Regional Distribution of Blood Flow during Arterial Hypertension Produced by Lesions of the Nucleus Tractus Solitarii in Rats

DAVID W. SNYDER, NOBUTAKA DOBA, AND DONALD J. REIS

SUMMARY Changes in the fractional distribution of cardiac output (FF), organ blood flow, and regional vascular resistance were measured by the isotope dilution technique of Sapirstein using ⁸⁷Rb as indicator in unanesthetized rats during acute arterial hypertension produced by bilateral lesions of the nucleus tractus solitarii (NTS). After NTS lesions, the FF was significantly reduced in skin, muscle, and colon, increased in ventricular myocardium, spleen, and adrenal glands, and was unchanged elsewhere. Because of a marked reduction in cardiac output (CO) during hypertension, the absolute organ blood flow (FF x CO) was reduced in lesioned rats to 30-40% of control in skin, muscle, and colon and between 60% and 75% of control in most of the remainder of the gastrointestinal tract and renal cortex; it was unchanged in myocardium and endocrine glands. Resistance was substantially increased (4- to 6-fold) in skin, muscle and colon but was only moderately increased (1.5- to 2.5-fold) in the remaining organs. The results indicate that, while NTS lesions will increase resistance in most vascular beds, the response is unequally distributed, influencing skin, muscle, and colon disproportionately to other tissues. Because of an interaction between a reduction in CO and little autoregulation, blood flow is reduced primarily in skin, muscle, and colon. The pattern of redistribution of CO was consistent with the interpretation that NTS hypertension results from interrupting baroreceptor reflexes centrally. The pattern of redistribution of blood flow in rats with NTS lesions differs from that produced by deoxycorticosterone acetate-salt and renal ischemia.

IN RATS, bilateral lesions of the nucleus tractus solitarii (NTS) results in the rapid development of arterial hypertension.¹ In this model, termed NTS hypertension, the rise of blood pressure is presumed to be due to increased vasoconstrictor discharge resulting from central deafferentation of arterial baroreceptors by destruction of their primary synapse within NTS. As a result, the total peripheral resistance is markedly increased, leading to ventricular overload, reduction in cardiac output, progressive heart failure, and death associated with pulmonary edema within 3-4 hours.¹²

In the present study, we measured the changes in regional blood flow and in vascular resistances after lesions of NTS. Our objective has been 2-fold. First, we sought to determine whether the increase in total peripheral resistance produced by the lesion could be attributed to changes in vascular resistances within specific vascular beds reflecting, in turn, a differential activation of sympathetic neurons. Second, NTS lesions abolish arterial baroreceptor reflexes,³⁴ and arterial baroreceptor activity is not uniformly distributed to all vascular beds, since vasoconstrictor activity in skeletal muscle is under greater baroreceptor control than that in kidney, skin, or the gastrointestinal tract.⁵¹⁰ Evidence of appropriate changes in resistance and flows in vascular beds after NTS lesions would provide additional evidence that the effect of NTS lesions, in large measure, can be attributed to defective arterial baroreceptor reflex function. Finally, we sought to determine whether the pattern of change in blood flow in rats, made hypertensive by NTS lesions, was comparable to changes in regional flow produced in other models of hypertension in rats, including the deoxycorticosterone acetate (DOCA)-salt,¹¹ renal,¹¹¹² and genetic¹³ models.

Methods

General Procedures

Experiments were performed on male Sprague-Dawley rats weighing 300-400 g. While the rat was anesthetized with halothane (2% in 100% O₂ blown over the nose through a face mask), a polyethylene catheter (PE 50, 0.023-inch inside diameter) containing saline with heparin (20 U/ml) was inserted into the ventral artery of the tail for direct measurement of arterial pressure. The catheter was fixed with sutures to the soft tissue and connected to a strain gauge transducer (Statham P23Db). Pulsatile and mean arterial pressures were displayed on a Beckman polygraph (type R). The peak of the arterial pressure pulse was used to trigger a cardiostachometer (Beckman 9857), and heart rate was simultaneously displayed. A second catheter was threaded down the right external jugular vein until its tip was estimated to lie in the right atrium. The venous cannula was fixed in deep tissue, externalized through a stab wound in the neck, and fixed to the skin.

NTS Lesions

NTS lesions were then made by methods described in detail elsewhere.¹ In brief, the rat was placed in a stereotaxic apparatus with its head flexed to 45°. The region of the obex was exposed by a limited occipital craniotomy. A monopolar electrode consisting of a Teflon-coated...
stainless steel wire (diameter, 0.015 cm) with the tip
exposed (0.2 mm) was placed in the brainstem visually
with the aid of a dissecting microscope. Bilateral lesions
were placed in NTS by passing an anodal DC current of 5
mA for 1-3 seconds; the cathode was a clip placed in an
adjacent muscle. The rat was moved from the stereotaxic
frame to a small cage, and the arterial cannula was
connected to the pressure transducer. Cardiovascular ac-
tivity was continuously monitored after cessation of the
anesthesia.

**Measurement of Blood Flow Distribution**

To measure the distribution of blood flow to different
tissues in the unanesthetized rat, the isotope-dilution
method was employed with 86Rb as the tracer.14,15 The
principle of the method is that 86Rb, like K, is rapidly
distributed to the intracellular tissue compartment (with
the exception of the central nervous system) and remains
at a constant concentration for over 1 minute. Thus, the
administration of 86Rb can be used to reflect the pattern
of the distribution of cardiac output.

In the unrestrained rat, 30 minutes after cessation of
the anesthesia, 10 μCi of 86Rb (0.2 ml) was rapidly
injected into the venous cannula and flushed with 0.3 ml
of saline. One minute later, a bolus of saturated KCl was
injected into the right atrium and resulted in almost
instantaneous death from cardiac arrest.

The following samples of tissue were dissected by the
same individual to ensure reproducibility of sampling
from animal to animal. Small areas (about 1 cm²) of the
skin were sampled from the lateral, upper right hindleg,
and lumbar region of the back. The right forepaw was
removed. The skeletal muscles consisted of the upper half
of the right soleus and right medial gastrocnemius. Small
samples (1 cm in length) were taken from the lower
region of the esophagus, from the region of the lesser
curvature of the stomach leading toward the esophagus,
anterior region of the jejunum, posterior region of the
ileum, and transverse section of the colon. Samples were
taken from the middle section of the spleen and pancreas
and from the right lobe of the liver. Samples of the right
kidney consisted of the outer cortex and inner medulla.
Both whole adrenals were removed. Lateral section of
the right atrium and lateral regions of the right and left
ventricles were sampled. The right lobe of the thyroid
and the neural hypophysis were removed. After dissec-
tion, the samples were blotted gently on absorbent paper,
weighed, and placed in plastic test tubes. The test tubes
were counted in a well-type gamma scintillation spectrom-
eter (Nuclear-Chicago) and expressed as counts/min per
100 g of tissue.

**Measurement of Cardiac Output**

The cardiac output (CO) of another group of rats with
sham and NTS lesions was measured at a similar time (30
minutes) after cessation of anesthesia by a thermal dilution

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<table>
<thead>
<tr>
<th>Table 1 Fractional Flow, Total Blood Flow and Regional Vascular Resistance in Unanesthetized Control Rats</th>
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<tbody>
<tr>
<td><strong>FF</strong></td>
</tr>
<tr>
<td>Skin</td>
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<td></td>
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<td>Skeletal muscles</td>
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<td>Heart</td>
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<td>Other organs</td>
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</table>

**FF** = fractional distribution of cardiac output; **TBF** = total blood flow estimated on the basis of an average cardiac output of 119 ml/min as measured in a different group of five unanesthetized rats and reported elsewhere; **RVR** = regional vascular resistance.

Values are mean ± 1 SEM. Numbers in parentheses, number of rats in group.
technique described in detail elsewhere. The CO of five sham-lesioned controls was 119 ± 5 ml/min and of five NTS-lesioned rats was 74 ± 7 ml/min. These figures were used as constants to derive approximate regional blood flows and vascular resistances.

Calculations

The fractional distribution (FF) of the cardiac output (CO) to any tissue was calculated as:

$$\text{FF} = \frac{\text{Organ activity (counts/100 g per min)}}{\text{Total injected activity (counts/min)}}$$

Absolute blood flow (TBF) to any organ/unit weight was calculated as: TBF (ml/min per 100 g) = FF × CO.

Regional vascular resistance (RVR) was calculated as:

$$\text{RVR} = \frac{\text{Pm}}{\text{organ blood flow}}, \text{where Pm is mean arterial pressure.}$$

Pm = (Ps + 2Pd)/3, where Ps = systolic blood pressure and Pd = diastolic pressure.

Results

Fractional distribution of the cardiac output, calculated absolute blood flows, and regional vascular resistances in various tissues of control rats are indicated in Table 1 and are in agreement with values obtained by others using comparable methods of whole organ analysis. In confirmation of other studies, bilateral lesions of NTS resulted in a significant elevation of arterial pressure (control 114 ± 3 mm Hg; NTS-lesioned, 164 ± 4 mm Hg; P < 0.001) and in a reduction of cardiac output (control 119 ± 5 ml/min; NTS-lesioned, 74 ± 7 ml/min; P < 0.001) within 30 minutes after cessation of halothane anesthesia. The changes in the distribution of cardiac output to various tissues in NTS hypertensive rats are shown in Table 2.

In hypertensive rats there was a significant decrease in the fraction of the cardiac output (fractional flow) delivered to the colon (61% of control), both red soleus (65% of control) and white gastrocnemius (62% of control) skeletal muscles, and skin (51-59% of control). In contrast, fractional flow to the myocardium, adrenal gland and spleen was significantly increased to approximately 140% of control. No change in fractional flow was observed in the forepaw, hypophysis, esophagus, small intestine, liver, pancreas, kidney (medulla and cortex), thyroid, or stomach.

The changes in absolute blood flow to these tissues during hypertension are presented in Table 2. Because of a substantial reduction in cardiac output during NTS hypertension, there was a significant reduction (P < 0.05) in nutritional blood flow in most tissues. The exceptions were myocardium, spleen, hypophysis, adrenals, esophagus, thyroid, liver, and renal medulla where

### Table 2 Changes in Fractional Flow, Total Blood Flow, and Regional Vascular Resistance during Acute NTS Hypertension in Rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>FF % of control</th>
<th>TBF % of control</th>
<th>RVR % of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td>58.7*</td>
<td>36.8†</td>
<td>28.91 ± 4.54</td>
</tr>
<tr>
<td>Hindleg</td>
<td>50.5†</td>
<td>31.0†</td>
<td>31.60 ± 7.06</td>
</tr>
<tr>
<td>Forepaw</td>
<td>71.8 (NS)</td>
<td>42.8†</td>
<td>47.05 ± 6.89</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>64.9†</td>
<td>40.3†</td>
<td>11.10 ± 3.63</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>61.6*</td>
<td>38.4†</td>
<td>36.02 ± 3.18</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrium</td>
<td>130.4 (NS)</td>
<td>81.2 (NS)</td>
<td>1.81 ± 0.17</td>
</tr>
<tr>
<td>RV</td>
<td>154.4*</td>
<td>96.0 (NS)</td>
<td>1.06 ± 0.07</td>
</tr>
<tr>
<td>LV</td>
<td>139.9*</td>
<td>87.0 (NS)</td>
<td>0.85 ± 0.05</td>
</tr>
<tr>
<td>Digestive system</td>
<td></td>
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</tr>
<tr>
<td>Esophagus</td>
<td>190.8 (NS)</td>
<td>118.2 (NS)</td>
<td>6.14 ± 1.14</td>
</tr>
<tr>
<td>Stomach</td>
<td>101.8 (NS)</td>
<td>63.3*</td>
<td>1.98 ± 0.24</td>
</tr>
<tr>
<td>Jejunum</td>
<td>93.9 (NS)</td>
<td>58.4*</td>
<td>1.87 ± 0.14</td>
</tr>
<tr>
<td>Ileum</td>
<td>113.9 (NS)</td>
<td>70.98</td>
<td>2.63 ± 0.19</td>
</tr>
<tr>
<td>Colon</td>
<td>61.4†</td>
<td>38.1†</td>
<td>4.71 ± 1.62</td>
</tr>
<tr>
<td>Pancreas</td>
<td>90.4*</td>
<td>56.3†</td>
<td>3.58 ± 0.34</td>
</tr>
<tr>
<td>Liver</td>
<td>147.2 (NS)</td>
<td>91.3 (NS)</td>
<td>5.38 ± 0.47</td>
</tr>
<tr>
<td>Other organs</td>
<td></td>
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<tr>
<td>Renal cortex</td>
<td>108.6 (NS)</td>
<td>67.5*</td>
<td>0.38 ± 0.03</td>
</tr>
<tr>
<td>Renal medulla</td>
<td>120.6 (NS)</td>
<td>75.0 (NS)</td>
<td>0.76 ± 0.11</td>
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<tr>
<td>Spleen</td>
<td>146.8§</td>
<td>91.3 (NS)</td>
<td>2.83 ± 0.34</td>
</tr>
<tr>
<td>Hypophysis</td>
<td>165.0 (NS)</td>
<td>103.8 (NS)</td>
<td>3.55 ± 0.54</td>
</tr>
<tr>
<td>Thyroid</td>
<td>111.4 (NS)</td>
<td>69.4 (NS)</td>
<td>1.24 ± 0.17</td>
</tr>
<tr>
<td>Adrenals</td>
<td>155.3§</td>
<td>96.9 (NS)</td>
<td>0.82 ± 0.07</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Numbers in parentheses, number of rats in group. FF = fractional distribution of cardiac output; TBF = total blood flow estimated on the basis of an average cardiac output of 74 ml/min as measured in a different group of five NTS-lesioned rats and reported elsewhere; RVR = regional vascular resistance; NS = not significantly different from control.

* P < 0.01, significantly different from control.
† P < 0.001, significantly different from control.
§ P < 0.05, significantly different from control.
the change in flow did not differ significantly from controls.

In the lesioned rats, there was a significant increase in vascular resistance in all tissue beds except the hypophysis (Table 2). Most striking was the increase of resistance in the vascular beds of skin (to 432-488% of control), the soleus, a red skeletal muscle (to 627% of control), the gastrocnemius, a white skeletal muscle (to 366% of control), and colon (to 476% of control).

Discussion

In the present study we analyzed the change in the redistribution of blood flow to various tissues in rats during acute hypertension produced by lesions of the NTS. Changes in blood flow distribution have been measured by use of the isotope dilution method of Sapirstein, using 86Rb as the indicator. The validity of the method as applied to this study is based in the assumption that the extraction ratio for 86Rb in a given vascular bed, and whole body, remains constant during the first minute after administration of the indicator and that the extraction is not modified by conditions altering blood flow and/or resistance to the tissue. It has been experimentally demonstrated by Sapirstein and by Goldman that, except for the brain, the uptake of 86Rb remains constant in selected tissues of the rat between 10 and 60 seconds after administration of the indicator. Moreover, when the peripheral resistance or cardiac output is altered as, for example, by infusion of norepinephrine, the extraction ratio over time is unaffected. In view of these observations and our own finding that the blood flow to one organ, the hypophysis, did not change during NTS hypertension, we conclude that the 86Rb method is an accurate indicator of changes in organ blood flow under the conditions of this experiment.

The acute phase of NTS hypertension in the unanesthetized rat is associated with changes in the pattern of distribution of the cardiac output. These changes are characterized by a decrease in the fraction of cardiac output distributed to the vascular beds of skin, colon, and skeletal muscles, and by an increase in fractional flow to myocardium, adrenal glands, and spleen. The distribution of cardiac output delivered to other tissues is not significantly altered.

These changes in the distribution of cardiac output reflect variations in local blood flow and peripheral resistances. Under conditions in which cardiac output is unchanged, a reduction in the fractional distribution of the cardiac output supplying an organ corresponds to a decrease in that organ's total blood flow and an increase in its vascular resistance. Conversely, an increase in fractional flow reflects an increase in that organ's total blood flow and a decrease in its vascular resistance. However in NTS hypertension, during which cardiac output is reduced, the absolute blood flow falls in any tissue not showing an elevation of fractional flow proportionate to the diminished cardiac output. The greatest fall occurs in those tissues in which fractional flow is most substantially reduced.

During the acute arterial hypertension produced by NTS lesions, the various vascular beds of the systemic circulation do not contribute to the same degree to the overall change in the peripheral vascular resistance. Although there is a significant increase in resistance in all vascular beds studied, except for the hypophyseal bed, a much greater increase is observed in the vascular beds of the skin, colon, and skeletal muscles than in other organs. Consequently, the greatest fall in blood flow was seen in these same three vascular beds.

Except for the colon, we did not observe a significant change in the blood flow pattern to the intestine during NTS hypertension. This may be due to the well-developed autoregulatory responses that can occur within 1-2 minutes after the onset of sustained sympathetic stimulation of the intestine. In support of this interpretation, we studied blood flow distribution 30 minutes after deafferentation of the baroreceptors, thereby allowing ample time for autoregulation to occur in the face of a sustained hypertensive crisis. The autoregulatory response in the colon is less pronounced than in other segments of the intestine, and in fact, it may fail to develop during sustained vasoconstrictor discharge.

The fact that there was much less vasoconstriction in kidney than in skin or muscle following lesions of NTS is due probably to powerful autoregulators of the renal blood flow even in the face of increased sympathetic discharge. It is well established that renal autoregulation will counteract baroreceptor control of the renal circulation.

Experimental evidence has shown that the arterial baroreceptor reflex responses of the skin vasculature are very small, if present at all, and that the cutaneous vasculature acts in a passive manner in response to pressure changes. However, strong stimuli, e.g., hemorrhage, will produce intense cutaneous vasoconstriction in man and animals. Moreover, catecholamines released from the adrenal medulla play a dominant role in vasoconstriction associated with hemorrhage in dogs. Thus, the uncontrolled release of sympathetic outflow after NTS lesions may have been so intense that the cutaneous vascular beds were affected directly, or circulating catecholamines released from the adrenal medulla may have contributed to the vasoconstriction.

In contrast to the skin, the large increase in regional vascular resistance to the skeletal muscle beds in the NTS hypertensive rat is of neurogenic origin and not due to vasoactive agents circulating in the bloodstream. This is supported by the observation that unilateral denervation of the hind limb blocked the reduction in blood flow and the elevation of vascular resistance in skeletal muscle in the denervated, but not the innervated, hind limb of the same animal during NTS hypertension. There was great variability in the blood flow pattern of the cutaneous beds in the denervated hind limb, probably due to circulating catecholamines.

These observations indicate that bilateral lesions of NTS result in increased sympathetic vasoconstrictor discharge which is not uniformly distributed to regional vascular beds. The results are consistent with the interpretation that NTS lesions produce an elevation of arterial pressure by central impairment of baroreceptor reflex.
mechanisms. Baroreceptor-induced inhibition of sympathetic activity exerts a differentiated pattern of control over vasoconstrictor outflow and withdrawal of baroreceptor input leads to a reflex increase in resistance, mainly in the vascular beds of skeletal muscle, to a lesser degree in the intestine and kidney, and least of all in the skin. If the response of the cutaneous beds were due to catecholamines released from the adrenal medulla, then the redistribution patterns of blood flow produced by NTS lesions and baroreceptor denervation would be comparable. However, since NTS lesions also will abolish chemoreceptor reflexes and possibly interrupt activity descending from intrinsic pathways in the area of NTS, disruption of other central cardiovascular systems may contribute to the cardiovascuar events.

The redistribution of blood flow during hypertension produced by NTS lesions in rats appears to differ in its pattern from that seen in DOCA-salt or Goldblatt models of hypertension in the same species or in the spontaneously hypertensive rat. Bralet et al. used the isotope dilution technique in anesthetized rats (1973) and reported that, in Goldblatt hypertensive animals, the fractional flow to the heart, aorta, colon, lungs, and skeletal muscles increased, whereas flow to the skin and liver decreased. Dahners et al. (1972) employed labeled macro-aggregated albumin in DOCA-salt and Goldblatt hypertensive anesthetized rats. They reported an increase in the fractional flow to heart and lung and a decrease in flow to the liver and kidney. The hemodynamics of spontaneous hypertensive rats were examined by using Rb dilution method under pentobarbital anesthesia. Although absolute values of organ blood flow showed an increase only in the thyroid, with decreases in skin and gastrointestinal tract in that study, the direct effect of the anesthetic agent should not be neglected.

It should be noted, however, that our studies were made during an acute phase of hypertension, in contrast to the aforementioned studies in which blood flow distribution was measured in chronically hypertensive animals and compensatory and adaptive mechanisms could modify the responses. The blood flow distribution remains to be established in animals such as the cat with chronic NTS lesions to truly distinguish the peripheral cardiodynamics in various forms of hypertension.

References

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