Effect of Mean Circulatory Filling Pressure and Other Peripheral Circulatory Factors on Cardiac Output

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If one studies curves which depict the relationship of cardiac output to mean right atrial pressure (one of the forms of Starling's curves), it is obvious that, within the normal range of function of the heart, cardiac output can change tremendously while the right atrial pressure changes only slightly. This fact led to the early belief that it is not the function of the heart itself which controls cardiac output but instead that cardiac output is controlled by the various factors in the peripheral circulatory system which regulate the return of blood to the heart.

Though it is not entirely true that cardiac output is independent of the function of the heart (1), nevertheless, it is hoped to emphasize in the present paper the special importance of the peripheral circulatory factors which affect venous return. In order to do this, a mathematical circuit analysis of the closed circuit circulatory system has been made. This circuit analysis has been specifically simplified so that the factors derived would be amenable to experimental test. Two of the factors which have proved to be of importance, as shown both by this circuit analysis and by experimental data, are a) 'capacitance' and b) 'mean circulatory filling pressure.' As used in these studies the term capacitance means dV/dP or, in other words, the change in volume of a particular part of the circulatory system with each unit change in pressure. This term has been used in the present paper because there is at present no term in common usage in hydrodynamics which means dV/dP. This is different from the term 'distensibility' which is commonly used to mean dV/dP/V. The term mean circulatory filling pressure (MCFP) has been defined previously (2), and it means the pressure determined as follows: If one should dissect the circulatory system into infinitesimal parts and then determine the mean of the pressures in all of these parts, weighting each pressure directly in proportion to the capacitance of the respective segment, then the pressure so determined would be the mean circulatory filling pressure. Mathematically this pressure should be equal to the pressure which would be measured if the heart should suddenly stop pumping blood and all the pressures in the entire circulatory system should be brought to equilibrium instantaneously. The mean circulatory filling pressure of the peripheral circulatory system has been considered in the present study to be approximately equal to the mean circulatory filling pressure of the entire circulatory system, which, as discussed previously (2), is reasonable.

METHODS

Forty-seven dogs anesthetized with sodium pentobarbital and heparinized with 3 mg/kg of heparin were used in the present experiments. Arterial and right atrial pressures were measured by mercury and water manometers through catheters inserted into the arterial and venous systems, respectively. In 15 of the experiments the dogs' hearts were stopped by asphyxiation, a special cannula was fixed by a purse string suture in the wall of the right atrium, blood was pumped through an external circuit by a variable propulsion pump, blood flow was measured by a stromuhr type flowmeter, and the blood was eventually returned through a cannula directly into the proximal aorta. Experiments in these animals were not performed until all signs of vasomotor activity were gone. In these experiments the mean circulatory filling pressure was varied by increasing or decreasing the blood in the circulatory system, and the right atrial pressure was varied by changing the propulsive force of the external pump or by changing the degree of resistance in the external system.

Experiments similar to those performed above on dead animals were performed on 21 live dogs while blood was pumped from cannulae in the superior and inferior vena cavae through an external circuit and then back into the right atrium through the cardiac end of the superior vena cava.
In nine live, intact dogs the relationship of mean circulatory filling pressure and right atrial pressure to venous return and cardiac output were studied by giving to the dogs massive transfusions and studying the changes in mean circulatory filling pressure, right atrial pressure, and cardiac output during the course of the experiments. In these experiments the mean circulatory filling pressure was determined by electrically fibrillating the heart, pumping blood rapidly from a catheter in the aorta into a catheter in the venous system, and considering the mean circulatory filling pressure to be the pressure at which arterial and venous pressures come to equilibrium, which procedure has been described previously (2). Following measurement of the mean circulatory filling pressure, the hearts were defibrillated by intense electric shock through the chest wall by a method also described previously (3). Cardiac outputs in these animals were determined by the direct Fick method. Six of the dogs were rendered ‘areflex’ by total spinal anesthesia and simultaneous continuous epinephrine infusion, which has been discussed previously (2).

RESULTS

Mathematical Circuit Analysis of the Major Circulatory Factors Which Control Venous Return to the Heart. In order to be completely accurate in any mathematical analysis of the circulatory system, it would be necessary to consider in the analysis all the discrete, infinitesimal parts of the circulatory system. Such a mathematical analysis would not be amenable to experimental test of its validity because measurements cannot be made in each infinitesimal part of the circulatory system. Therefore, a simplified analysis has been made based on the schema of figure 1 which illustrates the major portions of the circulatory system. In this schema $C_3$ is the capacitance of the arterial tree, $P_3$ is the mean arterial pressure, and $R_3$ is the arterial and arteriolar resistance. $C_2$ and $P_2$ are the capacitance and mean pressure respectively of the capillary and venular storage pool of blood, and $R_2$ is the resistance from this venular storage pool to the major veins. $C_1$ and $P_1$ are the capacitance and mean pressure, respectively, of the major veins, and $R_1$ is the resistance to blood flow from the veins to the right atrium. $RAP$ is right atrial pressure.

The essential steps for this mathematical analysis are given in the appendix to this paper, and the formula for venous return (VR) as derived from this circuit analysis is:

$$VR = \frac{MCFP - RAP}{R_1 C_1 + (R_1 + R_2) C_2 + \cdots + (R_1 + R_2 + \cdots + R_n) C_n}$$

in which $C$ is capacitance of the entire peripheral circulatory system. When the circulatory system is divided into $n$ portions instead of 3 portions as in the schema of figure 1, the formula becomes:

$$VR = \frac{MCFP - RAP}{R_1 C_1 + (R_1 + R_2) C_2 + \cdots + (R_1 + R_2 + \cdots + R_n) C_n}$$

As the value of $n$ in formula 2 approaches infinity, this formula approaches absolute validity for a system of distensible tubes.

It will be noted that the numerator of both of these formulae is a difference between two pressures. This may be called the 'pressure gradient for venous return.' On the other hand, the denominator in each instance is dependent upon the resistance and capacitance values of the different portions of the peripheral circulatory system. This denominator may be considered to be the 'impedance to venous return,' and a general formula may be expressed as follows:

$$VR = \frac{\text{pressure gradient for venous return}}{\text{impedance to venous return}}$$

Effect of mean circulatory filling pressure on the ‘impedance to venous return.’ Because the vessels of the circulatory system are elastic,
increasing the pressure within their lumina increases the diameter of these vessels. Therefore, it is obvious that the resistances in the denominators of equations 1 and 2 should decrease at least to some extent as the mean circulatory filling pressure increases. Therefore, it would be expected that increasing the mean circulatory filling pressure, in addition to its increasing the pressure gradient for venous return, should also decrease the impedance to venous return.

Experimental Test of the Formula for Venous Return. Relationship of mean circulatory filling pressure to venous return. Figure 2 illustrates a typical experiment performed in 12 dogs without any remaining vasomotor reactivity and with a variable pump used in place of the heart as described under METHODS. By varying the degree of pumping, a constant right atrial pressure was maintained while each of the curves depicted in figure 2 were determined. On the other hand, the mean circulatory filling pressure was varied by increasing or decreasing the quantity of blood in the circulatory system.

It is obvious from the curves in figure 2 that when other factors are maintained under constantly controlled conditions, the venous return increases approximately in proportion to the increase in mean circulatory filling pressure. However, there is a slight inflection in the curve which indicates, as predicted in the above paragraph, that the impedance to venous return decreases as the mean circulatory filling pressure increases, thereby allowing greater venous return at high mean circulatory filling pressures than would occur if the vessels were rigid. However, it is obvious from the curves of figure 2 that the effect of the mean circulatory filling pressure on the impedance to venous return is not excessively great.

Relationship of right atrial pressure to venous return. Observing figure 2 once again, it is immediately evident that the right atrial pressure also affects venous return greatly so that for any given mean circulatory filling pressure, the greater the right atrial pressure, the less is the venous return. In other words, as predicted from the formula, right atrial pressure acts as a reverse force, approximately in proportion to the right atrial pressure, to retard venous return.

As illustrated in figure 2, when the right atrial pressure falls to less than zero, decreasing this pressure below atmospheric pressure does not further increase venous return. This has been shown to be true by other experimental methods (4, 5), and this occurrence is obviously due to the collapsibility of the veins entering the thorax which causes the pressure in the emptying veins to remain approximately zero with respect to atmospheric pressure regardless of how negative the right atrial pressure falls.

Mean circulatory filling pressure as a limit to right atrial pressure. It would be predicted from the formula for venous return that, as venous return and cardiac output decrease to zero, right atrial pressure should rise to equal the mean circulatory filling pressure. Furthermore, at no time would it be possible for the right atrial pressure to rise to a value greater than the mean circulatory filling pressure. Figure 2 illustrates this principle—that mean circulatory filling pressure is the upper limit to the right atrial pressure—for in each curve, when the venous return becomes zero, the mean circulatory filling pressure is equal to right atrial pressure. Furthermore, at no time in any of the present experiments or other similar ones has it ever been possible to increase the right atrial pressure above the mean circulatory filling pressure.

Effect of peripheral resistance on venous return. Though the impedance to venous return, as expressed by the denominator in the formulae, is the most difficult factor to test experimentally, a few general principles...
have been observed. If one observes the denominator of formula 1, it becomes obvious that the resistances in the venous circuit (R₁ and R₂) are highly important in determining the over-all impedance to venous return, whereas the resistance in the arterioles and arteries (R₃) is relatively unimportant in the determination of the over-all impedance to venous return. These principles have been tested by, first, compressing the large veins and, second, increasing the resistance in the small arteries by injection of large quantities of 250 micron glass beads. It has been found in three dogs whose hearts had been replaced by a perfusion pump that increasing the total peripheral resistance 70% by injection of beads decreased the cardiac output only an average of 12%, whereas increasing the total peripheral resistance in three dogs 70% by pressure on the major veins decreased the cardiac output an average of 75%. This agrees with the prediction from the formula that changes in venous resistance should affect venous return considerably more than should changes in arterial resistance.

Finally, in three dogs increasing the viscosity of the blood by diluting it increased the venous return approximately in proportion to the calculated decrease in viscosity.

Test of the relationship of 'pressure gradient for venous return' to cardiac output in intact dogs. Figure 3 illustrates a typical experiment in an intact dog in which a massive transfusion of blood was administered and the cardiac output, the mean circulatory filling pressure, the right atrial pressure, and the arterial pressure were determined intermittently after the transfusion. Eleven similar experiments were performed. It will be noted from this experiment that massive infusion caused a simultaneous increase in right atrial pressure, mean circulatory filling pressure, cardiac output, and arterial pressure. Also, there occurred a similar increase in the pressure gradient for venous return (MCFP-RAP).

Figure 4 illustrates the relationship of the pressure gradient for venous return (MCFP-RAP) to cardiac output, but in most of the curves there is a slight curvature similar to that in figure 2 as would be predicted from the fact that increasing the mean circulatory filling pressure is certain to increase the dimensions of the peripheral vessels and thereby progressively decrease the resistances of the different vessels.

Effect of arterial pressure on venous return. In the different individual experiments the arterial pressure varied as much as 250% at times while the venous return remained constant. This occurred especially in experiments in which the resistance of the small arteries was greatly increased by occluding these with 250 micron beads. This is the effect predicted, for arterial pressure is proportional to venous return times the total peripheral resistance, whereas it is evident from formula 1 that the most important resistances in the circulatory system for governing venous return are not those in the arteries but are those in the venous circuit (R₁ and R₂), which resistances represent only a small fraction of the total peripheral resistance. Consequently, it is not expected that there should be a direct correlation between arterial pressure and venous return except when the resistances and capacitances in the different parts of the circulatory system remain constant.

DISCUSSION

The fit of the predictions from the mathematical circuit analysis with experimental results has been highly encouraging that the analysis itself is reasonable. Obviously, there are many factors which have been neglected in the present analysis for the sake of simplicity. These include especially the mean circulatory filling pressure of the pulmonary
circulatory system, the capacitance of the pulmonary circulatory system, and the capacitance of the heart. However, these factors apparently are not especially important except under special conditions such as inordinate shift of blood from the lungs into the peripheral circulatory system, etc.

The effects of mean circulatory filling pressure and right atrial pressure on venous return seem to be very clear-cut, for all experiments have indicated that increasing the mean circulatory filling pressure increases the rate of venous return and that increasing the right atrial pressure decreases the rate of venous return. Furthermore, experiments both in animals with the heart replaced by a pump and in intact animals have indicated that the rate of venous return is approximately proportional to the mean circulatory filling pressure minus the right atrial pressure which difference is called the 'pressure gradient for venous return.'

Many other experiments which correlate highly with the experiments of the present study have been performed in this laboratory and elsewhere. First, it has been shown that massive transfusion causes the mean circulatory filling pressure, the venous pressure, and the pressure gradient for venous return to rise immediately and then to return toward an asymptotic lower value during the ensuing 20–30 minutes (2, 6, 7). Also, it has been shown that the cardiac output following massive transfusion increases immediately and then falls toward an asymptotic level along approximately the same exponential curve (8). This indicates once again the relationship between mean circulatory filling pressure, right atrial pressure, and venous return. These same relationships occur in patients following either transfusion or hemorrhage. Hemorrhage decreases the mean circulatory filling pressure, and it is well known that when hemorrhage proceeds to the point that compensation by vasomotor constriction can no longer occur the cardiac output decreases as the degree of hemorrhage increases. On the other hand, rapid transfusion causes an immediate increase in cardiac output (9).

A very important prediction of the derived circuit analysis is the effect of blood viscosity on cardiac output, for, other factors remaining constant, the venous return and cardiac output should be inversely proportional to the peripheral resistance and consequently inversely proportional to blood viscosity. It is quite interesting that in clinical patients with severe anemia, in whom the viscosity of the blood may be decreased by a factor of some two to three times, the cardiac output is increased roughly in proportion to the decrease in viscosity (10). Obviously, other factors, such as vasomotor reflexes caused by the anemia, enter into this effect, but it would appear from the present experiments that viscosity plays a very important direct role in the control of cardiac output.

The present experiments may also be of value in explaining the changes in cardiac output which occur in myocardial failure. When the myocardium fails acutely and the right atrial pressure begins to rise, ordinarily there occurs a simultaneous decrease in venous return (11, 12), which would be predicted from the rising right atrial pressure. In general, the cardiac output increases during the ensuing few days following the initial failure of the myocardium. This is associated with retention of fluid (13) which, theoretically, should increase the mean circulatory filling pressure. Thus, it appears that initial myocardial failure, theoretically, should, and actually does, decrease the cardiac output, whereas the subsequent retention of fluid, theoretically, should increase the mean circulatory filling pressure and should return the cardiac output back toward normal; this is a usual finding. However, this does not mean to imply that excessive retention of fluid might not, when the heart becomes overloaded, decrease the cardiac output.

Fig. 4. Relationship of the pressure gradient for venous return to cardiac output in 7 intact dogs.
SUMMARY

The factors which were found by mathematical circuit analysis to be important in the control of venous return have been tested experimentally in dogs. The following important factors have been noted: a) when other factors remain constant, the venous return is approximately proportional to the mean circulatory filling pressure minus the right atrial pressure, which pressure difference is called the 'pressure gradient for venous return.' b) The increase in venous return due to an increase in mean circulatory filling pressure is not absolutely proportional to this pressure gradient, however, because the mean circulatory filling pressure not only is a force tending to push blood toward the right atrium, but, also, it apparently increases the diameters of the blood vessels, decreasing the 'impedance to venous return.' Consequently, as mean circulatory filling pressure increases, the cardiac output increases more than would be predicted should the peripheral resistances remain constant. c) The upper limit to right atrial pressure is the mean circulatory filling pressure. d) Changing the resistance to blood flow in different regions of the peripheral circulatory system causes less and less effect on venous return at progressively farther and farther distances along the peripheral circulatory system from the right atrium. This means that changes in venular and venous resistances affect venous return greatly while changes in arteriolar and arterial resistance have considerably less effect on venous return. e) When other factors remain constant, venous return is approximately inversely proportional to the viscosity of the blood. f) Venous return is proportional to arterial pressure only when all peripheral resistances and capacitances remain constant.

APPENDIX

Derivation of Formula for Venous Return. When blood is flowing through the peripheral circuit of figure 1, the following relationships hold for the pressures in the three different chambers:

\[ P_1 = VR(R_1) + RAP \]  
\[ P_2 = VR(R_1 + R_2) + RAP \]  
\[ P_3 = VR(R_1 + R_2 + R_3) + RAP \]

Because the quantity of blood in a chamber \( Q \) is equal to the pressure in the chamber times the capacitance, \( dV/dP \), the following formulae hold for the quantities of blood in each of the three respective storage chambers of figure 1:

\[ Q_1 = [VR(R_1) + RAP]C_1 \]  
\[ Q_2 = [VR(R_1 + R_2) + RAP]C_2 \]  
\[ Q_3 = [VR(R_1 + R_2 + R_3) + RAP]C_3 \]

The formula for the filling pressure (MCFP) of the entire peripheral circulatory system of the schema in figure 1 is:

\[ MCFP = Q_1 + Q_2 + Q_3 \]

Substituting the values for \( Q_1 \), \( Q_2 \), and \( Q_3 \) into formula 6 and solving for venous return (VR), formula 1 as presented in the text of this paper is derived.

REFERENCES