Differential neural control of intrarenal blood flow

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Leonard, Bridget L., Roger G. Evans, Michael A. Navakatiykan, and Simon C. Malpas. Differential neural control of intrarenal blood flow. Am J Physiol Regulatory Integrative Comp Physiol 279: R907–R916, 2000.—To test whether renal sympathetic nerve activity (RSNA) can differentially regulate blood flow in the renal medulla (MBF) and cortex (CBF) of pentobarbital sodium-anesthetized rabbits, we electrically stimulated the renal nerves while recording total renal blood flow (RBF), CBF, and MBF. Three stimulation sequences were applied: (1) varying amplitude (0.5–8 V), (2) varying frequency (0.5–8 Hz), and (3) a modulated sinusoidal pattern of varying frequency (0.04–0.72 Hz). Increasing amplitude or frequency of stimulation progressively decreased all flow variables. RBF and CBF responded similarly, but MBF responded less. For example, 0.5-V stimulation decreased CBF by 20 ± 9%, but MBF fell by only 4 ± 6%. The amplitude of oscillations in all flow variables was progressively reduced as the frequency of sinusoidal stimulation was increased. An increased amplitude of oscillation was observed at 0.12 and 0.32 Hz in MBF and to a lesser extent RBF, but not CBF. MBF therefore appears to be less sensitive than CBF to the magnitude of RSNA, but it is more able to respond to these higher frequencies of neural stimulation.

Renal sympathetic nerve activity (RSNA) plays a significant role in the regulation of renal hemodynamics and excretory function (8, 23, 26). However, little is known about the influence of renal nerves on regional kidney blood flow, and in particular, blood flow in the renal medulla. This issue is important because although only ∼10% of renal blood flow (RBF) enters the medulla (28), the medullary microcirculation appears to play a critical role in the long-term control of arterial pressure. This appears to be mediated chiefly through the influence of medullary blood flow (MBF) on tubular reabsorption of salt and water (7). Thus renal nerves may have a profound effect on the long-term control of arterial pressure mediated via effects on the medullary microcirculation.

Previous experiments investigating the effects of electrical stimulation of the renal nerves on blood flow in the renal medulla relative to that in the cortex have produced conflicting results. For example, in studies where the renal nerves were stimulated at or close to maximum, similar reductions were observed in both MBF and cortical (or total renal) blood flow (CBF) (1, 4). However, in studies in which the renal nerves were stimulated at a range of frequencies, the authors concluded variously that either MBF is sensitive to low-frequency renal nerve stimulation (15), or in contrast, that the medullary microcirculation is relatively insensitive to renal nerve stimulation (30). In agreement with this latter study, Ledderhos et al. (19) recently found that CBF, but not MBF, was reduced by chemical stimulation of arterial chemoreceptors in conscious rats. A range of factors may have contributed to the differences between these studies, including the methodology used to assess regional kidney blood flow, the species studied, and the precise physiological conditions during the experiment (e.g., volume status and anesthesia). Importantly, only one of these previous studies (15) administered graded levels of nerve stimulation ranging from threshold to maximum. However, Rubidium-86 uptake was used to measure regional kidney blood flow, the validity of which has since been questioned (14). A study using graded nerve stimulation together with valid methods for determination of regional kidney blood flow seems critical for a full understanding of the relative impacts of renal nerve stimulation on CBF and MBF. Therefore, in this study we examined the effects on total RBF and on CBF and MBF determined by laser-Doppler flowmetry, of graded stimulation of the renal nerves at amplitudes (0.5–8 V) and frequencies (0.5–8 Hz) that produced renal vascular effects across the entire range from threshold to maximum.

In the intact animal, neural control of renal hemodynamics may be dependent not only on the mean level of RSNA, but also on the pattern of RSNA. Different patterns or oscillations in nerve activity may have different functions, and RSNA has been shown to contain oscillations over a range of frequencies from 0.1 to 10 Hz (22). Lower frequencies (<0.6 Hz) directly induce oscillations in RBF, whereas faster frequencies (>0.6 Hz), associated with respiration or the cardiac cycle,

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appearance to set the degree of vascular tone (25). Thus one possible means by which the renal nerves might differentially regulate CBF and MBF is through different frequency response characteristics of the vasculature in these two regions. Differences in vessel structure (18, 28), density and distribution of innervation (2, 13), or the kinetics of smooth muscle contraction between cortical and medullary vascular sites may result in a difference in the ability to respond to the different frequencies in RSNA. To investigate the possibility of differences in frequency responses, we also examined the responses of total RBF, CBF, and MBF to stimulation of the renal nerves with an oscillating pattern of stimulation. With the use of this technique, we have previously observed resonance at 0.16 Hz in RBF in the rabbit (25). The present experiment allowed us to test whether this resonance is specific to the cortical or medullary vasculature.

METHODS

Experiments were performed on New Zealand White rabbits (n = 8, mean weight 3.06 ± 0.1 kg) and were approved by the University of Auckland Animal Ethics Committee. Animals were allowed food and water ad libitum until the experimental procedures began.

Surgical Procedures

Induction of anesthesia was by intravenous administration of pentobarbital sodium (90–150 mg Nembutal; Virbac Laboratories, New Zealand) and was immediately followed by endotracheal intubation and artificial respiration. Anesthesia was maintained throughout the surgery and experiment by pentobarbital sodium infusion (30–50 mg/h).

During surgery, 154 mmol/l NaCl solution was infused intravenously at a rate of 0.18 ml·kg⁻¹·min⁻¹ to replace fluid losses. A heated blanket was used throughout the surgery and experiment to maintain body temperature at ~36°C. A catheter was inserted into the central ear artery for monitoring arterial pressure. The left kidney was approached via a retroperitoneal incision, and the renal artery and nerves were carefully exposed. A transit time flow probe (type 2SB, Transonic Systems, Ithaca, NY) was placed around the renal artery. The kidney was then freed from the peritoneal lining and surrounding fat and placed in a stable cup. The renal nerves were identified with the use of a surgical microscope and placed across a pair of hooked stimulating electrodes. The nerves were then sectioned proximally to the stimulating electrodes. Paraffin oil was applied to the nerves throughout the experiment to prevent dehydration. Medullary perfusion was monitored with the use of a 24-gauge, needle-type laser-Doppler flow probe (DP4s, Moor Instruments, Millwey, Devon, England) inserted into the kidney with the use of a micromanipulator (Narashige, Tokyo, Japan) so that its tip lay 10 mm below the midregion of the lateral surface of the kidney, within the “white” inner medulla. For monitoring cortical perfusion, a standard plastic straight probe (DP2b, Moor Instruments) was placed on the dorsal surface of the kidney, and it was secured in place with the use of gauze packing.

Experimental Protocol

Electrical stimulation of the renal nerves was produced with the use of purpose written software in the LabVIEW graphical programming language (National Instruments) coupled to a LabPC+ data acquisition board (National Instruments). Three series of stimulation were applied, all using a pulse width of 2 ms. In the first sequence, the following voltage stimulations were applied in a random order 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, and 8.0 V at a constant frequency of 5 Hz. The second stimulation sequence used a constant voltage with step changes in frequency. The following sequences were applied in random order 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, and 8.0 Hz. The voltage used in this sequence was the minimal voltage required to produce a maximal RBF response. In both of these sequences, stimulation was of a 3-min duration per step with a 5-min recovery period before delivering the next stimulus. The final stimulation sequence used a base frequency of 5 Hz (2-ms pulse width) and an amplitude varying in a sine fashion. A full description of this stimulation approach has been described previously (25). The amplitude chosen was the minimal voltage required to produce a maximal RBF response. This ensured that the sinusoidal stimulation patterns were not supramaximal and thus being clipped, which would result in a nonsinusoidal stimulation pattern. The modulated sine stimulation was delivered at the following frequencies applied in a random order 0.04, 0.08, 0.12, 0.16, 0.2, 0.25, 0.32, 0.4, 0.5, and 0.72 Hz for periods of 7 min with 5-min recovery periods. At the conclusion of the experiment, each animal was killed with an intravenous overdose of pentobarbital sodium (300 mg).

Data Acquisition

The ear artery catheter was connected to a pressure transducer (Cobe, Arvarda, CO), the transit time flow probe was connected to a compatible flowmeter (T106, Transonic Systems), and the laser-Doppler flow probes were connected to a laser-Doppler flowmeter (DRT4, Moor Instruments). These analog signals were digitized and continuously displayed by the nerve stimulation program, allowing continuous sampling of mean arterial pressure (MAP; mmHg), RBF (ml/min), and CBF and MBF perfusion (perfusion units; equivalent to the instrument output in mV/10). Heart rate (HR, beats/min) was derived from the MAP waveform. During each experiment, data were saved continuously as 2-s averages of each variable and as the mean value per heartbeat. This latter file was used for spectral analysis. Each experiment was saved to videotape via a digital recorder (Instrutech). Levels of CBF and MBF recorded in the 60 s after the animal was humanely killed (but still being artificially respired) averaged 29 ± 10 and 41 ± 8 perfusion units, respectively. Before analysis, these offset values were subtracted from the values obtained throughout the experiment.

Data Analysis

Steady state. Steady-state results were calculated from the files of 2-s averages. Mean results show average blood flow for the minute before the stimulus began (control) and the percentage decrease from this control value during the final minute of stimulation.

Spectral analysis. The beat-to-beat data were resampled at 10.24 Hz with the use of a cubic interpolation and no prefiltering. Data were then partitioned into segments of 100-s (512 points) length, overlapping by 50 s (25). Each segment was subjected to detrending to remove the underlying mean value and windowed with a tapered cosine. This was subjected to an overlapped Fast Fourier Transform according to methods described by Berger et al. (3). The resulting frequency resolution was 0.05 Hz.
Because RBF was measured in milliliters per minute and CBF and MBF were measured as perfusion units, changes in these variables during renal nerve electrical stimulation were first normalized as percentages of the 1-min control period before each stimulation. This allowed us to make comparisons between responses to different stimulus parameters and between the different vascular beds. All values are expressed as means ± SE, and P values ≤ 0.05 were considered significant. Statistical analyses were performed with the use of ANOVA, the factors comprising rabbit, flow (i.e., RBF, CBF, and MBF), and the stimulus level (i.e., frequency or amplitude of the stimulus). We tested whether the responses to nerve stimulation differed for the different flow variables by performing separate analyses for each comparison (i.e., RBF vs. CBF, RBF vs. MBF, and CBF vs. MBF). The main effect of flow (P\text{flow}) from these analyses tested whether flow responses to graded nerve stimulation differed for the different flow variables. To protect against the increased risk of experiment-wise type 1 error associated with multiple hypothesis testing, P values were conservatively adjusted with the use of the Dunn-Sidak correction (21).

**Statistical Analysis**

**Stability of Renal Hemodynamic Responses to Nerve Stimulation**

To test whether the sensitivity of the renal vasculature to renal nerve stimulation was stable throughout the experiment, a single 5-V, 5-Hz stimulus of 30-s duration was applied at the completion of each stimulation sequence in five of the rabbits. The magnitude of the reductions in RBF, CBF, and MBF were similar at all three trials (P\text{time} ≥ 0.07) and averaged 81 ± 8%, 80 ± 10%, and 71 ± 12% of their baseline levels, respectively.

**Laser-Doppler Validation**

A separate series of experiments was undertaken to compare flow measurements between the two different types of flow probes used (i.e., needle-type probe vs. plastic-straight probe). Four New Zealand White rabbits (2.74 ± 0.12 kg) were prepared identically to those in the main experiment, except that the renal nerves were not stimulated, and a catheter was placed in a side branch of the renal artery for renal arterial infusion of endothelin-1 (American Peptide, Sunnyvale, CA). Also, the needle probe was not placed in the renal medulla, but it was instead positioned 1 mm below the cortical surface.

In the four rabbits in which it was tested, renal arterial infusion of endothelin-1 (2 ng·kg⁻¹·min⁻¹) produced slowly developing reductions in RBF and CBF, as we have described previously (10). The percentage reductions in CBF measured with the use of the two types of laser-Doppler flow probe were similar. Model II regression analysis (20) of the data, expressed as percentage change from control, demonstrated strong correlations between the two methods (r = 0.86–0.92) and an overall relationship with a slope not different from unity (1.06 ± 0.17; Fig. 1).

**RESULTS**

**Baseline Cardiovascular Variables**

The baseline levels, as measured during the final 1 min of the control periods before each electrical stimulation period, of MAP, heart rate, RBF, CBF, and MBF averaged 67 ± 2 mmHg, 224 ± 6 beats/min, 26 ± 3 ml/min, and 319 ± 24 and 109 ± 13 perfusion units, respectively. None of the stimulation sequences caused significant changes in MAP or heart rate, which remained relatively stable across the course of each experiment. RBF, CBF, and MBF all returned to resting levels during the 5-min control period between stimulations. Hematocrit also remained stable throughout the experiment, averaging 31 ± 3%.

**Effects of Varying Amplitude of Renal Sympathetic Nerve Stimulation**

For each of the flow variables, there was a clear curvilinear relationship between the amplitude of renal nerve stimulation and the percentage reduction in blood flow (P\text{level} < 0.001 for each flow variable; Fig. 2). All amplitudes of nerve stimulation produced a decrease in RBF and CBF from control levels. For example, stimulation at the minimum amplitude of 0.5 V produced a mean decrease in RBF of 21 ± 8%. A 2-V stimulus produced a near maximal RBF response (84 ± 3% decrease from control levels), and further increases in amplitude to 8 V produced further minimal decreases in RBF (91 ± 3%). CBF responses were not significantly different from RBF responses (P\text{flow} = 0.25), but MBF responses were significantly less than those of RBF and CBF (P\text{flow} < 0.001). For example, a 0.5-V stimulus decreased MBF by only 4 ± 6%, and the maximum stimulus of 8 V decreased MBF by only 81 ± 7%.
Effects of Varying Frequency of Renal Sympathetic Nerve Stimulation

Increasing the frequency of nerve stimulation while maintaining a constant, near maximal amplitude of stimulation caused progressive decreases in blood flow in all three regions ($P_{\text{Level}} < 0.001$ for each flow variable; Fig. 3). RBF was decreased by $11 \pm 1\%$ from control levels at 0.5 Hz and by $87 \pm 4\%$ at 8 Hz. RBF and CBF responses were not significantly different ($P_{\text{Flow}} = 0.99$), but MBF responses were significantly less than both RBF and CBF responses ($P_{\text{Flow}} < 0.001$), especially at lower frequencies of stimulation. For example, stimulation at 0.5 Hz caused only a $2 \pm 1\%$ decrease in MBF.

Sinusoidal Stimulation

Although each modulated sine pattern of electrical stimulation varied in the frequency of modulation (0.04 to 0.72 Hz), the base frequency remained the same (5.0 Hz) as did the range of amplitude of stimulation (0–5 V), thus the mean voltage applied to the nerves at each sinusoidal frequency was the same. Consistent with this, the mean decrease from control for each flow variable was not significantly affected by the frequency of the modulated sine pattern (Fig. 4), and it averaged $40 \pm 1$, $42 \pm 1$, and $19 \pm 2\%$, respectively, for RBF, CBF, and MBF across all stimulus frequencies. To allow comparison between animals, the absolute spectral power was normalized against the spectral power
at 0.04-Hz stimulation. The mean frequency response curve for RBF (Fig. 5A) shows that sinusoidal stimulation at 0.4 Hz produced an oscillation with an amplitude only 3% of that at 0.04 Hz. Although mean RBF always decreased in response to the nerve stimulation, at higher frequencies (<0.32 Hz) it did not oscillate ($P_{\text{level}} < 0.001$). CBF and MBF also failed to oscillate at higher frequencies.

Mean and individual frequency response curves (Figs. 5 and 6, respectively) also showed differences in the ability of the vasculature to respond to the different sinusoidal frequencies of nerve stimulation. An increased amplitude of oscillation in the medullary vasculature was seen over two frequency bands, as evidenced by the two peaks in the mean frequency response curve for MBF (Fig. 5C). Although these peaks occurred at different frequencies in individual animals (Fig. 6C), mean results show them centered around 0.12 and 0.32 Hz in MBF. They were also present, but less obvious, in the RBF frequency response curve. Neither peak was evident in the CBF frequency response curve (Figs. 5B and 6B). Thus the mean frequency response curve for MBF was significantly different from that for CBF ($P_{\text{Flow}} < 0.001$), but
not that for RBF \((P_{\text{Flow}} = 0.96)\). Furthermore, the mean frequency response curves for RBF and CBF were also significantly different from each other \((P_{\text{Flow}} < 0.001)\). As the input stimulus to the nerves was the same at all sinusoidal frequencies, the spectral power of the resulting oscillation in blood flow reflects the transfer function. However, in addition to spectral power, we also calculated the gain and phase between the electrical stimulation and the respective blood flow response (Fig. 7). RBF and MBF showed similar decays (20 dB per frequency decade), whereas CBF decayed at 40 dB per frequency decade. The phase delay between stimulus and response was not significantly different between the different vascular regions. The minimum time delay was between 1.1 and 1.5 s after stimulation at 0.72 Hz. This indicates the minimal time for a decrease in flow to occur in response to the electrical stimulus.

**DISCUSSION**

By electrically stimulating the renal sympathetic nerves and simultaneously recording RBF, CBF, and MBF in anesthetized rabbits, we have shown that the renal nerves can influence blood flow in both the renal cortex and medulla. However, rather than exerting the same effect on these two vascular territories, there appear to be at least two ways in which the renal nerves can differentially control MBF and CBF. First, MBF appears to be less sensitive than CBF to a mean increase in renal nerve activity. That is, for a given steady-state frequency or amplitude of nerve stimulation, the MBF response was always less than the CBF response (Figs. 2 and 3). Our examination of the frequency response characteristics of each region, with the use of sinusoidal electrical stimulation, revealed another more subtle mode of differential control. Our results indicate that the medullary microvasculature is more able to respond to higher frequencies in renal nerve stimulation than the cortical vasculature (Fig. 5). This raises the possibility that, although the medullary circulation only accounts for a small proportion of total RBF, it makes an important contribution to the previously reported resonant properties of total RBF (25).

The previous few studies that have examined the role of the renal nerves in control of intrarenal blood flow have provided conflicting results. Rudenstam et al. (30) used graded electrical nerve stimulation and laser-Doppler flowmetry in anesthetized rats and found RBF and CBF responded with similar percentage decreases at 0.5, 2, and 5 Hz, whereas papillary blood flow showed small and variable changes at all levels. They concluded that, whereas total RBF and CBF are profoundly influenced by extrinsic neural in-
put, blood flow in the papilla is likely to be under strong local control. These conclusions are at odds with those of Hermansson et al. (15), who used Rubidium-86 extraction to determine the effects of renal nerve stimulation (at 2, 5, and 10 Hz) and renal denervation on levels of intrarenal blood flow in anesthetized rats. They found that blood flow in all regions of the kidney was reduced by nerve activity in a stimulus-dependent manner, with MBF being more sensitive to lower frequency (0–2 Hz) stimulation. After renal denervation, percent changes in blood flow were greatest in the medulla. They concluded from this that MBF is more sensitive to neural activity than CBF. In contrast, Aukland (1), with the use of anesthetized dogs and a local hydrogen gas clearance method, found that electrical stimulation of the renal nerves (1 ms, 5–15 V, 3–20 Hz) reduced outer MBF by a similar magnitude to total RBF.

Our present results provide evidence of stimulus-dependent reductions in mean MBF after step changes in the frequency or amplitude of renal nerve stimulation. However, MBF appears to be less responsive than CBF, particularly with smaller mean changes in the level of renal nerve stimulation. Differences between our results and those of the studies described above may be partially attributed to the techniques used to record MBF. In a critical review of methods for measurement of MBF, Hansell (14) refers to 10-fold discrepancies between reported control values for MBF with the use of different measurement techniques and concludes particularly that the Rubidium-86 at best gives only a qualitative indication of RBF and its distribution. Although Rudenstam et al. (30) used laser-Doppler flowmetry, they measured papillary blood flow with the use of a “papillary window” technique. This may have resulted in renal nerve scarring thus influencing their results. Alternatively, a hypothesis consistent with the findings of both Rudenstam et al. (30) and the present study is that the renal nerves have less influence on papillary blood flow than on blood flow in other regions of the renal medulla. This hypothesis merits further investigation in future studies.

Consistent with our observations, anatomic and functional data from other studies support a role for RSNA in the control of MBF. For example, both the afferent and efferent arterioles of juxtamedullary glomeruli and the outer medullary descending vasa recta receive neural innervation (6, 28) and constrict in response to application of norepinephrine or stimulation of sympathetic nerves (5, 33). The inner medullary vasa recta gradually loses sympathetic innervation as the smooth muscle cells of the efferent arteriole are replaced by pericytes (27, 28). Thus MBF could be reduced in response to vasoconstriction of juxtamedullary afferent and efferent arterioles, their upstream interlobular arteries, and the outer medullary portions of the descending vasa recta.

We propose that RSNA can now be added to the growing list of factors that differentially regulate intrarenal blood flow, including local and/or circulating hormones that reduce MBF more than CBF [e.g., vasopressin (11, 12)] or reduce CBF more than MBF [e.g., endothelin (10)]. However, we can only speculate at present as to the physiological mechanisms underlying this differential sensitivity of CBF and MBF to RSNA. Regional differences in innervation density (2, 13), the postjunctional responsiveness to norepinephrine or in the amount of vascular smooth muscle (18, 29), may also contribute. Alternatively, as juxtamedullary afferent and efferent arterioles have significantly greater diameters than those in other regions of the cortex (28), Poiseuille’s relationship predicts that for equivalent levels of smooth muscle fiber shortening, smaller
changes in vascular resistance should occur than in the smaller vessels outside the juxtamedullary region (17).

In addition to finding that MBF and CBF are differentially regulated by the steady-state activity of the renal nerves, our use of a modulated sinusoidal stimulation pattern [which better reflects the frequency-rich nature of endogenous sympathetic nerve activity (SNA) (22)] demonstrated differences in the dynamic control of blood flow in these two vascular territories. Neither CBF nor MBF was able to follow high (>0.5 Hz) frequencies of sinusoidal stimulation. It has been proposed that this loss of oscillation in the vasculature at higher frequencies of nerve stimulation or activity (16, 31) is due to time delays in the rates of smooth muscle contraction (16, 25). Whereas the vascular contraction rate is too slow to follow oscillations in SNA above 0.5 Hz, decreases in steady-state flow occur due to the tonic constriction of the vessel. Slower frequencies of neural stimulation allow the vasculature to oscillate, albeit with some delay period, in synchrony with RSNA. Our results demonstrate an increased ability of the medullary microvasculature (but not cortical vasculature) to constrict in response to nerve stimulation at frequencies ~0.12 and 0.32 Hz. This increased amplitude of oscillation was also seen in RBF. Earlier studies in our laboratory (25) suggested that RSNA reveals resonance in the vasculature where the input stimulus, in this case electrical nerve stimulation, contains the frequency components necessary to induce resonant oscillations in the vasculature. Our interpretation of the current data is that the resonance seen in RBF [also observed by us previously (25)] is due chiefly to resonance in the medullary microcirculation. However, as we measured CBF only in the outer cortex, we cannot discount the possibility that these resonant frequencies are present in vascular territories deeper in the renal cortex. Nevertheless, our results clearly show different frequency response characteristics for outer CBF compared with MBF. In vivo recordings in rabbits have shown oscillations in RSNA and
RBF ~0.3 Hz, which increase in strength during hemorrhage (24) and hypoxia (16). Possibly this is reflected in our current results in the increased oscillation in MBF and RBF around this frequency.

The mechanisms underlying the differences in frequency response characteristics between CBF and MBF are undefined. Electrical stimulation allows non-selective recruitment of all nerve fibers without any functionally specific recruitment as may occur during reflex stimulation (9). Therefore, we are confident that our electrical stimulation was activating the nerves innervating the cortex and medulla similarly, and the reasons for the different responses are likely to reside within the vasculature itself. This notion is supported by a study by Navar et al. (27) that describes differences in activation mechanisms, in response to mechanical and vasoactive stimuli, between vascular smooth muscle cells in different renal microvascular segments. Staub et al. (32) also describes potential time-limiting steps in sympathetically mediated smooth muscle contraction (including neurotransmitter release rates, adrenergic cleft width, receptor type and densities, calcium entry mechanisms, intracellular electrochemical coupling, and neurotransmitter re-uptake), and it is possible that any one of these steps might differ between cortical compared with medullary vascular sites thus contributing to the difference in frequency response characteristics. Described differences in lumen diameter, smooth muscle thickness (18, 29), and density of innervation of vessels (2, 13) may also contribute. Juxtamedullary efferent arterioles have larger lumen (18, 29), more layers of smooth muscle cells (18, 29), and more extensive adrenergic innervation (2, 13) than superficial or outer cortical efferent arterioles.

**Perspectives**

It is likely that the ability of RSNA, along with circulating and locally acting hormonal factors, to differentially regulate CBF and MBF allows considerable precision in the regulation of regional kidney blood flow under physiological conditions. Precise control of MBF is crucial to long-term blood pressure regulation as evidenced by the fact that chronic decreases in MBF (independent of changes in CBF) can lead to the devel-
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REFERENCES


