Relative importance of venous and arterial resistances in controlling venous return and cardiac output

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Guyton, Arthur C., Berry Abernathy, Jimmy B. Langston, Berwind N. Kaufmann and Hilton M. Fairchild. Relative importance of venous and arterial resistances in controlling venous return and cardiac output. Am. J. Physiol. 196 (5) : 1008-1014. 1959.—In dogs with cardiovascular reflexes completely blocked by total spinal anesthesia, the total peripheral resistance was increased five- or more fold in two ways: first, by injecting small plastic microspheres into the arteries, thereby increasing the arterial resistance, and, second, by inflating pneumatic cuffs around the major veins, thereby increasing venous resistance. A small increase in venous resistance decreased cardiac output eight times as much as an increase in arterial resistance of similar magnitude. This difference was caused principally by a) a marked rise in systemic arterial pressure when arterial resistance was increased; this maintained the cardiac output at almost normal levels and b) a fall in systemic arterial pressure when venous resistance was increased; this promoted even more fall in cardiac output than increased total peripheral resistance alone would have caused.

In a previous mathematical analysis of the factors that affect venous return, it was shown that an increase in venous resistance should depress venous return far more than an increase in arterial resistance of the same magnitude (1). To study this problem, preliminary experiments were performed several years ago in which microspheres were injected into the arterial circuit to increase the resistance of the small arteries; in other experiments various degrees of obstruction were applied to the venous circuit by progressive ligation of veins returning to the heart (2). These preliminary experiments, though few in number, in general corroborated the mathematical analysis, indicating that an increase in venous resistance does reduce cardiac output many times more than a similar increase in arterial resistance. The present study has been carried out to establish even more accurately the quantitative difference between the effects of venous resistance and arterial resistance on cardiac output and also to determine, if possible, the cause of the difference.

Methods

Thirty-one experiments were performed in dogs averaging 17.2 kg in weight, anesthetized with sodium pentobarbital and heparinized with 5 mg/kg of heparin. An open-chest procedure, the principal details of which have been described in previous studies on the regulation of cardiac output, was used; the following is a brief summary of this procedure: the right atrium is cannulated with a large glass cannula in its lateral wall, and blood flows from this through an external circuit consisting of a) a thin collapsible rubber tube that can be raised or lowered to regulate right atrial pressure, b) a pump that pumps all the blood which succeeds in passing through the collapsible tube, c) a heater and thermostat circuit to maintain appropriate temperature of the blood and d) a rotameter to measure continuously the rate of venous return and cardiac output. After passing through this circuit the blood returns through a cannula into the pulmonary artery, bypassing the right ventricle entirely. Because all the blood entering the right atrium flows into the external circuit, the rotameter measures the total cardiac output, including even that passing through the coronary system. And the pump in the circuit nullifies all resistance; this allows the preparation to function in an almost normal physiological state for several hours. Appropriate pressures are measured from different parts of the circulation or external circuit by means of catheters connected with recording mercury or strain gauge manometers.

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To increase arterial resistance, plastic microspheres of 50–100 microns diameter were suspended in blood and then injected into the aorta a few centimeters distal to the coronary arteries. In this way the microspheres passed into all portions of the arterial tree except into the heart, causing a generalized increase in resistance rather than sectional increases. A total of 3–10 cc of microspheres, divided into small increments at a time, were injected into each animal.

Venous resistance was increased by placing two inflatable cuffs around the superior and inferior venae cavae, respectively. The cuff around the superior vena cava was placed below the entrance of the azygos vein so that venous return by this route could also be impeded. The pressures to which the two cuffs were inflated were at all times identical so that proportionate increases in resistance would occur in all sections of the venous circuit.

In all animals total spinal anesthesia was instituted by intraspinal injection at L2 or L4 of 30 mg of piperocaine hydrochloride (Metycaine) diluted in 20 cc of saline. This has been shown many times previously to eliminate all vasomotor reflexes (3). Also, this procedure eliminates vasomotor tone and in these experiments decreased the mean arterial pressure to an average of about 40 mm Hg which is approximately the normal acute ‘spinal’ level. In some experiments the loss of tone was nullified by continuous intraephrine drip of epinephrine which will be discussed later. These animals were normotensive even though all reflexes were absent. For the purposes of the present study, the results were the same whether epinephrine drip was used or not. In most experiments the epinephrine was not used because a far more extensive range of resistance changes could be effected in animals that had no initial vascular tone.

RESULTS

Degree of fall in cardiac output when arterial resistance was increased. The upper curve of figure 1 illustrates the effect in 15 dogs of progressively increasing the arterial resistance by injecting plastic microspheres into the arterial circuit. Because it is impossible to measure arterial resistance, the change in cardiac output is plotted against the percentage increase in total peripheral resistance. The control cardiac output averaged 840 cc/min.; the control arterial pressure averaged 48 mm Hg; and the control total peripheral resistance averaged 2.9 P.R.U. Here again the change in cardiac output is plotted against the percentage increase in total peripheral resistance. An increase in total peripheral resistance to only 25% more than control decreased the cardiac output by about 30 %, which is the same decrease that was recorded with an increase of 400 % in total peripheral resistance when caused by arterial embolization.

It is evident then that increasing the peripheral resistance by obstructing the veins causes far more decrease in cardiac output than does a similar increase in resistance caused by arterial obstruction. On analyzing the top and bottom curves in figure 1, one finds that the slope (ΔCO/ΔTPR) of the top curve at its origin is only one-eighth the slope of the bottom curve at its origin, thus indicating that the effect on cardiac output of small increases in resistance in the venous system is quantitatively eight times more significant than similar increases in arterial resistance.

Degree of fall in cardiac output when arterial and venous resistance are both increased simultaneously. The middle curve of figure 1 illustrates the effect in 15 dogs of simultaneously increasing both arterial and venous resistance. In these experiments the increases in resistance in the arterial and venous portions of the circulation were adjusted to be approximately equal. The curve of decline in cardiac output is approximately midway between that caused by increasing arterial resistance alone and that of increasing venous resistance alone.
Rise in arterial pressure as arterial resistance is increased. If the pressure gradient across an area of resistance in a flow circuit rises at the same time that the resistance is increased, the rise in pressure can compensate partially or totally for the increase in resistance; as a result, the decline in blood flow can be partially or totally prevented. Therefore, in an attempt to explain the failure of increased arterial resistance to decrease cardiac output greatly, the pressure gradient from the aorta to the right atrium was studied simultaneously with the changes in resistance and cardiac output. The upper solid curve of figure 2 illustrates the change in this pressure gradient in 10 dogs caused by embolization of the small arteries. The initial pressure gradient (the spinal level) averaged 34 mm Hg, but this rose rapidly as the small arteries were embolized. These results illustrated that for each incremental increase in arterial resistance there was also a very marked increase in systemic pressure gradient. The dashed curve of the figure illustrates the calculated rise in pressure that would have been required to compensate completely for the increased resistance; comparing this with the actual rise in pressure, it is evident that the actual rise did not fall far short of complete compensation.

Fall in systemic pressure gradient caused by increased venous resistance. Also, in figure 2, and in contrast to the effects of increasing arterial resistance, is shown the effect on the systemic pressure gradient in ten dogs caused by increasing the venous resistance. The control mean pressure gradient in these experiments (the spinal level) was 48 mm Hg. Instead of rising, the pressure fell, contributing even more to the decline in cardiac output rather than helping to compensate for the increased resistance.

Effect of increased arterial resistance in areflex normotensive dogs. In six dogs a constant drip of small amounts of epinephrine was given in addition to the total spinal anesthesia. This maintained the control arterial pressure at nontensive levels (mean 125 ± 7 mm Hg) though the spinal anesthesia still kept the dog in an areflex state. Then microspheres were injected into the arterial tree as before. The initial mean cardiac output was 1500 cc/min. and the initial mean total peripheral resistance was 5.8 P.R.U. Because the resistance in the small arteries was already several times that in the other dogs, the percentage changes caused by injection of microspheres were not as great as could be effected in the total spinal animals; nevertheless, the nature of the results was identical in the range that could be studied.

Figure 3 illustrates the very slight diminution of cardiac output as the total peripheral resistance increased to as high as 160% of the control value. Simultaneously, the arterial pressure increased from a mean of 125 mm Hg up to a mean of 208 mm Hg.

Effect of increased arterial resistance on venous return at different right atrial pressures. In previous experiments in which we have studied the factors that affect blood flow through the systemic circulation it has been demonstrated many times that very minute changes in right atrial pressure can greatly affect venous return and cardiac output (4). For this reason, we have used the so-called 'venous return curve' as a means for expressing the effects of different peripheral circulatory factors on venous return. This curve depicts the venous return at a succession of right atrial pressures rather than at a single pressure and, therefore, eliminates the uncertainty of the effect of right atrial pressure when one is analyzing the effects of other factors. Figure 4 illustrates a typical normal control venous return curve and three additional curves measured respectively after injecting three successive 1-cc doses of microspheres into the arterial system. This study was performed six times with essentially the same results. It is evident from the figure that the microspheres caused very marked increase in arterial pressure, from 112 mm Hg up to 210 mm Hg. However, the simultaneous over-all diminution in the plateau of the venous return curve was only 12% of the control value. It can be seen, therefore, that at all right atrial pressure levels increasing the arterial resistance decreases venous return only to a very slight extent but increases arterial pressure markedly.

Statistical analysis. The probable errors of the means of the different experimental curves are shown by the dotted areas in figures 1-3. The narrow distributions of
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Fig. 3. Effect of increased total peripheral resistance on cardiac output and arterial pressure when microspheres were injected into areflex normotensive dogs. Shaded areas indicate probable errors of the means.

Fig. 4. Effect of intra-arterial injection of microspheres on venous return curve and on arterial pressure, illustrating that venous return curve is hardly changed, though arterial pressure becomes greatly increased.

these probable errors show the consistency of results and also the distinct difference between the effects of arterial and venous resistance on cardiac output. However, additional analyses of the probabilities of significance in these studies showed the following: in 93 individual recordings of the effects of increased arterial resistance on cardiac output, in only one instance was the output measured to be even within the upper range of the cardiac output measurements resulting from increases in venous resistance. Also, in 46 individual recordings of the effect of increased venous resistance on cardiac output, in only one instance was the output measured to be within the lower range of the output measurements resulting from increases in arterial resistance. Therefore, the probability that the difference observed between the effects on cardiac output of increased arterial and venous resistance occurred by chance rather than being a true effect was less than one in 10^16 times. The extreme degree of these probabilities provides a very high degree of confidence in the results.

DISCUSSION

The present study concerns the effect of resistance in different parts of the systemic circulation on cardiac output. In any discussion of factors affecting cardiac output one must remain constantly aware that the circulation is a closed circuit and that the cardiac output is determined by a balance between the ability of the heart to pump blood and the ability of the vascular system to transmit the blood. Obviously, increasing the resistance in the systemic circulation can increase the load against which the heart must pump, in this way affecting the amount of blood that is pumped. It is equally obvious that increasing the resistance at different points in the systemic circulation can impede the flow of blood through the circulatory system, in this way affecting the ability of the vascular system to transmit blood back to the heart to be pumped around the circuit again and again. Therefore, in analyzing the effect of either systemic arterial resistance or systemic venous resistance on cardiac output, one must consider both of these factors, a) the loading effect on the heart and b) the impedance to flow through the systemic circulation itself.

Relative effects of arterial resistance and venous resistance on cardiac output. The total peripheral resistance was increased in two ways in these experiments: a) by injecting microspheres into the arterial system and b) by impeding the return of blood from the great veins to the heart. In the first of these instances it can be assumed that the increase in total peripheral resistance was caused by increased arterial resistance while in the second the increase was caused by increased venous resistance. Even though the changes in total peripheral resistance were equal in the two different studies, the effects on cardiac output were vastly different. Small increases in venous resistance diminished the cardiac output eight times as much as similar increases in arterial resistance. The major question that must be answered in this discussion is: why does increasing the venous resistance cause far greater decrease in cardiac output than increasing the arterial resistance?

Before attempting to answer the above question we must recognize three essential facts. First, if the vascular system were composed of rigid tubes the effect of
resistances anywhere in the systemic circuit would be the same, and there would be no difference between the effect of increased venous resistance or increased arterial resistance on the cardiac output. However, the vascular system is not composed of rigid tubes, and the distensibilities of the different parts of the system play an important role in determining this difference, as will be discussed below. Second, it must be realized that following an acute change in resistance in the circulation there is not a concomitant and immediate change in blood volume. If an increased resistance at some point in the circulation causes one vascular segment to distend, this removes blood from the other areas of the circulation. Third, it must be recognized that the venous portion of the vascular system has far greater distensibility and also far greater volume than the arterial portion, and, since the capacitance \( [d(volume)/d(pressure)] \) is the product of volume times distensibility, the capacitance is vastly greater in the venous system. Consequently, increasing the resistance from the veins to the heart can cause tremendous storage of blood in the veins and removal of like amounts from other portions of the circulation. On the other hand, increasing the resistance in the small arteries a similar amount causes relatively little increase in blood in the arterial system because its capacitance is far less than that of the venous system. For this reason increased arterial resistance does not remove excessively large quantities of blood from the remainder of the circulation even though it does elevate the arterial pressure greatly.

Now, let us examine the relative effects of increasing either arterial or venous resistance on the ability of the heart to pump. In the present experiments the total peripheral resistance was increased an equal amount whether this was achieved by increasing arterial or venous resistance. Therefore, the resistance load against which the heart had to work was increased the same in either instance. Obviously, the difference between the effects of the two resistances on cardiac output cannot be attributed to different resistive loading of the heart. For this reason, we must consider factors in the systemic circulation rather than in the heart as the cause of the different effects of arterial and venous resistance.

Let us use figure 5 to help explain this difference. This figure depicts symbolically the systemic circulation as well as the heart and pulmonary circulation. For the time being it will be assumed that the heart pumps all the blood that returns to it from the systemic system and that none of the blood is dammed either in the heart chambers or in the pulmonary circulatory system. Obviously this is not true, but it was shown by Patterson and Starling long ago that within physiological limits this state of events holds almost true (5). The system will be analyzed, first, making the above assumption and, second, allowing for damming of large quantities of blood in either the cardiac chambers or the pulmonary vascular system.

In figure 5 the two major storage areas of the systemic circulation are shown to be the arterial system and the venous system. \( R_v \) is the summated resistance from the veins to the heart, while \( R_a \) is the summated resistance from the arterial storage chamber to the venous storage chamber. In other words, \( R_v \) is comparable to the venous resistance and \( R_a \) is comparable to the arteriolar resistance plus capillary resistance. If \( R_v \) is increased, large quantities of blood will begin to dam up in the venous reservoir because it has a very high capacitance. Since we are for the present assuming that the same amount of blood remains in the heart and lungs at all times, the blood which dam in the venous system must come from the arterial reservoir, which has a very low capacitance. As a result, the arterial pressure falls greatly, and the total pressure gradient through the systemic circulation becomes far less than previously. In addition to this, the total peripheral resistance is increased because of the increase in \( R_v \). Thus, we have two factors decreasing the flow of blood through the systemic circulation when the venous resistance is increased: first, an increase in total peripheral resistance and, second, a decrease in total pressure gradient from the arteries to the right atrium. In the present experiments both of these effects were shown to be operative in the decrease in venous return when venous resistance was increased.

Now let us consider the effect on venous return of increasing the resistance \( R_a \) from the arterial reservoir to the venous reservoir. An increase in \( R_a \) will dam blood in the arterial system. However, since the capacitance of the arterial system is slight in comparison with that of the venous system, only a small amount of blood will actually be dammed in the arteries, though the arterial pressure rises markedly. Also, only a slight amount of blood is removed from the veins so that the peripheral venous pressures will not change greatly. For this reason, the venous inflow to the heart decreases only slightly. It can be seen that two major changes have taken place: first, the total peripheral resistance has increased because of the increase in \( R_v \); this obviously would tend to decrease the flow of blood through the systemic circulation. But, second, the systemic pressure gradient has at the same time increased almost in proportion to the increase in total peripheral re-
sistance, and this almost totally compensates for the increased resistance. Therefore, the cardiac output is decreased only a very slight amount. Both of these effects were shown to occur in the present experiments when the arterial resistance was increased.

The above discussion gives the basic cause of the difference between the effects of arterial and venous resistances on cardiac output, but this explanation still lacks the precision that can be attained on the basis of presently known data. Using the same schema as that shown in figure 5 and the same assumption that no blood becomes dammed in the heart or lungs, the following approximate relationship for computing venous return, \( VR \), was found in a previous study (1):

\[
VR = \frac{P_{\text{net}} - P_{\text{tr}}}{R_v + R_a}
\]

in which \( P_{\text{net}} \) is the mean circulatory pressure, \( P_{\text{tr}} \) is right atrial pressure, \( R_v \) is the venous outflow resistance, \( R_a \) is the resistance between the arterial system and the veins, \( C_v \) is the capacitance \([d(\text{volume})/d(\text{pressure})]\) of the venous system, and \( C_a \) is the capacitance of the arterial system. In still another study it has been shown that the average capacitance of the venous system is approximately 18 times that of the arterial system (6). Substituting this value in the above formula we find the following:

\[
VR = \frac{P_{\text{net}} - P_{\text{tr}}}{R_v + 18R_a}
\]

From this analysis it appears that a slight increase in venous resistance should theoretically cause the venous return to decrease 19 times as much as an increase in arterial resistance of the same magnitude. Yet, in the present study an increase in venous resistance actually caused only eight times as much diminution in venous return as a similar increase in arterial resistance. To explain this difference we must stop assuming that increased load in the systemic circulation fails to increase the amount of blood dammed in the cardiac chambers and pulmonary vessels; obviously, this is not true anyway. When arterial resistance is increased any blood that is dammed in these chambers must be considered along with that dammed in the arterial system, for this blood as well as that stored in the arteries is lost from the veins. This is equivalent to increasing the capacitance \( C_a \) of the arterial system, which in turn decreases the magnitude of the difference between the effects of venous and arterial resistance on cardiac output. Thus, the theoretical 19-fold difference derived above becomes some smaller value. Appropriate measurements have not yet been made to determine how much blood is usually stored in the cardiac and pulmonary chambers when arterial back pressure increases, but studies involving acute total obstruction of the aorta indicate that the amount is about equal to that stored simultaneously in the arteries (6, 7). If the amount dammed in the heart and lungs in the experiment with microspheres should have been slightly greater than that dammed in the arteries, then the measured eight-fold difference is approximately that which would be predicted by the mathematical analysis.

Importance of difference between effects of arterial and venous resistance on cardiac output. From the above considerations one can conclude that an increase in arterial resistance hardly affects cardiac output, though it causes a tremendous increase in arterial pressure. In contrast with this, only a slight increase in venous resistance decreases the cardiac output very greatly and also decreases the arterial pressure.

The results of these studies help to explain many hitherto poorly understood observations on venous blood flow. As an example, among the most difficult of all experiments to perform on the circulation are those having to do with venous flow, for even the slightest obstruction to flow invariably greatly reduces venous return. In our own experience we were never able to attain satisfactory flow of blood through an external circuit inserted into the major veins until the resistance of the circuit was nullified by simultaneously pumping the blood. When the pump is used, however, normal cardiac outputs and many hours of experimentation can be attained. This same effect has also been observed innumerable times in human patients when various factors such as cardiac tamponade, hemorrhage into the mediastinum, and mediastinal tumors compress the venous inflow into the heart; all of these are very likely to result in rapid and profound shock.

Long-term effect of venous resistance changes on cardiac output. In the present experiments only the acute effects of venous and arterial resistance changes on cardiac output have been studied. In such acute experiments the blood volume cannot change greatly, but it can change over long periods of time. Adequate studies are available to show that the volume will eventually be readjusted until the average mean capillary pressure \( (P_c) \) reaches an equilibrium state in accordance with the law of the capillaries (8, 9). That is:

\[
P_c = P_{\text{coo}} + P_t - P_{\text{tr}}
\]

in which \( P_{\text{coo}} \) is plasma colloid osmotic pressure, \( P_t \) is tissue pressure, and \( P_{\text{tr}} \) is tissue colloid osmotic pressure. Also, the following formula relates cardiac output \( (CO) \) to mean capillary pressure, right atrial pressure \( (P_{\text{tr}}) \), and venous resistance \( (R_v) \) from the mid-point of the capillaries to the right atrium.

\[
CO = \frac{P_c - P_{\text{tr}}}{R_v}
\]

Combining the above two formulae we find the following relationship for long-term control of cardiac output:

\[
CO = \frac{P_{\text{coo}} + P_t - P_{\text{coo}} - P_{\text{tr}}}{R_v}
\]
These last two formulae describe the relationship for long-term regulation of cardiac output. It will be noted that arterial resistance does not appear at any single place, and all of the determinants of cardiac output in these formulae except right atrial pressure are entirely independent of arterial resistance. Therefore, the only means by which arterial resistance could affect the long-term regulation of cardiac output would be by its effect on right atrial pressure, and this does not occur significantly under normal conditions because the heart usually compensates almost completely for load. Yet, it can occur when the arterial resistance becomes great enough to make the heart fail and thereby increase right atrial pressure. Thus, in normal operation of the circulatory system venous resistance is extremely important as a determinant of cardiac output, while arterial resistance has relatively little significance. On the other hand, in the case of a failing heart, arterial resistance, by virtue of its cardiac loading effect, can also become an important factor in affecting cardiac output.

REFERENCES


Unfortunately, several of the factors in the above formulae cannot be measured, but, nevertheless, this analytical approach provides interesting explanations for a great many problems in circulatory physiology such as: a) it helps to explain why essential hypertensive patients have normal cardiac outputs despite very high arterial resistance (10), b) it helps to explain the general correlation between decrease in cardiac output in congestive heart failure and increase in right atrial pressure (11); this is opposite to the normal relationship between right atrial pressure and cardiac output, c) it helps to explain the ability of retained fluids and increased tissue pressure to compensate partially for a weakened heart in congestive failure (12, 13), and d) it helps to explain the tendency for persons with hypoproteinemia to faint or even develop shock (14, 15). Thus, the principles of the above formulae are substantiated by circumstantial evidence even though all their facets will probably never be proved by direct experimentation.

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