Hemodynamic Effects of Quantitatively Varied Experimental Mitral Regurgitation

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Mitral regurgitation was produced in the open-chest dog by permitting blood to flow from left ventricle through a flow meter into the left atrium during systole. The hemodynamic effects of known amounts of regurgitation were studied. Two liters per minute of mitral regurgitant flow had relatively little effect on effective cardiac output, aortic pressure, left atrial pressure and on the left ventricular function curve.

The relative simplicity of characterizing stenotic valvular lesions of the heart has facilitated the analysis of this type of lesion. Valvular regurgitation, on the other hand, has presented a more challenging problem since the essential hemodynamic parameter, namely regurgitant flow, has been difficult to quantify. Attempts were directed towards devising experimental means whereby mitral and aortic regurgitant flow could be produced in a manner such as to permit not only their precise measurement and control but also an appreciation of their influence on circulatory dynamics. This communication deals with hemodynamic effects of mitral regurgitation.

Method

Sixteen mongrel dogs weighing 16.8 to 28.2 and averaging 23.7 Kg. were anesthetized with morphine, chloralose and urethane. A thoracotomy in the fifth left interspace was done under intermittent positive pressure breathing. Figure 1 is a schematic diagram of the preparation. Following pericardiotomy, the left ventricular apex was intubated with a polished lucite prosthesis (11 mm. internal diameter) in a manner described in detail elsewhere. After a waiting period of 10 min., 1 Gm. of mepesulfate was injected intravenously as anticoagulant and 250 mg. given each hour thereafter. The outer end of the prosthesis was then connected to a Potter turbine flow meter which, in turn, was connected to the cannulated left atrial appendage. A check valve in the line was oriented to permit a flow of blood (hereafter referred to as mitral regurgitant flow) from left ventricle to left atrium only during systole. This circuit permitted the continuous metering of left ventriculoatrial regurgitation, the amount of which could be regulated by graded constriction of the regurgitant path by a screw clamp. Effective cardiac output (systemic blood flow) was simultaneously metered with a second turbine flowmeter inserted into the aorta. Pressures in the left atrium, left ventricle and aorta were measured with strain gage transducers. Heart rate was continuously recorded and, in some experiments, controlled by atrial stimulation either with or without high cervical vagotomy. All values were continuously recorded on a multi-channel, direct-writing oscillograph at a paper speed of 1 mm./sec. Left atrial and left ventricular pressures were also intermittently recorded at a paper speed of 25 or 50 mm./sec. on a separate oscillograph.

When desired, the resistance to left ventricular forward outflow was increased by graded aortic constriction proximal to the systemic flowmeter. A reservoir containing blood was connected to the right femoral vein permitting infusion and bleeding, and thereby the adjustment of total aortic flow. Ventricular function curves, which show the relationship between filling pressure (either end-diastolic left ventricular and/or left atrial (Z point) pressure) and left ventricular stroke work, were obtained by stepwise infusion. When ascertaining the effects of mitral regurgitation on the left ventricular function curve, these data were obtained with the regurgitant pathway alternately opened and closed after each infusion.

Effective left ventricular minute work in gram meters was calculated as the product of mean aortic pressure in centimeters of water and effective cardiac output in liters per minute divided by 100. Peripheral resistance was calculated as the quotient of the mean aortic pressure in millimeters of mercury and effective cardiac output in liters per minute. Total cardiac output was the sum of effective cardiac output and mitral regurgitant flow.

Results

Hemodynamic Effects of Graded Mitral Regurgitation (fig. 2). Regurgitant flow was increased from zero to 4.24 L./min., a value...
more than double the effective cardiac output present before regurgitation was induced. Surprisingly modest changes in effective cardiac output, aortic pressure and left atrial mean and "Z" point pressures occurred. Calculated peripheral resistance rose only slightly. These data are representative of 23 similar experiments in 10 dogs.

Effect on Mitral Regurgitant Flow of Increased Resistance to Ventricular Ejection. With any given mitral regurgitant orifice, a stepwise increase in the resistance to left ventricular outflow produced approximately parallel changes in mitral regurgitant flow with a reciprocal fall of forward flow. The results of 1 such experiment are shown in figure 3 and are representative of 23 of the 26 such experiments performed in 11 dogs.

Influence of Mitral Regurgitation on the Effective Left Ventricular Function Curve. Results representative of the 9 such experiments in 6 dogs are shown in figure 4. Only a slight depression of the ventricular function curve was observed in the presence of substantial regurgitant flows (2.1 to 2.4 L./min.). In the single experiment in which a series of ventricular function curves was obtained with serially increased mitral regurgitant volumes, progressive depressions of the ventricular function curves occurred.
Relative Influence of Mitral Regurgitant Flow and Effective Cardiac Output on Ventricular Filling Pressure. These data suggested that the filling pressure required to provide any given increment of effective cardiac output exceeded that which was required for a similar increment of mitral regurgitant flow. The results of an experiment designed to examine this hypothesis more critically are illustrated in figure 5. By the appropriate adjustments of aortic resistance, mitral regurgitant orifice size and blood volume, it was possible to decrease forward and increase mitral regurgitant flows reciprocally so as to maintain mean left atrial, left atrial Z point and aortic pressures, and heart rate at a constant or almost constant level. Little change in filling pressure occurred while the increase in mitral regurgitant flow was 3.7 times as great as the decrease in effective cardiac output. Total flow doubled. These results are representative of the 7 such experiments in 5 dogs.

Influences which Modify the Effect of Mitral Regurgitation on Left Atrial Pressure. The effect on left atrial Z point pressure of progressively increasing mitral regurgitant flow was examined at 2 levels of effective cardiac output (650 and 1750 ml./min.) at comparable aortic pressures and heart rates (solid curves in figure 6). Before mitral regurgitation was induced, when effective cardiac output was maintained at a low level, left atrial Z point pressure was 3.5 cm. H$_2$O. Regurgitation of 4.74 L./min. raised left atrial Z point pressure by 4.5 cm. H$_2$O. In contrast, when effective cardiac output was maintained at a higher level and left atrial Z point pressure was 10 cm. H$_2$O before regurgitation was induced, 4.09 L./min. of regurgitation raised left atrial Z point pressure by 11.5 cm. H$_2$O. It was consistently observed in the 10 comparisons of
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Fig. 5. Effects of reciprocally varying forward and regurgitant flows at constant left atrial pressure; heart rate constant at 170/min. Dog weight, 25.9 Kg.

Fig. 6. Solid lines show the effect on left atrial Z point pressure of increasing regurgitant flow (M.R.F.) while holding forward cardiac output (S.F.) constant. Triangles, change in L.A. Z point pressures while increasing regurgitant flow when forward flow was constant at 0.65 L./min. Open circles, effect of increasing regurgitant flow when forward flow was held constant at 1.75 L./min. Broken lines, effect on L.A. Z point pressure of increasing total flow by increasing effective flow while regurgitant flow was held constant at 0 (solid dots) and at 2.6 L./min. (open triangles). Asterisk denotes value held constant during any given run. M.A.P., range of mean aortic pressure; H.R., range of heart rates.

This type performed in 9 dogs that the higher the ventricular filling pressure prior to regurgitation, the greater was the subsequent elevation of filling pressure produced by any given amount of regurgitation.

Fig. 7. Effects on L.A. mean and Z point pressures, forward flow, regurgitant flow, aortic pressure, stroke work and heart rate following the administration of 0.4 mg./Kg. of mephentermine sulfate. Dog weight, 25.9 Kg.

Figure 6 also confirms the data in figure 5 in that a given increase in total flow produced by increasing effective cardiac output (broken lines) required much greater elevations in filling pressure than did similar increases in total flow produced by increasing regurgitant flow (solid lines).

Effect on Left Atrial Pressures of Pharmacologically Elevating the Ventricular Function Curve in the Presence of Increasing Mitral Regurgitation. Figure 7 shows the results of 1 experiment in which, after mitral regurgitation had been produced, 0.4 mg./Kg. of mephentermine sulfate (Wyamine) was injected intravenously. The administration of this agent, which has been shown to elevate the ventricular function curve, was followed by a substantial fall in mean left atrial and Z point pressures even though mitral regurgitant flow increased and aortic pressure and effective stroke volume were also elevated.
DISCUSSION

The application to disease states in man of data derived from acute canine experiments which simulate such states is necessarily limited. This is largely because of possible species differences and the lack of the gradual development of the lesion together with whatever compensatory factors may come into play. Nevertheless, certain palpable advantages are obtained from the type of preparation described in which (a) the hemodynamic consequences of valvular regurgitation are effectively produced, (b) the regurgitant flow is directly metered, and (c) various hemodynamic parameters, including the volume of regurgitant flow, can be independently controlled. A more complete analysis of the hemodynamic effects of changing one of the variables can thus be obtained.

It was of considerable interest to observe the relatively small changes in forward cardiac output and aortic pressure when mitral regurgitation was induced. Further, these were accompanied by only small changes in mean left atrial and left ventricular filling pressures. Total cardiac output increased markedly and little depression of the effective ventricular function curve occurred at the levels of mitral regurgitation studied (fig. 4). If ventricular distensibility remained essentially unchanged, then these observations could be best explained by more complete systolic emptying when this degree of mitral regurgitation is present. These views are also supported by the data shown in figure 5 in which, with filling pressure held constant, the ventricle could eject substantially larger volumes through the regurgitant pathway than into the aorta. More complete systolic emptying is facilitated not only by the high pressure gradient between ventricle and atrium but also by the continuation of regurgitation during protodiastole and isometric relaxation as shown by Wiggers and Feil.4 It is clear, however, that the primary compensatory mechanism of more complete systolic emptying must gradually be exhausted when mitral regurgitant stroke volumes increase. Under such circumstances, an increase in end-diastolic ventricular volume must occur. This is suggested not only by the slight depression of the left ventricular function curve which is always observed when mitral regurgitant flow approximates resting effective cardiac output but also by progressive depression of ventricular function curves as mitral regurgitant volumes are further augmented.

It was not anticipated that the mitral regurgitant flows produced would be as high as those observed nor that they would be associated with such small elevations of left atrial pressure, since striking elevations of this pressure are observed when mitral valve injury is experimentally induced4,6 and also in the naturally occurring disease state in man. Further, if left ventricular hypertrophy is associated with mitral regurgitation, in the absence of other myocardial disease, it might be anticipated that the volume of regurgitation that the ventricle can endure would be greater than in the absence of such hypertrophy.

The observation that the effect of any given regurgitant volume on left atrial pressure is a function of the filling pressure prior to the induction of regurgitation may be helpful in the interpretation of hemodynamic findings in clinical mitral insufficiency. With the heart operating on any given left ventricular function curve,1 its specific position on that curve is of importance. As can be seen in figure 6, when regurgitant flows were induced with the preregurgitant filling pressure initially low, the consequent rise in left atrial pressure was substantially less than when the same range of regurgitant flows were induced with the ventricle higher on its ventricular function curve. Further, the particular ventricular function curve on which the heart is operating will also substantially influence the filling pressure at which the ventricle is doing its effective stroke work. That is to say, if the left ventricle is operating on a depressed function curve because of disease, the filling pressure and left atrial pressures will be higher at any given stroke work. Under such circumstances, the effect of any given mitral regurgitant volume will be to elevate left atrial pressure more than if the ventricular function curve were not depressed (fig. 7). An ancillary consideration is the rate of development of ventricular systolic pressure which is slower in hearts with a
depressed function curve. As suggested by Wiggers and Feil, a "hypodynamic" systolic contraction would tend to augment mitral regurgitation.

The increase of left atrial pressure which occurs with any given regurgitant stroke volume will also be a function of that point on the pressure-volume curve of the left atrium and pulmonary vascular bed obtaining at that time. If, as recently suggested, changes in pulmonary vascular distensibility do occur with mitral insufficiency, such changes will also modify the extent of the rise in left atrial pressure.

The observation of elevated left ventricular filling pressures in patients with pure mitral insufficiency when viewed in the light of the above data could be explained by the presence of (a) mitral regurgitant flows relative to cardiac output grossly in excess of those observed herein, (b) depressed ventricular function curves due to myocardial disease, or (c) changes in ventricular distensibility secondary to myocardial hypertrophy. In this connection it is of interest that Haynes et al., using the Korner-Shillingford method for the estimation of mitral regurgitant flow, observed regurgitant flows averaging 165 per cent of the effective cardiac output in patients with predominant mitral regurgitation in whom left ventricular end-diastolic pressures were not elevated.

Wiggers and Feil demonstrated striking elevations of the left atrial V wave when aortic pressure was increased in the presence of mitral regurgitation. The data shown confirm their interpretation that mitral regurgitation is augmented under these circumstances, as was also indicated by the model studies and the aortico-left atrial fistula preparation of Rodbard et al. Such augmentation of mitral regurgitant flow and the consequent striking elevation of the V wave when resistance to aortic ejection is increased has also been observed in patients with mitral regurgitation when aortic pressure was elevated by noradrenaline infusion. This response has proved helpful as a diagnostic test for the presence of even mild degrees of mitral regurgitation which were not otherwise hemodynamically apparent.

We have recently reported that the oxygen consumption of the heart is determined largely, if not solely, by the tension-time index (mean aortic systolic pressure times the duration of systole), and is independent of the stroke volume except insofar as the latter changes the duration of the tension developed by the myocardium. Planimetric integration of the systolic pressure curve provided the tension-time index in 3 of the experiments in which stepwise increases in mitral regurgitation were produced. No significant change in the tension-time index occurred. These data strongly suggest that the oxygen consumption of the left ventricle is not greatly increased by the volumes of mitral regurgitation studied and may help to explain the clinical observation that angina pectoris is relatively rare in patients with mitral insufficiency.

**SUMMARY**

Experimental technics were devised in the anesthetized, open-chest dog by means of which the regurgitation of blood from left ventricle to left atrium and from aorta to left ventricle could be metered and varied over wide ranges.

Mitrail regurgitant flows from 0 to 3 times resting cardiac output were tolerated with only slight alterations of effective cardiac output, aortic, left atrial and left ventricular pressures and total peripheral resistance. There was little depression of the effective left ventricular function curves with mitral regurgitant flows of approximately 2 L./min. Any given increase in mitral regurgitant flow required substantially smaller increments in ventricular filling pressure than did similar increases in effective cardiac output. These observations suggest that ventricular emptying is more complete in the presence of mitral insufficiency. Further observations revealed that, with any given mitral regurgitant orifice, regurgitant flow was a function of aortic pressure.

In other experiments, left atrial pressures were initially elevated by producing high effective left ventricular work levels, and these work levels were held constant during progressively increased mitral regurgitation. Under such circumstances, mitral regurgitation did produce substantial increments in mean left atrial and left ventricular filling pressures.
The extent of this rise, resulting from any given degree of mitral regurgitation, was a function of the mean left atrial and ventricular filling pressures prior to the induction of mitral regurgitation. These observations suggest the importance of the relationship between myocardial contractility and the hemodynamic effects of any given mitral regurgitant lesion.

REFERENCES