until 1975. In fact it can be considered as a sort of statement of our beliefs and is reprinted as chapter III.

Since so much emphasis has been placed on the advantages and versatility of the on-line computer system in the cardiac catheterization laboratory, details of the off-line analysis of coronary arteriograms and ventricular angiograms as well as a review of the atrial pacing stress test as an intervention during cardiac catheterization deserve special attention. Since these "packages" form an essential part of the entire procedure they are set apart in chapter IV.

As experience grew, it became evident that quantitative assessment of

global cardiac function was of limited value in patients with coronary artery disease. In fact, more often than not this disease is segmental or regional by nature, so that localized disturbances of contraction must be sought for even when overall measurements appear to be normal. Akinesis or dyskinesis of one or more segments of the left ventricular wall can occur in the presence of normal global parameters, such as an ejection fraction between 50 and 70%. This analysis of regional and segmental wall motion is detailed in chapter V, not only from the analysis of contours of the left ventricular angiogram, but also by the detailed measurement of epicardial markers, implanted at the time of surgery and restudied by cine-fluoroscopy in the years following surgery.

One of the great advantages of the automated system is that its analysis can be carried out on-line and that beat-by-beat changes in cardiac function can be analysed. Thus the assessment of slight beat-to-beat variations with a series of continual changes, even with normal sinus rhythm, has now become within reach. Some results are detailed in chapter VI, which, as was the case with the previous chapter, is based on a publication earlier submitted to peer-review. It was found that these small fluctuations in pressure and other signals, which usually disappear in the averaging process routinely employed, in fact provide significant information, the full extent of which has not yet been explored.

As alluded to above, global function of the left ventricle in rest often does not yield any abnormality in coronary artery disease. With the development of the atrial pacing stress test a powerful tool has become available to load the heart without undue discomfort. A doubling of the heart rate will often unmask, well before the patient experiences any symptoms, gross changes in cardiac performance. New statistical techniques were required which are described in chapter VII. They improve the yield of the atrial pacing stress test by data reduction and standardization. It is now felt that the atrial pacing stress test has become a highly sensitive and specific measure of the reserve capacity of the heart, which should be included in every investigation.

In chapter VIII an overall evaluation is carried out of the 1,664 cardiac catheterizations, analyzed by means of the computer assisted system in the Thoraxcenter over the period 1972 to 1976. A description is given of the dedicated diagnostic coding system, which permits all patients to be classified in distinct diagnostic groups. Of the many, at times up to 54, hemodynamic variables measured, nine have been selected on the basis of their discriminatory value. An approach was made to assess their relative value and contribution to the definition of the "hemodynamic state". From this a catheterization index was developed to simplify the classification of patients.

In chapter IX the catheterization index derived from the learning population described in chapter VIII, is applied to a testing population, obtained from the independent data bank collected by the Interuniversitary Cardiological Institute. The conclusion is that this new index has a useful function, particularly in the assessment of the subgroup of patients with impaired left ventricular function.

In summary, the eleven chapters of this thesis contain the life-story of one facet of computer application in a medium sized Universitary medical center. It describes the woes and the throes in the design, development, introduction and daily running of such an automated system. The general conclusion that can be derived from the thesis, is that such application of automation is eminently sensible and useful because it not only improves the quality of the cardiac catheterization procedure, but also provides additional and highly relevant information that otherwise would not be available to the diagnostician. And that is a good thing since, as Murphy has stated, "The patient is the center of our medical universe, around which all our work revolves, and towards which all our efforts tend".

CHAPTER 2

A REVIEW OF PERTINENT LITERATURE

PART A.

The history of the development of automation in cardiac catheterization systems parallels and is interwoven with the advances in computer sciences and the search for better assessment of the hemodynamic state of the human heart. Ever since the first recording of intracardiac pressures by Chauveau and Marey A1) in the animal and the first cardiac catheterization in the human by Forssmann A2), investigators have tried to describe the performance of the heart and of the contractile state of the cardiac muscle. Many models have been proposed, each successive one more complex than the other and requiring more calculations. As the significance of these parameters gained in stature and cardiac catheterization became a main avenue towards cardiac surgery, the need for quantitative information increased. Comparisons with the normal state and with individuals in various disease categories were collected and the study of the performance of the human heart under stress conditions, such as exercise or infusion of pharmacological agents, was introduced. Each successive step required more and more calculations before proper interpretation of the data became possible. Often data did not become available in time nor was their true significance revealed until the catheterization had been terminated and the patient had left the laboratory. Not infrequently, the investigator then had to conclude that he had failed to obtain information which was most relevant to his diagnostic efforts.

Small wonder, therefore, that the computer was called in to assist in cardiac catheterization at a relatively early stage. The first evidence of this is to be found in the publication of Sanders et al. A3) in 1967, in which the group of Stanford University in Palo Alto, California, described their first effort to use a computing device in the cardiac catheterization procedure. The workers in Stanford remained quite active in the field and followed their first publication by a more definitive description by Stenson et al. in 1968, which was published in the then very new Journal "Computers and Biomedical

Research" A4). From the introduction of that paper we quote:

"In recent years interest in the use of both analog and digital computers in cardiology has expanded rapidly. Considerable experience has been developed in the use of computer systems for interpretation of electrocardiograms for studying cardiovascular physiology, for determination of cardiac outputs from dye dilution curves, and for on-line monitoring of patients in intensive care units. The introduction of time-sharing capabilities which allows multiple investigators the simultaneous use of the high-speed capacity and large memory of digital computers has made their use economical for many investigators".

It is interesting to view their general system diagram:
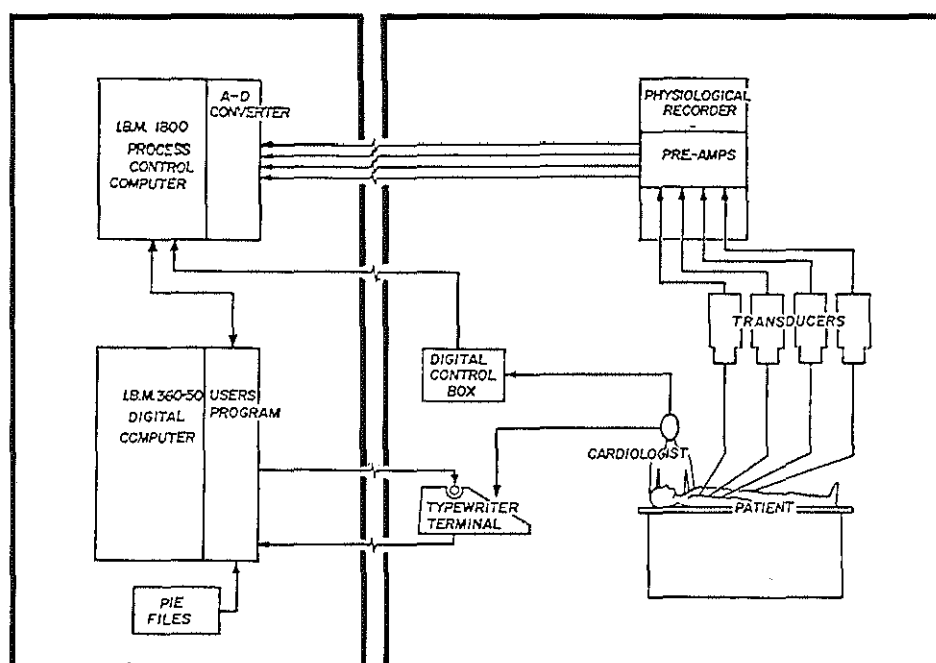
General system diagram: Cardiac catheterization laboratory is on the right and the computer room is on the left.
(Copied with permission from Stenson et al., Computers and Biomedical Research, 1,605-614, 1968).

This diagram clearly shows the for 1968 classical way of thinking where the computer was placed in a distant location and used on a time-sharing basis for multiple purposes. Communication with the computer was either through a typewriter terminal or some digital control box. In short, the

cardiologist used the computer as an additional tool and not as one that was integrated into the measurement system. Yet, the computer-cardiologist interaction was a great potential stumbling block and a considerable part of that publication is devoted to the discussion of a possible solution.

The authors were clearly not satisfied with their efforts because in none of their subsequent publications returns a reference to this "special control box". One may question whether the title of this first description of "on-line analysis" of cardiac catheterization data is correct, because the authors end with the statement that the use of data forms to transmit information from transducers in remote laboratories for on-line analysis of the data had not yet been attempted. We will find that the problem of interaction with the machine and the success of on-line processing of all data is the central feature which determines the acceptance of a computer system in most cardiac catheterization laboratories of today.

When designing computer programs to analyze data from cardiac catheterization laboratories, first of all a careful definition of the values most meaningful to the cardiologist, is necessary. Also, programs have to cope with non-ideal situations that may occur during a catheterization procedure. These include the frequent occurence of transient arrhythmias, especially premature ventricular contractions and the influence of respiratory mechanics on hemodynamic events. The Stanford group A5) introduced for minimizing distortion of data that dysrhythmic beats can cause, the concept of "representative beats". This concept involved analyzing a series of successive beats, ranking the peak pressure for each beat in terms of increasing magnitude and disregarding the highest and lowest third in the series. The middle third in the series of beats was then averaged and the results printed out as representative of the series of beats analyzed. This concept has been shown to be very effective in excluding ventricular premature beats. It also copes effectively with respiratory variations in a reproducable way. Now, 11 years after this publication, we consider this technique still as completely valid.

In the same period of time, a whole series of publications appear, such as that by Kyle et al A6) on computer identification of brachial arterial pulse waves, Freis et al. A7) on computer analysis of carotid and brachial pulse waves, Mirsky et al. A8) on assessment of myocardial contractility in man from ventricular pressure recordings, Hugenholtz et al. A9) on myocardial force-velocity relationships in clinical heart disease and Falsetti et al. A10) on V_{max} as an index of contractile state in man. All have utilized computer systems in an effort to arrive further information from the interplay between left ventricular pressure and cardiac dimensions. The latter were usually

derived from angiocardiograms on which measurements of the intracardiac volume and ventricular wall were made in an off-line fashion throughout the cardiac cycle so that from the interaction of pressure and dimension parameters, the condition and behaviour of the left ventricular wall could be studied.A11)

The development of these parameters and their clinical usefulness gained rapid confidence to the extent that they were suggested as useful indicators to assess the contractile state of the human heart. This in turn led to several warnings as to the reliability of these derived parameters, which is evident from a letter to the editor which appeared in Circulation in 1971 by Mirsky A12). In fact, a whole discussion in the then fashionable journals was stirred up as is testified to by the letter printed in Circulation of April 1972 by Katz A13), from which we quote:

"The exchange of letters between Dr. I. Mirsky and Drs. H.L. Falsetti et al. appears to me to miss the major question raised by the many derived indices of myocardial contractility examined by Falsetti et al. This question, in my opinion, is not the extent to which these indices correlate with each other, but, instead, their usefulness in evaluating the state of the myocardium in patients with heart disease" and "More important, are these criteria of any value in evaluating individuals with LV volume overload, in terms of state of compensation?"

It is evident that the availability of a whole range of new measurements to describe hemodynamic function of the human heart has brought about a greatly renewed interest in the potential usefulness of cardiac catheterization data but that their relevancy and accuracy was still in doubt. The new wave of enthusiasm of contractility indices was to increase considerably further and there is no doubt that the availability of on-line cardiac catheterization systems played a major part in this development, even though skepticism had already set in.

At the same time, angiocardiographic assessment of left ventricular function in patients with various forms of heart disease rapidly expanded and, consequently, the number of cardiac catheterization laboratories, in which modern angiocardiographic equipment was available, mushroomed. Many papers on the usefulness of quantitative angiography appeared, typefied by that from Chatterjee et al. in 1970 A14) on angiographic assessment of left ventricular function in patients with ischemic heart disease without clinical failure. Also, Hamilton et al from the group in Seattle reported in 1972 A15) on quantitative angiocardiography in ischemic heart disease and Hugenholtz et al. A16) referred to the need for complex computing equipment. However, all data still had to be obtained and processed

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in an off-line fashion and the significance of much of the derived information became available too late to influence the decision making during a given cardiac catheterization.

This continuing need for on-line information led to the development of real-time analysis of cardiac catheterization data with the help of computers. A first example of such a system was published by Harrison et al in 1971. again from the group in Palo Alto A17), and it is of interest to quote from that work where he discusses timesharing systems:

"..... several major problems were encountered."
"The cost of being connected to the time-sharing system during the entire catheterization procedure was prohibitive."
"..... the procedures to put data into the time-sharing system did not allow the laboratory personnel in the cardiac catheterization laboratory to use the system conveniently."
"..... the "down time" of the large system gave a lack of reliability and availability, at time critical for real-time analysis of data .....".

In the same period a cardiac catheterization system was developed in Rotterdam. The first results were published in 1971 by Meester et al. A18). As the disadvantages of time-sharing systems were clear from the outset, the Rotterdam configuration was based on a dedicated, small computer with special emphasis on the interaction facilities between cardiologist and computer. This in turn led to the design of a functional catheterization keyboard and a versatile display. To achieve this, the video output of the X-ray equipment was also used for digital and graphic computer display. Several hardware devices, which at that time were unavailable, had to be developed for this purpose.

Cost-effectiveness proved a major stumbling block. In the paper of Harrison et al. in 1971 A17), by that time with three years experience in computer analysis of catheterization data, many essential remarks are to be found, some of which still hold true today. We quote as considerations essential for the succesful operation of an automated system:

"That there be no increase in the staffing of the laboratory, ...".
"that the complexity of the operation of the catheterization laboratory should not be increased;"
"that the data analyzed by the computer system be made available to the operator instantaneously, ...".
"that adoption of the system not require extensive training .....".
"that the data analysis performed by the computer be at least as accurate as that performed by a trained physician;

that the cost of the computer system be commensurate with the operation of a catheterization laboratory .....".

Yet, the acceptance of computerization in the cardiac catheterization laboratory continued to gain, with simultaneously augmenting challenge from the economical perspective. It is of interest to see what is written for the cardiopulmonary technologist in the Journal of Cardiovascular and Pulmonary Technology by Gorham in 1978 [A19]. This is an opinion expressed for those who, perhaps even more than doctors, work with the equipment in the cardiac catheterization laboratory, namely the technicians. We quote here a number of passages from that brief publication:

"Recently many labs have been computerizing - a development that presages a sharp upswing in patient benefit. Computers can virtually eliminate calculation error and inconsistency, and if wired directly (hard wired) to the diagnostic instrumentation, they can provide standardized, real-time results".

"Installation of a computer with real-time capacity, according to practitioners and spokesmen for leading companies, almost always represents an investment of above $ 100,000, either initially or as an addition to an existing facility. As a result, such a purchase is subject to mandatory certificate-of-need (CON) review.

According to the *Federal Register*, (vol. 43, no. 14, January 20, 1978, p. 3067 ff) for a cath lab to receive CON approval,

"..... a minimum of 300 cardiac catheterizations, of which at least 200 should be intracardiac or coronary artery catheterizations, (should be) performed annually .....".

"Computer-purchase approval: the calculation time could well require almost all of a staff technologist's time in addition to a heavy commitment of physician time for supervision. Ability of the computer to perform calculations instantaneously represents more than a convenience to physicians and technologists, experts say; it also results in direct benefits to the patient. The safety factor: the computer is performing calculations in real-time so that the physician is cognizant of the patients condition while the study is being run.

Not only is the time-saving ability of the computer of benefit to the patient, but the computer can also upgrade care, practitioners attest, by improving accuracy of the calculations".

"Increased efficiency: we determined that the computer would add about $45 to the price of each procedure..... Since the per-patient share of computer coast adds little to the price of catheterization, computerization can actually be a positive factor in cost control".

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While it is clear that in the field of cardiac catheterization computer application has contributed much to the changing face of cardiology, in many closely related areas developments came about simultaneously. Of this testifies the perceptive editorial by Wallace and Rosati [A20]) entitled: "Computers can change cardiology". In this editorial the successful practice of medicine is stated to be a science of problem solving. For this purpose the doctor's job is first of all to collect data. Each piece of these data is a descriptor, "some discrete and some categoric, some hard and some soft. Together, these data serve to characterize the problem and the patient in whom the problem exists".

The next job is to perform a function of pattern recognition, as for example in acute myocardial infarction. Here they state "to accurately predict the outcome and to select a form of treatment, we need to know more than the diagnosis..... the prognosis, and even a first approximation of the plan, depend upon many descriptors, and almost always upon more information that that which is required to make the traditional diagnosis".

After elaborating om mechanisms of communications between doctors and patients, the pooling of descriptors into syndromes, such as "angina pectoris". Wallace and Rosati conclude that "as consequence, pattern recognition cannot take place except at the most superficial level". The authors feel that here is an area, where computers can change cardiology. "The computer forces upon data gatherers a degree of discipline", leading to more complete records and more accurate data. "Finally, the computer forces upon its users the discipline of more precise definitions. Terms such as shock, heart failure and anginal syndrome become relatively useless unless they are accompagnied by more precise descriptors, which document the problem and characterize its severity".

"The difficulty is that .... coronary disease, is probably multifactorial in cause, takes years to pass from a pre-symptomatic stage to a symptomatic stage and, even when manifest by specific signs or symptoms, has a tremendously variable prognosis". The authors conclude: "The information system, and its use, have and will continue to improve medial record keeping. To the extent that a more carefully kept record reflects more accurate observations of patients, patient care should improve...".

"The computer will force the clinical investigator to keep records as assiduously as he would if he did a laboratory experiment. The computer can provide the memory extension which is necessary for the doctor to recall the pertinent variables, which describe patients, who constitute his own experience and that of this colleagues. Computer-based records can be interfaced to powerful statistical technics which will aid the investigator in

defining subgroups of patients who are sufficiently homogeneous in their outcome so that therapeutic trials will be meaningful".

This brought about some reactions A21): "Computers can change cardiology, only if we recognize the factors that have prevented them for doing so during the past 15 years...."

As occurs with all developments sooner or later, by the end of the seventies a period of reflection and criticism of the computer had set in. These are perhaps best reflected by the article, published in 1977, by Covvey et al. A22) entitled "Look before you leap". The author concludes after having looked at all the available commercial cardiac catheterization laboratory systems:

"Currently at least nine companies are marketing computer-based products in North America to support on-line data acquisition, processing, and reporting in the cardiac catheterization laboratory".

"The products have been compared on the basis of the functions they support. System features and a spectrum of capabilities are noted. With the differences will come a finite problem in system selection to be faced by each laboratory considering such technology".

"Finally, an average cost per patient processed, ranging from a minimum of $ 20 to $ 37 is considered relative to the problem of cost-benefit justification. Although the analysis done here is relatively superficial, it does not appear possible to cost-benefit justify such systems. Therefore it would appear that work must be done to explore their potential in enhancing the effectiveness of various types of laboratories, to reduce their cost, or to seriously challenge their value".

Later, in 1978, the same author has provided an updated review A23) "A review of commercial computer-based systems in the cardiac catheterization laboratory (1977)", where he concludes that a computer based catheterization laboratory system (CCLS) is best suited to two situations: "....first, in the strictly service laboratory with a high patient volume and a large number of cardiologists utilizing the facilities".

"Second, laboratories in which sophistication in data analysis is desired (research-oriented labs), should benefit from the installation of a CCLS although in this case considerable modification of available systems may be necessary and fairly sophisticated in-house computer expertise may need to be available".

This first section contains only a selection of the extensive world literature on the subject. A more extensive listing of references, which for reasons of space is not discussed, is appended in part C.

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Work carried out in the Thoraxcenter (1972-1978) Part B

This list of publications, whether in the form of abstracts, contributions to proceedings, chapters in books or as articles, reviewed by peers in official journals, has been generated from this laboratory by various workers involved in the project to implement computerization in the Rotterdam cardiac catheterization laboratory. No attempt is made to extract part of this material or to summarize it, as the common denominator of all these papers is contained in the text of chapter III, which describes in detail the system as it is currently operating.

The list is, however, reproduced in its entirety to acknowledge the many people involved in the design, in its construction and implementation as it evolved over the years. The careful reader will be struck by the parallelism between developments in the literature at large, reported in part A of this chapter, and the steps taken by our group. Clearly, here is an example of parallel development in medicine, which, in many ways, is so typical of the current decade. But it was a justified development, and the fact that the Rotterdam system is now utilized in many places throughout the world and that in at least 23 laboratories the same system is currently operative, testifies to the applicability of the system elsewhere. The unique characteristic of direct interaction between the person who carries out the cardiac catheterization and the computer, the possibility of real-time calculation and direct recall of data obtained earlier, as well as the facility to integrate the system with off-line angiocardiographic information makes it still among the most attractive, currently commercially available.

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Part C

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CHAPTER III

A COMPUTER SYSTEM FOR REAL TIME ANALYSIS OF CARDIAC CATHETERIZATION DATA

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In the past three decades the cardiac catheter has provided ever increasing opportunities for the study of circulatory physiology (1,2). As experience was gained, additional procedures were introduced so that at present all chambers of the heart and most arterial and venous vessels are accessable for study. At the same time technological development of transducers, oximeters, densitometers and X-ray methods kept pace and provided more accurate measurements. With these developments, the collection and handling of reliable data out of the many signals became increasingly complex. The reduction of the raw data to relevant information and the derivation and interpretation of the calculated information became more and more a time-consuming and yet tedious effort.

As data compression and complex calculations may be performed more rapidly and accurately by a computer than by the scientist, the introduction of a digital computer in the catheterization laboratory was only a matter of time. Since the original contribution by Henry (3) in 1968, reports have been published (4,5,6,7,8) about the application of the digital computer in the catheterization

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laboratory. Starting with off-line procedures, developments led to on-line calculations of pressures, indicator dilution tracings (9) and many other signals, of which the instantaneous representation was deemed useful. It became clear that the computer could not only save a large amount of time, but also provide a system with which the course of the cardiac-catheterization could be guided, quality control enhanced and the diagnostic procedures improved. As data reduction and processing is performed immediately, unusual results can be re-checked instantaneously, at the same time, provide the cardiologist with a comprehensive overview of the recorded data at any moment during the catheterization.

The present report details the design, and 3 year experience with a dedicated on-line system, developed especially for a clinical cardiac catheterization laboratory.

METHODS

Hardware

The small digital computer was introduced in the catheterization laboratory in the middle of 1971 on the basis of several requirements detailed in the discussion. The configuration chosen is illustrated in figure 1. The central facility consists of a PDP 11 with 16K core, a digital tape unit, an 8-channel analog-digital convertor, as well as a number of devices, including keyboard and display, especially designed for the catheterization laboratory. The digital tape unit is used for the storage of various program modules, which make up the system (executive, application programs and utilities). It also acts as a temporary storage medium for the required physiological signals, which serve as input for the various data analysis programs, and as a semi-permanent or permanent medium for the storage of derived parameters, patient records, and the catheterization log.

A special display device was developed to provide the system with powerful graphic and alphanumeric facilities. This device generates a standard video signal which, connected to the existing X-ray video monitor, can alternatively be used for the display of the computer image or the X-ray image. Slaving of video-displays is relatively inexpensive and is used to great advantage for communication and teaching purposes. The display image can be altered rapidly making it possible to display the data being acquired as a moving trace. (Fig. 2B)

A special interface unit was designed to couple the catheterization laboratory preprocessors (which were of various well known equipment makers) and the computer, placed in a remote position.

This interface consists of an analog section, which provides electrical isolation of the patient signal as a safety precaution and a series of digital input and output signals to inform the computer of events taking place in the laboratory. It also controls remote equipment such as stripchart recorders and tape recorders.

A physician keyboard was developed to direct all communication between cardiologist and the computer. The Technician Panel and the Physician Keyboard communicate with the computer through a special interface, which functions as a parallel/serial converter greatly reducing the number of cables

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required between the lab itself and the computer. A separate panel allows the technician working within the non-sterile recording area also to control system function without having to disturb the ongoing catheterization procedure. With the keyboard the physician exercises complete control over the system during the entire catheterization with minimal effort. The keyboard functions in a sterile environment and it contains its own lighting system for key selections. The lay-out of the keyboard is so organized that functional sections can readily be recognized in a darkened room.
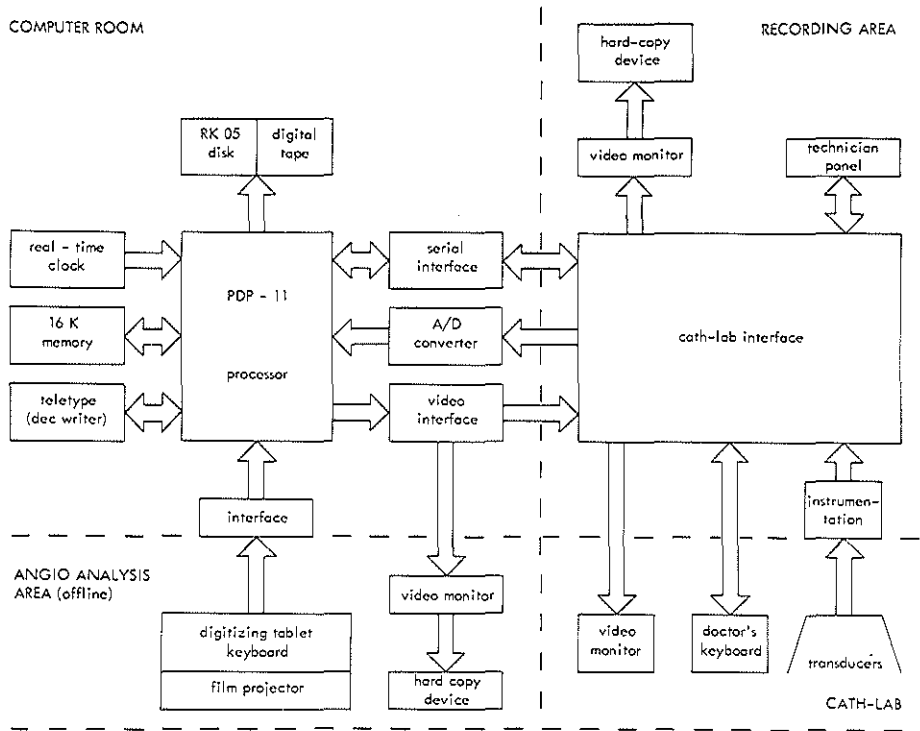
Fig. 1. Configuration and lay-out of computer assisted catheterization system.

Software

It was anticipated that the system would require continuous modification if it were to retain its relevance as a useful tool in daily practice. Such changes were anticipated in two areas: up-dating and expanding the computer facility itself, with new peripheral equipment and future inclusion of advanced medical-electronic techniques, such as videometry and extensions in the data-analysis domain. Therefore a modular system was developed. Application programs were all programmed exclusively in Fortran to facilitate off-line development, testing and documentation.

The system comprises several major subsystems, each containing a number of functional modules. The Supervisor sub-system is responsible for the scheduling

of tasks, the allocation of computer resources and the manipulation of peripheral devices including data acquisition activities. It provides for orderly communication and linkages of programs. It is essential that this sub-system be well designed since its operation affects all higher level sub-systems in both their implementation and performance. The Data Analysis sub-system is a collection of individual application modules which perform the major activity by the Supervisor and communicate via tables with other application programs and the dynamic patient data base. The communication sub-system is the only part of the system which communicates directly with the physician. It provides him with a simple mechanism for instructing the system and with extensive data retrieval and display facilities including graphic displays. A Utility sub-system exists to facilitate activities such as System Generation (modification and expansion) and to form a bridge between the systems' representation of the patient's cumulative record and the needs of any "non-system" computational processes which might be applied to this data when using the PDP 11 either as a general computer or to format and communicate the data to another computer (such as a large central machine).

Fig. 2. Composite of 6 examples of video-images. A: Stylized heart, used as quick overview for intermediate results. B: Video-image during datacollection, pressure-tracings are written from left to right. Calibration of channel is shown in window. Abbreviations: AO = Aorta; LV = Left ventricle. C: Results from LV pressure determination. Heading always contains date, time and patient identification. In small square at top right, number of minutes of catheterization. D: Thermodilution. Calibration data and results are given. The tracing starts with the automatic calibration signal shown as a square wave. The extrapolation is superimosed on the actual dilution signal. E: Atrial Pacing Stress Test. Results are presented in tabular form. For each pacing increment the computer adds a line of results to the Table. F: Graphical output. This is presented automatically at the end of the stress test. Horizontal axis : heartrate, vertical axis enddiastolic pressure and Vmax of left ventricle. Chosen time domain is specified at bottom of picture. This may be selected at will.

System Operation

Survey mode During cardiac catheterization a considerable period of time is spent in obtaining conventional hemodynamic measurements from simple pressure signals. Such measurements are typically carried out more than once to insure their reliability. They are routine in most laboratories. They require simple information such as the position of various catheters in the patient. It therefore seemed logical to split the operation of the computer system into district modes of operation. As the standard pressure measurements, require little interaction from the physician they were organized into a fixed set to run as ``survey-mode``.

Survey-mode is the dominant mode of the system and allows acquisition and analysis of up to three simultaneous pressure signals. The system itself selects the programs from those available. For instance, if two catheters are positioned, one in the right atrium and one in the right ventricle, pressing the corresponding keys on the keyboard, starts simultaneous data acquisition of both pressure signals and successively selects the following programs:
a. right ventricular pressure
b. right atrial pressure and
c. tricuspid valve parameters

After a one second calibration period, the computer analyses the pressure curves and displays the results from these programs immediately. They are then stored in the patient record if deemed acceptable by the cardiologist. Fig. 2C

Special procedure mode All programs using either non ``survey-mode`` data acquisition or specialized catheterization techniques have been termed ``special procedures``. These provide a facility for several techniques, oxymetry, cardiac output measurements, indicator dilution techniques, drug studies, pacing tests, and an easy overview of results for the physician to be used during the catheterization. Fig. 2A

Display mode This series of programs provides most of the graphical display. It allows graphs to be built up out of four dependent variables and one independent variable. An example is given in figure 2E. The variables can be selected from each of the time-related parameters acquired or calculated during the catheterization. The desired time-interval can also be selected independently. Display mode therefore provides a large number of possible combinations. To reduce the time taking in selecting a desired combination, an initial menu has been chosen with nine most commonly requested graphs.

Data Analysis

Pressures To minimize distortions and artefacts of pressure wave patterns, pressures are ideally measured by ``high fidelity`` catheter tip manometers. However, their usage is not yet generally accepted because of their cost. The alternative approach of fluid filled catheters, connected to a distal pressure transducer introduces a certain distortion of the signal, depending on the characteristics of the particular system employed (10,11,12). Movements of the catheter and resonances in the fluid column institute additional artefacts.

The occurrence of arrhythmias, especially premature ventricular contractions,

during catheterization is an additional source of distortion. Stenson (4) introduced the concept of "representative beats", in which from a series of consecutive beats the peak pressure for each beat is ranked in terms of increasing magnitude. By discarding the highest and lowest third part of the values in this series, the middle third, whose average is considered representative for the entire series of beats, is analysed. In this system data are collected over periods of maximally 20 seconds, until 12 beats are present. After ranking of the values of peak pressure, the four highest and lowest values are rejected. The average of the remaining four beats is presented as the pressure, representative for that series of beats.

In order for the digital computer to be able to calculate various pressure parameters, exact definitions have to be given. For example, to find the end-diastolic pressure, an important indicator of the preload of a ventricle, the computer calculates a series of dP/dt values and then selects a point on the pressure trace within certain preset limits. Details of the method are given in appendix I (also for calculation of peak systolic pressure, isometric contraction and Vmax).

Similarly the appendix contains the detailed definitions for the derivation of right ventricular pressure, pressures in the great vessels, atria and veins.

Cardiac output Cardiac output measurements from the Fick principle or from indicator dilution techniques lend themselves readily to computer calculation. With the introduction of the Swan-Ganz thermodilution catheter (13, 14) regular cardiac output measurements are preferred by this method. With thermo-dilution automatic calibration is initiated by the computer by switching on a calibrating resistor in the circuit. After injection of a premeasured quantity of cold saline, the program integrates the thermal curve, and calculates cardiac output with the Stewart-Hamilton equation (Fig. 2D) Again details are given in the appendix.

Oximetry An option for computer analysis for off-line acquired oxygen saturation samples for the detection and quantification of cardiovascular shunts is also provided. The programs are based on statistical evaluation of saturation values by means of the Students T test.

Angiocardiography The field of quantitative angiocardiography leans heavily on the computer. Dimensional information of the cardiac chambers, especially of the left ventricle is provided by left ventricular angiocardiography. In single or bi-plane mode, mostly one or two heartbeats are used for calculations. The left ventricular contours in the consecutive frames over this period of time, are manually traced and synchronized with intra-cardiac pressure. Details of this system are described elsewhere (15).

Stress test Imposed changes in the steady state may give additional insight into the characteristics of the cardiovascular system. Usually these tests are carried out by exercising the patient, by a forced increase in heartrate by means of a pacemaker or by administration of certain drugs. The atrial pacing stress test (16,17) is often applied for the evaluation of coronary heart disease. After selection of the stress test on the keyboard, the computer asks for specifics of the test. It will then calculate all possible parameters at the locations indicated by the catheter matrix.

This is done for each stress level with numerical output displayed concur-

rently. After completion of the test a graphical summary of results is shown. (Fig. 2E and F).

DISCUSSION OF RESULTS

Design Philosophy

In order to specify criteria for the design of a dedicated computer system in the cardiac catheterization laboratory, the following goals were defined:

A high degree of accuracy and speed in data-handling In order to achieve this goal, data-processing should be automatic, as far as possible, with minimal interaction between operator and computer required. Where ever possible calibration procedures should be automatic. Display should be fast, in standard format, and readily recallable.

A reduction in the duration of the catheterization To reach this aim the digital computer should "optimize" the course of catheterization. Results available in an easy overview, preferably in a graphical or alphanumeric form, should be utilized to direct the course of the investigation.

Limited costs To obtain this target, the system had to be economical in purchase cost and it should not place extra demands on staff or space. The aim was to add per patient no more than $ US 50,= per procedure on the basis of 1.000 procedures a year assuming a 5 year write off and to simultaneously reduce administrative staff.

The program should be modular in form This requirement should permit modifications and additions while the system is in daily use.

A dedicated computer facility It was felt in making computational power available to the cardiac catheterization laboratory, that the design and implementation of the system would be simplified and more straightforeward when it needed to consider the specific requirements of the catheterization laboratory only. In addition, such a design would greatly increase the potential of the system to find acceptance elsewhere.

The selection of a computer system with outstanding reliability and flexibility Reliability since the entire organization of the laboratory had to be reoriented in its daily activities to depend on the machine in all data processing, making such stand-bys as direct records, tape recorders etc. superfluous. Flexibility, since medicine is an extremely dynamic field and one must always anticipate that a functional system will need to undergo many substantial changes both in terms of equipment and in computer programs during the course of the years. A variant of the left ventricular pressure determination could for instance be used on a beat-to-beat basis in order to establish the spontaneous variation of pressure parameters in the resting steady state (18).

Validation

This system has been used in the cardiac catheterization laboratory in 1.058 patients until March 1975. Performance tests of all programs were carried out. (Fig. 3).

Consecutive series of patients were used for the evaluation of programs. No

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tracings were excluded. Computer processing was possible in all cases, no tracings had to be rejected.

The decision rules for manual and automatic measurements were equal in maximum and minimum pressure determinations. This also applied for the integration of indicator dilution curves. For manual determination of ventricular end-diastolic pressure the post-A wave pressure was used.

All hand calculated values were independently checked by two other individuals. Correlations between manual and computer measured data were excellent (Table I). As previously outlined by Pipberger and Cornfield (19), when using the same decision rules an "accuracy" of 95-100% may be expected. The small failure rate may be attributed to technical errors. This does not apply to the end-diastolic pressure correlation, where different criteria in manual and automatic recognition were used, because of the lack of a precise definition. It is evident that the computer program is more reproducible and coincides with manual recognition in 97%. This, however, does not provide an answer to the accuracy of the actual interpretation of the end-diastolic pressure point.

Evaluation

Performance characteristics of such a computer system include reproducibility and speed (20,21). No subjective interference with the programs is possible, the operator can either accept or reject the calculated data. We felt that interaction with the running programs for instance by means of movable indicators to manually select data was highly undesirable. Such a method introduces an element of subjectivity and makes reproducibility a fallacy. Speed is another characteristic of computer processing. Results of calculations should be immediately available and optimize the catheterization procedure.

In our experience the rapid availability of the data has failed to shorten the duration of the catheterization. Apparently events have a tendency to fill the

TABLE I. Statistical comparison of manual and automatic determinations.

Parameters	No observations	Correlation coefficient	Range	Slope of regression line	Standard error of estimate
LV peak systolic pressure	147	0,97	81 – 248 mmHg	0,95	9,4 mmHg
LV end-diastolic	136	0,97	0 – 53	0,92	2,6
PA diastolic	164	0,97	0 – 68	0,98	1,9
PA systolic	200	0,99	11 – 110	0,99	1,2
RA max	166	0,99	3 – 21	0,98	0,6
RA min	164	0,98	–1 – 15	0,96	0,6
AO systolic	244	0,96	93 – 241	0,98	9,0
AO diastolic	225	0,99	52 – 127	1,00	1,2
Thermodilution cardiac output	296	0,91	2,1–13,5 1/min	0,81	0,69 1/min

Statistical comparison of manual and automatic determinations.
Abbreviations: LV, left ventricle; PA, pulmonary artery; RA, right atrium; AO, aorta.

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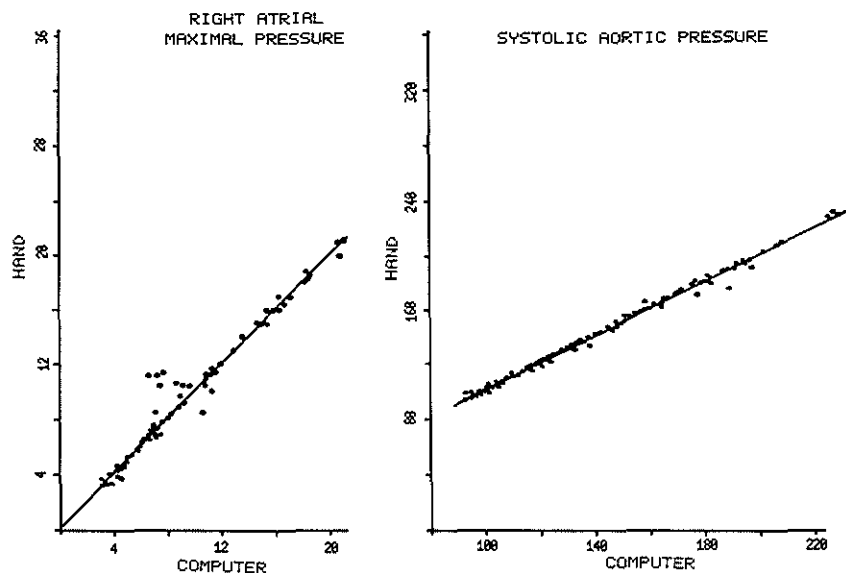
Fig. 3. Comparison of computer versus manual calculations. For numerical results see Table 1. A : Results and regression line for Right Atrial (RA) maximal pressure in mmHg. B : Systolic Aortic pressure.
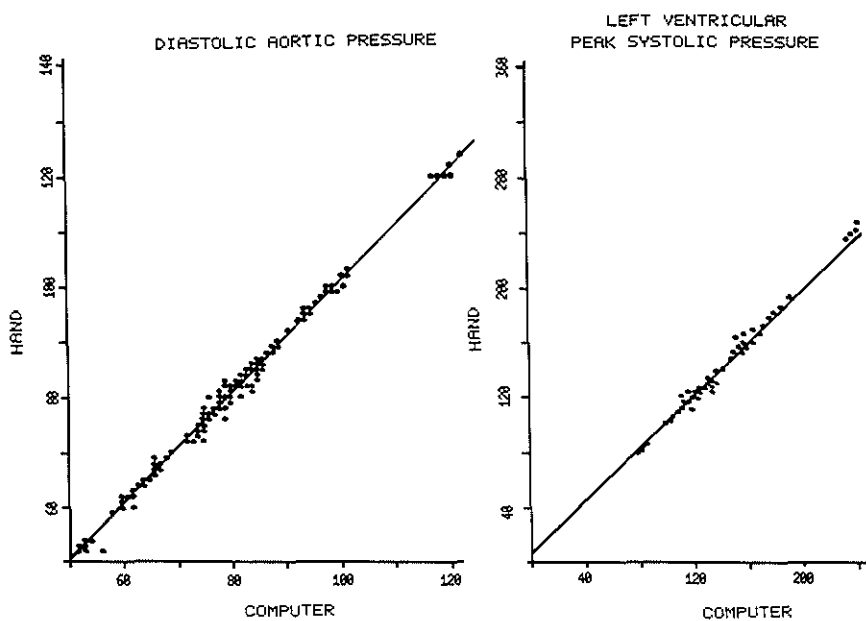
C : Diastolic Aortic pressure. D : Left ventricular peak systolic pressure.

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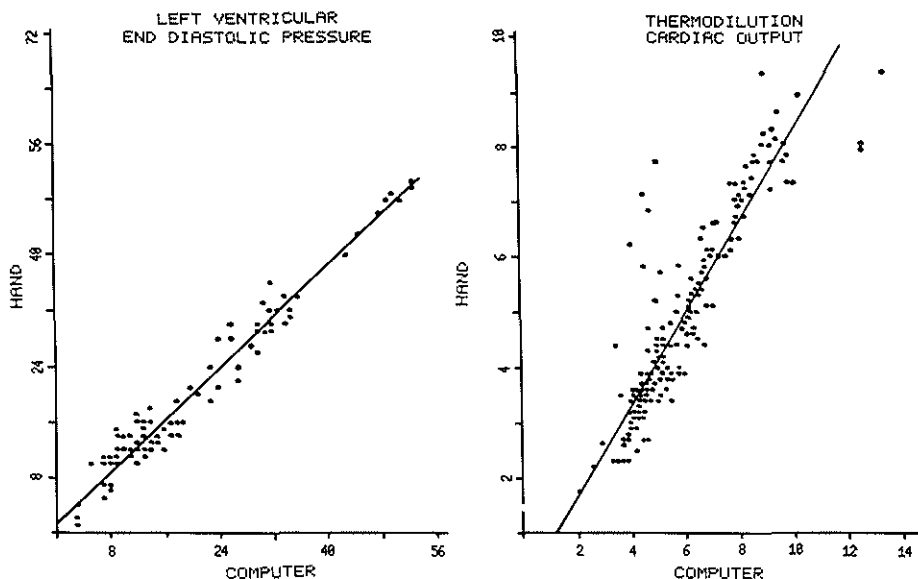
E : Left ventricular enddiastolic pressure. F : Thermodilution in L/min.

available time! However, more data are acquired, they are far more rapidly calculated and averaged. The number of missing bits of information is drastically reduced, inconsistencies in recording are immediately noted and corrected. All of these are advantages, because the computer enables one to carry out the catheterization more systematically.

CONCLUSION

Acceptance of the system by the medical staff has been good. They now increasingly depend on computer processing as, print-outs of the results are immediately available at the end of the procedure. At this moment manual data processing actually has become superfluous. Furthermore the computer system has been as an integral part of the catheterization equipment. It does operate as the main instrument for data collection and retrieval. There have been no technical break-downs in the last one and a half year. Specific evaluation of costeffectiveness is impossible, except in general terms. Computer processing and filing have allowed us to employ only one technician for all data processing, including quantitative angiography, of at least 300 procedures per year.

SUMMARY

A dedicated computer system is described for the on-line analysis of cardiac catheterization data. The system has been in practical use for over three years in a medium sized University Hospital and has been employed in the study of 1058 patients.

The system is based on a PDP-11 computer with 16K word core, a digital tape

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unit, an 8 channel analog to digital convertor and a television display device for graphic and alphanemeric information. A special keyboard operated by the physician brings the entire system under his control.

The designs and performance of various programs for pressure measurement, cardiac output determination, oximetry and various stress tests is described, validation tests show that very high degrees of correlation (between 0.91 and 0.97) are achieved.

The system proved to be a readily accessible and presently an indispensable tool in the catheterization laboratory not only for standard calculations but also for the frequent and rapid execution of various complex tests presently in use in most laboratories.

APPENDIX

Calibration Procedure

Calibration is performed electronically and automatically under computer control. The computer uses the initial comparison between the electronic calibration and the hydraulic calibration as a check on the gainsetting of the carrier amplifiers. All transducers are positioned at mid-thoracic level. At the start of data-collection calibration is checked automatically and adjusted if the signal is not within the range of the A-D converter. The calibration is shown in the data window on the video output (figure 2B).

Heart Rate

All survey mode programs estimate heart rate by measuring the total duration of the twelve beats in addition to the normally computed haemodynamic parameters. ECG R wave detectors are considered inadequate for this purpose in a cardiac catheterization laboratory. The R wave is not used as a means for identifying pressure phenomena. We feel that pattern recognition in a pressure trace should not be based on another signal with different characteristics.

Ventricular Pressures

Normally a catheter tip manometer is employed with the bandwidth limited electronically to 100 Hz (critically damped), A-D sampling rate is 250 samples/sec and the resolution is better than 0.1% full scale. Fluid filled manometers can be used, with consequent errors in several measured and derived quantities (10,11,12,22).
Ventricular data are processed on the basis of the following definitions:
a. End-diastolic pressure, for a given complex, is defined as that point on the pressure trace, after the beginning of diastole, at which the derivative of the pressure first exceeds 100 mm Hg/sec for the right ventricle or 200 mm Hg/sec for the left ventricle and continues to exceed this threshold level until the pressure has risen to 30 mm Hg above begin-diastolic pressure for the left ventricle, and 10 mm Hg for the right ventricle.
b. Peak-systolic pressure is defined as the highest numerical value of the ventricular pressure for a given complex.

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c. Begin-diastolic pressure for a given complex is defined as that point on the pressure trace, after the pressure peak, at which the derivative first exceeds -100 mm Hg/sec. Begin-diastolic pressure is always assumed to be < 10 mm Hg for the right ventricle and < 40 mm Hg for the left.

d. Isovolumic contraction period for a given right ventricular pressure complex is defined as that portion of the complex lying between peak V_{CE} and 2 mm Hg below peak systolic pressure.

e. Isovolumic contraction period for a given left ventricular pressure complex is defined as that portion of the complex lying between peak V_{CE} and the value of aortic end-diastolic pressure, if known, otherwise 20 mm Hg below peak systolic pressure.

f. dP/dt is calculated digitally using a 5 point Lagrange polynomial approximation with a 4 ms increment between steps (sampling rate = 250 samples/sec), that is,

$$\left. dP/dt \right|_{t=T} = \frac{P_{T-4} + 8(P_{T+2} - P_{T-2}) - P_{T+4}}{0.096} \quad \text{mm Hg/sec}$$

where $T \pm j$ signifies $t = T \pm 4j$ ms.

dP/dt/P is calculated using the above definition for dP/dt and measured P (23). In addition developed pressure (P-EDP) is used for the evaluation of developed V_{max}. V_{max} from measured pressure is estimated with a linear extrapolation using the least squares criterion over the isometric contraction period (defined above). V_{max} from developed pressure follows a similar pattern. In all cases the extrapolation for measured and developed dP/dt/P ignores data for measured $P < 20$ mm Hg. As an additional index, dP/dt/P is evaluated at 40 mm Hg.

Pulmonary Wedge and Central Venous Pressures

Because of the inherent variability in pulmonary wedge and central venous pressure recordings, and the presence of catheter artifact (fluid filled cath-manometer systems are used here), no true pattern recognition has been attempted on these signals. Twelve beats are recorded, and maximum and minimum pressure are calculated. Only gross errors checks are made, so it is up to the clinical staff to assume quality control.

Aortic Pressure

From the aortic pressure recording peak systolic pressure, mean pressure, end-diastolic pressure, and heart rate are computed according to the following rules: a. aortic end-diastolic pressure occurs at the point where the derivative goes positive and remains so until pressure has increased by 5 mm Hg.

b. peak systolic pressure is the first maximum greater than 10 mm Hg above the previous end-diastolic pressure.

c. the mean is calculated for all recorded data.

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Pulmonary Artery and Peripheral Artery Pressure

From the pulmonary artery pressure recording systolic, diastolic, and mean pressure are calculated according to:
a. systolic pressure is the peak pressure
b. diastolic pressure is the minimum pressure
c. pulse pressure must be at least 5 mm Hg
Similar rules hold for the peripheral arterial measurements, but here the criterion for rule c. is set to 10 mm Hg. Heart rate is determined as described above. Special care is taken to minimize the influence of artefacts.

Left Atrial and Right Atrial Pressure (24)

The inherent variability in atrial pressures is so great that it was decided to implement pattern recognition with the aid of the ventricular pressure recording measured simultaneously. The following definitions are used in addition to those described above for the LV and RV pattern recognition:
a. Atrial A wave pressure is the last atrial maximum before ventricular end-diastole,
b. Atrial X through pressure is the last atrial minimum before ventricular begin-diastole,
c. Atrial V wave pressure is the first atrial maximum after the X through
d. Atrial Y through pressure is the first atrial minimum after the V wave
Twenty seconds of data are recorded and the representative beat method is employed. Another program gives only mean, minimum and maximum values for the atrial pressures.

Cardiac Output

Cardiac output may be determined by several techniques, in the right heart, the most frequently employed method is thermo-dilution. The catheter is placed with its thermistor in the pulmonary artery (13,14), the indicator is injected through a separate lumen of the same catheter in the right atrium.
The computer is informed through the keyboard about:
1. Thermistor characteristics: ohms/degree celsius
2. Volume of injectate
3. Temperature of injectate
Heart rate is taken as the most recent determination while body dimensions (weight and height) were keyed in at the beginning of the cardiac catheterization. Calibration of the sensitivity of the thermistor bridge has been automated by introducing a standard resistor instead of the thermistor through a computer operated relay. The following sequence of distinct events is recognized:
1. A smooth baseline temperature for at least 2 seconds
2. A steep upslope in the signal corresponding to the onset of the calibration step
3. A smooth top to the calibration step for at least 1 second
4. A return of the signal to baseline level for at least 0.5 seconds (after which integration of the thermal curve begins)
5. A return of the signal to less than 40% of peak deflection after which

integration stops and cardiac output is calculated using an exponential fit to the descending limb of the measured data

The Stewart-Hamilton Equation modified for thermodilution is used to calculate cardiac output.

$$C.O. = \frac{V \times 1.08 \times (TB - TI) \times 0.825 \times 60}{\int \Delta TB \, dt \times 1000}$$

where C.O. = cardiac output in l/min
V = volume of injectate in ml corrected by 0.5 ml for residue left in catheter
1.08 = a constant incorporating specific heats and densities saline and blood
TB = initial temperature of patient (blood)°C
$\int \Delta TB \, dt$ = area under thermal curve in °C × sec
60/1000 = conversion factor for l/min
0.825 = correction factor to allow for heat exchange within the catheter, RA and RV

Cardiac output can also be evaluated by the direct Fick method, but here individual variables are measured off-line and keyed in by the technician.
The formula used is:

$$CO = \frac{O_2 \text{ consumption}}{(A-V)O_2 \text{ difference (vol \%)}}$$

where O_2 content = 1.34 Hemoglobin × O_2 saturation
(in gm %)

As an additional option cardiac output itself, determined by any other method may be directly entered into the cath record at any time during the procedure. On-line processing of indicator dilution techniques using fiber optics is being developed (25).

Body Surface Area

Body surface area (BSA) in m^2 is calculated by the formula of DuBois:

$$BSA = .00718 \times W^{.425} \times H^{.725}$$

where W is weight in kilograms and H is height in cm (25), all appropriate cardiac parameters and variables are normalized for BSA.

Valve Areas

Using the measured pressure gradient and the cardiac output, valve areas are

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determined by the formula of Gorlin (1,2), for stenotic mitral and aortic values.

For the mitral valve the mean diastolic gradient $\triangle P_{mv}$ is determined and the valve area (in cm^2) is estimated by:

$$MVA = \frac{Flow_{mv}}{31\sqrt{\triangle P_{mv}}} \ , \ Flow_{mv} = \frac{CO \ (ml/min)}{diast. \ filling \ period \ (sec/min)}$$

Similarly for the aortic valve:

$$AVA = \frac{Flow_{aov}}{44,5\sqrt{\triangle P_{aov}}} \ , \ Flow_{aov} = \frac{CO \ (ml/min)}{syst. \ ejection \ period \ (sec/min)}$$

where $\triangle P_{aov}$ represents mean the systolic gradient.

Resistance to Flow (26)

Mean systemic and pulmonary resistance are calculated by dividing mean pressure gradient by mean flow using the latest data available:

$$S.V.R. = \frac{\overline{AO} - \overline{RA} \times 80}{C.O.} \quad dynes \quad sec \quad cm^{-5}$$

$$P.V.R. = \frac{\overline{PA} - \overline{LA} \times 80}{C.O.} \quad dynes \quad sec \quad cm^{-5}$$

where   S.V.R.   = systemic vascular resistance
        P.V.R.   = pulmonary vascular resistance
        $\overline{AO}$ = mean aortic pressure in mm HG
        $\overline{PA}$ = mean pulmonary arterial pressure in mm Hg
        $\overline{RA}$ = mean right atrial pressure in mm Hg
        $\overline{LA}$ = mean left atrial pressure in mm Hg
        C.O.   = cardiac output in l/min

Oximetry

A program to perform all the generally accepted oximetry calculations has been developed and documentation is in preparation. The basic approach taken here is one of statistical evaluation of the significance of changes in mean values using the student T-test.

Final Patient Record

At the end of the procedure a final patient report may be requested. This gives in chronological order all those measurements made during the procedure. For inclusion in the patient file a summary is produced, listing all relevant parameters (figure 4).

```
                    SUMMARY CATHETERIZATION DATA
                       CATH. LAB. M. F. R.
     CODE NR. : 9281 REG. NR.          DATE:26-MAR-75
     NAME:                 MALE        LENGTH 1. 83 M
     AGE :48:07 YRS   WEIGHT  73 KG    B. S. A 1. 94 SQ. M
     PROCEDURE :
     DIAGNOSIS :
     SITE    PRESSURE    O2 CARDIAC OUTPUT          RESISTANCES
             PHASIC MEAN     O2 UPTAKE     : 244 ML/MIN PULM.  : 340 DSC-5
     S. C. V.              74 CARDIAC OUTPUT: 5. 8 L/MIN SYSTEM:1940 DSC-5
     I. C. V                 CARDIAC INDEX :2. 98      SHUNTS
     R. A.     3/ 0     1  76 HEARTRATE    :  81 B/MIN R-L:        L/MIN
     R. V.              76                            L-R         L/MIN
     P. A.    12/ 5    8  77
     P. C. W.  7/ 3    6                         MITRAL   AORTA
     L. A.                 MEAN GRADIENT                    MM HG
     L. V.  109/ 1/10     97 VALVE AREA                     SQ. CM
     AO.    121/ 76  97     HEART RATE                      B/MIN
     A. B.

     L. V. FUNCTION: P=PRESSURE , V=VIDEOMETRY , A=ANGIO
                      P
     EDV                          ML/SQ. M 50-90
     ESV                          ML/SQ. M 15-35
     TOTAL S. V.                  ML/SQ. M32-58
     FORWARD S. V.                ML/BEAT 75
     REGURG. FLOW                 L/MIN 0
     EJEC. FRACTION               0. 56-0. 78
     HEART RATE         74        B/MIN
     DP/DT PEAK        1423       MM HG/SEC 1500
     STRESS PEAK                  GR/SQ. CM 250-450
     VCE PEAK           38        SEC-1 40-75
     V-MAX              47        SEC-1 42-76
     L. V. MASS.                  GR/SQ. M 76-108
     L. V. WTH.                   CM 0. 8-1. 8
     ATRIAL PACING STRESS TEST:                  ANGIO
     PAIN AT            :     B/MIN              INJ.      RESULT
     ECG POS. AT        :     B/MIN
     WENCKEBACH BLOCK AT:     B/MIN
     RATE  LVP   LVEDP   PK DP/DT  PK VCE   VMAX
       83  113    11      1776      51. 6    58. 7
       90  117    10      1810      48. 8    56. 2
      101  113     9      1956      52. 5    58. 6
      111  113    10      2048      57. 7    56. 9
      119  115     6      2081      61. 6    66. 4
      129  114     5      2001      62. 1    68. 5
      140  113     5      2048      58. 2    74. 6
      150  116     4      2343      58. 3    83. 1
      161  119     4      2727      66. 7    95. 4
      169  123     5      2805      67. 7    93. 6
```

Fig. 4. Summary of catheterization for patient file, listing pressures, oxygen saturations and derived parameters. Results of quantitative angiocardiography and stress tests are also given. Another more extensive summary containing all acquired catheterization data is filed on digital tape as well as in written form.

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CHAPTER IV

QUANTIFICATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE

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METHODOLOGY: AUTOMATIC DATA PROCESSING

ATRIAL PACING STRESS TEST
   Materials and Methods
   Results
   Left Ventricular Systolic Pressure and Cardiac Output
   Left Ventricular End Diastolic Pressure
   Contractility Indices
   Conclusions for the APST

REGIONAL LEFT VENTRICULAR WALL MOTION
   Patient Material and Ventriculography
   Data Acquisition Hardware
   Characterization of the Normal Ventriculogram
   Quantification of Regional Shortening
   Failure Mode
   Regional Shortening in Normals
   Identification of the Apex
   Conclusions for Regional Shortening

DYNAMIC VENTRICULOGRAPHY

Evaluation of left ventricular function using conventional hemodynamic measurements in patients with chronic coronary artery disease (CAD), except in the late stages of the disease, is often not effective in separating normal and abnormal individuals (Hugenholtz et al., 1976). The reason for this seems to be the nature of the disease and the tremendous reserve capacity of the heart. In the majority of patients CAD is manifested as a localized narrowing in one or more of the main coronary arteries. The limited regions distal to the obstruction are affected, while other, possibly well-perfused, regions are able to compensate for any diminished performance by their neighbors. The resulting reduction in reserve capacity may not be manifest, except during moderate physical activity or stress. If the early functional consequences of CAD are to be determined, diagnostic methods must be developed that consider the two concepts of diminished reserve capacity and coexistent regional dysfunction.

Recent developments in this field have been aimed toward developing sensitive stress tests of reserve capacity and methods for directly detecting regional disturbances in myocardial wall motion. For the stress tests we shall limit the scope of this chapter to variables directly measured from left ventricular pressure and exclude indirect measurements of hemodynamics.

Several stress or functional testing techniques have been developed for estimating reserve capacity. These include: bicycle ergometry (McCallister et al., 1968; Weiner et al., 1968; Redwood et al., 1977; Thadani et al., 1977), isometric handgrip (Amende et al., 1972; Krayenbuehl, 1974; Krayenbuehl et al., 1974; Ludbrook, Karliner, and O'Rourke, 1974), a variety of medications [isoprel (Ross and Braunwald, 1964; Chiong et al., 1972), nitroglycerine (Dove, Shaw, and Schreiner, 1974; Klausner et al., 1976)], and atrial pacing (Cross, 1970; Forrester et al., 1971; Linhart, 1971; Graber et al. 1972; Pasternac et al., 1972; McLaurin et al., 1973a,b; Piessens et al., 1974; Krayenbuehl et al., 1975a,b; Van den Brand et al., 1975). For reasons discussed below, we shall concentrate on the atrial pacing stress test (APST). Basically, the procedure (Figure 1) calls for placing a bipolar pacing catheter in the right atrium of the subject, and a high fidelity tip manometer in the left ventricle (LV). As the atrium is paced, with increasing frequency in steps of 10–20 bpm increments every 2 min from basal heart rate (HR) to the highest sustainable rate, hemodynamic variables, such as end diastolic pressure, peak rate of change of pressure, etc., are recorded from the LV. The automatic data processing equipment (Figures 1 and 2) greatly assists in the systematic
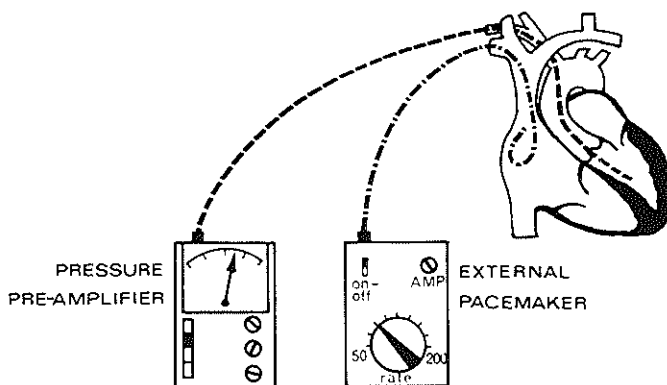
Figure 1. The methodology for performing the atrial pacing stress test includes a bipolar pacing catheter positioned in the right atrium, and a high fidelity tip manometer placed in the left ventricle. As the pacing is increased to the highest sustainable rate, automatic data processing equipment determines such quantities as end diastolic pressure and peak rate of change of pressure throughout the test.

and rapid on-line analysis of these data.

In principle these same measurements can be carried out on all five of the previously mentioned stress tests. However, the first three present some ambiguities about the actual stress seen by the heart. They all produce significant concomitant reflex, hormonal, and biochemical changes that are not easily measured or controllable. For the exercise tests, in particular, the ultimate stress endured by the patient is profoundly affected by such nebulous factors as his cooperativeness, patience, mood, pain threshold, and the tenacity of the clinician. The atrial pacing stress test avoids many of these difficulties. The test can be applied to the patient at rest, thus obviating any unwanted systematic change caused by muscular exercise, and the stress (increased HR) can be controlled exactly, both in duration and amplitude, thus removing most psychic factors completely. Nevertheless, all these methods are currently being explored.

There is one further property of the APST that is attractive to the control engineer. That is, by pacing the heart, we decouple the ventricle from nervous control of HR, which is a complex feedback system including the baroreflexes and the CNS. This ability to override the physiological signal controlling HR presents the possibility to study, in greater isolation, the performance of the ventricle directly. The first part of this chapter is therefore devoted to describing the recent research establishing the clinical value of the atrial pacing stress test.

Work on the second and interrelated aspect of the regional short-

ening pattern has been based, until recently, exclusively on angiographic measurements (Zimmerman, 1966; Gensini, 1975). A viscous radiopaque contrast material is injected into the left ventricle through a catheter introduced via either the femoral artery (percutaneous) or brachial artery (arteriotomy). This contrast material is filmed in either monoplane (right anterior oblique, then left anterior oblique projections) or biplane (anterior-posterior and lateral simultaneously) at 12–60 frames/sec (Yang et al., 1972). Until the recent introduction and systematic evaluation of quantitative techniques for analyzing these data, the film was reviewed entirely ''by eye'' and coded subjectively (Austen et al., 1973). Indeed, this procedure is followed today in the majority of clinics in spite of the serious and known problems with observer variability (Armitage et al., 1966; Zir et al., 1976). The latter half of this chapter is devoted to examining these advanced techniques for quantifying segmental wall motion from cine ventriculograms.

METHODOLOGY: AUTOMATIC DATA PROCESSING

Manometry and ventriculography are among the most important and direct diagnostic activities in the cath lab. Both are time consuming and yet employ well-established analytic methodologies (Yang et al., 1972), the introduction of automatic data processing in these two areas was a logical development (Henry et al., 1968; Groth et al., 1975; Meester et al., 1975; Brower et al., 1977). Because much of this work has appeared in specialized journals, and then only in the last few years, it would be useful at this stage to review those areas pertinent to the two major themes of this report. This serves not only as a description of the technology employed in our laboratory but sheds some light on the growing area of automatic data processing in the clinic.

The hardware organization for our cath lab is illustrated in Figure 2, with emphasis on the information processing hardware. The four major divisions (computer room, angioanalysis, recording area, and cath lab), with one exception, correspond to the actual location of the system components. The A-D converter actually resides in the cath lab near the analog equipment. Thus all data transmission to the computer is in digital form. The centralized and dedicated computer consists of a PDP 11/20 (16 K core + 4 K TV display), RK05 disc with DEC tape backup, teletype, and an eight-channel analog-digital converter as well as a number of specially constructed interface devices to handle information transfer to or from display and data acquisition

COMPUTER ROOM   RECORDING AREA
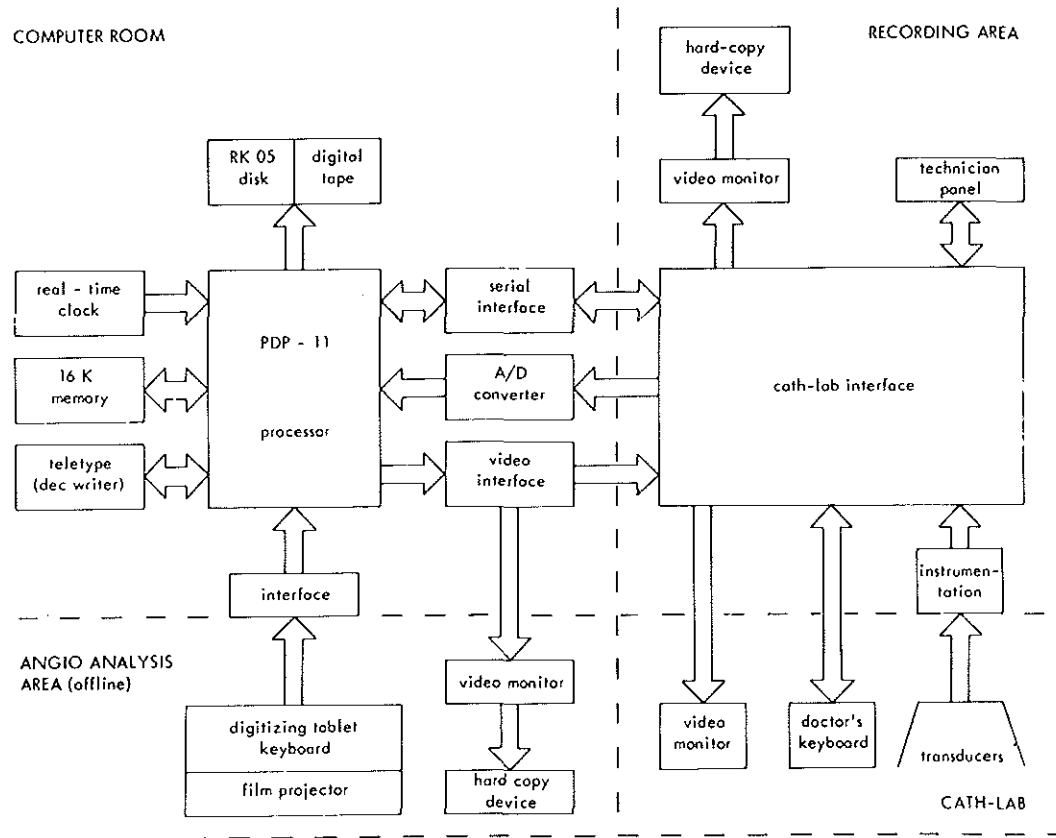
Figure 2. The organization of the hardware for the on-line analysis of the catheterization data is shown here separated into the catheterization laboratory, computer room, recording area, and angioanalysis area. The computer consists of a PDP 11/20, 16 K core, RK 05 disc, and ancillary DEC tape units.

devices. The disc is used for the storage of program modules (executive, applications programs, and utilities). It also is a temporary storage medium for physiological signals that serve as input for some analysis programs. The digital tape unit serves as a permanent medium for the storage of derived parameters, patient records, and the catheterization log.

The video interface was developed to provide a standard video signal that could be connected to the existing x-ray video monitor. While the x-ray equipment is in use, the TV monitor is automatically switched to the x-ray image intensifier. The video monitor and hard-copy facilities are identical for both on-line (manometry) and off-line (ventriculography) activities. The TV monitor resolution is 256×256 points, allowing up to 25 lines of text of 36 characters each. The same device is used for graphics display, and a TV display driver program has been written specifically for this task.

A physician keyboard handles all communication between the cardiologist and the computer. This can consist of: the site of the catheters (LV, aorta, left atrium, etc.) for manometry, blood sampling or flow measurement (data from up to three catheters may be used simultaneously); choice of special functions or procedures (e.g., thermal dilution cardiac output, atrial pacing stress test, oximetry); and process control (accept or reject measurements, calibration, final report, graphics, registration of a new patient). In total there are 13 distinct survey mode modules capable of carrying out most routine manometry calculations. The catheter position(s), as indicated on the physician keyboard, automatically make available the appropriate survey mode software. This is summarized in the first column of Table 1.

A separate panel also allows the technician working in the non-sterile recording area to control system function without disturbing the ongoing cath-room activities. Both the technician panel and the physician keyboard communicate with the computer through a parallel-serial interface, greatly reducing the number of cables required between the cath lab and the computer.

The analog or "front end" equipment is controlled by the technician in the recording area. This includes the electrical isolation, preamplifiers, and filters for the ECG, temperature, flowmeters, fiber optics, pressure, or off-line entry of tape-recorded signals.

Pressure calibration is performed electronically and automatically under computer control. The computer uses the electronic calibration and the hydraulic calibration (as provided by the technician) as a check on the baseline and gain setting of the carrier amplifiers. All trans-

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Table 1. Summary of software modules used by the on-line catheterization laboratory computer system at the thorax center

Survey mode		Special procedures mode
Program	Catheter location(s)	
Left ventricular pressure	LV	Thermal dilution
Right ventricular pressure	RV	Oximetry
Aortic pressure	Ao	Pull back
Pulmonary artery pressure	PA	Pacing test
Left atrial pressure	LA	Calibration
Right atrial pressure	RA	Beat to beat
Peripheral artery pressure	AR	Trace
Central venous pressure	CV	Heart overview
Pulmonary wedge pressure	PW	Summary (last data)
Aortic valve	LV,Ao	Patient report
Pulmonary valve	RV,PA	
Mitral valve	LV,LA	
Tricuspid valve	RV,RA	

ducers are positioned at mid-thoracic level (Brower et al., 1973). At the start of data collection calibration is checked automatically and adjusted if the signal is not within range of the A-D converter. The calibration is shown in the pressure recording by the pressure analysis modules called into core. The R wave of the ECG is not used as a means for identifying pressure phenomena because R wave detectors are considered inadequate for this purpose. We feel that pattern recognition in a pressure trace should not be based on another signal with different characteristics.

Normally a catheter-tip manometer is employed with the bandwidth limited electronically to 100 Hz (critically damped), A-D sampling rate is standardized at 250 samples/sec for all signals and the resolution is better than 0.1% full scale. Fluid-filled manometers can be used, with consequent errors in several measured and derived quantities (Shapiro and Krovetz, 1970; Brower, 1973; Brower et al., 1975). The occurrence of arrythmias during catheterization, especially premature ventricular contractions, is a complicating factor in the analysis of the pressure data. Such beats are generally discarded before analysis. This approach is implemented in the software by using the "representative beat method" introduced by Stenson (Stenson et al.,

1968; Henry et al., 1968; Harrison et al., 1971). A sequence of consecutive beats is ranked in terms of increasing magnitude of peak pressure. The higher third and lower third of the values in this sequence are rejected and the average of the middle third of the values in this sequence is computed. As a compromise between the time required for the measurement, accuracy of the estimate, and computer storage space, the total sampling period is limited to 20 sec or until 12 beats are digitized.

Although the precise definition of the indices for quantifying the atrial pacing stress test is presented in later sections, some aspects of this software are pertinent to the present discussion. For example, the rate of change of pressure, dP/dt, is calculated digitally using a 5-point Lagrange polynomial approximation with a 4-msec increment between steps (sampling rate = 250 sec^{-1}):

$$dP/dt \mid_{t=T} = \frac{P_{T-4} + 8(P_{T+2} - P_{T-2}) - P_{T+4}}{0.096} \text{ mm Hg/sec}$$

where $T + j$ signifies $t = T \pm 4j$ msec. All the contractility indices (peak dP/dt, peak $dP/dt/P$, and V_{max}) employ this basic measurement of dP/dt. The further explanation of these variables and those employed in ventriculography is given below.

The ventriculographic data acquisition hardware, in the angioanalysis area, consists of a digitizing table (Graf/Pen) with a built-in keyboard (see Figure 3). The principle of operation is that a hypersonic pulse is generated at the tip of a cursor and the transit time to two linear microphones is determined by an internal clock. The resolution of the x-y coordinates is better than 0.3 mm (0.1 mm in the most recent apparatus). The active digitizing area is 70 × 70 cm, but units of 32 × 32 cm are more commonly used. This device also contains a keyboard. It also operates on the ultrasonic transit time principle, but the software keyboard driver interprets coordinates coming from the keyboard area as containing alphanumeric information. The keyboard follows the standard teletype format with 10 special function keys that are generally used for process control instructions. Programs also exist whereby this same hardware can be used for the off-line analysis of pressure tracings, thermal dilution curves, and echocardiogram recordings. The TV monitor (Figure 3) is used for quality control and for reporting results of the calculations. A hard copy unit, not shown, is used for recording the angiographic report.

This brief review of our cath lab computer system provides some idea of the level of complexity at its current stage of development.

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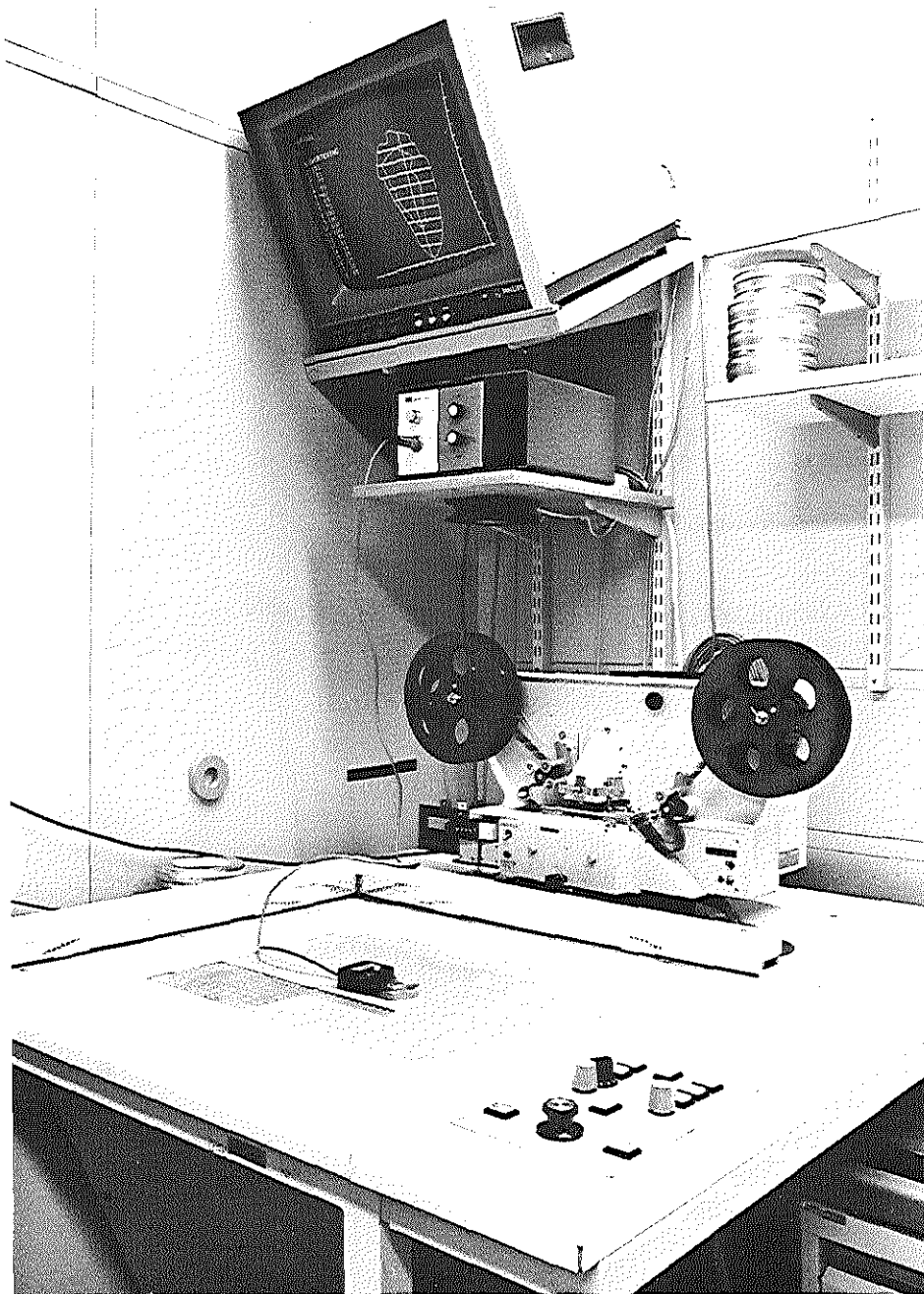
Figure 3. The Graf/Pen digitizing system is used to determine the coordinates of a left ventricular (LV) contour traced by a cursor. The coordinates are determined by the transit time of a hypersonic pulse from the cursor to two linear microphones. This equipment is used for data acquisition of ventriculograms.

The major reasons for its use and continued support are improved quality control, greater reliability of the results, consistent pattern recognition and calculation rules, and increased productivity of the staff.

ATRIAL PACING STRESS TEST

The analysis of the atrial pacing stress test (APST) first introduced by Sowton et al. in 1967 has been greatly facilitated by the introduction of automatic data processing systems. The systematic and rapid analysis of the mass of data emerging from this procedure has done much to advance the state of the art in this field. Nevertheless, the evidence demonstrating the diagnostic value of the APST has not been conclusive (Dwyer, 1970; Khaja et al., 1970; Parker, Khaja, and Case, 1971). The majority of studies have been limited to small groups of patients without a clear definition of the normal range or the most sensitive and specific ways of analyzing the data.

In this context a brief review of the status of pressure-derived contractility indices would be helpful. LV pressure (P) is related to mid-wall circumferential stress by:

$$\sigma = \frac{P(M + h)}{2h} \left[1 - \frac{(M + h)^3}{2L^2(M + 2h)} \right] \tag{1}$$

as derived by Sandler and Dodge (1963) and further developed by McHale and Greenfield (1973). M is the minor axis; h, wall thickness; and L, major axis. If we consider only the isovolumic period and assume that M, h, and L do not change during this period, then:

$$\frac{d\sigma/dt}{\sigma} = \frac{dP/dt}{P} \tag{2}$$

where this construct has totally removed the geometric factors. Thus the easily measured quantity $dP/dt/P$ is directly related to a fundamental property of the myocardium, the normalized rate of stress development in the LV wall during the isovolumic period.

This fact alone would justify interpreting and using $dP/dt/P$ as a contractility index, but the historical basis extends somewhat further into muscle physiology. It is in this area that the greatest controversies have arisen. The derivation of the contractility indices is included here because it has formed a framework within which much of the most critical work has focused. The Maxwell muscle model is shown in Figure 4. During systole, the stress (σ) is carried primarily by the

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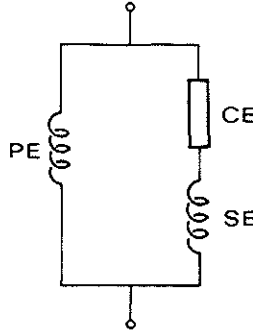
Figure 4. The Maxwell muscle model, originally developed for skeletal muscle, was adopted for cardiac mechanics and used in the development of the V_{max} concept. It is now largely disputed as a valid model for this purpose, but is of historical interest. The contractile element (CE) is in series with an undamped nonlinear series elastic (SE) element. The CE does not contribute to resting tension, which is borne by the parallel elastic (PE) element.

series elastic (SE) and contractile element (CE). Sonnenblick (1962, 1964, 1967), studying cat papillary muscle, reported that the velocity of shortening, V_{CE}, is load-dependent, but that a hypothetical maximum velocity of shortening (V_{max}) exists under zero loading, which is relatively independent of initial stretch or after loading.

The SE stress-strain relationship (Brady, 1967; Sonnenblick, 1964; Parmley and Sonnenblick, 1967) is governed by:

$$\frac{d\sigma}{dl} = K\sigma + C \tag{3}$$

Assuming that the contractile element shortens by extending the series elastic during isovolumic contraction:

$$V_{CE} = dl/dt = \frac{d\sigma/dt}{(K\sigma + C)} \tag{4}$$

During systole $K\sigma \gg C$, hence:

$$V_{CE} = \frac{d\sigma/dt}{K\sigma} \tag{5}$$

Generally, K is found to be a constant between 28 and 32, but more often the quantity $K \cdot V_{CE}$ is determined, and for the sake of brevity is referred to as V_{CE}.

Thus if one were to plot $K \cdot V_{CE}$ versus σ and extrapolate to $\sigma = 0$ (no loading) an estimate of the contractility index (V_{max}) would be obtained. Because σ is not easily measured in man, Equation 2 is
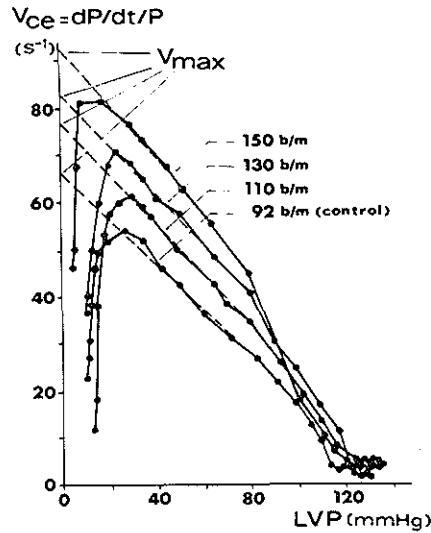
Figure 5. $K \cdot V_{max}$, usually referred to as V_{max} for brevity, is determined by extrapolating the isovolumic phase of the $(dP/dt)/P$ versus P curve to $P = 0$. Four recordings from the same normal subject (man, 32 years) are shown. They correspond to a pacing rate of 92, 110, 130, and 150 bpm. In our laboratory this calculation is now generally performed by automatic data processing equipment.

substituted. Thus $K \cdot V_{max}$ is determined as shown in Figure 5. This illustrates the $(dP/dt)/P$ versus P plots and how the computer extrapolates to $P = 0$ to obtain V_{max} at the four indicated heart rates. The constant K is dropped.

The constant K, as determined by "quick release" experiments (Sonnenblick, 1967; Noble, Bowen, and Hefner, 1969) in cat papillary muscle, has not been directly measurable in man. There is also no basis to assume that it does not vary with the extent of disease. Indeed, Muise, Wong, and Rae (1977) have shown that it increases with severity of CAD and, when properly estimated, causes a further reduction in the quantity $K^{-1}(dP/dt)/P$.

As mentioned above, this derivation is interesting mostly for historical reasons. The most recent work has focused on the validity of the assumptions, the concept of V_{max}, and the muscle model itself (Pollack, 1970; Pollack, Huntsman, and Verdugo, 1972; Noble, 1972, 1973). Indeed, 7 element models have been proposed to describe all the known mechanical characteristics of the myocardium. Current use of such parameters as dP/dt and $(dP/dt)/P$ is largely based on empirical findings and the assumption that Equation 2 still allows one to indirectly measure the contractile properties of the myocardium during

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routine cardiac catheterization. Recently several studies have appeared comparing the dP/dt based indices (Kreulen et al., 1975; Blumlein et al., 1976; Naqvi et al., 1976; Quinones, Gaasch, and Alexander, 1976; Spadaro et al., 1976; Brower et al., 1977). It seems that V_{max}, in spite of the valid criticisms of its derivation, is less dependent on extraneous loading factors than max $(dP/dt)/P$, or any parameter based on developed pressure, but not greatly superior to peak dP/dt. It is also clear that a great deal of the conflicting literature on this subject is due to a lack of standardization on high fidelity tip manometry and in the analytic techniques used to extrapolate (linear, exponential, and hyperbolic fits) to zero loading. As a result there has been a return to the more straightforward measurements, such as peak dP/dt (Quinones, Gaasch, and Alexander, 1976), which had earlier been shown to be unsatisfactory as too dependent on preload (Mason, 1969; Mason et al., 1971). In this report both peak dP/dt and V_{max} (linear extrapolation) are reported. Our approach is to consider V_{max} and dP/dt as normalized measurements of the rate of pressure development with, in some cases more than others, relative independence of preload and afterload.

This short review of the basis for the contractility indices notwithstanding, the APST in practice requires establishing the range in normals and limits for values associated with unambiguous pathology. Therefore, the remainder of this section on the APST is devoted to establishing the normal response and showing in what ways this is different in patients suffering from symptomatic coronary artery disease.

Materials and Methods

Patients A total of 217 patients were studied. Fifty-seven were found to be free of coronary artery disease (mean age = 44 years; 39 males, 18 females). None of these, hereafter referred to as "normals," had signs of a previous myocardial infarction.

The resting ECG was normal. Cardiac catheterization showed normal ventricular function [mean ejection fraction (EF) = 67%, SD ± 6%] and normal coronary vasculature. Cardiac output for the normal group was 6.65 liters/min (SD ± 1.47). The ratio of 57 normals in 217 cases is not the fraction of normals usually seen in our catheterization laboratory as an effort was made to include every normal seen since the introduction of the APST over a 6-year period.

160 patients (153 males, 7 females, mean age = 50 years) having

CAD of at least 50% obstruction were entered consecutively over a 2-year period. Cardiac output was 6.10 liters/min (SD ± 1.54). These patients could be further classified as follows. Forty-three had a single vessel diseased, 61 had two vessels diseased, and 56 had three or more vessels diseased. Of the 160 proven CAD cases, 120 had technically adequate ventriculograms: 68 had normal EF (>56%), 24 had a moderate EF (56% > EF ≥ 44%), and 28 had a low EF (<44%). Finally, 77 of the CAD cases had a history of infarction, while 83 did not. With one exception, all patients with an EF less than 44% had a history of previous infarction.

Atrial Pacing Stress Test Beta blockade was withdrawn at least 24 hr before catheterization. Following right heart catheterization and measurement of cardiac output (thermodilution) a bipolar pacing electrode catheter was placed high in the right atrium. Left ventricular pressures were recorded by either a Dallons-Telco MMC 8F or a Millar Instruments 7F tip micromanometer catheter.

After control determinations of left ventricular pressure, the APST was started at a level just above control heart rate. One to two minutes was allowed for stabilization. The pacing rate was then increased in steps of 10–20 bpm and measurements repeated. Pacing was continued until: 1) a rate of 180 bpm, 2) the onset of chest pain, or 3) atrial-ventricular node (AV) dissociation occurred or recurring extra systoles made the interpretation of the results doubtful. The following left ventricular pressure-derived variables are reported:

1. peak LV systolic pressure (LVSP, mm Hg)
2. LV end diastolic pressure (LVEDP, mm Hg)
3. peak positive first derivative of LV pressure (*PK dP/dt*, mm Hg/ sec)
4. $(dP/dt)/P$ extrapolated to $P = 0$ (V_{max}) using a linear least squares fit from peak $(dP/dt)/P$ to the beginning of ejection

Analysis Methods The following analytic tests were used to quantify the measurements from the APST:

1. Basal values, the value of the test variable at the basal heart rate.
2. HR range $R_1 - R_2$, the value of the test variable at the heart rate closest to $(R_1 + R_2)/2$, but not exceeding the range R_1 to R_2.
3. Heart rate R_x, the value of the test variable at rate R_x, interpolated between R_a and R_b, $R_a < R_x < R_b$

$$V_x = V_a + (R_x - R_a)(V_b - V_a)/(R_b - R_a) \tag{6}$$

4. Highest paced value, the value of the test variable at the highest paced heart rate.

5. Slope all data, the mean slope of the test variable against HR as estimated by linear regression over the entire paced HR range

$$\text{Slope} = \frac{\Sigma R i \Sigma V i - N \Sigma (R i \ V i)}{(\Sigma R i)^2 - N \Sigma R i^2} \tag{7}$$

6. Curvature at HR = 100, the effective curve at HR = 100 bpm as estimated by fitting the parabolic equation $V = A + B \times R + C \times R^2$ over the entire HR range where V represents the test variable and R the heart rate. Curvature K at a HR of 100 bpm was defined as

$$K = \frac{d^2 V / dR^2}{[1 + (dV/dR)^2]^{3/2}}$$
$$= \frac{2C}{[1 + (B + 2 \cdot C \cdot 100)^2]^{3/2}} \tag{8}$$

Items 1–6 were calculated for each pacing test and the results for each major group of patients averaged. The standard deviation, median, and 67% range were also calculated. The 67% range represents the range included by the lower one-third and upper one-third of the measurements rank ordered about the median.

Results

The results of the atrial pacing stress test for the 57 normals and 160 patients with CAD are listed in Table 2. The first three columns in Table 2 list the mean value, standard error of the mean (SE = SD/ $n^{1/2}$), and the 67% range for the normals, while the second three columns give the same determinations for the CAD group. The final column lists the probability that the difference in mean values between the normals and CAD group arises by chance.

As shown in Table 2, the basal HR for the normals is 74.5 ± 1.2 bpm while the highest paced HR is on average 147.5 ± 2.6 bpm, which is a 98% increase from basal conditions. In 27 cases pacing was terminated before reaching a rate of 150 bpm because of AV dissociation. For the CAD group the basal rate is 71.9 bpm, which is not significantly different from the normal group. However, the highest paced rate for the CAD group is approximately 137 bpm, which is significantly less than that for normals ($P < 0.001$). In fact, the measurements for the heart rate range 130–150 bpm for the CAD group

is deleted in Table 2, because one-half could not be paced beyond 140 bpm. This difference in the highest paced rate between normals and CAD is primarily because of the onset of ischemia, but AV block is also seen. Thus, the failure to reach a high paced HR in many cases of CAD is attributable to multiple causes, the most frequent of which is pain, while in normals the reason is predominantly AV dissociation.

Left Ventricular Systolic Pressure and Cardiac Output

For normals LVSP shows a small and physiologically unimportant drop of 8 mm Hg (-6.2%) from basal to the highest paced rate. For the CAD group this is even less (-5.2%). In no instance does peak systolic pressure show a significant difference between normals and the CAD group. The relatively small variation of LVSP with HR for both groups is consistent with previous reports (Bahler and MacLeod, 1971; Krayenbuehl et al., 1975a,b; Schmidt et al., 1976). LVSP is reported to increase slightly, but not significantly, with HR. However, our data show a slight decrease. This discrepancy may be caused by our consistent use of tip manometry. Fluid-filled manometers over-estimate peak systolic pressure and the error is greatest at high heart rates (Shapiro and Krovetz, 1970; Brower, 1973; Brower et al., 1975). It is known that cardiac output does not vary significantly with paced HR (Dwyer, 1970; Khaja et al., 1970; Parker, Khaja, and Case, 1971) except for an initial transient increase when the pacing rate is increased. As peripheral resistence is not directly affected by pacing, the relative constancy of LVSP is a reasonable expectation.

Whatever changes occur in LV myocardial stress at the beginning of ejection can be attributed to changes in wall thickness and chamber dimensions. That is, stress as shown in Equation 1 is given by the product of pressure and geometric factors. If peak pressure, and presumably aortic end diastolic pressure, does not change with pacing, a decrease in stress can be anticipated from the simultaneous decrease in internal dimensions and an increase in wall thickness.

Left Ventricular End Diastolic Pressure

The data in Table 2 shows that LVEDP for normals is reduced by 56% from basal HR to the highest paced rate, while for the CAD group there is a 28% decrease. There is a significant difference between normals and the CAD group at all pacing rates, but the difference is

greatest at the highest paced rate ($P < 0.00001$). As shown by the positive curvature, LVEDP has a tendency to curve upward, but retains a negative slope throughout the paced HR range. Whether or not the LVEDP increases at the highest paced rate is often taken as a sign of the severity of CAD.

This possibility is explored further in Figure 6, which shows LVEDP for normals and for the CAD group subdivided into three groups by the value of the ejection fraction: group 1, normal EF (>56%); group 2, moderate EF (44–56%); and group 3, low EF (<44%). The data are plotted over the entire HR range, which extends slightly beyond the mean basal HR, and mean highest paced HR. For normals this clearly shows the tendency for LVEDP to decrease with increasing HR, but to level off at 140 bpm. In general the CAD group starts at a higher basal LVEDP value, decreases with increasing HR in parallel with that of normals, and for those patients with a low ejection fraction LVEDP actually shows an increase at the highest rates. It is remarkable that even for those CAD patients with a normal EF there is an apparent shift in the LVEDP measurements compared to normals. However, there is no important difference within the CAD
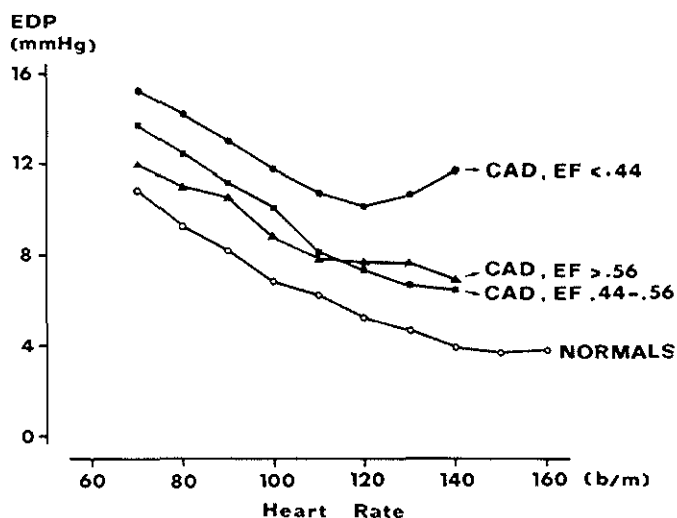
Figure 6. End diastolic pressure (EDP) versus HR is shown for the normals (SE = 0.50 mm Hg, n = 57), and three groups of patients with coronary artery disease (CAD) classified by ejection fraction (EF): EF < 0.44 (SE = 1.72 mm Hg, n = 26); EF 0.44–0.56 (SE = 1.18 mm Hg, n = 24); EF > 0.56 (SE = 0.67 mm Hg, n = 65). EDP decreases in parallel for low heart rates, but the difference becomes greatest at the highest paced rate. The most severely ill show an increase in EDP at the higher paced rates.

Table 2. Hemodynamic measurements during the atrial pacing stress test for 57 normals and 160 patients with coronary artery disease

Variable	Normal			Coronary Artery Disease			Significance
	mean	SE	67% Range	mean	SE	67% Range	
Heart rate (bpm)							
basal HR	74.5	1.2	68–80	71.9	0.9	60–83	NS[a]
highest paced	147.5	2.6	130–170	136.8	1.5	117–156	0.001
LVSP (mm Hg)							
basal HR	130	2.4	114–140	135	2.2	113–157	NS
70–90 bpm	129	2.5	110–140	134	2.2	112–156	NS
100–120 bpm	127	2.2	112–141	130	1.9	108–152	NS
130–150 bpm	123	2.3	108–137				
highest paced	122	2.2	107–136	128	2.2	106–146	NS
LVEDP (mm Hg)							
basal HR	10.6	0.48	7–14	13.0	0.46	8–17	0.005
70–90 bpm	9.5	0.48	6–12	11.8	0.46	7–16	0.005
100–120 bpm	6.5	0.44	3–9	9.0	0.46	4–13	0.005
130–150 bpm	4.4	0.52	1–7				
highest paced	4.7	0.54	1–8	9.4	0.56	4–13	0.00001
slope	−0.0815	0.0076		−0.0576	0.0086		NS
curvature	0.00280	0.00058		0.00303	0.00049		0.02

Pk dP/dt (dynes cm^{-2} sec^{-1})

basal HR	1897	55	1,465–2,255	1628	35	1,230–1,975	0.0001
70–90 bpm	1933	53	1,546–2,408	1675	34	1,292–2,022	0.0001
100–120 bpm	2151	56	1,725–2,545	1879	39	1,500–2,260	0.001
130–150 bpm	2440	87	1,800–2,995				
highest paced	2554	87	1,800–3,200	1996	50	1,472–2,530	10^{-6}
slope	9.00	0.653	4.40–13.5	5.66	0.436	1.13–9.62	0.0001
curvature	0.00021	0.00047		−0.0079	0.0061		NS

V_{max} (sec^{-1})

basal	57.3	1.4	49–67	48.1	0.86	39–58	10^{-6}
70–90 bpm	58.4	1.3	50–67	50.4	0.92	41–61	10^{-5}
100–120 bpm	67.2	1.6	56–79	57.2	1.1	45–70	10^{-6}
130–150 bpm	77.2	2.6	62–92				
highest paced	79.8	2.4	63–96	57.7	1.9	45–72	10^{-6}
slope	0.308	0.024	0.165–0.436	0.184	0.012	0.047–0.320	10^{-6}
curvature	0.00097	0.0015		−0.0027	0.00082		0.05

[a] NS = not significant.

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group between those with normal ejection fraction and a moderate EF. The discriminatory power of LVEDP seems most marked at the highest paced HR. The derived quantities, such as slope and curvature, show relatively little discriminatory power.

The decrease in end diastolic pressure (EDP) during pacing is generally interpreted as due to reduced diastolic filling. The most obvious hypothesis is that EDP declines along a heart rate-independent pressure-volume curve. Diamond and Forrester (1972) have shown that the diastolic pressure-volume relationship is governed by:

$$dP/dV = aP + b \qquad (9)$$

where P and V are end diastolic pressure and volume, respectively, and a and b are muscle parameters constant for any ventricle or group of similar ventricles. Recognizing that P and V vary with HR (here abbreviated as R):

$$dP/dR = (aP + b)dV/dR$$

Stroke volume, and thus filling volume, is given by CO/R. Previous studies have shown that for the majority of patients cardiac output (CO) does not change significantly during pacing (Dwyer, 1970; Khaja et al., 1970; Bahler and MacLeod, 1971; Parker, Khaja, and Case, 1971). Assuming that the reduction in volume is primarily caused by reduced filling volume, as heart rate increases:

$$dV/dR = -CO/R^2$$

Thus,

$$dP/dR = -(aP + b)CO/R^2$$

Integration leads to:

$$P = \frac{C \cdot \exp(aCO/R) - b}{a} \qquad (10)$$

where C is an integration constant that can be found by substituting measurements at the basal heart rate. Cardiac output for our group of normals is 6,650 ml/min, and in the CAD group 6,100 ml/min. Diamond and Forrester (1972) give values for a and b in normals ($a = 0.005$ ml^{-1}, $b = 0$ mm Hg/ml) and CAD patients ($a = 0.001$ ml^{-1}, $b = 0.12$ mm Hg/ml). The basal data for EDP and HR in Table 2, together with the above parameters, allow a direct evaluation of the equation for normals and CAD patients. The results are shown in Figure 7.

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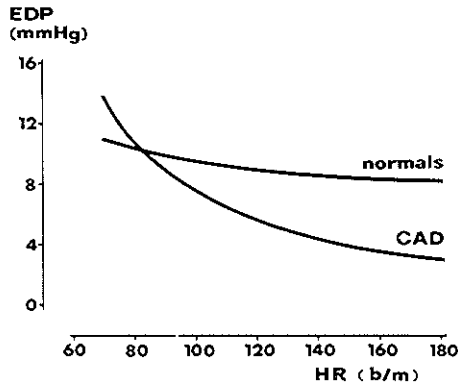
Figure 7. This predicted response of end diastolic pressure (EDP) during the atrial pacing stress test (APST) is based on a simple nonlinear compliance model. EDP decreases for both normals and coronary artery disease (CAD) group, but because the compliance in CAD is less than that in normals the model incorrectly predicts that EDP decreases more in the CAD group than in normals.

As expected, the simple model predicts that EDP decreases with HR for both groups. However, the analysis also predicts that pressure decreases more for CAD than in normals, which is the opposite of what has been shown to actually occur. In retrospect, the reason the model fails is apparent. For a given volume change (HR increase) the pressure change is the least in the most compliant ventricle. In chronic CAD compliance is less than in normals; thus for a simple but nonlinear compliance model the greatest pressure change is predicted for the CAD patient. Therefore, the simple compliance model is rejected. Three hypotheses emerge: 1) The compliance parameters a and b depend on HR, contrary to the conventional concept of compliance. 2) Incomplete relaxation causes a reduction in the early diastolic filling (Armitage, Blendis, and Smyllie, 1966). 3) Viscoelastic effects become significant at the higher heart rates. Grossman and McLaurin (1976), in a comprehensive review, have clearly summarized the current situation. None of these mechanisms can be ruled out, but current speculation is that there is a shift in the pressure-volume curve, i.e., that compliance is HR-dependent, possibly through a mechanism involving a long-time constant (>10 sec) and incomplete relaxation (Dwyer, 1970; McLaurin, Rolete, and Grossman, 1973a,b). However, such a result can also involve viscoelastic phenomena (Templeton, Echer, and Mitchell, 1972). There is some experimental justification for the pressure-volume curve shift from our laboratory. Figure 8 shows two diastolic log pressure-volume curves from the same patient, but at two

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different heart rates (a paced ventriculogram was performed). The shift of the curve toward lower volumes and a slight increase in slope can be interpreted as a HR-dependent increase in the parameters a and b of Equation 9, which presumably would return to control values after termination of pacing. This may also explain the observation that EDP often rises to a value greatly in excess of the basal EDP when HR is abruptly returned to the basal rate at the end of the APST. The shifted compliance curve is still in effect and the time course of EDP in the post-APST period follows the return of the parameters a and b to their basal values. In summary, a simple nonlinear compliance model fails to predict the difference in the EDP versus HR curve for normals or the CAD group. Other mechanisms, heretofore largely unexplored in this context, may be governing a shift in the diastolic compliance relationship, possibly coupled with incomplete relaxation.

Contractility Indices

The two isovolumic phase, pressure-derived indices (dP/dt and V_{max}; see Table 2) behave similarly. They increase with HR in normals and, to a lesser extent, in the CAD group. V_{max} shows the greatest percent increase, 39%, while peak dP/dt is slightly less sensitive, with a 35% increase. The standard errors for the isovolumic phase indices are
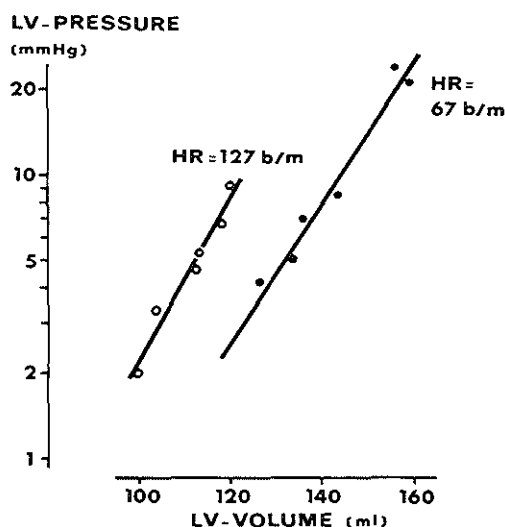
Figure 8. The log P-V curve (pressure-volume) during diastole is approximately linear when plotted in this manner. The relationship shows a shift toward higher pressure during pacing in this individual who had a normal atrial pacing stress test (APST). In this case, the parameters a and b of Equation 9 are heart rate dependent.

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generally less than 3% of the mean of the measured values, which is comparable to the measurement error (Brower, Roelandt, and Meester, 1971, 1974). V_{max} shows less overlap between normals and CAD, compared to peak dP/dt, especially at submaximal paced HR. For the purpose of discrimination between a normal individual and one with CAD, V_{max} seems superior to peak dP/dt. Figure 9 shows the V_{max}
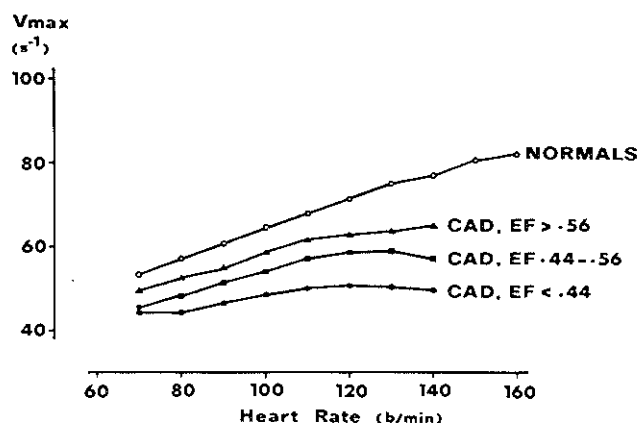
Figure 9. V_{max} is greater in normals than in the coronary artery disease (CAD) group and shows a nearly linear response over the paced heart rate (HR) range (SE = 1.91 sec^{-1}, $n = 57$). For the CAD group the basal value is least for the lowest ejection fraction (EF) group, shows little increase with pacing, and actually declines at the highest rate, reflecting the very limited reserve capacity in the low EF group. The pooled standard errors for the CAD group are: EF > 0.56, SE = 1.59 sec^{-1}, $n = 65$; EF 0.44–0.56, SE = 2.26 sec^{-1}, $n = 24$; EF < 0.44, SE = 2.56 sec^{-1}, $n = 26$.

versus HR curve for the normals and the CAD group, classified according to ejection fraction following the same criteria as in Figure 6. For normals, V_{max} increases linearly with HR over the range from 70–160 bpm. However, V_{max} for the CAD group starts at a lower value, increases to a lesser extent with increasing HR, and seems to plateau at a HR of 110 bpm for the moderate and lower EF group.

The apparent linear response of the normal's V_{max}, throughout the entire paced HR range, justifies the use of a straight line fit for calculating slope. For all the normal data taken:

$$V_{max} = 0.319 \times HR + 32.8 \ (s^{-1})$$

$$r = 0.75, \quad \text{SE} = 10.7, \quad n = 392. \tag{11}$$

Both V_{max} and peak dP/dt show their greatest discriminatory power at the highest paced HR, and the least at the basal rate. The slope of

the V_{max} versus HR response, as a measure of reserve capacity, is also more discriminatory than the slope of dP/dt.

Although V_{max} seems to have a straight line relationship with HR in normals, it is concave downward in CAD. This is also shown by the negative curvature at 100 bpm. However, the slope does not become negative for the CAD group as a whole. This is usually only manifest for the most severely ill CAD patient and, in part, justifies examining the shape of the pacing curves rather than looking only at specific paced values.

The physiological basis for the increase in performance with HR is generally ascribed to the Bowditch effect (Bowditch, 1871; Covell et al., 1967). While this predicts the direction of change, the prediction of the response curve in normals is severely handicapped by the lack of an adequate muscle and ventricle model. In view of the fact that the experimental findings prohibit the formation of a consensus on a realistic cardiac muscle model, the quantitative prediction of the dP/dt and V_{max} versus HR response curves is not likely. The mechanism by which CAD effects the V_{max} versus HR curve is generally ascribed to either changes in "series elastic" stiffness or a reduction in contractility because of ischemia. These are useful concepts, but at the moment, at least, do not lead to a quantitative prediction of the APST in CAD or even normals. Thus, the V_{max} versus HR curve, as is V_{max} itself, is an empirical index.

These results show once again the often observed fact that at rest hemodynamic measurements of about one-third of patients with CAD do not differ from those of normals. Of the 160 patients with angiographically proven CAD, over 25% had only one vessel diseased, 52% had no history of a previous infarction, and 57% had a normal ejection fraction. Because the major complaint in these patients was episodes of angina pectoris, it is not surprising that the hemodynamic measurements at rest are often normal.

The rationale for considering the APST as a pertinent factor in the evaluation of the CAD patient is that there is a significant difference in hemodynamic function between normals and at least some clinically important subgroups of the CAD patients, not apparent at basal HR. The fact that the greatest difference between normals and the CAD group is elicited at the highest paced rate is unambiguous support of the concept that reserve capacity is reduced in the CAD group. Thus, the APST is viewed as a practical means of stress testing the ventricle of the patient, under relatively well-controlled circumstances, for which the functional consequences of the disease are

Table 3. V_{max} and end diastolic pressure (EDP) at the basal and highest paced heart rate for coronary artery disease patients classified by: ejection fraction less than 44%, previous infarction, pain during test, presence of three diseased vessels, and EF greater than 56%

| | V_{max} | | | | EDP | | | |
| | basal HR | | highest paced HR | | basal HR | | highest paced HR | |
	mean	SE	mean	SE	mean	SE	mean	SE
EF < 44%	44.6	(2.0)	51.0	(2.7)	15.2	(1.5)	12.0	(2.2)
Previous infarct	46.2	(1.3)	52.8	(2.5)	13.2	(0.7)	10.1	(0.9)
Pain	47.7	(1.4)	57.8	(2.0)	12.7	(0.8)	10.7	(1.1)
Three-vessel disease	48.8	(1.5)	58.9	(2.3)	12.9	(0.8)	10.0	(1.0)
EF ≥ 56%	51.4	(1.4)	59.4	(3.9)	12.1	(0.6)	8.8	(1.7)
All CAD	48.1	(0.9)	57.7	(1.9)	13.0	(0.5)	9.4	(0.6)
Normals	57.3	(1.4)	79.8	(2.4)	10.6	(0.5)	4.7	(0.5)

reflected in the APST measurements. We have found that the extent of the disease, as reflected by the ejection fraction, number of vessels diseased, previous infarction, or precordial pain, generally correlates with the result of the APST, as can be seen in Table 3 and Figures 6 and 9. Table 3 is instructive in that we find the APST is most often depressed in the presence of a low ejection fraction or a previous infarction, while the number of vessels involved is less pertinent in terms of the hemodynamic measurements. Figure 9, on the other hand, shows the response of V_{max} to pacing in normals and in CAD patients, graded as to functional severity of CAD by ejection fraction. It is clear that for the lowest EF, the V_{max} curve barely increases over basal values during pacing, reaches a plateau, and shows a much greater tendency to decline at the highest paced rates. The development of pain during the test is also important (Graeber et al., 1972; McLaurin, Rolete, and Grossman, 1973a,b; Schmidt et al., 1976) and our results (Table 3) show that it ranks just after "previous infarct" in terms of a depressed APST result. Thus, the basis for performing the APST is first to determine if ischemia is producible, a specific sign of coronary artery disease, and second, to quantify the functional severity of the disease in terms of reduced myocardial reserve.

Conclusions for the APST

To establish the normal range and bounds for a positive atrial pacing stress test, the measurements from 57 normal individuals and a group of 160 patients with CAD were investigated. The test variables included left ventricular peak systolic pressure, end diastolic pressure, peak dP/dt, and V_{max} measured during 10- to 20-bpm pacing increments from basal rate to the highest sustainable rate. It is apparent that the greatest difference between normals and patients with CAD is elicited at the highest sustainable pacing rates. Furthermore, the difference within the CAD group is most clearly demonstrated at the highest paced rates. The slope of the response curve of EDP and V_{max} versus HR as well as the shape of the curve contains discriminatory information. The information in the shape of the response curve is obscured, however, by treating all CAD patients as one group; for example, dividing the CAD group into normal, moderate, and low ejection-fraction groups shows more clearly the differences in response among normals and the most severely ill.

The least difference is seen at the basal heart rate. Such measurements show that approximately one-third of CAD patients have values in the normal range, a finding similar to other hemodynamic measurements performed at rest. This fact, together with the increased discriminatory power at the highest paced rates, justifies the use of pacing as a stress test to quantify the pathophysiological significance of CAD as manifested by reduced reserve capacity.

Although further work is required to establish the relative specificity among the various forms of stress testing, these findings support the use of the APST as a practical clinical test replacing the predominantly empirical approach with a more rationally based analysis. This should lead to a better understanding of the fundamental physiological basis of the response curves, and especially deviations from the normal pattern.

REGIONAL LEFT VENTRICULAR WALL MOTION

In view of the long-standing clinical use of angiography, conventions already exist for coding the pattern of contraction. Herman et al. (1967) summarized the current practice as illustrated in Figure 10A: "Hypokinesis is a generalized reduction in normal degree of contraction." There are four classifications for local abnormalities: falling under the major heading of asynergy (derived from the Greek *a* (negative), *syn* (together), and *ergon* (work)); akinesis, total lack of motion

of a portion of left ventricular wall; dyskinesis, paradoxical systolic expansion of part of the wall; asyneresis, diminished or inadequate motion of part of the wall; and asynchrony, disturbed temporal sequence of contraction. To this day, regional wall motion is most often assessed by inspection of cine ventriculograms. Although it is not surprising, it is at least remarkable that quantitative techniques have not become more firmly established, especially in view of the known
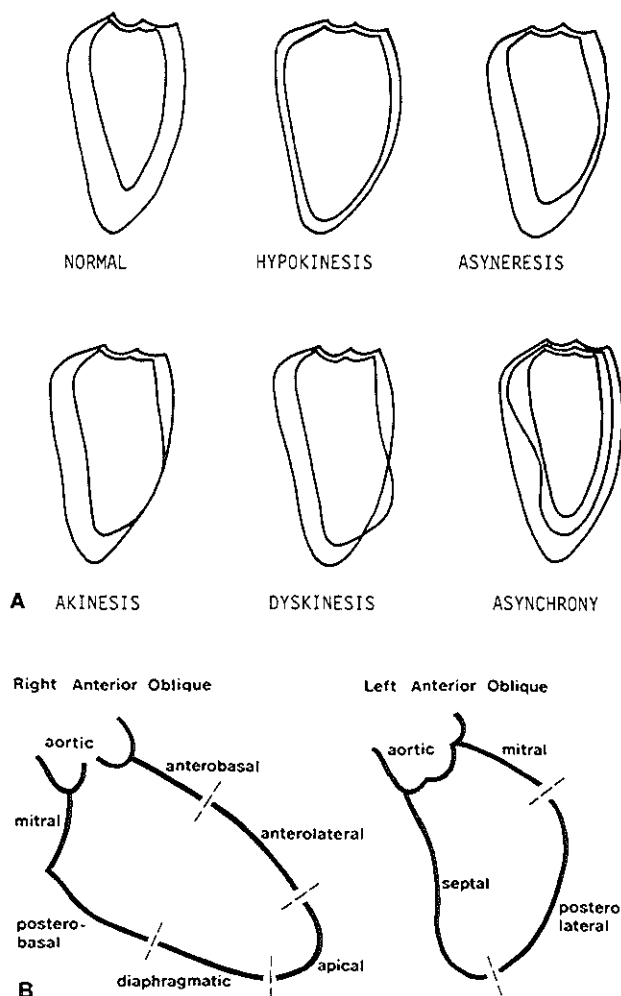
Figure 10. A, the ventriculogram is generally coded by inspection as being normal, hypokinetic, or one of four forms of asynergy: asyneresis, akinesis, dyskinesis, or asynchrony. B, in the right anterior oblique (RAO) projection the left ventricle (LV) is divided into the aortic region, mitral valve region, and five myocardial segments: anterobasal, anterolateral, apical, diaphragmatic, and posterobasal. In the left anterior oblique (LAO) projection the major segments include the posterolateral wall and septum.

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observer variability. Zir et al. (1976) invited four experienced physicians to independently examine 20 ventriculograms [right anterior oblique (RAO) projection exclusively]. "The ventricle was divided into five segments and the degree of wall motion abnormality graded into six categories of increasing severity from normal to dyskinesis" (see Figure 10B). "There was a 42% mean disagreement among all four observers where a disagreement between observers was defined as any difference in grading wall motion abnormalities." They went on to conclude: "In some cases, one man's dyskinesis was another man's normal motion. The results of this study underscore the need for objective methods of quantifying left ventricular wall motion abnormalities so that data among several institutions will be based on similar scales of interpretation and studies from several institutions can be compared in a meaningful way."

This appeal notwithstanding, the clinical value of quantifying regional shortening still requires reliable and well-understood analysis methods, which up to now have been too arbitrarily defined. In the last decade at least eight different methods have been proposed (Ueda et al., 1969; Hamilton, Murray, and Kennedy, 1972; Chaitman, Bristow, and Rahimtoola, 1973; Kitamura et al., 1973; Schelbert et al., 1973; Sniderman, Marpole, and Fallen, 1973; Baltaxe et al., 1974; Dyke et al., 1974; Leighton, Wilt, and Lewis, 1974; Schönbeck et al., 1974; Krayenbuehl et al., 1975a,b; Bulawa et al., 1976). A recent study has shown that they all give quite different results (Brower and Meester, 1976).

The theoretical solution to this problem seems nearly insurmountable. It requires an accurate three-dimensional model of the entire heart, including the elastic boundary conditions (pericardium, lungs, diaphragm) as well as the important tethering points (aorta and pulmonary artery). Although there have been impressive advances in three-dimensional computer models of the heart (Pao, Ritman, and Wood, 1974; Ghista and Hamid, 1977), we know of no such model that incorporates the minimal conditions necessary for a realistic prediction of regional motion. Out of necessity we must turn to empirical findings to provide the basis for the analytic techniques for quantifying regional wall motion.

A fundamental problem in designing a method to quantify regional left ventricular wall motion is the choice of an appropriate reference system. Unlike most boundary value problems in physics, this choice is not obvious from the geometrical constraints. Most systems may be classified as employing either rectilinear coordinates or radial coordi-

nates. As exceptions there are methods that employ neither coordinate system; they were all developed for special applications where a method was needed to code certain special pathological developments, such as aneurysms resulting in akinesia or dyskinesia. The basic approach was to overlay the end diastolic (ED) and end systolic (ES) contours, using anatomical landmarks (rib cage or diaphragm) and measure that portion of the perimeter showing dyskinesia. These methods are not useful for quantifying hypokinesis or asyneresis.

A problem related to the choice of a coordinate system that all systems have in common is how to align separate cine frames. Errors can be introduced by several routes. Gross motion of the heart caused by intended motion of the x-ray beam or patient can create a problem. Slack in the projection apparatus can cause frame repositioning errors. Motion caused by the ventricle vigorously ejecting blood, under a number of mechanical constraints, can result in a systematic rotation and translation not directly ascribable to contractile motion of the wall elements per se. The first problem, gross motion, can be largely controlled by aligning external markers or anatomical landmarks such as the rib cage or diaphragm.

For all the methods employing a radial coordinate system an assignment must be made for each frame with regard to the origin and orientation of the coordinates. The operative assumption for the radial coordinate system is that, over the ejection fraction range for normal ventricles, elements of the wall move toward a single point whose position may vary during contraction or with ejection fraction. This possibly movable point is the logical position for the center of the radial coordinate system. Such a point has not been directly measured, but is generally assumed to coincide with such constructs as the geometric center of gravity, or major axis midpoint. The orientation of the coordinate system, i.e., angular coordinate reference ($\theta = 0$), most often chosen is the mitral valve–aortic valve (MV-AoV) junction or the AoV midpoint, following the convention for planimetry.

Those methods employing a rectilinear coordinate system presume a fundamentally different pattern in LV wall motion during systole. In all such systems a number of hemi-axes are constructed perpendicular to a major axis. It is this major axis to which elements of the wall are presumed to travel. Apparent shortening at the apex is interpreted as apical obliteration caused by opposite sides coming into contact. A number of different definitions also exist for the position of the major axis. All, however, assume that the major axis passes through the apex, which is usually identified by inspection. The other

point establishing the major axis is usually placed at the base of the ventricle. A number of possibilities have been used: junction of the MV-AoV; midpoint of the AoV; or that point dividing the intersected LV area into two halves. To further complicate matters, some authors use only ES major axis, others only the ED major axis, and some use both. This choice is interconnected with the above-mentioned problem of how to correct for systematic motion of the ventricle. In view of this brief introduction to the field of regional wall motion, it would be appropriate now to turn to the clinical measurements. We must investigate the pertinent properties of LV wall motion and consider to what extent they guide the development of an analytic methodology.

Patient Material and Ventriculography

Thirty-one adult patients (21 men, 10 women, age range, 20–53 years) were referred for cardiac catheterization with complaints of atypical angina pectoris and were subsequently found to be clinically and anatomically normal. All patients underwent left ventriculography in the 30° RAO projection at 50–80 frames/sec using 0.75 ml/kg radiopaque contrast media (Isopaque). A grid calibration technique was used to correct for nonparallel beam distortion but not for forms of optical distortion. All data were analyzed with the computer system previously described. End diastolic and end systolic frames were analyzed. These were defined as the frames having the largest observed area and the minimum observed area, respectively.

Thirteen other patients, who had been shown to have serious coronary artery disease, were selected as representative examples of unambiguous akinesis. The apex was involved in ten patients, the anterolateral wall in eight, and the diaphragmatic region in two. In some patients disease extended over two regions. Ventriculograms from these thirteen patients were used to probe the failure mode of the analytic methods used for defining shortening patterns.

Data Acquisition Hardware

Contours were traced on paper from the viewing screen of the Tagarno 3500 projector and digitized using the graft pen system (Brower et al., 1975; Brower, Meester, and Hugenholtz, 1975; Brower et al., 1977) (Figure 3). This system provides equal arc length digitization with a resolution of 0.3 mm. Reproducibility is limited primarily by operator contour tracking. The contour data are stored in two integer arrays of 300 elements each and this is reproduced at reduced resolution on the

TV monitor for purposes of quality control. A Tektronix hard copy unit is used for copying the TV picture.

Characterization of the Normal Ventriculogram

The end diastolic volume, ejection fraction, and wall mass indexed for body mass and surface area are summarized in Table 4. Volume was calculated using the area-length method of Dodge (1971), but without any correction formula applied to correct for systematic errors in the volume estimate. This differs from the usual practice in our clinic of correcting for the overestimate made by this method; thus the normal range is somewhat greater than previously reported (Brower, Meester, and Hugenholtz, 1975; Brower et al., 1977). Volume was calculated by:

$$V = \frac{\pi}{6} LM^2$$

where L is the major axis (from apex to the junction of the mitral and aortic valve) and M is the effective minor axis. End diastolic wall mass was calculated by:

$$WM = \frac{\pi 1.05}{6} [(L + 2h)(M + 2h)^2 - LM^2]$$

where h is the ED wall thickness and the other dimensions are measured at end diastole.

The motion of the ED and ES major axes for the 31 normals, superimposed using an external reference system, is illustrated in Figure 11. All dimensions are normalized with respect to the ED major axis (length = 100%). The reference point at the base of the heart is the junction of the mitral and aortic valves. It seems that during the contraction the junction descends toward the apex along the ED major axis by about 12% ± 4% SD. This is accompanied by an overall ES

Table 4. End diastolic volume, wall mass, and ejection fraction in 31 normal adult ventriculograms

	EDV	Wall mass	EF
Uncorrected	130–209 cm³	133–258 g	0.67–0.80
Indexed (BSA = 1.78 m², SD = 0.18)	74.3–112 cm³/m²	76.7–133 g/m³	
Indexed (Weight = 67.4 kg, SD = 12)	1.83–2.96 cm³/kg	2.11–3.26 g/kg	

major axis shortening to a length of 76% ± 10% SD and an anterior rotation of 3.8°.

This rotation is consistent with that reported by others. For example, Dodge et al. (1966) state that the angle is about 5° in six normals, Chaitman et al. (1973) 5.5° also in six normals, and Leighton, Wilt, and Lewis (1974) report an average angle of 2.7° (range 0–9.2) in 20 normals. The majority of these reports are based on a small series: nevertheless, a consistent anterior rotation during systole is found.

The ED and ES centers of mass (CM) are also shown in Figure 11, near their respective major axis midpoints. The ventricle is shaped so that the CM is shifted slightly toward the anterolateral wall from the major axis midpoints. Total systolic motion of the CM is 1.4% ± 0.82% SE of the ED major axis, in the direction of the mitral valve. This motion is not large, but is statistically significant ($p < 0.04$). The major axis midpoint rotates anteriorly with the major axis and traverses a distance equivalent to 3.3% of the ED major axis, in a direction perpendicular to the motion of the center of mass.

The apparently small rotation of the major axis is significant for determinations of segmental shortening. McDonald (1970) and Kong, Morris, and McIntosh (1971) using, respectively, implanted and anatomical markers on the epicardium have shown that the regional contraction pattern of the epicardium depends on location. McDonald reports mean epicardial shortening, in the basal area, to be 15.8% ± 2.0% SD while midway along in the major axis mean shortening is
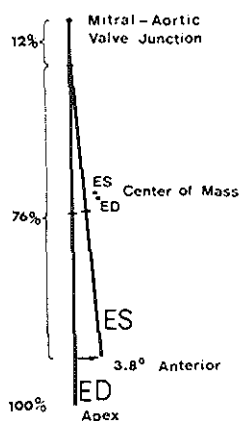
Figure 11. During systole the major axis rotates anteriorly by 3.8° and shortens over all by 76% (this corrects a typographical error in a previous communication (Brower and Meester, 1976)). The junction of the mitral valve–aortic valve (MV-AoV) descends along the end diastolic (ED) major axis by 12% while the apex apparently shortens by another 12%.

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12.0% ± 1.6% SD. Using biplane coronary cine angiograms from five individuals diagnosed as normal, Kong et al. (1971) find a regional variation in transverse epicardial shortening. At the base, shortening ranges from 13–14%, at the equator from 12–19%, and at the apex from 16–20%. This indicates that the apical region contracts slightly more than the equator and the equator more than the base, but all remain within the range 12–20%. In any event, discontinuities in the shortening pattern of normals ought not to exist and have never been reported. That this apparently small rotation can give rise to this sort of discontinuity is shown in Figure 12. This figure shows segmental shortening determined with respect to the ES major axis. The apparent discontinuity between segments 9 and 11 occurs at the apex, where the method is most sensitive to the effects of rotation. It is apparent that if no correction is made for systolic rotation of the apex, inferior wall shortening in the apical region is overestimated and anterior wall shortening is underestimated.

In summary, a number of patterns emerge in the overall motion of the normal ventricle (30° RAO projection) as it contracts from ED to ES. 57–80% of the ED volume is ejected. The major axis shortens by 76% of its initial length and rotates anteriorly by 3.8°. The MV-AoV junction descends along the ED major axis by 12% of the ED axis length. Apical shortening apparently represents another 12%. The
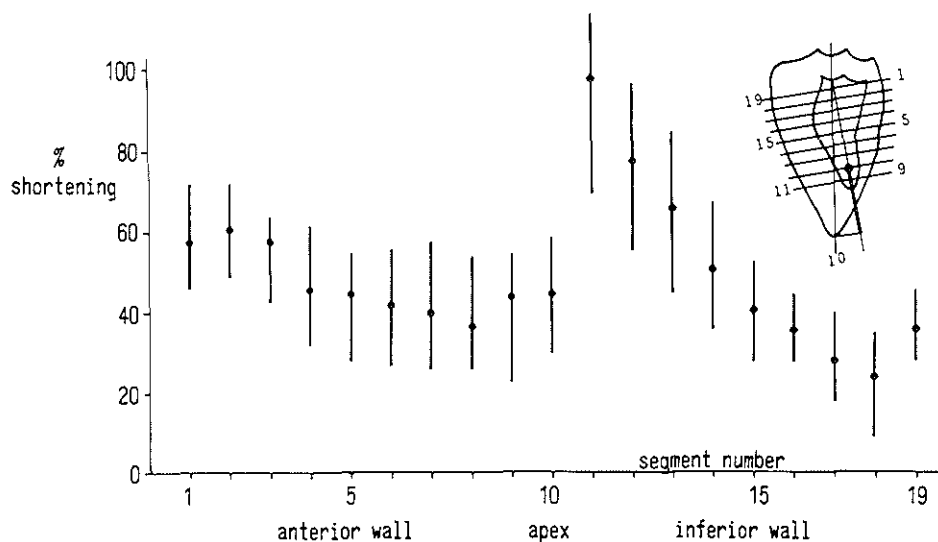
Figure 12. With equally spaced segments, defined as perpendicular to the end systolic major axis, the anterior rotation of the apex causes an apparent discontinuity in segmental shortening at the apex. Compare segments 9 and 11.

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center of mass, located anterior to the major axis midpoint, shifts towards the mitral valve, but only by 1.5% of the ED major axis. The axis midpoint rotates anteriorly, with the major axis traversing a distance of 3.3% perpendicular to the motion of the center of mass.

Quantification of Regional Shortening

Returning to the question of the coordinate system and alignment procedure, at least three previously described techniques seem attractive in view of the above results:

Method A, first proposed by Leighton, Wilt, and Lewis (1974), employs hemi-axes defined with respect to the ES major axis (Figure 13A). The ED major axis is defined as a line from the apex to the base dividing the LV area in half. The ES major axis is defined as a line from the ES apex to the point where the ED major axis intersects the ES contour at the base of the ventricle. The ES and ED major axes are then aligned, thereby correcting for the systematic anterior rotation, which is found to be an important source of variation.

Method B, first proposed by Clayton et al. and Harris et al., both in 1974, employs a radial coordinate system, with its origin at the midpoint of the respective major axes (Figure 14A). Major axes are defined by the apex and junction of the mitral and aortic valves for each contour. The angular coordinate is defined as positive clockwise from the MV-AoV junction. This approach inherently corrects for the rotation effect, and is also attractive in the sense that the major axis midpoint is relatively fixed, i.e., its motion is negligible once the rotation correction is made.

Method C, first proposed by Rickards, Seabra-Gomes, and Thurston (1977), is a radial coordinate system with its origin at the ES center of mass (Figure 15A). The ED contour is translated, but not rotated, so that the junction of the mitral and aortic valves at ED and ES coincide. The rationale for this approach is that the valves themselves are noncontractile and any apparent motion on their part must be artifactual and in need of correction. From the results presented above, this would represent a 12% motion of the MV-AoV junction.

Method R, first described by Chaitman, Bristow, and Rahimtoola (1973), uses a rectilinear system with axes defined from the ED major axis (Figure 16A). No correction for systolic motion is made, and this technique is included here for the sake of comparison.

Failure Mode

Results from the analysis of the 13 patients with frank akinesis are

Method A

ed

es

19 ——— 1

15 ——— 5

11 ——— 9

A · 10

$$Ld(n) = ed\ hemi\text{-}axis\ n$$
$$Ls(n) = es\ \ \ \ ''$$

$$FS(n) = \frac{Ld(n) - Ls(n)}{Ld(n)}$$

Method A

%
shortening

100

80

60

40

20

0

segment number

1   5   10   15   19

anterior wall   apex   inferior wall

B
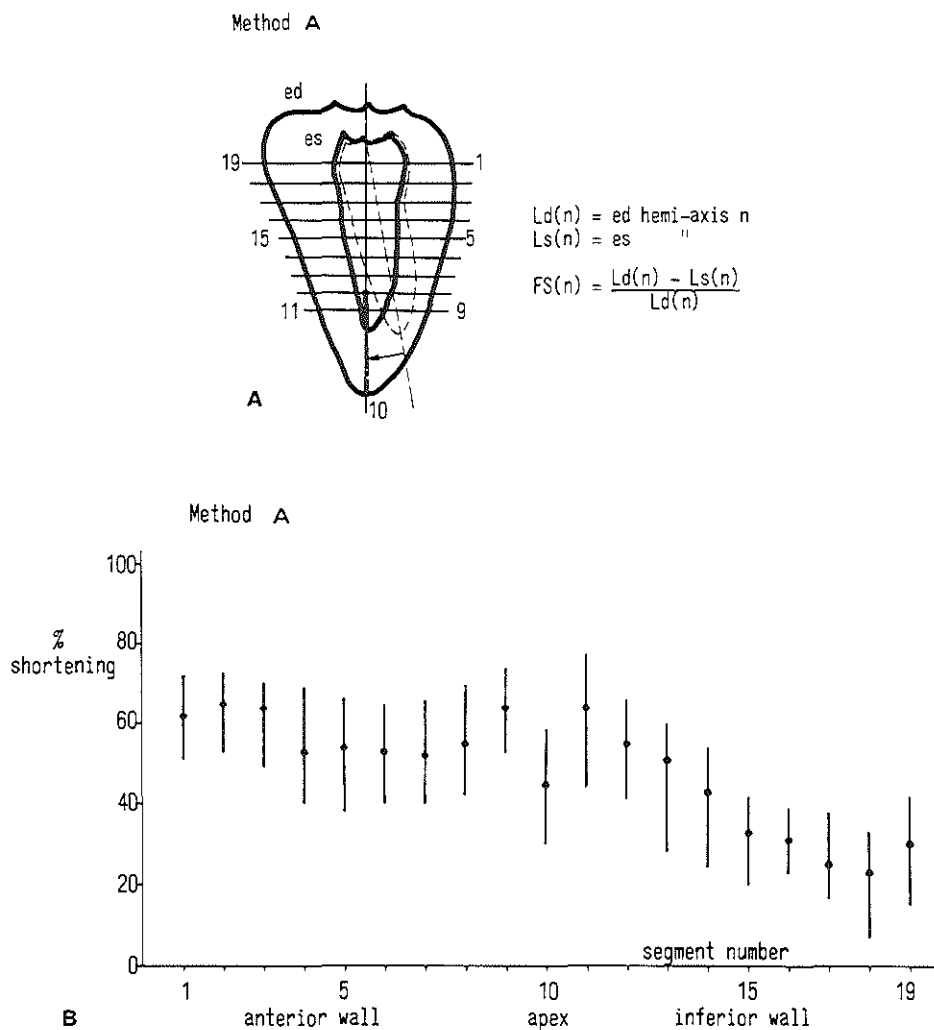
Figure 13.   A, method A defines equally spaced hemi-axes perpendicular to the end systolic (ES) major axis, then aligns the end diastolic (ED) and ES major axes. B, using method A the segmental shortening is determined in 31 normal adult ventriculograms.

summarized in Table 5. The location of the akinetic region is identified in the first column. In the next four columns the results are coded as a positive finding (+) if all segments in the akinetic region showed no more than ±5% motion. An ambiguous finding (0) means that at least one segment in the akinetic region was calculated to contract more than 5% but less than the normal range for that segment. A negative finding (−) means that at least one segment in the akinetic region fell into the normal range.
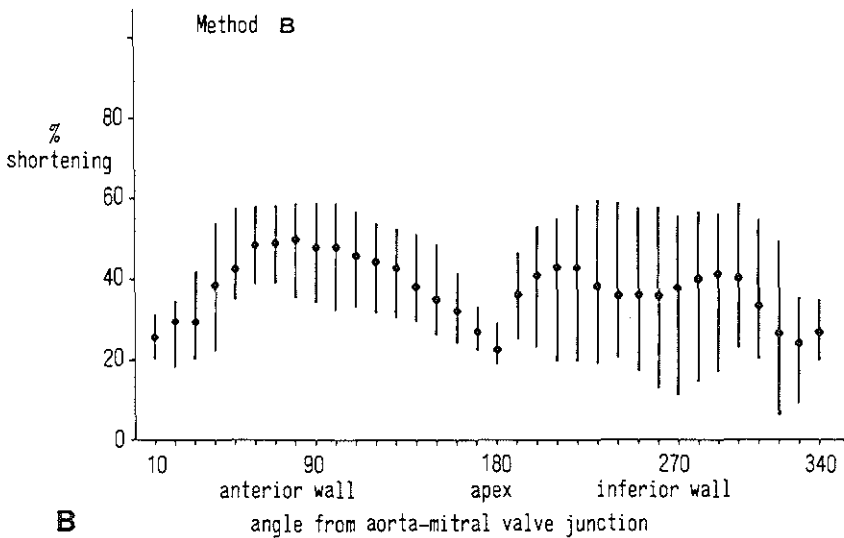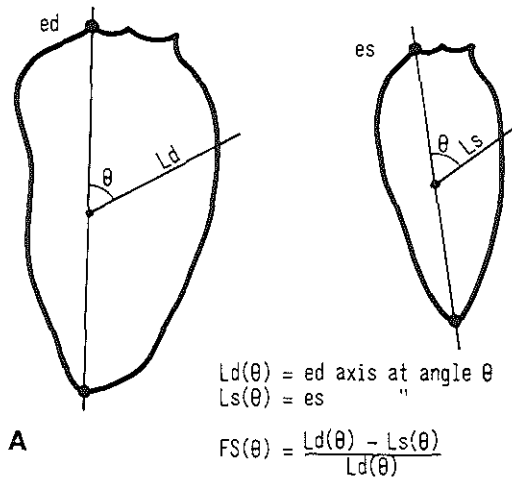
Figure 14. A, method B employs a radial coordinate system with the center at the major axis midpoints. $\theta = 0$ position is the mitral valve-aortic valve (MV-Aov) junction. The major axes are effectively aligned by this technique. B, using method B the segmental shortening is determined in 31 normal adult ventriculograms.

Method R had 13 positive findings out of 13 ventriculograms. Method A had 11 positive findings, followed by method B (six positives), and method C (three positives). The majority of the nonpositive

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findings are classified as ambiguous, which has resulted in a coding of asyneresis rather than akinesis in practice. Klein, Herman, and Gorlin (1967), who also studied 13 cases of aneurysm, found a distribution of four apical, eight anterior, and one inferior. Our results differ from theirs primarily in that seven of our anterior akinesis cases at least partially also involved the apex. Feild et al. (1972) also report frequent

Method C

$$FS(\theta) = \frac{Ld(\theta) - Ls(\theta)}{Ld(\theta)}$$
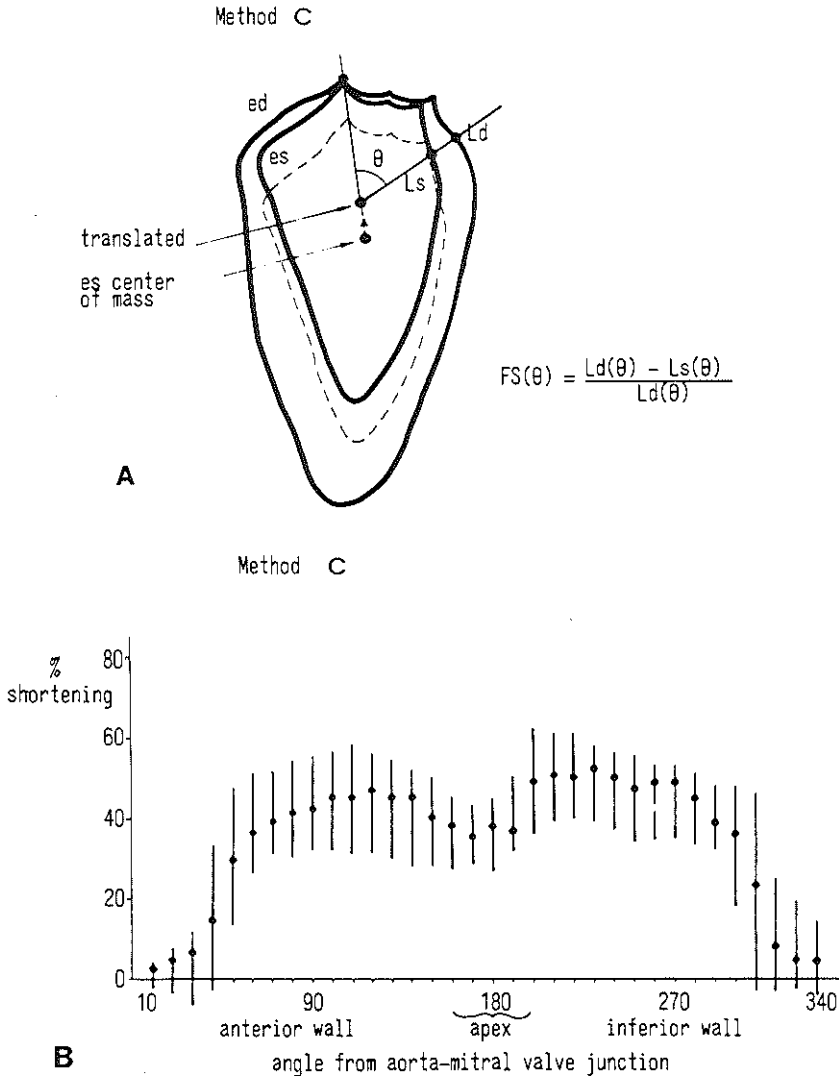
Method C

Figure 15. A, method C employs a radial coordinate system with the center at the end systolic (ES) center of mass. Contours are aligned by superimposing, via translation only, the aortic valve. $\theta = 0$ is defined at the mitral valve–aortic valve (MV-AoV) junction. B, using method C the segmental shortening is determined in 31 normal adult ventriculograms.

involvement of the apex in inferior or anterior akinesis. Herman et al. (1967) report most frequent involvement of the apex in asynergy, but Baxley and Reeves (1971) report most frequent involvement of the diaphragmatic and anterior regions for dysynergy. There seems to be little consensus.

Method R

$$Ld(n) = ed \; hemi\text{-}axis \; n$$
$$Ls(n) = es \qquad ''$$

$$FS(n) = \frac{Ld(n) - Ls(n)}{Ld(n)}$$

A

Method R

B
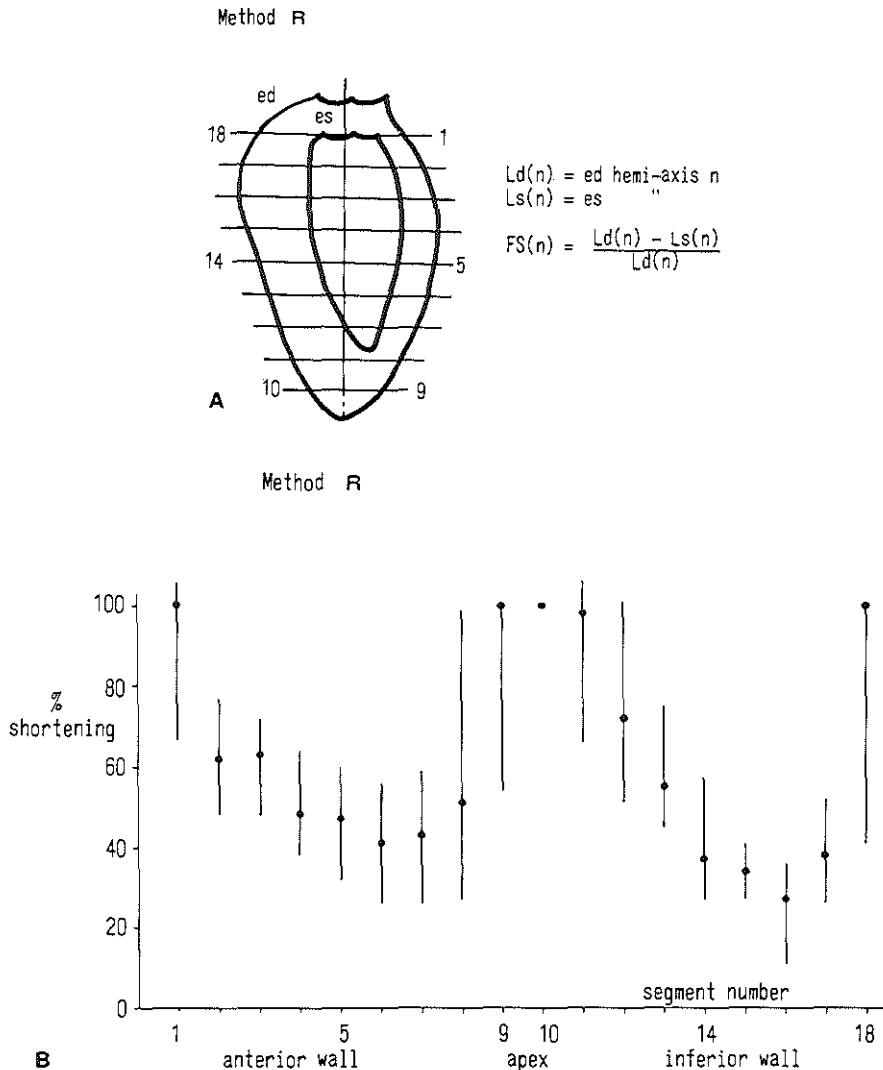
Figure 16. A, method R is included here for reference. It makes no attempt to correct for systolic motion. It employs equally spaced segments defined perpendicular to the end diastolic major axis. B, using method R the segmental shortening is determined in 31 normal adult ventriculograms.

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In a recent study of 134 patients with angiographically proven coronary artery disease we examined the distribution of wall motion abnormalities. The ventriculograms (RAO projection) were coded following the scheme shown in Figure 10B. The results are summarized in Table 6: in 34% (46 patients out of 134) all five segments were coded as normal. The anterolateral segment was coded as abnormal (hypokinetic, akinetic, or dyskinetic) in 46% of all CAD patients, the apical segment in 40%, posterobasal segment in 34%, diaphragmatic segment in 28%, and anterobasal segment in 8%. The sum exceeds 100% because more than one segment was frequently involved. The situation is altered when we look specifically for dyskinesis or akinesis: the apical segment was involved in 11% of patients, both the diaphragmatic and posterobasal in 6%, and the anterolateral in 4%. The anterobasal region was not found to be either akinetic or dyskinetic in this series. In summary, the anterolateral and apical segments are most often coded as abnormal, but akinesis or dyskinesis is seen most frequently in the apical region. Thus, a failure mode for regional shortening involving the apex as a pertinent factor will have the more serious consequences.

Although the distribution of akinesis in Table 5 is not atypical, the sample is not large enough to allow ranking the methods. Rather, these results are useful for probing the failure mode.

Method R, which uses only external markers for alignment, has 100% agreement, as it must, for unambiguous akinesis. This only confirms the fact that physicians, when coding the ventriculograms, do not explicitly take into account the systematic systolic motion of the ventricle. Method A fails for pure anterior and inferior wall akinesis when the apex seems to be pulled toward the akinetic area during systole. Alignment of the major axes effectively makes the akinetic area move toward the ED major axis. Methods B and C fail primarily when there is a relatively strong contraction in the basal area with poor contraction elsewhere. This causes the MV-AoV region to descend toward the apex. Using either the aortic valve or major axis midpoints as a reference effectively makes the valve area stand still, with apparent motion transferred to the apex. It must be emphasized that this part of the study only gives the failure mode. The distribution of disease for akinesis must be known and a larger sample used to judge the clinical importance of the actual frequency of occurrence of the failure mode, but, as we show above, the apex does seem to be predominately involved in akinesia or dyskinesia.

Table 5. Positive, ambiguous, and negative findings for unambiguous ventriculograms with large akinetic regions

Location akinesis[a]		Method[b]			
		R	A	C	B
1	Ap-AL	+	+	0	0
2	Ap-AL	+	+	0	0
3	AL	+	0	0	0
4	Ap-AL	+	+	+	0
5	D	+	−	0	0
6	Ap-AL	+	+	+	+
7	AL	+	+	0	0
8	Ap-AL	+	+	0	+
9	AL	+	+	0	+
10	Ap-AL	+	+	0	+
11	AL	+	+	0	0
12	Ap-AL	+	+	0	+
13	Ap-D	+	+	+	+
total positive		13	11	3	6
total ambiguous		0	1	10	7
total negative		0	1	0	0

[a] Ap = apex, AL = anterolateral, D = diaphragmatic.

[b] + = all segments in the akinetic region showed < ± 5% motion; 0 = ambiguous finding, at least one segment in the akinetic region was calculated to contract >5% but greater than the normal range for that segment; − = at least one segment in the akinetic region fell into the normal range.

Regional Shortening in Normals

There are several properties desirable in a method for quantifying regional shortening. These include the following. The method should provide a clear separation in fractional shortening between normal contracting regions and noncontracting regions. The reference system must be unambiguous, correlate consistently with the anatomy, and be relatively immune to changes, in the sense that the variation in repeated measurements is small compared to the normal range. The results must be consistent with independent direct methods for quantifying regional shortening, and the failure mode should be known and subject to quantification.

Table 6. Relative distribution of segmental wall motion coded visually following Figure 10B[a]

	Normal		Hypokinetic		Akinetic		Dyskinetic	
	Number	%	Number	%	Number	%	Number	%
Anterobasal segment	123	92	11	8	0	0	0	0
Anterolateral segment	72	54	57	42	5	4	0	0
Apical segment	81	60	38	28	12	9	3	2
Diaphragmatic segment	97	72	29	22	7	5	1	1
Posterobasal segment	89	66	37	28	8	6	0	0

[a] Segments are coded either as normal, hypokinetic, akinetic, or dyskinetic. The group consists of 134 consecutive patients with coronary artery disease. All segments were coded normal in 46 patients (34% of the total).

Method R (Figure 16, A and B) introduces a significant artifact in the regional shortening of normals. There is an apparent discontinuity in hemi-axis shortening, ascribable to rotation of the apex anteriorly. It is precisely because this method makes no correction for systolic rotation that there are 100% positive findings for the akinetic group. In this case, the primary objection to this method is the apparent inconsistency between the results shown in Figure 16B and what is known from independent studies of regional wall motion. The figure shows a highly nonsymmetric contraction pattern, which has virtually 100% contraction of segments 1, 18, and 9, 10. The latter represent motion of the apex such that no ES intersection is located, which the algorithm recognizes as 100% contraction. The fact that the shortening becomes 100% in the apical region is not an important objection to this method, because this represents actual obliteration of the apex, which contains useful information. Segment 1 intersects the anterior wall close to the aortic valve and segment 18 intersects the mitral valve. Both have larger ranges than the other hemi-axes and are generally the least reliable. Hemi-axes to the inferior wall seem to be systematically higher near the apex than the opposite hemi-axes to the anterior wall (i.e., 11-8, 12-7, and 13-6). The significance of systolic rotation anteriorly has been previously discussed.

Method A (Figure 13, A and B) presents a more uniform pattern than that of method R, but shows some systematic reduction in the inferior-basal region. Segments 18 and 19 often fall into the mitral valve area and are therefore subject to a great deal of variability. The apex contraction appears as a discontinuity, but this represents its arbitrary point of reference (1/5 ES major axis from the apex). This method aligns the major axes and uses the ES major axis as a reference line. This automatically avoids the problem of segments failing to intersect the ES contour when defined from the ED major axis, as in method R.

Table 5 reveals only two nonpositive findings for the akinesis check. This occurred when the akinesis, which did not involve the apex, resulted in motion of the apex toward the akinetic area. Alignment of the major axes then introduced an artificial contraction in the akinetic area. With apical involvement in the akinesis, the ES and ED apex points are the same and there is no effective alignment executed.

There is one theoretical objection to this method. Regardless of how many axes are used, the ES contour is not uniquely defined with respect to the ED contour. In other words, many different contraction patterns can give rise to the same segment shortening, depending on

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the motion of the aortic valve and ES major axis shortening. Related to this is the fact that the segment number alone fails to identify precisely what point is being analyzed on the ED contour. In this connection the apical contraction (segment 10 of method A) is most important. In practice this is not a serious problem because the contours are easily displayed. Finally, there appears a systematic trend toward reduced shortening in the posterior wall, suggesting that the half area axis lies closest to the anterior wall in this region.

Method B (Figure 14, A and B) employs a radial coordinate system, with the center at the major axis midpoints. By taking the $\theta = 0$ position to coincide with the major axis, the ED and ES axes are effectively aligned. There appears a well-defined notch at 180°, a relatively uniform and symmetric pattern on either side of 180°, but an apparent doubling in the standard deviation in the inferior wall.

Method B has seven ambiguous findings in Table 5. It is somewhat better than method C, but is subject to the general problem of a strong basal contraction pulling the valve ring toward the apex, shortening the ES major axis, and suggesting an apical contraction when distances are determined with respect to the midpoint. The doubling of the range of shortening in the inferior region may be attributable to the greater uncertainty in the area in quantifying papillary muscle attachment.

Method C (Figure 15 A and B) also employs a radial coordinate system and shifts the contours to overlap at the junction of the mitral and aortic valves; hence the fact that the contraction in the basal area (segments 10–30° and 320–340°) is minimized. The remainder of the pattern is remarkably uniform, with some slight systematic increase in the inferior wall. In this method the apex angles are not precisely the same in each contour and this results in some spreading of the apex for 170–190°. This method gives the most uniform pattern of contraction, except in the basal region, which the method inherently minimizes.

Table 5 reveals that this method fails when there are akinetic areas at the apex for which a basal contraction pulls the valve ring toward the center of mass at ES. When the ED contour is aligned, the akinetic area seems pulled toward the center of mass, resulting in an overestimate of its actual motion. Hence, there are only three positive findings in Table 5 and 10 ambiguous findings. The very desirable feature of having a small variation compared to the normal value is directly attributable to shifting the contours so that the valves overlap. The cost of this maneuver seems to be too large a proportion of false negatives, and we therefore must advise caution in interpreting results

from this method. A second, less serious objection is that in many of the normals the apices of the two contours are not necessarily in alignment, resulting in basal shortening being calculated from corresponding anatomically inappropriate locations. Depending on the anatomy, 180° may represent a point 10° on either side of either apex. Nevertheless, the median values agree well with independent tests of this method (Rickards, Seabra-Gomes, and Thurston, 1977), but the range is somewhat larger here.

Identification of the Apex

In previous communications (Brower, Meester, and Hugenholtz, 1975; Brower et al., 1977) the apex was determined automatically as the longest axis, with the mitral-aortic valve junction as a fixed point. This proved impractical in some instances for segmental shortening. Hence, the apex point was indicated manually via the digitizing pen. However, this is consistent with the majority of reports on segmental shortening where manual apex recognition was also used. This made little difference for the 31 normals, but for the 13 cases of akinesis it was important; in globular hearts the apex is not sharply defined and the computer latches onto the noise peak, which may be several degrees removed from the apex. Relatively little work has been reported on the automatic recognition of the apex. This is not a fundamental limitation, but one that must be solved in parallel with the development of quantitative techniques for regional wall motion.

Conclusions for Regional Shortening

In the last decade a variety of analytic methodologies for quantifying regional wall motion from cine ventriculograms have emerged. These methods are all labor intensive, time consuming, and yet follow well-defined rules for analysis. Automatic data processing techniques should be able to make a useful contribution toward speeding up the analysis while introducing a greater degree of standardization and objectivity. Granted that the computer may be helpful, it is necessary to make an objective decision about which method provides the most useful results.

Normal ranges are established for four previously described methods for quantifying segmental shortening from cine ventriculograms. It was shown that, on average for the 31 normal adults studied, the apex rotates anteriorly about the junction of the mitral and aortic valves during systole by 3.8°. This apparently small rotation had significant consequences with respect to determining segmental short-

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ening. Method R, which uses external fixed points, shows a systematic bias toward underestimating anterior wall motion and overestimating inferior wall motion at the apex. This becomes manifest as a clear discontinuity in the contraction pattern in some other methods if the correction for rotation is not applied.

In order to investigate the failure mode of these methods, 13 ventriculograms from patients with unambiguous akinetic areas were processed. These do not necessarily represent an unbiased sample with respect to location of akinesis. Nevertheless, all the methods that correct for systolic rotation can give significant false positive or false negative results for akinesis. The least false positive occurred in method A.

The apex point could be satisfactorily identified automatically in the normals, but the akinesis cases required manual apex identification. Video techniques that digitize the ventricle such that the apex is poorly defined seem to preclude those methods requiring accurate apex recognition. In this study only method C meets this criterion.

Of the methods investigated, none can be declared ideal for all clinical applications. Method R is unsatisfactory because of nonphysiological values for segmental shortening in normals, and all the others are liable to false positive or false negative findings in severe akinesis. The least errors occurred in method A, which aligns the major axes. Method C is indicated for videometric processing for technical reasons.

These methods seem very useful for quantifying the observed contraction pattern, providing the observer takes into account the failure mode in each instance. This suggests that a more successful approach to the detection of regional shortening would involve some form of pattern recognition of the contours before processing for segmental shortening. For example, this could include checks for rotation of the apex and translation of the major axes or center of mass in an effort to detect conditions suggestive of non-normal contraction patterns. This would also suffice to indicate the presence of conditions that involve the known failure mode.

Ad interim, method A has been adopted for routine clinical use in our laboratory and method C is being considered for implementation in the software for video signal processing, but without translation or superimposition of the aortic valve.

This chapter would not be complete if the logical extensions of atrial pacing and segmental wall motion were not explored. If it is true that the early functional consequences of coronary artery disease are most specifically manifest as reduced reserve capacity coupled with regional dysfunction, then it would be only logical to examine regional wall motion during stress testing. There have been a few reports on this subject that have, at least, established the validity of this conjecture.

In 1970, Dwyer examined segmental wall motion in 10 patients during pacing-induced ischemia. He found that asynergy could be induced acutely during angina, as manifested by regional akinesis or hypokinesis. In many cases a correlation could be established between the regional dysfunction and an associated coronary lesion. Pasternac et al. (1972) also examined 10 patients during pacing-induced ischemia. They concluded that pacing may reveal segmental disease not apparent at rest, with the majority of patients showing either an increase in severity or in the topographic distribution of abnormality. They also suggest that induction of asynergy may help to localize areas of myocardial ischemia. The most recent reports by Krayenbuehl et al. (1975a, b) further support these findings and identifies their concept of the therapeutic importance: "Since the temporarily dysfunctioning, not yet infarcted, myocardial areas are those that will most benefit from coronary bypass surgery, their preoperative identification is of great importance."

These persuasive findings notwithstanding, the measurement of segmental wall motion during pacing-induced ischemia has not been widely adopted. This is caused, in part, by the recognition of observer variability in ventriculography, which quantitative methods have not yet entirely resolved. Furthermore, contrast material is mildly toxic and cannot be given in large doses repeatedly. Finally, up to now, quantification of ventriculography has been a tedious and time-consuming task, which most practicing cardiologists cannot afford in terms of either time or ancillary manpower.

The challenge in this field is threefold. First, to further develop, along the lines discussed above, reliable methods for quantification of regional wall motion. Second, to confirm the early and positive findings of several laboratories concerning the detectability of significant wall motion abnormalities during ischemia. Third, to develop an effective and economical technology whereby ventriculograms can be acquired and processed at least semiautomatically.

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CHAPTER V

CLINICAL USEFULNESS OF RADIOPAQUE MARKERS IN LEFT VENTRICULAR FUNCTION*

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Abstract

Restoration of coronary blood flow following successful bypass surgery would be expected to lead to improvement of regional contraction. Several methods have been described for the quantitative assessment of regional or segmental left ventricular wall motion from the left ventriculogram. All methods need a reference point as a basis for their coördinate systems or to compensate for movement of the patient, relative to the film camera. Morphological abnormalities, such as aneurysms or akinetic areas influence the location of the reference point, resulting in artifacts when measuring wall motion. Localized abnormalities of contraction are not always reflected in "overall" measurements. Akinesis and/or dyskinesis of one or more segments can occur in the presence of normal end diastolic volume or ejection fraction. Such overall parameters will, however, gradually go into pathological ranges with an increase in the number of abnormally contracting segments. Another approach to the quantification of local wall motion uses radiopaque markers. In this study marker pairs are implanted during bypass surgery in the area of newly perfused regions as well as in control regions. Sequential cineradiograms at 50 fr. per second were made at intervals over a period of one year. It was found that direct traumatic effects of the surgical intervention overwhelm the expected improvement of myocardial function in the first three postoperative months. At present the quantitative approach to segmental cardiac function is mainly one of image analysis in one or two pre-selected planes. Subjective visual interpretation of these images should be replaced by objective data analysis.

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Introduction

Tennant and Wiggers suggested as early as 1935 [1]) the association between insufficient coronary blood flow and regional disturbances of ventricular contraction. When coronary blood flow after sucessful coronary bypass surgery is restored, improvement of local wall motion can therefore be expected. This result, however, is not so clearly present in the available extensive and somewhat conflicting literature of today. This is partly due to extraneous factors such as peri-operative infarctions, graft closure, or the influence of concomitant medical treatment, but also to the methodology involved. It is the purpose of this paper to review some of these factors and discuss alternative pathways.

Methodology

The assessment of regional shortening from cinéventriculograms is open for semi-automatic data processing. This includes manual outlining of ventricular contours. Several methods involving angiographic data processing have been described. [2—14]) Essentially a reference point or frame is selected from which rectilinear or radial coordinates are drawn with or without correction for systolic rotation or displacement. The reference points are usually taken from the contour itself: centre of mass, end diastolic major axis, or from external markers recorded on the film frame.

In a comparison of six methods [15]) in 31 normals and 13 patients with akinesis no method could be declared ideal for all clinical applications. All methods showed some false positive or false negative findings in severe akinesis. Results however, indicated that all methods were useful for quantifying the observed contraction pattern in normal man. When conditions of non-normal contraction patterns exist, the failure mode of the method can be defined.

In this context, the interobserver variability, in assessing visually the location and degree of left ventricular wall motion abnormalities, should be taken into account. Zir et al, investigating this phenomenon, found a 42% mean disagreement among four experienced observers. [16]) Angiograms were graded in five segments and six categories of increasing severity from normal to dyskinesis in their study.

"In some cases, one man's dyskinesis was another man's normal motion". Seen from this angle, even six different but objective semi-automatic methods, are an important step towards meaningful comparison between patient groups and institutions.

Overall and Regional Measurements

One segment of the ventricular contour contracting in an abnormal fashion will not always lead to abnormal pump function. [17]) It may be estimated that there is a linear relation between the non-normal contracting area and the results in pump parameters. [18])

Table I: Mean values of left ventricular end diastolic pressure (EDP), end diastolic volume (EDV) and ejection fraction (EF) compared to the extent of segmental wall motion abnormalities.

Segmental wall motion in 216 patients

Mean values

	EDP mm Hg	EDV ml/m²	EF%	n
All segments normal:	12.3	65.3	67.7	77
1 segment abnormal:	14.5	72.5	61.3	49
2 segments abnormal:	14.2	83.2	54.5	48
3 segments abnormal:	18.7	89.9	45.3	23
4 segments abnormal:	24.1	92.6	37.6	14
5 segments abnormal	27.6	132.0	28.5	5

Angio in RAO projection
Abnormal: Akinesis, dyskinesis or hypokinesis

These data indicate that with up to two abnormally contracting segments, end diastolic volume and ejection fraction remain normal. [19]). In the presence of more abnormal segments, parameters reach the pathological range. This, however, might be an oversimplification in itself; probably these data should be refined for asynchrony, normalization of loading conditions and contractility. [17]) The clinical application of pump parameters has been greatly enhanced by coronary bypass surgery (CBS). The effects of this type of surgery on myocardial function remain controversial.

Table II: Left ventricular end diastolic volume before and after CBS. Patients with all grafts open have smaller volumes one year post-operative than patients with one or more closed grafts.

End-diastolic volume in CBS

	Pre-op.		1 year Post-op.		
	mean	SD	mean	SD	
Open grafts: (60 pts)	70.5	14.8	82.5	20-9	ml/m²
Closed graft(s): (42 pts)	79.5	18.8	91.6	30.9	ml/m²

Table III: Ejection fraction before and after CBS. Improvement of normal values can not be expected. No significant deterioration is demonstrated in patients with closed grafts.

	Ejection fraction in CBS				
	Pre-op.		1 year Post-op.		
	mean	SD	mean	SD	
Open grafts: (43 pts)	57.8	10.9	58.0	10.9	%
Closed graft(s): (34 pts)	56.2	12.3	52.8	13.9	%

These data show that ejection fraction, with a pre-operative mean within the normal range, remains essentially unchanged after bypass surgery. When one or more grafts are occluded, there is a small, insignificant decrease after operation. These ejection fractions, however, should be read in conjunction with the results from end diastolic volume determinations. One year after surgery end diastolic volume increased by about 10% in the presence of open as well as closed grafts. These volume determinations are still within the accepted normal limits.

The conclusion of both observations would lead to a somewhat larger ventricle post-operatively with the same ejection fraction, resulting in a slight increase in stroke volume one year after the operation. Whether this effect is due to the operation, the drug regimen or other external factors remains unestablished. A 10% change might also be considered to fall within the biological range and as such to be of only theoretical importance.

It is clear, however, that the effects of CBS on ventricular function cannot be identified in this manner. The interaction of many variables, some local, some general, with a disease essentially localized in nature, with a nonuniform rate of progression will necessitate more detailed observations.

The relative contribution of specific segments to the overall ventricular performance is explored in table IV. These data again show that end diastolic pressure (EDP), end diastolic volume (EDV) and ejection fraction (EF) are dependent on the extent of regional disease. The regions, however, do not appear to be of equal influence. The posterior region (in the RAO position) is associated with a rise in EDP in the single region group. The anterior contour shows, on the contrary, the smallest contribution to the overall performance as indicated by EDP, EDV and EF.

Radiopaque Markers [20,21,22])

Another approach to regional wall motion studies is by the usage of

epicardial markers implanted at surgery.[23]) In our series of 56 patients with coronary artery disease a total of 120 marker pairs were implanted in bypassed myocardial regions and 31 pairs in control regions. In follow-up studies marker motion was filmed over the course of one year at regular intervals (fig. 1 and 2).

This method was also used to further define the early myocardial depression after CBS. For this purpose clinical variables, such as cardiothoracic ratio, cuff blood pressure and heart rate were determined as well as epicardial marker motion (fig. 3 and 4).

Table IV: Influence of specific segmental motion abnormalities on EDP, EDV, and EF. Abnormal motion: akinesis, dyskinesis, or hypokinesis.

Mean values and standard deviations

	EDP		EDV		EF		n
	mean	SD	mean	SD	mean	SD	
Normals	12.3	8.3	65.3	16.6	68	7.5	77
1 Region:							
Anterior	12.6	5.7	68.2	11.7	65	7.5	34
Apex	13.0	6.2	78.2	14.3	65	7.4	21
Posterior	16.2	8.8	77.0	20.4	60	8.4	44
2 Regions:							
Ant. + Apex	15.1	7.9	72.7	22.9	61	11.0	32
Ant. + Post.	15.4	7.9	82.2	20.4	52	8.3	14
Apex + Post.	15.3	16.3	82.6	14.4	54	9.6	16
3 Regions:							
Ant. + Post.							
+ Apex	17.3	10.6	92.1	33.2	46	12.0	71
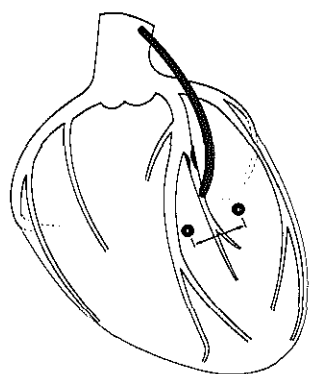
Fig. 1. Two epicardial markers in bypassed region, ± 2 cm apart.
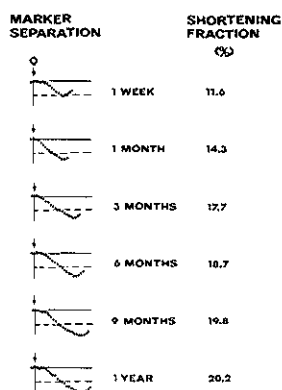
Fig. 2. Marker separation and shortening fraction. Follow-up results of one patient over 1 year after CBS.

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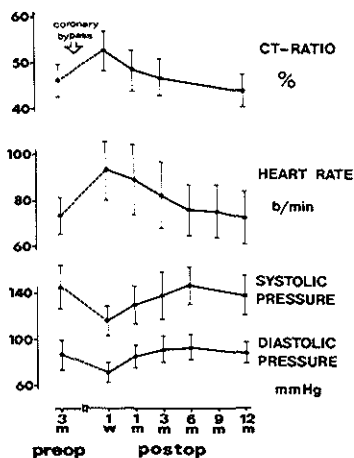
Fig. 3. Timecourse of cardiothoracic-ratio (CT), heart rate from ECG and cuff blood pressure. Pre- and postoperative data. Note depression to 3 months post-op.
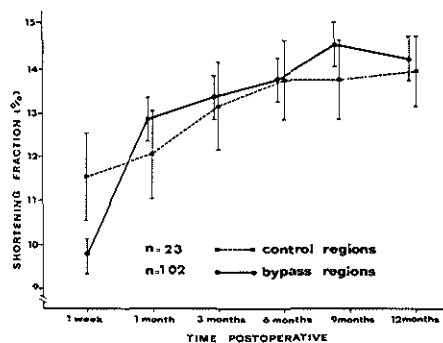
Fig. 4. Shortening fraction from epicardial markers after CBS. Markers are implanted in normal control regions and bypass regions. Bypassed regions have less than normal shortening immediately after CBS, normal regions are also depressed initially.

These data show a consistent enlargement of cardiac size for the first three months post-operatively, with a concomitant increase in heart rate and a decrease in blood pressure. In the first month post-operatively, shortening fraction of marker pairs differed slightly between control regions and bypassed region. Over 6 months both groups showed a slow and highly significant rise in shortening fraction. One year post-operatively, CT ratio, heart rate and bloodpressure were at pre-operative levels, with a shortening fraction of 14%. It can be concluded that bypassed regions have improved their shortening activity. It also shows that the depressive effects of CBS on the cardiovascular system are demonstrable over a period of up to six months post-operatively.

Shortening fraction from marker pairs can be easily used as an indicator in short-term follow-up studies. This application is shown in fig. 5. A coronary vasodilating drug (Nifedipin), also known to reduce afterload was tested during pacing induced tachycardia in 11 patients with 28 marker pairs. Shortening fraction was measured at each increment in heart rate. Results show that following Nifedipin there was an increase in resting heart rate, and shortening fraction also increased. The effects of such a drug have to be explained in terms of afterload, contractility and possible preload interaction.*)

*) see also litterature list B30 and B62.

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SF
%
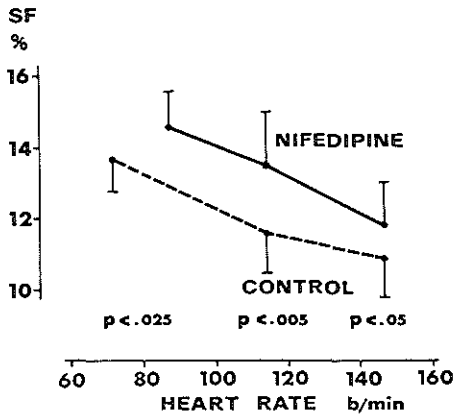
Fig. 5. Shortening fraction (SF) versus paced heart rate before and after Nifedipin. SF increases due to increased afterload. Higher level after Nifedipin might indicate increased contractility.

Automated Contourdetection

A few systems for semi-automatic detection of ventricular outlines in angiocardiograms have been published. [26], [27], [28], [29]) Their clinical, day-to-day application, however, is limited. Preliminary results from the Contouromat, a hardwired contour detector, have been published elsewhere. [28]) Due to the consistency and the detailed information a new application might emerge. In a series of automatic detected outlines over a cardiac cycle small details of the contour can be followed over a trajectory. In this way "spontaneous" endocardial markers can be identified over up to 20 locations in the ventricular contour.
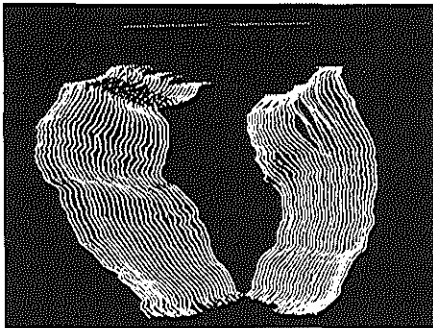
Fig. 6. Automatically detected ventricular contours (50 fr/sec.). Ventricle in upright position. RAO view. Outer contours: end diastole, inner contours: end systole. To avoid superimposition, every next contour is halved and displaced laterally by a fixed distance indicated by dots forming line above contours.
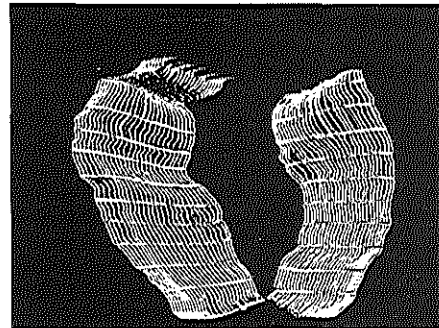
Fig. 7. Spontaneous marker trajectories as seen in fig. 6, manually sketched in. Trajectories must be adjusted for lateral displacement of contour halves.

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STANDARD DEVIATION

RAO - VIEW

LV SYSTOLIC MOTION IN 15 NORMALS
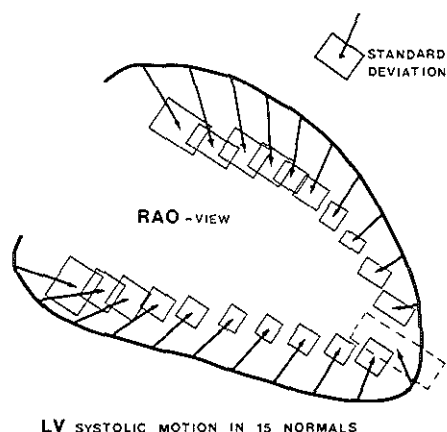
Fig. 8. Composite drawing of spontaneous marker trajectories in 15 normals. Mitral and aortic valves are not drawn. Arrows indicate direction and distance of endocardial motion; squares, standard deviation at end of arrow.

These marker trajectories have been used to plot endocardial wall motion in 15 normal RAO angiograms (fig. 8).

The markers are seen to follow consistent pathways. From this a normalized pattern of marker motion.could be constructed. Results show that the upper parts of the left ventricle contract mainly concentrically while the apex shows a more transverse contraction.

Information of this kind will eventually provide an additional impetus for the development of such devices and algorithms, apart from other reasons such as processing speed, accuracy and reproducibility.

Conclusions

The field of quantitative angiocardiography, based on contrast injections or markers, is moving to a place where normalization in methods and patient conditions is necessary. The "tricks of the trade" are fairly well established. Clinical and pathophysiological conclusions are within reach. It is expected that this experience in medical image analysis will lead to further developments in associated areas.

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CHAPTER VI

BEAT-TO-BEAT ANALYSIS OF LEFT VENTRICULAR FUNCTION PARAMETERS*

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MEESTER, G.T., ZEELENBERG, C., GORTER, S., MILLER, A.C. and HUGENHOLTZ, P.G. (1973): Beat-to-beat analysis of left ventricular function parameters.
Systemic correlation could not be demonstrated in the steady state, between cycle length on the one hand, and left ventricular pressure, end-diastolic pressure, and end-systolic pressure on the other. These results seem to indicate a more random behavior of total pressure V_{max}, i.e. independent of cycle length, and end-diastolic and end-systolic pressure in the resting state.

steady state; cycle length; total pressure V_{max}

Introduction

Most cardiac parameters show slight beat-to-beat variations even in normal sinus rhythm. After interventions, either 'spontaneous' as extrasystoles or artificial with drugs or pacemakers, the cardiovascular system needs several beats to find a new equilibrium. In cardiac catheterization these small fluctuations in pressure and other data are commonly compensated for by taking the mean of the required parameters over several beats.

With the introduction of the digital computer in the catheterization laboratory a more sophisticated normalization of the averaging procedure is possible. This can be done by the Representative Beat Technique (Harrison), where the computer samples the pressure signal for a certain period and after ranking the data, discards the highest and lowest values. The mean of the remaining beats is presented as final output.

Methods

In the present study, the computer sampled the data (left ventricular pressure from a catheter tip manometer, Telco or Millar) with a speed of 250 Hz for a period of 2 minutes (Fig. 1).

BEAT TO BEAT PROGRAM
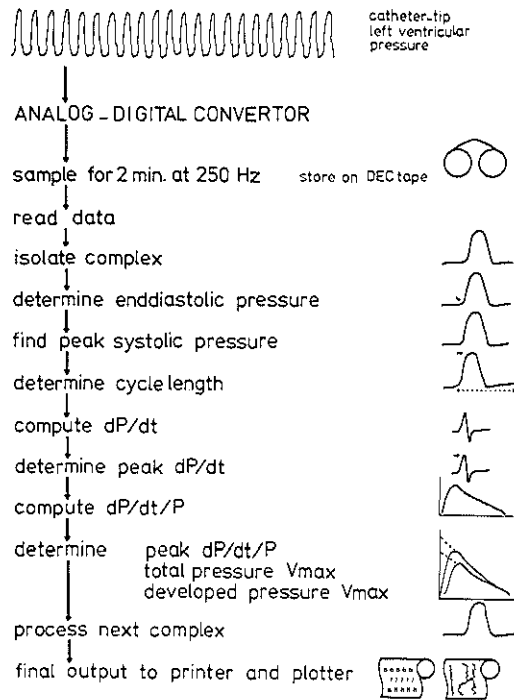
Fig. I. Beat-to-beat program.

On every beat the following calculations were performed:

- *end-diastolic pressure (EDP):* defined as the place in the pressure tracing where dP/dt starts to exceed 200 mm Hg/sec over a pressure rise of at least 30 mm Hg;

- *end-systolic pressure (ESP):* recognized as a negative slope of 100 mm Hg/sec or more with a concomitant pressure below 40 mm Hg;

- *peak-systolic pressure (PSP):* maximum of pressure tracing;

- *peak dP/dt:* maximum of calculated dP/dt values;

- *cycle length:* interval between end-diastolic pressure points of consecutive beats;

- *total pressure* V_{max}: Calculated as $(dP/dt)P$ with straight-line extrapolation after least square fitting of the descending slope between the 15 and 80 mm Hg pressure points;

- *developed pressure* V_{max}: same extrapolation after correction for end-diastolic
pressure.

The computed data are presented in tabular and graphical formats.

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Auxiliary programs provide for later statistical analysis.

This program was used in 23 patients. In each patient, one to three periods of two minutes were recorded in the 'steady state', and during interventions such as intraventricular contrast injections, coronary angiograms were made.

Results

Data on 5 patients in the 'steady state' are shown; all were in sinus rhythm. Results (Table 1) show that EDP, cycle length and total V_{max} may show variations of 10-30% of mean values. Histograms of cycle length and total V_{max} show a random distribution over this period (Figs. 2 and 3).
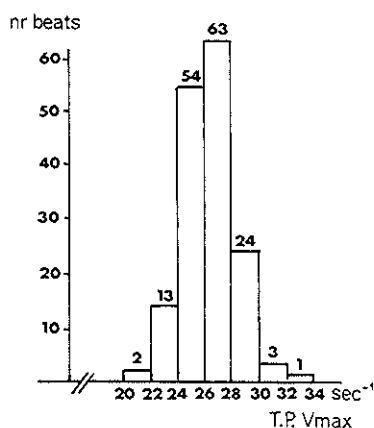
Fig. 2. Total pressure V_{max} of 160 consecutive beats (patient K, sinus rhythm).
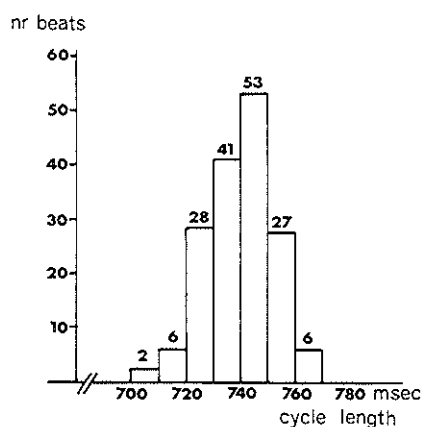
Fig. 3. Cycle length of 160 consecutive beats (patient K, sinus rhythm).

Table 1. Spontaneous variations in LV pressure during 1- or 2-min periods.

Patient	Nr. beats	Cycle length (msec)			Total pressure V_{max} (sec^1)			LVEDP (mmHg)		
		mean	SD	% of mean	mean	SD	% of mean	mean	SD	% of mean
K.	110	1012.4	208.9	20.6	29.8	2.2	7.3	24.8	2.6	10.5
van E.	184	612.5	52.8	8.6	67.3	5.2	7.7	5.5	1.7	30.9
K.	160	733.7	41.2	5.6	26.1	2.4	9.2	15.6	2.9	18.5
de W.	99	644.6	265.9	41.2	45.7	4.8	10.5	27.8	6.8	24.6
V.	91	743.0	224.0	30.1	37.6	4.5	11.9	23.0	7.9	34.3

Recordings during left ventricular angiograms were also made in 5 patients; 1 of them is shown in Figure 4. Beats 22-25 are extrasystoles induced by the contrast injection. Approximately 15 beats later total and developed
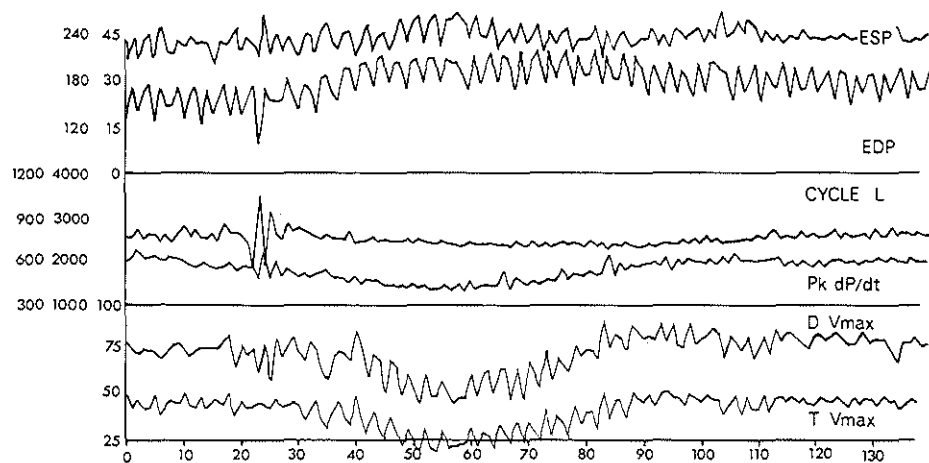
Fig. 4. Recording during left ventricular angiograms in 1 patient.

Table 2. Correlation coefficients for total pressure V_{max} and cycle length.

| | Cycle | | | | |
	N-1	N-2	N-3	N-4	N-5
van E.	+0.21	—0.38	+0.04	—0.09	—0.11
V.	—0.45	+0.20	—0.22	+0.45	—0.32
de W.	+0.13	+0.02	+0.05	+0.04	+0.09
K.	+0.56	+0.06	—0.19	—0.08	—0.05

Table 3. Correlation coefficients for total pressure V_{max} and EDP.

| | Cycle | | | | |
	N-1	N-2	N-3	N-4	N-5
van E.	+0.05	—0.34	+0.41	+0.09	—0.07
V.	+0.22	—0.35	+0.35	—0.03	—0.00
de W.	—0.09	—0.02	—0.03	+0.20	+0.22
K.	+0.02	+0.30	+0.32	+0.24	+0.19

Table 4. Correlation coefficients for total pressure V_{max} and ESP.

| | Cycle | | | | |
	N-1	N-2	N-3	N-4	N-5
van E.	—0.09	+0.00	+0.02	+0.06	+0.13
V.	+0.27	—0.24	+0.26	—0.38	+0.16
de W.	+0.03	—0.06	—0.06	—0.13	—0.07
K.	—0.09	—0.03	+0.00	+0.10	-0.01

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pressure V_{max} decrease from a mean of 72 and 45 sec-[1] to 60 and 25 sec-[1]. The depression of V_{max} lasts for 40 beats. Thereafter, a 10% overshoot is evident for the remaining period of 70 beats.

This supports the conclusions derived from quatitative left ventricular angiocardiography, were depression of functional parameters is not seen in the first 5 beats after injection of contrast. The effects of the contrast medium and its volume load, as evidenced by the behavior of V_{max} and EDP take at least 1 minute to disappear.

Finally, regression lines and correlation coefficients were calculated for total pressure V_{max}, end-diastolic pressure, end-systolic pressure, and cycle length. Each value of V_{max} was compared with the other parameters from the same beat and from 9 consecutive preceding beats.
A summary of the results in 5 patients is presented in Tables 2, 3 and 4. All were calculated in the steady state over periods of 100-150 beats. Correlation is not systematically present in the observed range of these parameters.

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CHAPTER VII

THE ATRIAL PACING STRESS TEST (APST)

I. Introduction

Parameters which describe circulatory function, when measured in the resting state, are often not reflecting the differences between normal subjects and patients with coronary artery disease (CAD). Explanations for this phenomenon are the regional nature of the cardiac disease, the reserve capacity of the heart and the extensive compensatory mechanisms in the peripheral vascular bed.

In patients with coronary artery disease a localized narrowing of one or more of the major coronary arteries can lead to subnormal perfusion of regions distal to the obstruction, with decreased mechanical function as a result, while other, well perfused regions, are able to compensate by increased performance. A reduction in overall reserve capacity may not become manifest except during physical activity or other types of stress.

Therefore, if the early functional consequences of reduced coronary artery perfusion are to be detected, diagnostic methods should be able to test the reserve capacity of the heart. This chapter is dedicated to this exploration with a stress-technique, extensively developed in this laboratory. The use of atrial pacing as a stress test to investigate the dynamic response of the heart in patients with coronary artery disease has emerged in the last decade as a very useful and attractive method. Our initial experience with it has been detailed in chapter IV. Several reasons continue to justify the choice of this stress, even if it does not constitute a maximal form of loading.

Atrial pacing increases myocardial oxygen consumption, by means of an increase in heart rate and as a consequence of augmented wall stress, although cardiac dimensions decrease[1-4], without affecting peripheral hemodynamics[5-7] or sympathetic drive[8]. The duration of diastole, during which the major part of coronary flow takes place, is decreased, so that the test also challenges the ratio of oxygen supply and demand in the cardiac mass.

Other advantages of the test are its rapid reversibility, its precise control in both duration and cardiac frequency, and the removal of psychological factors, since the patient can be left unaware that the test is carried out until he feels the equivalent of angina pectoris.

A vast literature has emerged on specific aspects of the APST. For example, the influence of APST on anginal pain threshold[9]), left ventricular pump and muscle function [7,10-14]), left ventricular compliance [11]), segmental wall motion [11, 15-17]), regional perfusion [18, 19]) and cardiac metabolism [20, 21]) have been described in considerable detail.

However, direct correlations between the extent of CAD as determined from the coronary angiogram and the level of myocardial function have been unsatisfactory[22-31]). This lack of correspondence is to be expected since their relation is obviously only indirect. The response in a particular patient depends for one not only on the presence and extent of collateral circulation and the occurrence of arterial spasm but also on the degree of myocardial damage.

Many techniques have been introduced to test reserve capacity. These include the bicycle (i.e. dynamic) ergometer test [32-35]), the isometric handgrip test [36-39]) pharmacological tests such as isoprenaline infusion [40,41]), nitroglycerine administration [42, 43]), and a primarily inotropic challenge as atrial pacing [8, 14, 16, 25, 26, 44-47]). Hemodynamic measurements can be carried out during all these types of stress tests, but the first three present difficulties in quantifying the actual load of the heart [50-53]). Concomitant hormonal and biochemical reactions are not easily measured or accounted for. The exercise test in particular may be profoundly affected by factors such as the cooperativeness and the extent of exercise training of the patients as well as the tenacity of the clinician in charge of the test. Pharmacological tests vary widely in their response. Only handgrip may have a reasonable reproducibility. The atrial pacing stress test avoids most of these difficulties, since the test can be applied to the patient in the recumbent state under controlled conditions.

II. Patient population

The records of 600 patients in whom complete APST-data were available provided the basis for this chapter.

Group 1

In 44 individuals no symptoms or signs coronary artery disease or hypertensive heart disease were found. Their mean age was 43 years; there were 28 males and 16 females. None of these "normals" had other signs of cardiovascular disease. The cardiac index was 3.9 l/min./m² with standard deviation (S.D.) 0.75, mean ejection fraction was 67% with a 8% S.D. They were considered as a control group.

Group 2

Seventy-one patients (mean age 51 years, 67 males, 4 females) were considered to have severely compromised myocardial function. This was based on angiographically proven CAD with one or more coronary obstructions exceeding 75% *and* one or more of the following conditions: an ejection fraction below 40%, one or more regions with akinesis or dyskinesis*) in the ventriculogram, four or more proven myocardial infarcts in their history and an end diastolic volume in excess of 110 ml/m².

Group 3

The third group consisted of 25 patients (mean age 46 years, 22 males and 3 females) where a single coronary artery bypass graft was placed and APST-data were available pre-operatively and one year after operation. Here the effect of revascularization upon myocardial function could be analyzed.

Group 4

This group consisted of 27 patients with CAD, who had undergone multiple graft bypass surgery. Their mean age was 48 years, all were male. Cardiac catheterization data were available before and one year after the operation, as well as data of maximal work performance during bicycle-ergometry, again before and after bypass surgery.

Group 5

Whether maximum work performance is indeed the best parameter to compare with cardiac performance, as assessed with the atrial pacing stress test, remains to be proven. To analyze this situation eight additional patients were selected. Their mean age was 55 years, all were male. All had severe

* as defined by the American Heart Association [48])

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ischemia as based on four coexisting criteria: a perfusion defect on thallium scan after exercise, ST-depression during exercise, angina during exercise and maximal work performance less than 85% of normal. The mean ejection fraction by angiocardiography was 0.56 (S.D. 0.14).

III. Methodology

All patients were studied after an overnight fast without premedication. Drugs with beta-blockade effect were withdrawn at least 24 hours prior to catheterization. After right heart catheterization and cardiac output measurement, a bipolar pacing electrode catheter was positioned high in the right atrium. The left ventricle was usually approached via a right brachial arteriotomy. Left ventricular pressures were recorded by either a Dallons Telco MMC 8F or a Millar Instruments 7F tip-manometer catheter. Calibration of the tip-manometer was performed electronically and automatically under computer control. The R-wave of the electrocardiogram or pacing spike was not used as a means for the definition of phenomena in the ventricular pressure tracing, rather than the characteristics of the pressure signal itself.

The reference level was set at the mid-thoracic position and adjusted with the fluid channel for base line correction. After control values had been recorded, the APST was started with a heart rate just above the resting value. During the test, left ventricular end diastolic pressure, peak rate of change of pressure and other data were recorded at varying heart rates until the highest attainable paced rate (fig. 1). Automatic data processing equipment is essential for the systematic on-line analysis of these data.

IV. Analysis

Previous papers have shown that in normals and coronary artery disease patients, the relationship between pressure derived parameters and heart rate is variable [7, 13, 24, 25, 29]. However, general tendencies prevail and within the individual patient a more consistent pattern can be observed.

The APST cannot always be carried out over an equal heart rate trajectory in every patient; for example, one patient can be paced over a range from 70 to 120 and another from 100 to 180 beats/min. Therefore, comparison between results of individual patients should include a

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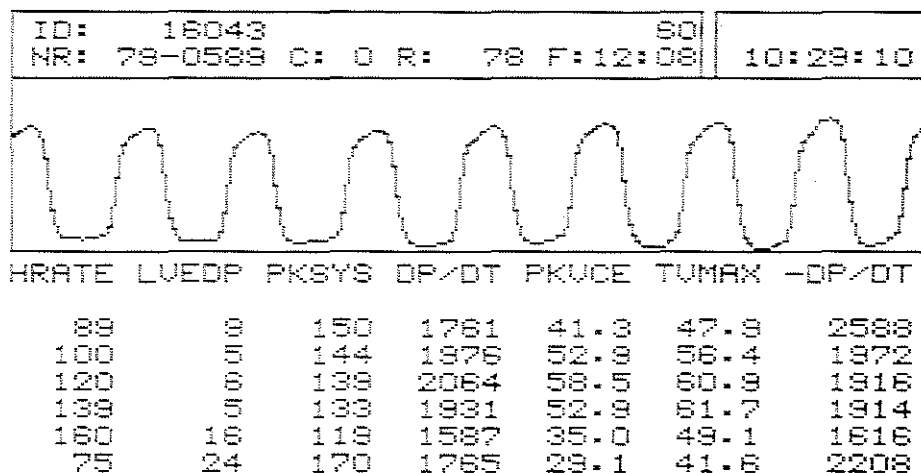
Fig. 1. Video output of computer analysis during an atrial pacing stress test. At the top: patient identification data and timing information, followed by a graphic representation of the last analyzed pressure trace. Underneath: results in columns.
Abbreviations: HRATE = heart rate, LVEDP = left ventricular end diastolic pressure, PKSYS = left ventricular peak systolic pressure, DP/DT = left ventricular peak dP/dt, PKVCE = peak value of dP/dt over P plot, TV_{MAX} = extrapolated V_{max} based on total pressure, -dP/dt = negative peak dP/dt.

normalization procedure.

Furthermore, measurement noise will influence the results. In order to alleviate these difficulties, a solution was sought to "normalize" the APST of an individual patient. After data acquisition, linear regression lines were calculated for every variable in each patient. From these regression lines the values of the variable at heart rates 70 and 140 were determined and assessed in the final analysis. The interdependence between left ventricular pressure derived parameters and heart rate appeared to be well described by a relationship which is linear within the range of 70 to 140 beats/min. Results of an individual patient can therefore be expressed as the value of that parameter at heart rates of 70 and 140. Seventy was chosen because this value is close to the resting heart rate of the majority of patients, 140 presents a 100% increment of this value, is well within the physiological range and was reached by nearly all patients.

Statistical analysis was carried out with the linear discriminant analysis technique. In this technique, the data of two learning groups are used to find that function of a given variable, on which classification of an individual patient into one of the groups can best be based. A geometrical interpretation

of discriminant analysis can be given by plotting each case as a point in space where each variable is a dimension. The points are separated by a hyperplane, selected such that the projections of the groups onto a line perpendicular to that plane, have maximum separation. The discriminant analysis procedure is the more successful the more the learning groups are conceptionnally distinct entities and separated from each other.

For this evaluation the Biomedical Computer Programs developed at the Health Sciences Computing Facility, UCLA [49]) were employed.

The following left ventricular pressure derived variables are included here:

1. Left ventricular end diastolic pressure (LVEDP in mmHg) is defined from the representative beat technique, as that point on the pressure trace after the beginning of diastole where the derivative of left ventricular pressure exceeds 200 mmHg/sec. and continues to exceed this level until the pressure has risen to 30 mmHg above initial diastolic pressure.
2. Peak positive first derivative of left ventricular pressure (pk dP/dt) in mmHg/sec., calculated from a five point Lagrange polynomial approximation with four msec. increments between steps.
3. dP/dt/P derived from the dP/dt and measured P. The peak value of this relationship is the peak VCE. V_{max} is estimated with a linear extrapolation using a least squares fit over the isometric contraction period (see chapter III).

V. Results

There are several sources of variability which must be discussed first. The response of measured values of end diastolic pressure, V_{max}, VCE and pk dP/dt to atrial pacing in 44 normal subjects is shown in fig. 2. From this data it is evident that considerable inter-patient variability exists between basal resting heart rate and highest paced rate.

For example, the record of an individual patient as shown in fig. 3, demonstrates the physiologically relevant range. Notwithstanding the apparant linear pattern, the data also show scatter, suggesting intra-patient variability and/or random measurement error. The V_{max} at heart rate 120 is 69 sec.$^{-1}$, at 140 is 68, and at 150 is 94. With linear regression a value of 81 sec.$^{-1}$ is calculated for heart rate 140, which is much more in line with preceding data and also in a close relationship with the post-operative
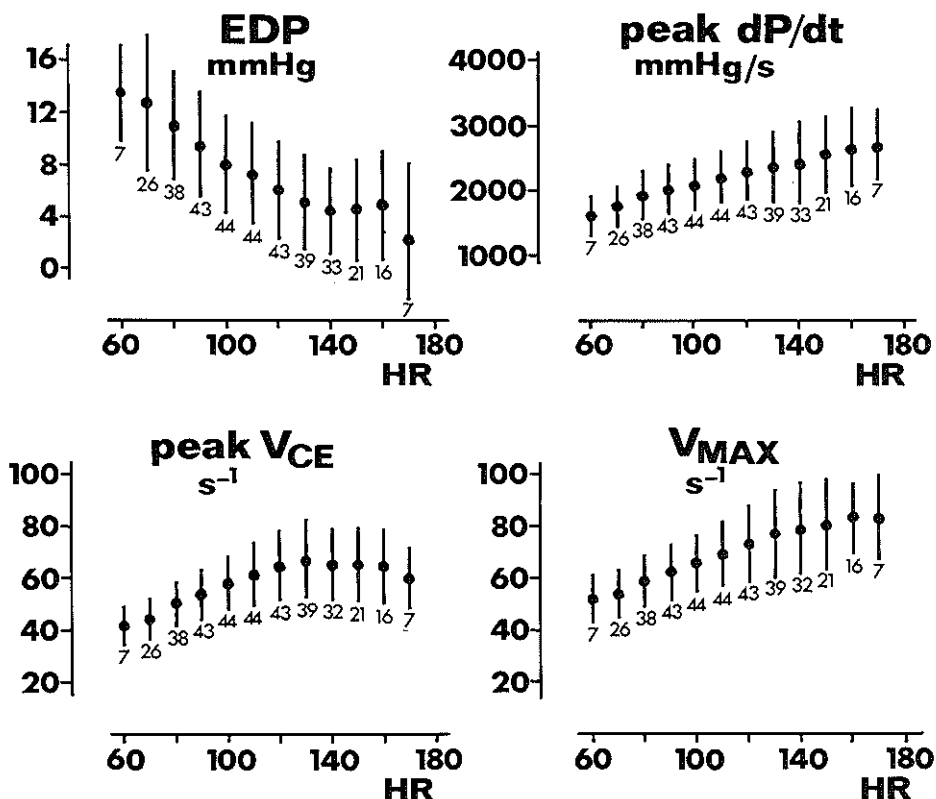
Fig. 2. Summary of APST results in 44 normals. Four variables over the available heart trajectory are plotted as mean with 67% range. The number of observations is provided for all ranges. Abbreviations: EDP = end diastolic pressure, HR = heart rate, peak VCE = peak of dP/dt/P versus P plot.

assessment of 80 sec.$^{-1}$ at the identical heart rate of 140. It is likely therefore that the V_{max} of 94 sec.$^{-1}$ while within the normal range, is a result of random measurement error. The usefulness of linear regression between heart rate and the four pressure derived variables can, to a certain extent, be appreciated from the correlation coefficients. As shown in fig. 4, where cumulative histograms of results in 125 patients with CAD are presented, practically all exceed 0.50. One should keep in mind, however, that a completely horizontal regression line, where the variable does not change with the increase in heart rate, will lead to a correlation coefficient of zero. In addition, pk VCE, the single highest sample of the dP/dt/P tracing will be more sensitive to measurement errors than V_{max} (fig. 5). The latter value is calculated from up to 100 samples in the declining part in the dP/dt/P versus P relation.

Since the histograms of correlation coefficients from the group of

normals and the groups of CAD patients do not show a systematic difference, it is indicated that, also under pathological conditions, the linear regression technique is applicable between heart rates of 70 and 140 beats/min.

During the atrial pacing stress test four interdependent variables are recorded at five to eight levels of heart rate. One test can therefore yield up to 32 measured values. If one compares pre- and post-operative results, this amount is doubled. However, data reduction through linear regression of the variables over the heart rate trajectory, provides two descriptive values per variable and so the results of the atrial pacing test can be condensed to eight descriptive parameters.
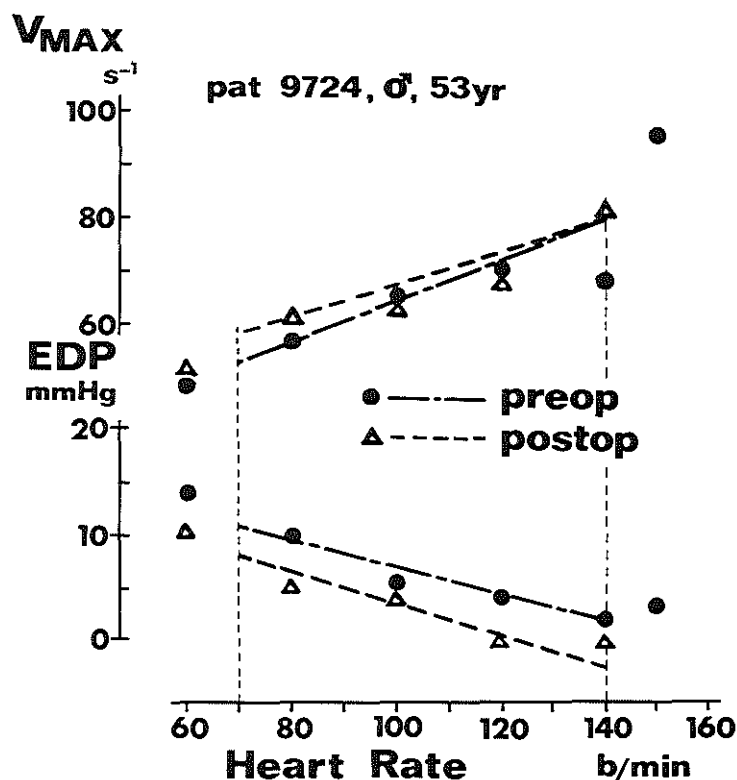
Fig. 3. Atrial pacing stress test of patient ID 9724. The results of V_{max} and end diastolic pressure (EDP) are presented before and after coronary bypass surgery. Regression lines based on these data are drawn in between heart rates 70 and 140 (see text).

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CUMULATIVE DISTRIBUTION
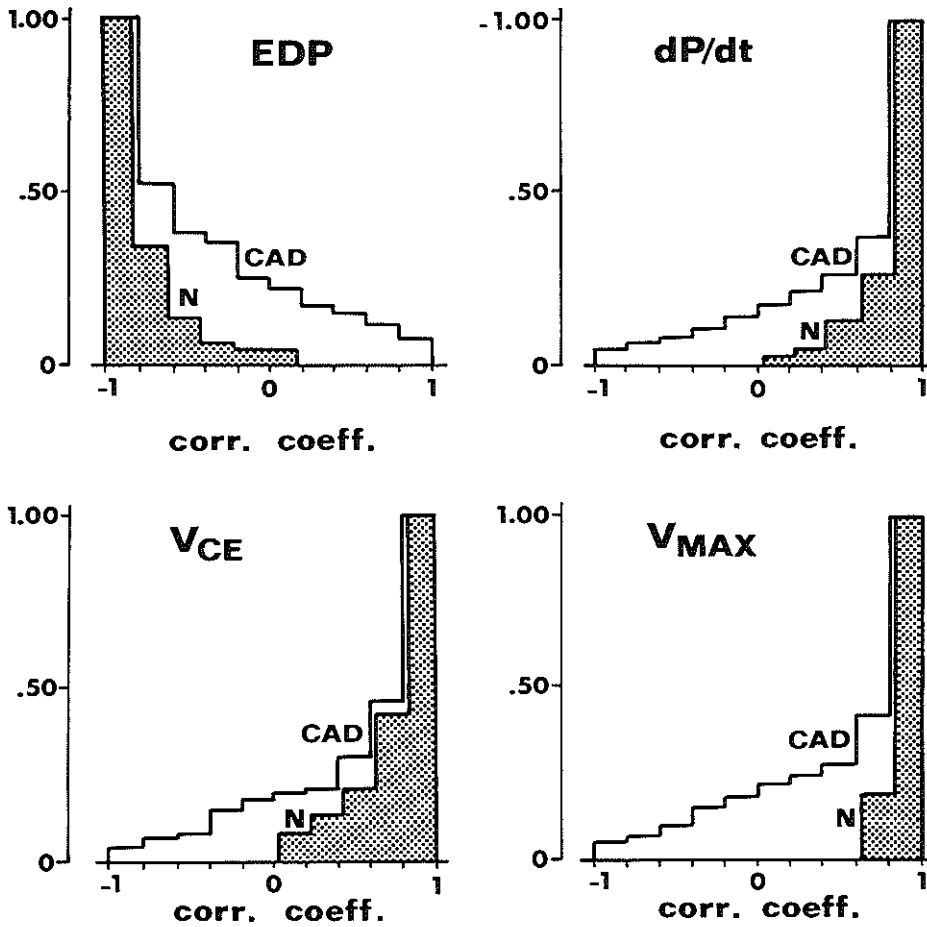
Fig. 4. Cumulative distribution of correlation coefficients obtained from linear regression of EDP, dP/dt, VCE and V_{max} in 44 normals (N) and 125 patients with coronary heart disease (CAD). *Note* high coefficients in both groups indicating the validity of the procedure.

Lineair discriminant function analysis of the eight descriptors was carried out in two learning groups, one consisting of normals (group 1), the other of patients with the most severe forms of coronary heart disease (group 2). The performance of this discriminant function will be described for each of the separate groups of patients.
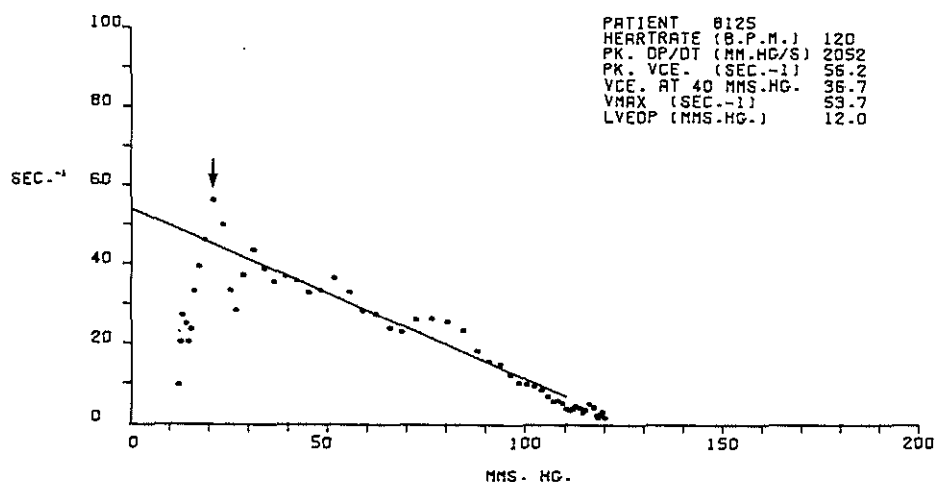
Fig. 5. Plot of calculated dP/dt versus P. Results in patient ID 8125 at heart rate of 120 beats/min., sampling rate: 250 Hz. Results of regression for V_{max} and extrapolated value of 53.7 sec.$^{-1}$ is presented.
Note: single highest sample (pk VCE) at higher level than extrapolated V_{max} due to measurement noise.

Table I.   APST: summary of results after linear regression of rough data in 44 normals and 71 patients with coronary artery disease. The values at heart rate 70 and 140 as mean and standard deviations.

MEAN VALUES AND STANDARD DEVIATIONS IN 44 NORMALS

	EDP mmHg	dP/dt mmHg/sec.	VCE sec.$^{-1}$	V_{max} sec.$^{-1}$
HR 70	9.8 ± 3.7	1824 ± 356	48.8 ± 10.5	55.3 ± 9.9
HR 140	3.6 ± 3.2	2459 ± 563	68.0 ± 14.2	78.8 ± 17.0
n	44	44	44	44

IN 71 CAD PATIENTS

	EDP mmHg	dP/dt mmHg/sec.	VCE sec.$^{-1}$	V_{max} sec.$^{-1}$
HR 70	15.3 ± 8.2	1595 ± 375	36.3 ± 10.8	46.4 ± 9.2
HR 140	12.8 ± 8.7	1847 ± 452	44.0 ± 13.8	52.4 ± 13.3
n	71	71	71	70

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EDP	=	$15.4 - 0.082$ x HR mmHg
pk dP/dt	=	$1140 + 9.44$ x HR mmHg/sec.
pk VCE	=	$59.2 + 0.24$ x HR sec.$^{-1}$
V_{max}	=	$33.6 + 0.32$ x HR sec.$^{-1}$

N.B.: Only in heart rate range of 70 - 140 B/min.

Group 1

The results of the group with 44 normals are summarized in mean values
with their standard deviations for heart rates of 70 and 140 beats/min. in
table I. The resulting regression equations for calculation of the left
ventricular pressure derived variables are presented in table II. It can be seen
that, when heart rate is increased from 70 to 140, on the average EDP falls 6
mmHg, pk dP/dt rises 635 mmHg/sec. and pk VCE and V_{max} both rise
approximately 20 sec.$^{-1}$

Discriminant analysis based on the descriptors as defined above (fig. 6a),
was carried out. When VCE was excluded both at heart rate 70 and heart rate
140 (fig. 6b) discriminatory power was practically the same as with the full set
of eight variables. When end diastolic pressure, pk dP/dt and V_{max} at heart
rate 140 alone were used (fig. 6d) results were somewhat worse. This is also
clear from the classification matrix in table III where the number of false
positives and false negatives is seen to increase when the variables are
progressively excluded from the function.

Group 2

This group consists of 71 patients with coronary heart disease where
impairment of left ventricular function was considered to be present, based
on one or more independent abnormalities. Results of the atrial pacing stress
test are also summarized in table I. Mean values of the group differ
considerably from values of the normal group (fig. 7). Several individuals,
however, fall within the normal range for one or more parameters. In fig. 8
histograms of the four pressure derived variables in this group of patients are
shown at a common heart rate of 140 beats/min. The distribution of these
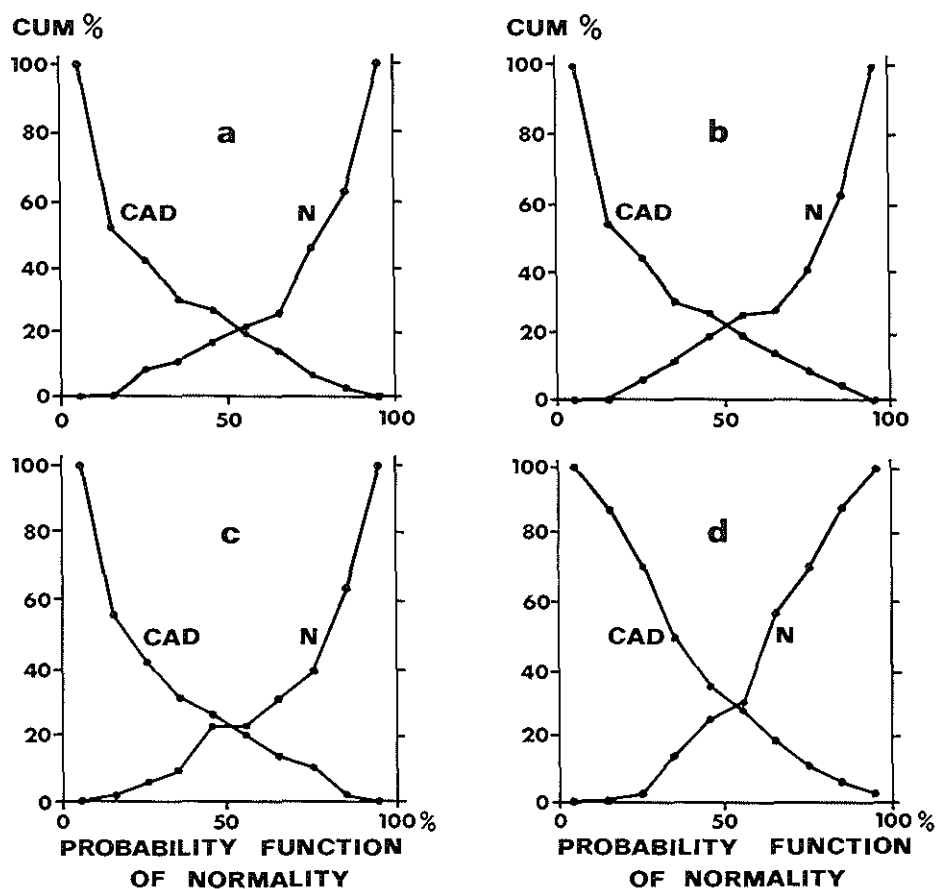
Fig. 6. Distribution in cumulative percent of the probability function after discriminant function analysis in 44 normals (N) and 71 patients with coronary artery disease (CAD). Results are expressed in the chance of being normal. Zero % indicating completely abnormal. 100% indicating maximum probability of normality.

Fig. a) calculated with four variables at two heart rates

Fig. b) calculated with three variables at two heart rates

Fig. c) calculated with three variables at heart rate 140

Fig. d) calculated with three variables at heart rate 70 (See text).
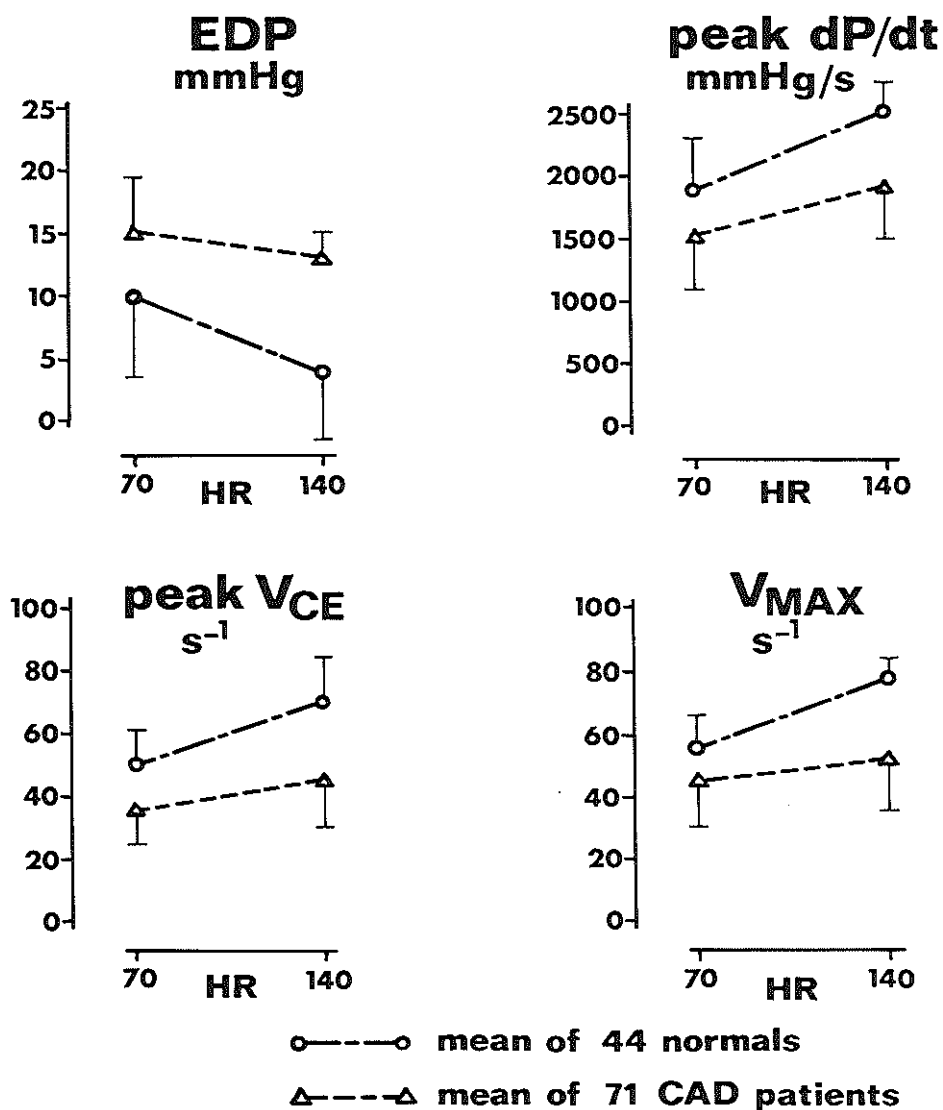
Fig. 7. Results of APST after linear regression of raw data expressed as means and standard deviations at heart rates 70 and 140, in 44 normals and 71 patients with coronary artery disease. The values at heart rates of 70 and 140 are calculated from the regression equation.

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Table III. Classification matrix: results of multivariate discriminant analysis of APST results in two learning groups: 44 normals and 71 patients with coronary artery disease (normal and CAD). Classification of patients in percent of total group in normal (n) or abnormal (abn). First column: EDP, dP/dt, V_{max} and VCE at heart rate 70 and 140 used as discriminant function variables. Second column: VCE excluded. Third column: results with EDP, dP/dt and V_{max} at heart rate 70. Fourth column: EDP, peak dP/dt, peak VCE at heart rate 140.

	n. %	abn. %	n. %	abn. %	n. %	abn. %	n. %	abn. %
44 Normals	84	16	82	18	75	25	77	23
71 CAD pts	22	78	19	81	28	72	20	80
	(8 variables)		(6 variables)		(3 variables) at HR 70		(3 variables) at HR 140	
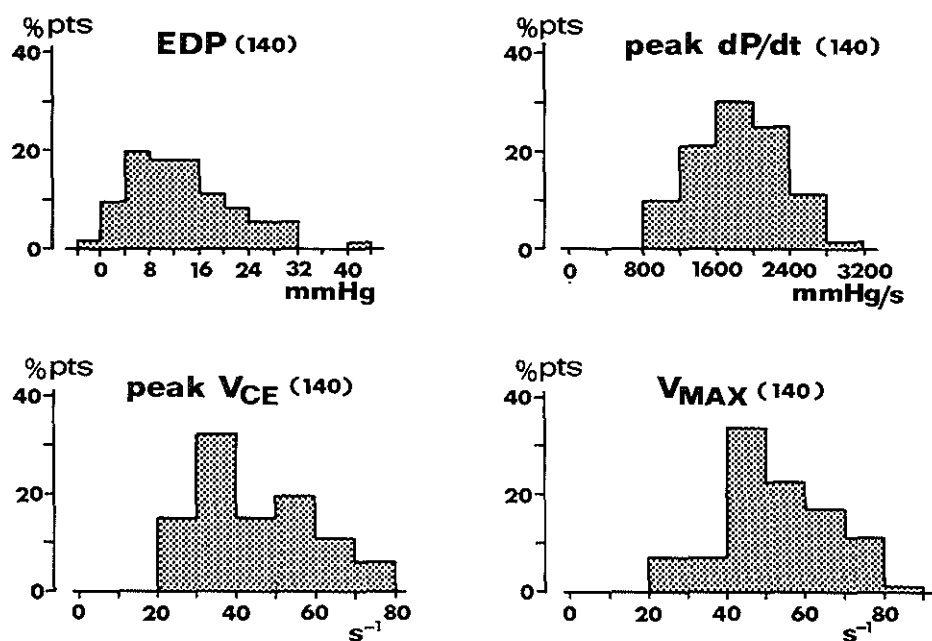
Fig. 8. APST-results in 71 patients with severe coronary artery disease. Histograms for EDP, dP/dt, VCE and V_{max} at heart rate 140 after linear regression in % of patients (% PTS).

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variables is more or less symmetrical across the range, indicating that some patients in this group are able to respond in a normal manner to atrial pacing at 140 beats/min., while others present extremely disturbed values. Discriminant function analysis was carried out between the group of 44 normals and 71 patients with severe CAD. End diastolic pressure, dP/dt, VCE and V_{max} at heart rate 70 and 140 were included in the analysis. From these data the probability of being normal can be calculated for each individual. This probability in classes of 10% is shown in fig. 9. The majority of individuals are correctly classified as normal or abnormal with clear separation between the two groups. There is some overlap, because not all "normals" will have truly normal cardiac function, while also in the abnormal group a few patients can be expected to have normal myocardial performance.
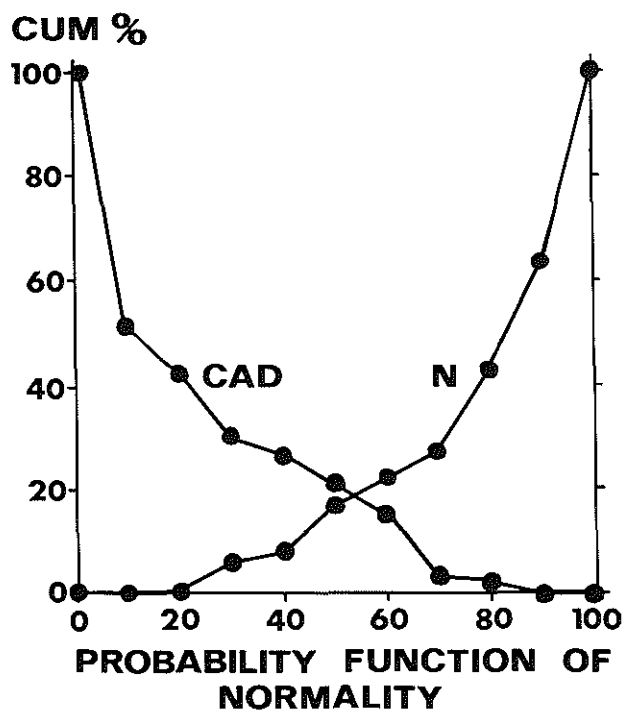
Fig. 9. Distribution in cumulative percent of 115 individuals (44 normals and 71 patients with severe coronary artery disease) after discriminant function analysis of eight variables EDP, V_{max}, VCE and dP/dt at heart rates 70 and 140. Results are expressed in chances of being normal, 100% indicating maximum chance of normality, 0% indicating abnormality.

Group 3

In 25 patients with a single bypass graft, an atrial pacing stress test was available before and after the operation. In 20 patients the graft was shown to be open one year post-operatively. In one of the patients post-operative APST data were incomplete. Fifteen of these grafts were placed on the left anterior descending, four on the right, one on the left circumflex coronary artery. In five patients the graft was closed one year post-operatively; four of these grafts were placed on the left anterior descending coronary artery, one on the right coronary artery. Although the single bypass graft surgery usually implies that there was only one significant lesion in the coronary artery system, in 12 patients additional lesions were shown to be present. These lesions did usually not exceed a 50% narrowing. In fig. 10 results of the V_{max} values at heart rate 140 are shown both before and after operation in five patients with a closed single graft. Three patients have a V_{max} value which is about equal before and after operation. In one patient (R) V_{max} decreased from 83 to 53 sec.$^{-1}$ after operation. This patient had a peri-operative infarct. In another patient (T) V_{max} improved from 68 to 93 sec.$^{-1}$. This patient was pre-operatively catheterized under the clinical syndrome of impending infarction. In table IV results are listed of all 25 patients with data before and after operation.

Eight patients had a normal V_{max} at heart rate 140 before operation. *) Four patients showed an improved value (to normal range) of V_{max} (140) after operation. In four V_{max} (140) worsened; of these, patient no. 10 had an infarct between cardiac catheterization and the operation (77 to 44 sec.$^{-1}$).

Patient no. 12 with a bypass graft on the right coronary artery had one year post-operatively, four additional areas of narrowing in the left coronary artery (of $<$ 50%) and V_{max} (140) moved from 85 to 50 sec.$^{-1}$.

Patient no. 14 had, apart from a grafted lesion in the right coronary artery, also total obstruction of the right coronary artery and additional lesions in left anterior descending and posterolateral branches. In addition there was postoperatively severe systemic hypertension with progressive signs of left ventricular hypertrophy. The new lesions here are probably responsible for the fall in V_{max} (140) from 88 to 68 sec.$^{-1}$.

In table IV are also shown the results of discriminant analysis expressed as the percent chance of an individual APST to fall in the normal group. Five patients have improved chances of being normal ($>$ 20%), four patients worsened after operation. In six patients results of V_{max} (140) alone and

*) V_{max} (140) expressing the quantity V_{max} after extra- or interpolation from the regression equation for an heart rate of 140 beats/min.

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discriminant function coincide. Two patients (no. 1 and 20) have diminished chances of normality after operation, in the presence of a normal V_{max} (140). A rise in EDP is present in both patients. Patient no. 1 still has some angina pectoris with limited exercise tolerance. Patient no. 20 is doing well. He has, apart from the bypassed lesion, six lesions less than 50% in his coronary tree.
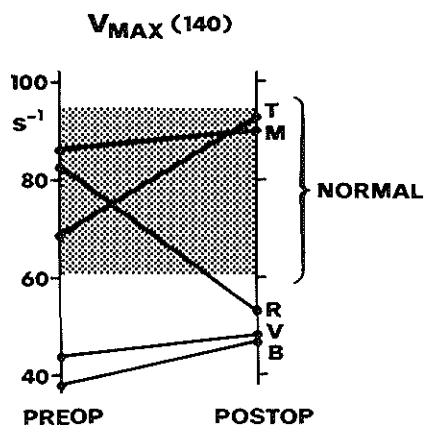
Fig.10. V_{max} at heart rate 140 after linear regression of the APST-results in five patients with closed single graft, before and one year after operation. Letters indicating individual patients (see text).

Group 4

This group consists of 27 patients in whom an atrial pacing stress test was carried out before and one year after multiple coronary bypass surgery and in whom also data were available from bicycle-ergometry, carried out just before the cardiac catheterization. From the ergometry test the maximum performance level W_{max} and maximum heart rate reached at the test are recorded. W_{max} is then adjusted for age, body size and sex. The exercise test is carried out to a maximal load just sustainable by the individual. Whether at that time maximum cardiovascular performance had in fact been reached or whether the exercise was interrupted just before this point, can perhaps be derived from the recorded heart rate at the moment the patient stopped the exercise test. Results of 27 patients in whom these data were available, are presented in table VI. It is clear that patient no. 2 at the post-operative exercise test did not reach his maximum performance since the heart rate at that time was only 90 beats/min. As the relationship between heart rate and V_{max} is essentially linear in the physiological range, it is possible to predict from the atrial pacing stress test the linear estimate of V_{max}, prevailing at the same heart

rate as at the moment of maximum work performance on the bicycle. This "corrected" estimate for V_{max} is also provided in the table.

The results of the previous discriminant analysis with the eight variables of the atrial pacing stress test were again applied. On the basis of the two previous learning groups, the probability of being normal was calculated and presented in the final column of table V. In an effort to relate these values with other indices of circulatory performance, various comparisons were made, one of which is demonstrated in fig. 11. As is the case with several other parameters, no correlation is present. The comparison between V_{max} at heart rate 140 and W_{max} from ergometry is presented in the form of a scattergram in fig. 11a. In fig. 11b the relation between end diastolic pressure at heart rate 140 and maximum performance on ergometry is shown. Again, any association between the two parameters is absent. The probability of belonging to the normal group calculated from all eight variables in the APST, as related to the maximum performance on the bicycle, is shown in fig. 12.

This scatter-gram shows a vertical orientation of the observations implying that between 50-100% of W_{max} various chances of being normal can occur. Correlation analysis performed on these parameters confirms the lack of any association.
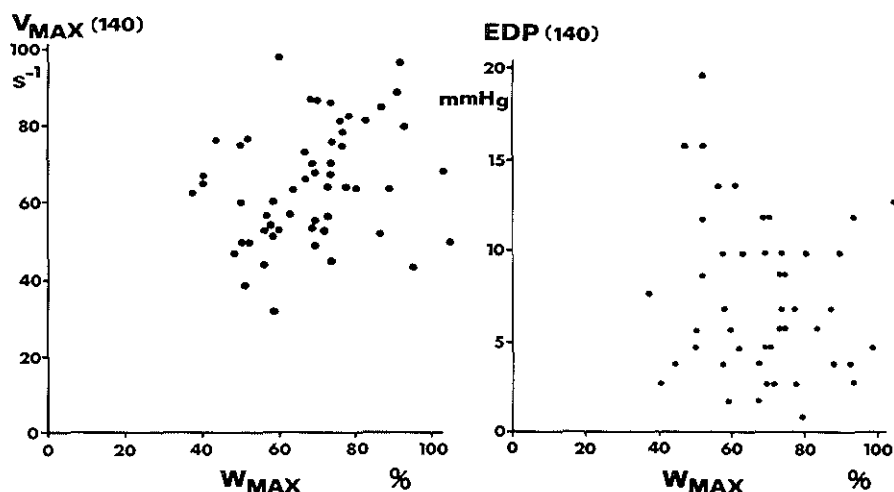
Fig.11. Comparison between APST-results and maximum performance with bicycle ergometry (W_{max}) in 27 patients with coronary artery disease, both before and after bypass surgery.
a) Relation between V_{max} at heart rate 140 and W_{max}.
b) Relation between EDP at heart rate 140 and W_{max}.

Table IV. Listing of patients with single graft coronary bypass surgery and APST before and after operation. Results of the APST after the regression analysis for heart rate 70 and 140 are provided. In the final column the probability index of being normal is given, all data before and one year after operation. At re-catheterization 20 patients had a functioning coronary bypass graft, in five patients it was closed.

APST RESULTS AFTER REGRESSION IN PATIENTS WITH SINGLE GRAFT BYPASS SURGERY

OPEN GRAFTS: PREOP AND 1 YR POSTOP.

ID. no	HR 70				HR 140				%Prob. index
	EDP	dP/dt	VCE	Vmax	EDP	dP/dt	VCE	Vmax	
2	10	1719	49	53	3	2377	75	88	93
	19	1881	42	51	12	2826	59	77	72
3	13	1289	36	46	5	1664	64	70	66
	15	1934	38	46	4	2507	72	83	81
4	11	1370	39	46	4	1748	57	64	54
	11	1557	40	46	3	2140	63	66	67
7	17	2300	43	57	7	2777	68	82	76
	23	2964	44	49	9	2706	58	82	30
31	9	1594	43	41	4	1993	51	65	51
	16	2005	44	-	6	2760	66	-	-
38	11	1377	41	51	3	2215	61	81	89
	8	1341	43	55	0	1694	64	80	88
61	13	1830	29	49	10	2172	55	64	26
	18	1974	35	44	6	2211	60	63	34
78	9	1427	39	47	4	2167	69	83	88
	17	1761	37	42	16	3268	80	96	92
88	14	1742	38	56	12	2045	42	61	24
	12	1574	41	45	6	1955	48	62	39
93	10	1656	45	58	1	2114	63	77	27
	21	891	21	32	4	1071	38	44	12
96	7	1656	45	58	1	2114	63	77	85
	11	2115	55	61	10	3009	55	76	77
102	15	1980	47	64	14	3156	60	85	87
	24	2696	37	57	17	3625	41	50	11
104	13	1403	33	42	6	1705	48	61	31
	14	1210	35	46	5	1528	46	58	38

ID. no	HR 70				HR 140				%Prob. index
	EDP	dP/dt	VCE	Vmax	EDP	dP/dt	VCE	Vmax	
131	21	2017	35	55	3	2470	80	88	90
	12	1276	40	50	5	1713	58	68	67
150	13	1603	35	47	11	1699	60	64	27
	24	1939	30	53	4	2602	82	91	96
155	11	2187	47	56	5	2482	54	70	52
	14	1491	37	51	7	1732	56	65	45
159	12	2051	44	56	9	2641	55	73	58
	9	1569	53	50	6	2353	62	83	89
175	10	1401	35	42	7	1847	59	61	42
	21	1476	31	41	10	2693	54	67	63
181	15	1685	39	48	9	1925	53	62	32
	20	1721	35	48	7	2638	61	90	90
188	7	1762	57	56	2	2196	70	79	86
	23	1389	25	40	9	2084	62	72	60

CLOSED GRAFTS: PREOP AND 1 YR POSTOP.

ID. no	HR 70				HR 140				%Prob. index
	EDP	dP/dt	VCE	Vmax	EDP	dP/dt	VCE	Vmax	
8	13	1731	40	54	3	2220	63	68	70
	20	2386	46	59	5	3370	75	93	95
15	14	1146	31	35	17	1352	34	38	03
	10	1663	31	37	11	1979	47	47	07
108	7	1944	55	57	9	2940	70	86	91
	7	1673	49	56	8	2414	75	90	95
126	13	1274	37	41	13	1249	36	44	05
	12	1312	33	36	10	1227	42	48	07
179	12	1490	46	57	4	2021	61	83	72
	6	1039	39	44	10	1820	49	53	56

Group 5

Results of the atrial pacing stress test in the eight ischemic patients, who performed an exercise test, are shown in table VI. The APST data have again been normalized for heart rate 70 and 140. From the data itself, it is clear that on the average, end diastolic pressures, both at heart rate 70 and 140, are elevated in these patients and that the other variables are all at the lower side of normal or below normal. The probability of being normal based on the discriminant function of APST-variables is also shown in table VI. One patient no. 6, is especially remarkable because he has normal APST-values at both heart rates for al parameters resulting in a 98% change of being normal. This patient was a male of 44 years, with a cardiac index of 3.3 l/min./m², left ventricular end diastolic volume of 63 ml/m² and an ejection fraction of 0.73. He had a 75% obstruction of the left main coronary artery with two lesions of less than 50% narrowing in the left anterior descending and diagonal branch respectively. Furthermore, there was a grade II mitral regurgitation. He had been admitted to the hospital with an impending infarction and after "cooling off", cardiac catheterization and coronary bypass surgery were carried out. This analysis shows that he can be considered as an ideal candidate for this procedure, because he was shown to have an 98% chance of having normal myocardial reserve.

This is the patient to identify in time before cardiac muscular damage occurs.

A contrast provides patient no. 5 in whom the APST was classified as 0% chance of being normal. This patient, a male of 50 years, had a cardiac index of 4.2 l/min./m², an end diastolic volume of 90 ml/m², an ejection fraction of 0.46 with three vessel coronary disease. There were in the left anterior descending artery two 75% lesions, in the left circumflex and the right coronary artery a 100% lesion. The patient suffered in addition from severe systemic hypertension (peak left ventricular pressure 170 mmHg) with left ventricular hypertrophy. The estimated left ventricular muscle mass was 244 ml/m², i.e. three time the normal value. The patient had angina pectoris over a period of eight years with a myocardial infarct three years ago. ts. Early a period of eight years with a myocardial infarct three years ago. From these data can be concluded that the combination of severe left ventricular hypertrophy and triple vessel coronary artery disease has reduced myocardial reserve capacity to practically nil. Even so, he underwent bypass surgery recently with three grafts, and the early postoperative results are good, thus far.

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Table V. Listing of results of APST and maximal performance on bicycle-ergometry in 29 patients before (first line) and 1 year after operation (second line).

APST AND ERGOMETRY BEFORE AND AFTER CBS

ID. no.	HR 70 EDP	dP/dt	VCE	Vmax	HR 140 EDP	dP/dt	VCE	Vmax	Wmax	at HR	Vmax estim.	%Prob. index
1	8	1782	49	58	16	1796	40	48	47	110	52	0
	11	1677	52	57	4	2586	77	95	92	115	82	97
2	10	1719	49	53	3	2377	75	89	69	140	89	93
	19	1881	42	51	12	2826	59	77	52	90	59	72
3	13	1269	36	46	5	1664	63	70	69	115	61	66
	15	1934	139	46	4	2507	1165	85	87	140	85	100
6	13	1746	37	52	4	2064	51	57	57	100	54	36
	13	1277	31	45	6	1742	47	56	73	147	58	32
16	15	2299	44	60	0	2262	82	86	73	105	73	86
	11	1844	47	59	6	2315	68	81	83	135	79	83
17	32	1375	33	43	4	2153	69	76	44	125	68	88
	23	1628	27	46	5	2027	52	64	62	114	57	43
19	8	2418	62	56	4	2629	70	74	67	130	72	72
	11	2049	49	53	2	2266	74	70	74	170	79	77
20	14	1199	34	46	12	1502	39	53	69	-	-	16
	16	1817	42	56	5	2277	55	70	69	115	65	66
21	8	1459	53	59	8	1967	53	63	37	-	-	62
	18	1991	36	51	6	2809	62	71	50	150	71	74
29	16	1045	29	35	10	1247	35	47	57	155	50	68
	13	812	30	30	10	1186	38	54	69	180	66	16
38	11	1377	41	51	3	2215	61	81	77	170	93	89
	8	1341	43	55	-1	1694	64	80	94	180	94	85
42	10	1296	38	42	5	1848	53	60	50	110	52	47
	11	1216	37	45	5	1604	46	63	69	136	63	45
43	6	1525	50	66	4	2197	84	98	60	100	80	99
	7	2318	59	64	2	2496	80	87	67	160	95	91

ID. no.	HR 70 EDP	dP/dt	VCE	Vmax	HR 140 EDP	dP/dt	VCE	Vmax	Wmax	at HR	Vmax estim.	%Prob. index
47	19	1802	33	44	14	2329	42	54	60	-	-	12
	18	1367	28	40	13	1847	40	50	105	156	51	11
56	10	1687	42	50	10	1857	53	58	63	125	56	24
	21	1719	29	41	7	2110	59	61	58	87	46	33
57	11	1794	44	54	7	2019	56	75	77	160	81	58
	12	1530	38	52	3	2104	67	88	93	160	97	90
58	34	1835	26	55	16	2110	36	61	52	110	60	09
	23	2023	36	55	5	2125	58	68	98	145	69	49
61	13	1830	29	49	10	2172	55	64	80	-	-	26
	18	1974	35	44	6	2211	60	63	74	-	-	31
62	16	1271	29	44	14	1491	34	44	56	145	44	05
	13	1623	36	48	6	1762	47	54	59	111	52	21
63	13	1453	40	51	9	1611	47	50	51	100	50	20
	13	1385	37	43	12	1563	42	49	70	113	47	10
85	8	1732	50	56	7	1563	45	56	87	128	56	22
	13	1454	33	40	9	1730	45	52	73	105	46	14
87	11	954	29	36	9	937	36	45	74	160	47	07
	23	747	15	31	2	1245	44	52	59	150	55	30
90	10	2335	53	66	7	2695	68	84	73	140	84	85
	12	2209	49	64	5	3117	83	112	70	96	82	98
91	11	1728	42	56	3	2158	58	67	40	128	65	64
	17	1458	32	41	12	1651	39	47	93	133	46	07
96	10	1656	45	58	1	2114	63	77	79	150	80	85
	11	2115	55	61	10	3009	55	76	73	121	72	77
99	14	1568	42	49	3	1850	58	65	71	95	54	58
	16	1632	39	46	10	2322	51	68	89	155	73	50
106	9	1396	37	40	20	1199	30	39	51	110	39	01
	36	1272	17	34	40	1406	19	31	58	151	31	01

VI. Discussion

The atrial pacing stress test, as it is usually carried out with increments in the heart rate of 10 or 20 beats/min., with the four pressure derived variables described earlier, can result in as many as 32 values per test. Comparison between results before and after an operation necessitates the assessment of twice this amount of data. With the application of the linear regression method, the results of an atrial pacing stress test are reduced to eight parameters, thus simplifying matters considerably.

The experience with multivariate analysis shows that the measurement of VCE, as it is carried out at present, probably does not contribute to the diagnostic power of the atrial pacing stress test. Although improvements in the measurement technique may be of help, it seems better to eliminate this part of the test.

Still, further reduction with discriminant analysis of the resulting eight or six parameters can be carried out, leading to a "summary probability index". To be of practical value, a large data base is necessary. Work along these lines is at present in progress. Improvement may also be expected from efforts at normalization and standardization, pari passu with the increase of the data base. Factors such as age, sex, resting heart rate and others, should also be included in this normalization procedure.

Yet, even without these refinements available at present, the linear regression technique is shown to be valid between the limits of heart rates of 70 and 140, both in normals and patients with CAD. Although not demonstrated here, this linear relation cannot be expected to be present at heart rates of 150 and above. Between the above mentioned limits, the existence of a linear relation can be used as an indicator for the validity of the test, as carried out in the individual patient.

The results of the APST in the group of patients with severely compromised myocardium show that the coronary artery disease patients have a different offset and slope, as compared to the normals, for all four measured variables. This difference in offset for the groups, however, falls within the standard deviations at heart rates of 70; but, at heart rates of 140/min. there is a clear separation between normals and CAD patients.

The relationship between the probability index and the degree of functional impairment, hopefully still more accurately defined with growing
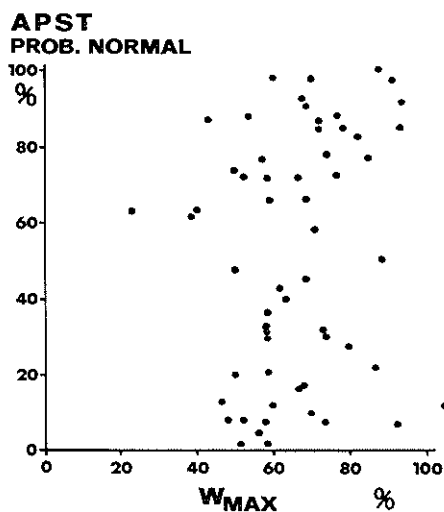
Fig.12. Comparison between discriminant function analysis of APST-results and maximum performance with ergometry (W_{max}) in 27 coronary artery disease patients before and after operation. Results expressed in probability of being normal for APST, in percent of normal for W_{max}.

Table VI. Eight patients with severe ischemia during exercise. Results of APST and probability index of normality. For comparison, mean values and standard deviations of normals are also provided.

Pat. no.	Heartrate 70				140				Prob. Index.
	EDP	dP/dt	VCE	V_{max}	EDP	dP/dt	VCE	V_{max}	
1	14	1402	35	37	12	2076	53	63	32
2	17	1835	37	49	10	2454	54	65	43
3	21	1429	33	48	10	1684	36	45	10
4	14	1371	35	43	14	1609	36	47	07
5	2	2611	39	67	28	1772	22	32	00
6	10	1514	50	59	4	2763	75	84	98
7	12	1705	38	46	11	2146	43	53	17
8	11	2146	43	53	7	2531	58	62	43
mean	12.6	1751.6	38.7	50.2	12.0	2125.7	47.1	56.4	
Normal:	9.8	1824	48.8	55.3	3.6	2495	68.0	78	
S.D.:	3.7	356	10.5	9.9	0.5	85	14.2	2.6	

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test populations, is easily determined in the same computer configuration as is employed for the calculation of the APST-results. The discriminant function can be provided at the end of the atrial pacing stress test, reducing the result to a single number between 0 and 100%. This value will also express the distance of the individual patient from the mean of the normal group, in other words, it can be regarded as a scaled factor.

The group of patients with a single graft, either open or closed, illustrates best the application of the atrial pacing stress test. In some patients, who had a closed graft, one year post-operatively, the worsening of the APST-results indicated intervening incidents, such as additional myocardial infarcts.

Comparison of the atrial pacing stress test with maximum performance on the bicycle in the ergometry test did not reveal any systematic relationships. It is highly likely that concomitant reflex changes of nervous, hormonal or biochemical nature obscure the results during exercise tests to such an extent, that no quantitative cardiac information is present in the "maximal" exercise tolerance. Criteria to assess the degree of exercise tolerance, such as a maximal pulse rate normalized for age and sex, may improve results. When a sub-maximal test has been conducted or when the test has been interrupted, the work produced at a desired pulse rate, estimated by extrapolation, will reflect the exercise tolerance better than the actual work produced.

Physical training is known to lower the pulse rate for given levels of exercise or to cause the maximal pulse rate to be reached at a higher load.

Whether the same phenomenon applies to the atrial pacing stress test has never been demonstrated. The fact that for this test a left and right cardiac catheterization have to be carried out, is an important draw-back.

Comparison between myocardial ischemia as assessed by independent indicators such as perfusion defects on thallium scan after exercise, ST-depression during exercise, angina during exercise and reduced maximal exercise tolerance, with the atrial pacing stress test, suggest that both sets of criteria have a common denominator in this group. Since the number is small, only eight patients with a limited range of variables, no major conclusions can be drawn.

VII. Summary

Data processing in the atrial pacing stress test and the assessment of its results has been complicated by the excessive numerical output of the test as well as by the lack of normalization. The technique outlined in this chapter, based on linear regression methods for smoothing the data, reduces the rate dependent events to measurements at heart rates of 70 and 140. With four left ventricular pressure derived parameters at the two proposed levels of heart rate, discrimimant function analysis was carried out, resulting in a probability index "indicating the distance between normals and patients with coronary artery disease". This index was derived from two test groups and afterwards applied in three other groups of patients with coronary artery disease. This index has the advantage of being quantitative, to supply a single number and to be easily incorporated in the computer configuration of the catheterization laboratory.

Additional advantages are the possibility of improved quality control, through the regression technique, as well as the total objectivity of the results. The technique may further improve when the learning groups of normals and patients with coronary artery disease increase.

Whether the APST results are indeed a measure of reserve capacity of the heart cannot be established directly because of the lack of an independent measurement of this quantity. APST-data in groups of normals and patients with varying degrees of functional impairment of the heart as selected on the basis of clinical criteria are presented in this chapter. Results show that the APST is sensitive to these criteria, after discriminant function analysis and normalization of the variables used in the test. It is likely that the APST remains the most useful stress test inasmuch as it is so simple to carry out and so reproducible in its daily use.

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            CATHETERIZATION DATA SUMMARY
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                  THORAX CENTRE
            ERASMUS UNIVERSITY ROTTERDAM

ID NR       :               DATE      : 29-MAR-79
NAME        :               MALE

CATH NR     : 79-           AGE       : 18-03-1925 [54]
AZRD REG  NR :              LENGTH    : 170    CM
AZRD COMP NR :              WEIGHT    : 60     KG
CATH TYPE   : PRE-OPERATIVE B S A     : 1 69  M2
PROCEDURE   :               BLOOD GRP : A POS
FLUOR  TIME : 13 MIN        H B       : 14     GM %
PHYSN  CODE :               (H B      : 8 75   MMOL)
DIAGN  CODE :
DIAGNOSIS   : COR 2


---------------------------------------------------------------------
S I T E         < P R E S S U R E >               < O 2   % >
---------------------------------------------------------------------
                  PHASIC      · MEAN                       · MEAN
S V C       ·   6 / 2     ·    4    ·                       · 73  %
I V C       ·  -- / --    ·   --    ·                       · 73  %
R  ATRIUM   ·      /       ·         ·                      · 79  %
R  VENTRICLE · 24 / 0 / 3 ·   --    ·                       · 78  %
PULM  ARTERY · 26 / 12    ·   16    ·                       · 76  %
PULM  WEDGE ·  10 / 7     ·    9    ·
L  ATRIUM   ·      /       ·         ·
L  VENTRICLE · 137 / 8 / 21 ·  --   ·                       · 96  %
AORTA       · 135 / 85    ·  113    ·
---------------------------------------------------------------------

---------------------------------------------------------------------
     > CARDIAC OUTPUT <          I     > RESISTANCES <
---------------------------------------------------------------------
O2 CONS  EST  ·   321   ML/MIN   I  SYS  VASC  RES          DSC-5
A-V DIFF      ·    18   %        I  PUL  VASC  RES    160   DSC-5
CARDIAC OUTPUT·   5 3   L/MIN    I  PUL  ARTE  RES          DSC-5
CARDIAC INDEX ·  3 14   L/MIN/M2 I---------------------------------
HEART RATE    ·   102   B/MIN    I
STROKE VOLUME ·  30 8   ML/BT/M2 I---------------------------------
                                 I  QP/QS RATIO    1 : 1
---------------------------------------------------------------------

---------------------------------------------------------------------
              MITRAL    AORTIC    PULMONARY   TRICUSPID
---------------------------------------------------------------------
MEAN GRADIENT ·         ·         ·           ·            MMHG
VALVE AREA    ·         ·         ·           ·            CM2/M2
HEART RATE    ·         ·         ·           ·            B/MIN
CARDIAC INDEX ·  3 14   ·  3 14   ·           ·            L/MIN/M2
DFP/EP        ·         ·         ·           ·            SECS/MIN
---------------------------------------------------------------------

---------------------------------------------------------------------
              LEFT VENTRICULAR FUNCTION       I    ANGIO NR: 79-
---------------------------------------------------------------------
                PRESSURE    ANGIO             I INJ ·         RESULTS
                                              I
HEART RATE    ·   102   ·    69    B/MIN       I COR · LAD 75 + 90 %
EDV           ·   --    ·    86    ML/M2 50-90 I     · L MARG 75 %
ESV           ·   --    ·    44    ML/M2 15-35 I     · RCA 50+50 %
TOTAL S V     ·   --    ·    42    ML/M2 32-58 I
EJEC  FRAC    ·   --    ·    46    0 56 - 0 78 I
FCI/TCI       ·  3 14   ·   5 4    L/MIN/M2    I
FORWARD S V   ·   --    ·    --    ML/M2       I
REGURG  S V   ·   --    ·    --    ML/M2       I
REGURG  FRAC  ·   --    ·    --    %           I
L V  WTH      ·   --    ·   1 0    CM 0 8 - 1 0 I LV. · HYPOKIN ANT WALL
L V  MASS     ·   --    ·    92    ML/M2 76-108 I     · HYPOKIN APEX
LV WEIGHT     ·   --    ·    86    GM/M2 80-102 I     · NO M R
DP/DT PEAK    ·  1320   ·   --     MMHG/SEC 1500 I
VCE PEAK      ·   31    ·   --     SEC-1 40-75  I
V MAX         ·   42    ·   --     SEC-1 42-76  I
---------------------------------------------------------------------I
          LEFT VENTRICLE (ATRIAL PACING STRESS TEST)                I
---------------------------------------------------------------------I
RESTING HEART RATE    62    B/MIN                I
PAIN AT  ·            --    B/MIN                I
ECG POS  AT          --    B/MIN                 I
WENCKEBACH BLOCK AT   --    B/MIN                I
                                                 I
RATE   PKSY   EDP  PK DPDT  PK VCE  VMAX          I
 62    132   13    2874      40      45           I
 69    139   12    2896      43      48           I
 80    129   11    1311      41      49           I
101    126   11    1311      41      49           I
120    120    7    1450      50      56           I
                                                 I
---------------------------------------------------------------------
```

Fig. 1. Output of computer analysis for clinical file. Angiography results are added after catheterization.

CHAPTER VIII

THE CLINICAL USEFULLNESS OF COMPUTER ANALYSIS OF
1,664 CATHETERIZATIONS

I. Introduction

The dedicated system for analysis of cardiac catheterization data developed in the Thoraxcenter between 1971 and 1972 (chapter III) *) became available for clinical application at the end of 1972. After testing the system for one year in 1973, it has been used ever since. In this chapter an analysis is made of the physician's experience with 1,664 catheterizations carried out between 1974 and 1978. The analysis programs written in 1971 and 1972 have remained unchanged in all but a few details, which were mainly of cosmetic nature. However, the computer hardware configuration was updated in 1978, after 7 years of nearly flawless performance, since newer and cheaper components had by that time become available.

During cardiac catheterization, measurement of 40 to 50 variables has to be carried out, some variables as a single measurement, others over prolonged periods of time, such as during interventions or stress tests. In addition, angiograpic, i.e. morphological data, must be added to the hemodynamic measurement. The assessment of such a great number of variables is to a large extent a problem of pattern recognition. Sometimes, results are obvious and easily recognized, in many other cases they remain doubtful or even controversial. Artefact, motion of the patient, wide physiological variations such as during respiration, all may confuse the interpretation. At the insistence of the users an attempt has been made to evaluate the clinical relevance of this type of objective analysis and data reduction. The aim of such an approach is not just the introduction of a new "diagnostic index", since a patient who is subjected to cardiac catheterization is usually reasonably categorized by extensive pre-catheterization assessment, but more the simplification of the final report. Many

*) for literature references see pp. 23)

noninvasive techniques are nowadays available which classify the nature of the disease, so that cardiac catheterization has largely become a method for assessment of the severity of the disorder. The results reported in this chapter must be seen as a step towards data reduction, the establishment of a simplified index of the severity of hemodynamic impairment and as a clinical judgment on the relevance of the entire enterprise.

It should have become evident by now that computer based systems are ideal for data processing of cardiac catheterization data. There is for one the possibility that the investigator can be continuously informed about the status of the variable he has measured so far, as well as about the totality of data obtained. He can immediately deduce any interactions between such parameters and retrieve data from the earlier part of the catheterization.

He can ask instant graphical displays either in the form of tables or as plots. The computer system presents the available data in compressed form in a facile survey (fig. 1). In the near future, it should be possible to provide the clinician also with the direction and strength of the results acquired by weighting the data obtained in that particular patient, against stored information obtained for similar patients, as described in chapter VII.

II. Patient population and Material

On the first of August, 1978, the data bank contained records on 1,664 patients between 5 and 76 years of age with a mean of 48.6. There were 1,226 males and 438 females. To the patient file of hemodynamic parameters, measured during cardiac catheterization, a descriptive anatomic diagnosis from one of six main categories is added. Each category is subdivided according to additional details as provided in fig. 2. For example, coronary heart disease is coded under letter C, followed by an indicator M (for main trunk) or 1, 2 and 3 (for respectively one, two and three vessel disease). This simple system has the advantage that specific diagnostic subgroups can be added at will at a later time, without disturbing the main structure.

The computer configuration was designed in 1972 from then available hardware. It consisted of a central processor, a Digital Equipment Corporation (DEC) PDP 11 mainframe with 16 K core with a digital tape-unit, an 8-channel analog to digital convertor and a specially developed video display device. The details of this configuration have been given in chapter III. The progress in hardware development in recent years has made it possible to update the system in 1978. It is now based on a DEC mini-computer, a LSI-11 (fig. 3) with 16 K core, two floppy disk units, an 8-

```
normals   N

          M main trunk
coron.    C ⪋  1 one vessel
h.dis.         2 two    „
               3 three  „

          M mitral        S stenosis       L light
valvular  V A aortic   <  I insufficiency ⪋ M moderate
          P pulmonary                        S severe
          T tricuspid.
                                 A atrial
          S shunts      ⪋  V ventricular
congenit  K F Fallot       P pulmonary
          O others

others    O

non-
cardiac   X
```

Fig. 2. Structure of diagnosis of cath. lab. system. The diagnosis is based on one or more of six main categories, subdivided for additional details. For example: VMSS, valvular heart disease, mitral stenosis, severe.
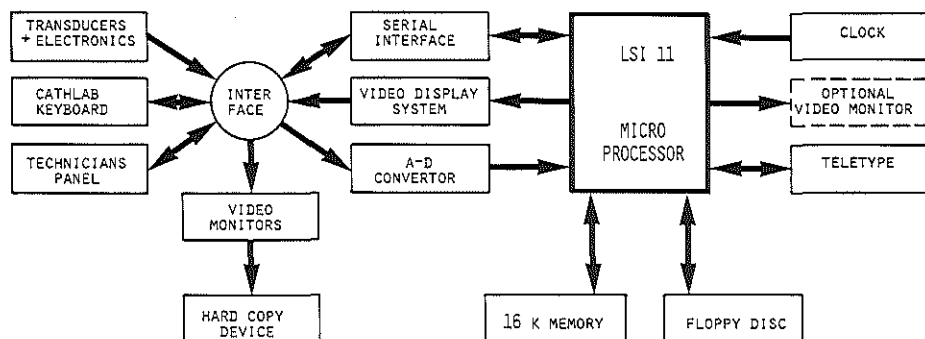

Fig. 3. General lay-out of updated computer system for cardiac catheterization (1978).

channel A.D. convertor, a special keyboard and a display video generator.

After data processing all the results of the analysis programs are sent to the Thoraxcenter Utility System (TUS) where other clinical and laboratory data are stored in a common data base. The transfer is done in the Massachusetts General Hospital Utility Multi-Programming System (MUMPS) language.

Here, data remain accessible either as segments or through one of three index files which contain name, identification number and diagnosis. The MUMPS language has been used to program the entire TUS system so that it provides a communication device between the various divisions within the Thoraxcenter. In the near future, it is foreseen that these blocks of information on cardiac patients will be transferred to the "Ziekenhuis Informatie Systeem" (ZIS), currently being implemented in the various University Hospitals in The Netherlands.

Of the 40 to 50 available hemodynamic parameters, nine major variables were selected because they were clinically judged to be of greatest potential diagnostic relevance and importance for the future management of the patient. Five of these originated from left heart catheterization, three from right heart catheterization, one, the stroke volume index, from cardiac output corrected for body surface area.

Cardiac output, measured with the thermodilution technique was available in 1,335 patients in whom up to four consecutive measurements were carried out.

III. Methods

Reliable normal values for hemodynamic variables as discussed here are hard to provide, since "normal" patients are rare. Yet, for the analysis techniques, outlined later, control values are necessary. For this purpose all patients in the "normal" category of the diagnostic file, where all nine hemodynamic variables were available, were selected and their data tabulated. The values in the resulting 71 individuals are listed in table I. Initial heart rate is included as an indicator of the patient's condition at the onset of the catheterization procedure. As far as can be judged from this parameter, a nearly basal state prevailed in all with a mean resting heart rate of 74.8 beats/min. Since all patients had been extensively prepared for the procedure both by an instructional movie [97] and individual counseling no sedation proved necessary.

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Table I.   Normal values: mean, minimum, maximum and standard deviation.

Normal values; 71 patients.

	Mean	SD	Min.	Max.	
Initial Heart rate	74.8	8.4	54	110	B/min.
Stroke Volume Index	49.0	8.5	25	74	ml/m^2
Pressures:					
Left ventricle, syst.	122.0	13.6	72	149	mmHg
end diast.	10.4	2.8	2	16	,,
V_{max}	53.0	9.3	34	75	sec^{-1}
Aorta syst.	125.3	12.9	63	151	mmHg
diast.	74.8	8.7	42	99	,,
mean	97.5	10.4	51	117	,,
Pulm. wedge mean	7.5	2.9	1	14	,,
Pulm. Art. syst.	19.7	4.3	12	34	,,
diast.	7.1	2.6	2	14	,,

Table II.   Normal values for oximetry in saturation % for sampling sites. Mean, minimum, maximum standard deviation.

Site:	SVC	IVC	RA	RV	PA	LV	
n:	98	25	100	99	101	85	patients
mean:	76.0	82.7	78.0	78.2	78.0	95.9	
S.D.:	4.3	6.5	4.2	3.9	3.9	1.6	
Min.:	67	58	59	58	58	88	
Max.:	88	92	89	87.5	88	99	

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Oxygen saturation of intracardiac blood was measured in many patients. In 101 normals complete oximetry data were available. Results are presented in table II. M.R. Hoare [399]) has employed these data to determine, with a least squares fit, an estimate for the mixed venous saturation sample. The best fit was provided by the formula: 0.45 x IVC + 0.55 SVC*). This estimate is used in the program for shunt detection.

As mentioned in the introduction a special index was sought in order to obtain a simplified, yet objective assessment of the patient's state, when several variables are involved. The "CHOP-index", introduced as a trauma-index [31, 43, 46]) is calculated from a number of selected variables as the square root of the sum of the squares of the deviations from the normal average value for each variable. In mathematics this quantity is called the Euclidean distance and it is believed to reflect the distance between an actual patient's state and a desired patient's state. Apart from the individual measurement of the patient's variables, the average values of normals with their standard deviations are included in the measurement. As a trauma-index, it is used in the Maryland Institute for Emergency Medicine in Baltimore to predict mortality rate in traumatic shock, to serve as a basis for patient triage and to evaluate the usefulness of care. The advantage of such an index is that it can be quantified from an unlimited number of variables. Furthermore, the index is simple to compute by pocket calculator or even from a nomogram, depending on the number of variables used.

The name "CHOP-index" was derived from the four variables, used in the initial publication: serum creatinine (C), hematocrit (H), serum osmolality (O) and systolic blood pressure (P). Because neither the literal implications of the word CHOP nor its four constituent variables suggest that this abbreviation is appropriate in the catheterization laboratory, the term utilized in this study was changed to CATH-index, where the capital letters stand for Cardiac, Angiographic and THermodilution determinators. This index will from now on be considered to represent a condensed description of the hemodynamic state in a patient undergoing cardiac catheterization.

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*) IVC: Inferior Vena Cava, SVC: Superior Vena Cava.

IV. Results

1. General data inventory

First of all, a general overview of the data bank provides results from the several diagnostic groups. In the period of six years the indications for cardiac catheterization have gradually changed. Currently the relative contribution of valvular disease to the population of patients for catheterization has decreased and coronary heart disease is now the prevalent indication for catheterization.

Over six years 6.2% of the patients undergoing cardiac catheterization was classified as normal (table III). The largest groups of patients consisted of those with coronary heart disease and with valvular heart disease. Both are about equal in size (55 and 57%). The total percentage of diagnosis exceeds 100 because several patients (36.2%) have more than one diagnosis.

Data on cardiac output are provided in table IV. Results of the thermodilution cardiac output measurement are shown as the mean values of up to four consecutive measurements. The standard error of the mean is extremely low. From these results can be deduced that there is no systematic error in the results of consecutive thermodilution cardiac output measurements.

Table III. Data inventory per August 1, 1978; Diagnostic categories with no. of patients.

Total Nr. Patients 1.664   Age: 5-76 years,
                male   1.226   (mean 48.6 years)
                female   438

Normals	104	6.2%
Coronary Artery disease:	923	55.4%
one vessel	225	13.5%
two vessel	360	21.6%
three vessel	338	20.3%
Valvular Heart disease	923	57.3%
Congenital Heart disease	195	11.7%
Others	63	3.8%
Multiple lesions	602	36.2%

2. Overview of six consecutive years of computer analysis.

As stated before, since the introduction of the computer system in the cardiac catheterization laboratory in the Thoraxcenter in 1973, the analysis programs have not been changed. The question may be considered whether changes in the patient population over the years are of relevance. In table V the numbers of patients are listed, as they are classified over the years, in one of five diagnostic groups. As can be seen from this table, the percent contribution to the patient population over the year does show important changes. The relative contribution of coronary heart disease to the patient load of the cardiac catheterization laboratory has clearly increased, mainly at the expense of valvular heart disease and this must have influenced our data. Currently, coronary heart disease is present in more than 60% of the patients undergoing cardiac catheterization.
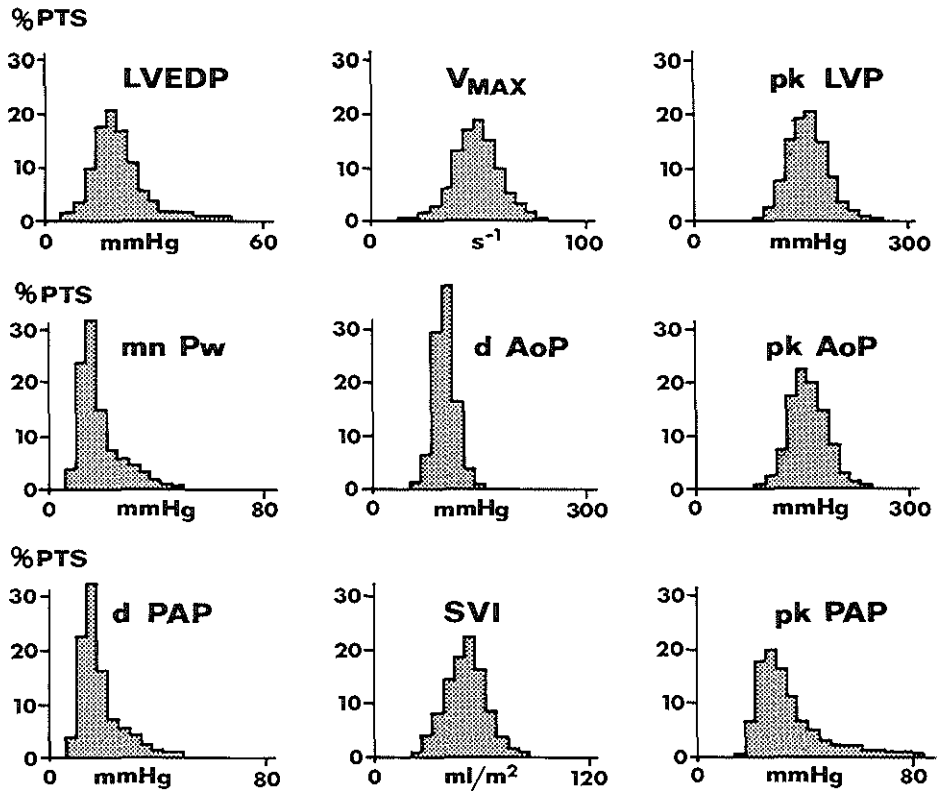

Fig. 4. Frequency histograms of nine hemodynamic variables as they occur in total file of 1.355 patients, expressed in percent of observations.
Abbrevations as in table VI.

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Table IV. Thermodilution cardiac output. Results of up to four consecutive measurements expressed as mean of total group with standard error of mean.

	1st	2nd	3d	4th	
n	1355	1320	633	186	patients
mean	5.7	5.7	5.7	5.7	l/ min.
S.E.M.	0.04	0.04	0.07	0.16	l/ min.

N.B. A paired t.test between consecutive individual measurements did not show a significant difference.

Table V. Overview of patient load during six years of computer analysis. Patients are categorized under their main diagnosis when multiple lesions existed.

	1973		1974		1975		1976		1977		1978 part		
	%		%		%		%		%		%		
Normals	6	(7)	5	(11)	6	(13)	8	(28)	5	(18)	14	(15)	
CAD	45	(50)	36	(75)	43	(96)	45	(153)	66	(216)	61	(90)	
Aortic VD	8	(9)	20	(42)	15	(34)	9	(32)	8	(25)	8	(12)	
Mitral VD	21	(23)	23	(48)	23	(50)	25	(85)	11	(36)	7	(11)	
Others	20	(22)	16	(33)	13	(29)	12	(39)	10	(34)	13	(19)	
n	111		209		202		337		329		147		Patients

% of patients in that year
( ) absolute number of patients.

In table VI mean and standard deviation of nine variables are listed over the same time span, as they were calculated in all patients from that year. These data do not show essential changes over the years. So, the final column, listing mean and standard deviations of the total population in the data bank, can be taken as representative for all data. Frequency histograms of the same nine variables in the total patient file, are shown in fig. 4.

It might be of some interest to have a closer look at some of the patients, where one or more variables reached extreme results. For this purpose, an "extreme result" was defined as a parameter deviating more than 3 x the standard deviation from the mean value of normals. In the entire group of 1,355 patients, where all nine variables were available, 164 were found responding to this criterium (see table VII). From this group of patients 125 had a single parameter in excess of three standard deviations from the mean, 35 patients had two parameters and 4 patients were found with three

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Table VI. Results in means and standard deviations of six years of computer analysis with identical algorythms in nine selected variables.
Abbreviations:

LVEDP	left ventricular end diastolic pressure in mmHg
V_{max}	extrapolated $dP/dt/P$ to zero P in sec.$^{-1}$
pk LVP	peak systolic left ventricular pressure in mmHg
pk AOP	peak systolic aortic pressure in mmHg
d AOP	diastolic minimum aortic pressure in mmHg
mn Pw	mean pulmonary capillary wedge pressure in mmHg
pk PAP	peak systolic pulmonary artery pressure in mmHg
d PAP	diastolic minimum pulmonary artery pressure in mmHg
SVI	stroke volume index in ml/m^2.

Year	1973	1974	1975	1976	1977	part 1978	Total	
Patients	111	209	222	337	329	147	1355	
LVEDP	16.8 ± 8.5	14.9 ± 8.9	14.7 ± 7.0	14.6 ± 7.3	14.9 ± 6.8	15.3 ± 8.0	15.0 ± 7.6	mm Hg
V_{max}	47.0 ± 14.3	46.9 ± 11.0	45.7 ± 11.6	47.2 ± 11.9	47.9 ± 11.2	48.0 ± 12.3	47.1 ± 11.8	sec-^{1}
pk LVP	136.4 ± 31.6	144.4 ± 40.8	135.5 ± 33.0	136.6 ± 30.0	145.2 ± 31.3	138.3 ± 27.0	139.9 ± 32.8	mm Hg
pk AoP	133.8 ± 27.6	136.0 ± 27.7	129.9 ± 25.2	133.7 ± 28.1	145.0 ± 28.4	139.4 ± 26.8	136.7 ± 27.9	mm Hg
dia AoP	77.9 ± 16.6	78.7 ± 15.3	75.0 ± 14.5	76.7 ± 14.8	83.0 ± 15.4	79.6 ± 12.5	78.6 ± 15.2	mm Hg
mn Pw	15.9 ± 10.3	12.6 ± 7.4	12.5 ± 8.2	12.8 ± 8.4	11.7 ± 7.5	11.9 ± 7.4	12.6 ± 8.1	mm Hg
pk PAP	29.5 ± 15.8	29.4 ± 18.5	27.0 ± 15.1	31.0 ± 17.8	28.9 ± 13.4	29.3 ± 14.4	29.3 ± 16.0	mm Hg·
dia PAP	15.2 ± 9.7	14.4 ± 11.2	12.8 ± 8.6	13.7 ± 9.8	11.4 ± 7.6	11.8 ± 8.0	12.9 ± 9.2	mm Hg
SVI	45.4 ± 14.4	41.5 ± 13.4	41.3 ± 11.8	41.5 ± 11.8	42.2 ± 10.0	44.0 ± 11.0	42.3 ± 11.9	ml/m^2

Table VII. Extreme values of one or more of the selected variables in this patient file. "Extreme" is defined as greater or smaller than the mean ± three standard deviations. Abbreviations as in table VI.

Variable		⩾ Mean + 3 SD			⩽ Mean - 3 SD		
		Treshold Value	Patients Nr.	%	Treshold Value	Patients Nr.	%
LVEDP	mmHg	37	18	1.3	0	-	-
V_{max}	sec-¹	83	7	0.5	11	2	0.1
pk LVP	mmHg	238	19	1.4	41	-	-
pk AoP	"	220	10	0.7	60	1	0.0
d. Aop	"	124	6	0.4	33	4	0.2
mn Pw.	"	37	20	1.4	0	-	-
pk PAP	"	77	36	2.6	0	-	-
d. PAP	"	41	33	2.4	0	-	-
SVI	ml/m²	78	8	0.5	7	-	-

In 1355 pats data are available:
    164 pats (12%) have one or more extreme values.
    125 pats (9%) have only one extreme value.
     35 pats (3%) have two extreme values.
      3 pats have three extreme values.
      1 pat has four extreme values.

abnormal parameters. Additional details of one of these patients are presented below. Pulmonary arterial hypertension was the most common extreme finding (2.6%), followed by elevated mean pulmonary wedge pressure and left ventricular peak pressure, probably associated with mitral and aortic valve disease, respectively.

(ID 50 333) Foreign Eurasian female, 30 years

    She was admitted for acute pulmonary circulatory congestion resulting from mitral valve disease, with active rheumatic heart disease as suggested by high sedimentation rate, fever, a pericardial friction rub and arthritis of both hands. Symptoms of breathlessness and nocturnal orthopnoe had been increasing over a period of 4 years prior to admission. After one month of medical treatment, cardiac catheterization was carried out. The mitral valve was severely stenosed (0.46 cm²/m²) with a cardiac index of 2.7 l/min./m² and pulmonary hypertension. Pulmonary arterial pressure: 90/50 mmHg. The mean Pulm. wedge was 44 mmHg. Left ventricle: V_{max} 41 sec.-¹, end diastolic volume 84 ml/m², ejection fraction 0.54,

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Table VIII. Mean values and standard deviations of the nine selected variables in five diagnosis groups.
Abbreviations:
CAD   coronary artery diseases
Mitral VD mitral valve disease
Aortic VD aortic valve disease

Variable	Normals	CAD	Mitral V.D.	Aortic V.D.	Others	
LVEDP	10.5 ± 2.9	14.9 ± 6.7	11.9 ± 6.0	20.0 ± 9.6	13.2 ± 6.5	mm Hg
V_{max}	53.1 ± 9.9	48.3 ± 10.4	47.5 ± 12.7	40.0 ± 11.8	49.6 ± 14.3	sec^{-1}
pk LVP	122.2 ± 16.1	139.6 ± 26.0	124.6 ± 30.9	176.4 ± 43.4	137.6 ± 41.4	mm Hg
pk AoP	125.5 ± 16.4	141.2 ± 26.6	129.6 ± 28.9	131.2 ± 24.0	133.0 ± 31.9	mm Hg
diast AoP	75.0 ± 10.5	81.7 ± 14.4	78.3 ± 14.6	65.1 ± 13.1	82.5 ± 15.5	mm Hg
mean Pw	7.5 ± 2.7	9.6 ± 5.6	20.7 ± 8.8	13.4 ± 7.1	11.2 ± 7.1	mm Hg
pk PAP	19.7 ± 4.5	23.7 ± 8.2	44.6 ± 23.7	28.1 ± 11.5	29.2 ± 19.5	mm Hg
diast. PAP	7.1 ± 2.7	9.5 ± 4.9	22.4 ± 13.7	12.8 ± 6.6	12.6 ± 11.6	mm Hg
SVI	49.0 ± 9.9	43.5 ± 10.1	36.4 ± 12.48	45.4 ± 14.1	44.6 ± 14.6	ml/m^2
Nr. patients	71	441	102	75	127	

mass 70 ml/m². There was no angiographic evidence for mitral or aortic regurgitation. In conclusion: severe isolated mitral stenosis secondary to rheumatic heart disease.

The patient underwent mitral commissurotomy with good results. These extreme values for pulmonary arterial and wedge pressures are indicative for the severity of the mitral stenosis, They have become as such a rare phenomenon in the Netherlands.

From table VII is also evident that many more patients are found in the higher than normal group, relative to the lower than normal group. In fact, among the 12% of patients, whose variables deviated more than three standard deviations from the normal mean, 11.7% were at the high side of the mean and only 0.3% at the low side of the mean.

3. Results of nine selected variables.

As stated earlier, nine variables acquired at cardiac catheterization were selected for the evaluation of their patterns in the several diagnostic groups.

For further evaluation only patients with a single diagnostic entry were used. In table VIII the nine variables are listed with their mean values and standard deviations, as measured in a group of 71 normals, 441 patients with coronary heart disease, 177 patients with valvular heart disease and a group of patients with miscellaneous disorders. As can be seen from this table, the ranges of the variables in these diagnostic groups show considerable overlap. The greatest absolute differences are found in peak left ventricular pressure, between the group of normals and the patients with aortic valvular disease, and the pressure in the pulmonary wedge position, the peak systolic and diastolic pulmonary artery pressure in mitral valve disease relative to normals.
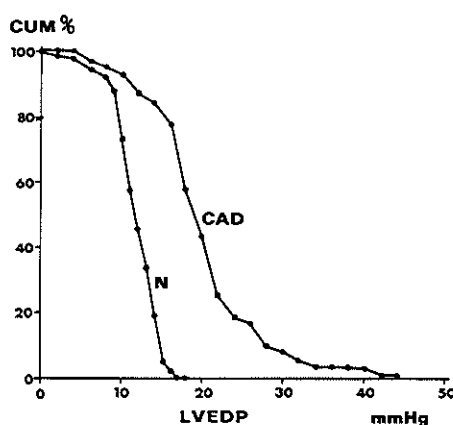
Fig. 5. Cumulative % histogram of LVEDP as measured in 71 normals (N) and 441 patients with coronary artery disease (CAD).

When the standard deviations are considered extensive overlap is shown to be present. From these results it can be expected that no single variable will have enough discriminatory power to permit selection of groups and that the final evaluation of the hemodynamic situation, based on these and other parameters, should include directional changes of more than one variable, with as many variables as practical.

Furthermore, the results expressed in the means and standard deviations obscure part of the information present in these data. To illustrate this point, in fig. 5. a cumulative histogram is presented of left ventricular enddiastolic pressure in normals and patients with coronary artery disease. The overlap in enddiastolic pressure at levels below 16 mmHg is evident, although it is somewhat surprising that over 70% of patients with coronary heart disease have a LVED-pressure in excess of 16 mmHg.

Table IX. Classification matrix after discriminant function analysis in several diagnosis groups.
Groups: AI: aortic insufficiency
          AS: aortic stenosis
          MI: mitral insufficiency
          MS: mitral stenosis
          COR: coronary artery disease
Function: classification by function
?:   no classification possible (probability < 60%)

A.

Diagn.:	1	2	3	4	?	n
1 AI	8	-	1	-	2	11
2 AS	-	4	-	-	1	5
3 MI	-	1	4	-	3	8
4 MS	-	-	1	18	7	26

B.

Diagn.:	1	2	3	4	5	?	n
1 AI	8	-	1	-	-	2	11
2 AS	-	4	-	-	-	1	5
3 MI	-	1	3	-	2	2	8
4 MS	-	-	1	17	4	4	26
5 Norm.	-	3	-	-	57	11	71

C.

Diagn.:	1	2	3	4	5	6	?	n
1 AI	8	1	-	-	-	-	2	11
2 AS	-	4	-	-	-	-	1	5
3 MI	-	1	3	-	1	-	3	8
4 MS	-	-	2	16	2	-	6	26
5 Norm.	-	3	1	-	22	4	41	71
6 CAD	8	10	7	7	53	106	252	441

D.

Diagn.:	1	2	3	4	?	n
1. A	46	5	4	1	10	66
2. M	1	42	5	3	16	67
3. Norm.	-	-	41	-	30	71
4. CAD	10	16	78	210	30	441

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4. Discriminant function analysis of nine variables

For this purpose learning populations had to be defined. From the existing data base, six groups of patients were selected, based on the presence of all nine variables, listed in table VIII, as well as to their classification into a single diagnostic group.

As groups were chosen: normals, coronary heart disease, pure aortic valvar insufficiency, pure aortic valvar stenosis, isolated mitral valve insufficiency or mitral valve stenosis. All nine variables were included in the calculations.

From these a probability function could be calculated for every patient expressing the probabilities of belonging to one of the learning groups. Arbitrarily, a threshold level of 60% probability was used as the lower limit. Patients with probability functions below 60% were classified in the undefined group. Results of these calculations are presented in table IX. This table contains classifications matrices, resulting from the discriminant analysis of four, five and six test populations.

The selection criteria lead to small groups, especially for valvular heart disease. This hampers the accuracy of the discriminant technique in these diagnostic groups. It is evident, however, that in all sets the category mitral insufficiency is relatively hard to define as a probability function. Also the group of normals and coronary heart disease show considerable overlap, as evident e.g. from matrix C, where 12% of patients with coronary heart disease are classified as normal, while in 57% no classification could be established.

These results are, of course, not surprising because of the regional distribution of coronary heart disease, where impairment of resting hemodynamic parameters may become evident only relatively late in the time course of the disease. This is one of the arguments for the introduction of a stress test for the proper evaluation of the hemodynamic situation in coronary heart disease, as discussed in chapter VII.

The ultimate aim of the usage of hemodynamic variables, is to employ them as a descriptor of the hemodynamic state, rather than as a separator between diagnostic groups. In this way, overlap between results of normals and patients with coronary heart disease is not only acceptable but may be considered a necessity. Yet, two additional questions remain to be answered.

First of all, whether the selected variables are applicable as sole descriptors of the hemodynamic situation, separate from all clinical experience. The relative weight of each of the variables in the discriminant function technique can be assessed from their coefficients (see table X). The coefficients of course, are dependent on the scale of measurement. This

Table X. Variables used in discriminant function analysis.

Variable	Mean value normals (1)	Mean value CAD (2)	D.F. (3)	Weight (4)	t value (5)
1. LVEDP	10.5	14.9	0.73	3.2	5.0
2. V_{max}	53.1	48.3	0.68	–3.2	3.4
3. pk LVP	122.2	139.6	0.02	0.3	5.1
4. pk AoP	125.5	141.2	0.06	0.9	4.1
5. d. AoP	75.0	81.7	0.23	1.5	3.3
6. mn Pwedge	7.5	9.6	–0.01	–0.02	2.7
7. pk PAP	19.7	23.7	0.22	0.8	3.6
8. d. PAP	7.1	9.5	0.37	0.9	3.5
9. SVI	49.0	44.1	0.48	–2.6	3.9
nr. patients	71	441			

(1) Mean value of normals.
(2) Patients with coronary artery disease.
(3) Discriminant function coefficient.
(4) D.F. adjusted for scale of variable [(2) - (1)] x (3)
(5) For 512 degrees of freedom.

difficulty can be partly overcome by multiplying each coefficient by the difference in mean values of that variable. These date are presented in column (4) table X. In this way the lowest weights have mean pulmonary wedge, peak LVP, peak PAP and diastolic PAP. The strongest variables for separating normals from CAD patients are LVEDP, V_{max}, stroke volume index and diastolic Aortic Pressure.

The next question is how far the nine variables are independent of each other, both in normals and in patients with coronary artery disease. The fact that discriminant function coefficients in excess of zero were established for all nine variables, implies, that they all have discriminatory power and independent contributions to the final results. The degree of independency has also been tested with linear regression. Results are presented in table XI. A linear correlation between 0.60 and 0.80 is shown to be present between peak aortic pressure and peak left ventricular pressure and between mean pulmonary wedge pressure and diastolic pulmonary artery pressure, both in normals and patients with coronary artery disease. In the latter group also correlations are present between diastolic aortic pressure and peak aortic pressure, as well as diastolic pulmonary artery pressure and peak pulmonary artery pressure. The relation between V_{max} and LVEDP is -0.40 in normals

Table XI. Matrix of linear correlation coefficients between nine hemodynamic variables in 71 normals left upper number in box) and 441 patients with CAD (right lower number).

	LVEDP	V_{max}	pk LVP	pk AoP	d. AoP	mn. Pw	pk PAP	d. PAP
V_{max}	-.40 / -.52							
pk LVP	.21 / .06	0.6 / .10						
pk AoP	.03 / -.04	-.02 / .7	.72 / .77					
d. AoP	.04 / .01	-.30 / .14	.36 / .60	.57 / .77				
mn Pw	.36 / .56	-.27 / -.40	.40 / -.04	.40 / -.04	.34 / .03			
pk PAP	.34 / .40	-.06 / -.21	.17 / .01	.07 / .05	-.03 / .07	.49 / .78		
d. PAP	.23 / .45	-.03 / -.33	.29 / -.05	.11 / -.05	.01 / .06	.64 / .83	.52 / .81	
SVI	.30 / -.17	-.03 / .19	-.02 / .13	-.02 / .13	.15 / .04	.22 / -.27	-.03 / -.28	-.05 / -.34

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and -0.52 in coronary artery patients. This indicates that V_{max} has a tendency to relate to LVEDP, a measure often used to estimate pre-load of the left ventricle. The relation between peak left ventricular pressure and peak aortic pressure reaches only a correlation coefficient of 0.75. It should be kept in mind, however, that these two parameters are seldomly measured simultaneously in these patients groups. In the patients with coronary artery disease, usually an atrial pacing stress test is carried out in between the two measurements.
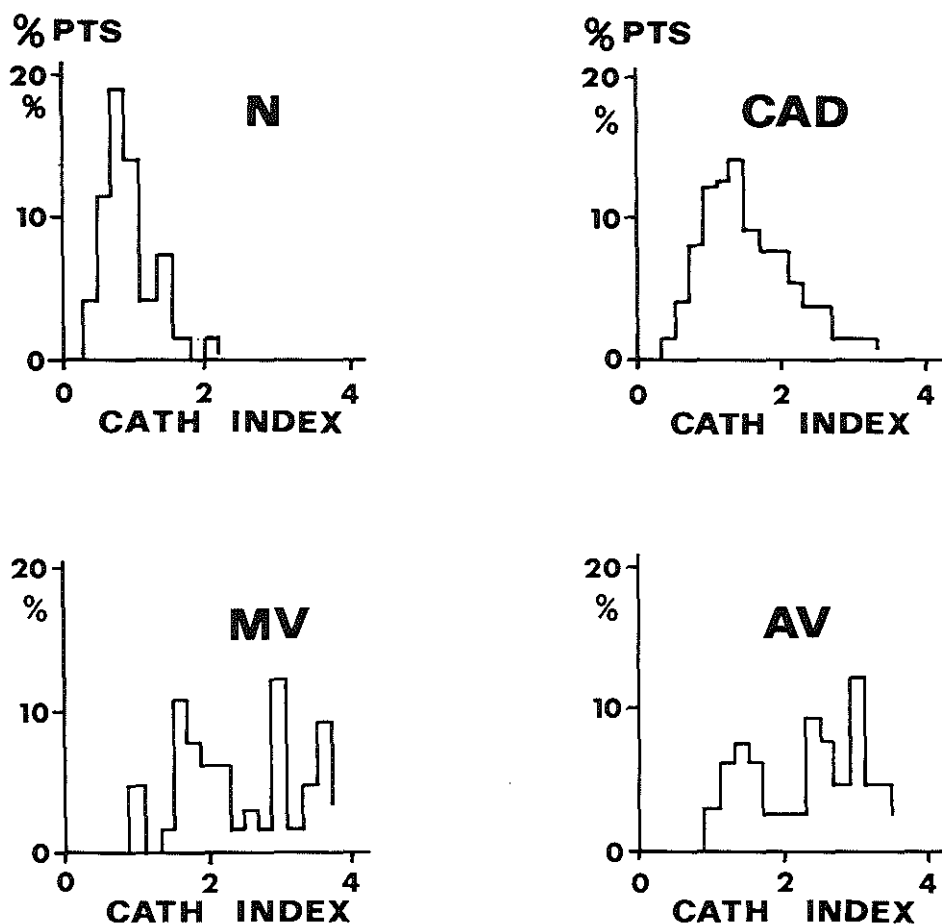
Fig. 6. Frequency histograms of CATH.-index based on all nine hemodynamic variables in four diagnostic groups, expressed in percent of observations.
    A) 71 normals (N), mean 0.93, range 0.38 - 2.08
    B) 441 patients with coronary artery disease (CAD), mean 1.74, range 0.29 - 7.53
    C) 67 patients with mitral valve disease (MV), mean 3.59, range 0.92 - 9.75
    D) 66 patients with aortic valve disease (AV), mean 2.96, range 1.05 - 7.48.

5. The CATH.-index

The index is essentially based on the sum of the deviations of the nine variables from their mean normal values. In normals, the mean value of this index can be established at 0.93. Results were evenly distributed around this mean as is evident from fig. 6. The coronary population had a mean value of 1.74, approximately twice the normal. Minima of both groups were practically equal: 0.4 and 0.3. The maximum of 7.5 in the coronary group was far beyond the range of normals. The histogram of the indices in the coronary group in fig. 6b is assymmetrical with a steep incline towards the peak value at 1.4 and then a slower decline in the higher ranges of the index.

In the group of patients with stenosis and regurgitation of the mitral valve (fig. 6c) and of the aortic valve (fig. 6d) mean values of both groups are clearly in excess of normal. Also the range of the index in mitral valve disease is in general in excess of the coronary group. Histograms show an uneven, double peaked distribution. Whether this phenomenon is due to the combination of valvular insufficiency and stenosis in one group is unclear. As the number of patients with pure isolated valve disease in this data base was very limited, this observation was not explored any further. The data of normals and coronary artery disease patients are summarized in the form of a percent cumulative distribution. (fig. 7). This indicates that 1 out of 5 patients with coronary artery disease has an index of 2.2, not found in normals. The tendency for higher index values in the coronary group as a whole is also clear.
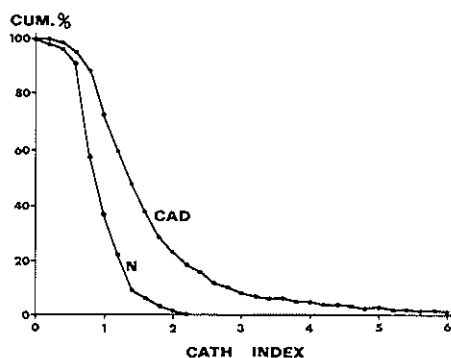

Fig. 7. Cumulative % histograms of CATH.-index, based on nine hemodynamic variables as measured in 71 normals (N) and 441 patients with CAD.

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6. Comparison between CATH.-index and discriminant function analysis.

For the purpose of this comparison discriminant function analysis was carried out in 71 normals and 441 patients with coronary artery disease. Results of the discriminant function analysis was expressed as the probability of being normal for all individuals in both groups. The function was based on the nine hemodynamic variables, as indicated above. From these variables the CATH.-index was also calculated. The relation between the calculated CATH.-index and the discriminant function in 71 normals is presented in fig. 8. It is evident that the group of normals is within the range of 60 to 90% of normality. No patients have a greater than 90% chance of being normal. The CATH.-index ranges from 0.5 to 1.5, leading to a reasonably well defined normal area.

The relation between the two indices, as found in 441 patients with coronary artery disease, is shown in fig. 7b. In a subgroup of 130 patients results from the atrial pacing stress test were also available. When these are added to the calculation of the CATH.-index, it can be expected that the sensitivity of this index increases. Results of the comparison between this CATH.-index and the discriminant function analysis from the nine resting variables alone, are presented in fig. 8 and show indeed a clear relation. These scattergrams indicate that in normals and many CAD patients the two methods show concordant results. However, in part of the patients a low probability of being normal coincides with a normal CATH.-index (fig. 8 and 9), either with or and without inclusion of APST data. Because the two methods agree well in normals, this is probably to be explained as a difference in sensitivity of the two tests.. The discriminant function detects abnormality in individuals where the CATH.-index is (still) normal.

There is, of course, a relationship between the two methods themselves. Furthermore, the variables used, are to some extent dependent on each other as was earlier demonstrated. Finally, the atrial pacing stress test is not "a steady state" but a dynamic event. However, with the regression technique as outlined in chapter VII, the results of the APST are brought back to indicators of offset and slope of the regression line (in practice expressed as values at heart rates 70 and 140). For both measurements the distance between "desired state and the individual patient's state", as expressed in the CATH.-index would seem to be applicable.

7. Case histories

The average CATH.-index calculated in the normal group was 0.93. From the coronary heart disease group, three patients were selected with an
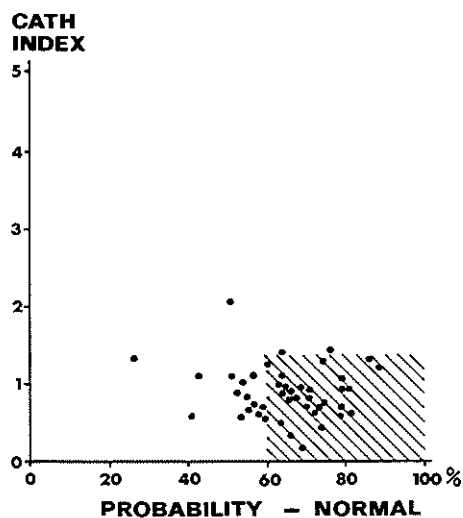
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Fig. 8. Relation between CATH.-index and probability of being normal, calculated with discriminant function analysis in 71 normals. All data based on nine hemodynamic variables as listed in table VI.
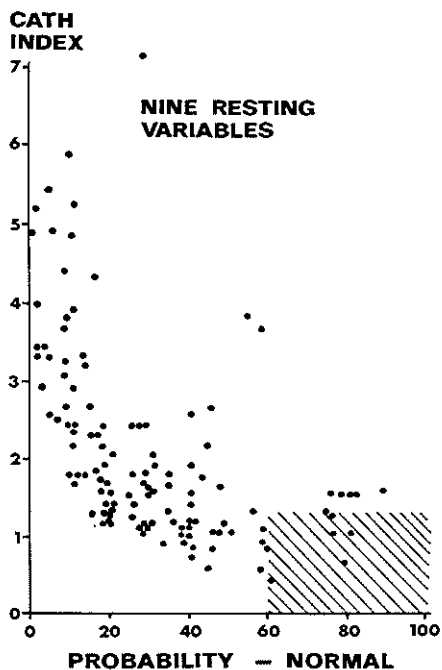

Fig. 9. Relation between CATH.-index and probability of being normal in a group of 130 patients with CAD. Calculations based on nine resting hemodynamic variables (see also fig. 10). Shaded area indicates normal ranges.
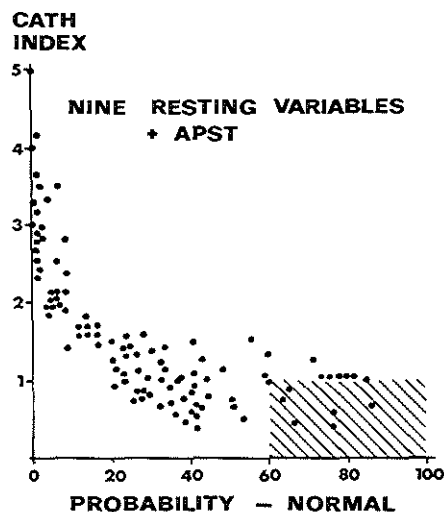
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Fig.10. Relation between CATH.-index and probability of being normal in the same group of 130 patients with CAD as fig. 9. Calculations here based on nine resting variables together with atrial pacing stress test data at heart rates 70 and 140, corrected as outlined in chapter VII.

index between 2 and 6. Their case histories may serve to illustrate the clinical picture of the CATH.-index.

Patient (ID 2840) is a 48 year old male with a CATH.-index of 2.1. He has angina pectoris and sustained three infarcts in one year. There are no signs of heart failure. On the angiograms a normal right coronary artery and circumflex are seen, as well as 95% narrowing of left anterior descending, 75% of left marginal branch. Both are non-graftable and surgery is not contemplated. There is hypokinesis of anterior and posterior wall with dyskinesis at the apex. The ejection fraction is 0.41, the resting LVEDP 21 mmHg; all other hemodynamic variables are within normal range.

The second case is a male of 55 years (ID 2710). His CATH.-index is 3.9. He has had two infarcts, but no angina pectoris. There is fatique, dyspnoea et rest and noctur nal orthopnoea. The angiograms show right coronary artery obstructions of 75%, 90% and 100%. In the left anterior descending there is 95% narrowing with three additional narrowings of less than 50% in other arteries. There is hypokinesis of anterior, septal wall and apex, also akinesis of posterior wall. The ejection fraction is 0.33, the EDV 93 ml/m², the LVEDP 35 mmHg. Bypass surgery was not carried out because the lesions were considered non graftable.

The last patient (ID 9612) is a male of 55 years with a CATH.-index of 6.4. There were three previous infarcts with mild angina pectoris. The angiograms show the right coronary artery to be 100% occluded with collateral flow from the left coronary artery. Left anterior descending also has a 100% occlusion, also with collateral flow. The diagonal branch and the circumflex artery are narrowed to 75% and near 100%. There is a large left ventricle with EDV of 144 ml/m². There is hypokinesis of the anterior and septal wall with akinesis of the posterior wall. The ejection fraction is only 0.19. LVEDP is 14 mmHg. The APST shows no rise in V_{max} (46 sec.$^{-1}$), while the

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LVEDP is 22 mmHg at a heart rate of 140. After medical treatment with digitalis and diuretics, bypass surgery was carried out with grafts on the right coronary, left anterior descending and marginal branch. One year later there were still symptoms and signs of heart failure with impaired renal function. Since then he has progressively deteriorated with peripheral edema, ascites and jaundice, notwithstanding rigorous medical therapy.

These three examples may serve to relate the overall clinical picture to the value of the CATH.-index. The normal value of the CATH.-index is 0.93 ± 0.37 as established in a retrospectively determined group of normals. Whether these "normals", in whom an indication for cardiac catheterization was judged to be present, are really normal is believed to be close to the truth.

The first patient has no signs of heartfailure, there is, however, some evidence of functional impairment of the left ventricle (hypo- and dyskinetic wall motion with a high LVEDP). His index was 2.1 (twice normal). The second patient has mild but definite signs and symptoms of left ventricular function disturbance, the index is four times normal (3.9).

The third patient with overt heart failure, responding barely to therapy, including bypass surgery, has an index of 6.4.

Thus, the hemodynamic scoring classifies these patients reasonably well.

By the nature of the calculation of the index, an individual "better" than normal (if he or she exists), would be classified as "worse" than normal, in deviating from the mean of normals. The data base, therefore, was examined for "supernormals"; one individual was found, who could be considered as a possible "supernormal" in the hemodynamic sense.

This was a 27 year old male (ID 8799), a professional bicycle racer. After several races he had paroxysms of atrial fibrillation. By clinical exams there were no signs of valvular heart disease. The resting and exercise ECG were normal. At catheterization all resting variables were within normal range, except Pulmonary Artery pressure which was slightly elevated, 30/12 mmHg and a cardiac index of 5.6 l/min./m² at heart rate 72. Quantitative angiocardiography showed the Left Ventricle to have an EDV of 119 ml/m². Ejection fraction was 0.68 and LV muscle mass 128 ml/m². The APST at heart rate 70 and 140 showed a LVEDP of 12 and 4 mmHg, peak dP/dt of 880 and 2451 mmHg/sec., VCE of 36 and 58 sec⁻¹ and V_{max} to rise from 41 to 72 sec⁻¹. The angiograms of coronary arteries were normal. The CATH.-index of nine resting variables was 1.53, and the CATH.-index of the APST was 1.50 (mean of normals 0.93, range 0.2 - 2.1).

These index values are within the normal range and not indicative of a special situation. The problem of "supernormals" is in reality a theoretical one, because even if they do exist in the hemodynamic sense of the word, catheterization data will become available only very rarely (1 in 1.664).

V. Summary and conclusions

A computer based system for the analysis of cardiac catheterization data has been in clinical use for six years in 1.664 cardiac catheterizations. The system has proven to be reliable and it functions at this moment as an integral part of the laboratory. The patient load has slowly shifted to coronary artery disease as the current main indication for cardiac catheterization, while valvular heart disease provides a reduced numbr of patients per year. Congenital heart disease has receded into the background. Within the patient population over this time span, a small number of normal individuals could retrospectively be identified, to provide normal values as a basis for further calculations in the patients group.

Based on clinical experience, nine hemodynamic variables in the resting state were selected for further analysis. The variables consisted of five left heart parameters, three from right sided cardiac catheterization data and the last of the stroke volume index. Mean values and range of the variables differed within the diagnostic groups and their ranges showed considerable overlap. Discriminant function analysis provided functions for classification of patients into one of each diagnostic test groups. The sensitivity of this method as a diagnostic tool proved to be low. When the discriminant function analysis is restricted, to two groups, normal individuals and coronary heart disease patients, the calculated probability of belonging to the normal group can be used as a reverse indicator how far an individual patient is ranged from the normal situation. Function analysis can in this way be used as an indicator of the patient's hemodynamic state.

Another method was also assessed, the CATH.-index which is based on the sum of all the differences from normal of the nine parameters involved. This CATH.-index proved to be easy to calculate and gave an average value for normal of 0.93. In the group of coronary artery disease patients, values for this index ranged from 0.3 to 7.2. The CATH.-index exceeded normal in approximately 40% of the observations in patients with coronary heart disease and thus did not provide clear separation between groups. A comparison between the results of discriminant function analysis and the CATH.-index, both calculated from variables in the resting state and the APST variables, corrected for heart rates 70 and 140, showed a clear tendency for the patients with a high CATH.-index and bad APST results to have very low chances of being normal.

Both methods of analysis have their intrinsic draw-backs and advantages. Discriminant function analysis of an individual patient's data can only be carried out in computer supported laboratories. The

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CATH.index is easily calculated by hand when normal values are available. The author, therefore, tends to prefer this index in general. Parameters can be added at will in the future, while it can be corrected for missing data by dividing the final index through the number of observations. The index should be improved upon by the assessment of weighting factors for each variable. The clinical usefulness of the nine selected variables is first of all dependent on the diagnostic groups where they are applied. In this chapter results in normals and patients with CAD are emphasized, the latter disease providing the majority of our patient load.

Based on the discriminant function analysis, the t values and the correlation coefficients, as determined in these two groups, the following conclusions can be made for normals and CAD patients:

1. The best separators out of the nine tested variables are left ventricular end diastolic pressure and V_{max}. They are only slightly interrelated.

2. The next best variables are stroke volume index and diastolic aortic pressure.
   Stroke volume index is independent of others, while diastolic aortic pressure relates to peak left ventricular pressure and peak aortic pressure.

3. Mean pulmonary wedge pressure and pulmonary arterial pressures have little discriminant power and can be discarded.

4. Therefore, the only requirement for right heart catheterization in coronary heart disease, stems from the need for cardiac output measurement with thermodilution and the introduction of the atrial pacing catheter.

CHAPTER 9

APPLICATION OF THE SCORING SYSTEM
IN ANOTHER DATA BANK *)

I. Introduction

In January 1976 three University hospitals in The Netherlands began a co-operative study to evaluate the effects of Coronary Bypass Surgery on left ventricular function. The study is supported by the Dutch Government and is executed as a project of the Interuniversitary Cardiological Institute (ICI). The participating centers are the Departments of Cardiology in Leyden, Nijmegen and Rotterdam.

The extensive knowledge which has accrued, relates mostly to symptomatic relief [1-10] and the matter of survival in coronary disease [11-26]. This in contrast with the limited insight in the aspects of cardiac function [27-33].

Therefore, emphasis is placed in this project on the time course of cardiac function. Various other aspects of Coronary Bypass Surgery such as (peri-) operative mortality, morbidity, complication rates and subjective results are also evaluated. The project requires that each patient in the study agrees to undergo repeat cardiac catheterizations at one year and three years after surgery. The data bank design allows for a total of nearly 1,000 patients, whose data are to be collected over a six year period. The new patients are entered into the data bank over the first three years, with follow-up information collected up to three years after surgery.

The study aims at the objective documentation of the following items:

1. Cardiac pump function, especially left ventricular function, before and after bypass surgery in order to provide answers to three questions:
   a. What are reliable and predictive left ventricular function parameters in the pre- and postoperative assessment of the patient?
   b. What are the changes in the coronary arteries and bypass circuits after surgery?

c. What is the relation between the possible changes in left ventricular function and the patency of the implanted bypass?

2. Mortality and morbidity data for all patients in the study over at least three years in order to provide answers to two major questions:
   a. Which patients are most likely to benefit from surgery?
   b. Who are the high-risk patients in whom pharmacological treatment might be preferred?

The design goal is for each of the three participating university centers to contribute at least 100 patients per year to this study. These patients have all followed the same pathway:

1. A standardized history and physical examination with various laboratory and biochemical determinations.
2. A standardized coronary angiographic investigation which utilizes the classification system of the American Heart Association.
3. A standardized left ventricular catheterization procedure, quantifying pump and muscle function, including an atrial pacing stress test, where data analysis is carried out in an identical manner by a hard- and software configuration, which is the same in all three participating centers. This system corresponds to that described in chapters III and IV.
4. A standardized description of the electrocardiogram and chest x-ray.
5. A report on surgical technique, with exact description of the surgical procedure in an effort to keep the procedure as consistent as possible.

The management of such a large amount of data requires careful data collection and processing. In order to handle all the data from the three participating institutions, an interactive data bank system based on the MUMPS-11 DBMS language was developed. It is organized into 18 sections with separate data sheets:

1. history of chest discomfort.
2. associated conditions and social data.
3. current therapy.
4. physical exam and Rx thorax.
5. ECG.
6. biochemical data.
7. catheterization data.
8. atrial pacing stress test.
9. quantitative ventriculography.
10. contractility.
11. coronary arteriogram.

12. angiography of coronary bypass graft.
13. mortality form.
14. autopsy pathology.
15. autopsy coronary arteries.
16. autopsy bypass graft.
17. special events.
18. surgical report and post-operative data.

In total, a list of 171 numerical or coded variables and 156 descriptors is completed, for every patient.

II. Patients and methods

On November 1, 1979 the data bank consisted of 684 patients where pre-operative catheterization information was available. Details of these patients are given in table I. Out of this group of patients a subgroup was selected, where impaired left ventricular function could be suspected, based on the same criteria as used for the patient identification in group 2 of chapter VII. Accordingly, all patients were included in whom one or more of the following conditions were present: ejection fraction $< 40\%$, left ventricular end diastolic volume in excess of 110 ml/m², four or more myocardial infarcts in the history and the presence of akinetic or dyskinetic areas on the left ventricular angiogram in the RAO position.

The data base provided 84 patients (12% of the total group), in whom one or more of these criteria were met. The scoring system described in the previous chapters was applied in these 84 patients.

The catheterization index, which is based on the distance between the individual variables and their mean values in normals, expressed in units of their respective standard deviations, was again calculated for all patients.

Table I.   Project IV of the Interuniversitary Cardiological Institute. Data bank per November 1, 1979.

Databank per nov. 1. 1979 of project IV, Interuniversitary
Cardiological Institute, the Netherlands.

Pre-operative catheterizations	:	684 patients
Coronary bypass surgery in	:	676 patients
1th year recatheterization	:	346 patients
3d year recatheterization	:	48 patients

Average age at surgery: 52 years
(627 males and 57 females)

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Calculations were performed separately for the atrial pacing stress test data and the nine hemodynamic variables used in chapter VIII. The APST-data were adjusted for heart rates 70 and 140 as previously described. Results of the CATH.index were compared with those of the group of normals, as identified in chapters VII and VIII.

III. Results

A summary of the data in the form of the means and standard deviations of the calculated CATH.-indices and APST is given in table II. It is evident that the mean value of the index as derived from the basal hemodynamic variables in the 84 patients with impaired left ventricular function is twice that of the 71 normals. This also applies for the index calculated from the atrial pacing stress test data, where the mean indices of the patient group are 1,82 and 1.87 respectively versus 0.93 and 0.91 for the 44 normals.

A histogram of the CATH.-index based on the APST (fig. 1a), shows that the group as a whole is distributed over a higher range of the index than the normals. About half of the patients have an APST-score in excess of normal.

Histograms of the CATH.-index, based on the nine hemodynamic variables, measured in the resting state are shown in fig. 1c and 1d. Results are comparable to the atrial pacing stress test data. The patient group as a whole is shifted to the higher ranges of the index, although the separation between the normals and the patient group is not as clear as with the atrial pacing stress test.

The relative contribution to these results for each of the variables involved, is shown in table III. In this table the average deviation from the

Table II. Results of CATH.-index calculation. Mean values and standard deviation in normals and 84 patients. APST: atrial pacing stress test.

Cath Index: Mean values and standard deviations

	Basal Haemodynamic Variables	APST
normals	0.93 ± 0.37	0.91 ± 0.39
84 patients with compromised ventricular function	1.82 ± 0.90	187. ± 0.92

normal mean for each separate variable is listed, as found in the group of 84 patients. The deviation is expressed in units of the standard deviations in the normal group. For example, in the atrial pacing stress test data, the LVEDP at heart rate 140 is the most powerful variable, showing an average deviation

IMPAIRED LV FUNCTION

CATH INDEX : ATRIAL PACING STRESS TEST
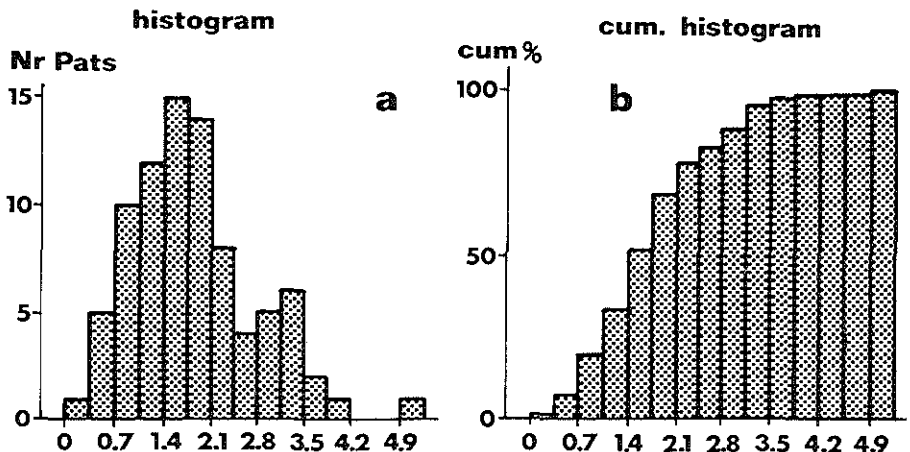
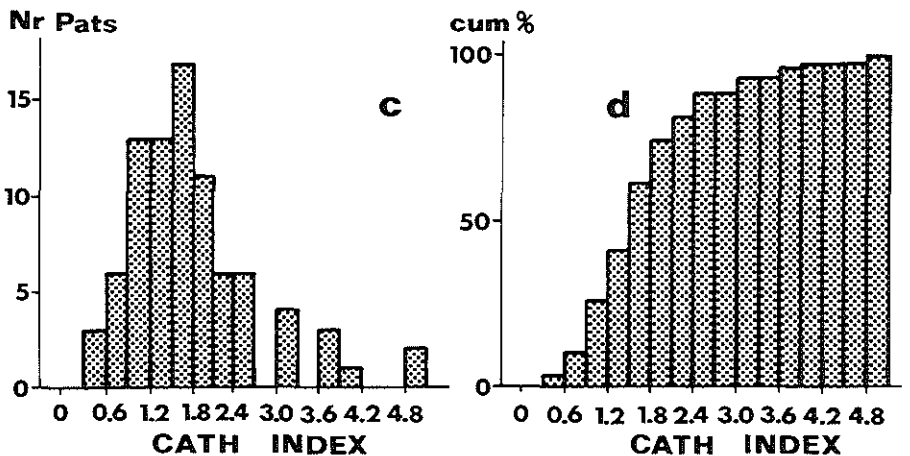
CATH INDEX: NINE HAEMODYNAMIC VARIABLES

Fig. 1. CATH.-index of atrial pacing stress test in 84 patients of project IV (ICI) with impairment of left ventricular function as a) Frequency histogram b) Cumulative percent histogram c, d) CATH.-index in the same group of patients calculated from nine hemodynamic variables in the resting state, also as frequency and cumulative percent histograms.

Table III. Deviation from normal mean in 84 patients of project IV (ICI). Results in basal hemodynamic variables and APST expressed in standard deviations of normal group.

Abbreviations: pk LVP = peak systolic left ventricular pressure, pk AoP = peak systolic aortic pressure, d AoP = diastolic aortic pressure, mn Pw = mean pulmonary capillary wedge pressure, pk PAP = peak systolic pulmonary artery pressure, d PAP = diastolic pulmonary artery pressure, SVI = stroke volume index, LVEDP = left ventricular end diastolic pressure, pk dP/dt = peak positive first derivative of left ventricular pressure, VCE = peak dP/dt/P, V_{max} = extrapolated dP/dt/P over P to zero P.

Average deviation from normal mean of 84 pats of project IV, ICI, expressed in standard deviations of normal group.

Basal Variables						
Pk LVP	Pk AoP	d. AoP	mn Pwedge	pk PAP	d PAP	SVI
1.59	1.34	0.89	1.49	1.95	1.68	- 0.38

APST: Variables				
Heart rate	LVEDP	dP/dt	Vce	V_{max}
70	1.48	- 0.62	- 1.20	- 0.92
140	2.81	- 1.09	- 1.69	- 1.44

of 2.81 standard deviations from normal, while dP/dt at heart rate 70 is the least powerful with a deviation of -0.62 from normal mean. In the group of basal hemodynamic variables, peak Left Ventricular pressure and peak Pulmonary Artery pressure contribute most to the results of the score. The smallest contribution comes from the diastolic Aortic Pressure and Stroke Volume Index.

However, this univariate method of assessing the relative contribution is not sensitive to interdependent directional changes of more than one variable.

These results, when compared with the discriminant function of table X (chapter VIII) indicate that the high deviation from normal mean for Pulmonary Artery pressures is to be adjusted for interdependency. The Stroke Volume Index, on the contrary, although deviating only -0.38 standard deviations, is still a strong separator, being independent of other variables.

Also note the impressive increase in contribution of the APST-variables, when heart rate is increased from 70 to 140, indicating the information gain of the pacing test.

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IV. Discussion

Results are presented of the CATH.-index calculations in an independent (testing) group of patients with impaired left ventricular function. The index is found to be elevated to a significant degree in about 50% of these patients, both in the resting state as well as during atrial pacing. The results show that the index can be used as a reliable indicator of the hemodynamic state.

Since for every patient in the data bank of this project 327 descriptors are used, a total of about 1,000 descriptors per patient will be in the data bank, when the two follow-up investigations are performed. Since, in roughly 900 patients one is dealing with 2,700 data sets, data reduction, earlier alluded to, is now imperative. Data of the cardiac catheterization can be classified into four groups:

1. basic hemodynamic variables.
2. the atrial pacing stress test.
3. the coronary arteriogram.
4. the quantitative ventriculogram.

Reduction of data can be carried out in the first two groups by the CATH.index system as described above, to compress the data of the atrial pacing stress test, as well as of the standard hemodynamic variables. Some amplifications for scoring of the coronary arteriogram and ventriculogram will be necessary. A scoring system for the coronary arteriograms has been designed and first data are currently in press 49).

Furthermore, a strategy for coping with missing data will have to be designed. Also, improvement is possible with the introduction of "weighting factors". Statistical techniques for the calculation of such weighting factors are available and will be introduced in this system in the near future.

Some variables are interdependent to some extent (for example, peak Left Ventricular pressure and peak Aortic Pressure) while others (Left Ventricular end diastolic pressure) contribute strongly to the results. Since the CATH.-index is essentially a counting technique of abnormal variables and is easily performed and adjusted, it is ideally suited for incorporation in data analysis programs in a cardiac catheterization computer system.

V. Summary

The catheterization index, details of which have been described in earlier chapters has been tested in an independent file of 84 patients, all with coronary artery disease and impaired left ventricular function.

The results indicate that the index system, based on the atrial pacing stress test and selected hemodynamic variables in the resting state, can be used as a score for indicating the state of cardiac performance. We expect, with additional refinements to effectuate a sizable and sensible data reduction for the evaluation of patients. This will not only benefit the individual patient but is a necessity for handling a large data base as in this multicenter study.

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CHAPTER X

OVERZICHT EN SAMENVATTING VAN DIT PROEFSCHRIFT

In dit proefschrift worden het ontwerp, de ontwikkeling en de eerste zes jaren van toepassing beschreven van een computersysteem voor de verwerking van hartcatheterisatiegegevens. Dit systeem is op het ogenblik in dagelijks gebruik in het Thoraxcentrum van het Academisch Ziekenhuis Rotterdam-Dijkzigt, Rotterdam.

Gedurende de laatste drie decennia is hartcatheterisatie geleidelijk een steeds meer ingewikkelde en complexe procedure geworden, die als een noodzakelijke fase wordt beschouwd bij de voorbereiding en de indicatiestelling van de hartchirurgie. Gezien de eis van nauwkeurigheid is de behoefte aan automatisering bijna vanzelfsprekend. De fases waarin de opbouw van dit computersysteem plaatsvond, zijn in de verschillende hoofdstukken van dit proefschrift weergegeven.

In hoofdstuk II is de beschikbare literatuur besproken en samengevat in drie verschillende onderdelen: eerst een selectieve beschrijving van de meest belangrijke publicaties, die aan het ontwerp en de ontwikkeling van het systeem vooraf gingen; vervolgens een tweede deel, waarin alle betrokken publicaties van de Rotterdamse groep die op dit onderwerp betrekking hebben zijn genoemd, maar niet in detail besproken. Tenslotte een lijst met alle belangrijke literatuurreferenties die in de loop der jaren tijdens de ontwikkeling zijn geraadpleegd.

Een gedetailleerde beschrijving van dit catheterisatie-systeem werd gepubliceerd in 1975. Het vormt een samenvatting van vele jaren werk en geeft details over alle componenten van het systeem. In dit hoofdstuk wordt ook ingegaan op het dagelijks gebruik van deze opstelling met een weergave van de ervaringen daarmee, zoals die in 1975 konden worden samengevat. Deze tekst kan in feite worden beschouwd als een soort hoeksteen van dit proefschrift en is als hoofdstuk III hierin opgenomen. Aangezien hierin veel nadruk valt op de voordelen en de flexibiliteit van een on-line computersysteem in het catheterisatielaboratorium, zijn details over de off-line analyse van ventrikel-angiogrammen, alsook een overzicht van de

belastingstest met behulp van atrial pacing, als delen van de catheterisatieprocedure, apart behandeld. Aangezien deze onderdelen een essentiëel deel van de ingreep uitmaken, zijn zij in hoofdstuk IV gebundeld. Met het groeien van de ervaring, werd het geleidelijk aan duidelijk, dat kwantitatieve bepalingen van de globale hartfunctie bij patiënten met coronaire hartziekten van beperkte betekenis zijn. In feite is deze ziekte heel vaak segmenteel of regionaal van karakter; waardoor plaatselijke stoornissen in de contractie soms kunnen worden aangetoond, zelfs wanneer de gegeneraliseerde metingen van de hartfunctie normale resultaten geven. Akinesie of dyskinesie van één of meer segmenten van de linker vertrikelwand kan optreden in de aanwezigheid van normale, globale parameters, bijvoorbeeld een ejectie fractie tussen 50 en 70%. Deze analyse van regionale en segmentale wandbeweging is weergegeven in hoofdstuk V, gebaseerd op de analyse van contouren van het linker ventrikelangiogram, maar ook uitgaande van metingen van epicardiale markerbewegingen, geïmplanteerd tijdens operatie en vervolgd met cine-radiografie in de jaren na de ingreep.

Een van de grote voordelen van een geautomatiseerd systeem is dat de analyse "on-line" kan bijgehouden worden en dat veranderingen in de hartfunctie van slag tot slag kunnen worden geanalyseerd. Op deze wijze kunnen de kleine wijzigingen die van slag op slag optreden, zelfs tijdens het normale sinusritme, worden vervolgd. Enkele resultaten worden in hoofdstuk VI beschreven, wat evenals het vorige hoofdstuk gebaseerd is op een eerder verschenen publicatie. Vastgesteld werd dat deze kleine wijzigingen in druk en andere parameters, die gewoonlijk door het middelen van gegevens verdwijnen, belangrijke informatie kunnen herbergen, hetgeen nog verdere exploratie verdient.

Zoals boven beschreven laat globale functiebepaling van het hart in rust bij coronaire ziekte vaak geen afwijkingen zien. Met de ontwikkeling van atrium pacing als belastingtest, is een techniek ter beschikking gekomen die het hart kan belasten zonder bijkomende onaangename sensaties voor de patient. Een verdubbeling van de hartfrequentie zal vaak, ruim voordat symptomen optreden, ernstige tekortkomingen in de hartfunctie aantonen. Een nieuwe statistische benadering van deze verschijnselen was noodzakelijk, welke beschreven wordt in hoofdstuk VII. Op deze wijze kan tegelijk data-reductie en standaardisatie worden uitgevoerd, waardoor de waarde van de atrium-pacing-stress-test wordt verhoogd. Deze test kan worden beschouwd als een zeer gevoelige en specifieke maat van de reservecapaciteit van het hart en zou bij iedere catheterisatie moeten worden uitgevoerd.

In hoofdstuk VIII wordt een evaluatie besproken van de 1.664 catheterisaties, die met het boven beschreven computer-gesteunde systeem in het Thoraxcentrum zijn uitgevoerd tussen 1972 en 1978. Een beschrijving wordt gegeven van het toegepaste diagnose-code systeem, waarmee alle patiënten geclassificeerd kunnen worden in verschillende diagnostische groepen. Van de vele, soms tot 54 toe, haemodynamische variabelen die bij catheterisatie worden gemeten, zijn er 9 uitgekozen op basis van hun discriminerende eigenschappen. Een aanvang werd gemaakt met het vaststellen van hun relatieve waarde bij het kwantificeren van de "haemodynamische situatie". Voor dit doel werd een z.g. Catheterisatie-Index ontwikkeld.

De Catheterisatie-Index die uit de leergroepen zoals beschreven in hoofdstuk VIII, is afgeleid, wordt vervolgens in een andere populatie toegepast. Deze toepassing is beschreven in hoofdstuk IX, bij patiënten die voorkomen in een andere data-bank, verzameld door het Interuniversitair Cardiologisch Instituut. Hieruit valt te concluderen dat deze nieuwe index een nuttige functie kan vervullen, speciaal bij de beoordeling van patiënten met afgenomen functie van de linker ventrikel.

Samenvattende, de tien hoofdstukken van dit proefschrift bevatten het wel en wee van een facet van computertoepassing in een middelmatig groot universiteitsziekenhuis. Er wordt ingegaan op ontwerp, ontwikkeling, toepassing in de kliniek en het dagelijkse gebruik van een dergelijk systeem. De algemene conclusie die uit dit proefschrift naar voren komt, is dat een dergelijke automatisering niet alleen redelijk en nuttig is, maar ook de kwaliteit van de hartcatheterisatieprocedure verhoogt. Daarenboven komt relevante informatie ter beschikking die anders niet voor de clinicus bereikbaar zou zijn. Tenslotte is dit ons doel, zoals door Murphy omschreven: "The patient is the center of our medical universe, around which all our work revolves, and towards which all our efforts tend".

CURRICULUM VITAE

De auteur werd geboren op 9 maart 1929 in Eindhoven. Hij volgde de gymnasium-B opleiding aan het Gemeentelijk Lyceum in Eindhoven, eindexamen in 1947. Daarna medische opleiding aan de Rijks Universiteit te Utrecht, arts-examen in 1957. Tijdens de studie was hij $1^1/_2$ jaar student-assistent op de afdeling Cardiologie waar zijn belangstelling voor dit terrein werd gewekt. Na militaire dienst specialisatie in het Zuiderziekenhuis te Rotterdam en de afdeling Cardiologie van de Rijks Universiteit te Utrecht. Na 1963 aan deze afdeling verbonden, speciaal voor de catheterisatie-laboratoria. Van 1968 tot heden werkzaam in het Thoraxcentrum, Erasmus Universiteit, Rotterdam. In 1973 aanvaardde hij een bijzonder lectoraat in de klinische pathophysiologie van het cardiovasculaire systeem.