Arterial Baroreflex Control of Renal Hemodynamics in Humans

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Background  Control of renal hemodynamics by the arterial baroreflex has never been proved in humans. Apart from the physiological viewpoint, this issue is relevant because altered baroreflex function has been implicated in the pathogenesis of human hypertension.

Methods and Results  Renal function studies were performed in seated healthy volunteers (n=12; age range, 20 to 34 years) during sustained neck suction at ~60 mm Hg, aiming to selectively activate the carotid sinus arterial baroreceptors. Two protocols were followed. One group of 6 volunteers taking a 20 mmol/d sodium diet underwent 90 minutes of neck suction. Compared with a time-control study, neck suction decreased arterial pressure and heart rate; increased glomerular filtration rate (inulin clearance) from 104±6 to 114±8 mL/min (P<.01), renal plasma flow (para-aminohippurate clearance) from 616±52 to 665±42 mL/min (P<.01), and renal blood flow (from 1120±95 to 1209±77 mL/min, P<.01); and decreased renal vascular resistance (from 86±8 to 76±6 mm Hg · min · L⁻¹, P<.01). Neck suction had no effect on plasma renin activity, aldosterone, atrial natriuretic peptide, catecholamines, and renal sodium excretion. The other 6 volunteers took a normal sodium diet and underwent sustained neck suction for 60 minutes. In this group, no effects on renal hemodynamics could be discerned, despite a modest decrease in blood pressure and heart rate.

Conclusions  These data show, for the first time, that the arterial baroreflex is involved in the control of renal hemodynamics in humans. However, basal arterial baroreflex control of renal hemodynamics is probably low, and arterial baroreflex activation with subsequent renal vasorelaxation may be found only in conditions in which basal arterial baroreflex control of kidney function is significant, as is presumably the case in seated sodium-restricted subjects. (Circulation. 1994;90:1883-1890.)

Key words  • carotid arteries  • reflex  • kidney  • hemodynamics

The method of negative neck pressure ("neck suction") has been applied to study the effects of selective arterial baroreceptor activation on cardiovascular function in humans. Selective arterial baroreflex activation obtained in this way decreases heart rate and blood pressure and vascular resistance in the calf and decreases peripheral sympathetic nerve activity often with a correlation between magnitude of negative pressure and change in monitored parameter. The relation with renal function has not been studied. Acute natriuretic challenges such as volume expansion, recumbency, or head-out water immersion probably activate the arterial baroreflex, but whether this plays any role in the renal response is uncertain. Selective arterial baroreflex activation, obtained by unilateral carotid sinus traction, has been demonstrated to increase sodium excretion in rats. Prior carotid sinus denervation could prevent these effects. The dog, baroreflex activation through selective elevation of carotid artery perfusion pressure was shown to increase renal blood flow. A role for the arterial baroreflex in the control of renal function may thus be suspected.

The question whether the arterial baroreceptor participates in the control of renal function in humans is important because of the possible relation between the baroreflex responsiveness and hypertension. Decreased baroreflex-cardiac sensitivity but not baroreflex-vascular sensitivity has been demonstrated in hypertensive humans and rats. Decreased baroreflex-renal sensitivity, that is, insufficient renal vasorelaxation after arterial baroreceptor stretch, could theoretically contribute to the genesis of hypertension. Arterial baroreceptor deafferentation has been shown to cause hypertension in some animal studies but this is not a consistent finding. The relevance of these findings remains uncertain until we know whether the arterial baroreflex plays a role in the control of renal function in humans. Conversely, the idea that attenuated baroreceptor responsiveness could play a role in the genesis of hypertension is not tenable if the baroreflex does not control renal function. Thus far, however, direct information on this relation in humans is not available. The goal of this study was to assess in humans the effect of vigorous neck suction, sustained for at least 1 hour, on renal function. We hypothesized that neck suction, through arterial baroreflex activation and subsequent sympathetic deactivation, can uncover prevailing renal sympathetic control and cause renal vasodilatation. However, normal subjects at rest probably operate at low levels of sympathetic activity. Therefore, our studies included subjects examined during sodium restriction and in the seated position, assuming that this

Received March 22, 1994; revision accepted June 13, 1994.

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would increase basal arterial baroreflex control of kidney function.

Methods

Studies were carried out in two groups of six healthy volunteers, 20 to 34 years old, after informed consent had been obtained. One group received a normal-sodium diet (200 mmol Na/24 hours) and the other a low-sodium diet (20 mmol Na/24 hours). These diets (see below) were provided by the metabolic ward, to which the subjects returned daily for weighing and delivery of 24-hour urine collections. All subjects underwent two clearance studies on separate days. The protocol was approved by the Hospital Ethical Committee for Studies in Humans. The protocol included sustained neck suction at −60 mm Hg for 60 or 90 minutes. To familiarize the volunteers with the rather inconvenient procedure of prolonged vigorous neck suction, each subject underwent trial experiments in the weeks before the actual experiments.

Clearance Technique

Clearance studies were performed in the morning after an overnight fast, in a quiet room, and with the subjects in the seated position. Antecubital veins were catheterized bilaterally for blood sampling and infusion. At 9 AM, a priming dose of a solution containing 100 mg/mL insulin to measure glomerular filtration rate (GFR) and 25 mg/mL para-aminohippurate (PAH) to measure estimated renal plasma flow (ERPF) was given, followed by a maintenance infusion of this solution by infusion pump throughout the remainder of the study at a rate of 0.005 mL·kg⁻¹·min⁻¹. The total amount of fluid infused was 16 to 20 mL/h. The subjects were supplied with water (300 mL/h) to ensure adequate urine flow. After 90 minutes of equilibration, urine was collected each 30 minutes by spontaneous voiding, and blood samples were drawn halfway through each 30-minute period until the end of the clearance study.

Neck Suction in Sodium-Restricted Subjects

The 6 volunteers, 4 men, 2 women, took a diet containing 20 mmol/d sodium. Each participant underwent a clearance study on days 5 and 7 of this diet. One of these studies included a 60-minute baseline period, followed by 90 minutes of neck suction and a 60-minute recovery period. The other clearance study concerned a time-control study (random order). During the neck suction experiment, a static negative pressure of −60 mm Hg was applied by means of a neck suction device described in detail by others. Each 30 minutes, blood and urine samples were assessed for sodium, inulin, and PAH. Additional blood samples for plasma renin activity, aldosterone, atrial natriuretic peptide, and catecholamines were obtained at the end of the baseline period, at 22 and 67 minutes of the experimental phase, and at 20 minutes of the recovery phase. Throughout the clearance study, blood pressure and heart rate were recorded continuously by means of finger plethysmography (Finapres 2300, Ohmeda) and stored in computer files for later analysis.

Neck Suction in Sodium-Replete Subjects

The 6 volunteers (5 men, 1 woman) participating in this study consumed diets containing 200 mmol/d sodium. Each participant underwent a clearance study on day 5 and day 7 of this diet. One of these studies included a 60-minute baseline period, followed by 60 minutes of neck suction at −60 mm Hg and a 60-minute recovery period. The other study concerned a time-control study (random order). In view of the inconvenience of sustained vigorous neck suction, we limited the duration of the experimental phase in this study to 60 minutes, having learned from the above-mentioned experiment that effects could be expected within this period (see "Results").

Blood and urine samples for clearance determinations were taken as described above. Additional blood samples for deter-

| TABLE 1. Baseline Values During Normal- and Low-Sodium Diet |
|-------------------------------------|----------------|----------------|
|                                    | Normal-Sodium Diet | Low-Sodium Diet |
| MAP, mm Hg                         | 94±1             | 93±2           |
| GFR, mL·min⁻¹·m⁻²                   | 58±2             | 55±2           |
| ERPF, mL·min⁻¹·m⁻²                  | 316±11           | 322±21         |
| FF, %                              | 18.7±1.0         | 17.1±0.4       |
| RVR, mm Hg ·min·L⁻¹                | 91±4             | 87±9           |
| PRA, fmol·L⁻¹·s⁻¹                  | 222±73           | 661±77*        |
| Aldosterone, pmol/L                | 224±53           | 617±175*       |
| ANP, pmol/L                        | 9±1              | 8±1            |

MAP indicates mean arterial pressure; GFR, glomerular filtration rate; ERPF, estimated renal plasma flow; FF, filtration fraction; RVR, renal vascular resistance; PRA, plasma renin activity; and ANP, atrial natriuretic peptide. Values are mean±SEM.

*P<.01 compared with normal-sodium diet.

Analytical Techniques

Sodium was determined by standard flame photometry. Inulin was hydrolyzed to fructose and determined photometrically with indolacetic acid.29 PAH was determined photometrically by a chromogenic aldehyde reaction.30 Plasma renin activity, aldosterone, and atrial natriuretic peptide were determined by standard radioimmunoassay.31 Plasma catecholamines were assayed by high-performance liquid chromatography with fluorometric detection after isolation from plasma by a specific liquid-liquid extraction method and derivation with the selective fluorogenic agent 1,2-diphenylethylene-diamine.32

Statistical Analysis

Values are given as mean±SEM. Means of plasma renin activity and aldosterone were calculated after logarithmic transformation. Statistical analysis of differences within the two studies was performed by repeated-measures ANOVA, with the presence or absence of neck suction and time as independent variables. When the variance ratios obtained by this method reached statistical significance, the differences between the means were analyzed at 1% and 5% significance levels by the least-significant-difference test. Differences in baseline values between sodium-restricted and sodium-replete groups were tested by means of an unpaired t test. Blood pressure and heart rate data were averaged per 15 minutes, except for the period after starting or stopping neck suction, when the values were averaged for 3-minute periods.

Results

Comparison of Basal Values in Sodium-Restricted and Sodium-Replete Groups

Twenty-four-hour sodium excretion before the studies was 16±2 mmol in sodium-restricted subjects and 188±14 mmol in the sodium-replete subjects (P<.01). Other basal values, averaged for the time-control and neck suction experiments, are given in Table 1. For comparison, data for renal hemodynamics were normalized for body surface. No significant differences in blood pressure and renal hemodynamics were found between
the sodium-restricted and sodium-replete groups. In particular, the filtration fraction, known to increase during volume depletion, was not higher in the sodium-restricted subjects. Absence of a difference in filtration fraction probably reflects the limited number of subjects within each group. Plasma renin activity and aldosterone were both elevated in the sodium-restricted subjects (P<.01), whereas plasma atrial natriuretic peptide concentrations were not different.

**Neck Suction in Sodium-Restricted Subjects**

Heart rate fell from 62±3 to 56±4 beats per minute (P<.01) in the first half hour of neck suction (Fig 1). Thereafter, heart rate gradually increased again to 60±4 beats per minute before cessation of neck suction. Immediately after discontinuation of neck suction, heart rate rose to 65±4 beats per minute (P<.05). Neck suction also caused a decrease in arterial pressure from 93±2 to 88±4 mm Hg (P<.05) in the first half hour of suction (Fig 1). Blood pressure remained low but differed significantly from control only in the first 45 minutes of neck suction. After cessation of neck suction, a transient increase in blood pressure from 89±4 to 95±4 mm Hg (P<.05) was observed. During the time-control study, no consistent changes in heart rate and blood pressure were observed.

Compared with the time-control experiment, neck suction caused significant increments in ERPF and renal blood flow in the second and third half-hour periods of neck suction (Table 2). The calculated renal vascular resistance was decreased throughout the neck suction experiment. The GFR increased in proportion to the increments in ERPF, as reflected by the absence of a change in filtration fraction. Neck suction had no effect on renal sodium excretion.

Neck suction caused no change in plasma renin activity, aldosterone, or atrial natriuretic peptide (Table 3). Plasma norepinephrine decreased in four of the subjects but overall did not change significantly during neck suction. No change was found in plasma epinephrine.

**Neck Suction in Sodium-Replete Subjects**

Effective stretch of the carotid sinus throughout the suction period was evidenced from the immediate fall in heart rate after initiation of suction (from 56±3 to 51±3 beats per minute, P<.05) and the immediate increase in heart rate after discontinuation of suction (from 54±2 to 60±2 beats per minute, P<.05) (Fig 2). Similarly, blood pressure fell from 92±2 to 88±2 mm Hg (P<.05) immediately after initiation of neck suction and increased from 89±3 to 94±3 mm Hg (P<.05) after discontinuation of neck suction. No consistent changes in heart rate and blood pressure were found during the time-control study.

Neck suction had no effect on renal hemodynamics and sodium excretion (Table 4). Plasma renin activity, aldosterone, and plasma atrial natriuretic peptide also did not change (Table 5).

**Discussion**

The main finding in this study is that sustained neck suction at −60 mm Hg causes renal vasorelaxation in seated salt-restricted healthy humans. As far as we know, this is the first direct demonstration of a relation between arterial baroreceptor stretch and renal hemodynamics in humans, in the sense that increased stretch can cause renal vasorelaxation. Information available thus far is based on techniques such as volume expansion, posture change, or changes in lower-body pressure. Such maneuvers activate or deactivate multiple neurohumoral pathways, and the single contribution of arterial baroreceptor stretch to changes in kidney function cannot be discerned. Infusion of vasoactive drugs such as phenylephrine and nitroglycerin, useful to evaluate the effect of selective arterial baroreceptor (de-) activation on cardiovascular function, cannot be used for this purpose because of the direct effect of these drugs on the kidney.  

Neck suction has been used mainly to study the acute influence of the arterial baroreceptor reflex on cardiovascular function. For this purpose, neck suction is applied for several seconds or a few minutes at most. The overall conclusion drawn from these studies is that neck suction causes a prompt decrease in heart rate and blood pressure, and sympathetic activity. Our study confirms the immediate effect on heart rate and blood pressure and also shows that these changes tend to remain during continued neck suction, although differences are small and often not significant. Previous studies have demonstrated that during sustained neck suction, the heart rate and blood pressure adapt rapidly but only partially. However, as mentioned, these studies covered only a few minutes of suction. In equally short studies, no effect of neck suction on spontaneous or stimulated plasma norepinephrine concentrations was found. Our study confirms this finding, although some tendency
for decreased plasma norepinephrine could be recognized throughout the neck suction phase in the sodium-restricted subjects.

Suspecting that it would take some time to detect changes in renal hemodynamics with clearance techniques, we applied neck suction for at least 60 minutes. Changes in renal hemodynamics can usually be demonstrated within this period during maneuvers such as water immersion. In the sodium-restricted subjects, an increase in GFR, ERPF, and renal blood flow and a fall in renal vascular resistance was found throughout the entire 90-minute period of neck suction. This indicates that the carotid stretch caused sustained renal vasodilation. It has been demonstrated that during continued neck suction, the decrease in muscle sympathetic activity adapts fully, reaching baseline values within seconds. For this reason, it was suggested recently that sympathetic muscle activity responds to a changing arterial pressure rather than correlating with absolute pressure levels.

The absence of an effect of neck suction on renal function in sodium-replete subjects compared with sodium-restricted subjects suggests a difference in prevailing arterial baroreflex control of kidney function. It is assumed that in normal sodium-replete humans, basal renal nerve activity is low and has little or no influence on renal hemodynamics.

A decrease in effective blood volume has been shown to increase renal nerve activity in rats. Although we are not aware of direct data in humans showing that sympathetic control of renal hemodynamics becomes significant during sodium restriction, this is a conceivable option, particularly in subjects examined in the upright position. Studies exploring the relation between arterial baroreceptor activity and blood pressure or muscle sympathetic activity in humans also suggest that sodium-replete subjects at rest operate at low levels of sympathetic excitation. It has been demonstrated recently that dietary sodium restriction increases the arterial baroreceptor control of heart rate and blood pressure in normal subjects studied with neck suction. In parallel, we suggest that sodium restriction may also enhance arterial baroreflex control of renal hemodynamics and that neck suction can uncover such control, particularly in this condition.

It is unlikely that the discrepant findings in sodium-replete subjects compared with sodium-restricted subjects were associated with a methodological difference. Although the experimental period in the sodium-replete subjects was relatively short, neck suction of similar duration caused consistent renal vasorelaxation in the sodium-restricted subjects. Also, in both groups, discontinuation of neck suction promptly increased heart rate, indicating adequate carotid stretch throughout the experimental phase. It is also unlikely that the difference
in renal hemodynamic response was related to a greater degree of angiotensin II suppression in the sodium-restricted subjects, even though baseline activity of the renin-angiotensin system was greatly stimulated in this group. Neck suction had no effect on plasma renin activity in both groups (see below). Besides, the vaso-dilation associated with angiotensin II suppression is characterized by a greater increase in ERPF than in GFR and thus with a decrease in filtration fraction.41,42 In the present study, the increases in ERPF and GFR were proportional, which is consistent with a change in renal nerve activity. Experiments in rats have demonstrated that variation of renal nerve activity is associated with proportional effects on GFR and ERPF.43,44

The present study was not designed to detect brief transient changes in renal hemodynamics. For this purpose, clearance methods are evidently too slow. Therefore, it remains possible that sudden carotid stretch caused renal vasorelaxation also in sodium-replete subjects but that this response is followed by rapid adaptive loss in vasodilatory response. If such adaptation indeed occurs, it is incomplete in the sodium-restricted subjects, since a decrease in renal vascular resistance was found throughout the period of neck suction in this group. This is in clear contrast with the reported transient effect on muscle sympathetic activity.5,13,15 Nearly all previous reports on the relation between arterial baroreflex and renal hemodynamics are limited to the instantaneous effects of alterations in baroreflex activity. However, in the study by Karim et al18 in dogs, the effect of selective elevation of carotid sinus pressure on renal hemodynamics was recorded during 20 minutes, and sustained increments in GFR and renal blood flow were found. These data and the findings in our study suggest that changes in arterial pressure can have sustained effects on renal hemodynamics via modulation of arterial baroreceptor activity.

Direct information on the relation of arterial baroreceptor activity and renal function in other species is relatively scarce. In the dog, it was found that deactiva-

### Table 3. Plasma Hormone Values During Time Control and Neck Suction on Low-Sodium Diet

<table>
<thead>
<tr>
<th></th>
<th>Baseline, min</th>
<th>Test, min</th>
<th>Recovery, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-15</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>PRA, fmol·L⁻¹·s⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>589±69</td>
<td>631±90</td>
<td>692±136</td>
</tr>
<tr>
<td>Neck suction</td>
<td>741±70</td>
<td>851±70</td>
<td>891±105</td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>646±174</td>
<td>708±201</td>
<td>708±237</td>
</tr>
<tr>
<td>Neck suction</td>
<td>589±187</td>
<td>646±184</td>
<td>776±234</td>
</tr>
<tr>
<td>ANP, pmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>8.3±1.3</td>
<td>7.0±1.0</td>
<td>7.7±1.1</td>
</tr>
<tr>
<td>Neck suction</td>
<td>8.1±0.8</td>
<td>7.6±0.8</td>
<td>8.2±0.9</td>
</tr>
<tr>
<td>NE, nmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>1.46±0.12</td>
<td>1.53±0.27</td>
<td>1.43±0.33</td>
</tr>
<tr>
<td>Neck suction</td>
<td>1.56±0.17</td>
<td>1.35±0.24</td>
<td>1.38±0.21</td>
</tr>
<tr>
<td>E, nmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>0.17±0.05</td>
<td>0.17±0.05</td>
<td>0.15±0.03</td>
</tr>
<tr>
<td>Neck suction</td>
<td>0.13±0.05</td>
<td>0.13±0.05</td>
<td>0.14±0.05</td>
</tr>
</tbody>
</table>

PRA indicates plasma renin activity; ANP, atrial natriuretic peptide; NE, norepinephrine; E, epinephrine. No significant changes were found, and no difference existed between time control and neck suction studies. Values are mean±SEM.

**FIG 2.** Graphs showing changes in heart rate (left) and mean arterial blood pressure (right) from baseline values during neck suction (closed circles) compared with time control (open circles) during 200 mmol/d Na diet. Neck suction was applied for 60 minutes. The start and finish of this period are indicated by the dotted lines. Values are mean±SEM. ##P<.05, ###P<.01 compared with time control. bpm indicates beats per minute.
tion of renal sympathetic activity by volume expansion depends on cardiopulmonary baroreceptors rather than arterial baroreceptors. However, it was also found that selective elevation of carotid sinus pressure increased renal blood flow. In rabbits, it has been shown that both aortic and carotid baroreceptors take part in the control of renal nerve activity. In rats, arterial baroreceptor stimulation by carotid traction has been shown to stimulate sodium excretion without affecting renal hemodynamics. In regard to primates, it has been difficult to demonstrate a role for cardiopulmonary baroreceptors in the renal response to volume expansion or atrial stretch in intact monkeys, but such a role could be shown if the animals had undergone sinoaortic denervation. In humans with a functioning heart transplant, the renal vascular resistance is elevated but decreases during water immersion. Considering that this condition is associated with denervation of cardiopulmonary receptors, this finding suggests that in humans, arterial baroreceptors are also involved in the control of renal hemodynamics.

In regard to the magnitude of the renal response observed here, two other points may be relevant. First, neck suction leaves the aortic baroreceptors undisturbed, and these were shown to be of prime importance for the magnitude of the arterial baroreflex-cardiac and -vascular response in humans. Therefore, it is quite possible that a more pronounced renal response would be obtained (in sodium-restricted as well as -replete subjects) if the entire arterial baroreflex were activated. The only way to accomplish this is the administration of hypertensive drugs, but this is complicated by direct drug actions on the kidney. Second, it is not unlikely that the arterial baroreflex effect on the kidney is potentiated by simulta-
neous activation of the cardiopulmonary baroreflex. Such interaction, which has been shown in humans for the baroreflex cardiac and vascular response,\textsuperscript{11,52} can explain why renal vasorelaxation is more commonly found during water immersion,\textsuperscript{31,38} which engages both cardiopulmonary and arterial baroreflexes.

In view of the above, carotid stretch may at most lead to partial deactivation of renal sympathetic nerve activity. If renin secretion is high, partial deactivation of renal sympathetic activity can cause renal vasorelaxation without influencing the stimulated renin secretion rate,\textsuperscript{23} in correspondence with our findings. Absence of renin suppression and the fact that neck suction, in contrast to challenges such as volume expansion, posture change, or water immersion, does not increase plasma atrial natriuretic peptide may also explain the absence of a natriuretic response in this experiment.

The relevance of the present data extends to pathophysiological conditions, hypertension in particular. Decreased baroreflex-cardiac sensitivity but not baroreflex-vascular sensitivity has been demonstrated in hypertensive humans\textsuperscript{19,20} and hypertensive rats.\textsuperscript{21,22} Transient baroreflex dysfunction and hypertension have been observed in patients after carotid endarterectomy\textsuperscript{26} and Takayasu's arteritis,\textsuperscript{57} whereas baroreceptor deafferentation has been associated with hypertension in some animal studies.\textsuperscript{23-25} The questions whether baroreflex-renal sensitivity is altered during hypertension and whether altered baroreflex sensitivity can cause or contribute to human hypertension on a long-term basis are relevant only if it is assumed that the arterial baroreflex is involved in the control of renal function.\textsuperscript{26,27} The present data support this assumption and also provide a model to examine the relation between the arterial baroreflex and kidney function in physiology and pathophysiology.

Acknowledgments

This study was supported by the Dutch Kidney Foundation, grant 91.1108. We acknowledge the assistance of R.P. Rab and H.L.C.J. van Strien from the Instrumental Service and Development Department in our hospital.

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Circulation. 1994;90:1883-1890
doi: 10.1161/01.CIR.90.4.1883

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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