Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves[1]

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THE CONCEPT that the heart responds with increasing cardiac output when there occurs increasing venous return was popularized by Starling and, indeed, has come to be known as Starling's law. There are many different forms in which Starling's law can be expressed, including the relationship of cardiac output to right atrial pressure, the relationship of cardiac output to the degree of distention of the right ventricle at the end of diastole, the relationship of cardiac work to right atrial pressure or right ventricular distention, the relationship of left ventricular work to right atrial pressure or right ventricular distention, etc. For the determination of cardiac output, the form of Starling's law which will be used in the present discussion is the relationship of cardiac output to mean right atrial pressure, and this type of cruve will be called the "cardiac response curve" to right atrial pressure.

It is well known that many factors in the peripheral circulatory system combine together to determine the rate of venous return to the heart. These include the quantity of blood available, the degree of vascular resistance in various parts of the peripheral circulatory system, and the back pressure from the right atrium. It is with these factors that this paper is especially concerned, and it is hoped that this presentation will demonstrate how cardiac output is determined by equating the peripheral circulatory factors with the cardiac response curves.

Cardiac Response Curves Under Different Conditions

It is very difficult to determine cardiac response curves in the intact animal, for changing the right atrial pressure or cardiac output from normal results almost immediately in tremendous compensatory activity tending to correct these abnormal conditions. Nevertheless, by the technique of administering massive transfusions very rapidly and making measurements before complete readjustments can occur, approximate cardiac response curves have been obtained in this laboratory as illustrated in figure 1 (1). The central curve of figure 1 is approximately the response curve of the heart of an average-size dog whose vasomotor reflexes have been completely abrogated by administration of total spinal anesthesia, normal blood pressure being maintained by continuous infusion of small quantities of epinephrine. The first curve of figure 1 is approximately the response curve of a dog during generalized sympathetic stimulation or during continuous infusion of epinephrine. Finally, the lower response curve of figure 1 is approximately that which occurs in a dog with a moderately damaged myocardium.

The various factors which affect the cardiac response curve have been adequately reviewed many times throughout the past fifty years, and especially has

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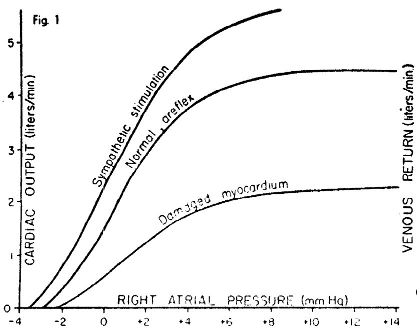
Sarnoff emphasized in the present symposium the variability of different types of Starling's curves under various conditions. Suffice it to say that the following and many other factors can change the cardiac response curve from beat to beat and from time to time: *1*) the phase of respiration at onset of cardiac contraction; *2*) the interval of time elapsing between two successive heart beats; *3*) the degree of sympathetic stimulation; *4*) the effect of many drugs on the heart, such as digitalis, epinephrine, cholinergic drugs etc.; *5*) myocardial damage; *6*) cardiac fatigue; *7*) the degree of oxygenation of the blood, etc. However, when the heart is operating under conditions of light respiration, constant degree of sympathetic stimulation, and with a constant source of nutrition, the cardiac response curve remains relatively constant from beat to beat.

Venous Return Curves

The factors affecting venous return are even more elusive and more difficult to study than are the factors which determine the cardiac response curve. However, figure 2 illustrates venous return curves obtained under relatively well-controlled conditions—namely, in a recently dead dog with a pump replacing the heart. It will be observed from these curves that there are two major pressure factors which determine the quantity of blood which returns to the heart from the peripheral circulatory system. These are the *right atrial pressure* and the *mean circulatory filling pressure.* It is quite obvious that the greater the right atrial pressure, the greater is the back pressure in the veins preventing the return of blood to the heart. On the other hand, the principle of mean circulatory filling pressure is not yet well established in physiological circles, and this needs additional explanation. The term, mean circulatory filling pressure, means the mean integrated filling pressure throughout the circulatory system when one appropriately weights the volumes and degrees of elasticity of the different portions of the circulatory system. This mean circulatory filling pressure in the normal dog averages 6.3 mm. Hg (2, 3) and can be measured by momentarily stopping the pumping of blood by the heart and allowing the pressures throughout the circulatory system to come to equilibrium. The pressure measured when all blood flow has stopped has also been called 'static blood pressure' for obvious reasons. With this concept of mean circulatory filling pressure in mind



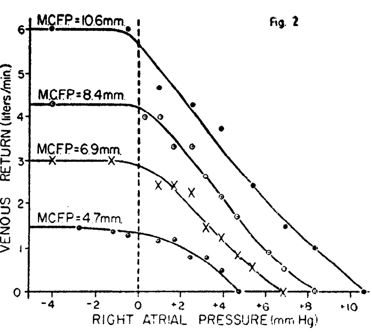


FIG. 1. Cardiac response curves to right atrial pressure with the heart under different conditions.

FIG. 2. Venous return curves illustrating the effect of right atrial pressure on venous return when the mean circulatory filling pressure is maintained at different levels.

the effect of the various factors on the venous return curve can be explained as follows:

Effect of Right Atrial Pressure on Venous Return. The curves of figure 2 were obtained by varying the right atrial pressure and the mean circulatory filling pressure. In place of the heart a perfusion pump was connected from the right atrium to the aorta, and the level of right atrial pressure was varied by increasing or decreasing the minute capacity of the pump. On the other hand, the mean circulatory filling pressure was varied by increasing or decreasing the total quantity of blood in the circulatory system. It will be noted that for each of the four curves of figure 2 the mean circulatory filling pressure was maintained at constant levels of 10.6, 8.4, 6.9 and 4.7 mm. Hg, respectively.

Observing the uppermost curve of figure 2, it is immediately obvious that when the right atrial pressure rose to a value of 10.6 mm. Hg, which was equal to the mean circulatory filling pressure, the cardiac output was zero. In other words, as the right atrial pressure approaches the mean circulatory filling pressure the cardiac output approaches zero. Consequently, *the mean circulatory filling pressure constitutes the upper limit to which the right atrial pressure can rise.*

Observing once more the upper curve of figure 2, it will be noted that, as the right atrial pressure falls below the mean circulatory filling pressure, blood flows from the peripheral vessels which have a mean pressure higher than the right atrial pressure toward the right atrium, and the rate of flow into the right atrium continues to increase as the right atrial pressure falls progressively more and more below the mean circulatory filling pressure.

Effect of vein collapse on venous return. After the right atrial pressure falls below zero mm. Hg, the return of blood to the heart does not continue to increase, as is illustrated in figure 2. On directly observing the major veins entering the thorax, one notes that these vessels suddenly collapse as the right atrial pressure falls below zero. It has been well documented that such collapse causes the pressure in the veins where they first enter the chest cavity to remain approximately zero mm. Hg regardless of how much negative the pressure becomes in the right atrium (4, 5). Therefore, decreasing right atrial pressure below zero mm. Hg, in general, does not continue to increase the venous return to the heart.

Effect of Mean Circulatory Filling Pressure on Venous Return. If the vessels of the peripheral circulatory system are well filled with blood, this causes the mean circulatory filling pressure to rise. The increased pressures in the peripheral vessels in turn cause greater tendency for the blood to flow toward the low pressure area of the right atrium. Therefore, for any given right atrial pressure the greater the mean circulatory filling pressure, the greater the venous return should be. Thus in figure 2 it is noted that for each level of right atrial pressure the venous return increases almost directly in proportion with the level of mean circulatory filling pressure.

Pressure gradient for venous return. From the above discussions and from figure 2 it can be seen that right atrial pressure opposes the return of blood to the heart while the mean circulatory filling pressure promotes the return of blood to the heart, though as right atrial pressure rises to approach the mean circulatory filling pressure the return of blood to the heart approaches zero. It can be shown mathematically that, provided the peripheral resistances remain absolutely constant, the momentary rate of venous return will be proportional to the mean circulatory filling pressure minus the right atrial pressure. This difference between mean circulatory filling pressure and right atrial pressure can be called the *pressure gradient of venous flow*. However, negative right atrial pressures must be considered simply as zero pressure because of the collapse factor as discussed above.

Figure 3 illustrates an experiment in a normal dog which has received a very large and rapidly administered transfusion of whole blood (1). Following this transfusion the heart was stopped approximately every 2 minutes by electrical fibrillation; then the mean circulatory filling pressure was measured within a few seconds; and thereafter the heart was electrically defibrillated. By measuring right atrial pressure and cardiac output simultaneously it was possible to plot the pressure gradient of venous flow (MCFP-RAP) against cardiac output (venous return) as illustrated in the figure. This figure illustrates that the venous return and cardiac output are approximately proportional to the pressure gradient of venous flow, though there is an inflection in the curve. This inflection is to be expected, for one would expect the peripheral resistances to decrease as the filling pressures throughout the peripheral vessels increase and consequently distend the respective vessels. Thus this experiment and many other similar experiments have correlated beautifully with the concepts presented above (6).

Effect of Peripheral Resistances on Venous Return. The effect of the peripheral resistances on venous return is the most difficult factor relating to venous return to understand and to assess, and it will be impossible to give a thorough discussion of this factor at the present time. In general, when there occurs an increase in vascular resistance between the major blood reservoirs and the right atrium, this decreases the cardiac output tremendously; on the other hand, when there occurs an increase in resistance between the left ventricle and the major blood reservoirs, this affects the left ventricular blood pressure tremendously but affects the venous return to only a slight extent. This latter effect is illustrated in figure 4. The experiment of figure 4 was performed on a freshly dead dog by the method described for figure 2 (1). The peripheral resistance was changed from one curve to the next by injecting into the arterial system large quantities of 250 micron glass beads which plugged the minute arteries. It is obvious from figure 4 that even though the total peripheral resistance increased 2.6 times, the maximal venous return decreased by only 10 per cent. This is approximately the decrease in venous return which one would mathematically predict, for there occurs as a consequence of the increased resistance in the small vessels a small amount of pooling of blood in the elastic arterial blood reservoir, thereby decreasing to a slight extent the effective filling pressures of the vessels in the venous side of the circulatory system and thus decreasing venous return slightly.

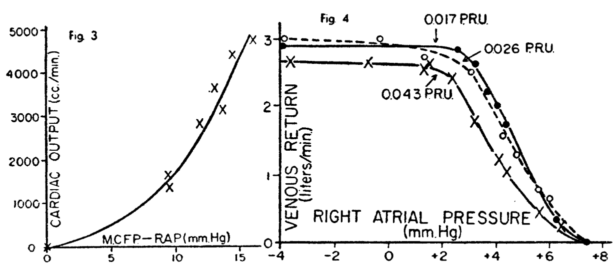


FIG. 3. Effect of the pressure gradient for venous return (MCFP-RAP) on cardiac output

FIG. 4. Effect of increasing peripheral resistance on venous return when the peripheral resistance is increased by occluding the small arteries with 250 micron glass beads.

An additional experiment was performed in the same manner as that illustrated in figure 4 except that the increasing resistance was applied by progressive occlusion of the veins entering the right atrium. In this experiment the total peripheral resistance increased only about 10 per cent, but the venous return decreased four times.

Thus both mathematically and experimentally it can be shown that changes in vascular resistance which occur near the right atrial end of the peripheral circulatory system greatly affect venous return to the heart, while changes in vascular resistance at progressively greater and greater distances away from the right atrium exert progressively less and less effect on venous return until finally resistance changes in the arterial tree affect venous return only slightly.

A Formula for Expressing Venous Return. Venous return may be expressed by the formula

$$\text{V. R.} = \frac{f(\text{MCFP})\cdot f(D)}{v}\cdot(\text{MCFP} - \text{RAP})\cdot C$$

which may be explained as follows: the factor, C, is simply a constant for mathematically relating the other factors. The factor (MCFP−RAP) is the pressure gradient for venous flow as discussed above, illustrating that the greater the difference between the mean circulatory filling pressure and right atrial pressure, the greater will be the venous return. The factor, $\frac{f(\text{MCFP})\cdot f(D)}{v}$, is an expression for determining the conductivity of the peripheral circulatory system for venous return, and this factor is the reciprocal of the resistances which resist the return of blood to the heart. The function, $f(\text{MCFP})$, illustrates that the greater the mean circulatory filling pressure, the greater will be individual filling pressures in the different vessels and the greater will these vessels be distended; as the mean circulatory filling pressure increases, this factor alone should decrease the resistance to venous flow and increase the return of blood to the heart. Measurements thus far, however, have indicated that this factor is not as important as might have been expected. The function, $f(D)$, is a function of the different dimensions of the peripheral circulatory system, illustrating that the greater these dimensions, the greater will be the venous return. This factor is so complicated that it is doubtful that it will ever be completely understood, though the general principles as discussed above relating it to venous return are not necessarily difficult. The expression, v, illustrates that the greater the viscosity of the blood, the less will be the venous return.

Equating Venous Return Curves With Cardiac Response Curves

Figure 5 illustrates a number of different types of venous return curves at different peripheral resistances and at different mean circulatory filling pressures. On the same graph are shown the three cardiac response curves illustrated in figure 1. If a normal-size dog is operating with approximately a normal cardiac response curve as illustrated by the heavy response curve of figure 5 and at the same time the various peripheral factors are approximately normal so that his venous return curve is that illustrated by the heavy venous return curve, it is obvious that these two curves equate with each other at *point A*, at which point the cardiac output is approximately 1525 cc/min., and the right atrial pressure is approximately zero. The heavy points on the graph illustrate the different possible equating points for respective venous return and cardiac response curves.

Obviously, except under momentary conditions the venous return and the cardiac output must be equal. For instance, if the myocardium is damaged, the cardiac response curve under which the heart is momentarily operating would be similar to the lower cardiac response curve, and, if the mean circulatory filling pressure is greatly increased, then the venous return curve would be affected in some manner similar to that illustrated by the venous return curve to the right in figure 5. The only point on these two curves at which the venous return and cardiac output are equal is at *point B*, at which the cardiac output is approximately 2050 cc/min., and the right atrial pressure is 6.2 mm. Hg.

It will have been noted in the above discussion that right atrial pressure is a common factor in both the cardiac response curve and in the venous return curve. When these curves are equated with each other, the right atrial pressure becomes an exact value at the same time that the equilibrium value of venous return and

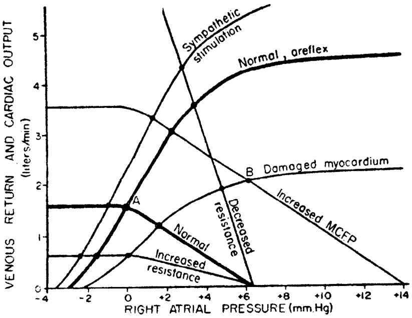


FIG. 5. Equilibration of various venous return curves with different cardiac response curves.

cardiac output becomes an exact value. Though it is impossible to discuss the mathematics at the present time, it can be shown that *right atrial pressure is not one of the primary determinants of cardiac output but, instead, is itself determined simultaneously along with cardiac output*. The factors which determine cardiac output and right atrial pressure simultaneously are, first, the shape of the cardiac response curve under which the heart is momentarily operating and, second, the peripheral circulatory factors which affect venous return, these including the mean circulatory filling pressure, the momentary dimensions of the peripheral system, and the viscosity of the blood.

SUMMARY

The factors which affect the ability of the heart to respond with increasing cardiac output as the right atrial pressure rises have been discussed briefly. On the other hand, the less popularized factors which affect venous return of blood to the heart have been discussed at greater length, it having been pointed out that right atrial pressure opposes return of blood to the heart, whereas the mean circulatory filling pressure promotes return of blood to the heart. The difference between mean circulatory filling pressure and right atrial pressure represents a *pressure gradient of venous flow*. It has been pointed out that changes in peripheral resistance occurring near the right atrium greatly affect venous return, whereas changes in peripheral resistance occurring at progressively greater distances from the right atrium have progressively less effect on venous return.

The various factors affecting venous return have been expressed in a formula. Also, it has been illustrated how venous return curves can be equated with cardiac response curves; by equating these curves both the cardiac output and the right atrial pressure are simultaneously determined.

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