Peripheral Resistance after Cardiac Output Reduction in the Barodenervated Cat

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SUMMARY. Studies on the nervous or humoral control of total peripheral resistance are often complicated by concomitant changes in cardiac output. We studied the influence of cardiac output on peripheral resistance in the absence of modulating reflexes. In barodenervated and vagotomized cats, cardiac output was varied by graded inferior caval vein occlusion or by arterial bleeding. Total peripheral resistance was obtained with an analogue device which continuously divided the pressure difference between aorta and caval vein by cardiac output (electromagnetic flowmeter). Cardiac output reduction caused a decrease in peripheral resistance, followed within 2 minutes by a slow increase. Resistance stabilized at preocclusion levels within 5.8 (range 4-9) minutes. The relative changes in resistance and cardiac output were linearly related, when cardiac output was reduced by less than 40%. With larger reductions, the relation became nonlinear, and with a drop of more than 65%, no further change was noticed. These changes in resistance could not be explained by variations in blood viscosity as measured by Hct. They were nonnervous in nature: when all reflexes were abolished by ganglionic blockade, a similar pattern was found. Humoral mechanisms like the vasopressin or the renin-angiotensin system, known to be activated by hypotension, probably played no role, since arterial osmolality remained stable and captopril did not influence the resistance response. The involvement of metabolic autoregulation could not be excluded, but was unlikely because O₂ consumption and serum lactate did not change. (Circ Res 52: 7-15, 1983)

IN STUDIES on nervous or humoral control of total peripheral resistance, it often remains uncertain whether a change in resistance has resulted from the stimulus alone or is also a consequence of a concomitant change in cardiac output. A reduction of cardiac output (with a subsequent fall in blood pressure) is known to increase peripheral resistance when the baroreflexes are intact. When cardiac output is reduced after elimination of these reflexes, no change (Levy et al., 1954; Sagawa and Eisner, 1975; Rumberger et al., 1978), or a decrease in resistance (Fol- kow, 1953a; Granger and Guyton, 1969; Shepherd et al., 1973; Liedtke et al., 1973), is found.

In some of these studies, resistance had not been calculated continuously. In others, the use of circulatory pump devices or artificial blood reservoirs may have prevented active changes in vascular tone (Folk- kow, 1953b; Green et al., 1963; Falotico and Zimmerman, 1978). In the present investigation on cats, we measured resistance continuously after a fall in cardiac output until a steady state was reached. Reflex modulation of resistance was abolished by barodenervation and vagotomy or by ganglionic blockade. Surgical trauma and invasive interventions were kept to a minimum.

Methods

Preparation

Thirty two cats (weight 3-5.2 kg) were anesthetized with sodium pentobarbital (35 mg/kg, ip). They were artificially ventilated with a mixture of room air and oxygen (2:1) at a rate of 20/min. Tidal volume was adjusted such that the capnometer (Godart, type 146) indicated an end-expiratory CO₂ content of 3.6%. Blood samples, taken at regular intervals, showed that this percentage corresponded with an arterial CO₂ pressure of about 3.7 kPa (28 mm Hg), which is normal for the cat (Fink and Schoolman, 1963).

Blood pH and PaCO₂ ranged from 7.30 to 7.42 and 13.3 to 18.6 kPa (100-140 mm Hg), respectively.

During the surgical preparations, we added 1.5% halothane to the ventilation gas. After completion of surgery, a light anesthesia was maintained by a continuous intravenous infusion of sodium pentobarbital (3-6 mg/kg per hour). The infusion rate was adjusted so that the pupillary light reflex remained present and slight responses were obtained from the eyelid, the larynx, and the interdigital reflex.

Body temperature was kept at 37°C by a servo-controlled warming device. To avoid gross changes in body fluid volume, urine production was measured continuously by means of a urethra catheter and the same amount of saline was continuously infused into the left femoral vein. After barodenervation, production of urine increased considerably. The infusion procedure resulted in hematocrit values which varied less than 5 units over a period of 4 hours.

Stiff polyethylene catheters were introduced into the aorta via the left femoral artery and into the inferior caval vein (below the diaphragm) via the right femoral vein for measurement of pressures.

The chest was opened in the 4th intercostal space on the left and the pericardium incised. An electromagnetic flow transducer was placed around the ascending aorta. This transducer had a diameter which guaranteed good contact between electrodes and vessel wall.

After completion of surgery, a long-acting local anes-
thentic (5% xylocain salve) was applied to skin incisions and cut intercostal muscles.

The circulation of the animal was allowed to stabilize for half an hour before measurements were started.

**Measurements**

Aortic and venous blood pressures were measured with Statham P23Db pressure transducers, calibrated against a Wallace and Tiernan (model D-62-A) precision manometer. Heart rate was derived continuously from the aortic pressure pulse. Blood flow in the ascending aorta was measured with an electromagnetic flowmeter (Skalar transflow 601-system, model 400). Zero-drift of the flow measuring system was corrected by automatic zero adjustment during diastole (Dijkema and Elzenga, 1973).

Total peripheral resistance ($R_p$) was determined from:

$$R_p = \frac{\text{mean arterial pressure} - \text{mean venous pressure}}{\text{mean aortic flow}}$$

For a continuous recording of this ratio, venous pressure was subtracted from aortic pressure by means of a differential amplifier; the output of this amplifier and the flow signal were integrated on a beat-to-beat basis and filtered by identical first order low-pass filters with a time constant of 5 seconds. The filtered signals were fed into an analogue divider made in our laboratory.

When peripheral resistance is calculated continuously in this way, errors may result, particularly during transients. Because of arterial compliance, a change in aortic flow will not instantaneously be accompanied by a change in pressure. Dividing pressure by flow will then erroneously suggest a change in peripheral resistance. The size of this possible error was estimated from the fastest transient available in this investigation. For that purpose, the arterial system of the cat was modeled by an electrical analog of a three-element windkessel (Westerhof et al., 1971). The aortic blood flow transient measured in the cat was used (playback from tape) as a current input to the model. The resulting voltage is comparable to ascending aortic pressure in the cat (Fig. 1). The values of the elements of the model were those found in the cat during the control situation.

Pressure generated by the model was divided by flow with the same filters and divider, as in the actual experiment. Fluctuations in the quotient must result from the compliance effect in the non-steady state condition because resistance of the model is kept constant. The magnitude of the error is directly related to the rate of change of mean aortic flow and the magnitude of arterial compliance.

In the chosen example, mean aortic flow changed 0.25 ml/sec⁻¹. The resulting error in the calculation of peripheral resistance was less than 4% and had a time course of about 12 seconds with the filter setting used (Fig. 1). This error was considerably less when flow changes were smaller and slower. We conclude that continuous calculation of $R_p$ in the manner described above accurately reflects the changes in vascular resistance of the systemic arterial tree.

Amplitude, as well as time course of changes in peripheral resistance, was studied during flow reduction. The time necessary to reach 95% of the steady state amplitude was defined as stabilization time.

All variables were recorded on a direct-writing recorder (Hellige) and an analog tape (SE 7000). Measurements were made by hand from the tracings.

Arterial $P_{O_2}$, $P_{CO_2}$, and $pH$ were determined with a Radiometer 3 BMS 3 MK. Serum osmolality was measured by the freezing-point-depression method. For the calculation of $O_2$ extraction (arteriovenous oxygen difference, vol %) and $O_2$ consumption (cardiac output × $O_2$ extraction, ml/min), we measured arterial and mixed venous oxygen content (Lex-O2-6). Lactate concentration (UV test) was measured in mixed venous blood only. This blood was sampled from the right ventricle via a catheter introduced in the left femoral vein.

**Interventions**

Cardiac output was varied in two different ways. One method involved partial occlusion of the inferior caval vein. To this end, the 6th right intercostal space was opened and a string placed around the caval vein, about 1 cm above the diaphragm. The string was pulled up with a micromanipulator which could be blocked up. This assured graded and stable occlusions. Cardiac output was also reduced by arterial bleeding. Blood was rapidly (5-50 ml in less than 1 minute) removed from an arterial line with a large heparinized syringe. Before reinfusion, the blood in the syringe was stirred.

To eliminate baro- and chemoreflex activity from the aortic and cardiopulmonary region, the aortic nerves and vago-sympathetic trunks were cut just caudal to the carotid sinus (Guazzi et al., 1962; Pillsbury et al., 1969; Öberg and White, 1970). Carotid barodenervation was accomplished by cutting the sinus nerves at their junction with the glossopharyngeal nerve near the jugular foramen. In addition, all nervous connections between the common carotid arteries and the central stump of both the aortic nerves and vago-sympathetic trunks were cut to prevent baroreflex activity from the common carotid region (Heymans and Neil, 1958). Carotid barodenervation was assumed to be complete if bilateral common carotid occlusion did not elevate aortic blood pressure by more than 12% of control (Borgdorff and van den Horn, 1980).

Ganglionic blockade was obtained by an initial intravenous injection (25 mg/kg), followed by a continuous infusion of hexamethonium bromide (0.5 mg/kg per min). In addition, 1 mg atropine sulphate was given (Brown, 1967). The blockade was assumed to be complete if electrical stimulation (20 Hz, 5 m/sec., 1.5 mA) of the peripheral cut end of the vago-sympathetic trunk evoked no heart rate deceleration and stimulation of the central cut end produced no pupil dilation. To reestablish the control values of blood pressure, cardiac output, and peripheral resistance, noradrenaline (0.4-0.9 µg/kg per min) was continuously infused into the left atrium. The concentration was 33 µg noradrenaline per ml saline, with 10 mg ascorbate per 50 ml solution to prevent oxidation. According to Stjarne (1980), the concentration and not the absolute amount of neurotransmitter is the decisive factor at the receptor site. To avoid an increase of the concentration of circulating noradrenaline when flow was reduced by caval vein occlusion, the speed of the infusion pump was controlled by mean aortic blood flow, as described by Engel (1977).

The renin-angiotensin system was blocked with captopril* (3-mercapto-2-0-methylpropanoyl-l-proline), an angiotensin-converting enzyme inhibitor (Vollmer and Boccagni, 1977). Effectiveness of the dose selected (1 mg/kg, iv) was tested in three animals by injection of angiotensin I (0.3 µg/kg, iv).

**Results**

Partial occlusion of the inferior caval vein increased venous pressure peripheral to the site of occlusion by

* Captopril (Sp 14,225) was kindly supplied by Squibb, Princeton, New Jersey.
Borgdorff/Resistance and Cardiac Output in Barodenervated Cats

0.13 to 1 kPa and reduced cardiac output. As a result, aortic pressure fell. When the baroreflexes were intact, these changes were accompanied by an increase in heart rate and peripheral resistance (Fig. 2A). Sometimes cardiac output tended to a slow recovery, but this never exceeded 15% of the previous fall.

Barodenervation and vagotomy decreased cardiac output but increased heart rate, blood pressure and

**Figure 1.** Arterial compliance and the continuous calculation of peripheral resistance as the ratio of mean pressure and cardiac output. Left panel: in the intact barodenervated cat, decreased aortic flow causes fall in systemic blood pressure and peripheral resistance. Possible role of arterial compliance cannot be identified. Right panel: aortic flow signal from this cat fed into analogue model of systemic circulation in which $R_p$ (peripheral resistance) is kept constant. Fall in flow causes smaller pressure drop than in intact cat. Resistance as measured with divider is constant as it should be since $R_p$ had been fixed. Small changes at beginning and end of occlusion must be attributed to arterial compliance. Figure shows that divider measures $R_p$ accurately, that the change in cardiac output in the intact cat causes $R_p$ to fall, and that the role of arterial compliance is negligible. Parameter values of the model:

$$R_p = 76 \text{kPa/liter}\times \text{min}$$

$$R_e = 2 \text{kPa/liter}\times \text{min}$$

$$R_p \times C = 1 \text{sec}$$

(The conversion factor from hemodynamical to electrical units is: 0.1 kPa/liter $\times$ sec $= 1 \text{Ohm}$).

**Figure 2.** The effect of partial occlusion of the inferior caval vein on hemodynamics in a cat. A: intact baroreflexes; B: baroreflexes eliminated. Note that, in B, peripheral resistance declines during the first minute and then returns to control level within 5 minutes.
Peripheral resistance (Table 1). Now a reduction of cardiac output did not alter heart rate but decreased peripheral resistance after 10-15 seconds (Fig. 2B). Within 2 minutes, resistance started to rise again until it stabilized at or near its preocclusion level (101 ± 4.2%) between the 4th and 9th (mean: 5.8) minute. At the end of occlusion, the behavior of resistance was reversed: it increased and then returned slowly to control. When in four cats the occlusions were alternated with arterial bleeding to reduce cardiac output, a similar pattern was found.

The magnitude of the fall in resistance and the time needed for recovery varied with the amount of cardiac output reduction. With larger reductions, resistance decreased more and needed more time to recover. This is shown in Figure 3 by superposition of original tracings from one experiment. Sometimes, with larger falls in flow, resistance did not reach control again.

Figure 4 represents the mean time course of resistance after three different amounts of cardiac output reduction in seven cats.

The relation between cardiac output reduction and the maximal percentage fall in peripheral resistance was linear when cardiac output was reduced by less than about 40%. With further reductions, the relation became nonlinear: when cardiac output fell more than 65%, resistance decreased only 35% (Fig. 5).

The mean slope for the linear part of the individual curves is 0.83 (so: 0.29) and the mean $r^2$ is 0.97 (so: 0.018). These coefficients do not differ significantly from those found during arterial bleeding: 0.89 (so: 0.34) and 0.95 (so: 0.02), respectively (paired t-test, $\alpha = 5\%$).

Nature of Resistance Response

A change in resistance must have been caused by a variation in blood viscosity or a change in length or diameter of the vascular bed. Table 2 shows that hematocrit values before and during the 2nd and 8th minute of caval vein occlusion did not differ significantly. The changes in resistance can thus not be accounted for by variation of blood viscosity.

Since the length of the vascular bed is fixed, the changes in resistance must have resulted from vaso-
dilation and vasoconstriction caused by nervous control, humoral factors, or autoregulation.

**Reflex Effects**

To establish whether the initial fall and subsequent rise in resistance resulted from sympatho-sympathetic reflexes, the experiments were repeated on six other cats in which, after barodenervation and vagotomy, the ganglia were blocked. Since ganglionic blockade caused a dramatic fall in blood pressure, we restored pressure with an infusion of noradrenaline (0.4–0.9 \( \mu \)g/kg per min).

A mean cardiac output reduction of 40% decreased resistance to a same extent as in animals without ganglionic block, but recovery was slower and resistance did not reach control level within the time of study (Fig. 6).

Consequently, the fall in peripheral resistance after reduction of cardiac output seems not nervously mediated. Though the depression of resistance recovery apparently points to the elimination of a nervous component, it is unclear whether the depression resulted from ganglionic blockade or from the noradrenaline infusion. We therefore varied the rate of noradrenaline infusion in another group of six cats and found resistance recovery increasingly inhibited with higher rates (Fig. 7; see Table 1 for preocclusion (\% of control) .

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Thus, decrease and recovery of resistance after a cardiac output reduction are of a nonnervous nature.

**Humoral Factors**

Resistance recovery might have been caused by a humoral mechanism.

The latency of the increase in resistance (1–2 minutes) could indicate activation of the vasopressin system (Cowley et al., 1980) or of the renin-angiotensin system (Cowley et al., 1971). Vasopressin release is evoked either by cardiopulmonary and arterial baro- and stretch receptors or by changes in plasma osmolality in the hypothalamus. The baro- and stretch receptors were denervated in our experiments, and osmolality of arterial blood did not change during cardiac output reduction (see Table 2). Involvement of this system is very unlikely.

The role of the renin-angiotensin system was studied in a separate group of six animals. Cardiac output was reduced by 27 ± 12\% (mean ± se) before and by 29 ± 10\% after blockade of this system by intravenous administration of captopril (1 mg/kg). Effectiveness of the blockade was tested in three animals by iv injection of angiotensin I (0.3 \( \mu \)g/kg). This dose raised blood pressure by 6.3 ± 2.7 kPa before and by 0.4 ± 0.7 kPa after captopril administration.

Captopril decreased blood pressure from 21.2 ± 3.5 kPa to 14 ± 1.7 kPa. This was entirely due to a fall in resistance, cardiac output remaining unchanged (from 213 ± 32 to 210 ± 45 ml per min). Blood pressure was not further reduced by a higher dose (3 mg/kg) of captopril. As shown in Figure 8, cardiac output reduction evoked similar changes in resistance before and after captopril (analysis of variance, \( \alpha = 5\% \)). Consequently, the restoration of resistance is not caused by the renin-angiotensin system.

**Autoregulation**

To determine whether the decrease in resistance after cardiac output reduction was part of metabolic autoregulation or was caused by changes in blood

![Figure 6. Peripheral resistance after a 40% cardiac output reduction without (solid line) and with (dashed line) ganglionic blockade. Means and SEM of two groups of six cats.](image)

![Figure 7. Effect of noradrenaline on the response of peripheral resistance to cardiac output reduction after ganglionic blockade. Means and SEM. In each of six cats, cardiac output was reduced by 21–31\% (mean 26\%) during three different rates of noradrenaline infusion (solid lines). The dotted line is transposed from Figure 4 and represents resistance after a comparable (mean 28\%) reduction of cardiac output without ganglionic blockade and noradrenaline. During a low rate of infusion (top solid line), decrease and recovery time of resistance do not differ significantly from control (dotted line). This indicates that the change in resistance is not nervously mediated. With higher rates of infusion recovery is increasingly depressed.](image)

![Figure 8. Effect of cardiac output reduction on peripheral resistance before (dots) and after (triangles) captopril. Means and SEM, n = 6. Cardiac output was reduced by a mean of 27 and 29\%, respectively. Captopril did not significantly influence the response of resistance.](image)
Resistance after a mean cardiac output reduction of 29% in seven cats from which blood was sampled at the times indicated by arrows. Resistance showed a normal return to control. Means and sem.

**TABLE 2**

Blood Values before and during Cardiac Output Reduction

<table>
<thead>
<tr>
<th>Arterial</th>
<th>P02 (kPa)</th>
<th>Pco2 (kPa)</th>
<th>pH</th>
<th>Hct (%)</th>
<th>Osmolality (mosm/kg H2O)</th>
<th>O2 cons (ml/min)</th>
<th>O2 extr (vol %)</th>
<th>Lactate ven (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>19.1 ± 3.1</td>
<td>3.55 ± 0.44</td>
<td>7.35 ± 0.04</td>
<td>37.3 ± 5.3</td>
<td>303.8 ± 2.0</td>
<td>14.5 ± 2.5</td>
<td>6.6 ± 1.3</td>
<td>2.00 ± 1.28</td>
</tr>
<tr>
<td>Occlusion</td>
<td>20.0 ± 3.7</td>
<td>3.13 ± 0.48*</td>
<td>7.38 ± 0.06*</td>
<td>37.2 ± 5.6</td>
<td>303.0 ± 1.4</td>
<td>13.7 ± 2.4</td>
<td>9.8 ± 0.9*</td>
<td>1.95 ± 1.22</td>
</tr>
<tr>
<td>2nd min</td>
<td>20.8 ± 3.3</td>
<td>3.27 ± 0.44*</td>
<td>7.38 ± 0.04*</td>
<td>36.2 ± 5.1</td>
<td>303.2 ± 1.5</td>
<td>14.8 ± 3.5</td>
<td>9.7 ± 0.4*</td>
<td>2.07 ± 1.31</td>
</tr>
</tbody>
</table>

Means ± se, n = 7.

* Significantly different from control (paired t-test, α = 5%).

slowly until it stabilized at its control level after 4 to 9 (mean: 5.8) minutes. Consequently, the time at which the change in resistance is determined can greatly influence results.

Folkow (1953a) studied peripheral resistance in spinal kittens in which the aorta was perfused with blood from adult cats. He found flow regulation during the first 2-3 minutes after a pressure drop but did not report what happened later.

Liedtke et al. (1973), who measured 3 minutes after changing cardiac output in the dog, also found flow regulation. Some measurements after 10 minutes, however, still showed a decreased resistance during reduced cardiac output. Sometimes we did not find recovery either, when cardiac output was reduced by more than 50%. Unfortunately, Liedtke et al. did not indicate the amount of cardiac output reduction during their 10-minute observation period.

Levy et al. (1954) measured cardiac output in the 8th minute only, and observed no change in resistance. This finding seems consistent with our results.

In three studies (Granger and Guyton, 1969; Shepherd et al., 1973; Sagawa and Eisner, 1975), cardiac output and aortic pressure were monitored continuously after a change in pressure or flow. The first two groups of authors reported flow regulation which, in contrast to what we have found, was slight in the first minute and became increasingly strong during the next 35 minutes. The third group found no flow regulation at all. Possibly, experimental conditions in these studies were not suited to elicit a drop in resistance during the first minutes after cardiac output reduction. The animals were connected to extracor-
Borgdorff/Resistance

FIGURE 10. Resistance after a mean cardiac output reduction of 37% during ganglionic block and noradrenaline infusion. Note that the resistance did not return to control. Arrows: time of blood sampling. Means and sem, n = 7. Same animals as in Figure 9.

poreal pump devices or blood reservoirs. As pointed out by Folkow (1953b) and Green et al. (1963), even the mere passage of normal arterial blood through rubber tubes or glass cannulas causes slight trauma to red blood cells. This results in release of vasodilator substances which depress reactive relaxation of smooth muscle in the vessel wall. Later, Falotico and Zimmerman (1978) could demonstrate that one of the substances was a prostaglandin.

The time-dependent changes in resistance demonstrated in our study have consequences for investiga-
tions in which the reflex regulation of peripheral resistance is studied in the presence of a fall of cardiac output. Short-term effects of reflex action on resistance must be corrected for a non-reflex decrease in peripheral resistance. To find such a correction, one might repeat the experiment with a same fall in cardiac output as in the actual experiment, but now when all reflexes have been abolished, e.g., by ganglionic blockade. Our results show that it makes no difference whether cardiac output is reduced by caval vein occlusion or by arterial bleeding.

Nature of Resistance Response

Although the results of our study did not show

1. Hematocrit before and during flow reduction was not significantly different (Table 2). The changes in resistance can thus not be accounted for by changes in blood viscosity.

2. They cannot be ascribed to a compliance effect of the large arteries. We showed in the Methods section that such a passive effect lasts only a few seconds and is opposite to the change in resistance we have actually found (Fig. 1).

3. The results with ganglionic blockade exclude a nervously mediated arteriolar dilation and constric-
tion.

4. Caval vein occlusion caused a rise in venous pressure peripheral to the site of occlusion. However, a vaso-vasomotor reaction would have resulted in increased rather than decreased peripheral resistance (Lutz, 1966). Moreover, resistance behaved in the same way with arterial bleeding as with caval vein occlusion.

5. Theoretically, the initial decrease in resistance could have been caused by a humoral agent. We did not study this possibility, but thought such a mecha-
nism unlikely because a fall in resistance was noticed already when we decreased cardiac output by only 17% (see, e.g., curve a in Fig. 3). This resulted in a blood pressure drop from about 23 to 17 kPa. We do not know a system in the body that releases a vasodilator substance in the presence of these still high blood pressure levels.

6. The recovery of resistance during reduced car-
diac output seems not to be caused by the vasopressin system because the baroreceptors were denervated and arterial osmolality did not change during occlusion. This last finding confirms the results of Cowley et al. (1980) with hemorrhage in the dog. The ex-
periments with captopril showed that the return of resis-
tance to control was not caused by the renin-angio-
tensin system either. One could wonder why, in our experiments, this system was not activated even when blood pressures were very low (e.g., 8 kPa). Probably this system was already maximally active before cardiac output reduction, as indicated by the dramatic fall in blood pressure (21.2 to 14 kPa) after injection of captopril. A similar large effect of captopril on pressure was found in the barodenervated conscious rabbit but not in sham-operated animals (Pettty and Reid, 1981). The high level of angiotensin may be a consequence of the increased sympathetic tone after barodenervation which enhances the release of renin from the kidney (Zanchetti et al., 1976).

7. The decrease of total peripheral resistance in response to a reduction of cardiac output could be a summated effect of autoregulation in local beds. Au-
toregulation generally has a metabolic or a myogenic nature. Since \( O_2 \) consumption did not decrease (14.5, 13.7, and 14.8 ml/min, respectively) and venous lactate did not rise (2.00, 1.95, and 2.07 mmol/liter), we assume that the tissues could meet their oxygen de-
mand and that the decrease in resistance was not caused by substantial accumulation of metabolites. Although \( O_2 \) consumption was not measured contin-
uously, it is unlikely that it had decreased between the first and the second measurement, since Shepherd et al. (1973) showed that restoration of \( O_2 \) consump-
tion is a slow phenomenon which takes 15–25 min-
utes. \( O_2 \) extraction increased during cardiac output reduction (from 6.6 to 9.8 and 9.7 vol%, respectively). We do not know if the stimulus that caused the increased \( O_2 \) extraction did not, at the same time, cause vasodilation.

These findings thus neither demonstrate nor ex-
clude a metabolic cause for the decrease in resistance. However, the short latency of this decrease (10–15 sec) makes the metabolic factor an unlikely candidate, since Johnson et al. (1976) could not detect metabolic vasodilation until some 30 seconds after a complete cessation of blood flow in skeletal muscle.

In our experiments with different rates of noradren-
aline infusion, the recovery of resistance was increasing more with higher rates of infusion (Fig. 7). Later experiments (Fig. 10; Table 3) on the animals
used for Figure 9 and Table 2 showed that this depression of recovery was accompanied by decreased \( O_2 \) consumption (17.0 to 12.1 and 12.7 ml/min) and increased venous lactate in the 8th minute (2.92, 2.99, and 3.96 mmol/liter). \( O_2 \) extraction, already high, increased from 9.0 to 10.3 and 10.6 only. In this situation, the tissues probably were short of oxygen. One thus would expect a slow vasodilation, as in the experiments of Shepherd et al. (1973). We assume that such a slow vasodilation demonstrated itself in our experiments indirectly by depressing resistance recovery.

The question why metabolic autoregulation would occur with higher rates of noradrenaline infusion only, may be answered as follows: Table 1 shows that an increase in the dose of noradrenaline raised the preocclusion level of cardiac output less than it increased peripheral resistance. With the highest rate of infusion, resistance reached the same value as before ganglionic blockade (89 kPa/liter \( \times \) min), but cardiac output was still diminished (220 vs. 266 ml/min). Noradrenaline could have changed the balance between oxygen supply and oxygen demand. Shepherd et al. (1973) demonstrated that metabolic blood flow control increased as “initial oxygen availability-to-demand ratio” was reduced. They calculated this ratio for the animals in which \( O_2 \) content and consumption were measured. During noradrenaline infusion, the initial oxygen availability-to-demand ratio was significantly lower (1.24 ± .37 vs. 2.79 ± .61).

In some experiments we increased initial flow levels with respect to peripheral resistance by adding adrenaline to the noradrenaline solution in a ratio of 1:5. With this mixture, recovery of resistance was the same as before ganglionic blockade. We conclude that noradrenaline promoted metabolic autoregulation by decreasing initial oxygen availability-to-demand ratio. Cardiac output reduction decreased resistance in the same way as without noradrenaline, but the consequence increase might have to compete with a slow metabolic decrease, resulting in suppression of recovery.

Whereas we could find no clear indication for a metabolic or humoral control of resistance after cardiac output reduction in control conditions (without noradrenaline), the resistance response shows some correspondence to a myogenic response described by Grande and Mellander (1978). These authors varied transmural vascular pressure in the sympathectomized lower leg of the cat by changing tissue pressure. In this way, arteriovenous pressure difference was not affected and changes in blood flow were kept so small that the metabolic control system would not be activated. A reduction of transmural pressure was followed within 10 seconds by a proportional decrease in microvascular resistance. After a maximal fall at 20–30 seconds, resistance gradually returned to a level just below control. A nearly symmetrical response was found when pressure was increased (end of caval vein occlusion in our experiments), and even small pressure changes (e.g., 0.7 kPa) were sufficient to evoke the response. However, the myogenic response had a shorter time course (1–2.5 minutes) than the reaction described by us.

In conclusion, the decrease and recovery of resistance after cardiac output reduction are definitely not caused by changes in blood viscosity, reflexes, or the renin-angiotensin system, but the involvement of a humoral, metabolic, or myogenic mechanism could not unequivocally be excluded or demonstrated.

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