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Left Ventricular Volume Measurements in Man by Thermodilution *

J. DAVID BRISTOW, RODNEY L. CRISLIP, CYRUS FARREHI, WALDO E. HARRIS, RICHARD P. LEWIS, DONALD W. SUTHERLAND, AND HERBERT E. GRISWOLD

(From the Division of Cardiology of the Department of Medicine, University of Oregon Medical School, Portland, Oreg.)

A safe, rapid method for estimating left ventricular volume in man during the course of hemodynamic studies should prove helpful in the assessment of cardiac disease and useful in physiological research. It is the purpose of this report to present left ventricular volume measurements in man that were obtained by an indicator dilution method which employs cold as the indicator. This circulatory indicator has been studied by several workers (1–4) and has been used for left ventricular volume determinations in animals previously (5–10). The method employed was adapted from those used by Rapaport and his co-workers for left ventricular volume measurements in the dog (7) and right ventricular studies in man (11).

Methods

Thirty-eight patients were studied during diagnostic left heart catheterization. The left ventricle was catheterized by the percutaneous transseptal method, utilizing a Teflon catheter which has four side holes near its tip (12). Left atrial pressure was measured before and after ventricular catheterization. A brachial artery was cannulated percutaneously with a 15-cm length of polyethylene tubing. A 6F Teflon catheter was introduced percutaneously into the right femoral artery and advanced until its tip was slightly above the aortic valve, as judged fluoroscopically. Left heart pressures were measured with a P-23G strain gage [1] and systemic arterial pressure with a P-23D gage.[1] These pressures and the electrocardiogram were recorded with a direct-writing four channel oscillograph.[2]

The measurement of left ventricular volume by indicator dilution requires determination of indicator concentrations in the proximal aorta during a sequence of beats after left ventricular injection. It is important that this dilution curve not be deformed by the sampling system and that it present an exponential series of decreasing, steplike concentrations. In these studies cold was used as the indicator and was delivered rapidly into the left ventricle by injections of 5 ml of cooled saline. Rarely, 10- to 15-ml injections were given in patients with extremely large ventricular volumes. A bead thermistor in the proximal aorta served as the sampling system. The thermistor catheter was of nylon (o. d., 0.97 mm) with a closed end and had a rapidly responding thermistor bead mounted at its tip.[3] This catheter was 1 cm longer than the radiopaque aortic catheter and was inserted into the latter when thermodilution curves were to be recorded. This placed the thermistor into the blood stream just above the aortic valve. Immediately after recording the thermodilution curves and cardiac output by dye dilution, the aortic catheters were removed to avoid the possibility of thrombosis.

The thermistor was employed as one arm of a Wheatstone bridge that was activated by a mercury battery. Approximately 0.1 v was presented to the thermistor itself. The resulting signal was amplified by a type 53/54 D preamplifier [4] and displayed with a type RM 565 oscilloscope.[4] The electrocardiogram was displayed simultaneously by a type 3 A 74 amplifying electronic switch.[4] Records were made by photographing the oscilloscope screen with 35-mm film.

The thermistors were calibrated against known temperature in a water bath. The peak change in aortic blood temperature produced by the cold injections was usually between 0.3° and 0.5° C. Since the changes in blood temperature were small, the thermistor could be used as a linearly responding system (7). The thermodilution curves were analyzed to obtain a dimensionless ratio, and therefore knowledge of the exact quantity of cold injected was not required.

The cardiac output was determined by the dye dilution method. Five mg of indocyanine green was rapidly flushed into the left ventricle, and continuous sampling of blood from the brachial artery was achieved with a cuvette densitometer [5] and a constant rate withdrawal pump.[6] The dilution curves were calibrated by passage of known concentrations of dye in arterial blood through

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[1] Statham Transducers, Inc., Hato Rey, Puerto Rico.

[2] Sanborn Co., Cambridge, Mass.

[3] Victory Engineering Corp., Springfield, N. J.

[4] Tektronix, Inc., Portland, Oreg.

[5] Colson Corp., Elyria, Ohio.

[6] Harvard Apparatus Co., Dover, Mass.

the densitometer. Stroke volume was calculated by dividing the cardiac output by the heart rate which was recorded during the dilution curves.

Left ventricular volumes were calculated by formulas adapted from those published by Holt (13). Two basic measurements are required. The first is the forward stroke volume, which was obtained from the dye dilution curves. The second is a series of indicator concentration ratios in the downslope of an aortic dilution curve produced by left ventricular injection of indicator. This was provided by the thermodilution curve. The formulas are:

$$EDV = \frac{FSV}{1 - \frac{T_{n+1}}{T_n}}, \qquad [1]$$

where EDV = end-diastolic ventricular volume, FSV = forward or effective stroke volume, and T_n and T_{n+1} = differences between base-line aortic blood temperature and that resulting at beats n and $n+1$ in the thermodilution curve. The average of 2 to 5 such ratios (T_4/T_3, T_5/T_4, T_6/T_5, and so forth) was used. The third beat after injection was the first one employed in curves with rapid downslopes, and the fourth was the initial one used in those with prolonged downslopes.

$$FSV/EDV(\%) = 1 - \frac{T_{n+1}}{T_n} \times 100 \qquad [2]$$

and

$$ESV = EDV - FSV, \qquad [3]$$

where ESV = end-systolic ventricular volume, and there is neither mitral nor aortic regurgitation. Expression 2 represents the fraction of the EDV that is ejected as the forward stroke volume. The formula for ESV can apply only when there is neither mitral nor aortic regurgitation. With aortic insufficiency, some of the indicator that left the ventricle with systole returns to it in the next diastole, and the curve appears as though the regurgitant indicator did not leave the chamber. Thus the calculated ESV also includes the regurgitant volume. However, the measurements of FSV/EDV and of EDV should remain valid. In the presence of mitral regurgitation it is not possible theoretically to measure ventricular EDV by this method. Indicator travels from the left ventricle to the left atrium with systole, and it is uncertain that it all returns to the ventricle in the following diastole. Thus volumes were not calculated in the four patients with mitral insufficiency who had thermodilution curves. Their results are stated as FSV/EDV, but the expression is interpreted empirically in this case.

The patients had a variety of cardiac diseases as shown in Table I. They were categorized on the basis of their clinical and catheterization findings. Five had apparently normal ventricular function at rest and are tabulated as the miscellaneous group. They had normal left atrial mean and left ventricular end-diastolic pressures and were free of any significant hemodynamic burden for the left ventricle. Four of these were studied several months after aortic commissurotomy or aortic valve replacement (two each), and three had small transvalvular systolic pressure gradients. The fifth patient in this group had an atrial septal defect. These five patients cannot be considered normal in a strict sense. The patients with mitral stenosis had no clinical or hemodynamic evidence of mitral regurgitation. Those listed with aortic stenosis had peak systolic pressure gradients between the left ventricle and the brachial artery of 24 to 120 mm Hg without evidence of severe aortic regurgitation. One patient in the aortic insufficiency group had a systolic transvalvular gradient of 30 mm Hg but had all other signs of gross regurgitation.

Patients came to the laboratory fasting and had received 100 mg of secobarbital or pentobarbital. From 1 to 7 thermodilution curves were obtained in each patient. The indocyanine green curve was recorded with or immediately before or after the thermal curves. The cooled saline and dye injections were usually accomplished within a 5-minute period.

Differences between various groups of patients were analyzed by the t test.

Results

The complete data are presented in Table I. The volume results are corrected for body size and expressed as milliliters per square meter body surface area.

Deleterious effects from the injections of cooled saline were not observed. Electrocardiographic changes were not seen, except for appearance of a premature contraction in some patients at the time of injection.

140 thermodilution curves were recorded in the 38 patients, and a steplike washout of indicator from the left ventricle was consistently recorded. Multiple curves were obtained in 36 patients, and the reproducibility of the test is shown graphically in Figure 1. For further analysis of reproducibility, the average ratio T_{n+1}/T_n for a single curve was compared with the average value for all of the curves in that patient. The difference was expressed as a percentage of this average, without regard to sign. The mean difference of T_{n+1}/T_n for a given curve from the average for that patient was $3.2 \pm 3.1\%$ (mean $\pm$ 1 SD). Duplicate curves from a patient are presented in Figure 2.

The consistency of the exponential downslope of the thermodilution curves was analyzed in detail in 84 curves from the first 23 patients studied. The ratio of each pair of downslope deflections (T_4/T_3, and so forth) was compared with the average of such ratios for that curve. The difference was

TABLE I

Results in all patients studied

Patient	Age	Heart rate	Cardiac index	Stroke index	EDV	ESV and aortic regurgitant vol	FSV/EDV	Pressures		
								Mean LA	LV†	BA
			L/min/m²	*ml/m²*	*ml/m²*	*ml/m²*	%		*mm Hg*	
Miscellaneous group										
1	45	76	2.28	30	100	70	30	6	136/7	122/74
2	18	72	3.00	41	124	83	33	7	112/7	104/68
3	12	102	4.58	45	83	38	54	6	160/10	164/60
4	32	64	2.96	46	100	54	46	2	140/5	122/72
5	33	103	2.44	24	89	65	27	5	100/4	102/72
Mean	28	83	3.05	37	99	62	38			
Pure or predominant aortic stenosis										
6	45	78	2.64	34	117	83	29	8	200/11	90/65
7	12	78	2.71	35	67	32	52	5	132/9	100/68
8	40	93	2.76	30	130	100	23	4	224/7	128/80 No
9	61	78	2.56	33	132	99	25	11	216/14	148/54 diastolic
10	49	68	2.35	35	97	62	36	12	172/16	116/72 murmur
11	62	78	2.84	36	136	100	26	3	180/3	116/72
12	27	70					41	8	160/11	80/54
13	57	80	2.71	34	179	145	19	10	162/18	104/64
14	17	68	3.53	58	152	94	38	9	124/10	90/52 Murmur
15	14	96	4.18	44	133	89	33	3	164/5	140/64 of
16	56	66	2.12	32	119	87	27	3	165/7	125/64 aortic
17	50	66	2.37	36	171	135	21	14	220/17	100/52 insufficiency
18	45	72	2.69	37	231	194	16	5	196/5	106/60
19	38	88	2.39	27	150	123	18	11	224/18	152/56
Mean	41	77	2.76	36	140	103	29			
Predominant aortic insufficiency										
20	46	94	1.92	20	143	123	14	4	104/8	120/32
21	31	72	2.10	29	322	293	9	9	148/14	118/56
22	42	63	2.07	33	114	81	29	8	108/8	117/62
23	53	63	3.04	48	267	219	18	12	136/18	144/48
24	20	78	2.76	35	350	315	10	7	116/15	144/44
25	43	74	1.89	26	144	118	18	4	130/7	164/56
26	18	84	4.42	53	183	130	29	4	120/6	128/72
Mean	36	75	2.60	35	218	183	18			
Mitral stenosis										
27	23	78	2.98	38	109	71	35	28	90/6	120/56
28	48	70	2.44	35	125	90	28	12	100/10	114/76
29	23	69	1.73	25	74	49	34	22	104/6	112/64
30	35	91	2.63	29	85	56	34	18	102/7	114/64
31	49	72	2.46	34	189	155	18	11	90/13	120/64
Mean	36	76	2.45	32	116	84	30			
Mitral insufficiency										
32	56	81	1.63	20			4	11	96/8	112/68
33	44	93	2.21	24			24	13	128/7	152/72
34	49	82	1.86	23			22	5	124/2	128/80
35	44	102	1.99	20			33	8	110/6	132/80
Mean	48	90	1.92	22			21			
Mixed valve disease										
36	51	63	2.12	34	106	72	32	17	182/11	112/54 AS, MS
37	49	93	2.13	23	177	154	13	22	160/7	96/62 AS, MS
38	44	86	2.45	29	126	103	23	19	120/7	102/60 MS, AS, AI
Mean	48	81	2.23	29	136	110	23			

* EDV = end-diastolic ventricular volume; ESV = end-systolic ventricular volume; FSV = forward or effective stroke volume; LA = left atrial; LV = left ventricular; BA = brachial artery; AS = aortic stenosis; MS = mitral stenosis; and AI = aortic insufficiency.

† The left ventricular diastolic pressure was measured at end-diastole (at the time of onset of ventricular contraction).

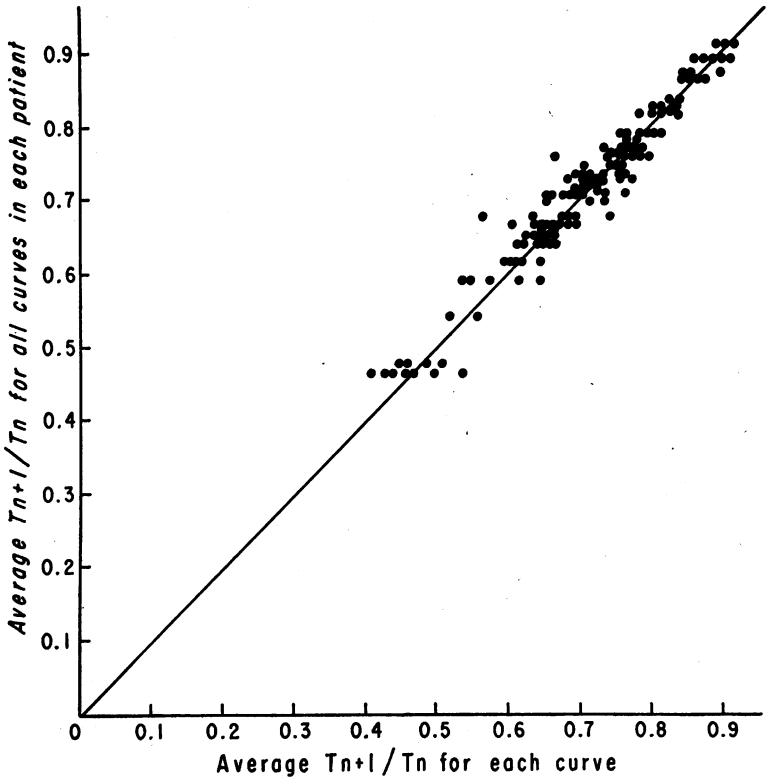

FIG. 1. REPRODUCIBILITY OF THE METHOD. The measurement obtained from the thermodilution curves was the ratio T_{n+1}/T_n, as explained in text. This ratio is plotted for each curve against the average for all curves in that patient. The variability is shown by the scatter on either side of the line of no difference.

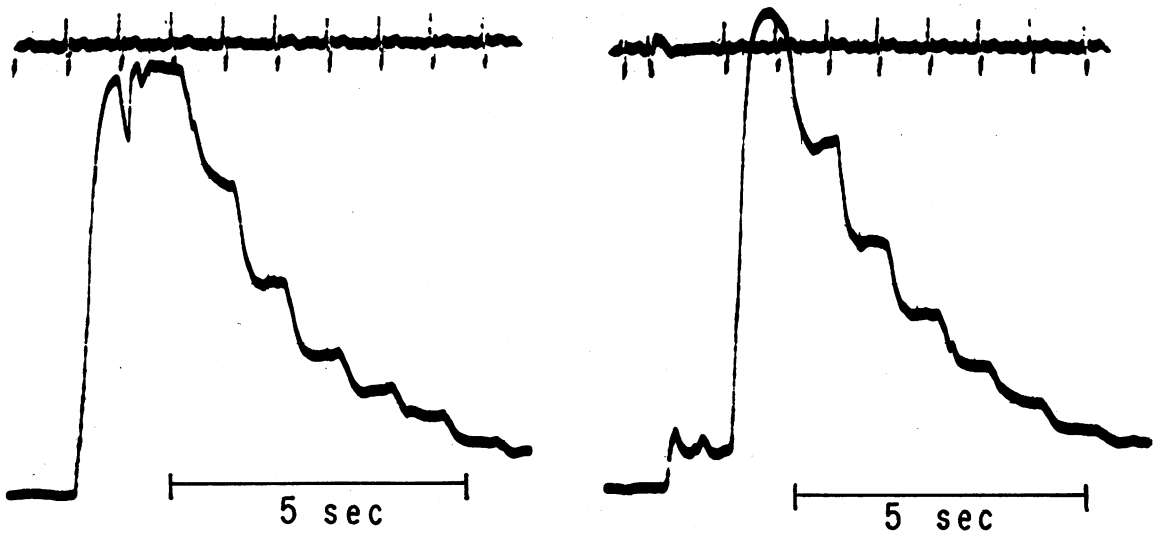

FIG. 2. DUPLICATE THERMODILUTION CURVES FROM PATIENT 16. A decrease in temperature is inscribed in an upward direction. T_{n+1}/T_n is 72% for the curve on the left and 71% for that on the right. The average of seven curves in this patient was 73% [forward stroke volume (FSV)/end-diastolic ventricular volume (EDV) = 27%]. In the example on the right, injection produced one premature contraction. The electrocardiogram is above.

compared to the average for the curve as a percentage, regardless of sign. In 300 such comparisons the mean difference was $3.8 \pm 3.4\%$. These findings are similar to those we obtained in a series of experiments in dogs (9).

The fraction of the EDV ejected as the FSV ranged from 27 to 54% in the five patients with "normal" ventricular function (miscellaneous group). An example is shown in Figure 3. Low ratios of FSV/EDV and the largest EDV's were found in the patients with predominant aortic insufficiency (Figure 4). The mean EDV for this group was 218 ml per m^2 BSA, and this value was significantly different from that of the miscellaneous group ($p < 0.01$). The value for the ESV and regurgitant volume combined was almost three times greater in the aortic insufficiency patients.

The findings in four of the five patients with mitral stenosis were similar to the miscellaneous category, and no difference between the groups for EDV was shown (Figure 5).

Patients with predominant aortic stenosis had a larger EDV than the miscellaneous group ($p < 0.01$). Seven of these 13 patients had a murmur of aortic insufficiency, although this lesion was not considered a prominent feature of their disease. These seven had a mean EDV of 162 ml per m^2 compared to 113 ml per m^2 for those with aortic stenosis and no regurgitant murmur ($p < 0.01$). When those with no aortic insufficiency were compared with the miscellaneous group, no difference was found. When the entire aortic stenosis group was compared to those patients with predominant aortic insufficiency, the latter had a larger EDV ($p < 0.05$).

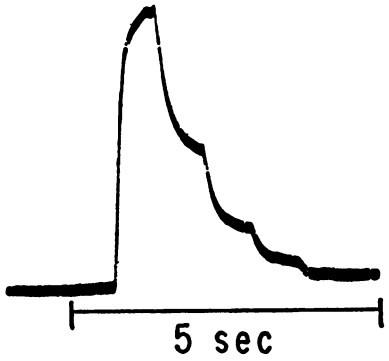

FIG. 3. THERMODILUTION CURVE FROM PATIENT 3, CLASSIFIED IN THE MISCELLANEOUS GROUP. T_{n+1}/T_n is 46% and FSV/EDV is 54%. The cold (indicator) is virtually cleared from the ventricle in four beats.

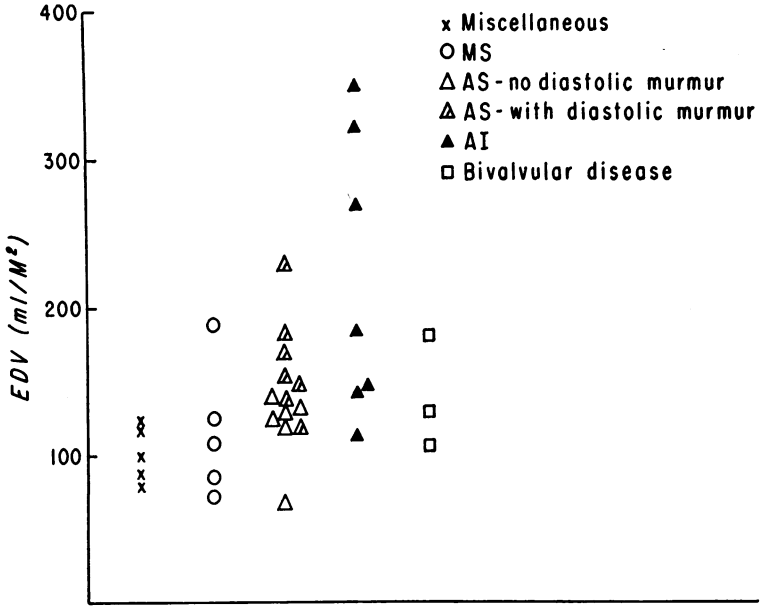

FIG. 4. LEFT VENTRICULAR EDV IN ALL PATIENTS IN WHOM IT WAS MEASURED. Abbreviations: MS = mitral stenosis; AS = aortic stenosis; AI = aortic insufficiency.

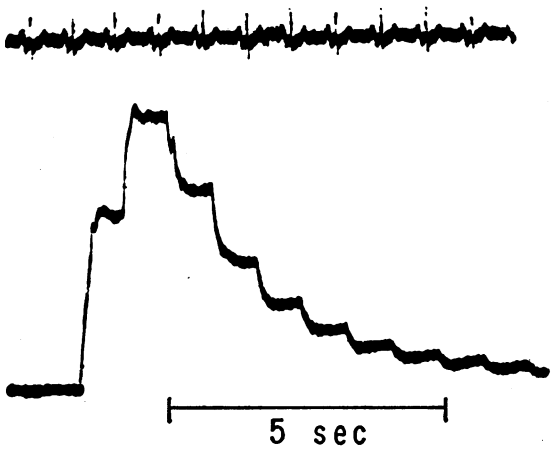

FIG. 5. THERMODILUTION CURVE FROM PATIENT 27, WHO HAD PURE MITRAL STENOSIS. Steplike temperature changes in the upslope of the curve resulted when injection was not confined to diastole. This did not influence temperature ratios in the downslope.

The thermal curves were employed empirically in the four patients with mitral insufficiency, and ventricular EDV was not calculated. Three of these four had atrial fibrillation with a fairly regular ventricular rate and were the only ones in the study who did not have sinus rhythm. Their values for FSV/EDV tended to be low.

There was a generally inverse relationship between the fraction of the EDV ejected as the FSV and the EDV itself, as shown in Figure 6. Thus when all the patients were compared, the FSV tended to fall or remain unchanged as the EDV increased.

Discussion

The measurements of left ventricular EDV correlated well with clinical observations in the patients studied. In general those with mitral stenosis or pure aortic stenosis had an EDV similar to the control group, and those with predominant aortic insufficiency had larger volumes, as expected. The miscellaneous group of five patients all had heart disease, which in four had been treated surgically with good results. It is possible, or even likely, that more complete systolic emptying of the ventricle and a smaller ESV occur in persons without heart disease. At present our data and those of Folse and Braunwald (14), using a somewhat similar approach, suggest that the normal EDV is below 150 ml per m^2.

An interesting finding in the patients with aortic stenosis was the difference between those with and those without an aortic insufficiency mur-

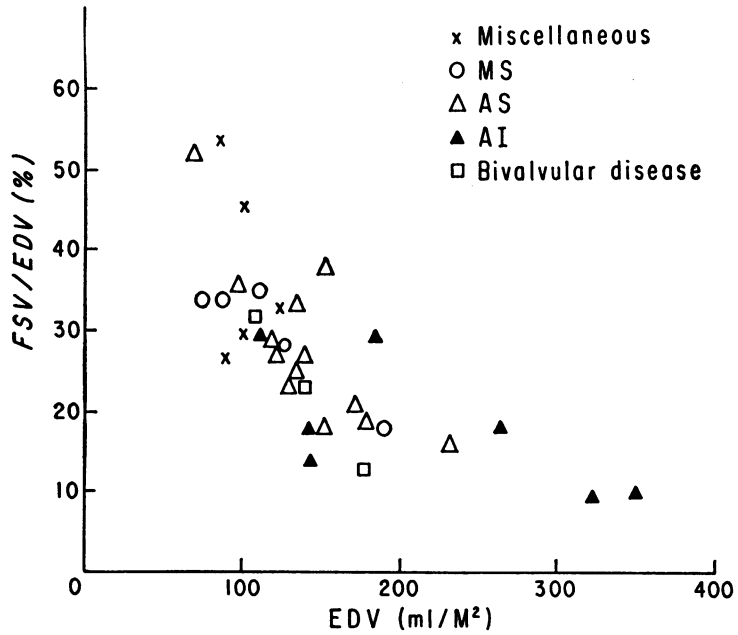

FIG. 6. FRACTION OF THE EDV EJECTED AS THE FSV IS PLOTTED WITH THE EDV ITSELF. With the larger EDV's FSV/EDV tended to be low. See text for discussion.

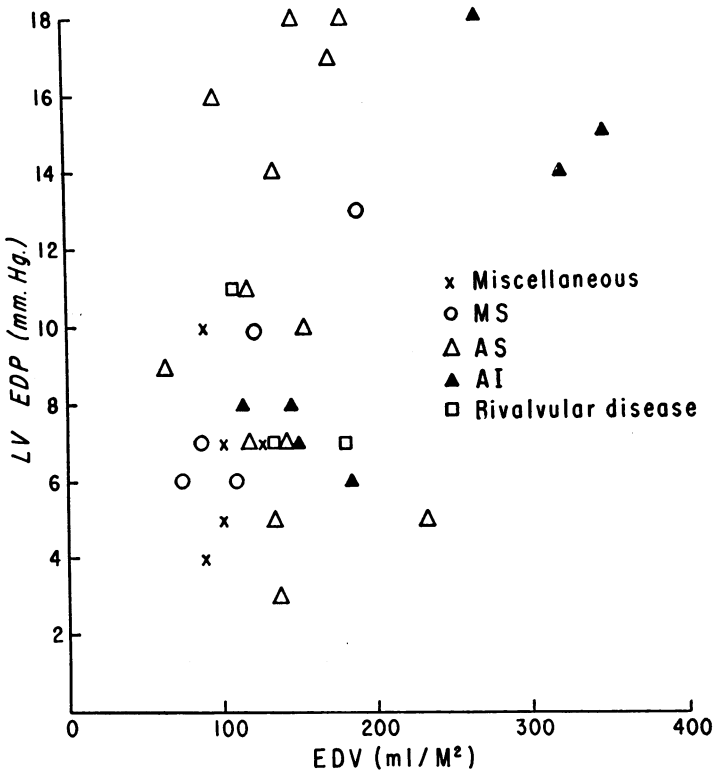

FIG. 7. LEFT VENTRICULAR END-DIASTOLIC PRESSURE PLOTTED AGAINST EDV. No correlation is discernible.

mur. In those with the murmur, the amount of regurgitation was judged to be minimal on the basis of clinical and hemodynamic evidence. Despite this, a larger EDV was found as well as a high value for the ESV and regurgitant volumes combined. Since the total left ventricular stroke volume in the presence of aortic regurgitation cannot be measured by our method, the degree of systolic ventricular emptying cannot be determined. However, a larger EDV in the presence of the regurgitant murmur strongly suggests that the regurgitant volume was greater than we would have predicted. Although ventricular failure due to aortic stenosis would be expected to produce the same findings, we do not believe it explains the difference in these patients.

We found no correlation between ventricular EDV and end-diastolic pressure, as shown in Figures 7 and 8. For example, in patients with aortic stenosis and equivalent EDV's, end-diastolic pressure ranged from 3 to 18 mm Hg. Normal end-diastolic pressure was found in a few patients with grossly increased EDV, and high end-diastolic pressure occurred in one patient with a normal EDV, associated with aortic stenosis. Presumably the muscular hypertrophy which occurs with aortic stenosis can decrease ventricular diastolic compliance. Because of the variability of the end-diastolic pressure when patients are compared, it seems unwise to diagnose ventricular failure on this basis alone. Work by Dodge, Hay, and Sandler is consistent with this conclusion (15), and a recent editorial has advised a reappraisal of the interpretation of ventricular end-diastolic pressure (16).

The generally inverse relation between FSV/EDV and EDV indicates the serious consequences of valvular heart disease for the left ventricle. To develop a given systolic pressure, a large EDV necessitates a large increase in the force of contraction by the ventricular muscle (17), simply to produce the same or even a smaller forward flow. The disadvantage for ventricular function can be enormous, and myocardial oxygen needs will be increased (18).

One of the patients with mitral stenosis de-

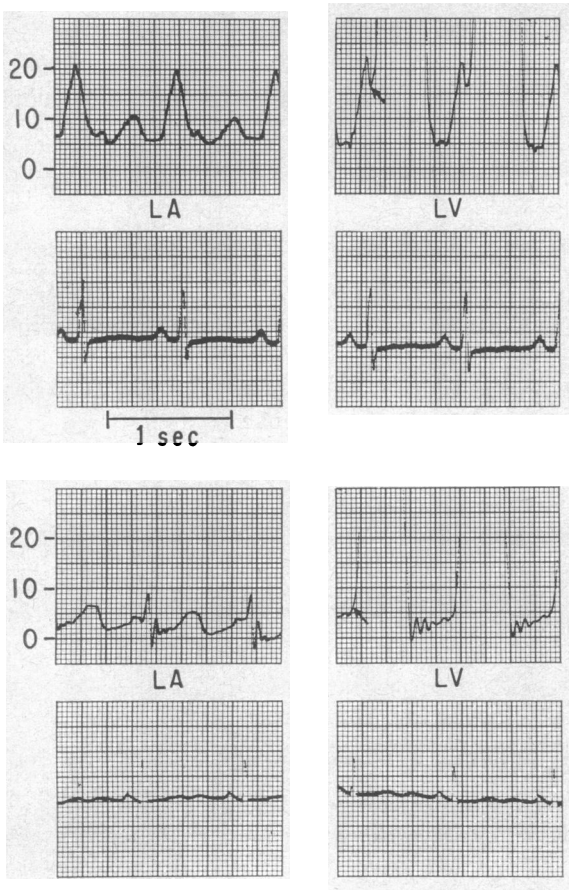

FIG. 8. ABOVE: LEFT ATRIAL AND VENTRICULAR PRESSURES IN PATIENT 13 WHO HAS AORTIC STENOSIS. End-diastolic pressure is elevated, as indicated by the arrow, and is associated with a tall left atrial "a" wave. BELOW: SIMILAR PRESSURES IN PATIENT 26 WHO HAS AORTIC INSUFFICIENCY. The pressures are normal. Despite the wide difference in end-diastolic pressures, both have almost identical EDV's (179 and 183 ml per m^2, respectively).

serves additional comment (Patient 31). This woman had a large EDV, slightly elevated left ventricular end-diastolic pressure, and a low FSV/EDV. Our other patients with mitral stenosis and those in the study by Folse and Braunwald (14) did not exhibit these findings. The possibility of primary left ventricular disease associated with mitral stenosis can be suggested to explain these abnormalities. Measurement of left ventricular volume in mitral stenosis should lead to a better understanding of ventricular function in this disease, an area which others have scrutinized (19).

The measurement of ventricular volume has presented theoretical and technical problems. Two different approaches have been by indicator dilution techniques and by angiocardiography. In both methods there are inherent assumptions concerning the geometry of the ventricle or the mixing of indicator in it. Although comparison of results in different patient groups studied by various methods has some obvious limitations, similarity or difference between results may contribute to a better understanding of the methods used. The study which is most comparable to the one herein reported was done by Folse and Braunwald (14). They injected radioactive iodine into the left ventricle and measured its clearance with a precordial counting technique. Our thermodilution results compare closely with their findings. Their normal group had ratios of FSV/EDV from 29 to 48%, compared with 27 to 54% in our miscellaneous group. The calculated EDV's also compared closely. In general, the findings with aortic valve disease were similar in the two studies. The similarity of the results and the reproducibility of both methods are encouraging.

Several investigators have reported left ventricular volume measurements in man obtained by angiocardiography (15, 20–22). In general, they found a smaller EDV and a greater FSV/EDV in the normal left ventricle than was observed in our miscellaneous group and the normal group of Folse and Braunwald's study. A higher FSV/EDV was found in several patients with heart disease by the angiographic approach than observed with the indicator dilution techniques. These comparisons suggest a systematic difference between the results obtained by these two methods.

Studies of mixing of indicators in the left ventricle have been done (23, 24), and the conclusion has been drawn that imperfect mixing occurs and can introduce errors in the calculations of ventricular volumes. Although this is true, there are considerations which suggest that serious errors do not often occur. The most important evidence is the consistency of the exponential washout of indicator from the ventricle, since incomplete mixing might be expected to produce a nonexponential series of aortic indicator concentrations. Randomly occurring errors of mixing might also make reproducibility difficult to demonstrate. Furthermore, as Holt has pointed out,

perfect ventricular mixing is not required for validity of the method (25). Rather, the series of decreasing aortic concentrations must equal a corresponding series of average ventricular end-diastolic concentrations, whether the indicator is well mixed or not. A misleading, reasonably pure exponential could occur, however, if blood entering the ventricle from the atrium during diastole gained a consistent (but insufficient) proportion of residual ventricular indicator and was preferentially ejected as the next stroke volume. In this situation, the degree of ventricular emptying could be underestimated. When empirical models of such situations are constructed mathematically, the errors in general do not change the order of magnitude of the results. The addition of aortic insufficiency to the system might be expected to improve ventricular mixing by turbulence in the chamber.

The method we employed was safe, reproducible, and easily performed during the course of transseptal left heart catheterization. The information obtained was useful in the clinical evaluation of the patients and in several cases helped to explain elevated left ventricular end-diastolic pressures that would otherwise have been attributed to ventricular failure despite the absence of any other signs. We believe that further application of the method in study of the circulation in man is warranted.

Summary

In 38 patients, left ventricular volume estimations were obtained from thermodilution curves recorded in the ascending aorta after left ventricular injection of cooled saline. The results were reproducible, and a discontinuous, steplike exponential function was consistently seen in the thermodilution curves.

Patients without significant abnormalities of left ventricular function were compared with groups with various valve lesions. These with "normal" ventricular function, with mitral stenosis, and those with pure aortic stenosis had similar end-diastolic ventricular volumes. Patients with aortic stenosis and the murmur of aortic insufficiency had larger volumes as did those with predominant aortic insufficiency.

There was no correlation between end-diastolic volume and ventricular end-diastolic pressure when patients were compared.

It is concluded that thermodilution offers a safe means of obtaining left ventricular volume estimations during left heart catheterization and that the information obtained is useful for clinical and investigative purposes.

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