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MODELLING OF THE DYNAMIC RELATIONSHIP BETWEEN ARTERIAL PRESSURE, RENAL SYMPATHETIC NERVE ACTIVITY AND RENAL BLOOD FLOW IN CONSCIOUS RABBITS

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Summary

A linear autoregressive/moving-average model was developed to describe the dynamic relationship between mean arterial pressure (MAP), renal sympathetic nerve activity (SNA) and renal blood flow (RBF) in conscious rabbits. The RBF and SNA to the same kidney were measured under resting conditions in a group of eight rabbits. Spectral analysis of the data sampled at 0.4 Hz showed that the low-pass bandwidth of the signal power for RBF was approximately 0.05 Hz. An autoregressive/moving-average model with an exogenous input (ARMAX) was then derived (using the iterative Gauss–Newton algorithm provided by the MATLAB identification Toolbox), with MAP and SNA as inputs and RBF as output, to model the low-frequency fluctuations. The model step responses of RBF to changes in SNA and arterial pressure indicated an overdamped response with a settling time that was usually less than 2 s. Calculated residuals from the model indicated that 79±5 % (mean ± S.D., averaged over eight independent experiments) of the variation in RBF could be accounted for by the variations in arterial pressure and SNA. Two additional single-input models for each of the inputs were similarly obtained and showed conclusively that changes in RBF, in the conscious resting rabbit, are a function of both SNA and MAP and that the SNA signal has the predominant effect. These results indicate a strong reliance on SNA for the dynamic regulation of RBF. Such information is likely to be important in understanding the diminished renal function that occurs in a variety of disease conditions in which overactivity of the sympathetic nervous system occurs.

Key words: mathematical model, ARMAX, spectral analysis, arterial pressure, blood flow, sympathetic nerve activity, rabbit.

Introduction

The kidney has long been known as an organ of homeostasis, which has been taken to imply that the steady state is the most appropriate condition in which to view the kidney. However, the kidney has an intrinsic rhythm (Holstein-Rathlou and Leyssac, 1987; Holstein-Rathlou and Marsh, 1989), and it is known that disorders of these rhythms are associated with at least some cardiovascular diseases, such as renovascular hypertension (Yip *et al.* 1991), and in spontaneous hypertension in rats (Wagner *et al.* 1997). Renal blood flow (RBF) and pressure mechanisms have been modelled using a range of dynamic system models (Holstein-Rathlou and Marsh, 1994*b*). This has improved our understanding of the controlling mechanisms, enabling the evaluation of models, and has been of use in determining the relative importance of various inputs in the control of RBF. However, in a comprehensive review paper, Holstein-Rathlou and Marsh (1994*b*) reveal that, even using a combination of the best existing modelling approaches, there are some significant discrepancies between the predictions of such models and the actual behaviour of the kidney. One explanation for this may be that previous work has given no consideration to the importance of sympathetic nerve activity (SNA) in regulating RBF.

Historically, it has been hypothesised that small variations in SNA occurring during normal daily events play little role in modulating renal blood flow RBF (Dibona and Kopp, 1997). This suggests that RBF, under basal conditions, is likely to be regulated by other factors such as arterial pressure, hormones and autoregulation. This hypothesis has been supported by a number of studies in both anaesthetised and conscious animals, in which RBF was generally estimated by the clearance of a substance across the kidney, and nerve activity increased and decreased in response to afferent stimuli (Hesse and Johns, 1984; Miki *et al.* 1989*a*,*b*). However, this approach does not take into account that SNA is an inherently dynamic signal, responding rapidly to

multiple afferent inputs. Measurements of RBF using clearance methods have time resolutions of 10–15 min, and techniques for the simultaneous measurement of SNA and dynamic RBF have not been applied. Thus, it has not been possible to study the actual input–output interaction between these variables and to test directly whether SNA and its rhythmical variations do modulate RBF at resting levels of activity. However, using the combination of a flow probe and a recording electrode, it is now possible to record SNA and blood flow to the same kidney in conscious rabbits (Janssen *et al.* 1997; Malpas *et al.* 1998). Data obtained from such an experimental approach allow the contribution of nerve activity to the regulation of RBF, and therefore to the control of arterial pressure, to be evaluated. In the present study, we test the hypothesis that SNA does play a role in the regulation of RBF and show that, by modelling its interaction with arterial pressure, it is possible to account for much of the variation in RBF.

Materials and methods

Animal preparation

Experiments were performed on eight rabbits bred at the Baker Institute (mass 2.3–2.8 kg) in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. Rabbits underwent surgery using halothane anaesthesia at least 7 days prior to the first experiment to implant a recording electrode around the renal sympathetic nerve and a transit-time flow probe around the left renal artery. The sterile surgical procedures used have previously been described in detail (Dorward *et al.* 1985; Malpas *et al.* 1996, 1998). Briefly, using an operating microscope, the left renal nerve and artery were exposed by a retroperitoneal approach, and the intact nerve was carefully fed through a coiled electrode. A Transonic flow probe (type 2SB; Transonic Systems Inc., Ithaca, USA) was placed proximal to the nerve electrode, taking care not to damage the renal nerves. The nerve electrode and flow probe arrangement was insulated from the surrounding tissue by Wacker Sil-Gel (Wacker-Chemie GmbH, Munich, Germany). The ends of the electrode and probe were tunnelled under the skin for retrieval on the day of the experiment.

Recording of RBF and SNA in conscious rabbits

Throughout the experiment, the animal was kept in a rabbit box (dimensions 15 cm wide, 40 cm long and 18 cm high), and catheters were placed in a central ear artery for the measurement of arterial pressure. The other ends of the renal blood flow probe and nerve electrode were retrieved from beneath the skin under local anaesthesia. Animals were subsequently left for 60 min before any measurements were made. Recordings of resting SNA, RBF and arterial pressure were then made for 15 min. Sympathetic activity was amplified, filtered between 50 and 5000 Hz, full-wave-rectified and integrated using a low-pass filter with a time constant of 20 ms (Malpas and Ninomiya, 1992). This processing of SNA means that the synchronized bursts of multifibre nerve activity appear as a series of peaks. This integrated rectified SNA signal, the RBF waveform and arterial pressure were continuously sampled throughout the experiment at 1000 Hz using an analog-to-digital data-acquisition card (National Instruments, Texas, USA). Calibrated signals were displayed on a computer screen and saved to disk using a program written in the LabVIEW graphical programming language (National Instruments, Texas, USA). Although all data were sampled at 1000 Hz, these were averaged over 400 ms periods (2.5 Hz) and saved to file.

Modelling

The data were preconditioned by removing outliers, detrending, decimation by a factor of 2 (i.e. resampled at a frequency of 1.25 Hz) and scaled to ensure that all data streams had unity variance. An autoregressive/moving average model with an exogenous input (ARMAX) was derived (using the iterative Gauss–Newton algorithm provided by the MATLAB identification Toolbox) by the two-inputs/single-output ARMAX representation shown in equation 1 and the assumed model structure in Fig. 1, with mean arterial blood pressure (MAP) and SNA as inputs and RBF as output. The dynamics were modeled, using the iterative Gauss–Newton algorithm provided by the MATLAB identification toolbox, by the two-input/single output ARMAX representation:

$$\begin{aligned} f(n) = {} & a_1 f(n-1) + a_2 f(n-2) + \ldots\ a_{\mathrm{na}} f(n-na) \\ & + b_{1,1} s(n-nk_1) + \ldots b_{\mathrm{nb}_1,1} s(n-nb_1-nk_1+1) \\ & + b_{1,2} p(n-nk_2) + \ldots b_{\mathrm{nb}_2,2} p(n-nb_2-nk_2+1) \\ & + c_1 e(n-1) + \ldots + c_{\mathrm{nc}} e(n-nc) + e(n) \end{aligned} \quad (1)$$

where the system variables are: f, renal blood flow (RBF); p, mean arterial blood pressure (MAP); s, renal sympathetic nerve activity (SNA); and e, random white noise, with zero mean and S.D. σ_e. a_i is the ith autoregressive constant, na the number of autoregressive constants, b_{ij} the ith moving average constant for jth input, nb_j the number of moving average constants for jth input, nk_j the transport delay for jth input, c_i the ith constant for moving average noise model and nc the number of noise constants. The exogenous variable, e, could have been due to measurement artifacts or the physiological variables considered in the Discussion.

Results

The power spectral densities of RBF from each rabbit are shown in Fig. 2 and illustrate a low-pass bandwidth of approximately 0.05 Hz with a decrease to less than 1 % of its low-frequency value by 0.5 Hz. There is evidence of resonance between 0.1 and 0.2 Hz for RBF. The spectrum for SNA was similar (Fig. 2).

The structure of the model [i.e. the variables na, (nb_1,nb_2), nc, (nk_1,nk_2)] was obtained by making a systematic search until

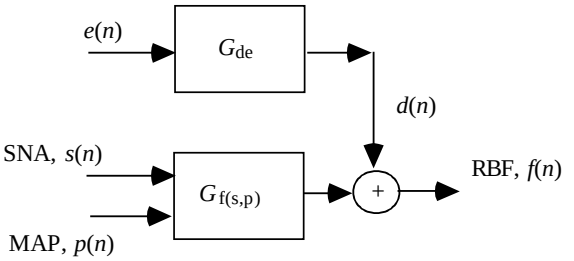

Fig. 1. The assumed model structure for the kidney. *e*, random white noise with zero mean; G_{de} and $G_{f(s,p)}$ are defined by equation 1; RBF and *f*(*n*), renal blood flow; SNA and *s*(*n*), sympathetic nerve activity; MAP and *p*(*n*), mean arterial pressure.

a white noise residual was obtained with negligible correlation between the two inputs and the residual and the variances of the parameter estimates were sufficiently small.

A third order model with zero transport lags was found to perform well for all the experiments (i.e. $na=nb_f=nb_2=nc=3$, $nk_1=nk_2=0$). Some correlation existed between the two inputs but the small parameter variances (see Table 1) indicated that the parameter estimates were nevertheless reliable. The

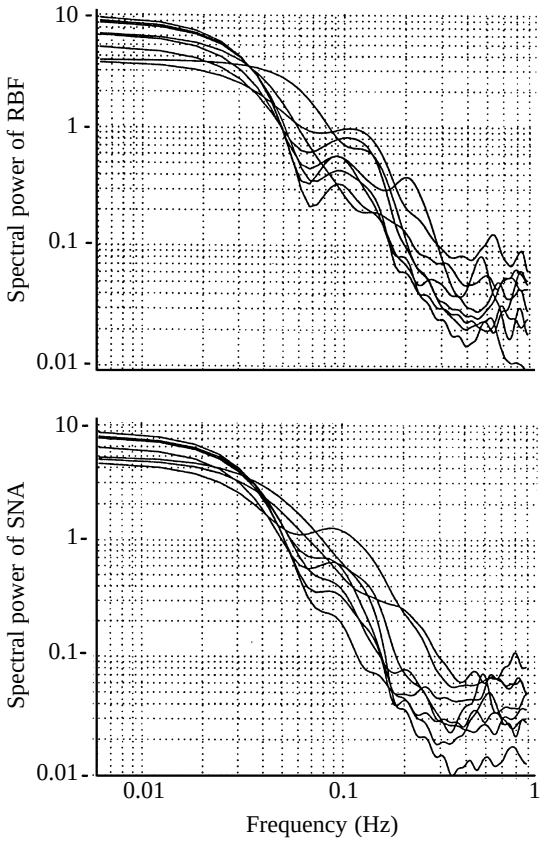

Fig. 2. Spectrograms of sympathetic nerve activity (SNA) and renal blood flow (RBF) data sampled at 2.5 Hz in eight rabbits. The power in the spectrum from each rabbit dropped to less than 1 % of the lowest-frequency power by 3 rad (0.5 Hz). There was evidence of a resonance at 0.1–0.2 Hz in RBF.

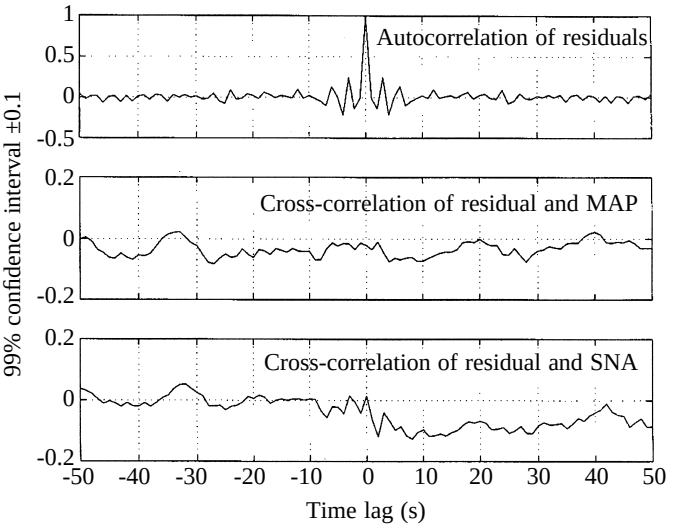

Fig. 3. Normalized correlation function for the resulting residual defined in equation 3 and the cross-correlation function between each of the inputs and residuals from rabbit 2. SNA, sympathetic nerve activity; MAP, mean arterial pressure.

efficacy of the model was measured by comparing the simulated model output, $\bar{f}(n)$, where:

$$\begin{aligned}\bar{f}(n) = {} & a_1\bar{f}(n-1) + a_2\bar{f}(n-2) + \ldots a_{na}\bar{f}(n-na) \\ & + b_{1,1}s(n-nk_1) + \ldots b_{nb_1,1}s(n-nb_1-nk_1+1) \\ & + b_{1,2}p(n-nk_2) + \ldots b_{nb_2,2}p(n-nb_2-nk_2+1) \end{aligned} \quad (2)$$

with the measured output *f*(*n*) using the standard deviation of the simulation residuals (J_s):

$$J_s = \sqrt{\frac{\sum_1^N [f(i)-\bar{f}(i)]^2}{N}}, \quad (3)$$

where *N* is the number of measured data points and the parameters in equation 2 are defined under equation 1.

The correlation function for the resulting residuals and the cross-correlation function between each of the inputs and the residuals are shown in Fig. 3 (for rabbit 2) and only slightly exceed the 99 % confidence levels for the hypotheses of white-noise residuals and zero correlation between the residuals and the two inputs.

The dynamics of the resulting models are shown by step responses for the two inputs in Fig. 4 (positive changes for step changes in blood pressure). Most responses are overdamped with settling times of less than 2 s. Percentage changes in SNA had a significantly larger effect ($P<0.05$, *t*-test) on the RBF response (gain −1.1±0.1; mean ± S.D., $N=9366$) than percentage changes in blood pressure (gain 0.66±0.12; mean ± S.D., $N=2$).

The simulation and actual output signals for a representative model are compared in Fig. 5, and the standard deviations of the residuals from all animals are given in Table 2. These

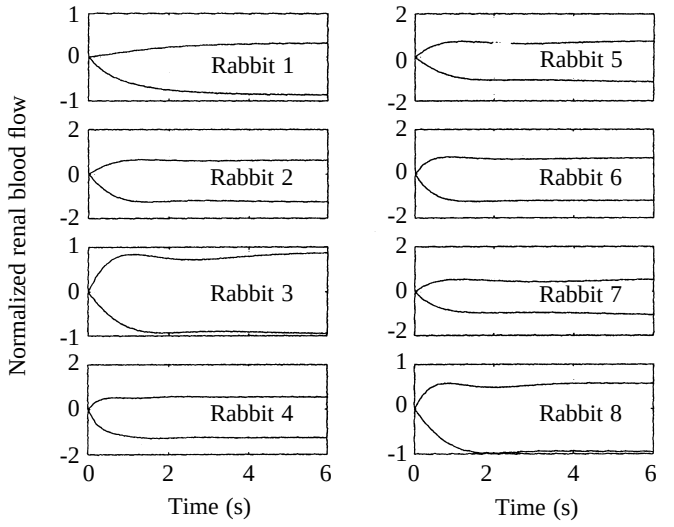

Fig. 4. Unit step responses *versus* time of renal blood flow (RBF) for each $G_{f(s,p)}$ model, defined in equation 1, from each of the rabbits [positive response of RBF to input step of mean arterial pressure (MAP); negative response to input step of SNA].

residuals indicate that 80 % (weighted mean over the eight independent experiments) of the variation in RBF can be accounted for by the variations in arterial pressure and SNA.

Two additional single-input models were also obtained for each of the inputs. The resulting standard deviations of the residuals are also shown in Table 2. The last column in Table 2, which gives the standard deviations of the residuals for all the rabbits, shows conclusively that using both inputs in the model is better than using each of the single-input models and that the SNA single-input model is better than the blood pressure input model.

Discussion

In the present study, we have developed an ARMAX model, using pressure and sympathetic nerve activity as inputs, which was able to predict 80 % of the variation in RBF in conscious rabbits. Percentage changes in SNA, calculated from the normalized gain, had a significantly larger effect on the RBF response than percentage changes in arterial pressure. On the basis of previous research, one might have expected that SNA would play only a minor role in the regulation of RBF (Dibona and Kopp, 1997). In a number of studies that have recorded the steady-state changes in RBF in response to stimuli designed to increase SNA, RBF was reduced only with large increases in SNA (Morita, 1986; Nelson and Osborn, 1993). In other studies on the dynamic control of RBF, a number of frequencies have been recorded in RBF, and the role of a variety of hormonal or intrinsic systems in regulating these oscillations has been examined; however, the role of the sympathetic nerves has generally been ignored (Holstein-Rathlou, 1993; Holstein-Rathlou and Marsh, 1994*b*; Holstein-Rathlou *et al.* 1991*a*,*b*). Recent work by our group, combined with the present study, suggests that this has been an oversight. With regard to the steady-state condition, we have shown that the resting level of SNA plays a major role in setting the resting level of RBF: in renal-denervated conscious rabbits, resting RBF averaged 54 ml min^{-1} compared with 38 ml min^{-1} in the innervated condition (Malpas and Evans, 1998). Furthermore, during a range of afferent stimuli, such as air-jet stress and hypoxia, designed to evoke small increases (10–20 %) in SNA, RBF was consistently reduced. With regard to the dynamic control of RBF, we have also shown that SNA is responsible for oscillations in RBF that occur between 0.2 and 0.4 Hz (Janssen *et al.* 1997) and that the presence of resting levels of SNA alters the transmission of oscillations in arterial pressure through the renal vasculature (Malpas *et al.* 1998). In

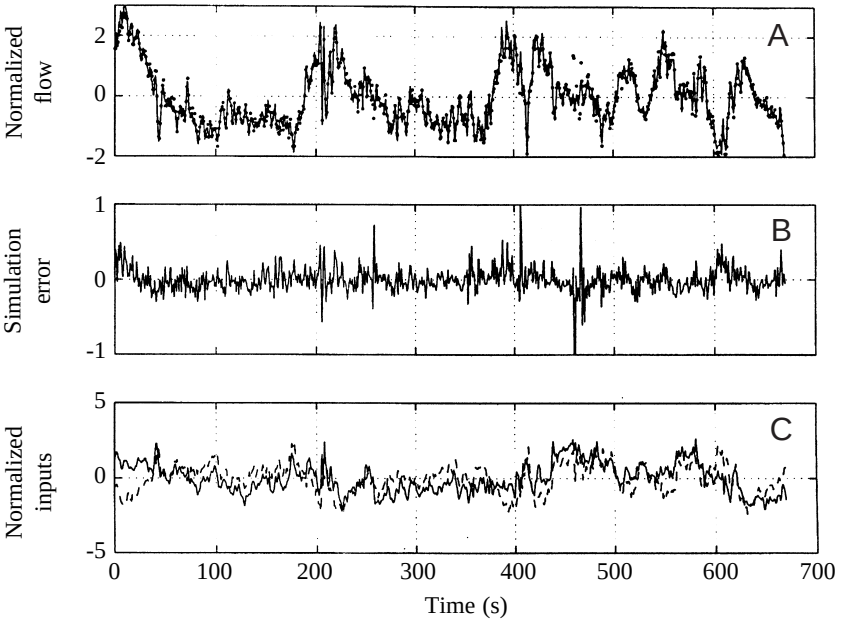

Fig. 5. The actual and simulated outputs from one rabbit (J_s=0.17) using the ARMAX model with arterial pressure (MAP; solid line in A) and sympathetic nerve activity (SNA; broken line) as the inputs (C) and the predicted renal blood flow responses (the solid line in A refers to the actual data and the dots the predicted values). The simulation error is shown in B. J_s, simulation residual.

Table 1. *ARMAX parameters and standard deviations for rabbit 2*

	a_1	a_2	a_3	b_{12}	b_{22}	b_{32}	b_{11}	b_{21}	b_{31}	c_1	c_2	c_3	σ_e
Parameter	1.09	–0.26	0.004	0.76	–0.89	0.28	–0.95	0.98	–0.21	–0.28	–0.76	0.48	0.015
S.D.	0.01	0.008	0.0003	0.0003	0.006	0.004	0.004	0.01	0.007	0.008	0.002	0.006	

Refer to the Materials and methods section for definitions of terms.

particular, we observed that the coherence between MAP and RBF signals in the innervated condition was significantly less than in the denervated condition. We suggested that this indicates multiple inputs, of which SNA was clearly important, although we could not assess its relative role compared with arterial pressure. The present study indicates that, somewhat surprisingly, SNA has a larger role in regulating RBF than arterial pressure. This finding is likely to be important in a range of pathological conditions where chronic increases in SNA are a factor or where the aim of different therapeutic regimes is to reduce SNA in order to lower arterial pressure.

We conducted experiments in conscious rabbits, so our data represent the integrated control over RBF from a potentially huge range of inputs, only two of which, MAP and SNA, were measured in the present study. It is therefore of considerable significance that the ARMAX model we developed was able to account for 80 % of the variation in RBF. Other factors that are likely to play a role in regulating RBF, although probably over longer time scales than the seconds and minutes of this study, are a variety of hormonal systems, notably renin. Future studies that incorporate blockade of such systems may produce improvements on the model.

In addition to describing an ARMAX model for the regulation of RBF, we characterised power spectral densities for RBF and observed a low-pass filtering response in the vasculature to a change in SNA where the spectral power was less than 1 % by 0.5 Hz. Such a response has been observed in the rat mesenteric blood flow (Stauss and Kregel, 1996) and was proposed to exist for the renal vasculature (Janssen *et al.* 1997), although it has not previously been quantified. The maintenance of an adequate glomerular filtration rate, and thus of urine flow, requires RBF to remain relatively stable. Oscillations in RBF caused by SNA or MAP that are faster than 0.5 Hz would be likely to diminish this ability. Conversely, a system that has no variability, and in which the inputs only adjust the mean level of RBF, is one with reduced controllability. The ability of RBF to respond to low-frequency inputs is, therefore, likely to assist in its dynamic control, ensuring that it responds rapidly and with a sufficiently high gain to the stimuli of daily life.

It is of interest to note that we observed evidence of resonance in RBF between 0.1 and 0.2 Hz. The autoregulatory phenomena of the renal vasculature have been shown to exhibit resonance between 0.1 and 0.25 Hz in rats (Holstein-Rathlou and Marsh, 1994*a*,*b*; Sakai *et al.* 1986), where oscillations in arterial pressure reveal resonance in the renal vasculature (Cupples *et al.* 1996). Previous studies, however, were conducted under anaesthesia conditions, and such phenomena do not appear to have been reported in conscious animals. This is significant because quantifying the resonant capabilities of the vasculature can illustrate the mechanical properties of the system, which may be altered under conditions such as hypertrophy. Previous approaches to determining such features have generally isolated the kidney both neurally and haemodynamically from the circulation and then applied discrete frequencies and amplitudes of renal perfusion pressure *via* a pump (Holstein-Rathlou *et al.* 1991*a*,*b*).

Although the maintenance, and the ability to adjust the overall level, of SNA in response to various stimuli is thought to provide the major mechanism for the short-term control of arterial pressure (Brooks and Osborn, 1995), understanding the dynamic relationship between sympathetic tone and arterial pressure is difficult because the reflex mechanisms act on several effector mechanisms simultaneously, including heart rate, cardiac contractility, systemic venous capacity and the levels of a variety of circulating substances. All these superimpose themselves in complex and often unpredictable ways. Thus, the combination of control mechanisms means that the global result may be quite different from the sum of the single effector actions, and modelling of this all-

Table 2. *Comparison of standard deviations of simulation residuals,* J_s*, for two-input and single-input models*

	Rabbit no.								
	1	2	3	4	5	6	7	8	Overall S.D.
J_s (two inputs)	0.29	0.17	0.21	0.13	0.18	0.33	0.21	0.16	0.2
J_s (SNA only)	0.45	0.67	0.53	0.61	0.88	0.56	0.41	0.61	0.65
J_s (MAP only)	0.86	0.95	0.91	0.90	0.82	0.87	0.89	0.59	0.86
No. of data points	1532	837	828	1145	2500	1065	944	515	9366

SNA, sympathetic nerve activity; MAP, mean arterial pressure.
Refer to the Materials and methods section for definitions of terms.

encompassing system may not provide the best approach to delineating the contribution of each input to circulatory control. In the present study, we have attempted to simplify these contributing factors by localizing the sympathetic control of arterial pressure to a single end organ and effector system. Through the development of an ARMAX model using MAP and SNA as inputs and RBF as the output, we conclude that in the conscious resting rabbit variations in arterial pressure and SNA are transmitted into changes in RBF. This showed conclusively that the changes in RBF, in the conscious resting rabbit, are a function of both SNA and MAP and that the SNA signal has the predominant effect. These results indicate a strong reliance on SNA for the dynamic regulation of RBF.

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