Oscillations in Mean Arterial Blood Pressure in Conscious Dogs

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SUMMARY Oscillations in mean arterial blood pressure (MABP) with periods near 1.5 hours were observed in conscious male dogs with pressure transducers implanted in their aortas. Cardiac output (CO) was measured with an electromagnetic flow probe implanted about the ascending aorta, and total peripheral resistance (TPR) was calculated as the ratio of MABP to CO. Heart rate (HR) was measured with a cardiotachometer. Coherence functions were calculated among the four variables (MABP, TPR, CO, and HR) to determine significant oscillations at the frequency of the MABP oscillation. Cross-spectral calculations produced phase relationships among the variables. TPR and CO were both oscillating at the same frequency as MABP. However, TPR lagged MABP by 63 degrees, whereas the phase angle for CO and MABP was not significantly different from zero. We concluded that CO must be producing the MABP oscillations, and that the TPR oscillations arose as a reaction to the MABP or CO changes. HR was oscillating in phase with CO, indicating that CO fluctuations were induced in part by HR changes and that the sympathetic nervous system was probably driving the heart. In further experiments, chronic dietary sodium changes did not alter the power spectra for MABP. Thus, the renin-angiotensin system (RAS) was not responsible for the oscillations; conversely, the oscillations were not acting as a signal to the RAS during sodium-deficient states, a condition known to stimulate the RAS.

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CARDIOVASCULAR periodicities have been known since man first felt his pulse, but the heart beat and circadian rhythms are the only frequencies that have attracted much attention. Rhythms lying between these two extremes have been reported for a number of physiological variables (Kleitman, 1963; Krieger et al., 1971; Lenfant, 1967; Ookhtens et al., 1974; Yamaji et al., 1972), but not for the circulation. We speculated, from very general considerations, that flows and pressures might fluctuate periodically at an intermediate frequency (Marsh, 1973), and the major purpose of this paper is to report observations of such oscillations in mean arterial blood pressure (MABP), cardiac output (CO), heart rate (HR), and total peripheral resistance (TPR) in conscious dogs. The period length is 1.5 hours.

An important unresolved question in the area of fluid volume regulation is the identification of the signal that triggers renin release when extracellular fluid volume is depleted, as during dietary NaCl restriction. Arterial blood pressure governs renin release, at least in part, but MABP remains normal over a wide range of renin secretion rates (Davis and Freeman, 1976). We therefore speculated that a blood pressure signal that varied in the frequency domain, rather than in the amplitude domain, might cause the change in renin release when extracellular fluid volume varies (Marsh, 1973). We have tested this hypothesis by examining the effect of dietary NaCl restriction on the MABP oscillations.

Methods

Male mongrel dogs weighing 22-32 kg were divided into two groups. The first was used only for MABP observations, and the second provided data on CO, HR, and TPR, as well as MABP.

Surgery

In the first group, consisting of 10 dogs, a strain-gauge pressure transducer (Konigsberg Instruments) was implanted through a left flank incision into the abdominal aorta under sodium pentobarbital anesthesia. The transducer was placed into the aorta, 7-8 cm distal to the origin of the renal arteries, after an incision had been made in the wall of the aorta large enough to accommodate the head of the transducer. The period length is 1.5 hours.

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flow probe was placed around the root of the ascending aorta through an incision in the 4th intercostal space on the left side. A pressure transducer was sewn into the descending aorta 3-5 cm distal to the origin of the left subclavian artery. The cables from both the flow probe and the pressure transducer were channelled subcutaneously to the back of the neck, where they emerged through a puncture wound in the skin. During an experiment, the transducer was connected to the transducer amplifier, and the flow probe was connected to an electromagnetic flowmeter (model BL 610, Biotronex Laboratory). A cardiotachometer (model 2170, Harvard Apparatus) was used to measure HR and was triggered by the blood pressure signal.

After both surgical procedures, an interval of at least 7 days was allowed for recovery before data were acquired. During this recovery period, three or four injections of 1,000,000 U of penicillin G were administered subcutaneously.

Experimental Procedures

When recordings of data were not being taken, the dogs were housed in an animal care facility where the lights were turned on at 6:00 a.m. and off at 6:00 p.m. Feeding (Purina lab chow) took place once a day near 8:00 a.m. On a recording day the dogs were allowed to eat that morning and were brought to the laboratory shortly thereafter.

On the day of a recording session, the electrical connectors were exposed and connected to appropriate instrumentation. The dogs were tethered by a chain 2 meters long. During the day, they were allowed to sit, lie, or stand as they wished within the 2-meter radius. Occasionally, water was offered to the dogs during an experiment. These sessions usually lasted 8.5 hours.

The measurements were made in a room approximately 5 by 5 m. The room was lit by artificial light and was air-conditioned from a central compressor in the building. The room contained only the measurement and recording equipment, and one investigator, who did not interact with the dog. No other persons were admitted. From the standpoint of temperature, light, noise, or other disturbance, we could detect no periodic external stimulus. No systematic record was kept of the dog's activity during the recording period.

During dietary sodium experiments, the dogs were fed either the normal lab diet or a diet with a low sodium content (Hartroft formula, General Biochemicals). The normal diet contained 0.5% NaCl by weight, whereas the salt-deficient diet is listed as having trace amounts of NaCl. Both specifications are the manufacturer's. Each dog was studied first on one diet, and then on the other. The order of presentation of the diet was varied randomly. The dogs on the low salt diet tended to eat less than when they were fed the normal diet, a response that reinforced the reduction in salt intake. These diets were fed a minimum of 4 days prior to a recording session. Urine samples were taken by suprapubic pressure after an experiment and analyzed for sodium and potassium concentrations to verify that the dogs were in the desired state of salt balance. The urine sodium levels during low and normal diets were about 5 and 140 mEq/liter, respectively. The corresponding urinary sodium-potassium ratios for dogs on these diets were approximately 0.05 and 1.0 for low and normal diets, respectively. Every dog used in this portion of the study showed this response to changes in dietary salt content. In addition, we measured plasma renin activity by radioimmunoassay in two of these dogs. Plasma renin activity increased in one dog by a factor of 4, and in the second by a factor of 2.9 when the low salt diet replaced the normal diet.

Analytical Procedures

Arterial blood pressure, CO, and HR were obtained as analog voltages from their respective amplifiers. The analog data were filtered by a low pass analog filter, then digitized by an analog-to-digital converter. In most cases, data points 20 seconds apart were used in the analyses. TPR was calculated point by point as the ratio of arterial blood pressure and CO. Each set of data was processed to a form suitable for entry into a fast Fourier transform (FFT) algorithm. This process included digital filtering by a low pass Butterworth filter, application of a cosine taper to the ends of the data set, removal of linear trends, and subtraction of the mean value from each data point so that the entire data set had a mean value of zero. The data were then Fourier-transformed by the FFT, and the results were used to calculate power spectral densities, cross-spectral densities, and coherence function estimates (Bendat and Piersol, 1971; Ottes and Enochson, 1972). These calculations are given in the Appendix. Figure 1 illustrates the data analysis scheme for MABP. Analogous procedures were used for CO, TPR, and HR. Computations were carried out on a PDP 8/1 laboratory computer.

Statistical tests involved the calculation of confidence intervals for coherence functions. Coherence is analogous to a correlation, but the coherence function is a more suitable measure for periodic phenomena than is the correlation coefficient. The coherence function can range from zero to one, zero indicating that the two variables are uncorrelated and a value of one that the variables are perfectly correlated. We wanted to know whether any coherence existed at all, i.e., whether the coherence function was different from zero. Thus a 95% confidence interval was calculated about the estimated coherence functions, and if the interval excluded zero, we accepted the coherence function as differing significantly from zero. For phase relationships it was also of interest to know whether variables were in or out of phase, i.e., whether the phase angle was different.
Results

MABP Oscillation

Figure 1 shows a filtered recording of MABP recorded from a dog over a period of slightly more than 8 hours. The record has been subjected to linear trend removal and cosine tapering and consists of 1024 discrete data points spaced equally in time. Figure 2 shows that the principal power from the time series of Figure 1 is in a bandwidth with a frequency of 114 minutes. The results of 33 experiments on 10 dogs were averaged to acquire the result pictured in Figure 3. The peak in this spectrum is at 102.4 minutes, but appreciable power is present in the range 85-256 minutes, indicating that the period of oscillation varies somewhat from the peak value.

Pressure, Flow, and Resistance Experiments

Figure 4 shows data from one experiment. As before, these are computer-generated plots of data that have undergone low pass filtering and have had cosine tapers applied to the ends and linear trends removed. The four panels represent MABP, mean CO, mean TPR, and mean HR, and are displayed as percent variations about the mean value. Similar sets of data were obtained from each experiment. Power spectra were calculated from each individual set of data, and then the spectra were averaged for each variable. The averaged power spectra for the four variables are shown in Figure 5. These spectra are ensemble-averaged over six experiments and frequency-averaged over four adjacent frequency bands. The six experiments were performed on four dogs; two of the animals were used twice. All spectra have the same general appearance, with most of the power at the low frequency portion of the spectrum and little power at the higher frequencies. For MABP, Figure 5A shows that a large amount of power is present in the frequency band centered at a period length of 78.8 minutes. Figure 5B displays the power spectral density for mean CO, and it is apparent that the largest amount of power is also in a frequency band whose period is 78.8 minutes, although there is substantial power in the adjacent frequency bands as well. The HR power spectral density shown in Figure 5C has its peak power at a frequency that is centered about a period of 204.8 minutes. The TPR power spectrum has the greatest amount of power at 48.8 minutes, as shown in Figure 5D.

In Figure 6, the magnitude portion of the cross-spectral density between MAPB and CO, MAPB and TPR, and CO and HR, is illustrated (see also Table 1). The phase angle is shown only at that frequency at which MABP is oscillating, namely 78.8 minutes (Fig. 5A). Since we are interested in the contributions of TPR and CO to the MABP oscillations, the portion of the cross-spectral densities with which we are concerned is that frequency at which MABP is showing a fluctuation. For MABP and CO, the magnitude of the cross-spec-

Figure 1 Typical MABP record from a dog receiving a normal diet. The plot is generated by computer from the raw data after low pass filtering, linear trend removal, and cosine tapering.

Figure 2 Power spectrum from the time series of Figure 1.

Figure 3 Ensemble average power spectrum for 33 MABP experiments. The peak power has a frequency of 0.6 cycle/hr.
A MEAN ARTERIAL BLOOD PRESSURE

PERCENT OF MEAN VALUE

0 -50% 0 50%

C CARDIAC OUTPUT

PERCENT OF MEAN VALUE

0 -50% 0 50%

D HEART RATE

PERCENT OF MEAN VALUE

0 -50% 0 50%

FIGURE 4 Computer-generated plots of raw data for one experiment with low pass filtering, cosine tapering, and linear trend removal applied. The four panels represent (A) mean arterial blood pressure, (B) cardiac output, (C) heart rate, and (D) total peripheral resistance. The data are plotted as percent variations of the mean value. The mean values are (A) 103 mm Hg, (B) 2.7 liters/min, (C) 118 beats/min, and (D) 2.2 peripheral resistance units-seconds.

The coherence function for MABP and CO at the frequency of MABP oscillation was estimated as 0.27. The coherence function estimate for MABP and TPR at the same frequency was 0.19 and for CO and HR was 0.20. We determined 95% confidence intervals for all three coherence function estimates, and all three were significantly greater than zero.

Dietary Sodium Experiments

Figure 7 shows the averaged MABP spectra from dogs on both normal and low sodium diets. Each spectrum is the average of 10 experiments. Both spectra show a strong oscillation with a period near 90 minutes, but there is no significant difference between them, either in power or in the location of the bandwidth with greatest power. There was also no difference between the two states when the comparison was made on an intra-animal basis.

Discussion

Our data reveal a persistent free-running oscillation in HR, CO, MABP, and TPR, all with periods of about 90 minutes. Several factors preclude a more precise specification of the frequency. Probably the most important of these is the problem of constancy of the oscillation, often referred to as stationarity. Application of the time series analytic methods we have used assumes that the periodic signal, however much corrupted by noise, remains constant over the period of observation. This duration in our experiments was over 8 hours. Since there is a circadian activity cycle that affects cardiovascular performance, and since our observation period lasted one-third of that period, it is a priori unlikely that the dogs in this study satisfied the criterion of stationarity completely. We have attempted to deal with this problem by removing linear trends from the raw data, but this procedure assumes that the oscillation of primary interest and the trend that is being removed simply add, i.e., that the underlying system is linear. The system regulating cardiovascular performance is highly nonlinear, so that if there is an oscillator driving the fluctuations we observed, it will probably become entrained in other rhythms, particularly slower ones, and the effect will be to broaden the peak in the power spectrum over several adjacent bandwidths.

Another reason that a precise frequency cannot be given is that we have averaged the power spectra from all the dogs in our study to arrive at an ensemble power spectrum for each variable. Inter-animal variability tends to broaden the power spectrum. The time series techniques also contribute to the imprecision of the estimate of period length. The power spectrum calculation partitions the variance of the original data set into equally spaced frequency bandwidths. Since the period length is simply the reciprocal of frequency, the length is shortest at the high frequency end of the spectrum and longest (or least precise) at the low frequency
end. We could have obtained better estimates by prolonging the length of the observation, but such a decision would have made the stationarity problem even more serious. The 8.5-hour observation therefore represents a compromise between these two conflicting demands.

Measurement noise probably contributed little to the imprecision of the estimates, particularly in the MABP determination. The transducers we used drifted less than 1 mm Hg over 8 hours when placed in saline, and the drift was not periodic. Of the four variables we examined, TPR is probably the most susceptible to measurement noise, because it is calculated as the quotient of two variables, and therefore contains the noise of both.

The phase angle relationships permit us to reach certain conclusions about the cause of the oscillations. Because of the low frequency of these changes, there should be no phase lag between MABP and whichever of CO and TPR is causal. Since there is a significant lag between TPR and MABP, we reject oscillations in TPR as the cause of MABP fluctuations. On the other hand, we could detect no phase lag between CO and MABP, and

Table 1 Summary of Phase Angles and Coherence Function Estimates

<table>
<thead>
<tr>
<th></th>
<th>Pressure-CO spectrum</th>
<th>Pressure-TPR spectrum</th>
<th>CO-HR spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase angle</td>
<td>33.75° (7.4)</td>
<td>-62.58° (-13.7)</td>
<td>-6.03° (1.32)</td>
</tr>
<tr>
<td>95% confidence interval for phase angle</td>
<td>-3.99° &lt; φ ≤ 71.49° (-0.88) (15.89)</td>
<td>-112.85° &lt; φ ≤ -12.31° (-24.76) (-2.72)</td>
<td>-54.63° &lt; φ ≤ 42.57° (-11.96) (9.32)</td>
</tr>
<tr>
<td>Coherence function estimate</td>
<td>0.2708</td>
<td>0.1904</td>
<td>0.1982</td>
</tr>
<tr>
<td>95% confidence interval for coherence function</td>
<td>0.0706 &lt; γ² ≤ 0.4729</td>
<td>0.0226 &lt; γ² ≤ 0.3290</td>
<td>0.0277 &lt; γ² ≤ 0.4004</td>
</tr>
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Estimates are computed at the frequency where arterial pressure is oscillating (period = 78.8 minutes).
The equivalent time periods for the phase angles (in minutes) are given in parentheses.
none between HR and CO. These phase relationships suggest that oscillations in CO, possibly caused in part by oscillations in HR, provide the primary cause of the MABP fluctuation. One plausible interpretation of the TPR oscillations is that they represent an autoregulatory adjustment to the variable peripheral flow caused by the MABP oscillations.

FIGURE 6 Average cross-spectra between mean arterial blood pressure and cardiac output as (mm Hg) (liters/min)/hr⁻¹, mean arterial blood pressure and total peripheral resistance as (mm Hg) (peripheral resistance units-seconds)/hr⁻¹, and cardiac output and heart rate as (liters/min) (beats/min)/hr⁻¹. The phase angle is shown in each spectrum at the frequency at which mean arterial blood pressure is oscillating (Fig. 5A).

It seems unlikely that variations in HR alone, as might be caused by variations in vagal efferent activity, could cause MABP to vary as much as it did in these experiments. Variable cardiac sympathetic activity that would induce both inotropic and chronotropic effects could produce the observed MABP oscillations. There is nothing in our data to rule out simultaneous and complementary changes in both cardiac vagal efferent and cardiac sympathetic activity. The significant phase lag between TPR and the other variables does suggest that if periodically varying cardiac sympathetic firing does occur, there is no concomitant variation in peripheral sympathetic vasomotor activity.

The sino-aortic baroreceptor system is either bypassed during the genesis of these oscillations or is ineffective in preventing them. In response to a rising pressure, cardiac slowing and a reduction in CO would be the expected responses of the baroreceptor reflex system. This behavior is not seen; MABP and CO rise in unison. Thus, changes in MABP due to hydrostatic changes, such as encountered in postural shifts (Lamberti et al., 1968), which are mediated by the baroreceptors, are not involved in the fluctuations. Any changes induced by TPR changes can be excluded also, since TPR changes appear to be secondary to MABP fluctuations rather than casual. This conclusion is at variance with the idea that CO is determined primarily by the sum of peripheral tissue needs (Coleman et al., 1974).

At this point we can only speculate about the origin of these oscillations. The question remains open as to whether they are intrinsic spontaneous oscillations of the blood pressure-regulating system or the result of entrainment by another system interacting in the central nervous system with the blood pressure-regulating system. A rest-activity cycle with a period of near 90 minutes that continues 24 hours a day has been proposed in man (Kleitman, 1963). Cyclical rapid eye movement
sleep is a reflection of this cycle during sleep, whereas, during wakefulness, activity waxes and wanes also with a period of near 90 minutes. This rhythm could reside in or be transmitted to the autonomic nervous system, where sympathetic and/or parasympathetic control of the heart could induce periodic CO changes that could affect MABP. Indeed, an oscillation in human HR with a period of near 90 minutes has been reported previously (Orr and Hoffman, 1974). Since no systematic observations were made of animal behavior during our experiments, we are unable to correlate a rest-activity cycle with our MABP oscillations. Other causal possibilities include: (1) an effect of changing reticular activating system drive to skeletal muscles, which would alter vascular capacity; (2) periodic changes in vasopressin secretion, which can be a significant pressure controller under some circumstances (Cowley et al., 1978); and (3) an effect of sympathetic drive, primarily on capacitance vessels. None of these possibilities excludes the others, and all appear to be consistent with our data. Whatever the cause of the oscillation, however, we wish to emphasize that these fluctuations affect flow and impinge on pressure-sensitive receptors everywhere, including those that mediate renin release. Whether the fluctuations in MABP affect renin release would depend on the frequency response of the renal baroreceptor. Other hormones are released at similar frequencies (Krieger et al., 1971; Yamaji et al., 1972).

The last series of experiments tested the possibility that variation in the frequency domain of MABP could provide a signaling pathway to the renin-angiotensin system during chronic sodium deficiency. The frequency content of the MABP power spectral density was compared during a normal diet and a sodium-deficient diet. No significant difference in the respective power spectra could be detected. Thus, whatever the signal may be that alters renin release during the change in sodium states, it does not involve an alteration in any aspect of the blood pressure we have examined. Altered responsiveness of the renal baroreceptor might be responsible, so that blood pressure might still be the signal, but the problem then remains to determine what alters receptor sensitivity.

**Appendix**

The time series analysis we performed to characterize the data included computation of power spectral densities, cross-spectral densities, and coherence functions. A fast Fourier transform (FFT) algorithm was used to calculate power spectral density and cross-spectral density estimates, and these, in turn, were used to derive coherence functions.

The data were first obtained in analog form and put through analog low pass filters. The filters used for the MABP and CO signals were fourth-order, two-stage, active filters. The corner frequency for these filters was near 0.06 Hz, so that higher frequencies in the signal were attenuated. These filters were designed to remove variations due to cardiac and respiratory cycles. Aliasing errors were eliminated by these filters so long as the sampling interval did not exceed 5 seconds. HR was filtered by using the analog filter supplied with the cardiotachometer.

The filtered analog signals were sampled every 5 seconds by analog-to-digital converters. By selecting every nth point of a data set, the sampling interval could be changed to 5n seconds. Varying the sampling interval, in turn, altered the range of frequencies observed later in the spectral analysis. Thus, the choice of sampling was dependent on the frequencies to be investigated. When we were confident that an oscillation existed with a period near 1-2 hours, a sampling interval of 30 seconds was used; every sixth data point was used for analysis. A total of 1024 data points were analyzed from each experiment.

From the data, now in the form of a set of discrete points, each separated by a constant time interval, TPR was calculated, point by point, from the MABP and CO data points. This procedure generated a new time series, so that in all there were now four sets of points, one each for MABP, CO, TPR, and HR. Since the analog filter could prevent aliasing only if the sampling interval was not more than 5 seconds, a digital low pass filter was applied to prevent aliasing with the large sampling intervals. A third-order Butterworth filter was employed for this purpose (Rader and Gold, 1967).

Linear trend removal, a procedure that applies a form of high pass filtering, was next applied to the data. A linear trend in the data is viewed as a small portion of a cycle whose period is large relative to the data record length. If not eliminated, such trends distort the spectral analysis in the low frequency range. Since the mean value of a data record does not affect the spectral analysis, the data are converted to zero mean to save computation time during FFT calculations. We used a linear least-squares fit to the data and then subtracted this fit from the data to create a data set with zero mean and zero slope.

A cosine taper was applied to the first and last 10% of the data to alleviate leakage in the spectral analysis. During spectral analysis, the data are viewed as an infinitely long record multiplied by a boxcar function which has a value of unity during the time the data record exists and zero at all other times. When the data and the boxcar function are subject to Fourier transformation, the sharp discontinuities at the ends of the boxcar cause leakage; power that should be attributed to one frequency becomes spread out onto adjoining frequencies. Thus, if the discontinuities were not smoothed by tapering, the resultant power spectrum might lead to a spurious result. Although leakage cannot be
totally eliminated, because the data record has finite length, tapering reduces this leakage considerably.

The data were subject to Fourier transformation with an FFT algorithm. The Fourier components, $X_k$, are defined as:

$$X_k = \sum_{i=1}^{n} x(i) \exp \left[ -j \frac{2 \pi k i}{n} \right].$$

where $x(i) =$ $i$th data point, $j = \sqrt{-1}$, and $n = 1024$ data points. These components are defined at the frequencies:

$$f_k = \frac{k}{nh},$$

where $h$ = sampling interval.

The particular FFT routine used computed $X_k$ from the data points, $x(i)$, by carrying out the following computations:

$$s(1) = \sum_{i=1}^{n} x(i),$$

$$s(k) = \sum_{i=1}^{n} x(i) \cos \left[ \frac{2 \pi (k - 1) i}{n} \right]$$

$$s(k) = \sum_{i=1}^{n} x(i) \sin \left[ \frac{2 \pi (k - n/2 + 1) i}{n} \right]$$

where $k = 2, 3, \ldots, k = n/2$.

$X_k$ are then computed from $s(k)$:

$$X_1 = s(1),$$

$$X_k = s(k) + js(k + n/2 + 1)$$

where $k = k - n/2 + 1, k = n/2 + 2, \ldots, n$.

From these values of $X_k$, the power spectral estimates, $G_k$, were formed:

$$G_k = \frac{2h}{n} |X_k|^2.$$

$G_k$ is the average power over the frequency band, $\frac{1}{nh}$, centered at a frequency $f_k$. These values were multiplied by the factor $\frac{1}{0.875}$, to compensate for the loss of variance due to the cosine tapering applied earlier. The power spectral density plot, or periodogram, is a graph of $G_k$ plotted as a function of frequency, $f_k$.

Cross-spectral densities were also computed from the output of the FFT routine. A cross-spectral density is calculated between two variables, $x(i)$ and $y(i)$. Both sets of variables are subject to Fourier transformation to create $X_k$ and $Y_k$. From these two, the cross-spectral density estimates are calculated:

$$G_{xy}(f_k) = \frac{2h}{n} \sum_{i=1}^{n} X_k^* Y_k,$$

where $X_k^*$ = complex conjugate of $X_k$. $G_{xy}(f_k)$ are complex numbers of the form:

$$G_{xy}(f_k) = C_{xy}(f_k) - jQ_{xy}(f_k).$$

The cross-spectral density has a magnitude and a phase angle determined by:

$$\text{Magnitude} = G_{xy}(f_k) = \sqrt{C_{xy}^2(f_k) + Q_{xy}^2(f_k)},$$

$$\text{Phase angle} = \phi(f_k) = \frac{360}{2\pi} \arctan \left[ \frac{Q_{xy}(f_k)}{C_{xy}(f_k)} \right].$$

$G_{xy}(f_k)$ was also multiplied by the factor $\frac{1}{0.875}$ to correct for cosine tapering.

Ensemble and frequency averaging were used to characterize the population to improve the spectral estimates. Ensemble averaging consists of combining spectral estimates computed from different time segments. In our studies, data recorded from different experiments were averaged together. If $G_{xy}$ are the spectral estimates from $i$ different experiments, then the averaged estimate, $\bar{G}_k$, is:

$$\bar{G}_k = \frac{1}{n} \sum_{i=1}^{n} G_{xy}.$$

where $n = \text{number of time segments averaged}$.

Frequency averaging is averaging over adjacent frequency bands in the power spectrum. The resulting averaged spectral estimate is now the value for a new frequency band which covers all the frequency bands averaged. If $m$ different frequency bands are averaged, the new estimate becomes:

$$\bar{G}_k = \frac{1}{m} \sum_{i=1}^{m} [G_{xy} + G_{xy+1} + \ldots + G_{xy+m-1}],$$

where $m = \text{number of frequency bands averaged}$. The new frequency band which results from frequency averaging is $\frac{m}{nh}$.

A coherence function, $\gamma_{xy}^2(f_k)$, was calculated between an input, $x(t)$, and an output, $y(t)$, of a system. In these studies, the output was considered to be MABP oscillations and the possible inputs to the system, CO and TPR oscillations. In addition, HR oscillations were viewed as a possible input to CO variations. The coherence function represented the fraction of the variance in the output that was due to variance in the input. If the coherence function was zero, none of the output variance was due to the assumed input, and thus this input was in
fact not an input to the system. Conversely, a coherence function with a value of 1.0 meant that all of the output variance was accounted for by the input variance. The coherence function was calculated from the cross-spectrum between the input and output and the power spectra of the individual input and output:

$$\gamma_{xy}(f_k) = \frac{|G_{xy}(f_k)|^2}{G_{xx}(f_k)G_{yy}(f_k)},$$

where $G_{xx}(f_k)$ is cross spectrum between x and y, $G_{xx}(f_k)$ = power spectrum of x, and $G_{yy}(f_k)$ = power spectrum of y.

The statistical testing in this study involved the computation of confidence intervals. A primary concern was whether the coherence function between CO and MABP or TPR and MABP equaled zero. If either was zero, CO or TPR could be excluded as being a contributing factor toward the oscillations in MABP. Thus 95% confidence intervals were estimated. If zero was excluded from this interval, the coherence function was accepted as being significantly different from zero, and vice versa. A transformation was used to facilitate a confidence interval calculation:

$$w(f) = \frac{1}{\ln \left( \frac{1 + \gamma_{xy}(f)}{1 - \gamma_{xy}(f)} \right)} = \text{tanh}^{-1} \gamma_{xy}(f),$$

where $\gamma_{xy}(f) = \sqrt{\gamma_{xy}^2(f)}$. The variable $w(f)$ has an approximately normal distribution. Thus, a 100 $(1 - \alpha)$% confidence interval for the coherence function is:

$$\tanh \left( w(f) - (n - 2)^{-1} - \sigma_z z_{n/2} \right) < \gamma_{xy}(f) < \tanh \left( w(f) - (n - 2)^{-1} + \sigma_z z_{n/2} \right),$$

where $n = \text{degrees of freedom}$, $\sigma_z^2 = (n - 2)^{-1}$ = variance of $w(f)$, and $z_{n/2} = 100\alpha$ percentage point of the standard normal distribution.

A confidence interval for the cross-spectrum phase angle was also calculated. For a 100 $(1 - \alpha)$% confidence interval, the quantity $\hat{r}(f)$ was first determined (Bendat and Piersol, 1971):

$$\hat{r}^2(f) = \frac{2}{n - 2} F_{2,n-2n} \left[ 1 - \gamma_{xy}(f) \right] \frac{G_{yy}(f)}{G_{xx}(f)},$$

where $n = \text{degrees of freedom}$, and $F_{2,n-2n} = 100\alpha$ percentage point of F distribution with $n_1 = 2$ and $n_2 = n - 2 \text{ degrees of freedom}$. The quantity, $\Delta \phi(f)$, is then found:

$$\Delta \phi(f) = \sin^{-1} \left[ \frac{\hat{r}(f)}{\sqrt{H(f)}} \right],$$

where $\hat{r}(f) = \sqrt{\hat{r}^2(f)}$, and $H(f) = \frac{G_{xx}(f)}{G_{xx}(f)}$. The confidence interval for the real phase angle, $\phi(f)$, was derived from the estimated cross-spectrum, phase angle, $\phi(f)$, and $\Delta \phi(f)$:

$$\phi(f) - \Delta \phi(f) \leq \phi(f) \leq \phi(f) + \Delta \phi(f).$$

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