Autonomic cardiovascular control in conscious mice

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Autonomic cardiovascular control in conscious mice. Am J Physiol Regulatory Integrative Comp Physiol 279: R2214–R2221, 2000.—Autonomic cardiovascular control was characterized in conscious, chronically catheterized mice by spectral analysis of arterial pressure (AP) and heart rate (HR) during autonomic blockade or baroreflex modulation of autonomic tone. Both spectra were similar to those obtained in humans, but at ~10× higher frequencies. The 1/f relation of the AP spectrum changed to a more shallow slope below 0.1–0.2 Hz. Coherence between AP and HR reached 0.5 or higher only above 0.3–0.4 Hz and also above 2.5 Hz. Muscarinic blockade (atropine) or β-adrenergic blockade (atenolol) did not significantly affect the AP spectrum. Atropine reduced HR variability at all frequencies, but this effect waned above 1 Hz. β-Adrenergic blockade (atenolol) slightly enhanced the HR variability only above 1 Hz. α-Adrenergic blockade (prazosin) reduced AP variability between 0.05 and 3 Hz, most prominently at 0.15–0.7 Hz. A shift of the autonomic nervous tone by a hypertensive stimulus (phenylephrine) enhanced, whereas a hypotensive stimulus (nitroprusside) depressed AP variability at 1–3 Hz; other frequency ranges of the AP spectrum were not affected except for a reduction below 0.4 Hz after nitroprusside. Variability of HR was enhanced after phenylephrine at all frequencies and reduced after nitroprusside. As with atropine, the reduction with nitroprusside waned above 1 Hz. In conclusion, in mice HR variability is dominated by parasympathetic tone at all frequencies, during both blockade and physiological modulation of autonomic tone. There is a limitation for further reduction but not for augmentation of HR variability from the resting state above 1 Hz. The impact of HR on AP variability in mice is confined to frequencies higher than 1 Hz. Limits between frequency ranges are proposed as 0.15 Hz between VLF (very low frequency range) and LF (low frequency range) and 1.5 Hz between LF and HF (high frequency range). The analysis of arterial pressure (AP) and heart rate (HR) variability by spectral methods has proved a useful tool in humans and conscious animals for the investigation of integrative cardiovascular regulation (28, 29), for the assessment of sympathovagal balance (7, 27, 28), and for diagnostic and prognostic purposes in cardiovascular disease (7). These methods have also been applied to rats (1, 9, 21, 31), and thorough evaluations have shown that they are valid in this species after adaptation of the frequency ranges by a factor of four, corresponding to the higher HR and respiratory rate (9, 21, 31).

Therefore, it seems plausible that spectral analysis of cardiovascular variability may also be transferable to mice. Indeed, spectral analysis of HR has already been used in mice (18, 20, 25, 37, 40). These studies investigated the responses to pharmacological blockade of the autonomic efferents but did not address the responses to physiological modulation of the autonomic nervous tone. Although the responses to a hypertensive stimulus have been assessed by methoxamine (40) or \( N^\text{ω}-\text{nitro-L-arginine methyl ester (L-NAME)} \) (20), no data are available for a modulation of sympathovagal balance into the opposite direction.

Furthermore, there is also growing interest in genetic targets potentially involved in the regulation of blood pressure (11, 15, 35). From its use in larger animals and humans (28, 29), the spectral analysis of AP is expected to be a valuable tool for the integrative investigation of such murine models, as it has already been in a recent study (35). Thus a more detailed understanding of the basic characteristics of the AP variability in the mouse would be highly desirable. This important point has been addressed in a recent detailed work on conscious unrestrained Swiss mice (20) by means of pharmacological autonomic blockade. However, information on the effects of autonomic influences during modulation of the sympathovagal balance within the physiological range is still missing.

Therefore, the aims of the present study were 1) to characterize the normal baseline spectra of both HR and AP in conscious freely moving mice of the C57BL/6J strain, the most widely used genetic background for studies on genetically modified animals, 2) to reassess for both spectra the effects of blockade of...
the autonomic nervous control in this strain of mice, and 3) to investigate the responses of baroreflex-mediated modulation of the autonomic tone within a physiological range.

METHODS

All experiments were performed in 14 female wild-type C57BL/6J mice (22–24 g, age 6 mo) in accordance with national guidelines for the care and use of research animals. After surgery, the mice were housed individually in plastic cages with free access to water and standard mouse chow. After completion of all experiments the animals were killed by an overdose of ketamine.

Surgical procedures. After anesthesia with ketamine and xylazine-HCl (100 and 4 μg/g ip; Rompun, Bayer), catheters were implanted aseptically into the left femoral artery and vein, tunneled subcutaneously, and exteriorized through a spring, sewn to the animal’s back. Cefazolin (10 mg im) was given for antibiotic prophylaxis. The catheters were manufactured as described by Mattson (26) comprising a dead space of 30–100 μl. The spring was connected to a swivel device at the top of the cage. The catheters were filled with heparin solution (50 IU/ml saline) and sealed until use.

Measurements. All experiments were done in conscious unrestrained mice in their own cage. AP measured via the catheter (transducer PRC-21K, amplifier MIO-0501; FMI, Seeheim, Germany) was continuously recorded on a computer (Pentium, DAS-16; Keithley-Metrabyte, Taunton, MA. Note-Book 10.2.1; Labtech, Wilmington, MA) at 500 Hz. Drugs were infused intravenously by a calibrated pump (Picodir 5003; Infors, Bottmingen, Switzerland).

Protocols. On day 2 (48 h) after surgery AP was recorded for 1 h (21–22 spectra) as a control. Subsequently, either nitroprusside (5 μg·kg⁻¹·min⁻¹; Merck, Darmstadt, Germany) or phenylephrine (5 μg·kg⁻¹·min⁻¹; Merck) was infused at a constant rate (250 nl·g⁻¹·min⁻¹ iv, i.e., <10% of estimated blood volume over the 30-min period). AP was recorded for 984 s (6 spectra) beginning 300 s after starting the infusion. After flushing and reloading of the catheter and recovery for at least 30 min, the infusion of the other drug was started and AP was recorded for 984 s beginning after 300 s. The order of nitroprusside and phenylephrine was randomly assigned. After flushing and recovery for at least 30 min, another control period was recorded for 984 s. Subsequently, a bolus of either atropine-methyl-nitrate (2 mg/kg, Sigma Chemicals) or atenolol (2 mg/kg, Sigma Chemicals) was given intravenously in 2.5 μl/g saline over 1 min. AP was recorded for 984 s starting 200 s after the bolus. On the following day, this scheme (984 s control, 984 s after bolus) was repeated for the other antagonist. The order of atropine and atenolol was randomly assigned.

In a separate group of five mice, prazosin (Sigma Chemicals) was given intravenously as a bolus of 0.1 mg/kg in 7.5 μl·g⁻¹·min⁻¹ saline over 3 min, followed by a continuous infusion of 0.2 mg·kg⁻¹·h⁻¹ in 2.5 μl·g⁻¹·min⁻¹ saline. AP was recorded for 984 s before the bolus as well as for 984 s beginning 120 s after the start of the infusion.

Data processing. From the 500-Hz AP data, pulse interval durations (PI), mean AP, and instantaneous HR were determined for each pulse from the systolic pressure upstrokes by a custom-designed program. The values of PI were stored at 500 Hz for spectral analysis, and mean AP and instantaneous HR were stored beat by beat for determination of total variability. The accuracy of the PI determination was tested by chronically implanted electrocardiogram (ECG) electrodes. In 1,369 pulses, the PI values determined from AP at 500 Hz differed by 0.64 ± 0.72 ms (mean ± SD) from those derived by ECG at 5,000 Hz. For spectral analysis, the 500 Hz files of AP and PI were then resampled at 10 Hz. Because power above 50 Hz was negligible, no anti-aliasing filter was applied. Power spectral density (PSD) of AP and PI as well as squared coherence between AP and PI were calculated from linear trend corrected blocks of 163.84 s from the 100 Hz data by the Blackman-Tukey algorithm. Subsequent spectra from each recording were averaged. Because spectral analysis from long periods of nonstationary data may be distorted by slow, nonharmonic components, the same analysis was also calculated from blocks of 16 times shorter duration (10.24 s). These spectra were confined to the high-frequency (HF) and low-frequency (LF) range (0.293–5.0 Hz) but in these ranges led to the same results as those from the longer blocks (data not shown). The direct current (DC) component and the lowest two frequencies of each spectrum were discarded. PI values longer than twice the previous one were automatically replaced by the previous value. If no pulse was detected for more than 10 s, or if other artifacts occurred (flushing of the catheter, interruption of data acquisition), these data segments were excluded from the analysis (altogether less than 3% of data were discarded). To allow statistical testing of changes in PSD, integrated values of PSD were derived by summing the PSD values in certain frequency ranges. The frequency ranges were chosen with respect to the results of the present study (see DISCUSSION) as follows: very low frequency (VLF) <0.15 Hz; LF, 0.15–1.5 Hz; and HF, 1.5–5.0 Hz. To assess total variability in the time domain, mean AP and instantaneous HR were determined for every single beat. From these beat-by-beat values, standard deviation (SD) and coefficients of variation (SD/mean × 100%) were calculated. Statistical analysis was done by one-way ANOVA followed by the Newman-Keuls test. Integrated spectral densities were logarithmically transformed before statistical testing. An error level of P < 0.05 was considered significant.

RESULTS

Normal variability under control conditions. An original trace of AP of one block (163.84 s) from the 1-h control recording in one of the mice is shown in Fig. 1A. Mean values of AP and HR from the 1-h control recordings (n = 9) were 106 ± 2 mmHg and 662 ± 12 beats/min, respectively (Table 1). Total variability in terms of SD from beat-by-beat values of AP and HR was in the range of 5% of the respective mean value (Table 1). The mean spectra of AP and PI are shown in Fig. 1, B and C. In both spectra, there is some accumulated variability between 2 and 5 Hz, whereas below 2 Hz, the spectra largely comprise a “1/f pattern,” i.e., increasing power with lower frequencies without discrete peaks of oscillation. Between 0.08 and 0.4 Hz of the AP spectrum, there appears to be some concentration of variability, causing the 1/f relation to change from a steeper to a more shallow slope with smaller frequencies. This change in slope is most prominent around 0.1–0.2 Hz. The frequency ranges, denoted in Fig. 1 by vertical lines, were derived from the pattern of the spectra and their responses to autonomic blockade and modulation, as described in more detail in DISCUSSION. It may be of note that in two single recordings (1 after atropine and 1 in the control before atenolol), prominent oscillations occurred at 0.9 Hz in the
absence of any other obvious abnormality. However, not any distinct oscillation could be detected between 0.7 and 1.5 Hz in all other of the 69 recordings.

Squared coherence between AP and PI during the 1-h control recordings of all nine mice is depicted in Fig. 2. The coherence was small between 0.7 and 1.5 Hz and reached levels above or close to 0.5 for frequencies higher than 2–3 Hz and smaller than 0.3–0.4 Hz.

Responses to inhibition of autonomic control. Inhibition of the parasympathetic branch of HR control by atropine did not lead to a significant tachycardia or alteration of mean AP (Table 1) compared with the 16-min control period recorded immediately before. The variability of AP was not altered after atropine (Fig. 3A; Table 1). In contrast to the AP spectrum, the variability of PI was dramatically reduced at all frequencies below 3–4 Hz after atropine (Fig. 3B), although it did not reach statistical significance in total variability (Table 1). This effect was most pronounced between slightly below 0.1 and 1 Hz (Fig. 3B) and waned above 1 Hz.

Inhibition of the sympathetic branch of HR control by atenolol resulted in a substantial reduction of mean HR by $119 \pm 28$ min$^{-1}$ without changes in mean AP (Table 1). Despite the strong effect on mean HR, the total variability of both AP and PI was not affected (Table 1). There was also virtually no change in the AP spectrum except for at most a very faint depression between 0.2 and 1.5 Hz (Fig. 3C). The PI spectrum displayed only a slight elevation, which was significant in the frequency range above 1.5 Hz (Fig. 3D).

Inhibition of $\alpha$-adrenergic vasomotor control by prazosin resulted in a drop of mean AP and an increase of HR (Table 1). The AP spectrum was depressed between 0.1 and 2.5 Hz (Fig. 4A). This effect was most prominent between 0.15 and 0.5 Hz. The spectral density of PI was reduced at all frequencies below 3 Hz (Fig. 4B). As with atropine, this effect waned above 1 Hz.

Responses to physiological modulation of the autonomic nervous tone. Both phenylephrine and nitroprusside caused moderate responses of mean AP and marked changes of mean HR compared with the 1-h control (Table 1).

The modulation of the autonomic tone toward sympathetic predominance during the hypotensive stimulus by nitroprusside led to a depression of AP variability between slightly below 1 Hz and up to 3 Hz (Fig. 5A, Table 1). There was also a drop of the variability, which was confined rather sharply to frequencies below 0.4 Hz, thereby unmasking a peak of rather discrete oscillations around 0.4 Hz. In contrast, the variability of PI was strongly depressed after nitroprusside at almost all frequencies (Fig. 5B). The same was seen in total variability (Table 1), although here the changes did not reach statistical significance. Similar to the observations after atropine, this reduction of variability waned above about 1 Hz and was absent above 3.5 Hz (Fig. 5B).

The modulation of autonomic tone toward parasympathetic activation by phenylephrine induced an increase of AP variability, which was almost exclusively confined to the frequencies above about 1.5–2 Hz (Fig. 5C) but was not sufficient to significantly affect total variability (Table 1). In contrast, the variability of PI was markedly enhanced over the entire frequency range reaching the same degree at all frequencies (Fig. 5D; Table 1).
humans), which are in parallel to respiration. All the frequency ranges above 1.5 Hz in mice (There was an accumulation of discrete oscillations in that the frequencies of the spectra are scaled according to HR (31). If this should also be true in the mouse, this finding also in previous investigations in mice (18, 20, 25, 35, 37, 40), and such oscillations were found in only two recordings of the present data. 1) There was usually no discrete oscillation in the frequency range of 0.8 and 1.0 Hz in mice, at which the “0.1-Hz Mayer waves” would be expected, which occur quite regularly in humans at 0.1 Hz (7, 27, 28, 36) and in rats at 0.4 Hz (1, 6, 9, 21, 31). The absence of a discrete oscillation at 0.8–1.0 Hz in the present results has been a consistent 0.15 Hz in. In accordance with the findings by Baseline spectra. In accordance with the findings by Janssen et al. (20) in Swiss mice, the baseline spectra of both AP and PI observed in the present study on conscious C57BL/6J mice were closely similar to those in larger mammals such as humans (7, 28), dogs (2, 27, 30), cats (14), and rats (1, 9, 21, 31). From previous studies comparing the spectra of AP and PI in rats to those in humans (1, 9, 21, 31), the picture had emerged that the frequencies of the spectra are scaled according to HR (31). If this should also be true in the mouse, then the frequencies from the human spectra would be scaled by a factor of 8–10. With this assumption, there are indeed major congruencies to the human spectra. 1) There was an accumulation of discrete oscillations in the frequency range above 1.5 Hz in mice (>0.15 Hz in humans), which are in parallel to respiration. Although respiratory frequency was not measured in the present investigation, in a previous study it had been found at 210 min⁻¹, i.e., at 3.5 Hz (37). 2) There was a transition of the 1/f relation of the AP spectrum from a steeper to a more shallow slope at 0.3–0.4 Hz (0.04 Hz in dogs; Ref. 38). However, there were two important differences to human spectra. 1) There was usually no discrete oscillation in the frequency range of 0.8 and 1.0 Hz in mice, at which the “0.1-Hz Mayer waves” would be expected, which occur quite regularly in humans at 0.1 Hz (7, 27, 28, 36) and in rats at 0.4 Hz (1, 6, 9, 21, 31). The absence of a discrete oscillation at 0.8–1.0 Hz in the present results has been a consistent finding also in previous investigations in mice (18, 20, 25, 35, 37, 40), and such oscillations were found in only two recordings of the present data. 2) The coherence between AP and PI was small at 0.8–1.0 Hz in the
present data as well as in a previous report on mice (20), whereas usually a peak is observed at 0.1 Hz in humans (27, 36) and at 0.4 Hz in rats (8, 31).

Baseline AP and HR in the present study were very similar to values found by other authors using chronic catheters (11, 15, 20, 26) or telemetry (18, 40). In a number of studies on mice, also, smaller values of HR have been reported (13, 22, 25, 35, 37). Although in one of the latter studies, only periods of quiet rest had been selected (35), and in another the animals were in a mouse holder (37), there is no obvious explanation for the differences in HR between the remaining studies. Although we cannot entirely exclude that HR in the present study may have been influenced by remnant effects from the implantation surgery, or from some isolation stress due to keeping the animals in separate cages after the surgery, it is important to note that a moderate tachycardic response to atropine of less than 5% (13, 20, 40) or maximally 10% (18) and a more pronounced bradycardic effect of \( \beta \)-adrenergic blockade by at least 20% (13, 18, 20) and up to 50% (40) has been a consistent finding in mice, whether the baseline HR was similar (18, 20, 40) or slower (13) than in the present study. This suggests that the autonomic nervous tone was probably not severely altered in the animals of the present investigation. A balanced response to atropine and propranolol has been reported only in one study, in which the animals were restrained in a mouse holder (37).

Modulation of the HR spectra by the autonomic nervous system.

In response to pharmacological blockade of the parasympathetic branch of HR control, there was a pronounced reduction of HR variability despite only minute effects on mean HR. This reduction af-

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In contrast to the pronounced impact of parasympathetic tone on HR variability, β-adrenergic inhibition had only faint effects on the PI spectrum despite a marked depression of mean HR. The same pattern of response has been found after β-adrenergic blockade by metoprolol (20). Other studies had reported variable results (18, 25, 40), but in these studies, propranolol had been used, which is less cardioselective (34) and more prone to central effects (12) than metoprolol or atenolol. Nevertheless, a prominent bradycardic response to β-adrenergic blockade was found repeatedly in mice (18, 25, 37, 40), indicating a predominance of sympathetic tone in murine control of mean HR (18). Thus the small responses of HR variability observed in the present study are unlikely to be due to an already small sympathetic tone during baseline. In contrast, even at enhanced levels of activation during the hypotensive stimulus, the sympathetic outflow to the heart does not play a major role for HR variability in the mouse. A slight increase of variability after β-adrenergic blockade between 0.4 and 2 Hz has also been found in a previous study (20) and may be explained by a suppressing effect of the sympathetic activity on vagally mediated fluctuations (17), which is alleviated after inhibition.

In contrast to larger animals, the capacity for a further reduction of HR variability from the resting state is limited in mice, while there is no such restriction for further enhancement of the variability during parasympathetic activation by the hypotensive stimulus. This limitation is most pronounced above 1 Hz, probably because here the variability in the resting state is already lower than in the other frequency ranges. The reason for this limited reduction of HR variability is not exactly clear. It is unlikely to derive from an insufficient resolution of the estimation of PI from the AP data, because the same limitations were found for PI values derived from ECG sampled at a much higher rate (40). This raises the possibility that there might be a biological limitation for the accuracy of HR control in mice. It should be noted that to reduce variability to below the limit of experimental detection from 500 (present study)- or 5,000-Hz data (40), the mouse would have to restrain variations in PI to less than ±1 ms or ±0.1 ms, respectively. The observation that variability after atropine may be further reduced in mice lacking the cholinergically controlled potassium channel (40) suggests that this conductance might play a role for the supposed noise in HR control.

**Modulation of the AP spectra by the autonomic nervous system.** The spectrum of AP was remarkably stable with regard to the large concomitant changes of HR variability. A comparison of the affected frequency ranges in the AP and HR spectra suggests that the impact of the fluctuations of HR on the variability of AP is restricted almost exclusively to frequencies above 1.5 Hz. This is similar to findings in humans (32, 36), dogs (2), and rats (9, 21) in which the AP spectrum is altered by the reduction of HR variability after atropine or pacing only in the HF range, i.e., above 0.15 in humans and above 0.6 Hz in rats, but not at lower frequencies.

The reduction of AP variability induced by prazosin demonstrates the frequency range of the impact of α-adrenergic vasomotor control. The reduction observed above 1 Hz, however, is unlikely to derive from a direct effect of the resistance vessels. Comparison to the spectral effects of nitroprusside rather suggests that this reduction was secondary to the depression of HR variability. The diminution of HR variability observed after prazosin, which was almost identical to that after nitroprusside, was most probably the baroreflex-mediated result of the hypotension induced by prazosin. The direct influence of vasomotor control is therefore probably confined to the frequency range below 1 Hz. The finding that this effect was most pronounced between 0.15 and 0.5 Hz nicely corresponds to the coherence between AP and PI, which reached 0.5 at 0.3–0.4 Hz. Both features were also reported in a previous investigation on mice (20).

An unexpected finding was the reduction of AP fluctuations in the VLF range after nitroprusside. This is unlikely to derive from the smaller variability of HR, because the reduction of AP variability was confined rather sharply to frequencies below 0.4 Hz, which was not the case for HR variability. The sharp onset at 0.4 Hz may suggest that this effect is related to sympathetic vasomotor control, because the corresponding frequency in dogs and humans (0.04 Hz) approximates the natural frequency of baroreceptor reflex and sympathetic vasomotor responses (33). This view would also be in congruence with the effect of prazosin in mice being most pronounced around 0.4 Hz. Furthermore, the marked augmentation of AP variability after baroreceptor denervation in cats and dogs, as a correlate of the regulatory effect of the baroreceptor reflex, is limited to a similar frequency range (<0.06 Hz) (14, 23). The effect observed in the present study may be specific to nitroprusside due to an attenuating action of NO on central outflow or peripheral transmission of sympathetic vasomotor activity (41).

**Derivation of characteristic frequency ranges.** To facilitate a possible transfer of knowledge from larger mammals to the spectra in mice, it is attempted in the following to derive the frequency ranges in accordance to the definitions in humans (7), dogs (27, 28), and rats (1, 9, 21, 31) based on the results of the present study. The HF range (0.15–0.5 Hz in humans and dogs, 0.6–3 Hz in rats) is characterized by its close association with the rate of respiration (7, 28), the impact of

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only parasympathetic control without sympathetic contribution (7, 27). In addition, the impact of HR variability onto the variability of AP has been found to be most pronounced in this frequency range in dogs (2) and humans (36). Based on these criteria, we would suggest the HF range in mice as 1.5–5 Hz.

In the LF range (0.04–0.15 Hz in humans and dogs, 0.2–0.6 Hz in rats) the impact of prazosin was found to be most prominent in most studies in rats (9, 21, 31). Furthermore, this range characteristically comprises a peak of high coherence between AP and PI (8, 27, 31, 36). Finally, the border between the LF and VLF range, at least in dogs, is typically associated with the change of the slope of the 1/f relation in the AP spectrum (38), which was the case between 0.1 and 0.2 Hz in mice in the present study. Accordingly, the LF range is proposed as 0.15–1.5 Hz. No attempt was made to delimit the ULF range, which might be expected around 0.03 Hz (<0.003 Hz in humans; Ref. 7). Therefore, we have ascribed in the present study all frequencies below 0.15 Hz to the VLF range.

In larger mammals, the relation between power in the LF and the HF range (LF/HF ratio) has been proposed as a marker of sympathovagal balance (7, 27). It must be emphasized, however, that in mice, because of the limited reduction of HR variability in the HF range, the LF/HF ratio of HR variability does not change with a shift to parasympathetic predominance, and it even moves in the direction opposite to that in larger mammals during a shift to sympathetic predominance. Therefore, the LF/HF ratio is not a valuable tool in mice.

A remark should be given concerning the LF range. Although the interpretation of the fluctuation at 0.4 Hz in mice as the correlate to the 0.1-Hz Mayer wave in humans has been proposed and experimentally supported by Janssen et al. (20), the occasional observation of a distinct oscillation at 0.9 Hz in the present study may suggest that it might be the latter oscillation which represents this correlate. It may be of note that in dogs oscillations at 0.05 Hz have been observed in addition to the fluctuation at 0.1 Hz (10). However, since the 0.1-Hz Mayer waves are believed to derive from feedback oscillations of the baroreceptor reflex (4), the attribution of the 0.1-Hz Mayer waves to the oscillations at 0.9 Hz in mice seems to implicate that the vascular smooth muscle in mice is capable of responses as fast as 1 Hz. Although no studies on the response times of smooth muscle in mice are available, such a fast response appears surprising. However, it should be noted that other authors have suggested that the 0.1-Hz Mayer waves derive from an interaction of the different response times of the components of the baroreceptor reflex (24), with the natural frequency of the sympathetic vasomotor response being slower (33) and that of vagal control of HR being faster (39) than the 0.1-Hz Mayer waves. In addition, the delays within the baroreceptor reflex seem to be a more important determinant for the frequency of the 0.1-Hz Mayer waves than the corner frequency of the feedback response (4). However, the question of the correct assignment of the fluctuations in the LF range cannot be settled from the present data. Therefore, the LF range was defined as including both the region of 0.4 Hz and that of 0.9 Hz.

**Perspectives**

In mice, the spectra of HR and AP variabilities are shifted to roughly 10 times higher frequencies compared with humans. This also includes the HF range and the upper limit of the LF range. In contrast, the features within the LF range, which differ slightly from those of larger mammals, suggest that the limit between the LF and the VLF range may be at slightly smaller frequencies than expected. The variability of HR is dominated by the parasympathetic branch of HR control and may thus serve as an indicator of parasympathetic tone, but not of sympathovagal balance. Because of a limitation for a reduction of HR variability in the HF range, the LF/HF ratio of HR variability is not a valuable tool in mice. Similar to larger mammals, the contribution of HR to the variability of AP is confined to the HF range. This provides an interesting extension on the significance of the cholinergically operated potassium channel, which has been shown in a recent study to be most important for HR variability in the LF and HF range (40). The present finding of the impact of HR on AP variability in the HF range suggests that this ion channel is not only important for HR variability, but may also contribute to the control of AP.

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