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Oscillations and Rhythms in the Neural Control of the Circulation

IDENTIFICATION OF BLOOD PRESSURE CONTROL MECHANISMS BY POWER SPECTRAL ANALYSIS

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SUMMARY

1. Blood pressure and organ perfusion are controlled by a variety of cardiovascular control systems, such as the baroreceptor reflex and the renin–angiotensin system (RAS), and by local vascular mechanisms, such as shear stress-induced release of nitric oxide (NO) from the endothelium and the myogenic vascular response. Deviations in arterial blood pressure from its set point activate these mechanisms in an attempt to restore blood pressure and/or secure organ perfusion. However, the response times at which different cardiovascular mechanisms operate differ considerably (e.g. blood pressure control by the RAS is slower than blood pressure control via the baroreceptor reflex).

2. Owing to these different response times, some cardiovascular control systems affect blood pressure more rapidly and others more slowly. Thus, identifying the frequency components of blood pressure variability (BPV) by power spectral analysis can potentially provide important information on individual blood pressure control mechanisms.

3. Evidence is presented that the RAS, catecholamines, endothelial-derived NO and myogenic vascular function affect BPV at very low frequencies (0.02–0.2 Hz) and that low-frequency (LF) BPV (0.2–0.6 Hz) is affected by sympathetic modulation of vascular tone and endothelial-derived NO in rats. In humans, LF BPV (0.075–0.15 Hz) is affected by sympathetic modulation of vascular tone and myogenic vascular function. The impact of the RAS and endothelial-derived NO on BPV in humans requires further investigation.

4. In conclusion, power spectral analysis is a powerful diagnostic tool that allows identification of pathophysiological mechanisms contributing to cardiovascular diseases, such as hypertension, heart failure and stroke, because it can separate slow from fast cardiovascular control mechanisms. The limitation that some cardiovascular control mechanisms affect the same frequency components of BPV requires the combination of blood pressure spectral analysis with other techniques.

Key words: baroreflex, blood pressure variability, heart failure, hypertension, myogenic vascular function, nitric oxide, renin–angiotensin system, shear stress, stroke, sympathetic nervous system.

INTRODUCTION

Pathophysiological mechanisms underlying cardiovascular diseases are often difficult to assess and, therefore, are frequently not considered for selection of cardiovascular therapy. For example, it has been suggested that uraemia-induced impairment of cerebrovascular myogenic function[1–3] contributes to the high incidence of haemorrhagic stroke in hypertensive patients on chronic haemodialysis.[4–7] Thus, assessment of myogenic vascular function may not only be useful to predict risk for haemorrhagic stroke in individual patients, but it may also assist in the selection of antihypertensive drugs (e.g. Ca^{2+} channel blockers may increase the risk of haemorrhagic stroke in hypertensive dialysis patients because these drugs further deteriorate myogenic vascular function[8–11]). This example illustrates the need for new techniques and strategies allowing investigation of cardiovascular mechanisms that are currently difficult to assess. We propose that cardiovascular variability has the potential to be one such technique. The focus of the present article is on blood pressure variability (BPV), although other cardiovascular variability measures, such as heart rate variability, are equally important.

Cardiovascular homeostasis is achieved by a variety of feedback systems, such as the baroreceptor reflex, hormonal systems, such as the renin–angiotensin system (RAS), and local mechanisms, such as the myogenic vascular response and the endothelial nitric oxide (NO) system. Almost all these mechanisms are affected by cardiovascular diseases,[12] such as hypertension,[13,14] heart failure[15–17] or stroke.[18,19] In order to maintain homeostasis, cardiovascular control mechanisms directly or indirectly affect arterial blood pressure. However, the response time of arterial blood pressure can vary markedly (e.g. slow-responding cardiovascular control systems, such as hormonal mechanisms, affect lower-frequency components of BPV than rapid-responding cardiovascular control systems, such as neuronal mechanisms). Thus, cardiovascular control mechanisms elicit specific patterns of BPV that can be assessed by power spectral analysis. The present article focuses on: (i) sympathetic modulation of vascular tone; (ii) the myogenic vascular response; (iii) the endothelial NO system; and (iv) the RAS.

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SYMPATHETIC MODULATION OF VASCULAR TONE

Time delays in sympathetic modulation of vascular tone include central nervous system processing, ganglionic transmission, sympathetic nerve conduction, release, diffusion and receptor binding of neurotransmitters, the intracellular signalling cascade and, finally, actin and myosin interactions. In previous studies, we investigated the frequency–response characteristic of sympathetic-mediated vasomotor waves in rats[20–23] and humans.[24] Sympathetic nerve stimulation experiments in conscious rats revealed that the mesenteric artery can respond to periodic sympathetic nerve stimulation with corresponding fluctuations in mesenteric vascular resistance only at stimulation frequencies below 1.0 Hz and that the greatest dynamic responses were found at 0.2 and 0.5 Hz. At higher stimulation frequencies, tonic vasoconstriction occurred.[20] Central processing, ganglionic transmission or nerve conduction do not limit this frequency–response characteristic because the same responses were obtained when the stimulation electrode was placed in the hypothalamic paraventricular nucleus, from which direct pathways project to preganglionic sympathetic neurons in the intermediolateral cell column.[21]

However, sympathetic modulation of vascular tone differs among individual vascular beds. Periodic electrical stimulations of the lumbar sympathetic trunk and concomitant laser Doppler recordings of blood flow to the plantar surface of the skin of the hind paws revealed that sympathetic modulation of skin blood flow is limited to frequencies below 0.1 Hz in rats. The strongest dynamic responses were observed at 0.05 and 0.075 Hz.[22] Interestingly, the same frequency–response characteristic of sympathetic modulation of skin blood flow was found in humans,[24] indicating that the apparent species differences in the frequency of sympathetic-mediated blood pressure Mayer waves (0.2–0.6 Hz in rats *vs* 0.075–0.15 Hz in humans) is related to different frequency–response characteristics of vascular beds other than the skin, such as the renal and mesenteric vascular beds. With regard to these two vascular beds, we demonstrated that the renal vasculature responds more sluggishly to sympathetic stimulation than the mesenteric vascular bed. The greatest dynamic response to periodic sympathetic nerve stimulation was found at 0.32 ± 0.03 Hz for the renal circulation and at 0.40 ± 0.02 Hz ($P < 0.05$) for the mesenteric vascular bed.[23] These and other studies[25] demonstrated that sympathetic-mediated blood pressure Mayer waves depend on the response time of the vasculature and occur at frequencies between 0.2 and 0.6 Hz in rats and between 0.075 and 0.15 Hz in humans.

Although the response time of the vasculature to sympathetic stimuli determines the highest frequency at which sympathetic modulation of vascular tone can occur, it does not explain the initiation and maintenance of sympathetic-mediated Mayer waves. As reviewed by Claude Julien,[26] two theories have been proposed. The pacemaker theory suggests that autonomic oscillators within the central nervous system generate periodic fluctuations in autonomic nerve activity that are translated into corresponding oscillations of arterial blood pressure and heart rate. However, the frequencies of central nervous system oscillators identified in most studies are different from the frequency of Mayer waves.[26] Second, the baroreflex theory implies that the arterial baroreceptor reflex exhibits a resonance frequency at the frequency of spontaneously occurring Mayer waves.[26] This theory is, indeed, well-supported by experimental data in rats, demonstrating that the frequency–response of arterial blood pressure to periodic stimulations of the aortic depressor nerve exhibits a resonance frequency close to the frequency of Mayer waves.[27]

MYOGENIC VASCULAR FUNCTION

In isolated arteries, myogenic vasoconstriction is considerably slower than sympathetic-mediated vasoconstriction. Figure 1a shows the time-course of constriction in response to the application of 10^{-5} mol/L noradrenaline in an isolated mesenteric artery, a vascular bed known for high α_1-adrenoceptor density.[28,29] Full constriction is reached within 5 s. In contrast, Fig. 1b shows the time-course of myogenic vasoconstriction in response to a step increase in intravascular pressure in a middle cerebral artery, a vascular bed known for exceptionally well-developed myogenic function.[30,31] Full myogenic vasoconstriction takes almost 1 min. Thus, one may assume that myogenic vascular function affects BPV at lower frequencies than sympathetic modulation of vascular tone.

However, response times obtained during *in vitro* conditions may not apply directly to the situation in an intact organism. Therefore, we recorded blood pressure in conscious normotensive Wistar-Kyoto rats under control conditions and during infusion of the L-type Ca^{2+}

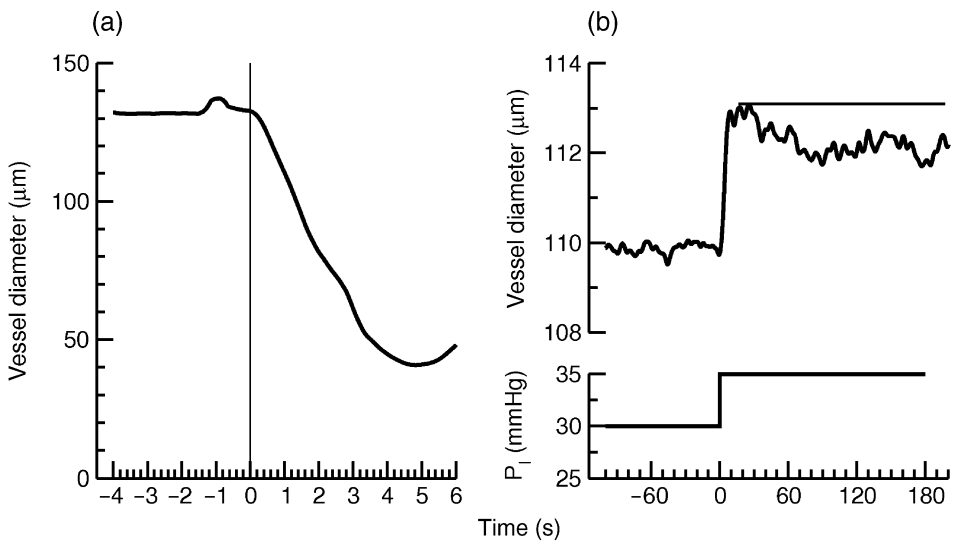

Fig. 1 (a) Contractile response of a rat mesenteric artery (second-order branch of the mesenteric artery) to the application of 10^{-5} mol/L noradrenaline. Maximum constriction is reached within approximately 5 s. (b) Myogenic vasoconstriction in response to a step increase in intravascular pressure (P_I) from 30 to 35 mmHg in a rat middle cerebral artery. Full development of myogenic tone is reached only after approximately 60 s.

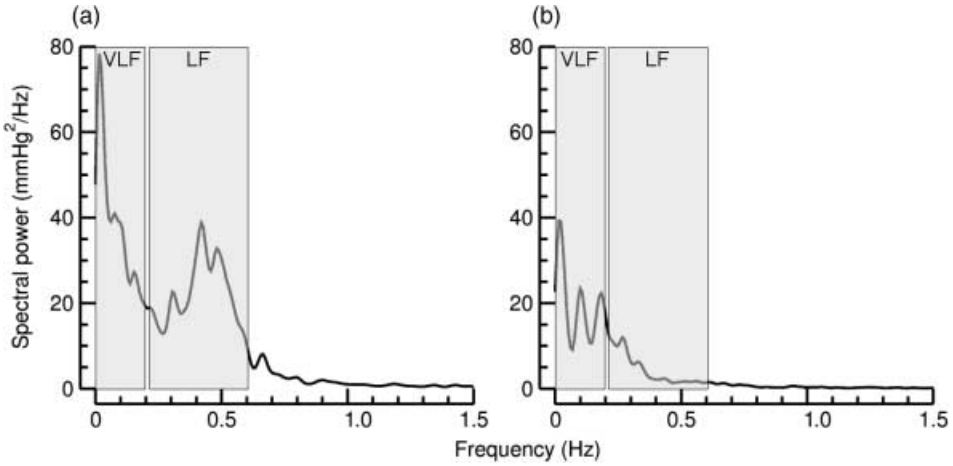

Fig. 2 Systolic blood pressure power spectra from a conscious Wistar-Kyoto rat (a) under control conditions (no drug infusion) and (b) during infusion of the Ca^{2+} channel blocker nifedipine (4 mg/kg per h, i.v.). Nifedipine markedly reduced very low frequency (VLF; 0.02–0.2 Hz) and low frequency (LF; 0.2–0.6 Hz) blood pressure variability.

channel blocker nifedipine, which inhibits myogenic vascular function.[7,8] Blockade of Ca^{2+} channels significantly reduced very low frequency (VLF; 0.02–0.2 Hz; 3.6 ± 1.1 *vs* 1.4 ± 0.3 $mmHg^2$; $n = 8$; $P < 0.05$) and low frequency (LF; 0.2–0.6 Hz; 1.22 ± 0.26 *vs* 0.68 ± 0.12 $mmHg^2$; $n = 8$; $P < 0.05$) BPV (Fig. 2). The reduction in VLF BPV during application of nifedipine is most likely not due to hypotension because hypotension, as well as activation of the RAS, increases VLF BPV in rats.[32–34] In addition to blocking the myogenic response, nifedipine also reduces α_1-adrenoceptor-mediated vasoconstriction via blockade of store-operated Ca^{2+} channels.[35] Therefore, we suggest that the reduction in LF spectral power is due to less sympathetic modulation of vascular tone, whereas the reduction in VLF spectral power is due to inhibition of myogenic vascular function. The frequency range for myogenic modulation of BPV in rats (0.02–0.2 Hz) is consistent with studies in rats demonstrating that myogenic function contributes to blood flow autoregulation at frequencies below 0.2 Hz in the renal circulation,[36–41] at 0.13 Hz in the mesenteric vascular bed[41] and below 0.1 Hz in the cerebral circulation.[42]

A recent study by Radaelli *et al*.[43] demonstrated that constant infusions of catecholamines enhance VLF BPV after ganglionic blockade in conscious rats. In addition, ganglionic blockade markedly reduced VLF BPV and abolished the dose-dependent reduction in VLF BPV in response to increasing doses of the L-type Ca^{2+} channel blocker nifedipine.[44] These findings suggest that the sympathetic nervous system elicits a permissive effect on myogenic vascular function and VLF BPV.[44] In contrast, Zhang *et al*.[45] demonstrated, over a decade ago, that guanethidine-induced sympathectomy enhances overall BPV via spontaneously occurring decreases in blood pressure associated with delayed vasodilation in the mesenteric and aortic vascular beds. The vascular responses to the depressor episodes were consistent with myogenic vasodilation. Only depressor, but no pressor episodes were observed after sympathectomy. Thus, a certain level of sympathetic nervous system activity may be necessary for myogenic vasoconstriction, but not for myogenic vasodilation. Indeed, it has been demonstrated that catecholamines enhance myogenic vascular responsiveness.[46–48] Interestingly, the myogenic vasodilation episodes in the study of Zhang *et al*.[45] lasted for approximately 15 s, corresponding to a frequency of 0.067 Hz, further confirming that VLF (0.02–0.2 Hz) BPV reflects myogenic vascular function in rats.

Information on myogenic function in humans comes from studies on dynamic autoregulation of cerebral blood flow. In these studies, transfer function analysis between blood pressure and cerebral blood flow velocity (middle cerebral artery, transcranial Doppler) was used to assess cerebrovascular myogenic function.[49–56] The gain of this transfer function is a measure of how much cerebral blood flow velocity changes for a given change in blood pressure. Thus, low gains indicate good autoregulation, whereas high gains indicate poor autoregulation. Using this technique, most studies demonstrated that dynamic autoregulation of cerebral blood flow is most efficient at frequencies below 0.07 Hz.[49–54] However, some studies suggested that autoregulation of cerebral blood flow in humans can operate at frequencies as high as 0.15 Hz.[55,56] The study of O'Leary *et al*.[56] is unique in that these investigators also performed transfer function analysis between mean blood pressure and total peripheral resistance. The gain of this transfer function can be seen as an index of myogenic vascular function of the whole circulation. At frequencies below 0.2 Hz, changes in mean blood pressure were followed by a directionally similar change in total peripheral resistance as expected from myogenic vascular function.[56] Thus, in humans, myogenic vascular function in the cerebral circulation appears to be most effective at frequencies below 0.07 Hz, corresponding to the VLF range in humans. However, myogenic vascular function of the whole circulation appears to affect both VLF and LF components of cardiovascular variability in humans.

ENDOTHELIAL NO

Another local vascular mechanism that affects BPV is the endothelial NO system.[57] In previous studies, we demonstrated that mice with functionally inactive endothelial NO synthase (NOS) have increased BPV in the frequency range 0.05–0.4 Hz.[58,59] Thus, the local vascular endothelial NO system can be seen as a mechanism that buffers BPV. A rise in blood pressure enhances endothelial shear stress and causes NO release from endothelial cells. Nitric oxide diffuses to the adjacent vascular smooth muscle cells, where it elicits vasodilation via activation of guanylyl cyclase.[57] Nafz *et al*. demonstrated that the endothelial NO system buffers BPV at frequencies between 0.2 and 0.6 Hz in rats[60] and between 0.1 and 0.5 Hz in dogs.[61] The study of Nafz *et al*.[60] demonstrating that NOS inhibition markedly increases LF BPV (0.2–0.6 Hz) in rats is unique in that the rise in arterial blood pressure caused by NOS inhibition was offset by a continuous infusion of the NO donor nitroprusside. In earlier studies investigating the effect of NOS inhibition on BPV

in rats, blood pressure was elevated during NO inhibition.[62,63] These earlier studies demonstrated an increase in VLF BPV (0.02–0.2 Hz) and a decrease in LF BPV (0.2–0.6 Hz) during NO inhibition. The reduction in LF BPV may have been secondary to baroreflex inhibition of sympathetic nerve activity resulting in reduced sympathetic modulation of vascular tone. Whether the increase in VLF BPV is secondary to the elevated blood pressure or directly related to the reduced NO release from the endothelium remained open. Unfortunately, the study by Nafz *et al*.[60] did not answer this question either, because these authors did not analyse VLF BPV. Based on these studies, NO appears to buffer BPV in the LF[60] and possibly VLF ranges[62,63] in rats.

In humans, inhibition of NOS decreased LF BPV (0.03–0.15 Hz).[64] However, in that study, NOS inhibition was associated with a reflex-mediated reduction in sympathetic nerve activity, as indicated by reduced plasma noradrenaline levels.[64] Therefore, the decreased LF BPV can be explained by reduced sympathetic modulation of vascular tone. In an attempt to overcome this problem, Cooke *et al*.[65] studied BPV during NOS inhibition in humans in the supine position and during 60° head-up tilt. In that study, NOS inhibition did not alter LF BPV in the supine or tilted positions. Therefore, the authors concluded that NO does not buffer BPV in humans.[65] However, because systolic and diastolic blood pressures were significantly elevated during NOS blockade in the supine and tilted positions, respectively, one may still argue that an increase in BPV caused by NOS inhibition was masked by baroreflex-mediated inhibition of sympathetic modulation of vascular tone.

The frequency ranges where endothelial-derived NO buffers BPV in mice, rats and dogs overlap at frequencies between 0.2 and 0.4 Hz. If this frequency range also applies to humans, endothelial NO would buffer BPV in the respiration-linked high-frequency (HF) range in humans. This possibility is supported by the finding that blockade of NOS in humans significantly increased normalized spectral power of systolic blood pressure in the HF range.[64] If endothelial-derived NO buffers BPV in the HF range in humans, it would be difficult to use BPV to assess endothelial function in humans because HF BPV is largely dependent on respiration. Maybe a protocol that involves controlled respiration could overcome this limitation.

RENIN–ANGIOTENSIN SYSTEM

Blood pressure regulation by the RAS depends on the synthesis and release of renin and angiotensinogen. Furthermore, angiotensinogen needs to be converted to the active metabolite, angiotensin II. Thus, it can be expected that the RAS affects BPV at lower frequencies than the sympathetic nervous system. Indeed, it has been suggested that the RAS modulates VLF (0.04 Hz in dogs) cardiovascular variability.[66] This suggestion is in line with studies by Elghozi *et al.*,[32–34,67–70] who demonstrated in conscious rats that VLF BPV (0.02–0.2 Hz) increased if the RAS was stimulated experimentally and that this increase in VLF BPV could be blocked by angiotensin AT_1 receptor antagonists.[33,34,69,70]

To test whether the elevated VLF BPV in renovascular hypertension is secondary to elevated blood pressure levels, we performed telemetric blood pressure recordings in conscious rats under baseline conditions (3 weeks), during renovascular hypertension (3 weeks; two-kidney, one-clip model) and during the recovery phase of another 3 weeks after surgical reversal of renovascular hypertension. Rats were treated with either placebo or hydralazine (40 mg/kg per day),

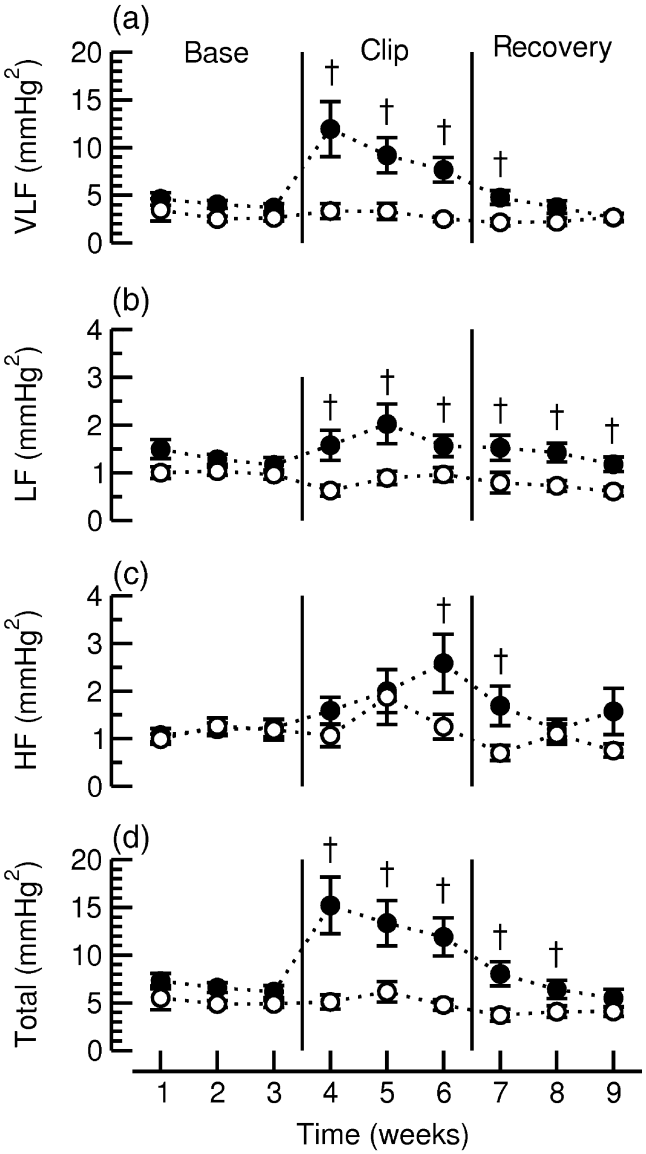

Fig. 3 Time-course of (a) very low frequency (VLF; 0–0.2 Hz), (b) low frequency (LF; 0.2–0.6 Hz), (c) high frequency (HF; > 0.8 Hz) and (d) total spectral power of systolic blood pressure. A 3 week baseline period (base) was followed by a 3 week phase of renal hypertension induced by renal artery clipping (clip) and a final 3 week recovery phase initiated by removal of the renal artery clip. During the renal hypertension phase, rats were treated with placebo (●) or 40 mg/kg per day hydralazine administered by gastric gavage (○).

a vasodilator that has been demonstrated to elicit no effects on short-term[68] or long-term[71] BPV. In contrast with placebo-treated rats, blood pressure did not increase after renal artery clipping in hydralazine-treated rats, although plasma renin activity was significantly elevated in both treatment groups.

Figure 3 shows the time-course of BPV over the 9 week observation period. In placebo-treated rats, total spectral power increased threefold during the 3 weeks of renovascular hypertension (Fig. 3d). This increase in total power was due to a strong increase in VLF BPV (Fig. 3a). Although significantly elevated, the LF (Fig. 3b) and HF (Fig. 3c) bands contributed only modestly to the increase in total BPV after renal artery clipping. After removal of the renal artery clip, VLF spectral power decreased gradually and reached baseline

levels at the end of the recovery period. In rats treated with hydralazine, neither total spectral power nor any component of systolic BPV changed significantly during the 9 week observation period. These results suggest that the increase in VLF spectral power of systolic blood pressure in severe chronic renovascular hypertension is secondary to the elevation in arterial blood pressure rather than a direct consequence of the stimulated RAS.

However, it is important to note that this finding is not necessarily opposing other studies demonstrating that the RAS can modulate VLF BPV.[32–34,67–70] In fact, intrarenal infusion of the β-adrenoceptor agonist isoprenaline caused a mild increase in plasma renin activity without increasing arterial blood pressure in rats. This mild activation of the RAS was associated with a marked increase in VLF (0.02–0.2 Hz) BPV that was abolished by pretreatment with the angiotensin AT_1 receptor antagonist valsartan.[69,70] Thus, small acute perturbations of the RAS can, indeed, elicit VLF BPV independent of the level of blood pressure. In contrast, the increase in VLF BPV that occurs during excessive stimulation of the RAS, such as during renal artery clipping, is secondary to hypertension.

The question remains how a constant increase in plasma renin activity,[69,70] a constant inhibition of NOS[62,63] or a constant infusion of catecholamines[43] can elicit VLF fluctuations in arterial blood pressure. Like catecholamines,[46–48] angiotension II[72–74] and NOS inhibition[75–78] have been demonstrated to enhance vascular myogenic responsiveness. Thus, one may speculate that myogenic vascular responses to spontaneously occurring perturbations of arterial blood pressure are the primary mechanism generating VLF BPV. Catecholamines, NO, the RAS and other factors affecting these systems (e.g. hypovolaemia and heat stress) may elicit their known effects on VLF BPV by altering myogenic vascular responsiveness. This idea is in line with the finding that the angiotensin II AT_1 receptor antagonist losartan prevented the increase in VLF BPV elicited by NOS inhibition.[62]

Data on the impact of the RAS on BPV in humans are scarce. Application of the angiotensin AT_1 receptor antagonist eprosartan did not alter LF or HF BPV in healthy volunteers.[79] The VLF BPV was not investigated in that study.[79] In patients with stimulated RAS due to severe heart failure (ejection fraction 24%), a 3 h infusion of the angiotensin-converting enzyme inhibitor enalaprilat did not change overall BPV or its LF or HF components.[80] Again, the VLF component was not studied. These two studies may suggest that inhibition[79] or activation[80] of the RAS do not affect LF and HF BPV in humans. Whether the RAS affects VLF BPV in humans remains to be elucidated.

SUMMARY AND PERSPECTIVES

Table 1 summarizes the frequency components of BPV that are affected by sympathetic modulation of vascular tone, myogenic vascular function, endothelial-derived NO and the RAS. Blood pressure fluctuations elicited by sympathetic modulation of vascular tone (so-called Mayer waves) occur in the LF band that is centred around 0.1 Hz in humans and shifted to higher frequencies (0.2–0.6 Hz) in rats. Myogenic vascular function affects VLF and LF BPV in humans, but only VLF BPV in rats. Thus, in humans, LF BPV may not exclusively reflect sympathetic modulation of vascular tone. Similarly, in rats, LF BPV does not exclusively reflect sympathetic modulation of vascular tone, because, in rats, the endothelial NO system also affects LF BPV. If and at which frequency endothelial-derived NO affects BPV in humans remains controversial. Finally, the RAS has the potential to increase VLF BPV in rats. However, VLF BPV does not exclusively reflect the RAS, because catecholamines, NO and myogenic vascular function also affect VLF BPV in rats. The impact of the RAS on specific components of BPV in humans is currently unknown.

Table 1 Frequency components of blood pressure variability in rats and humans that are affected by sympathetic modulation of vascular tone, myogenic vascular function, endothelial-derived nitric oxide and the renin–angiotensin system

	Rats	Humans
VLF	0.02–0.20 Hz	0.02–0.07 Hz
LF	0.2–0.6 Hz	0.075–0.15 Hz
HF	1.0–4.0 Hz	0.15–0.40 Hz
Sympathetic modulation	LF	LF
Myogenic vascular function	VLF	VLF and LF
Endothelial-derived NO	LF and VLF	Maybe HF
Renin–angiotensin system	VLF	?

VLF, very low frequency; LF, low frequency; HF, high frequency; NO, nitric oxide.

Different authors use slightly different frequency ranges for VLF, LF and HF. The values provided are used frequently.

Knowing which frequency components of BPV are affected by different cardiovascular mechanisms may aid in the diagnosis and treatment of patients with cardiovascular diseases. For example, hypertensive patients with elevated LF BPV may have enhanced sympathetic modulation of vascular tone and, therefore, may respond well to lifestyle modifications aimed at reducing stress or to sympatholytic drugs, whereas other patients without elevated LF BPV may not respond well to such treatment strategies. Another example is the selection of antihypertensive drugs in hypertensive patients with impaired cerebrovascular myogenic function, such as patients on chronic dialysis owing to end-stage renal disease and uraemia.[4–7] Because impaired cerebrovascular myogenic function increases the risk of haemorrhagic stroke,[2,81–83] drugs that further impair myogenic function, such as Ca^{2+} channel blockers,[8,9] may be harmful in this population of patients.[11] Because myogenic vascular function is reflected in VLF BPV, it may be possible to identify hypertensive patients with impaired cerebrovascular myogenic function prior to haemorrhage and, thus, prevent haemorrhagic stroke. These potential clinical applications of BPV are somewhat limited by the fact that different cardiovascular mechanisms can affect the same frequency components of BPV. Thus, to identify specific cardiovascular mechanisms, it is not sufficient to perform blood pressure spectral analysis under resting conditions. However, spectral analysis of blood pressure combined with other diagnostic tests (e.g. controlled breathing or perturbation or inhibition of specific cardiovascular mechanisms) may provide a wealth of information on cardiovascular regulation that is not assessable by any other clinical or experimental technique.

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