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Analysis and Prediction of Left Ventricular Performance under Load Changes during Cardiac Catheterization

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The applicability of a computer model, which relates the transmural mechanical distribution in the left ventricle (LV) to its global function at different loading conditions, was evaluated in patients with normal to near normal LV function undergoing cardiac catheterization. Left ventriculography and measurements of aortic and LV pressures were performed at baseline conditions and repeated following rapid volume expansion with intravenous infusion of 250 to 300 ml of physiologic saline and also after sublingual isosorbide-dinitrate (ISDN) administration. Twenty patients (18 men and 2 women, average age = 53 years) underwent coronary angiography and left ventriculography. Sixteen patients had coronary artery disease with one- to three-vessel involvement and 4 had normal coronary arteries. The measured input data into the model included the end-diastolic LV volume and wall thickness, aortic pressure, heart rate, and the peripheral resistance. The model parameters of myocardial contractility and arterial system capacitance for the control baseline conditions were estimated so that an accurate match was obtained between the predicted and the measured end-systolic (ES) volume and pressure. Using these parameters, model predictions for the two load perturbations were compared to the measurements. An excellent correlation was found between the predicted and measured LV ES volumes and peak-systolic pressures (PSP) ($R^2 > 0.994$). In four patients, who developed ischemic symptoms during saline injection, the prediction of end-systole volumes were lower than the measured values, suggesting an actual reduction in contractility during acute ischemia. There-

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fore, the model is sensitive to contractility changes. The model predicts global LV performance, under different loading conditions, including stroke work, peak developed wall stress, velocity of fiber shortening, and myocardial oxygen consumption.

Keywords—*Left ventricle, Computer model, Angiography.*

INTRODUCTION

Left ventricular (LV) function in health and disease is determined by the complex interaction between its geometry, the specific distribution of muscle fibers across the LV wall, and the mechanical properties of the fibers. However, global parameters such as pressure, volume, and their derivatives are commonly used in the clinical setup to quantify the LV function. The end-systolic (ES) pressure-volume relationship (ESPVR), originally proposed by Sagawa *et al.* (18) and Suga *et al.* (21,22) and validated by others (7,13–17), has been proposed as an index to assess ventricular function.

Various approaches have been used to adjust the ESPVR model to clinical data, and to define the data which is representative of the ESPVR. Grossman *et al.* (7), Mehmel *et al.* (15), and Marsh *et al.* (14) used the dicrotic notch pressure in the artery to represent the ES pressure. Grossman *et al.* (7), Dehmer *et al.* (5), and Nivatpumin *et al.* (17) used peak-systolic pressure (PSP) in the LV and aorta as an approximation of the ES pressure. To simplify these measurements, Nivatpumin (17) showed that the maximal ratio of the LV pressure and volume (determined by ventriculography) was similar to the ratio of peak LV pressure (measured before angiography) and ES volume (measured during angiography). When impedance was used to measure ventricular volume, it allowed to determine the PV loops over a large range of loads (10) showing that the ESPVR is nonlinear and that the slope is a function of the load. Therefore, the clinical value of the ESPVR as a load-independent index is in question.

Beyar and Sideman (1) developed a model of the LV that combines LV geometry and fiber transmural architecture with sarcomere mechanics. This model differs from the time-varying elastance model because it uses the sarcomere properties to predict the time-varying global ventricular function as well as distributed local transmural myocardial functions.

The advantage of the proposed model (1) lies in its ability to describe transmural myocardial properties such as stress distribution, velocity of fiber shortening, and local myocardial oxygen consumption (3). The latter is derived from the local stress-length loops of the sarcomeres, in analogy to Suga's global pressure-volume area concept for prediction of ventricular O_2 consumption (23). Obviously, the utilization of this model demands knowledge of some basic physiological parameters, such as sarcomere length and sarcomere mechanics, which cannot be evaluated in individual patients. *A priori* assumptions of these data must be made based on known physiological data so that the model can be combined with basic clinical data to yield meaningful quantitative description of the individual's ventricular function.

The purpose of the present study is to test the reliability of the model to predict and evaluate the *global response* of normal and ischemic hearts to different loading conditions. To achieve this aim, we have utilized data from cardiac catheterization in patients evaluated for chest pain. Left ventricular volumes and pressures were measured under three different loading conditions and compared to the model simulation results.

METHODS

Patient Selection

Twenty patients (18 men and 2 women, 18 to 72 years of age), with a mean age of 53 years, underwent cardiac catheterization for evaluation of chest pain. Because the study was aimed at the response to load of normal or near normal hearts, patients with a clinical history of congestive heart failure, valvular heart diseases (which modify afterload and preload), or atrial fibrillation were excluded. The studied patients and their clinical states are given in Table 1. Sixteen patients had coronary artery disease (CAD) and 4 had normal coronary arteries (NCA).

Experimental Protocol. The experimental protocol was approved by an international review board (Helsinki Committee), and each patient signed an informed consent prior to the study. Left ventricular angiography and the measurements of the aortic and LV pressures were performed after coronary arteriography and repeated three times in each patient for the following loading conditions:

1. Normal "baseline" conditions.
2. Acute volume load: Rapid (over 3 to 5 min) intravenous injection of 250 to 300 ml physiologic saline solution.
3. Acute afterload and preload reduction: Sublingual administration of 5 mg isosorbide-dinitrate (ISDN).

TABLE 1. Description of the studied subjects.

Patient Number	Sex	Age	Diagnosis and Duration of Disease	Number of Diseased Vessels
1	M	41	CAD, AP, 2 yr	2VD
2	M	62	CAD, AP, 4 yr	2VD
3	M	53	CAD, MI, 11 yr	3VD
4	M	55	CAD, AP, 1 yr	1VD
5	F	62	CAD, AP, 3 yr	2VD
6	M	54	CAD, MI, 2 yr	3VD
7	M	53	CAD, MI, 4 yr	2VD
8	M	50	CAD, AP, 10 yr	3VD
9	M	72	CAD, AP, 2 yr	3VD
10	M	56	CAD, AP, 1 yr	3VD
11	M	70	CAD, AP, 5 yr	3VD
12	M	58	CAD, MI, 10 yr	2VD
13	M	64	CAD, MI, 1 yr	3VD
14	M	45	CAD, MI, 1 yr	2VD
15	M	56	CAD, AP, 1 yr	3VD
16	M	52	CAD, AP, 3 yr	3VD
17(N)	F	18	Normal-chest pain	–
18(N)	M	19	Normal-chest pain	–
19(N)	M	44	Normal-chest pain	–
20(N)	M	46	Normal-chest pain	–

AP = angina pectoris; CAD = coronary artery disease; F = female; M = male; MI = myocardial infarction; VD = vessel disease; yr = years; N = normal coronary arteries.

Measurements were taken within a short period of time (1 to 2 min) after the intervention. In each case, 10 to 15 min were allowed to elapse in order to achieve complete stabilization before the next intervention.

Typical ischemic chest pain developed in four patients during or immediately after injection of the second contrast agent following the saline loading. The clinical symptoms of ischemia were verified by typical ECG changes in two of the patients. It is assumed that active ischemia was induced by the saline infusion. The ischemic changes resolved completely in all of these patients after ISDN administration. Therefore, it was assumed that the patients returned to normal before the third contrast agent injection was given, and it was within an acceptable catheterization risk to proceed with the third (25 ml) injection of contrast agent. The patients were informed in advance of the potential risk inherent in repeat examination of contrast ventriculography.

Catheterization Procedure. The catheterization of all patients was performed by the transfemoral Seldinger technique, using the Judkins catheters for coronary arteriography and a 7F pigtail catheter for left ventriculography and pressure measurements. Short pressure tubing and Statham pressure transducers were used. The frequency response of the system is typically up to 10 to 15 Hz, which is good enough to obtain end-systole as well as peak-systolic pressures but cannot be applied to dynamic pressure-volume changes. Single-plane, right anterior oblique ventriculography was performed on all the patients immediately after the pressure reading in each intervention using intraventricular injections of 25 ml of 76% urographin solution at a flow rate of 18 ml/s.

LV Measurements. A metal grid was routinely photographed in order to correct for X-ray beam magnification. End-diastole was defined as the frame just before the onset of contraction and ES as the frame preceding opening of the mitral valves. The latter could be visualized in most patients when aided by the subjective impression of a small silhouette. After manual tracing, the LV volume was calculated using the Sandler and Dodge (6,19,20) area-length method. A correction using the linear regression equation of Kennedy *et al.* (11) was employed. The following measurements were taken:

1. *Volume:* The LV silhouettes at the corresponding frames were traced twice. The two calculated volumes were averaged.
2. *ED Wall Thickness:* This was measured as the distance between the endocardial and epicardial borders at the corresponding frames and averaged for a segment of 3 cm. The endocardial border was defined as the edge between the contrast agent and the myocardium. The epicardial border was defined by the edge between the myocardium and the lungs. The short axis of the LV, M, at ED and ES was calculated utilizing the area length method proposed by Sandler and Dodge (19,20), that is,

$$M = A/\pi L \tag{1}$$

where A is the projected silhouette area and L is the long axis of the LV.

The Computer Model. A detailed description of Beyar and Sideman's model is given elsewhere (1), and only a short summary of the basic assumptions that characterize the model is presented here (see Fig. 1).

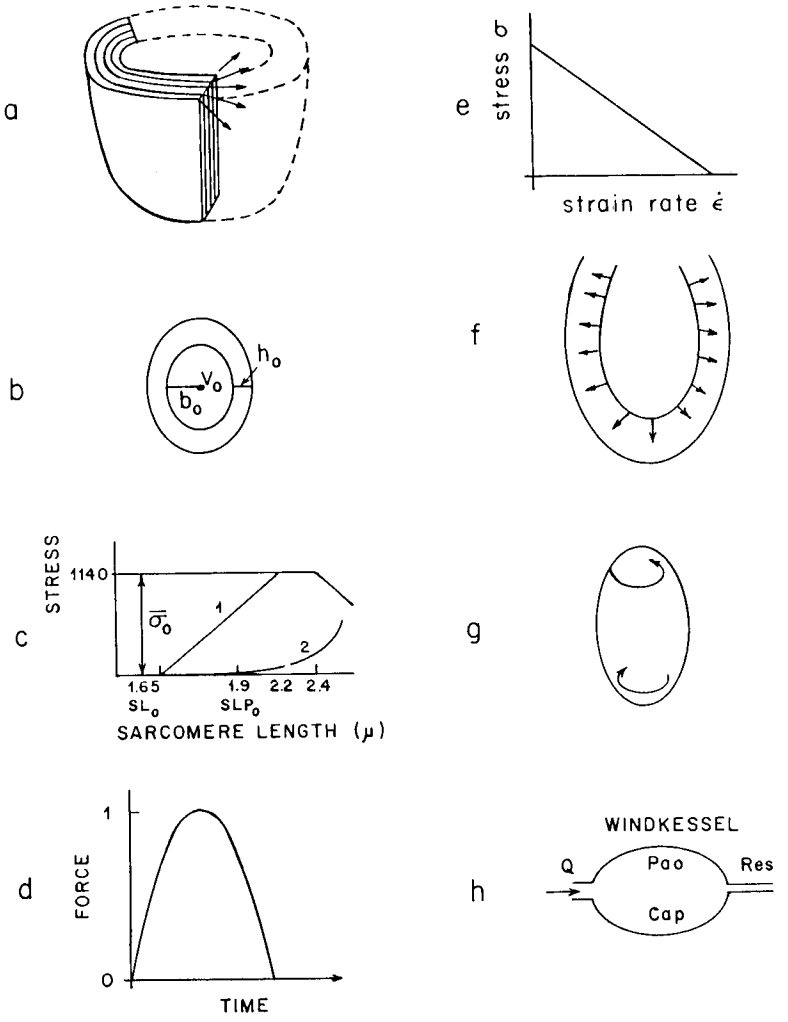

FIGURE 1. A schematic presentation of the assumptions used in this model (see text for explanation).

1. The LV is assumed to be a nested shell spheroid wherein the ratio between the semimajor and the semiminor axes at the endocardium is held constant. The LV shell is constructed of fibers with angles to the transverse plane that vary linearly from $+60°$ to $-60°$ throughout the wall thickness.
2. The reference resting state is defined as the state at which no transmural pressure exists across the LV wall in the fully passive state. It is assumed that at this value the sarcomere length (SL) is constant across the wall and equals 1.9μ. The semimajor, semiminor axis, wall thickness, and volumes at this state are defined as a_0, b_0, h_0, and V_0, respectively.
3. The fibers exhibit the classical sarcomere physiology: the force-length relationship is exponential for the passive state and linear for the fully active state from $1.65 < S1 < 2.2\mu$. The active stress plateaus between 2.2 and 2.4μ and declines

thereafter. Maximum sarcomere stress at the optimal length is expected to be 1140 mmHg (1500 g/cm^2) (1).

4. The muscle activation function, in terms of normalized force, varies from the passive to the fully active states. As a first approximation, half a sinusoidal activation function is assumed. The duration of the muscle activation time, TC, is assumed to equal the ventricular contraction time; the electrical propagation time is relatively small.
5. The force-velocity relationship is a linearly decreasing function of stress vs. strain rate.
6. The electrical activation in the nonischemic LV propagates radially from the endocardium to the epicardium at a velocity of 0.3 m/s.
7. The LV base twists 24° relative to the apex during contraction. This value, measured originally by Ingels et al. (9) by implanted markers in surgical patients, and further studied by Hansen *et al.* (8), was validated recently by noninvasive measurements utilizing magnetic resonance imaging (MRI) (4).
8. A simple Windkessel afterload model with a peripheral resistance and an arterial capacitance is assumed for the arterial load.

Contractility Index. The value of 1140 mmHg (1500 g/cm^2) for the maximum active sarcomere stress at the optimal sarcomere length was previously selected as the normal value (1) based on experimental work *in vitro* (12).

Oxygen Consumption. It is assumed that the local oxygen consumption relates linearly to the local stress-length-area of the sarcomere (3), parallel to the approach of Suga *et al.* (23), utilizing the pressure-volume-area to determine the oxygen consumption for the whole ventricle.

The measured input data to the model includes the heart rate, ED-LV dimensions and wall thickness, and ED aortic pressure. The arterial resistance was taken from calculations derived from the cardiac catheterization as previously described. Based on these input data, the reference dimensions of the model were adjusted assuming that the reference volume V_0 is 0.66 of the EDV in the control state. (This ratio is based on the known physiological data that sarcomere length at V_0 is 1.9μ and at end-diastole is roughly 2.05 to 2.1μ. Based on these data, one can calculate that $V_0/EDV = 0.66$.) The reference wall thickness, h_0, was calculated assuming muscle incompressibility.

The output data derived from the model includes the LV-ES volume and PSP, ES dimensions, cardiac output, ejection fraction (EF), stroke work, peak developed wall stress, maximum isovolumic pressure indexes, circumferential fiber shortening rate, cardiac oxygen consumption, maximum flow, and the maximum elastance. Pressure-time, volume-time, and pressure-volume curves are also determined.

The model parameters of the individual patients were determined by the following procedure. Given the ED dimension and pressures, and the reference dimensions, which were calculated as outlined above, the contractility index and the arterial capacitance were adjusted to match the model's calculated value of the ES volume and peak systolic pressure to the experimental ES volume and peak systolic pressure. There is only one combination of these two independent parameters that will yield the matching of both the peak systolic pressure and ES volume. These parameters were assumed to remain unchanged at the three different loading conditions tested here and were used to predict the ejection and ES parameters based on the ED input.

Statistical Analysis. Comparison of the results before and after the interventions of volume expansion and the sublingual administration of ISDN were analyzed using the paired *t*-test methods with the Bonferoni correction, using $p < 0.05$ to define significance. The fit of the predicted values with the measured data was determined by the linear correlation:

$$R^2 = 1 - \Sigma(\text{computed-measured})^2 / \Sigma(\text{measured})^2 \quad (2)$$

where R^2 of the ES values was calculated for each of the interventions.

RESULTS

Effects of Loading Manipulations

The measured responses of the patients with normal (NCA) and diseased coronary arteries (CAD) to the load manipulations are listed in Table 2. The response of the group as a whole to load manipulations is reported below.

Volume expansion by saline infusion caused, in the whole group of patients, significant increases of the LV-ED volume (EDV) (from 138 ± 32 ml to 162 ± 34 ml; $p < 0.001$) and the ED pressure (EDP) (from 18 ± 5 mmHg to 30 ± 5 mmHg, $p < 0.0001$). The heart rate, peak aortic pressure, and EF did not change significantly.

Significant decrease in EDV (from 162 ± 34 ml to 139 ± 29 ml; $p < 0.0001$) and

TABLE 2. The response of the two groups to load changes.

		1		2		3
Parameters/Loading State		Control State	Stats 1 vs. 2 p =	Volume Expansion	Stats 2 vs. 3 p =	ISDN
Heart rate (beats/min)	CAD	82 ± 10	NS	84 ± 10	NS	85 ± 9
	NCA	85 ± 10	NS	86 ± 12	NS	92 ± 12
Peak aortic pressure (mmHg)	CAD	139 ± 18	NS	143 ± 20	0.0002	131 ± 16
	NCA	122 ± 15	NS	124 ± 9	0.0002	115 ± 5
EDV (ml)	CAD	143 ± 32	0.0002	168 ± 34	0.0002	143 ± 29
	NCA	115 ± 16	0.0002	135 ± 14	0.002	121 ± 17
ESV (ml)	CAD	41 ± 12	0.0012	51 ± 14	0.002	42 ± 15
	NCA	28 ± 7	0.0008	30 ± 6	0.016	28 ± 5
Peak systolic pressure (LV) (mmHg)	CAD	135 ± 20	0.012	146 ± 19	0.0004	136 ± 18
	NCA	118 ± 11	0.004	124 ± 10	0.0002	120 ± 7
EDP (mmHg)	CAD	18 ± 6	0.0002	30 ± 6	0.0002	18 ± 6
	NCA	16 ± 1	0.0002	27 ± 2	0.0002	15 ± 4
EF (%)	CAD	71 ± 6	NS	69 ± 7	NS	71 ± 8
	NCA	77 ± 4	NS	79 ± 3	NS	78 ± 2

CAD = coronary artery disease ($n = 16$); EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; ISDN = isosorbide-dinitrate; NCA = normal coronary arteries ($n = 4$). Stats = paired *t* test with the Bonferoni corrections for multiple comparisons. The statistics were done for the 20 patients. No attempt to separate between the NCA and CAD patients was done due to the small numbers.

in EDP (from 30 ± 5 mmHg to 17 ± 5 mmHg; $p < 0.0001$) were observed following the ISDN administration. The peak aortic pressure decreased as well (from 142 ± 20 mmHg to 133 ± 18 mmHg; $p < 0.0001$). Heart rate and EF did not change significantly. There was no significant difference in the response to load manipulations between the patients in the NCA group and the CAD group.

Comparison of Calculated and Measured Results

Table 3 shows the comparison between the measured (M) and the model-based calculated results (CR) of the end-systolic volume (ESV), PSP, EDP, and EF in the three loading conditions: the control (C) state, after-volume expansion by normal saline (NS) infusion, and after the sublingual administration of ISDN for the whole group of patients. The data of the control condition were used to adjust the appropriate parameters of the computer model. An accuracy of ±3 mls was considered reasonable in volume adjustment. Note that the EDV given in this table was used as input, and therefore the CR and M are identical. As already stated, the values of the LV reference dimensions, contractility, and arterial parameters were extracted from the control state and kept constant throughout the various load manipulations.

The correlations between measurements and calculated ESV, PSP, and EF in the control group were high ($R^2 = 0.999$) for each parameter, reflecting favorably on the accuracy of the adjusted parameters. Obviously, this correlation of the control data does not provide information on the predictive power of the model. However, Fig. 2 shows a fairly linear correlation between the measured and calculated predictions of the ESV, PSP, EDP, and EF values after volume loading the heart. Note the excellent prediction of the systolic indices like ESV, PSP, and EF as compared with the diastolic (EDP) indexes, which show a somewhat lower correlation coefficient ($R^2 = 0.822$).

The correlation between the measured and computed results following the administration of ISDN are shown in Fig. 3. Again, an excellent correlation was obtained (the lowest R^2 was 0.99) for the systolic parameters, ESV, PSP, and EF. However, as before, a lower predicted value is noted for the EDP.

The capacitance, contractility parameter, and EF are detailed in Table 4 for the 20 patients. Note that the average capacitance is 1.46 ± 0.5 ml/mmHg. The average con-

TABLE 3. Comparison of the EDV, ESV, PSP, EDP, and EF between angiographic measurements (M) and computed (CR) results.

	Control		Volume Load		Isosorbide-Dinitrate	
Parameter	M	CR	M	CR	M	CR
EDV (ml)	138 ± 32	138 ± 32	162 ± 34	163 ± 33	139 ± 29	139 ± 29
ESV (ml)	38 ± 12	39 ± 12	47 ± 16	46 ± 16	39 ± 15	39 ± 14
PSP (mmHg)	132 ± 20	132 ± 18	142 ± 20	140 ± 17	133 ± 18	129 ± 18
EDP (mmHg)	18 ± 5	18 ± 5	30 ± 5	35 ± 5	17 ± 5	21 ± 19
EF (%)	72 ± 6	72 ± 6	71 ± 7	72 ± 8	72 ± 7	72 ± 7

M = measured; CR = computed results; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; PSP = peak-systolic pressure.

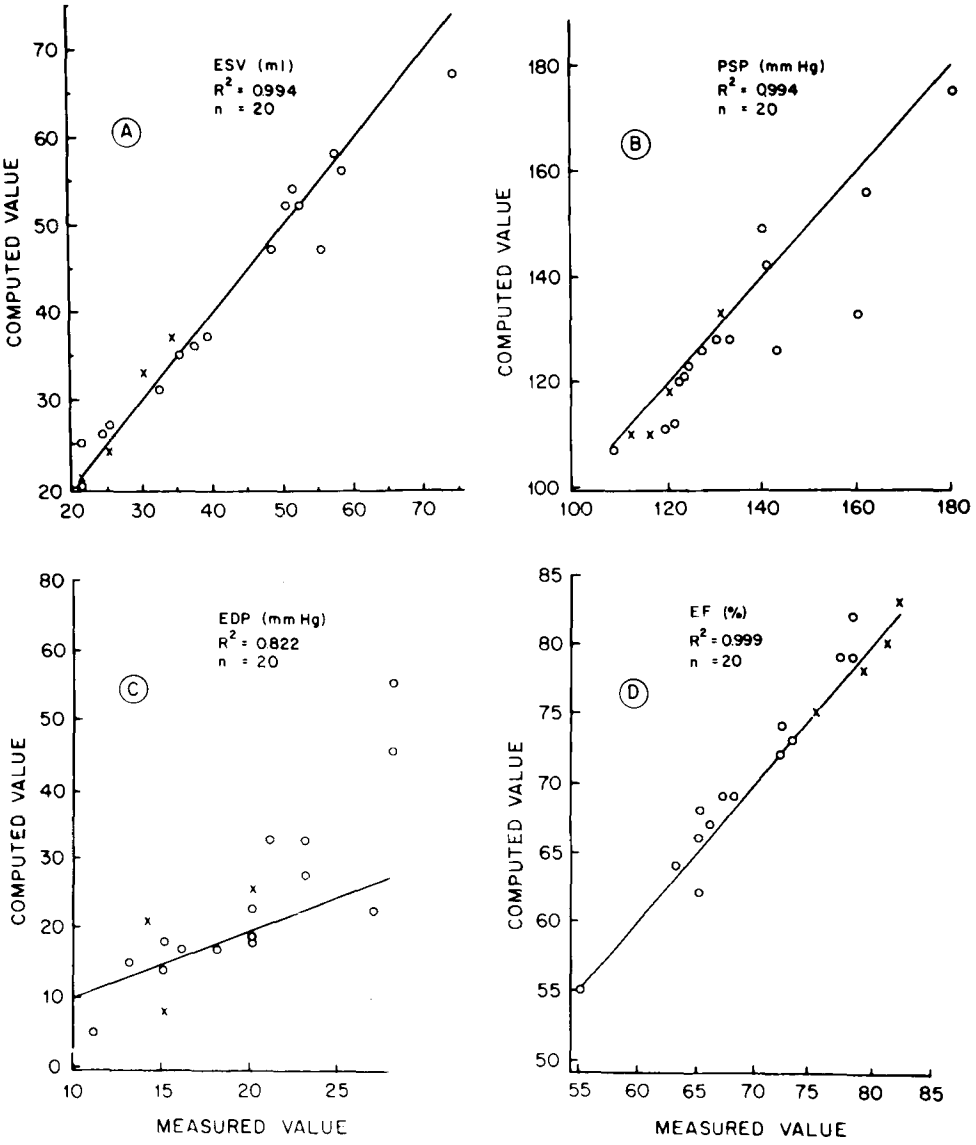

FIGURE 2. Comparison of left ventricular end-systolic volume (ESV), end-diastolic pressure (EDP), peak systolic pressure (PSP), ejection fraction (EF), determined by cineangiography (measured) and computer program (computed), after increasing preload with saline infusion. O—subjects with coronary artery disease (CAD). X—subjects with normal coronary arteries (NCA).

tractility index is 1683 ± 967, with a relatively high variability of the contractility index, ranging between 470 and 3720. The correlation between the contractility and EF is good with $r = 0.66$ ($p < 0.01$). The difference between the NCA vs the CAD groups is also given in Table 4. Note that the contractility and EF values are higher in the NCA group than in the CAD group; however, this difference is statistically insignificant.

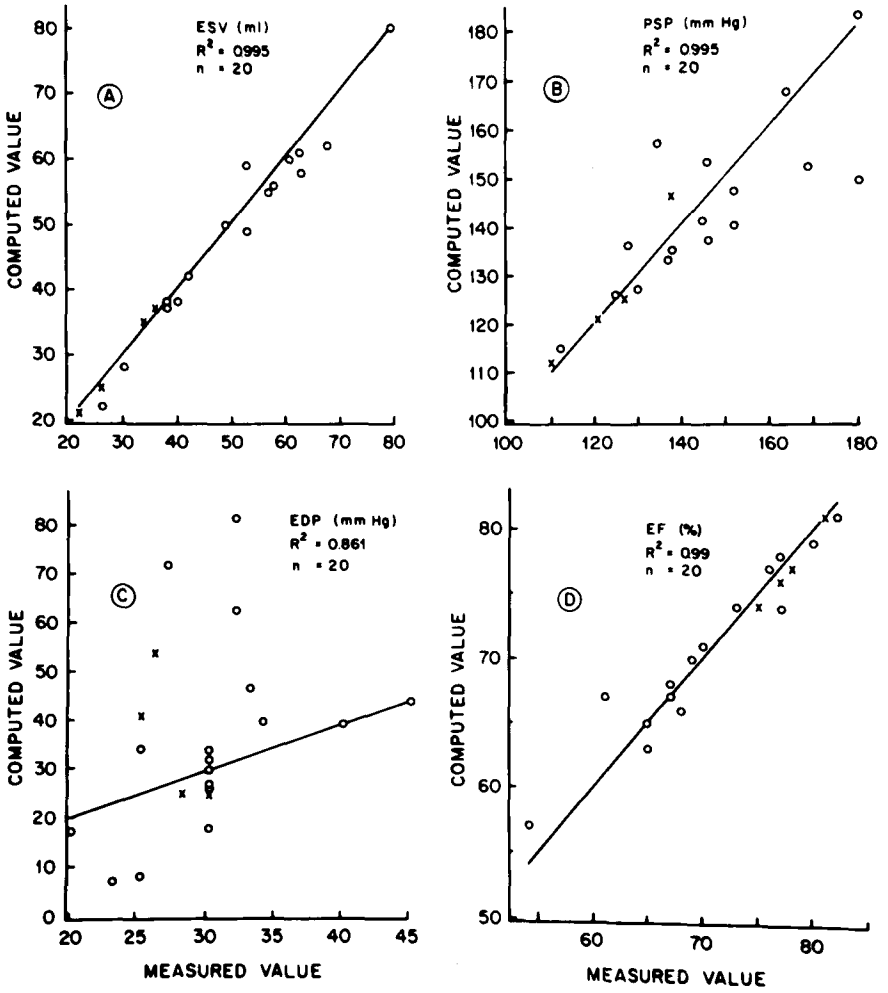

FIGURE 3. Comparison of left ventricular end-systolic volume (ESV), peak systolic pressure (PSP), end-diastolic pressure (EDP), ejection fraction (EF), determined by cineangiography (measured) and computer program (computed), after reducing preload. O—subjects with coronary artery disease (CAD). X—subjects with normal coronary arteries (NCA).

Table 5 lists the measured (M) and computed results (CR) of the ESV, PSP, and EF values in the 4 patients who developed typical ischemic pain following the NS infusion and volume expansion manipulation at the time of LV contrast injection. In all 4 patients, typical chest pain developed at the time or shortly after contrast agent injection and in two patients concomitant electrocardiogram (ECG) changes of acute ischemia evolved (ST depression). Both the ECG changes and the symptoms resolved shortly after the administration of ISDN. It is noteworthy that the measured ESV results in these 4 patients during volume expansion were much higher than the anticipated calculated results, obtained by utilizing the control-based contractility values that were used in the other 16 patients undergoing loading manipulations. These results indicate that the myocardial ischemia reduced the myocardial contractility in

TABLE 4. Capacitance, contractility, and ejection fraction values for the 20 patients studied.

Patient Number	Capacitance (ml/mmHg)	Contractility (mmHg)	Ejection Fraction
1 (CAD)	2.0	2500	72
2 (CAD)	1.1	600	63
3 (CAD)	1.5	1050	68
4 (CAD)	1.5	1040	65
5 (CAD)	1.0	3420	82
6 (CAD)	1.8	2400	73
7 (CAD)	1.9	1000	69
8 (CAD)	0.7	1140	67
9 (CAD)	2.5	2500	75
10 (CAD)	1.2	840	66
11 (CAD)	0.7	3720	75
12 (CAD)	1.2	1000	77
13 (CAD)	2.5	1500	77
14 (CAD)	1.6	980	67
15 (CAD)	1.0	470	61
16 (CAD)	1.0	1254	80
17 (NCA)	1.2	1687	79
18 (NCA)	1.6	1980	73
19 (NCA)	1.7	3420	80
20 (NCA)	1.5	1250	74
M ± SD (total)	1.46 ± 0.5	1683 ± 967	72 ± 6
NCA group (17-20)	1.5 ± 0.19	2074 ± 814	76.5 ± 3
CAD group (1-16)	1.45 ± 0.55	1585 ± 977	71 ± 6

CAD = coronary artery disease; M ± SD = mean ± standard deviation; NCA = normal coronary arteries.

TABLE 5. The measured (M) versus predicted parameters in four patients who experienced chest pain and ECG changes during volume load for control (C), saline infusion (NS), and isosorbide-dinitrate (IS). For volume load by saline infusion, model predictions are given using baseline contractility (CR1) and reduced contractility (CR2).

Patient Number:		1			10			11			12		
Load State		M	CR1	CR2	M	CR1	CR2	M	CR1	CR2	M	CR1	CR2
Contractility		–	2508	1482	–	840	760	–	3720	1700	–	1000	700
ESV (ml)	C	36	38	–	43	43	–	26	26	–	35	35	–
	NS	49	41	50	80	67	80	38	29	38	61	38	60
	IS	32	40	–	74	44	–	21	27	–	24	32	–
PSP (mmHg)	C	112	118	–	150	150	–	170	168	–	160	160	–
	NS	128	142	136	180	160	149	169	167	152	135	174	157
	IS	119	108	–	160	150	–	162	151	–	141	145	–
EF (%)	C	74	72	–	65	66	–	74	75	–	77	77	–
	NS	72	77	72	55	62	55	63	73	64	66	79	67
	IS	73	67	–	54	72	–	77	71	–	80	75	–

ESV = end-systolic volume; PSP = peak-systolic pressure; EF = ejection fraction.

these patients, leading to a higher ESV than the predicted values using baseline contractility (CR1). Indeed, reevaluating the contractility parameter to yield a close fit between the calculated and the measured values of ESV and EF shows an appreciable decrease in the contractility. The contractility changes yielding the best fit of the ES parameters (CR1) are shown in Table 5. Note that a decrease in contractility of $33 \pm 12\%$ during saline loading, which causes ischemia (probably by increased oxygen demand), is required for accurate predictions of the ES volumes.

The values of some of the model predicted indices are presented in Table 6. Note that volume load by saline infusion causes an increase in the cardiac output, stroke volume, and stroke work, as well as an increase in the velocity of shortening and the myocardial O_2 consumption. As expected, the ratio PSP/ESV did not change as these changes were not due to contractility changes. The predicted ratio of the endocardial/epicardial O_2 demand increased slightly with volume load. Interestingly, the endocardial/epicardial ratio of O_2 demand did not reverse after ISDN administration.

DISCUSSION

The purpose of this study was to examine the utility of a rather complex multiparametric model of the LV and evaluate its capacity to predict the response of the LV to various load manipulations performed during cardiac catheterization. The model parameters were evaluated based on the physiological baseline-loading conditions. The predictions for the two-load manipulations studied here, which utilized these parameters, were in excellent agreement with the experimental values (as long as no myocardial ischemia occurred). Note that the model's response to the maneuvers is conceptually related to the microscale sarcomere-level function in the LV.

Like all complex models related to physiological systems, the present model employs a set of "general" assumptions for the data that cannot be evaluated for each individual heart. The assumptions used here are clearly only first-order approximations. However, they are based on known physiological values, and it seems that the predictive value of the model for individual hearts does not diminish when the distributed local characteristics are integrated to yield the global performance characteristic of the individual LV. Note that the proposed model, based on the foregoing basic assumptions and the assumed sarcomere length at ED, requires only one experimental set of data at a fixed load in order to generate and extract the geometrical and contractility parameters. This necessitates the stipulation that the reference volume has some constant relationship to the baseline EDV. Obviously, this assumption may introduce some error. Note, however, that if three or more data sets at widely different loading conditions are available, the reference dimensions can be calculated uniquely, without the need for the reference volume assumption. In the current study, the nonlinearity of the ED pressure-volume relationship, the relatively narrow range of load manipulations, and problems with accurate pressure measurement at ED utilizing fluid filled catheters limited our reference parameter to one loading state.

The sensitivity of the parameters in a multiparametric model utilized here is obviously of interest. In general, the global results of the model are most sensitive to the volumetric and contractility parameters. In contrast, the twist of the LV does not effect the global results but affects the transmyocardial distribution of stress and O_2 consumption. The force velocity relationship of the sarcomeres effect the pattern of systolic flow but not the ESPVR. The transmyocardial electrical propagation veloc-

TABLE 6. Predicted hemodynamic indices in patient without the development of ischemia.

	CO (ml/min)	SV (ml)	SW (J)	dP/dt (mmHg/s)	PSP/ESV (mmHg/ml)	PDS (mmHg)	Max. EBDT (s^{-1})	MVO_2 (ml O_2/s −100 g)	Endo/Epi of O_2 Consumption
Control state	7504 ± 2034	90 ± 20	1.5 ± 0.4	2120 ± 601	4 ± 1.55	121 ± 22	2.78 ± 0.42	13.9 ± 2.0	1.3 ± 0.05
Volume load	9694 ± 1773	111 ± 18	2.1 ± 0.5	2503 ± 557	4 ± 1.53	152 ± 18	2.82 ± 0.35	19.1 ± 2.2	1.36 ± 0.06
Isosorbide-dinitrate	8273 ± 2034	96 ± 16	1.6 ± 0.3	1770 ± 430	4 ± 1.47	128 ± 21	2.83 ± 0.35	16.0 ± 4.7	1.36 ± 0.07

CO = cardiac output (ml/min); SV = stroke volume (ml); SW = stroke work (erg × 10^{-8}); *dP/dt* = maximum isovolumic pressure index (mmHg/s); PSP/ESV = peak systolic pressure – end-systolic volume ratio (mmHg/ml); PDS = peak developed stress (ml/min 100 g); Max. EBDT = maximal velocity of shortening (circum/s); MVO_2 = myocardial O_2 consumption (Ml/min 100 g); endo/epi ratio = endocardial/epicardial ratio of myocardial oxygen consumption.

ity has only a small effect on the global P-V relationship but has a significant effect on the transmural stress distribution. More details are given in our previous publications (1–3). Our approach was to use data from the literature for all the different parameters and then adjust only the parameters to which the model is most sensitive with respect to the present data.

Other models describing global LV performance obviously exist, each with its own inherent limitations. For instance, an alternative approach to the present model is the elastance model that utilizes global P-V relationship of the ventricle rather than myocardial properties (18,21,22). Although this approach is much simpler, the comprehensive model suggested herein offers the following advantages:

1. Based on basic physiological assumptions, the model parameters can be extracted from only one set of load trials and then used to predict subsequent loading states. This is not possible with the elastance model, which required at least two load manipulations to establish the appropriate system parameters.
2. The present model accounts for the wall thickness and myocardial mass and can thus be used to evaluate myocardial parameters such as fiber stress and myocardial oxygen consumption.
3. The present model can be used to calculate the local as well as the global LV parameters. The endo/epi ratio of O_2 consumption (3) is an example of the predictive capability of this model to determine the transmural distribution of O_2 demand. Indeed, it is predicted here that the natural metabolic gradient for O_2 demand will increase as the volume load increases.
4. A number of useful characteristic indices of LV performance are "automatically" derived by the present model, which is based on general microscale physiological parameters.
5. The proposed model represents a simulation tool that can be used to study the effect of many parameters on the LV performance in individual patients. Because the model is also coupled to a model of coronary flow (2), it can be used to study the complex effects of load manipulations on transmural coronary flow, which is difficult to measure in a clinical setup. Obviously these predictions are model dependent and have to be evaluated carefully.

With regard to the particular clinical procedure employed and studied here, it is noteworthy that the hemodynamics due to load manipulations achieving a new steady state are within the scope of the model's predictive range, suggesting that the contractility is not significantly altered under those conditions. Indeed, the data indicate only nonsignificant changes in contractility, unless ischemia occurs. As shown here, ischemia that developed following volume loading in four patients affects a significant reduction in the contractility index. Note that the model deals here only with the global implications of ischemia, and no attempt has been made in the present study to differentiate between the ischemic and nonischemic regions of the LV.

It is also noted that the EDP showed the least agreement with the predicted values. This is probably due to the exponential nature of the diastolic stress-length relationship and to the variability of the material properties in the different hearts. The identical general passive parameters used here for all the hearts are obviously only a fair approximation, at best.

Limitations

Apart from the uncertainty in the values of the physiological parameters that are impossible to measure in patients, this study has the following limitations:

1. Reflex changes in contractility may occur between the load manipulations and affect the results of the next intervention. However, the predictions of the model for the patients who did not suffer ischemia were good, and it is believed that these changes in myocardial contractility are minor.
2. Errors associated with the injection of contrast agents into the ventricle are obviously introduced. As is well known, the injection of contrast agent by itself modified LV-ED volume, and the effects of contrast agents on myocardial performance are well described. To minimize these effects, we employed minimal quantities of contrast agents. Also, the coronary arteriography preceding the intervention may in itself render the myocardium slightly impaired to start with, which may partly explain the relatively high LV-EDP in our study. Inaccuracies due to nonsimultaneous measurements of pressure and volume also exist. This unavoidable error is minimized by obtaining pressure measurements immediately preceding each contrast injection.
3. Neither load intervention has a singular "pure" effect. For example, ISDN causes both arteriolar dilatation (afterload reduction) and venular dilatation leading to decreased EDV (preload effect). Saline infusion by itself (pure preload effect) causes an increased blood pressure (afterload effects). However, in spite of these considerations, the study of the interventions, which generate three sets of loading conditions, was feasible because both LV volume and arterial pressure were measured, the model could deal with the complex load manipulations presented here.
4. Regional effects are unaccountable. The model assumes a spheroidal LV geometry. Although the normal heart may represent a relatively symmetric contracting structure, this is not true for the regionally ischemic heart. Consequently, the model describes the *average* global function of the ventricle and cannot relate to regional dysfunction phenomena at its present form. The resulting *global* performance index, however, may be clinically useful even if the exact local effects in each region are unknown.

SUMMARY

A comprehensive model of the LV mechanics is shown to predict the LV response to load manipulation in the clinical setup, as obtained by angiographic measurements. Ischemia seems to affect deviation from this predictive capability, suggesting that it affects the contractility as manifested by a reduced global performance. Although other models of global ventricular function can have similar predictive value, this model has the advantage that it can also predict the local parameter changes due to variations in load and give a better insight into the physiological phenomena under study. The proposed model, unlike all others, can provide insight and valuable information on the spatial transmural distribution of stresses, oxygen consumption, and myocardial blood perfusion while giving a good *a priori* description of the global performance characteristics. It is noteworthy that the applicability of the model extends

beyond the specific cath-lab application discussed here and can be easily related to other methods of clinical measurements such as echocardiography, magnetic resonance imaging (MRI), computer tomography (CT) imaging, and others.

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NOMENCLATURE

C = Control state
CAD = Coronary artery disease
CR = Calculated results
ED = End-diastolic
EDP = End-diastolic pressure
EDV = End-diastolic volume
EF = Ejection fraction
ES = End-systolic
ESV = End-systolic volume
ESPVR = End-systolic, pressure-volume relationship
ISDN = Isosorbide-dinitrate (IS)
LV = Left ventricle or left ventricular
M = Measured
MRI = Magnetic resonance imaging
NCA = Normal coronary arteries
NS = Normal saline infusion
PSP = Peak-systolic pressure
P-V = Pressure-volume
SL = Sarcomere lengths