Abstract

Mayer waves are oscillations of arterial pressure occurring spontaneously in conscious subjects at a frequency lower than respiration (~0.1 Hz in humans). Mayer waves are tightly coupled with synchronous oscillations of efferent sympathetic nervous activity and are almost invariably enhanced during states of sympathetic activation. For this reason, the amplitude of these oscillations has been proposed as a surrogate measure of sympathetic activity, although in the absence of a clear knowledge of their underlying physiology. Some studies have suggested that Mayer waves result from the activity of an endogenous oscillator located either in the brainstem or in the spinal cord. Other studies, mainly based on the effects of sinoaortic baroreceptor denervation, have challenged this view. Several models of dynamic arterial pressure control have been developed to predict Mayer waves. In these models, it was anticipated that the numerous dynamic components and fixed time delays present in the baroreflex loop would result in the production of a resonant, self-sustained oscillation of arterial pressure. Recent analysis of the various transfer functions of the rat baroreceptor reflex suggests that Mayer waves are transient oscillatory responses to hemodynamic perturbations rather than true feedback oscillations. Within this frame, the amplitude of Mayer waves would be determined both by the strength of the triggering perturbations and the sensitivity of the sympathetic component of the baroreceptor reflex.

1. Introduction

Arterial pressure (AP) oscillations have been the focus of a large number of studies since the introduction of computers in cardiovascular research. Of particular interest are the so-called Mayer waves (corresponding to the “10-s rhythm” in humans). From their very first description, these oscillations were referred to as vasomotor waves. Because Mayer waves are usually enhanced during states of sympathetic activation, several authors have proposed that these oscillations might provide an indirect measure of efferent sympathetic nervous activity (SNA). However, the identification of a precise mechanism underlying these oscillations has been, and still partly remains, elusive (for review, see [2–8]). In the following, we will try to summarize the recent advances in our knowledge of the physiology of these oscillations, especially by confronting experimental facts and modeling studies.

2. Characterization of Mayer waves

2.1. Definition

The application of spectral techniques to simultaneous recordings of AP and SNA in conscious experimental animals and humans has revealed the presence of spontaneous oscillations of both signals at frequencies slower than the respiratory movements. The calculation of coherence, which quantifies the strength of the linear coupling between
fluctuations of two variables in the frequency domain, has indicated that these rhythms are tightly correlated at particular frequencies. It can therefore be proposed to define Mayer waves as the AP oscillations slower than respiration that exhibit the strongest, significant coherence with oscillations of SNA. AP oscillations that meet this requirement have a characteristic frequency of ~0.1 Hz in humans [9–11], 0.3 Hz in rabbits [12,13], and 0.4 Hz in rats [14,15]. In humans, studies were based on muscle SNA recorded from the peroneal nerve whereas in rabbits and rats, studies were based on renal SNA recordings. In decerebrate cats, cardiac preganglionic SNA displays a strong rhythmicity at a frequency near 0.1 Hz [16]. In this study, coherence between SNA and AP was not reported. It is however likely that the actual frequency of Mayer waves in cats is near 0.1 Hz, or slightly above, especially because this is where a clear AP oscillation is seen in conscious animals [17,18]. To our knowledge, there are no data in the literature describing the spontaneous variability of SNA in conscious dogs. However, like in humans, a 0.1-Hz AP oscillation has been found in conscious dogs, the amplitude of which is augmented by maneuvers resulting in sympathetic activation [19]. By analogy with observations made in humans, it sounds logical to propose that Mayer waves have a characteristic frequency of 0.1 Hz in the dog. It should however be mentioned that slower (~0.05 Hz) AP oscillations have been described in conscious dogs subjected to hemorrhage [20]. The increasing availability of genetically engineered mice has prompted several investigators to study AP variability in this species. Although direct measurements of SNA have not been obtained in conscious mice, indirect evidence suggests that Mayer waves may have a central frequency of 0.4 Hz in this species [21,22].

2.2. Hemodynamic basis

Mayer waves result from an oscillation of the sympathetic vasomotor tone, as they are strongly attenuated, or even abolished, after acute alpha-adrenoceptor blockade [23–27]. In conscious rats, 0.4-Hz oscillations are observed in total peripheral resistances but hardly in cardiac output [28]. Oscillations in total peripheral resistances originate from synchronous oscillations of vascular tone in several regional circulations, including the kidney, mesentery and skeletal muscles [28,29]. In rabbits, the renal circulation appears to play a predominant role in producing Mayer waves, at least during sympathetic activation induced by hemorrhage [13].

The precise role of heart rate oscillations, and hence of cardiac output, in modulating Mayer waves in humans is complex and would deserve a thorough discussion. However, the enhancing effect of atrial pacing [30] and cardiac autonomic blockade [31] on Mayer wave’s amplitude suggests that heart rate oscillations buffer rather than reinforce Mayer waves in humans.

3. What determines the frequency of Mayer waves?

A common feature of Mayer waves is that their frequency is fairly stable within a given species. In particular, it has been shown in humans that this frequency does not depend on gender, age or posture [9,10,32,33]. Two theories have been proposed to explain the constancy of Mayer wave’s frequency.

3.1. The pacemaker theory

This theory is based on the observation that, in some instances, oscillations of SNA and/or hemodynamic variables can be observed at or near the frequency of Mayer waves in the absence of sensory inputs from the periphery. Such rhythmicity is then thought to derive from the pacemaker-like activity of an autonomous oscillator located within central nervous structures generating SNA.

Experimental support to the pacemaker theory came first from a series of observations in anesthetized animals. It was reported that slow waves in AP and lumbar SNA could be evoked in spinal, vagotomized dogs by raising spinal subarachnoid pressure [34]. This finding was taken to indicate that the putative central oscillator might be located in the spinal cord. However, the period of AP and SNA waves in this study was longer (20–40 s) than that of slow AP oscillations occurring spontaneously in the conscious dog [19]. In cats, Preiss and Polosa [35] reported the occurrence of slow fluctuations of preganglionic SNA during hemorrhage combined with common carotid artery occlusion. SNA oscillations persisted when AP oscillations were abolished, either mechanically or by means of alpha-adrenoceptor blockade with phentolamine. This led the authors to conclude that Mayer waves are generated independently of baroreflex influences, thus probably as a result of the activity of a central oscillator. However, in this experiment also, the period of the evoked oscillations varied within a broad range (between 9 and 60 s) with a mean value of ~25 s, which is longer than that of spontaneous Mayer waves in conscious cats [17]. More recently, Grasso et al. [36] observed that in dogs, during constant-pressure perfusion of the isolated hindlimb, iliac blood flow exhibited spontaneous slow oscillations coherent with systemic AP. As these oscillations were also observed when carotid sinus pressure was held constant, the authors concluded that they were of central origin. It is not clear in this study whether authors actually examined Mayer waves, as SNA was not measured and the reported frequency of hemodynamic oscillations was highly variable (from 0.01 to 0.18 Hz).

As far as we know, the direct demonstration of a central rhythm possibly related to Mayer waves has been provided on one occasion. Spectral analysis was applied to the ongoing activity of single medullary neurons from anesthetized cats that had undergone prior sinoaortic baroreceptor denervation and bilateral vagotomy [37]. A low-frequency
rhythm (around 0.1 Hz) was present in the discharge of some sympathetic-related neurons, but was also present in the activity of some sympathetic-unrelated neurons, raising the possibility that this rhythm could be a reflection of a generalized propensity of medullary neuronal networks to oscillate at this frequency. Later on, the same group reported the presence of a 0.1-Hz rhythm in the cardiac SNA of unanesthetized, decerebrate cats after bilateral vagotomy and C1 spinal section [38]. This rhythm was amplified during a sympathetic excitatory spinal reflex (aortic constriction). The possibility that Mayer waves might derive from a spinal rhythm has been examined in patients with spinal cord injury. These studies have been inconclusive, first because SNA was not measured, and second because conflicting results were reported. Specifically, slow AP oscillations referred to as Mayer waves were observed constantly [39], occasionally [40] or not at all [41] in tetraplegic patients. In addition, in some studies, these AP oscillations displayed a paradoxical behavior as their amplitude decreased during head-up tilt [40,42,43], contrary to what is consistently observed in healthy subjects [9–11]. In rats with spinal cord transection, the 0.4-Hz oscillation of AP was eliminated [44].

In summary, this review of the relevant literature does not allow us to draw a definitive conclusion about the contribution of a central oscillator to the genesis of Mayer waves. Nonetheless, there is no denying that, under some experimental conditions, central nervous structures can generate slow SNA rhythms independent of peripheral afferent inputs. However, under physiological conditions, Mayer waves are produced while AP control systems are operating. The arterial baroreceptor reflex is the most powerful and rapidly acting controller of AP. Therefore, even if an endogenous SNA rhythm were present, its direct feedforward effect on AP would necessarily be modulated by baroreflex responses. An obvious experimental approach to this question has been to examine the effect on AP oscillations of eliminating baroreflex influences by opening the baroreflex loop.

3.2. The baroreflex theory

3.2.1. Opening the baroreflex loop abolishes Mayer waves

In animals, opening of the baroreflex loop can easily be achieved by means of surgical denervation of aortic and carotid sinus baroreceptors. In conscious chronically sinoaortic baroreceptor denervated (SAD) cats and rats, spectral analysis of AP time series indicates that Mayer waves are absent [17,18,29,45,46]. Furthermore, the simultaneous recording of AP and regional blood flows in conscious SAD rats revealed that the residual AP power in the frequency band containing Mayer waves was not correlated anymore with corresponding fluctuations of regional vascular conductances, thus pointing to a major role of the baroreflex in synchronizing oscillations of vasomotor tone in this frequency band [29]. Several studies have indicated that the prominent oscillations of renal SNA associated with Mayer waves are strongly attenuated in SAD rats (Fig. 1) under both resting [47,48] and stressful [49] conditions. Although these data are in support of a major role of the baroreceptor reflex in the generation of Mayer waves, it is worth noting that in the frequency band containing Mayer waves, fluctuations of AP and SNA were not abolished in SAD rats, although they were not organized with a periodicity of 0.4 Hz. In addition, coherence between AP and SNA was reduced but not abolished [48,49]. Finally, it has been shown that in SAD rats, the residual AP power in the Mayer band was eliminated after acute ganglionic blockade [45]. All these observations suggest that SNA rhythms of small amplitude and apparently random frequency are still present after baroreceptor denervation in the frequency band containing Mayer waves.

Another method for opening the baroreflex loop is to interrupt the sympathetic transmission at the vascular neuroeffector junction. This has been done in humans [27] and in rats [50] with the use of the alpha-adrenoceptor antagonist, phentolamine. In both experiments, phentolamine decreased AP, increased SNA, and strongly depressed both Mayer waves and accompanying oscillations of SNA, thus further strengthening the hypothesis that SNA oscillations at Mayer wave’s frequency are of reflex origin.

The involvement of the baroreceptor reflex in the genesis of Mayer waves was proposed by Guyton and Harris in 1951 [51], although the authors did not formulate a mathematical modeling of their observations. Later on, several models predicting Mayer waves have been described [52–66]. All these models were based on a computer simulation of the cardiovascular system, and therefore incorporated a dynamic representation of the arterial baroreceptor reflex. Their physiological relevance has often been limited because of absent or erroneous data about the dynamic behavior of the various components of the baroreflex loop. The recent advances in the description of transfer functions of baroreflex pathways, especially in rats, now make it possible to propose realistic models.

3.2.2. Basic principles of resonance in feedback loops

In the following, we will consider simple linear input–output relationships in an arbitrarily chosen negative feedback control loop (Fig. 2). When the loop is opened, the output is related to the input through the transfer function of the loop. This transfer function includes an inverter which results in a 180° phase shift between the output and the input. In other words, the input and output tend to vary in opposite directions. The transfer function also includes one or several dynamic components that can generally be mathematically described by differential equations of filters (in this example, a low-pass filter). Finally, the transfer function includes a time lag (or dead time, latency, fixed or pure time delay, all these terms are synonymous). Under steady-state conditions or at very low frequencies, a change in the input will merely result in an
opposite change in the output, the amplitude of which depends on the static gain of the system. As frequency of the input fluctuation increases, the low-pass filter and time delay have an increasing influence on the response of the output, so that the output fluctuation is progressively delayed and its amplitude decreases. This holds true until, at a particular frequency, both signals are perfectly in phase. This frequency is called the resonance or resonant frequency of the loop. The resonance frequency of a feedback loop is the frequency at which the loop, when it is closed, can be unstable, i.e., can generate a self-sustained oscillation of the controlled variable. Let’s consider the fate of an external perturbation in the closed loop depicted in Fig. 2. If the perturbation contains a 0.1-Hz component, even if it ceases spontaneously, this component will be echoed by an opposite change delayed by exactly one-half cycle, which in turn will induce an opposite change with a one-half cycle delay, and so forth. Then, an oscillation is created and will continue provided that the gain is sufficiently high (see Section 4).

3.2.3. Resonance in the baroreflex loop

When considering the arterial baroreflex loop, the input is pressure at the baroreceptors and the output is systemic AP. For example, in the Moissejeff’s preparation [67], both carotid sinuses are isolated from the rest of the circulation and aortic baroreceptor afferents are denervated. Then, pressure at carotid sinuses is varied by a pump, either stepwise or sinusoidally. This experimental setup has been used for characterizing the static and dynamic properties of the baroreceptor reflex in dogs [68,69], rabbits [70] and rats [71]. In 1966, Levison et al. [69] described the transfer function from carotid sinus pressure to systemic AP in dogs. The resonance frequency of the loop was located at 0.13 Hz, which is close to the likely frequency of Mayer waves in this species (but the study also suggested that the dog baroreflex system is highly stable at this frequency, see Section 4). In rabbits also, the resonance frequency was close to that of Mayer waves [70], although this result was not noticed by the authors. Importantly, in these and some other [72–74] studies, the most consistent finding has been the presence of a low-pass filter and a fixed time delay between pressure at baroreceptors and systemic AP. In humans, low-pass filter properties of the baroreceptor reflex have been demonstrated (but not quantified) by using cyclic baroreceptor stimulation induced by neck suction [75]. By means of electrical stimulation of carotid sinus nerves, the time delay of human baroreflex responses has been evaluated to ~2.5 s [76], which would be compatible with the generation of a 0.1-Hz feedback oscillation in the loop (see Fig. 2). However, a precise determination of the resonance frequency of the baroreceptor reflex has not been reported in humans. This issue

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Footnote:
2 Actually, this term is rather unfortunate because it introduces confusion with resonance of second order filters.
has been addressed in rats. Transfer functions of baroreflex pathways have been determined in anesthetized rats either by electrically stimulating the aortic depressor nerve at discrete frequencies [15,77,78] or by randomly altering pressure in isolated carotid sinuses [71]. The phase of the transfer function identified by both methods fell to zero at 0.4 Hz (Fig. 3). From these observations, it could be concluded that the baroreflex loop of the rat exhibits a resonance frequency close to that of spontaneous Mayer waves. It is noteworthy that the transfer function from carotid sinus pressure to systemic AP (a preparation involving arterial baroreceptor nerve terminals, [71]) was quite comparable to the transfer function from aortic nerve stimulation to AP (a preparation excluding baroreceptor terminals, [15,77,78]). This indicates that the phase contribution from the arterial baroreceptors was negligible in the frequency range of interest (<1 Hz), which accords with previous studies indicating that baroreceptors do not introduce any significant time delay [79] and show dynamic properties that become important at frequencies above 1 Hz in rats [80].

3.2.4. Between-species differences in the frequency of Mayer waves

Some computer simulations suggest that the fixed time delay is the main factor determining the resonance frequency of the baroreflex system [54,60,77]. Therefore, if the time delay determines the resonance frequency of the loop, then between-species differences in the frequency of Mayer waves should be paralleled by between-species differences in the time delay. First, the latency of neural pathways (conduction time from baroreceptor afferents to postganglionic sympathetic nerves) has certainly an increasing importance as body size increases, because conduction velocity of unmyelinated sympathetic nerves is low (<1 m/s) and does not vary much among species [81,82]. Differences in conduction time are thus likely to account for part of the between-species differences in the overall time delay.
et al. [84,85] have compared the frequency responses of skin vascular smooth muscle cells differ among species. Stauss whether the kinetics of contraction and relaxation of renal SNA and AP fluctuations measured in anesthetized of iliac blood flow in rats [15]. The 0.5-s delay between stimulation of the lumbar sympathetic chain and responses 0.7 s, which is longer than the 0.4-s delay between nerve and responses of renal blood flow was of the order of rabbits, the time delay between stimulation of the renal baroreflex loop also derives from the delay of AP responses in the baroreceptor reflex. However, the frequency of Mayer waves can be similar in animal species with quite different body sizes (e.g., ~0.1 Hz in both humans and cats, and ~0.4 Hz in both rats and mice). Besides nervous conduction times, it has been shown that the overall time delay in the baroreflex loop also derives from the delay of AP responses to sympathetic fluctuations [15,64,83]. It is not known whether the kinetics of contraction and relaxation of vascular smooth muscle cells differ among species. Stauss et al. [84,85] have compared the frequency responses of skin blood vessels to sympathetic modulation in humans and rats and concluded that no species-specific differences are apparent. More recently, Guild et al. [86] reported that in rabbits, the time delay between stimulation of the renal nerve and responses of renal blood flow was of the order of 0.7 s, which is longer than the 0.4-s delay between stimulation of the lumbar sympathetic chain and responses of iliac blood flow in rats [15]. The 0.5-s delay between renal SNA and AP fluctuations measured in anesthetized and conscious rats [64,83] is shorter than the 1-s delay between cardiac SNA and AP fluctuations that has been reported in anesthetized rabbits [70]. It is therefore possible that some factors such as vessel size or geometry of the vascular tree would affect the time delay of the vasculature response.

Finally, it should be mentioned that the relative contribution of cotransmitters (ATP and noradrenaline) released at the vascular neuroeffector junction might also play a role in determining the latency of the vascular response to SNA, since the kinetics of vasoconstriction evoked by P2-purinoceptor stimulation is faster than that evoked by alpha-adrenoceptor stimulation [87,88].

### 4. What determines the amplitude of Mayer waves?

Within a given individual, the amplitude of Mayer waves varies considerably over time. In rabbits, Mayer waves are normally absent or hardly visible unless animals are placed in a hypoxic environment [12] or submitted to moderate hemorrhage [89], both situations resulting in sympathetic activation. In rats, Mayer waves are attenuated during pentobarbital sedation [90], amplified during exposure to an environmental stressor [49] and during moderate nitroprusside-induced hypotension [91], and thus seem to parallel the mean SNA level. In humans also, there appears to be positive relationships between the amplitude of Mayer waves, the strength of the corresponding SNA oscillations and the mean level of SNA [9,10,92]. However, these relationships have a limited within-subject reproducibility over the long-term [93] and are absent when considering groups of individuals [32]. Beyond this phenomenology, there has been very little direct experimental approach to the determinants of Mayer wave’s amplitude. Most of our current working hypotheses derive from modeling studies.

A negative feedback control loop is unstable, i.e., generates self-sustained oscillations of the controlled variable, when gain is unity at the resonance frequency of the loop. Applying this theory to the baroreflex loop, a stable AP oscillation can be sustained in the loop if the pressure-to-pressure open-loop gain is exactly equal to 1 at the resonance frequency. Most models attributing Mayer waves to baroreflex instability have not considered whether it is realistic or not [53,54,58,59,65]. It should be stressed that if the gain at the resonance frequency is >1, it is predicted that the feedback oscillation will progressively grow in amplitude, which theoretically would have destructive potentials. However, this does not happen because a limit is imposed on this amplitude, i.e., the baroreflex system contains nonlinearities [94]. Ringwood and Malpas [60] have shown that a nonlinear model is better able to predict a self-sustained feedback oscillation than does a linear model [57]. These authors are inclined to put the origin of the nonlinearity within the central nervous system. Another possibility is that the limit imposed on the amplitude of
Mayer waves would reflect the saturation of vascular responses, which could in turn be modulated by extrinsic factors.

In two recent modeling studies of cardiovascular variability [64,66], it was considered that the cardiovascular system is continuously exposed to random perturbations, which appear in the form of a 1/f noise in the power spectra of AP [95,96]. In the absence of baroreflex correction, the impact of these perturbations on AP variability is amplified, which is verified in SAD rats [45,46,48,97]. Renal SNA and AP data collected in conscious SAD rats have been used as inputs in a simplified model of the baroreflex system [64]. The baroreflex loop was then closed using the transfer function of nervous baroreflex pathways that had been characterized in a previous study [78]. It was found that the most accurate reproduction of actual SNA and AP variabilities observed in baroreceptor-intact rats was obtained when the pressure-to-pressure open-loop static gain was set at 20–30% of the value leading to instability in the loop, i.e., between 1.5 and 2.2 in absolute values. Such baroreflex gain values agree well with previous reports for the carotid sinus baroreflex gain measured in anesthetized cats and dogs [63], rabbits [94], and rats [71]. In this context, Mayer waves are transient oscillatory responses to hemodynamic perturbations and their amplitude depends both on the strength of these triggering perturbations and on the baroreflex gain. The limitation of this study is that it does not offer any explanation for the well-documented link between changes in the amplitude of Mayer waves and changes in the mean SNA level (see above). In an attempt to simulate Mayer waves in healthy humans, and using parameters derived mainly from dog experiments, it was concluded that the baroreflex system is fundamentally stable in the supine position (open-loop static gain of ~4) but verges on instability in the upright position (gain of ~7). The whole system was extremely sensitive to changes in the feedback gain controlling venous volume [66]. The limitation of this study is that the model does not explain the amplification of Mayer waves occurring in other situations of sympathetic activation such as mental stress [98] and arterial baroreceptor unloading [92]. In addition, the simulated feedback oscillations had a frequency of ~0.07 Hz. Oscillations with a similar frequency have been shown to coexist with 0.1-Hz oscillations [99], but it is not known whether they are also sympathetically mediated.

5. What is the function of Mayer waves?

One important feature of baroreflex transfer functions is that the low-pass filter properties of the vasculature are partly compensated for by the derivative properties of the nervous pathways [70,78]. It is likely that these derivative properties are of utmost importance for translating fast oscillations of baroreceptor afferent activity into fast oscillations of SNA, including those at the frequency of the heart beat. These high-frequency SNA oscillations set the level of sympathetic vasoconstrictor tone, hence contributing to sustain AP [91,100]. In rats, the corollary of the derivative properties is that the gain is amplified in the 0.1–1 Hz frequency range [78], where apparently it is of little or no use because there is little or no AP perturbation to correct [29]. That would mean that Mayer waves are an epiphenomenon of normal baroreflex operation, and have no specific function [64]. It has however been suggested that Mayer waves trigger the liberation of endothelium-derived nitric oxide through cyclic changes in vascular shear stress, which in turn would attenuate their amplitude [101]. This cyclic stimulation of nitric oxide release could be beneficial to end organ function [102].

6. Perspectives

The clinical usefulness of measuring Mayer waves is still awaiting a comprehensive physiological analysis of their underlying mechanisms. While the strength of these AP oscillations show some relationship with the SNA level in healthy subjects, it is strongly reduced in some cardiovascular diseases associated with sympathetic activation, e.g., in congestive heart failure [103,104]. Whether the absence of Mayer waves aggravate the disease or just reflect an impairment of the baroreceptor reflex and/or changes in vascular reactivity is an important unresolved question.

References


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