Effect of renal denervation on dynamic autoregulation of renal blood flow

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DiBona, Gerald F., and Linda L. Sawin. Effect of renal denervation on dynamic autoregulation of renal blood flow. Am J Physiol Renal Physiol 286: F1209–F1218, 2004.—Vasoconstrictor intensities of RNS that decrease basal RBF by ≥15–20% result in a progressive elevation of the autoregulatory threshold (“break point”), i.e., that level of renal arterial pressure (RAP) below which further reductions in RAP are associated with decreases in RBF. Correspondingly, basal RBF and stepwise and dynamic autoregulation of RBF are not affected by removal of basal RSNA by either renal denervation or ganglionic blockade with hexamethonium (1, 10, 14).

The in vitro physiological reality of RBF autoregulation is the moment-to-moment adjustments of the renal vasculature to the oscillations in RAP that are needed to maintain RBF constant. This spontaneous or dynamic RBF autoregulation spans the frequency range of RAP oscillations, which is 0–10 Hz.

Studies in normal dogs and rats indicate that neither basal RBF nor dynamic RBF autoregulation is affected by removal of basal RSNA by renal denervation or hexamethonium administration (1, 10, 14). However, it appears that the situation is different in the rabbit. In two studies, renal denervation resulted in increases in RBF of 42 (11) and 55% (12), suggesting that the basal level of RSNA in the rabbit is renal vasoconstrictor and significantly greater than that in the rat and dog. It was observed further that dynamic RBF autoregulation was impaired after renal denervation (transfer function gain was lower in innervated than denervated kidneys), suggesting that the vasoconstrictor intensity of basal RSNA was a factor contributing to the maintenance of normal dynamic autoregulation of RBF in the rabbit (12).

The current studies were undertaken to test the hypothesis that 1) removal of basal RSNA that is of subvasoconstrictor intensity does not affect dynamic RBF autoregulation; and 2) removal of basal RSNA that is of vasoconstrictor intensity improves dynamic RBF autoregulation. To test these hypotheses, dynamic RBF autoregulation was measured before and after acute renal denervation in rats where the basal level of RSNA is subvasoconstrictor, i.e., in control and Wistar-Kyoto (WKY), and in rats where the basal level of RSNA is vasoconstrictor, i.e., in congestive heart failure (CHF) (5, 7, 8) and spontaneous hypertension (SHR) (18).

MATERIALS AND METHODS

Adult male Sprague-Dawley, WKY, and SHR rats, weighing 250–300 g, allowed free access to normal sodium rat pellet diet and tap water drinking fluid, were used for all studies. All animal procedures were performed in compliance with the University of Iowa Policies and Guidelines Concerning the Use of Animals in Research and Teaching and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85–23, Revised 1985).

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IN NORMAL ANIMALS, BASAL RENAL sympathetic nerve activity is low (6). Under such circumstances, the renal functional responses to renal denervation consist of an increase in urinary sodium excretion and a decrease in renin secretion rate with no change in renal blood flow (RBF) or glomerular filtration rate (GFR). These responses suggest that, under basal conditions, there is tonic renal sympathetic neural tone to increase renal tubular sodium reabsorption and renin secretion but that there is no tonic renal sympathetic neural vasoconstrictor tone. These renal functional responses to renal denervation correspond well with the renal functional responses to graded intensity renal nerve stimulation (RNS). Low-intensity RNS (frequencies ≥1.0 Hz, subvasoconstrictor) results initially in an increase in renin secretion rate and then a decrease in urinary sodium excretion with no change in RBF or GFR. Only at higher intensity RNS (frequencies >1.0 Hz, vasoconstrictor) are RBF and GFR decreased.

Steady-state or stepwise RBF autoregulation is also differentially affected by subvasoconstrictor vs. vasoconstrictor intensities of renal sympathetic nerve activity (RSNA) (4, 15). Subvasoconstrictor intensities of RNS have little effect on stepwise RBF autoregulation. However, vasoconstrictor intensities of RNS that decrease basal RBF by ≥15–20% result in a progressive elevation of the autoregulatory threshold (“break point”), i.e., that level of renal arterial pressure (RAP) below which further reductions in RAP are associated with decreases in RBF. Correspondingly, basal RBF and stepwise and dynamic autoregulation of RBF are not affected by removal of basal RSNA by either renal denervation or ganglionic blockade with hexamethonium (1, 10, 14).

The in vitro physiological reality of RBF autoregulation is the moment-to-moment adjustments of the renal vasculature to the oscillations in RAP that are needed to maintain RBF constant. This spontaneous or dynamic RBF autoregulation spans the frequency range of RAP oscillations, which is 0–10 Hz.

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CHF was produced in Sprague-Dawley rats by left coronary artery ligation with subsequent myocardial infarction using a method established and validated in our laboratory (5, 7, 8). Control (Control or sham CHF), CHF, WKY, and SHR rats were studied 4–6 wk later.

Rats were anesthetized with pentobarbital sodium (50 mg/kg ip); an oral endotracheal tube was inserted, and mechanical ventilation with room air was instituted. A jugular vein was catheterized for the administration of additional anesthetic (10 mg/kg−1·h−1 iv) and isotonic saline at 0.05 ml/min. A carotid artery was catheterized for the measurement of arterial pressure [AP; pulsatile or mean (MAP)] and heart rate (HR). Via a left-flank incision, the left renal nerve bundle was gently dissected free (but not transected) and loosely snared with a suture for future identification and retrieval. To measure RBF, a noncannulating electromagnetic flow probe (1.5-mm circumference) was placed around the left renal artery and connected to an electromagnetic flowmeter (Carolina Medical Electronics). The flow probe was calibrated in situ by pumping heparinized rat blood at known flow rates through the cannulated rat renal artery (with the flow probe in place) at the end of the experiment.

After surgery, a 30-min period was allowed for equilibration and stabilization. This experimental protocol resulted in four experimental groups: Control (n = 8), CHF (n = 7), WKY (n = 9), and SHR (n = 10).

The experimental protocol consisted of a 30-min control (intact renal innervation) period during which continuous recordings of AP and RBF were made. Then, the left kidney was denervated by transecting the left renal nerves. The experimental period began 30 min later and consisted of 30 min during which continuous recordings of AP and RBF were made. Thereafter, a bipolar stimulating electrode was placed on the left lumbar sympathetic chain above the left kidney. A Grass S9 stimulator delivered conventional rectangular pulses of 0.2-ms duration, 15-V amplitude, and 4-Hz frequency for a total stimulation period of 1 min. The absence (<5% change) of a decrease in RBF was taken as evidence of the completeness of left renal denervation. Then, the carotid artery catheter was advanced into the left ventricle for the measurement of left ventricular end-diastolic pressure. The rats were killed with an overdose of pentobarbital sodium, and a 20-min recording of postmortem signals was made. The heart was removed and weighed.

Data analysis. AP and MAP were recorded via an electronic pressure transducer (Statham). HR was determined via a tachometer (Grass 7P4) driven by the pulsatile AP waveform. RBF, both pulsatile and mean, was recorded via the electromagnetic flowmeter, the output of which was low-pass filtered below 10 Hz by the built-in analog filter. The outputs of the pressure transducer, the tachometer, and the electromagnetic flowmeter were sent to a Grass model 7D polygraph recorder for graphic output and to VHS tape via a pulse code modulation adapter (Vetter, model 4000A PCM Recording Adapter) for later offline analysis.

Analog AP and RBF signals were sampled from the tape at 1,000 Hz. The postmortem signals were subtracted from the recorded control and experimental period data. For assessment of the effect of renal denervation on steady-state values of AP, RBF, and renal vascular resistance (RVR = AP/RBF), the averages of the values from the last 5 min of the control period were compared with the averages of the values from the first 5 min of the experimental period.

Subsequent processing of the data was performed with Matlab software (Matlab, release 12.1, MathWorks, Natick, MA). The 1,000-Hz data files were digitally low-pass filtered (3.5-Hz cutoff frequency, finite-impulse-response, order 50) and then decimated to a rate of 5 Hz. These 5-Hz data were split into blocks of 4,096 data points. The transfer function spectra were calculated from AP (input) and RBF (output) during both control and experimental periods. The transfer function was taken as the quotient of the cross spectrum of input and output divided by the power spectrum of the input. The algorithm involved mean detrending and a Hanning window with 50% overlap of the blocks. To permit comparison among rats, the transfer function gain (magnitude) values over the frequency range have been normalized to the value at 0-Hz frequency (direct current; i.e., to a value of 1). After conversion of the normalized transfer function gain values into decibels (20 log [gain]), a mean spectrum was calculated from the consecutive spectra in each rat, and these were subsequently averaged for all rats.

Coherence is a frequency domain estimate of a linear correlation (i.e., squared coherence, akin to coefficient of determination) between two signals indicating the degree to which the variance in one signal can be explained by a linear operation on the other signal. The coherence spectra were calculated from AP (input) and RBF (output) during both control and experimental periods. The coherence function was taken as the quotient of the square of the cross spectrum of input and output divided by the product of the power spectrum of the input and the power spectrum of the output. The algorithm involved mean detrending and a Hanning window with no overlap of blocks of 256 data points.

For assessment of RBF variability, the mean RBF was calculated for the entire 30-min control and experimental periods for each rat. Then, the change in RBF from this mean value was calculated for each RBF value within the respective control and experimental periods for each rat. The range of change in RBF from the mean value, −5 to +5 ml/min, was divided into 0.1 ml/min intervals (bins), and a histogram of percent occurrence was calculated for the control and experimental periods in each rat.

Statistical analysis was performed with analysis of variance with the subsequent use of Scheffé’s method for simultaneous comparisons within groups and the subsequent use of the F ratio and modified statistic for nonsimultaneous comparisons between groups (19). For a comparison of distributions, the Brandt-Snedecor χ2 test for comparison of arbitrary distributions was used. A significance level of 5% was chosen. Data are expressed as means ± SE.

RESULTS

During the control period (Table 1), CHF rats had decreased RBF and increased RVR compared with Control rats (P < 0.05 for both). SHR had increased MAP and RVR compared with WKY rats (P < 0.01 for both). Acute renal denervation did not affect steady-state values of MAP, RBF, or RVR in Control or WKY rats. Acute renal denervation increased RBF and decreased RVR without affecting MAP in CHF and SHR rats (P < 0.05 for all). The heart weight-to-body weight ratio was

<p>| Table 1. Effect of acute renal denervation on steady-state renal-hemodynamics |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MAP, mmHg</th>
<th>RBF, ml/min</th>
<th>RVR, mmHg/ml·min⁻¹</th>
<th>MAP, mmHg</th>
<th>RBF, ml/min</th>
<th>RVR, mmHg/ml·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>118±4</td>
<td>6.1±0.2</td>
<td>19.8±0.6</td>
<td>119±4</td>
<td>6.0±0.2</td>
<td>20.7±0.6</td>
</tr>
<tr>
<td>CHF</td>
<td>7</td>
<td>112±4</td>
<td>5.1±0.2†</td>
<td>22.2±0.6*</td>
<td>108±5</td>
<td>6.9±0.3‡</td>
<td>16.7±0.7‡</td>
</tr>
<tr>
<td>WKY</td>
<td>9</td>
<td>116±4</td>
<td>5.5±0.2</td>
<td>20.9±0.5</td>
<td>114±3</td>
<td>5.5±0.1</td>
<td>20.7±0.5</td>
</tr>
<tr>
<td>SHR</td>
<td>10</td>
<td>157±4*</td>
<td>5.8±0.2</td>
<td>27.0±0.6</td>
<td>151±5</td>
<td>7.0±0.2‡</td>
<td>21.1±0.5‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, No. of rats; MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance; CHF, congestive heart failure; WKY, Wistar-Kyoto; SHR, spontaneously hypertensive rat. *P < 0.01 SHR vs. WKY; †P < 0.05 CHF vs. Control. ‡P < 0.05 Experimental vs. Control.
0.65 ± 0.03% in CHF compared with 0.33 ± 0.01 in Control rats (P < 0.01). Left ventricular end-diastolic pressure was 13.6 ± 0.7 mmHg in CHF compared with 1.6 ± 0.2 mmHg in Control rats (P < 0.001). After acute left renal denervation, stimulation of the left lumbar sympathetic chain above the left kidney did not significantly decrease left RBF (<5%).

The effects of acute renal denervation on transfer function gain spectra for Control and CHF rats are shown in Fig. 1. Before acute renal denervation, there is a trend for gain to be greater in CHF than Control rats at frequencies <0.1 Hz, suggesting less efficient autoregulation of RBF in CHF than in Control rats, in agreement with previous studies (7). Both the nadir in transfer function gain between 0.06 and 0.07 Hz (slower tubuloglomerular feedback component) and the plateau between 0.15 and 0.3 Hz (faster myogenic component), seen in Control rats, were absent in CHF rats. After acute renal denervation, in both Control and CHF rats transfer function gain tended to be lower (not statistically significant) at frequencies <0.1 Hz and tended to be higher (not statistically significant) at frequencies >0.1 Hz. After acute renal denervation in CHF rats, the transfer function gain at frequencies <0.1 Hz became similar to that in Control rats with intact renal innervation.

The effects of acute renal denervation on transfer function spectra for WKY and SHR rats are shown in Fig. 2. Before acute renal denervation, the gain is greater in SHR than WKY rats at frequencies <0.1 Hz, reflecting less efficient autoregulation of RBF in SHR than in WKY rats. The nadir in transfer function gain between 0.02 and 0.03 Hz (tubuloglomerular feedback component) seen in WKY rats was absent in SHR rats. The plateau in transfer function gain (~0 dB) between 0.15 and 0.3 Hz (myogenic component) seen in WKY rats was shifted upward to positive gain values of +5 dB in SHR rats. After acute renal denervation in WKY rats, transfer function was slightly decreased (not statistically significant) below 0.1 Hz and slightly increased (not statistically significant) above 0.1 Hz. After acute renal denervation in SHR, there was a marked decrease in transfer function gain that was statistically significant at all frequencies <0.3 Hz. In addition, there was the reappearance of a distinct nadir at 0.02 Hz (tubuloglomerular feedback component), and the plateau in transfer function gain at between 0.1 and 0.2 Hz (myogenic component) was decreased to negative values, i.e., ~2 dB. After acute renal denervation in SHR rats, the transfer function gain over the entire frequency range shifted toward that of WKY rats with intact renal innervation.

In all experiments, the phase angle was positive, indicating that RBF (output) leads AP (input). The effects of acute renal denervation on phase-angle spectra for Control and CHF rats are shown in Fig. 3. Before acute renal denervation, the phase angle was positive but less in CHF than in Control rats at frequencies <0.05 Hz. In Control rats, the phase angle exhibited an initial peak at 0.02 Hz, falling toward zero at lower frequencies and to a nadir between 0.06 and 0.07 Hz (corresponding to the nadir in the transfer function gain; Fig. 1). There was a second local maximum of slightly less magnitude at 0.1–0.2 Hz. In CHF rats, the phase angle showed a peak at 0.08 Hz, with a plateau at frequencies below 0.001–0.04 Hz and above 0.1–0.2 Hz. Acute renal denervation significantly decreased the phase-angle peak at 0.02 Hz in Control rats but had no significant effect on the phase angle in CHF rats.

The effects of acute renal denervation on phase-angle spectra for WKY and SHR rats are shown in Fig. 4. Before acute renal denervation, the phase angle was positive in both WKY rats and SHR at frequencies <0.2 Hz. In WKY rats, the phase angle exhibited an initial peak at 0.02–0.03 Hz (corresponding to the nadir in transfer function gain; Fig. 2), decreasing at lower and higher frequencies with a second local maximum of similar magnitude at 0.1 Hz. In SHR rats, the phase angle...
exhibited a plateau at 0.02–0.3 Hz, ascending to a maximum peak at 0.07 Hz. Acute renal denervation did not significantly affect the phase angle in WKY but significantly decreased the phase angle at all frequencies <0.1 Hz in SHR, resulting in loss of definition of the 0.07-Hz peak.

The effects of acute renal denervation on coherence in Control and CHF rats are shown in Fig. 5. Before acute renal denervation, coherence was greater in Control than in CHF rats over the entire frequency range. Acute renal denervation had no effect on coherence in Control rats. After acute renal denervation in CHF rats, coherence tended to increase (not significant) toward that in Control rats.

The effects of acute renal denervation on coherence in WKY and SHR rats are shown in Fig. 6. Before acute renal dener-
vation, coherence was greater in WKY rats than in SHR over
the entire frequency range. Acute renal denervation had no
effect on coherence in WKY rats. After acute renal denervation
in SHR rats, coherence significantly increased at all frequen-
cies <0.5 Hz.

When acute renal denervation removed tonic vasoconstrictor
intensities of RSNA (i.e., in CHF and SHR rats), RBF vari-
ability was increased. Figure 7 (left) plots the change in RBF
from its mean value vs. the change in AP from its mean value
in one SHR before [Control (Con in figure); top left] and after
acute renal denervation (DNX in figure; bottom left). Over the
same range of changes in AP from its mean value, the changes
in RBF from the respective mean value were more variable
after acute renal denervation. For example, when AP increased
10 mmHg above the mean value (i.e., systole), the increases in
RBF above the mean value ranged from 0 to 1.5 ml/min in

Fig. 4. Effect of DNX on phase angle between
AP and RBF in WKY (left) and SHR rats (right).
For clarity of presentation, SE curves (shown
for SHR) are not shown for WKY rats.

Fig. 5. Effect of DNX on coherence between AP
and RBF in Control (left) and CHF (right). For
clarity of presentation, SE are not shown. con,
Control.
SHR-DNX compared with 0.3–0.5 ml/min in SHR-Con rats. In the histograms of RBF variability, before renal denervation SHR-Con (top right) showed a unimodal narrow distribution. After renal denervation, SHR-DNX (bottom right) showed a bimodal wide distribution.

The effects of acute renal denervation on RBF variability, as histograms of changes in RBF from mean, for Control and CHF rats are shown in Fig. 8. Before acute renal denervation, 100% of values are encompassed within the range −1.0 to +1.0 ml/min in CHF rats, whereas Control rats exhibit a negative shoulder with 7% of values being between −1.0 and −2.0 ml/min plus a positive shoulder with 7% of values between +1.0 and +3.0 ml/min. Acute renal denervation did not significantly affect variability in Control rats. However, in CHF rats, acute renal denervation significantly widened the distribution (i.e., increased the variability; P < 0.01) and

Fig. 6. Effect of DNX on coherence between AP and RBF in WKY (left) and SHR rats (right). For clarity of presentation, SE lines (shown for SHR) are not shown for WKY rats.

Fig. 7. Effect of acute renal denervation on RBF variability in one SHR rat. Left: changes in RBF from mean as a function of changes in AP from mean before (SHR-con; top left) and after DNX (SHR-DNX; bottom left). Right: distribution histograms of RBF variability before (SHF-con; top right) and after DNX (SHR-DNX; bottom right).
significantly decreased the peak percent occurrence from $9.6 \pm 1.2$ to $5.1 \pm 0.9\%$ ($P < 0.01$).

The effects of acute renal denervation on RBF variability for WKY and SHR rats are shown in Fig. 9. Before acute renal denervation, RBF variability was significantly greater in SHR than in WKY rats ($P < 0.05$). The distribution ranged from $-1.0$ to $+2.0$ ml/min in WKY and $-2.0$ to $+2.5$ ml/min in SHR rats. The peak percent occurrence was significantly lower in SHR ($5.5 \pm 0.9\%$) than in WKY rats ($9.6 \pm 1.2\%; P < 0.01$). Acute renal denervation did not significantly affect variability in WKY rats. However, in SHR rats, acute renal denervation resulted in even greater RBF variability, with the range of distribution widening to $-3.0$ to $+3.5$ ml/min. In addition, the peak percent occurrence was significantly decreased further to $4.0 \pm 0.6$ ml/min ($P < 0.05$).

Fig. 8. Effect of acute renal denervation on RBF variability (distribution histograms) in Control (left) and CHF (right) rats. For clarity of presentation, SE (shown for CHF) are not shown for Control rats.

Fig. 9. Effect of acute renal denervation on RBF variability (distribution histograms) in WKY (left) and SHR rats (right). For clarity of presentation, SE (shown for SHR) are not shown for WKY rats.
DISCUSSION

The main findings of this study are that acute removal of vasoconstrictor, but not subvasoconstrictor, intensities of RSNA by renal denervation improves dynamic autoregulation of RBF and increases RBF variability.

These results indicate that intensities of RSNA that produce tonic and sustained renal vasoconstriction (i.e., SHR) impair dynamic autoregulation of RBF, whereas subvasoconstrictor intensities do not (i.e., Control, WKY). However, acute renal denervation in CHF rats, which produced a similar increase in basal RBF to that seen in SHR, had no effect on dynamic autoregulation of RBF rats. An important difference between SHR and CHF rats is that the maximum duration of the increase in RSNA in CHF rats can be only 4–6 wk, whereas the increase in RSNA in SHR is of lifelong duration. It is also likely that the influence of RSNA on dynamic autoregulation of RBF involves an interaction with structural as well as functional components of the renal vasculature. While the increase in RBF after acute renal denervation reflects the response of functional components of the renal vasculature (vascular smooth muscle relaxation after removal of sympathetic neural vasoconstrictor tone), it seems clear that prolonged increases in RSNA can affect structural components of the renal vasculature. Sympathetic vasoconstrictor tone is known to contribute to structural remodeling and hypertrophy of arterial resistance vasculature (9, 17). Another important difference between SHR and CHF rats is that the level of AP with SHR having significant lifelong hypertension, whereas CHF rats are generally normotensive. Under the influence of chronic hypertension, the renal vasculature of SHR undergoes significant remodeling characterized by a marked increase in minimal renal vascular resistance, i.e., a decreased renal vasodilator capacity (9, 13). Thus it is likely that the longer duration of increased RSNA and hypertension in SHR compared with CHF rats contributes to the differences between SHR and CHF rats in the effect of acute renal denervation on dynamic autoregulation of RBF.

The slower tubuloglomerular feedback and faster myogenic components of RBF autoregulation, readily evident in Control rats, were seen in CHF rats only after renal denervation. The slower tubuloglomerular feedback component of RBF autoregulation, readily evident in WKY, was seen in SHR only after renal denervation, which also decreased the gain of the myogenic component. These results indicate that the vasoconstrictor intensities of basal RSNA in CHF and SHR rats interacted with both the tubuloglomerular feedback and the myogenic mechanisms of RBF autoregulation.

The effect of renal denervation on the dynamic autoregulation of RBF in WKY and SHR rats has been previously examined (1). Acute renal denervation did not significantly affect basal RBF in either WKY or SHR rats; i.e., the intensity of basal RSNA in both WKY and SHR rats was subvasoconstrictor. Acute renal denervation significantly increased admittance gain in both WKY (0.1 ± 1.0 to 4.1 ± 0.9 dB) and SHR rats (from 2.9 ± 0.4 to 5.4 ± 0.3 dB) but only in the frequency range faster than autoregulation (0.25–0.7 Hz) and had no effect on the admittance phase. Withdrawal of the subvasoconstrictor intensities of RSNA did not affect admittance gain at frequencies ≤0.2 Hz, wherein the slower tubuloglomerular feedback and faster myogenic components of RBF autoregulation operate in either WKY or SHR rats. These previous findings agree with the current results that withdrawal of subvasoconstrictor intensities of RSNA does not affect dynamic autoregulation of RBF.

These results are in agreement with the observations made in studies of dynamic autoregulation of RBF in the rat and dog (1, 10). Removal of basal RSNA by acute or chronic renal denervation or by hexamethonium administration in otherwise normal rats or dogs does not produce sustained alterations in the basal level of RBF and does not alter dynamic autoregulation of RBF. Using graded intensities of renal nerve stimulation (4, 14), intensities that were subthreshold for producing decreases in the basal level of RBF, there was no major effect on stepwise autoregulation of RBF. Higher intensities of renal nerve stimulation that decreased the basal level of RBF by ≥15–20% resulted in a progressive impairment of stepwise autoregulation of RBF, which was manifest as an elevation of the pressure threshold (break point). Similar results have been observed using carotid baroreflex activation (16) or renal arterial administration of methoxamine (15) to increase renal sympathetic adrenergic vasoconstrictor tone and decrease the basal level of RBF.

The new information from the current study concerns the influence of tonic vasoconstrictor intensities of RSNA on dynamic autoregulation of RBF. The tonic vasoconstrictor intensities of RSNA seen in CHF and SHR rats significantly worsened dynamic autoregulation of RBF in the frequency ranges of both the tubuloglomerular feedback component and the myogenic component. After renal denervation, the overall marked improvement in dynamic autoregulation of RBF was characterized by notable changes that occurred in the frequency ranges of these two components.

The similarity in results in the dog and the rat focuses on the different findings in the rabbit. In contrast to the dog and the rat where renal denervation has no sustained effect on basal RBF, the situation appears to be different in the rabbit. Compared with basal RBF in an innervated kidney, basal RBF in a denervated kidney was increased by 42 (11) and 55% (12) in two separate studies. These results suggest that, in these studies, basal RSNA in the rabbit was significantly increased, resulting in substantial tonic renal vasoconstrictor tone. Based on the results in rats and dogs, one would predict that assessment of dynamic autoregulation of RBF in these rabbit studies, wherein renal denervation markedly increased basal RBF, would show an improvement (i.e., change from a higher to a lower gain) after renal denervation. However, the opposite was observed, with gain being significantly greater in the denervated kidney than the innervated kidney across all frequencies (0.0–2.0 Hz) (12). These results would suggest that dynamic autoregulation of RBF in the rabbit is better in the presence of a tonic level of renal sympathetic neural vasoconstrictor tone. This might indicate that, in the rabbit, a tonic level of renal sympathetic neural vasoconstrictor tone, perhaps present throughout life, favorably impacts both the tubuloglomerular feedback and myogenic components of dynamic autoregulation of RBF. There is scant information on the effect of either acute or chronic renal denervation on the single-nephron characteristics of the tubuloglomerular feedback or myogenic mechanisms in the rabbit.

While the removal of a tonic renal vasoconstrictor level of RSNA had different effects on dynamic autoregulation of RBF...
in the rabbit (worsened) compared with the rat (improved), the effects on coherence were similar in the two species in that coherence increased significantly. This indicates that there was a tighter coupling between AP and RBF after renal denervation and that the presence of a tonic renal vasoconstrictor level of RSNA impaired the coupling (e.g., autoregulation) between AP and RBF.

In dynamic or spontaneous autoregulation, it is apparent that vasoconstrictor intensities of RSNA also interfere with the moment-to-moment adjustments of the renal vasculature that keep RBF nearly constant during the moment-to-moment changes in AP. This is reflected in the finding that, for the same change in AP from the mean value, the range of change in RBF from the mean value is far greater after acute renal denervation. It is important to note that this loss of fine adjustment is the same over the entire range of change in AP from the mean value, i.e., both during diastole when the changes in AP and RBF from their mean values are negative and in systole when they are positive. Therefore, the moment-to-moment changes in the vasoconstrictor intensity of RSNA appear to be involved both when RVR is rising (when change of AP from mean is positive) and falling (when change of AP from mean is negative).

Both the oscillations in AP as well as the rhythmic bursting discharge in RSNA contribute to the oscillations in RBF. In the rabbit, modeling the RBF oscillations as a single output with AP and RSNA as inputs indicated that ~80% of the variation in RBF could be accounted for by the variations in AP and RSNA (3). With the use of a single-input model, it appeared that the RSNA signal had a somewhat more dominant effect. In that regard, it was reasoned that plotting the simultaneous individual changes from the mean of RBF vs. the individual changes from the mean of AP before and after renal denervation would unmask the contribution of RSNA to RBF variability. In Control and WKY rats, wherein basal RSNA was vasoconstrictor, acute renal denervation did not affect RBF variability. However, in CHF and SHR rats, wherein basal RSNA was vasoconstrictor, acute renal denervation did not affect RBF variability.

Similarly, high-intensity renal sympathetic nerve stimulation decreases RBF and GFR, further increasing renal tubular sodium reabsorption and renin secretion rate.

This analysis receives support from simultaneous measurements of RSNA and RBF made in conscious, freely moving rats (20). Compared with non-rapid eye movement sleep, rapid eye movement sleep decreased RSNA by 39.0% and increased RBF by 4.8%. In contrast, moving and grooming increased RSNA by 29.4 and 65.3%, respectively, while decreasing RBF by only 5.4 and 6.6%, respectively. It is apparent that large increases in RSNA are required to elicit relatively small decreases in RBF in vivo. The slope of the relationship between percent change in RBF and percent change in RSNA was −0.079, indicating that RBF decreased only 0.79% for every 10% increase in RSNA. Thus this is consistent with the view that subvasoconstrictor intensities of RSNA are present in vivo; while these do not appear to affect RBF, it appears they are capable of influencing renal tubular sodium reabsorption and renin secretion rate.

In summary, these studies have shown that, before renal denervation 1) basal RBF was lower in CHF compared with Control rats and basal renal vascular resistance (RVR) was higher in SHR compared with WKY rats; and 2) dynamic RBF autoregulation was impaired in CHF and SHR rats compared with Control and WKY rats. In rats where basal RSNA was subvasoconstrictor (Control, WKY), renal denervation did not affect basal RBF, dynamic autoregulation of RBF, or RBF variability. In rats where basal RSNA was vasoconstrictor (CHF, SHR), renal denervation significantly increased basal RBF, improved dynamic autoregulation of RBF, and increased RBF variability.

**REFERENCES**


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