Circulatory Effects of Acute Expansion of Blood Volume: STUDIES DURING MAXIMAL EXERCISE AND AT REST

By Brian F. Robinson, M.B., M.R.C.P., Stephen E. Epstein, M.D., Richard L. Kohler, M.D., and Eugene Braunwald, M.D.

ABSTRACT

The maximum cardiac output that can be achieved during exercise might be limited either by extracardiac factors influencing ventricular filling, or by the heart itself. In order to investigate this problem, the effect on the cardiac response to maximum exertion of an acute expansion of blood volume was studied in six men with essentially normal cardiovascular systems. Augmentation of blood volume produced by infusion of 1000 to 1200 ml of the subject's own blood resulted in a small increase in central venous pressure at rest (avg = +1.9 mm Hg) and a substantial increase in cardiac output (avg = +1.47 liters/min). During exercise, however, the expansion of blood volume caused a large increase in central venous pressure (avg = +7.4 mm Hg), but no significant increase in cardiac output or maximum O2 uptake. This finding suggests that the maximum cardiac output is not restricted by extracardiac factors and that the upper limit must therefore be determined by the heart itself.

ADDITIONAL KEY WORDS maximum cardiac output cardiac rate control of cardiac output blood volume hypervolemia central venous pressure oxygen consumption man

The factors which limit the maximum cardiac output achieved during exercise are of considerable interest, since their identification would lead to an improved understanding of circulatory regulation. The problem can be reduced to a consideration of two fundamental possibilities; either extracardiac factors set a limit to ventricular filling at a time when the ventricles are still capable of augmenting their performance, or alternatively, the function of the heart itself may reach a maximum level in which case further increments in filling pressure would not augment cardiac performance.

Previous investigators have suggested that the maximum circulatory response to exercise is dependent on total blood volume, but much of the evidence is indirect. Taylor et al.1 2 demonstrated that prolonged bed rest was associated with reductions in both the maximum O2 uptake and blood volume, but a causal connection between these findings was neither established nor claimed. Subsequently, Danzinger and Cumming3 studied the effect of a deliberate reduction of blood volume induced with chlorothiazide; they found that the maximum O2 uptake was consistently lowered and that this change could be reversed with intravenous dextran. Conflicting results were obtained by Saltin4 who observed the effect of a reduction of blood volume induced by thermal dehydration; he found no decrease in maximum O2 uptake or cardiac output, but he did observe that the maximum time during which work could be continued was markedly reduced. Kjellberg et al.5 observed a strongly positive correlation between blood volume and the capacity for exercise on a bicycle ergometer in a group of subjects with normal cardiovascular systems. In subsequent studies, it was shown that the improvement in physical working capacity, following

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a period of training, was associated with an increase in total blood volume and it was inferred that this relationship was causal.\textsuperscript{6} The effects of deliberately augmenting the blood volume were studied by Gullbring et al.\textsuperscript{7} who infused a quantity of the subjects' own blood; they found that the heart rate was lower at any given rate of work, from which they concluded that the working capacity was increased, but they made no measurements of cardiac output or maximum O$_2$ uptake. It has also been shown that at a given submaximal O$_2$ uptake the cardiac output is higher when the exercise is done in the supine rather than in the erect position,\textsuperscript{8-10} suggesting that the improvement in ventricular filling provided by the supine position augments cardiac performance during exercise.

A review of previous studies thus suggests that the total blood volume and other factors influencing ventricular filling normally limit maximum cardiac performance. However, the effect of acute expansion of blood volume on the cardiac output during maximum exercise has not been determined, and this experiment, which might be considered crucial in resolving the question, forms the subject of this investigation.

**Methods**

Six men ranging in age from 19 to 36 years were studied. Five subjects had systolic heart murmurs, but following full investigation it was concluded that no cardiac abnormality was present. The sixth had had an atrial septal defect repaired several months previously, and had recovered completely from the effects of operation at the time of study. The techniques employed in the present investigation were identical to those used in a previous study.\textsuperscript{11} Exercise was performed at varying speeds and grades on a motor-driven treadmill. O$_2$ uptake was recorded by means of a continuous flow system using a paramagnetic O$_2$ analyzer, the details of which have previously been described.\textsuperscript{12} Cardiac output was measured by the dye dilution technique using indocyanine green. The indicator was injected through a polyethylene catheter which had been introduced percutaneously into a forearm vein and advanced to the superior vena cava. Brachial arterial blood was sampled through a Teflon catheter previously introduced by a modified Seldinger technique. Systemic arterial and central venous pressures were recorded by means of Statham pressure transducers with the base line set at the level of the mid right atrium. The electrocardiogram, mean arterial and central venous pressures, and indicator dilution curves were recorded with a photographic recorder. The O$_2$ demands of exercise were calculated by dividing the total excess O$_2$ consumed during and after running by the duration of the bout, and adding the O$_2$ demand per minute so obtained to the basal uptake. The O$_2$ debt was calculated as the quantity of O$_2$ above basal levels consumed after cessation of exercise. The O$_2$ uptake (VO$_2$ in table I) was the level determined just prior to the cessation of exercise; this level was always the maximum achieved during that particular bout of exercise.

All studies were performed in the postabsorptive state, and the subjects were completely familiarized with running on the treadmill before any definitive observations were made. During the preliminary studies each subject was exercised by running at increasing grades until there was no further rise in VO$_2$ when the grade was increased by 2.5%. This level of VO$_2$ was regarded as the maximum and the rate of work which had been required to produce it was that used in the subsequent investigation. When these preliminary studies had been completed, 1000 to 1200 ml blood were removed by venesection over a period of two days and the subjects were subsequently given oral iron to help restore their hemoglobin levels.

Approximately two weeks after the blood had been withdrawn the definitive study was performed. The cardiac output was determined in duplicate with the subject standing at rest on the treadmill. The values shown for this variable in table 1 are the mean of the two determinations; the second of the paired measurements differed from the first by an average of 10.4%. The subject then ran at the predetermined level and the cardiac output was determined at the third, fourth, and fifth minutes of exercise. VO$_2$ was recorded continuously during exercise and mean arterial and venous pressures were recorded except when the cardiac output was being determined. Following completion of the control study, the previously withdrawn blood (1000 to 1200 ml) was reinfused over a period of one hour. All measurements were then repeated both at rest and during performance of a second bout of exercise at the same level as before.

**Results**

1. **PRE-INFUSION STUDIES**

At rest in the upright position, the cardiac index ranged from 2.06 to 3.60 liters/min/m$^2$. 
Circulatory Effects of Augmentation of Blood Volume at Rest and During Maximum Exercise

<table>
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<tr>
<th>Subject</th>
<th>B.S.A. (kg)</th>
<th>Diagnosis</th>
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Mean*<br> C 84 174 178 178 5.34 21.48 21.66 21.68<br>I 75 165 168 173 6.81 21.54 20.91 22.40<br>P N.S. <.02 <.02 <.05 <.01 N.S. N.S. N.S.

B.S.A.: body surface area in m²; FM: functional murmur; Postop. A.S.D.: postoperative atrial septal defect; C: control study; I: post infusion study; R: rest; E: exercise; VO₂: oxygen consumption; N.S.: not significant (P > 0.05).
*Excluding J.O'R.
†Excluding H.C. and M.P.
‡Cardiac output data obtained under the same exercise conditions but on a different day from O₂ and pressure data.

Figure 1
Response of mean brachial arterial (B.A.) and right atrial (R.A.) pressures to commencement of treadmill exercise.

It was below the lower limit of normal for the supine position (2.5 liters/min/m²) in two subjects, but was within the normal range in the other three (table 1). Immediately following the commencement of exercise, the central venous pressure showed a sudden rise following which it either remained steady or declined slightly to reach a steady level by the end of the second minute of exercise (fig. 1); the change in central venous pressure with exercise averaged +1.2 mm Hg. The cardiac output increased from an average value of 5.34 liters/min at rest to 21.60 liters /min during exercise; heart rate rose from 84 beats/min to 176 beats/min and stroke volume from 65 ml to 123 ml. The maximal O₂ consumption averaged 3180 ml/min. In every subject the O₂ uptake was significantly less than the calculated O₂ demand and large O₂ debts, averaging 7083 ml, accrued.

II. POSTINFUSION STUDIES
A comparison of measurements at rest, be-
fore and after infusion of 1000 to 1200 ml of the subject's blood, showed that significant increases occurred in central venous pressure (+1.9 mm Hg), cardiac output (+1.47 liters/min) (fig. 2), and stroke volume (+26 ml). The hematocrit rose slightly in all subjects, the average value increasing from 42% to 44%.

With the commencement of exercise, there was a large increase in central venous pressure in all studies and the level finally achieved was an average of 7.4 mm Hg higher ($P < 0.01$) than during the control exercise period. The cardiac output, however, reached almost exactly the same level during each of the three measurements made during exercise as it had before the infusion. The average heart rate during exercise was slightly but significantly lower following infusion (8 beats/min). In all except one subject the stroke volume was slightly larger after infusion. The $O_2$ uptake during exercise, the $O_2$ requirements of exercise, and the $O_2$ debt were not altered significantly by the infusion (figs. 3 and 4).

**Discussion**

While the augmentation of blood volume produced a substantial increase of cardiac output in the upright position at rest, it did not elevate the output during maximum exercise, despite a considerably higher central venous pressure. The possibility that these findings were influenced by repetition of the study can be excluded, since in an earlier investigation utilizing identical techniques, no significant changes in any of the variables were observed between two bouts of maximal exercise done one hour apart.11 The absence of any significant rise in the maximum $O_2$ uptake following blood infusion confirms the
finding of an unchanged cardiac output during exercise; the small increases in \( \text{O}_2 \) uptake observed in some subjects can be explained by the slight rise in hematocrit following transfusion. The possibility that the work load after infusion might be of insufficient magnitude to evoke a maximum cardiac output response can also be excluded, since in each subject the \( \text{O}_2 \) demand during exercise exceeded the \( \text{O}_2 \) uptake achieved and a large \( \text{O}_2 \) debt accumulated. After infusion the latter was comparable to, and in fact tended to be slightly larger than, the \( \text{O}_2 \) debt which accumulated prior to infusion. Thus, the cardiac output failed to achieve higher levels during exercise after expansion of the blood volume despite the fact that the level of output was inadequate to meet the metabolic requirements.

Although expansion of the blood volume resulted in only a small increase in central venous pressure when the subjects were at rest, it nevertheless produced a substantial elevation both in the resting cardiac output and stroke volume. These observations made with the subjects in the upright position differ from those in which the effects of acute hypervolemia were determined in the supine position, when no consistent changes in cardiac output were observed. This difference in response is probably accounted for by the fact that the stroke volume and cardiac output fall on assumption of the upright position as a result of a reduction in central venous pressure; augmentation of the total blood volume restores the level of the central venous pressure and thus raises the level of the cardiac output. At rest in the upright position, the heart of intact conscious subjects thus responds to an increase in blood volume and of central venous pressure in accordance with the operation of the Frank-Starling mechanism.

When exercise was performed after the blood infusion, the central venous pressure was significantly and substantially higher than during the control period of exercise. Despite elevation of central venous pressure, however, the cardiac output did not rise any further. From this it appears that the extracardiac mechanisms controlling central venous pressure are not normally the factors which limit ventricular filling and cardiac output during maximal exercise. These findings place the limitation of the cardiac output during maximum exercise on the heart itself.

A number of specific mechanisms may be responsible for the inability of the heart to augment its performance during exercise in spite of an elevation of central venous pressure. First, it is possible that the right ventricle is operating at the peak or on a
flat portion of its function curve, in which case a rise in central venous pressure, although associated with an increased end diastolic fiber length, would not further augment cardiac output. Secondly, it is possible that the elevation of central venous pressure is not associated with an increase in end diastolic fiber length during maximum exercise. The duration of diastole is very brief at the rapid heart rates achieved during maximum exertion and it has been shown that the abbreviation of diastole during tachycardia may result in insufficient time for the ventricle to relax completely. Under these circumstances it might be expected that the end diastolic fiber length would be little affected by an increase in filling pressure. The observation of Kjellberg et al. that heart size appears to diminish with levels of exercise which elevate heart rate beyond 140 to 160/min is consistent with this hypothesis. Thirdly, it is possible that cardiac filling is limited by the pericardium during maximum exertion, in which case an increase in central venous pressure would not be associated with a greater effective ventricular filling pressure or end diastolic fiber length. A mechanism of this sort would provide an automatic safeguard against the development of pulmonary edema during exercise since any increase in the filling pressure and volume of the left heart would necessarily cause a reduction in the filling, and consequently the output, of the right ventricle.

Whatever the precise mechanism or combination of mechanisms by which maximum cardiac performance is regulated, the results of this study suggest that it is the right side of the heart which normally sets the upper limit. This inference is based on the observation that the "central blood volume," calculated by the mean transit time method, was essentially the same in the two exercise periods, averaging 2.70 liters prior to infusion and 2.65 liters afterwards. It is appreciated that this evidence is indirect since "central blood volume" includes not only the volume of blood between the injection and sampling sites, but also that contained in all temporally equidistant pathways, and can therefore be influenced profoundly by redistribution of cardiac output. Since the cardiac output, level of exercise, and O₂ uptake were essentially the same during the two bouts of exercise, it seems improbable that substantial alterations of distribution of cardiac output occurred. The absence of change in the calculated "central blood volume" thus suggests that the true central blood volume was essentially the same during both exercise periods, which implies that all of the infused blood was accommodated in the systemic venous reservoir. Had the function of the left heart been a limiting factor, it would have been expected that at least some of the infused blood would have accumulated in the pulmonary vascular bed, and that the "central blood volume" during exercise would therefore have been higher during the postinfusion study.

The main finding of this investigation is that an acute increase in blood volume and central venous pressure does not result in any increase in the response of cardiac output to maximum exertion; from this it may be concluded that the blood volume and central venous pressure are not the factors which limit the cardiac response to exercise in normal subjects.

References


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