Effect of Hematocrit on Venous Return

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THAT RESISTANCE to blood flow in the systemic circulation, especially in the veins, influences venous return very greatly has been known for many years, and this has been further emphasized by recent quantitative studies from this laboratory depicting the effects of venous or small arterial occlusion on venous return. Since viscosity is one of the many factors that determines resistance to flow, it is logical to believe that viscous changes in the blood resulting from high or low hematocrit could greatly influence the venous return to the heart and in this way also affect cardiac output.

The present experiments were designed to study as exactly as possible the effect of acute changes in hematocrit on venous return when other factors affecting venous return are controlled. Among these other factors are right atrial pressure, mean circulatory pressure, and nervous reflexes to the systemic circulation. Special procedures have been employed to eliminate these factors in the present studies, as will be explained below. These studies also shed light on the cardiac outputs reported both in animal and human anemia.

Methods

Eighteen dogs were used, weighing an average of 13.6 Kg., anesthetized with 30 mg./Kg. of sodium pentobarbital, and heparinized with 5 mg./Kg. of heparin. Measurements of venous return were made in each dog while its hematocrit was still normal and then again after it had been rendered either anemic or polycythemic. In 10 of the dogs, 450 to 900 ml. of blood was removed from the circulation and was replaced immediately by an equivalent amount of Tyrode's solution, establishing anemia. In 8 of the dogs, 400 to 700 ml. of blood was removed and was replaced immediately by the same amount of packed whole red blood cells, creating polycythemia. After allowing the circulation to stabilize for 10 to 15 minutes, adjustments were made in the blood volume to bring the mean circulatory pressure, which was measured as explained below, back to the control value.

Venous return in these animals was studied using a preparation that has been employed previously for determining the effects of right atrial pressure, mean circulatory pressure, and changes in peripheral resistance on venous return. This preparation consisted briefly of the following: The animal’s chest was opened and the wall of the right atrium was cannulated. Blood was pumped from this cannula through a flowmeter and an automatically controlled heater circuit back into the pulmonary artery, thus bypassing the right ventricle. By increasing the activity of the pump, the right atrial pressure could be reduced to any desired value, and by decreasing the activity, the pressure could be increased to any desired value. Appropriate pressures were measured from the right atrium and from the aorta through catheters, and the pressures were all referred to a hydrostatic reference level located 61 per cent of the thickness of the chest anterior to the back, a level at which rotation of the animal from the supine to prone position causes the least hydrostatic effect. Also, the mean circulatory pressure of the entire circulation was measured, when required, by temporarily stopping the pump and allowing the pressures in the aorta and right atrium to come to equilibrium. The purpose of this elaborate system for studying venous return was to provide very precise control of the right atrial pressure and the mean circulatory pressure, both of which have such extreme effects on venous return that any study of venous return without controlling these would be almost useless.

To prevent reflexes from occurring during the course of these experiments, total spinal anesthesia was instituted in all dogs, employing 150 mg. of metycaine in 20 cc. of normal saline injected at the level of the third lumbar vertebra. This immediately reduced systemic arterial pressure.
Effect of Anemia and Polycythemia on Venous Return at Various Right Atrial Pressures

Because previous studies on venous return have shown that even very slight changes in right atrial pressure can affect venous return greatly, we have found it necessary to measure venous return over a spectrum of right atrial pressures from very high to very low and then to plot this in the form of a “venous return curve.” Figure 1 illustrates (1) the mean control venous return curve for all 18 dogs, (2) the mean venous return curve for the 10 dogs that were rendered anemic, and (3) the mean venous return curve for the 8 dogs that were rendered polycythemic. The average hematocrit of the control dogs was 39, of the anemic dogs 21, and of the polycythemic dogs 59. In figure 1, it is apparent that each curve reached a level plateau when the right atrial pressure was decreased below -4 mm. Hg. Therefore, effects of hematocrit changes on venous return can best be analyzed by the levels of the plateaus in the venous return curves; these levels are independent of changes in right atrial pressure. The curves show that the maximum venous return for the normal animals averaged 1,200 ml. per minute; for the anemic animals, 1,630 ml. per minute (an increase of 36 per cent); and for the polycythemic animals, 760 ml. per minute (a decrease of 37 per cent).

In each of the average curves of figure 1, the venous return became zero at the same right atrial pressure, 6.3 mm. Hg. Since the right atrial pressure at which venous return becomes zero is a measure of mean circulatory pressure, one can see that on the average this factor, one of the major regulators of venous return, was controlled very exactly in these experiments.

Statistical Analysis of the Venous Return Curves

The shaded areas around the curves of figure 1 denote the probable errors of the means of the measurements. Seventy different measurements of venous return were made in the 10 anemic dogs at different right atrial pressures, and in not one of these was the venous return less than the corresponding value in the same dog prior to producing the anemia. Fifty-six different measurements of venous return were made in the 8 polycythemic dogs, and in not one single instance was the venous return as great as the corresponding value in the same dog prior to polycythemia. The values of \( P \) for the significance of these measurements were \( 10^{-21} \) for the anemic values and \( 10^{-11} \) for the polycythemic values. These
measures of reliability show the extreme constancy of the results.

Relationship of Hematocrit to Venous Return

Figure 2 illustrates the average effect of hematocrit on venous return when the right atrial pressure was more negative than -4 mm Hg. This curve was derived from 82 individual measurements, and the shaded area around the curve represents the probable error of the mean between the hematocrit limits of 20 and 62. Beyond these limits the number of points was not sufficient for statistical significance. If the curve were extrapolated downward, venous return would become zero at a hematocrit of about 90. This is also approximately the level at which one would predict zero flow on the basis of blood viscosity studies.

Minute Flow of Red Cells to the Tissues

The total volume of red cells transported to the tissues each minute, called the "minute flow of red cells," has been calculated at each hematocrit by multiplying the hematocrit by the rate of blood flow. The results, depicted in figure 3, show that the minute flow of red cells reaches a maximum at a hematocrit of 40 which is almost exactly the normal hematocrit for a dog. The decrease in minute flow of red cells in anemia was caused by the decreased volume of red cells in each unit quantity of blood flowing through the tissues. However, this was not as severe as it would have been had the overall venous return not increased, as illustrated in figure 1. The decrease in minute flow of red cells at hematocrits higher than 40 was caused by the very marked decrease in venous return in the polycythemic animals. This effect would have been much more severe had it not been for the increase in red cell mass per unit volume of blood. That is, in anemia the decrease in red cells outweighed the increase in venous return, while in polycythemia the decrease in venous return outweighed the increase in red cells. This same effect has been found previously by Crowell (optimal hematocrit of 39) in studying the effects of hematocrit on shock and by Richardson (optimal hematocrit of 40) in studying the effect of hematocrit on cardiac output in intact dogs.

Effect of Hematocrit on Total Peripheral Resistance

Figure 4 illustrates a plot of the total peripheral resistance against hematocrit in all the control, anemic, and polycythemic animals. These total peripheral resistances were calculated when the right atrial pressure was more negative than -4 mm Hg, a range in which venous return had reached its maximum value. The points in circles indicated those animals with initial arterial blood pressures higher than the range of pressures from the other animals; the points designated x's were from animals with arterial pressures below the range of the other animals.

It will be noted that the relationship of total peripheral resistance to hematocrit, particularly when the points from those animals with inordinately high and inordinately low arterial pressures are excluded, fall into a
Figure 3
Relationship of hematocrit to minute volume of red blood cells flowing to the tissues.

The general pattern, with relatively low total peripheral resistances at low hematocrits and relatively high total peripheral resistances at high hematocrits. The solid curve of the figure represents the best fit for all the points on the graph. The dashed curve represents the calculated change in total peripheral resistance which would be expected if total peripheral resistance should have changed proportionately with viscosity of the blood. In calculating this curve, viscosity values determined by Whittaker and Winton for bloods of different hematocrits were used. The high degree of correspondence between the two curves indicates that changes in viscosity probably played a major role in the changes in total peripheral resistance at different hematocrits, as will be discussed in more detail later.

Discussion
Mechanism by Which Hematocrit Changes Affect Venous Return

The data presented in this study illustrate that hematocrit has an extremely important effect on venous return, particularly when other factors known to enter into the regulation of venous return—such as right atrial pressure and mean circulatory pressure—are very exactly controlled. Yet, we now need to discuss the possible mechanisms by which hematocrit changes cause their effects on venous return. Some of the possibilities include: (1) cardiovascular reflexes, (2) local effects of hematocrit changes on vascular caliber, and (3) changes in viscosity of the blood.

One of the prevalent suggestions for the cause of increased venous return in anemia is that low tissue $P_a$ initiates autonomic reflexes which in turn cause vasodilation. The only such reflex ever proved beyond doubt is the chemoreceptor reflex involving the carotid and aortic bodies. Even these reflexes are rarely important in anemia because the chemoreceptors normally are not excited until the arterial $P_a$ falls low, whereas the arterial $P_a$ usually remains very high in anemia. In the present experiments, the chemoreceptor and all other vasomotor reflexes were eliminated by giving the animals total spinal anesthesia, which shows that, even in the absence of cardiovascular reflexes, hematocrit changes can still cause drastic alterations in venous return. However, for obvious reasons, these experiments do not rule out the possibility that cardiovascular reflexes could have played a part had they been present.

A second effect that could play a major role in altering the peripheral resistance, and therefore also venous return, would be local dilatation or vasoconstriction resulting from alterations in hematocrit. In the last few years, several experiments have shown that progressive diminishment of oxygen transport to the tissues causes dilatation of (a) coronary blood vessels, (b) the vascular tree of the dog’s hind limb, and (c) vessels of isolated skeletal muscles. Therefore, decreases in hematocrit could very readily have caused dilatation of the peripheral vessels by decreased oxygen transport to the tissues. Conversely, it might be suspected that an excess of oxygen transport to the tissues could have resulted in vasoconstriction at high hematocrits. However, reference to figure 3 shows that the minute flow of red cells to the tissues decreased in polycythemia as well as in anemia, the maximum transport occurring at a hematocrit of 40 and diminishing both above and below this value. Therefore, it can be assumed that the oxygen availability to the tissues decreased in polycythemia just as it
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If the peripheral resistance were controlled principally by local availability of oxygen, a decrease in peripheral resistance rather than the measured increase should have occurred in polycythemia. Since this was not true, excess tissue oxygenation can be ruled out as the cause of the decreased venous return in polycythemia.

Finally, viscosity is the remaining important factor altered by changes in hematocrit. Figure 4 illustrated that the total peripheral resistance increased with hematocrit approximately the same that blood viscosity increases with hematocrit. Unfortunately, measurements of viscosity in relation to hematocrit, including measurements made in this laboratory, have demonstrated that the relationship between hematocrit and viscosity varies tremendously with such factors as diameter of the viscosimeter and rapidity of flow in the viscosimeter. Therefore, in the absence of any known method to give the true viscosity of blood in the tissues, it can be pointed out that there is a general correspondence between the increase in blood viscosity and the decrease in venous return when the hematocrit rises.

Analysis of the Effect of Blood Viscosity on Cardiac Output

Up to this point in this paper we have discussed principally the effect of hematocrit on venous return. However, it has been demonstrated that it is neither the ability of blood to flow through the peripheral circulation alone nor the ability of the heart to pump blood alone that controls cardiac output; instead, it is the two of these acting simultaneously. The "venous return curve" is the complement to one type of Starling's function curves of the heart, namely, the type depicting cardiac output as a function of right atrial pressure. Therefore, to determine the importance of hematocrit as a regulator of cardiac output we now must analyze the venous return curves obtained in this study in relation to cardiac function curves that have been obtained elsewhere. This is done in figure 5 and can be explained as follows:

Figure 5 illustrates the three venous return curves determined in these experiments and extrapolated to the average 12-Kg. dog. It also shows the plot of cardiac output against right atrial pressure for the normal heart and for the same heart in a weakened state. To determine the effect of hematocrit on the cardiac output, we now choose, first the state of the hematocrit and, second, the state of the heart. If we choose a normal hematocrit and a normal heart, the two respective curves cross each other at point (A), representing the point at which cardiac output and venous return are equal (which is a necessary condition in the circulation except for momentary imbalances). If the blood should become anemic but the heart should remain normal, the cardiac output would rise to point (B), whereas if the animal should become polycythemic, the cardiac output would fall to point (C). Note that in the case of the normal heart, changes in hematocrit would be expected to cause very significant effects on cardiac output.
Anemic

Normal

Polycythemic

Weakened heart

RIGHT ATRIAL PRESSURE (mm. Hg.)

Figure 5

An analysis of the effects of hematocrit on cardiac output when the heart is normal and when it is weakened.

A somewhat different situation occurs when the heart becomes weakened, for the function curve of the heart itself might well reach a plateau or almost a plateau before it crosses the venous return curves, as is illustrated in the figure. Under these conditions, a change from the normal hematocrit to an anemic state would increase the cardiac output from point (A') to point (B'), which would be rather insignificant. However, there would be a very significant rise (1.5 mm. Hg) in right atrial pressure, an observation well known to occur in severe anemia. Also, a change to the polycythemic state would cause the cardiac output to change from point (A') to (C). Here again the effect is greater on the right atrial pressure than on the cardiac output. Thus, in the weakened heart the state of the peripheral circulation has little to do with determining the volume of blood that can be pumped by the heart, for then it is the heart itself that is the limiting factor. Therefore, it would be expected that changes in hematocrit would not necessarily cause significant changes in cardiac output when the heart is weak.

Cardiac Output in Chronic Anemia and Polycythemia

Many studies in human beings have shown that anemia almost invariably increases the cardiac output, the degree of increase being almost directly proportional to the degree of anemia. It is not unusual for the cardiac output to rise to as high as 10 L. per minute in a resting patient with a hematocrit one-third normal. If one considers the normal cardiac output to be 5 L. per minute, then he can calculate from this that the minute volume of red blood cells transported to the tissues (venous return times hematocrit) in such an anemic patient would be approximately two-thirds normal. Referring once again to figure 3, in the present experiments, in which all cardiovascular reflexes were completely eliminated, the minute volume of red cells transported to the tissues was about two-thirds normal when the hematocrit fell to approximately one-third normal. This is about the same finding as in anemic patients. Therefore, the possibility of nervous reflexes being the principal cause of the increased cardiac output in anemia must be seriously questioned.

On the other hand, on the basis of the present experiments, it would be possible to explain most of the increased blood flow in anemia by decreased viscosity of the blood, this causing increased ease of return of blood to the heart and consequently greater quantities of blood pumped by the heart. But the present experiments cannot rule out the possibility of local vasodilatation resulting from oxygen lack or from some other local factor initiated by the low hematocrit. Indeed, figure 4 illustrates that the correspondence between the measured total peripheral resistance and the postulated total peripheral resistance calculated from blood viscosity studies is not as good in the anemic range as in the higher hematocrit ranges. This would indicate that some factor other than viscosity does indeed cause local vasodilatation in serious anemia.
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Therefore, to summarize, we would conclude that most of the increased cardiac output in chronic anemia probably results from diminished total peripheral resistance consequent to diminished viscosity of the blood. On the other hand, the results of these experiments would also be consistent with the idea that diminished oxygen availability to the tissues might cause an additional significant decrease of total peripheral resistance.

Far fewer studies have been conducted on the effects of chronic polycythemia than of anemia on cardiac output. However, polycythemia in human beings is not associated with a diminished cardiac output as would have been expected from the findings in these experiments.17,18 Unfortunately, no information is available on the mean circulatory pressure in polycythemic patients. It is known that these patients have greatly increased blood volumes, in addition to greatly increased hematocrits. For this reason, it is reasonable to assume that their mean circulatory pressures are also far above normal because blood volume is one of the primary factors that determines mean circulatory pressure. Furthermore, it has been well established that an increase in mean circulatory pressure increases the venous return.6 Therefore, it is likely that the cardiac output remains normal in polycythemic patients because of a rise in mean circulatory pressure which balances the tendency for the increased hematocrit to decrease the venous return.

Summary

In 18 dogs, the major factors besides blood hematocrit that are known to affect venous return were exactly controlled, while the hematocrit itself was varied from 9.5 up to 65. In general, the changes in venous return in these experiments were approximately the reciprocal of the changes in blood viscosity, as estimated from standard blood viscosity curves. An interesting sidelight of these studies was the fact that the minute volume of red blood cells fell drastically in anemia because of decreased hematocrit and in polycythemia because of greatly reduced venous return.

References

