Effect of Acute Isovolemic Anemia on Cardiac Output and Estimated Hepatic Blood Flow in the Conscious Dog

By Gaston Chamorro, Jose A. Rodriguez, Barry Dzindzio, and Elliot Rapaport

ABSTRACT

The effect of acute isovolemic anemia induced by Dextran 70 exchange (40 ml/kg body weight) on estimated hepatic blood flow, cardiac output, and related variables was studied in 27 experiments on 24 unsedated dogs. Experiments were performed 5–10 days after implantation of an electromagnetic flow transducer around the aorta and catheters in the hepatic vein, jugular vein, and carotid artery. Bromsulphalein infusion was used to measure estimated hepatic blood flows, and electromagnetic measurements of stroke volume and cardiac output were calibrated using a simultaneous dye-dilution curve. With a mean fall in hematocrit from 34.8 to 17.0 ml/100 ml, estimated hepatic blood flow rose from 53.6 ± 15.3 (SD) to 76.3 ± 21.1 ml/min kg⁻¹ (P < 0.01). These changes were proportionately smaller than the increase in cardiac output (182 ± 80 to 350 ± 146 ml/min kg⁻¹) and the fall in systemic vascular resistance (37.0 ± 4.9 to 21.7 ± 4.9 mm Hg/liter min⁻¹), leading to a fall in the ratio of estimated hepatic blood flow to cardiac output from 34.3 to 25.7%. Bromsulphalein extraction ratio was significantly decreased, but Bromsulphalein clearance increased 44%. Splanchnic oxygen consumption did not change. Beta-receptor blockade in 6 dogs (propranolol 0.5 mg/kg body weight) failed to prevent or attenuate the increase in estimated hepatic blood flow or cardiac output when the blocking agent was given before induction of acute isovolemic anemia. Sixty minutes after accomplishment of anemia, estimated hepatic blood flow and cardiac output had returned toward but not to control levels. Induction of β-receptor blockade in the anemic dog did not influence the effects of time on estimated hepatic blood flow or cardiac output. We concluded that acute isovolemic anemia leads to a significant increase in estimated hepatic blood flow that is essentially independent of β-receptor stimulation.

KEY WORDS

beta-receptor blockade bromsulphalein clearance hepatic blood flow high output state splanchnic circulation splanchnic oxygen consumption blood viscosity dextran exchange

The effects of acute and chronic isovolemic anemia have been studied extensively in both man and animals (1–12). Cardiac output and flow through some of the major vascular beds rise during acute isovolemic anemia (10, 13, 14). Since changes in cardiac output represent the summation of changes in the various regional beds and since the hepatic blood flow is an important fraction of the cardiac output, we chose to study the effects of exchange anemia on hepatic blood flow. Unsedated dogs were employed to eliminate the known modifying effects of anesthesia and sedation on sympathetic nerve activity.

Furthermore, the increased cardiac output during isovolemic anemia is only partially adrenergically mediated (2, 6), and β-receptor blockade reduces but does not prevent this response (3, 6, 7, 12). Since controversy about the relative importance of β-adrenergic control of hepatic blood flow still exists, we also endeavored to define the role of β-receptor tone in the splanchnic vascular bed during acute isovolemic anemia.

Methods

Twenty-seven experiments were carried out on 24 mongrel dogs weighing between 13 and 20 kg. Under general anesthesia (sodium pentobarbital 30 mg/kg), an indwelling polyethylene no. 240 cannula was inserted into the left hepatic vein using the technique
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Effect of Acute Isovolemic Anemia on Cardiac Output, Estimated Hepatic Blood Flow, and Related Variables

Table 1 summarizes the effects of acute isovolemic anemia on estimated hepatic blood flow and related variables in 17 experiments and the effects on cardiac output and stroke volume in 6 experiments in which the electromagnetic measurement of cardiac output was calibrated with an indicator-dilution curve. Lowering the mean hematocrit from 34.8 to 17.0 ml/100 ml resulted in an average increase in estimated hepatic blood flow of 46.1%. (The average percent change was calculated throughout the paper by averaging the individual percent changes rather than by calculating the percent changes of the means.) Mean arterial blood pressure increased slightly but significantly; therefore, splanchnic vascular resistance dropped significantly (21.4%). The splanchnic arteriovenous oxygen difference varied inversely with the estimated hepatic blood flow (mean ± SD = 5.73 ± 1.45 and 3.81 ± 1.17 vol % for control and anemic conditions, respectively) and in such a way that there was no significant change in splanchnic oxygen consumption. During anemia the Bromsulphalein extraction ratio decreased an average of 17.3%, which was proportionately less than the increase in estimated

TABLE 1

Effect of Acute Isovolemic Anemia on Cardiac Output, Estimated Hepatic Blood Flow, and Related Variables

<table>
<thead>
<tr>
<th>Hematocrit (ml/100 ml)</th>
<th>Cardiac output (ml/min kg⁻¹)</th>
<th>SV (ml/kg)</th>
<th>HR (beats/min)</th>
<th>MAPB (mm Hg)</th>
<th>EHBFR (ml/min kg⁻¹)</th>
<th>SpVR (mm Hg liter min⁻¹)</th>
<th>Splanchnic O₂ consumption (ml/min)</th>
<th>BSP extraction ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>34.8</td>
<td>17.0</td>
<td>182</td>
<td>350</td>
<td>1.92</td>
<td>2.43</td>
<td>99</td>
<td>145</td>
</tr>
<tr>
<td>± SD</td>
<td>3.6</td>
<td>3.2</td>
<td>80</td>
<td>146</td>
<td>0.57</td>
<td>0.56</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
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</tr>
</tbody>
</table>

C = control, A = anemia, SV = stroke volume, HR = heart rate, MAPB = mean arterial blood pressure, EHBFR = estimated hepatic blood flow, SpVR = splanchnic vascular resistance, and BSP = Bromsulphalein. *P* values were calculated using Student’s paired t-test.

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hepatic blood flow. Therefore, the clearance of Bromsulphalein rose significantly (186 ± 74 to 270 ± 100 ml/min, P < 0.01).

The increase in cardiac output (average 95%) was more pronounced than the increase in estimated hepatic blood flow, leading to a significant fall in the ratio of estimated hepatic blood flow to cardiac output (34.3 ± 14.0 to 25.7 ± 11.3, P < 0.05). The systemic vascular resistance, which fell an average of 41.3%, consequently dropped more than the splanchnic vascular resistance. The increase in cardiac output resulted from an increase in both stroke volume (29.7%) and heart rate (48.5%, Table 1).

Although cardiac output was not calibrated directly in the remaining 11 experiments, the relative change could be measured from the electromagnetic signal and was observed to increase in a similar way in all dogs. Therefore, the increase in cardiac output for all 17 experiments was 92 ± 30% (mean ± SD).

To observe the ability of β-receptor blockade to modify the circulatory changes produced by acute isovolemic anemia, two sets of comparisons were made. Figure 1 shows the effect of acute isovolemic anemia on estimated hepatic blood flow in dogs that had received propranolol compared with that in dogs without blockade. Propranolol tended to produce a trivial decrease in estimated hepatic blood flow (44 ± 11.7 to 37.5 ± 9.8 ml/min kg⁻¹) that did not reach statistical significance (0.05 < P < 0.1). After induction of acute isovolemic anemia with similar mean falls in hematocrits (34.8 to 17.0 in the control group and 34.2 to 13.5 ml/100 ml in the group with β-receptor blockade), propranolol did not prevent or attenuate the increase in estimated hepatic blood flow, and the values achieved were not significantly different from those obtained in dogs with acute isovolemic anemia without β-receptor blockade.

Similarly, propranolol produced a small fall in cardiac output from 153 ± 23 to 139 ± 25 ml/min kg⁻¹ (P < 0.05) that was due exclusively to a decrease in resting heart rate (Fig. 2). After induction of acute isovolemic anemia, cardiac output increased similarly in the presence or the absence of β-receptor blockade. The ratios of estimated hepatic blood flow to cardiac output fell in a similar way with anemia in the presence or the absence of β-receptor blockade (29.9 ± 9.4 to 25.1 ± 9.4 vs. 34.3 ± 14 to 23.7 ± 11%, respectively).

Bromsulphalein extraction ratio was slightly increased after propranolol (33.0 ± 12.1 to 37.7 ± 14.1%, P < 0.05), although Bromsulphalein clearance and splanchnic oxygen consumption were not significantly modified. In none of these variables was the response to acute isovolemic anemia different in the group with β-receptor blockade compared with that in the group without blockade. As expected, there was a smaller increase in heart rate after β-receptor blockade which was compensated for by a greater increase in stroke volume.

Figure 3 shows the effect of propranolol administered to anemic dogs and compares the response in these dogs to that in a similar group of anemic dogs which did not receive the drug. The increased estimated hepatic blood flow present after acute isovolemic anemia was induced tended to return toward control levels without further intervention when the dogs were studied 30 minutes later. The addition of propranolol did not accelerate this return. Hematocrits for the propranolol-treated dogs (17.9 ± 2.7 ml/100 ml) and the nontreated dogs (17.8 ± 3.5 ml/100 ml) were essentially the same as those achieved immediately after anemia was induced (17.0 ± 3.2 ml/100 ml, Table 1).

Cardiac output behaved in a similar way during continued observation after induction of acute isovolemic anemia and, again, propranolol did not modify the effect of time on cardiac output in these dogs. From a 92 ± 30% increase immediately after anemia, the cardiac output decreased to 60 ± 33% and 78 ± 10% in the control and the propranolol-treated dogs, respectively.

**FIGURE 1**

_Effect of propranolol on the estimated hepatic blood flow (EHBF) in the resting dog and the response of estimated hepatic blood flow to acutely induced isovolemic anemia (right) compared with that in a group without β-receptor blockade (left). Each line represents one dog. The values of estimated hepatic blood flow achieved after anemia are not statistically different in the two groups (P < 0.1)._
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Effect of propranolol (P) on cardiac output (CO), ratio of estimated hepatic blood flow to cardiac output (EHBF/CO), heart rate (HR), stroke volume (SV), systemic vascular resistance (SVR), splanchnic vascular resistance (SpVR), Bromsulphalein extraction ratio (BSPER), and Bromsulphalein clearance (BSP/CI) in the resting dog and the subsequent response to acutely induced isovolemic anemia (A). White bars represent the mean value for the nonblocked group under control conditions (C) and after anemia (A). Stippled bars represent the mean value for the group that received propranolol and was then made anemic (A + P). Vertical lines represent 1 SD. The number of dogs in each condition is indicated below each bar. The only significant difference between the two groups after anemia was in heart rate. (P < 0.05).

Discussion

An increase in cardiac output following acute isovolemic anemia produced by exchange with dextran has been repeatedly observed in anesthetized dogs (1, 3, 7, 9, 10, 12) and has been also reported in awake dogs (6). Several regional flows are known to contribute to the increased cardiac output, namely, coronary (10), renal (14), and cerebral blood flows (13).

Estimated hepatic blood flow has been studied only during chronic anemia in man (8) and was found to be within the normal range. However, many of the patients had a normal cardiac output, which precludes a clear-cut conclusion. The present study demonstrated that a marked increase in estimated hepatic blood flow was produced by acute isovolemic anemia in dogs. The fall in the ratio of estimated hepatic blood flow to cardiac output was small, but it indicates that blood flow to other vascular beds increased proportionately more than estimated hepatic blood flow. The splanchnic circulation behaves similarly during exercise when estimated hepatic blood flow remains constant (18) or falls (19) as cardiac output and blood flow to exercising muscles markedly increase.

The contribution of enhanced myocardial contractility to the increased cardiac output during acute isovolemic anemia has been suggested in two studies (7, 12). However, it seems well established that the main determinant of the hyperkinetic circulation is the marked fall in peripheral vascular resistance resulting from the decrease in blood viscosity. The present study revealed that splanchnic vascular resistance also fell markedly. We made
no attempt to quantify the change in blood viscosity in vitro, since there is no predictable relation between the change in blood viscosity measured in vitro and the effective viscosity of blood flowing through the resistance vessels. For a given hematocrit, blood viscosity is highly dependent on the shear rate, and a decrease in shear rate from 20 to 0.2 sec\(^{-1}\) can produce a four- to fivefold increase in blood viscosity in vitro (20).

Since the increase in estimated hepatic blood flow was proportionately less than the increase in flow to other vascular beds after acute isovolemic anemia, some regulatory control over the corresponding vascular resistances must be operating. Alpha-adrenergic agents cause vasoconstriction of the hepatic arterioles (21) that can be blocked by phenoxybenzamine (22). The vasoconstriction caused by epinephrine and hepatic nerve stimulation converts to vasodilatation after \(\alpha\)-receptor blockade (23). The vasodilating effect of isoproterenol (21, 22) and experiments in the isolated perfused dog liver (24) suggest that \(\beta\)-receptor stimulation produces vasodilatation of the hepatic arterial bed. The nervous and humoral influences on the portal vein and its tributaries seem much less pronounced and, in general, more dependent on the changes induced in the intestinal and splenic arterial vasculatures in which the overall effect of \(\beta\)-receptor stimulation is also one of vasodilatation (23, 25).

The experiments with propranolol were designed to explore the regulatory role of \(\beta\)-receptor stimulation during acute isovolemic anemia. The adequacy of the \(\beta\)-receptor blockade may be inferred from the known effects of the dose used (4, 7) and from the smaller increase in heart rate after induction of acute isovolemic anemia in the propranolol-treated dogs. The effects of \(\beta\)-receptor blockade per se were minimal in the resting dog. Cardiac output fell slightly, mainly as a consequence of a decrease in heart rate, and there was a tendency for estimated hepatic blood flow to fall. This decline was accompanied by a significant increase in the Bromsulphalein extraction ratio and a tendency for the splanchnic arteriovenous oxygen difference to increase, changes that are opposite to those seen when significant increases in estimated hepatic blood flow occur. It was clear that propranolol did not prevent the increase in cardiac output after acute isovolemic anemia. The increase in estimated hepatic blood flow was not prevented in turn, and the actual values during anemia were not significantly different from those of the nontreated dogs.

Beta-receptor blockade by pronethalol and dichloroisoproterenol (3, 6, 7) also fails to prevent the increase in cardiac output after acute isovolemic anemia. Denervation of the heart, treatment with reserpine, or both do not completely block the rise in the cardiac output following acute anemia, and the adrenal glands need not be present for this response to occur (2). Failure of \(\beta\)-receptor stimulation to play a dominant role in the cardiac output and estimated hepatic blood flow responses to acute isovolemic anemia was further confirmed when these parameters returned toward control levels from the peak elevation obtained immediately after anemia was induced at a rate uninfluenced by \(\beta\)-receptor blockade. The fall in cardiac output shortly after acute isovolemic anemia was induced confirmed previous observations (3). The present study indicated a similar time course for response of the splanchnic circulation. There was no significant modification of the hematocrit 30–60 minutes after induction of anemia; any change in the relative concentration of dextran in the plasma would not be expected to influence the effective blood viscosity which was thus assumed to remain approximately the same during this period (20). It is highly likely, therefore, that a readjustment of vascular tone took place to bring the vascular resistance back toward control levels in a way that
appeared to be independent of the β-adrenergic system. A reasonable explanation would seem to be a secondary increase in α-adrenergic tone, thus accomplishing a decrease in the high output state, which is not necessary from a tissue perfusion standpoint but results primarily from the physical effects of decreased blood viscosity.

It is of interest that splanchnic oxygen consumption did not change after acute isovolemic anemia, since the splanchnic arteriovenous oxygen difference decreased in proportion to the increase in flow. Beta-receptor blockade did not modify this relation. Therefore, an increase in the hepatic metabolic rate can be ruled out as a determinant of the increase in estimated hepatic blood flow in acute isovolemic anemia.

The ability of the liver to excrete Bromsulphalein without impairment during acute isovolemic anemia was demonstrated in this study; in fact, the clearance of Bromsulphalein was significantly higher during anemia. Moreover, this response did not pair the ability of the liver to clear Bromsulphalein during control conditions or after induction of acute isovolemic anemia.

References
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