Effect of Blood and Saline Infusion on Ventricular End Diastolic Pressure, Stroke Work, Stroke Volume and Cardiac Output in the Open and Closed Chest Dog

By Thomas B. Ferguson, M.D., Oscar W. Shadle, M.D., and Donald E. Gregg, Ph.D., M.D.

Left and right ventricular end diastolic pressure, stroke work, stroke volume, and cardiac output were measured in open and closed chest dogs infused with blood and/or saline. The methods employed permitted repeated determinations of these factors during short time intervals. For nonfatigued hearts in the open chest preparation point to point correlation of end diastolic pressure with the other three variables was very good, but in closed chest animals a number of non-correlations occurred. Sufficient variation was seen to indicate that factors other than those measured in this study will have to be known before cardiac performance in the intact animal can be fully assessed.

The relationship between diastolic pressure in the atrioventricular cavity and the response of the ventricle during the following systole is not clear. Measurements by Patterson, Piper and Starling in the heart-lung preparation with constant heart rate and peripheral resistance revealed that with increasing venous return in nonfatigued hearts no constant correlation existed between diastolic pressure and the succeeding ventricular stroke volume; but in contrast Wiggers and Katz found in the open chest dog with saline infusion that changes in stroke volume were never dissociated from alterations in initial intraventricular pressure. In the intact dog and human, observations during infusion indicate both a correlation between cardiac output and mean right atrial pressure and a lack of correspondence of these parameters. The latter confusion could arise from the use of methods which give information only on mean atrial pressure and cardiac output measured over many minutes. Such measurements could well obscure the phasic response of the individual heart beat. The development of a photoelectric method for cardiac output by dye injection and the availability of a technic for measuring phasic pressure from a cardiac cavity make it possible to quantitate the response of the myocardium during a few cardiac cycles. Accordingly, investigations were made to determine the relationship of ventricular end diastolic pressure to stroke work, stroke volume, and cardiac output during intravenous infusion.

Methods

Experiments were set up in which infusions of whole blood and/or saline at varying rates and for varying periods of time were made intravenously into anesthetized closed or open chest dogs while cardiac outputs, phasic systemic and ventricular end diastolic pressures were recorded.

In the group of closed chest dogs several weeks before the experimental day, a left carotid loop was constructed to facilitate registration of arterial pressure and withdrawal of blood for the determination of cardiac output. At the same time, to aid in the measurement of left ventricular pressure through the intact chest wall, a segment of costal cartilage was removed and the apex of the heart sutured in the defect. On the day of the experiment, following premedication with morphine sulfate (3 mg. per kilogram), the dog was anesthetized intravenously with 0.25 cc. per kilogram of a 1:1 mixture of Dial-urethane and pentobarbital. Artificial respiration was maintained through an endotracheal tube.
catheter by means of a demand valve apparatus supplied by an oxygen tank. Prior to infusion, sinus arrhythmia was abolished and a regular rhythm maintained by a slow intravenous drip of 200 mg. proeaine amide in 50 cc. of saline. Needles attached to Gregg manometers were inserted into the left ventricular cavity and carotid loop and the respective pressure curves optically recorded. In all but one dog phasic intrapleural pressure was recorded with an optical segment capsule connected to a trocar in the left intrapleural space near the heart. Cardiac output was determined before and at intervals during and after infusion by the dye dilution technic using continuous photoelectric recording of the arterial dilution curve. Evans blue dye (5 to 10 mg. in 1 to 3 cc. volume) was injected very rapidly through a jugular catheter into the superior vena cava while blood was continuously withdrawn from the needle in the carotid artery. In early experiments a modification of the constant flow photometer of Friedlich, Heimbecker and Bing was used. Later a more stable densitometer with greater flexibility was employed, the details of which have been recorded elsewhere. After control determinations of pressure and cardiac output fresh heparinized dog blood and/or saline at approximately body temperature was infused into a leg vein. Infusion rates greater than 1 cc. per kilogram per minute were regarded as rapid, and rates less than this value as moderate.

In the group of open chest dogs after induction of anesthesia and artificial respiration as already described, the left chest was opened and intravenous heparin (10 mg. per kilogram) given, and one-half this amount repeated every 30 minutes. A cannula was tied into the midthoracic aorta and cardiac output measured by an optically recording rotameter connected to it. All branches of the aorta between the ostia of the coronary arteries and the rotameter cannula were ligated, and the right carotid artery was perfused from the output side of the rotameter. Since coronary inflow was not measured, the indicated rotameter flow was divided by 0.95 to give total cardiac output. Phasic pressure curves were obtained from a needle in the left ventricular cavity and a left carotid trocar whose tip was just inside the aorta. In several experiments pressure curves were also obtained simultaneously from the right ventricle with a Gauer manometer. Infusions were given in a similar manner to those in the closed chest dog.

Consideration of data was limited to those experiments in which pressure curves were obtained comparable to those shown in figure 1, and diastolic pressure values could be read from the record with an error of less than 0.5 mm. Hg, and flow and pressure calibration curves were linear. In all, 21 experiments were completed and of these 13 were considered adequate on the basis of the above criteria. Systemic blood pressure and heart rate were calculated from carotid pressure tracings taken immediately before and after each determination of cardiac output. Mean blood pressure was calculated as the diastolic pressure plus one-half the pulse pressure. Ventricular and diastolic pressure (point P, fig. 1) was averaged from 10 consecutive pulses during each output measurement. In most experiments this value was corrected for the simultaneously recorded intrapleural pressure fluctuations. Cardiac output was calculated in cubic centimeters per minute and stroke volume computed from it. Total peripheral resistance was computed as:

\[ \text{Mean BP in mm. Hg} \times 100 \]

\[ \frac{X}{100} \]

and expressed in large units (PRU). Since under the condition of heavy ventricular loading the ventricular end diastolic pressure can be as much as 40 per cent of the mean blood pressure, stroke work was calculated by the formula: Stroke work in Gm. meters/beat = stroke volume in cc. \( \times (\text{mean BP in mm. Hg} - \text{end diastolic pressure in mm. Hg}) \). Where necessary stroke, stroke volume and minute output were also expressed per square meter of body surface.
RESULTS

Prior to the infusion load the level of cardiac activity in the two groups of dogs was quite different (table 1). The closed chest animal was characterized by a higher mean blood pressure, minute cardiac index, stroke work index, stroke volume index, and left ventricular end diastolic pressure, but a reduced heart rate and total peripheral resistance.

Two types of response of these cardiac parameters to rapid blood infusion were observed in the open chest dog. These are illustrated in figures 2 and 3. In figure 2 as end diastolic pressure in both right and left ventricles is increased by infusion there is an accompanying rise in stroke work, stroke volume, and cardiac output. During this time heart rate decreases, mean blood pressure increases, peripheral resistance rises steeply and then falls somewhat. When infusion was stopped at 28 minutes, these changes reverse and all values approach preinfusion levels at 50 minutes. In figure 3 stroke work, stroke volume and minute output increase with right and left ventricular pressure through the fourteenth minute (vertical line). Thereafter, with further increase in pressure, the other three variables fall, with death of the animal occurring at the twentieth minute. During association of flow and work with pressure, heart rate is unaffected, peripheral resistance increases mildly and mean blood pressure greatly, but as dissociation occurs heart rate and blood pressure fall while peripheral resistance rises considerably.

Nine experiments with blood infusion were done in anesthetized closed chest animals. The results of six rapid blood infusion experiments are given in figure 4 and in table 2A. In figure 4 after an initial increase in diastolic pressure, stroke work and volume, all three values fall temporarily and then rise through the forty-third minute, while cardiac output rises progressively throughout. As infusion continues end diastolic pressure rises further in the presence of decreasing stroke work and minute output,
The data for three experiments with moderate rates of blood infusion are shown in table parameters. In the remaining two experiments no consistent pattern of response is discernible.

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* Minutes post-infusion.
† End diastolic pressure not corrected for intrapleural fluctuation.

2B. In the first experiment, with the exception of several equivocal correlations, there is a directional relationship between the four parameters. With rapid infusion of saline in the open and closed chest dog (table 2A experiment 6, 2C) the end diastolic pressure, stroke work, stroke...
volume and cardiac output rise continuously, as do mean blood pressure and heart rate, while total peripheral resistance declines. Later in the infusion in the open chest dog dissociation occurs, and end diastolic pressure continues to rise while the other parameters tend to return to their preinfusion value.

Right ventricular end diastolic pressure measured in two open chest and two closed chest dogs consistently followed left ventricular end diastolic pressure, although ordinate values were somewhat lower.

Thus, with rapid infusion into the open chest dog and before dissociation occurred, any change in end diastolic pressure was accompanied by similar directional changes in stroke work, stroke volume and minute output in 21 of 22 observations for each variable. In closed chest dogs given rapid infusions point-to-point directional correlation was found in 13 of 16 comparisons for stroke work and cardiac output and in 12 of 16 for stroke volume. In closed chest animals given moderate infusions directional correlation in response was observed in 5 of 10 comparisons for stroke volume and cardiac output, and in 7 of 10 for stroke work.

In figure 5 left ventricular end diastolic pressure and stroke work index are plotted as changes from preinfusion levels for all 13 experiments. The distribution of points suggests that the maximum response of stroke work occurs at an end diastolic pressure of about 20 mm. Hg above the preinfusion level. Similar plots of stroke volume index and cardiac index show the same general distribution, but with greater scatter of points.

Discussion

These results show gradation in the degree of directional correlation between end diastolic pressure and stroke work, stroke volume and cardiac output depending upon whether the chest was open or closed or whether the infusion rate was rapid or moderate. In the open chest dog with rapid blood or saline infusion the data are in accord with those of Wiggers and Katz, showing almost perfect correlation between end diastolic pressure and stroke vol-

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**Fig. 4.** Rapid infusion of blood and saline in an intact dog. Blood was infused for first 40 minutes and saline thereafter. (Description in text.)

**Fig. 5.** The effect of blood and saline infusion on ventricular end diastolic pressure and stroke work index. The values are plotted as changes from preinfusion levels. Circles, closed chest experiments; triangles, open chest experiments. Solid symbols are before, and open symbols after dissociation from overloading of heart.
ume, and in addition show the same correlation between end diastolic pressure, stroke work and minute output. Rapid infusion in the closed chest dog, however, resulted in a small number of noncorrelations, and these deviations became still more numerous with moderate infusion. Although with moderate infusion changes in measured variables were smaller than with rapid infusion, it is not believed that these noncorrelations are the result of variability in the methods.

With high rates of infusion initial association was sometimes followed by increasing divergence of stroke work, stroke volume, and minute output from end diastolic pressure. The mechanism responsible for such dissociation in heavily loaded hearts is not known. Apparently it is not related to a limitation of myocardial distensibility imposed by the pericardium, for in two open chest dogs, one with and another without a pericardium, the responses were identical. After dissociation, each animal showed a progressive decline in stroke work, stroke volume and output with increasing ventricular diastolic pressure.

These results are not pertinent to the question of the applicability of Starling's law to the heart of the intact animal. Starling stressed that the energy of cardiac contraction is a function of the diastolic length of the myocardial fibers. Subsequent observations by Lovatt-Evans and Matsuoka18 and Starling and Visscher19 indicate that in nonfatigued hearts the diastolic size is always correlated with the oxygen consumption and work of the heart. Since in the present study no measurements were made of oxygen usage, and since end diastolic ventricular volume cannot be accurately measured in intact animals, consideration of the mechanisms involved must be deferred.

SUMMARY AND CONCLUSIONS

The relationship of initial intraventricular pressure to stroke work, stroke volume and cardiac output was investigated by methods capable of measuring these responses during short time intervals.

The intravenous infusion of blood or saline into either the anesthetized closed or open chest dog elevates the end diastolic pressure in both the right and the left ventricle. Directional point-to-point correlation between end diastolic pressure, stroke work, stroke volume and cardiac output during infusion was present in 21 of 22 observations of each variable in the open chest dog. In closed chest dogs given rapid infusions (greater than 1 cc. per kilogram per minute), correlation of end diastolic pressure with stroke work and cardiac output was found in 13 of 16 comparisons, and in 12 of 16 comparisons with stroke volume. In closed chest animals given moderate infusions (less than 1.0 cc. per kilogram per minute), end diastolic pressure correlated with stroke volume and cardiac output in 5 of 10 comparisons, with stroke work in 7 of 10 comparisons. There was no consistent response in heart rate or total peripheral resistance.

With extreme loading of the heart, dissociation of stroke work, stroke volume and cardiac output from end diastolic pressure occurred. The end diastolic pressure continued to rise while the other three parameters fell.

The variability of the results in the closed chest dog emphasizes the need for knowledge of factors other than those measured in this study before cardiac performance in the intact animal can be fully assessed.

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