Reactive Hyperemia and Oxygen Extraction in the Feline Small Intestine

Nicholas A. Mortillaro and Harris J. Granger

SUMMARY Arterial flow and oxygen extraction were continuously measured from an in situ, denervated loop of cat ileum. Following release of arterial occlusion of varying time periods, oxygen extraction decreased transiently, returning to control levels as the hyperemia subsided. These results suggest that the hyperemia overcompensates in attempting to repay the oxygen deficit and, consequently, oxygen extraction is depressed. In the pump-perfused preparation (constant flow), oxygen extraction rose following the release of arterial occlusion indicating a shift to oxygen extraction as the mechanism for repaying the oxygen deficit in the absence of hyperemia. Following venous occlusion, reactive hyperemia failed to develop in the majority of cats and, when present, was highly blunted. In addition, oxygen extraction rose transiently suggesting that, as with constant flow, this is the mechanism of oxygen debt repayment in the absence of hyperemia. With venous pressure elevation, a decrease in blood flow was coupled to an increase in oxygen extraction that resulted in an overall increase in calculated oxygen consumption; oxygen extraction progressively increased for each level of venous pressure. Estimated oxygen consumption following occlusion suggests a decrease in oxygen demand during arterial occlusion and an increased demand during venous occlusion. However, during venous occlusion, the myogenic and metabolic control mechanisms would elicit opposite effects. Based on the results obtained following venous occlusion, we suggest that the blunted hyperemic response observed results from the net influence of both mechanisms acting in opposition, that is, a myogenic influence modulated by a metabolic one.

PREVIOUS STUDIES of reactive hyperemia in intestine have focused mainly on hemodynamic responses following release of arterial occlusion.1 Our experiments were designed to elucidate three questions. First, does vasoregulation during vascular occlusion reflect a unitary mechanism, either myogenic or metabolic in nature? To answer this question, the effects of venous vs. arterial occlusion were compared. Second, what mechanisms are used by intestinal tissue to reestablish normal blood-tissue O2 transport following release of vascular occlusion? Thus, blood flow and A-VO2 transients were monitored and the contributions of reactive hyperemia and altered O2 extraction to repayment of O2 debt were determined. Finally, what is the effect of vascular occlusion on intestinal aerobic metabolism?

Methods

GENERAL PROCEDURE (FIG. 1)

The procedure used in this study is similar, except for minor alterations, to that described in detail in a previous study.2 Briefly, the spleen, greater omentum, large intestine, and a portion of the small intestine were surgically removed through a midline abdominal incision and the superior mesenteric vein of the remaining intact ileal segment (20-50 g) was cannulated and the venous outflow passed into a reservoir before being returned to the cat through a jugular vein. Heparinized blood from a freshly killed donor cat was used to prime the extracorporeal venous circuit. Venous outflow pressure of the intestinal segment was set by adjusting the height of the reservoir and monitored from a T-connector located in the venous circuit. For continuous recording of intestinal arteriovenous oxygen difference, a small portion of the venous efflux (3-4 ml/min) and arterial blood from a carotid artery were pumped through a calibrated arteriovenous oxygen difference analyzer (Oxford Instruments).

Arterial perfusion of the in situ intestinal segment was accomplished by passing blood from a femoral artery to the superior mesenteric artery; the latter was stripped of the surrounding sympathetic nerve plexus. Inserted in the arterial loop was a flow probe (CME) and, distal to the probe, a T-connector through which intestinal perfusion pressure was monitored. The signal from the flow probe was used to drive a square wave electromagnetic flow meter (CME). Venous and arterial perfusion pressure were measured with Statham P23 pressure transducers. All parameters were recorded on a Beckman type 411 Dynagraph recorder.

We used a total of 28 cats, 15 for studies of occlusion and 13 for studies of elevation of venous pressure. Each cat weighed 2-3 kg and was anesthetized with sodium pentobarbital (35 mg/kg, ip); maintenance doses were given iv as required. In addition, atropine (1 mg/kg, iv) and heparin sodium (200 USP/kg, iv) were also administered.

For the series of experiments in which arterial inflow was constant, a small pump (Extracorporeal) was placed
in parallel to the arterial perfusion circuit thereby allowing the intestinal segment to be perfused normally or via the pump circuit (constant flow).

EXPERIMENTAL PROCEDURE

Following the procedure outlined above, the preparation was allowed to attain a steady state in which all parameters appeared to be stable and in a resting state. Occlusions were performed by clamping the extracorporeal loops at the appropriate point. Thus, for arterial occlusions a clamp was placed between the perfusion pressure transducer and the flow probe; for venous occlusions the clamp was placed between the venous pressure transducer and the outflow reservoir. In the case of the pump perfused occlusion studies, the normal perfusion pathway was clamped and perfusion transferred to the pump circuit. Occlusion of the pump circuit was accomplished by turning the pump off for the appropriate period of time. In addition, during all occlusion periods, the pump bringing arterial and venous blood to the arteriovenous oxygen difference analyzer was turned off for the entire period of occlusion and started at the time of release of occlusion. All occlusion studies were carried out for varying periods of time, i.e., 5, 10, 15, 20, 30, 45, 60, or 120 seconds.

Studies involving elevations in venous pressure were performed by allowing a control period at a venous pressure of 0 mm Hg and then rapidly elevating the reservoir in the venous outflow circuit to a level that yielded the desired venous outflow pressure of 15, 20, 25, or 30 mm Hg.

Values for oxygen consumption were determined in the following manner. After making corrections for lag times in the extraction curve, that is, corrections for the time required for venous blood to reach the A-VO\textsubscript{2} difference analyzer, the product of the instantaneous corresponding values for points along the blood flow and O\textsubscript{2} extraction curves were used to establish an oxygen consumption vs. time curve. The area under the resulting curve was then determined by planimetry and an estimate of total oxygen consumption was established for both the pre- (control) and postocclusion oxygen consumption curves.

Results

ARTERIAL OCCLUSION, NORMAL PERFUSION

The response of the intestinal vasculature to a 120-second occlusion of arterial inflow is shown in panel A of Figure 2. Upon release of occlusion, blood flow rose rapidly to nearly three times the control value, indicating a substantial dilation of the intestinal vasculature during the period of ischemia. In contrast to the blood flow response, the arteriovenous oxygen difference decreased following release of the occlusion, indicating a reduction in the oxygen extraction ratio.

Table 1 summarizes the vascular and oxygen dynamics following release of arterial occlusions of 5-120 seconds duration. Occlusions lasting only 5 seconds evoked a 1.5-fold increase in peak flow during the hyperemic period. Further increases in the duration of occlusion up to 45 seconds produced linear increments in peak hyperemic flow. For occlusions lasting more than 45 seconds, peak hyperemic flow did not increase significantly above the levels attained at 45 seconds. In contrast, the duration of the reactive hyperemia was essentially independent of occlusion times from 4 to 45 seconds but increased markedly with further increments in duration of ischemia beyond 45 seconds. The characteristic change in oxygen extraction for all periods of occlusion was a reduction in the extraction, the extent of the reduction increasing with duration of arterial occlusion. Assuming a constant oxygen demand during the period of occlusion (i.e., an oxygen debt incurred), repayment of the oxygen deficit was 93.2% for 10-second occlusions and decreased markedly to 43.8% for arterial occlusions lasting 120 seconds.

ARTERIAL OCCLUSION, CONSTANT FLOW

The response of the intestinal vasculature to an occlusion for 120 seconds of the arterial inflow for the pump-perfused preparation is shown in Figure 2, panel C. In contrast to the response shown in panel A, the postocclusion flow was kept constant (absence of hyperemia); however, the arteriovenous oxygen difference increased following the release of the occlusion, indicating a marked increase in the oxygen extraction ratio.

Table 2 summarizes the results of experiments on the pump-perfused preparation in response to arterial occlusions of 5-120 seconds. For all periods of ischemia, the elicited response was a rise in oxygen extraction, the extent of the elevation increasing with the duration of arterial occlusion. Assuming, as above, a constant tissue oxygen demand during the period of arterial occlusion, repayment of the estimated oxygen debt was 88.5% for 10-second occlusions and decreased to 41% for arterial occlusions lasting 120 seconds.
VENOUS OCCLUSIONS

The response of the intestinal circulation to release of an occlusion of the intestinal venous outflow lasting 120 seconds is illustrated in panel B of Figure 2. Note that during the occlusion the arterial inflow decays rather slowly to zero, presumably reflecting the translocation of arterial blood into the venous compartment to elevate venous pressure toward arterial levels. The dramatic reactive hyperemic response as seen in the postarterial occlusion studies (panel A) is conspicuously absent following the release of venous occlusion. In addition, the oxygen extraction rises dramatically in marked contrast to the reduction in oxygen extraction seen following release of arterial occlusion.

Table 3 summarizes the data for venous occlusion. The results show that following the release of venous occlusion, both the peak oxygen extraction attained and the duration of the augmented oxygen extraction were proportional to the duration of the occlusion. In most cases, reactive hyperemia was absent following venous occlusion, and in those few instances in which it was seen it was markedly blunted and of very short duration.

Again, assuming unchanged oxygen demand during the occlusion period, repayment of the estimated oxygen debt incurred was 101.3% for a 10-second occlusion and increased to 198.6% for occlusions lasting 120 seconds. These results indicate a gross overpayment of the estimated oxygen deficit incurred during the occlusion period. However, as shown below, studies of venous hypertension suggest that intestinal oxygen demand is modified by changes in venous pressure.

ELEVATION OF VENOUS OUTFLOW PRESSURE

Figure 3 illustrates the response of the intestinal circulation to venous outflow pressure elevations of 15 and 30 mm Hg. Although blood flow decreases during venous hypertension, oxygen extraction rises dramatically and consequently oxygen consumption is accelerated. The results of experiments on 13 cats in which venous pressure was elevated to 15, 20, 25, and 30 mm Hg are summarized
in Table 4. The results indicate that intestinal oxygen consumption rises significantly and progressively with increasing venous outflow pressure, e.g., elevation of venous outflow pressure to 15 mm Hg resulted in a mean increase of 18% in oxygen consumption over the control ($P_v = 0$ mm Hg). At a venous outflow pressure of 30 mm Hg, the consumption increased 98% over control.

**Discussion**

**MYOGENIC VS. METABOLIC CONTROL OF INTESTINAL VASCULATURE**

The reactions of the microvasculature to vascular occlusion have been explained in terms of metabolic and myogenic mechanisms.1, 4-8 According to the metabolic hypothesis, vascular tone is modulated by vasodilator metabolites released from parenchymal cells or by interstitial $P_O_2$ per se. On the other hand, the myogenic hypothesis proposes that vascular resistance is directly proportional to transmural pressure at the microvascular level, presumably due to the effect of stretch on vascular smooth muscle activity (Bayliss effect).

Although both the metabolic and myogenic hypotheses predict an active dilation of resistance vessels during arterial occlusion, several arguments can be made in favor of metabolic control. First, the effect of duration of occlusion on peak hyperemic flow and duration of hyperemia suggests that the vascular response is caused by metabolite accumulation or $O_2$ deficiency. Thus, the reduction of vascular resistance is proportional to metabolite accumulation or vascular smooth muscle energy depletion for periods of occlusion less than 45 seconds. For occlusion periods greater than 45 seconds, vascular resistance is at a minimum, and the proportionality between occlusion time and duration of hyperemia probably reflects the rate-limiting effects of metabolite washout or restoration of vascular ATP stores. Second, our observation of an increased duration of vasodilation when hyperemia is prevented by constant flow perfusion suggests that metabolite washout rate is a rate-limiting factor in the hyperemic response to arterial occlusion.

The evidence presented above in favor of metabolic control during arterial occlusion is circumstantial. To separate metabolic and myogenic factors in a more direct manner, analysis of vascular responses to venous occlusion is the method of choice. During venous occlusion, the metabolic and myogenic mechanisms elicit completely opposite microvascular responses. The metabolic scheme predicts a vasodilation secondary to accumulation of vasodilator metabolites during venous stasis. In our study the absence of any hyperemia following release of venous occlusion is difficult to reconcile with the metabolic theory.

**Table 1 Effects of Arterial Occlusion with Normal Perfusion**

<table>
<thead>
<tr>
<th>Occlusion time (sec)</th>
<th>No. of observations</th>
<th>Control blood flow† (ml/min per 100 g)</th>
<th>Peak reactive hyperemia (% control)</th>
<th>Duration of reactive hyperemia (sec)</th>
<th>Repayment of estimated oxygen debt (%)</th>
<th>Maximum change in $A-VO_2$ (% control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>7</td>
<td>30.9 ± 3.52 1.5 ± 0.11</td>
<td>18.1 ± 1.43 99.1 ± 1.33</td>
<td>0.93 ± 0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>32.7 ± 3.33 1.9 ± 0.08</td>
<td>20.0 ± 1.43 93.2 ± 2.09</td>
<td>0.89 ± 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>8</td>
<td>28.9 ± 3.12 2.2 ± 0.12</td>
<td>20.6 ± 1.06 84.0 ± 2.94</td>
<td>0.88 ± 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>33.6 ± 3.29 2.5 ± 0.07</td>
<td>21.2 ± 1.50 78.3 ± 3.79</td>
<td>0.87 ± 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>7</td>
<td>32.9 ± 3.98 2.9 ± 0.09</td>
<td>24.7 ± 1.91 58.6 ± 3.59</td>
<td>0.81 ± 0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>13</td>
<td>34.6 ± 2.87 3.1 ± 0.17</td>
<td>42.6 ± 3.38 53.2 ± 3.54</td>
<td>0.77 ± 0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>11</td>
<td>32.6 ± 2.95 3.1 ± 0.14</td>
<td>87.9 ± 4.21 43.8 ± 2.03</td>
<td>0.69 ± 0.010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values given in above table are mean ± se.
* From 15 animal experiments.
† Preocclusion blood flow.
‡ Based on the assumption that oxygen consumption during the ischemic period remains at preocclusion levels.
See text for details.

**Table 2 Effects of Arterial Occlusion with Constant Flow**

<table>
<thead>
<tr>
<th>Occlusion time (sec)</th>
<th>No. of observations</th>
<th>Blood flow† (ml/min per 100 g)</th>
<th>Repayment of estimated oxygen debt (%)</th>
<th>Maximum change in $A-VO_2$ (% control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>35.3 ± 2.87</td>
<td>98.5 ± 2.25</td>
<td>1.21 ± 0.044</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>37.3 ± 3.49</td>
<td>88.5 ± 2.01</td>
<td>1.24 ± 0.013</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>34.5 ± 3.32</td>
<td>82.3 ± 2.22</td>
<td>1.32 ± 0.011</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>32.3 ± 3.14</td>
<td>75.4 ± 2.14</td>
<td>1.35 ± 0.010</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>35.6 ± 3.10</td>
<td>65.2 ± 1.08</td>
<td>1.45 ± 0.013</td>
</tr>
<tr>
<td>45</td>
<td>4</td>
<td>37.3 ± 2.97</td>
<td>60.7 ± 0.41</td>
<td>1.48 ± 0.016</td>
</tr>
<tr>
<td>60</td>
<td>4</td>
<td>36.8 ± 3.79</td>
<td>51.8 ± 0.89</td>
<td>1.54 ± 0.009</td>
</tr>
<tr>
<td>120</td>
<td>4</td>
<td>36.6 ± 4.02</td>
<td>41.0 ± 0.79</td>
<td>1.71 ± 0.023</td>
</tr>
</tbody>
</table>

All values given in above table are mean ± se.
* From four of the 15 animal experiments.
† Pre- and postocclusion blood flows.
‡ Based on the assumption that oxygen consumption during the ischemic period remains at preocclusion levels.
See text for details.
of local vasoregulation. Others have suggested that reactive hyperemia following venous occlusion is less intense than the hyperemia observed following arterial occlusion of the same duration because arterial blood continues to flow through the capillaries for some time and, hence, the degree of tissue hypoxia is less severe. However, if the duration of the zero flow period during venous occlusion is used as a measure of degree of ischemia in our study, the flow responses following release of arterial and venous occlusions are still dramatically different. Furthermore, the elevation of metabolite levels should be rather substantial during venous occlusion because tissue metabolism appears to be accelerated. Thus, according to the metabolic hypothesis, the hyperemia following release of venous occlusion should be more dramatic than that observed on release of an arterial occlusion of the same duration.

Since we cannot account for the vascular response to venous occlusion on the basis of a metabolic mechanism, we now turn to a consideration of the possible involvement of myogenic factors. According to the myogenic hypothesis, vascular resistance should increase during venous occlusion due to elevation of intravascular pressure at the microvessel level. Consequently, immediately upon release of venous occlusion, arterial flow should be depressed below the control value and subsequently is expected to rise to the preocclusion level as transmural pressure falls to control. Such a short-lived reactive reduction in flow was not observed in our experiments and thus casts doubt on the sole involvement of the myogenic factor.

MECHANISMS OF O₂ TRANSPORT FOLLOWING RELEASE OF VASCULAR OCCLUSION

The present study is the first to focus on the relative contribution of reactive hyperemia and O₂ extraction to repayment of intestinal O₂ debt following release of vascular occlusion. Upon release of arterial occlusion, intestinal O₂ extraction is depressed throughout the hyperemic phase. Since both myogenic and metabolic control mechanisms would elicit increased effective capillary density during arterial occlusion, it is unlikely that the transient decrease in arteriovenous oxygen difference results from diffusion limitations. A more convincing argument can be made for "luxury perfusion" of the intestine following release of the ischemic stimulus. In other words, the vessels controlling vascular resistance are so sensitive to the effects of arterial occlusion that the resultant hyperemia, at any given instant after release of the

### Table 3

**Effects of Venous Occlusion**

<table>
<thead>
<tr>
<th>Occlusion time (sec)</th>
<th>No. of observations*</th>
<th>Control blood flow† (ml/min per 100 g)</th>
<th>Peak reactive hyperemia‡ (x control)</th>
<th>Duration of increased A-VO₂ (sec)</th>
<th>Repayment of estimated oxygen debt (%)</th>
<th>Maximum change in A-VO₂ (x control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>32.3 ± 4.24</td>
<td>1.03 ± 0.013</td>
<td>7.0 ± 1.45</td>
<td>100.3 ± 2.59</td>
<td>1.12 ± 0.005</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>30.3 ± 4.16</td>
<td>1.01 ± 0.017</td>
<td>18.7 ± 1.52</td>
<td>101.3 ± 1.42</td>
<td>1.26 ± 0.007</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>33.5 ± 4.36</td>
<td>1.02 ± 0.015</td>
<td>26.7 ± 2.72</td>
<td>102.7 ± 1.36</td>
<td>1.39 ± 0.012</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>35.7 ± 4.15</td>
<td>1.02 ± 0.017</td>
<td>61.3 ± 3.77</td>
<td>105.8 ± 2.07</td>
<td>1.47 ± 0.010</td>
</tr>
<tr>
<td>30</td>
<td>6</td>
<td>32.5 ± 5.45</td>
<td>1.01 ± 0.013</td>
<td>66.7 ± 4.06</td>
<td>107.3 ± 2.03</td>
<td>1.61 ± 0.016</td>
</tr>
<tr>
<td>45</td>
<td>6</td>
<td>30.2 ± 3.93</td>
<td>1.00 ± 0.006</td>
<td>95.0 ± 4.48</td>
<td>110.4 ± 2.59</td>
<td>1.68 ± 0.013</td>
</tr>
<tr>
<td>60</td>
<td>8</td>
<td>32.7 ± 4.82</td>
<td>1.04 ± 0.023</td>
<td>130.0 ± 6.14</td>
<td>126.8 ± 3.23</td>
<td>1.93 ± 0.027</td>
</tr>
<tr>
<td>120</td>
<td>7</td>
<td>38.3 ± 4.38</td>
<td>1.03 ± 0.020</td>
<td>198.6 ± 9.84</td>
<td>195.0 ± 5.77</td>
<td>2.36 ± 0.031</td>
</tr>
</tbody>
</table>

All values given in above table are mean ± se.

* From eight of 15 animal experiments.

† Preocclusion blood flow.

‡ Approximately 20% of observation showed any reactive hyperemia following venous occlusion; all were blunted and of short duration.

§ Based on the assumption that oxygen consumption during the ischemic period remains at preocclusion levels. See text for details.

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Figure 3. Response of the intestine to elevations in venous outflow pressure resulting in an increase over control of oxygen extraction at each level of elevated venous pressure. Calculated values of peak oxygen delivery (BF × A-VO₂) are 0.46 ml of O₂/min × 100 g at control, 0.84 at Pᵥ = 15 mm Hg, and 1.47 at Pᵥ = 30 mm Hg. Pᵥ and Pₐ are arterial and venous pressures. BF is blood flow, and A-VO₂ is the arteriovenous difference for oxygen.
occlusion, is greater in relative terms than the transient increase in O₂ uptake. If the hyperemia is prevented by constant flow perfusion, repayment of the oxygen debt is not compromised because oxygen extraction is substantially elevated for some time following release of arterial occlusion. Thus, our data suggest a two-component control mechanism for regulating transcapillary O₂ flux. The range of compensation of this two-component system is substantial since the compromise of one of the components is counterbalanced by an increased contribution of the other. Further support for this concept is provided by studies on venous occlusion; in this case, no reactive hyperemia occurs and repayment of the incurred O₂ debt is accomplished by a long-lasting augmentation of O₂ extraction.

**INTESTINAL METABOLISM AND VASCULAR OCCLUSION**

The apparent oxygen consumption patterns seen following arterial and venous occlusion are dramatically different. It should be noted that the resultant data, expressed as "estimated oxygen consumption," were computed on the assumption that intestinal tissue oxygen demand remained constant during the occlusion period. Based on the foregoing assumption, the resultant data would thus indicate that, following arterial occlusion, for both the normally perfused preparation and the constant flow preparation, the reactive hyperemia and/or modified oxygen extraction are of such magnitude and duration as to be inadequate to repay the estimated oxygen debt incurred during the ischemic period, the deficit increasing with duration of arterial occlusion. On the other hand, if the contrary assumption is made, that is, the oxygen deficit incurred during the period of ischemia is fully repayed postocclusively, regardless of the duration of occlusion, a more compelling argument emerges suggesting that oxygen demand does not remain constant during the ischemic period but decreases, and that the relative decrease in oxygen demand is proportional to the duration of arterial occlusion. In contrast, the gross overpayment of the "estimated oxygen debt" incurred during venous occlusion would indicate that intestinal tissue oxygen demand increases during the occlusive period. The increase in oxygen delivery seen with elevations of venous outflow pressure indicates that such is the case.

The nature of the elevated intestinal O₂ utilization during venous hypertension is unknown. Recent studies have demonstrated a similar phenomenon in cardiac muscle subjected to elevated coronary sinus pressure.²³ For myocardium the suggested mechanism is sarcomere lengthening and concomitant augmentation of force generation induced by elevated interstitial volume. Since the contribution of visceral smooth muscle O₂ uptake to total intestinal O₂ consumption is small,¹⁴ it is unlikely that the observed augmentation of ileal O₂ uptake results from increased motility induced by a rise in venous pressure. Furthermore, intestinal motility was not observed during venous hypertension in preparations placed in a sensitive fluid-filled plethysmograph.⁷ Although recent histochemical studies¹⁵ indicate a high aerobic capacity for blood vessels of the ileal submucosa, the small mass of the vascular tissue argues against increased vascular metabolism as an explanation for the acceleration of ileal O₂ consumption during venous hypertension. At present, lack of detailed information on the metabolic responses of intestinal tissue to venous hypertension precludes any type of analysis beyond mere speculation.

**Acknowledgments**

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Lack of Correlation of Plasma Norepinephrine and Dopamine-β-hydroxylase in Hypertensive and Normotensive Subjects

CHARLES R. LAKE, MICHAEL G. ZIEGLER, MICHAEL COLEMAN, AND IRWIN J. KOPIN

SUMMARY Dopamine-β-hydroxylase (DBH) and norepinephrine (NE) have been determined in over 350 plasma samples from 174 subjects while resting supine (basal sample), standing, or exercising. Although increments in both NE and DBH were found with postural change, the further increase in plasma levels of NE during exertion was not attended by any change in levels of DBH. There was no significant correlation between basal levels of DBH and NE nor was there any correlation in their increments after standing or exercising. DBH activity in plasma of subjects with moderate essential hypertension was not different from that of normotensive subjects. It is concluded that plasma DBH is a poor index of acute sympathetic neuronal activity.

THE ENZYME dopamine-β-hydroxylase (DBH), which is responsible for the formation of norepinephrine (NE) from dopamine,1 is released along with the catecholamines from the adrenal medulla2 and from stimulated sympathetic nerves in perfused organs.3-6 The enzyme is present in plasma of man and other animals.6 In animals, the levels of the enzyme are increased with stress7 and decreased after chemical destruction of the sympathetic nerve endings but not after adrenalectomy.8 Thus, DBH in plasma appears to come from sympathetic nerve endings. In man, levels of DBH in plasma are reported to be increased by procedures that increase sympathetic neuronal activity, e.g., exercise,9-11 immersion of the hand in cold water,10 and insulin-induced hypoglycemia.12 Basal levels of DBH vary widely between normal individuals, and the degree of elevation of the enzyme with stress is usually relatively small (10-25%), so increases in enzyme levels are not always observed after stress.13 Furthermore, during the cold pressor test, levels of the other large protein molecules increase in parallel with DBH.14 Thus, some investigators have found DBH to be a useful index of sympathetic function15-20 while others have not.11-13 Because of the controversy over the meaning of small changes in DBH activity, Noth et al.28 have stressed the need for the analysis of NE and DBH from the same plasma samples to determine whether DBH is an index of acute changes in sympathetic neuronal activity. In the present study, changes in plasma levels of DBH, total protein, a representative large protein molecule (prolactin), and NE are examined in normotensive, healthy subjects at rest, while standing, and after a standard exertion known to produce an increase in plasma levels of NE and pulse rate.25 Since some studies have found DBH activity to be elevated in hypertensive patients or correlated with blood pressure15-16-20-21-25-30 but other studies have not,17-20,24,31,25 we also measured DBH of subjects with essential hypertension under basal conditions and while standing.

Methods

Normotensive Caucasian volunteers (68 individuals of both sexes), without significant abnormalities on the basis of medical history and physical examination, and who ranged in age from 10 to 70 years, and 106 outpatients (age range, 16 to 78 years) with mild to moderate essential hypertension were asked not to take medication for 7 days nor tobacco, coffee, or tea for at least 3 hours prior to reporting for the test procedures. After a thorough explanation of the procedure, subjects gave written consent and they were asked to lie supine and relax in a quiet room. The needle of a “heparin lock” with a 3-way stopcock was inserted into an antecubital vein. A solution containing 30 units of sodium heparin (Upjohn) per milliliter sterile saline was used to flush the catheter and...
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