Published in final edited form as:

Physiol Meas. 2013 September ; 34(9): . doi:10.1088/0967-3334/34/9/1207.

Cardiac Output is Not a Significant Source of Low Frequency Mean Arterial Pressure Variability

F Aletti¹, RL Hammond², JA Sala-Mercado², X Chen³, DS O'Leary², G Baselli¹, and R Mukkamala³

¹Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Piazza Leonardo da Vinci, 31, 20133 – Milan - Italy

²Department of Physiology and The Cardiovascular Research Institute, Wayne State University School of Medicine, Detroit, MI, U.S.A

³Department of Electrical and Computer Engineering, Michigan State University, East Lansing, MI, U.S.A

Abstract

Spontaneous mean arterial pressure (MAP) variability may be mainly due to fluctuations in cardiac output (CO) and total peripheral resistance (TPR). While high frequency (HF ~ 0.25 Hz) oscillations in MAP are ultimately driven by respiration, the source of low frequency (LF ~ 0.1 Hz) fluctuations has not been fully elucidated. It is known that CO buffers these oscillations, but there is no evidence on its potential role in also generating them. The main goal was to determine whether CO is a source of LF variability in MAP. Six dogs were chronically instrumented to obtain beat-to-beat measurements of CO and MAP while the dogs were fully awake and at rest. A causal dynamic model was identified to relate the fluctuations in CO to MAP. The model was then used to predict the MAP fluctuations from the CO fluctuations. The CO fluctuations were able to predict about 70% of the MAP oscillations in the HF band but showed no predictive value in the LF band. Hence, respiration induces CO fluctuations in the HF band that, in turn, cause MAP oscillations, while TPR fluctuations appear to be the dominant mediator of LF fluctuations of MAP. CO is not a significant source of these oscillations, and it may only be responsible for dampening them, likely through the baroreflex.

Keywords

arterial blood pressure variability; cardiac output; mathematical model; total peripheral resistance

1. Introduction

It is well appreciated that arterial blood pressure (ABP) spontaneously fluctuates on a beat-by-beat basis about its average value. Spectral analysis has shown that these ABP oscillations appear both in the low frequency (LF ~ 0.1 Hz) and high frequency (HF ~ 0.25 Hz) bands (Akselrod *et al* 1981, Akselrod *et al* 1985, Pagani *et al* 1986). The sources of these fluctuations have captured the interest of a number of investigators.

Akselrod *et al.* measured beat-to-beat fluctuations in ABP and heart rate (HR) before and after atrial pacing in conscious dogs (Akselrod *et al* 1985). The elimination of HR variability caused ABP oscillations to (a) vanish in the HF band and (b) show a tendency to increase in

the LF band. Hence, HR variability induces ABP variability in the HF band. The origin of this variability is surely respiration. By contrast, ABP variability may be responsible for HR variability in the LF band via the baroreflex. These authors hypothesized that the source of this variability is total peripheral resistance (TPR) changes due to local control mechanisms.

O'Leary and Woodbury measured beat-to-beat fluctuations in mean arterial pressure (MAP) and cardiac output (CO) before and after the experimental elimination of CO fluctuations in conscious dogs (O'Leary and Woodbury 1996). To keep beat-to-beat CO virtually constant, they applied a previously developed technique (Wyss *et al* 1982), which involved induction of atrioventricular (AV) block followed by computer control of the ventricular rate by means of stimulating electrodes so that the product of the imposed ventricular rate and stroke volume (i.e., CO) did not vary over time. The elimination of CO variability caused MAP oscillations to (a) vanish in the HF band (which is consistent with the findings of Akselrod *et al.* (Akselrod *et al* 1981)) and (b) increase in the LF band. Since MAP is equal to the product of CO and TPR, the authors concluded that MAP oscillations in the LF band are due to TPR fluctuations and that CO fluctuations serve to buffer LF oscillations in MAP.

Elstad *et al.* measured beat-to-beat fluctuations in MAP and CO in healthy humans (Elstad *et al* 2011). They estimated TPR for each beat as the ratio of MAP and CO and then applied phase and coherence analysis to the measured and estimated oscillations in the LF band. TPR and MAP fluctuations were in phase, whereas CO variability was in opposition of phase with TPR oscillations. Hence, the authors concluded that TPR fluctuations are a source of LF MAP oscillations and that CO has a buffering effect on these oscillations in humans.

These and other investigators (e.g., Rimoldi *et al* 1990, Wang *et al* 1995, Cevese *et al* 1995, Just *et al* 1995, Julien 2006) have provided great insight into the origin of beat-to-beat ABP variability. However, to our knowledge, no one has studied the role of CO as another possible source of the slow beat-to-beat variability in ABP. Indeed, Elstad *et al.* left this problem open by stating that "CO variations could both produce and buffer variations in MAP" (Elstad *et al* 2011).

The main goal of this work was to shed light on the role of CO fluctuations as a source of MAP oscillations in the LF band. We measured beat-to-beat fluctuations in MAP and CO from conscious, resting dogs and analysed how well the CO fluctuations are able to predict the MAP variability in the LF and HF bands by means of a causal dynamic model. If CO turned out to be highly predictive of the MAP fluctuations, we could conclude that CO is a significant source of these fluctuations. Conversely, if CO turned out to show little predictive value, then we could conclude that CO is not a major source of the variability. Our results showed that CO poorly contributed to the prediction in the LF band, thus providing evidence that CO is not a significant source of slow oscillations in MAP during normal physiologic conditions.

A preliminary version of this manuscript has been reported in abbreviated form (Aletti *et al* 2010).

2. Materials and Methods

2.1. Experimental Protocol

Six adult mongrel dogs (20–25 kg) of either gender were studied on multiple days. The protocol was reviewed and approved by the Wayne State University Animal Investigation Committee and the Michigan State All University Committee on Animal Use and Care.

Chronic instrumentation was installed using a sterile surgical procedure under general anaesthesia. A thoracotomy was performed, and an ultrasonic flow probe (Transonic Systems) was placed around the aortic root for measurement of a CO signal. An indwelling 20ga. polyethylene catheter (Norton) was placed in the abdominal aorta for measurement of an ABP signal. To address aims beyond this study, pacing electrodes (Medtronic, Inc.) were placed on the right atrium and ventricle, and connected to an implantable DDD pacemaker (Medtronic, Inc.). The AV node was ablated by injection of formalin (Steiner and Kovalik 1968), and ventricular fixed rate pacing (VOO) was instituted at 90 beats per minute. After placing additional instrumentation, the chest was evacuated and closed in layers, with all leads, cables, and catheters tunnelled subcutaneously to the interscapular site for exit. The dog was then allowed to recover for 10–14 days. After the first post-operative night, neural control of HR was re-established by programming the implanted pacemaker to AV sequential mode (DDD). This mode was maintained thereafter, except for several two to three hour experiments that were unrelated to this study.

During the experimental sessions, the flow probe was connected to a flowmeter (Transonic Systems), and the aortic catheter was connected to a pressure transducer (Abbott Transpac IV) interfaced to a signal conditioner (Gould, 4600 series). The hemodynamic measurements were then continuously recorded for about 15 minutes at a sampling frequency of 300 Hz (Dataq Inst) while the dog lay quietly awake.

2.2. Pre-Processing of the Signals

Approximately 270 seconds of simultaneous, stationary segments of the ABP and CO signals were selected for each dog (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The CO signals were utilized to identify each cardiac cycle. The ABP and CO signals were then averaged over each cardiac cycle, thus obtaining MAP and CO beat series. The beat series were subsequently resampled to 2 Hz time series (Mukkamala *et al* 2003). More specifically, each beat series was transformed into a stepwise continuous-time process whose value corresponds to either the MAP or CO of the current cardiac cycle for a time period of that cycle. The continuous-time process was then sampled to 2 Hz with an anti-alias filter whose impulse response was a unit-area boxcar of 1 second duration. (The sampling frequency was chosen based on the observed Nyquist rate of the signals. Further, varying the sampling frequency from 1 to 4 Hz had negligible impact on the results.) Finally, zero-mean, unit-less MAP ($y(t)$) and CO time series ($x(t)$) were obtained by subtracting their respective mean values and dividing by these values.

2.3. Prediction of MAP Variability

In steady-state, MAP is simply the product of CO and TPR. On a beat-to-beat basis, the relationship between CO and MAP is much more complicated. This relationship is dynamic (i.e., characterized by a difference equation rather than an algebraic equation) with other variables such as arterial compliance involved. However, since the changes in these variables are relatively small during resting conditions, the dynamic relationship may at least be well approximated as linear and time-invariant (Xiao *et al* 2005). Further, CO and MAP fluctuations are related in a closed-loop manner.

The following parameterized impulse response model was therefore used to predict the present value of MAP oscillations from the past values of CO fluctuations:

$$y(t) = \sum_{i=0}^m h(i) \cdot x(t-i) + n(t) \quad n(t) = \sum_{i=1}^p a(i) \cdot n(t-i) + w(i) \quad (1)$$

Here, $h(t)$ defines the unknown impulse response coupling the fluctuations in CO ($x(t)$) to MAP ($y(t)$), whereas the unknown residual white noise error $w(t)$ and the unknown autoregressive (AR) parameters $a(t)$ specify the noise term $n(t)$. The term m defines the unknown duration of $h(t)$, while the term p indicates the unknown number of AR parameters. Note that for reliable identification of open-loop systems operating in closed-loop, causality of $h(t)$ is enforced by virtue of setting the lower limit of the summation to zero and the $n(t)$ model (lower equation) is employed (Baselli *et al* 1988, Baselli *et al* 1994, Xiao *et al* 2006). The noise term $n(t)$, by mathematical definition, is the component of the MAP fluctuations that is uncorrelated with, or cannot be predicted by, the CO fluctuations. This term is expected to largely represent TPR fluctuations (O'Leary and Woodbury 1996). For example, as frequency decreases, $n(t)$ should increasingly reflect fluctuations in TPR (that are orthogonal to the CO fluctuations). However, $n(t)$ may also be due to arterial compliance changes, the direct effects of respiratory-induced intrathoracic pressure variations on the aorta, signal measurement noise, and other factors. In the following, we will refer to $n(t)$ as the “non-CO” related component of MAP variability.

All unknowns are estimated from $x(t)$ and $y(t)$ by minimizing the energy in $w(t)$ using a weighted principal component regression system identification technique. This technique is described in detail elsewhere (Xiao *et al* 2006, Chen and Mukkamala 2008). The basic idea of the technique is to let the data determine the basis functions for $h(t)$ while invoking pre-knowledge that the present value of $y(t)$ is more dependent on the recent values of $x(t)$ than the distant values. The basis functions are specifically established as the major principal components of the covariance matrix of $x(t)$ pre-multiplied by a diagonal matrix whose non-zero elements decay exponentially so as to reflect this pre-knowledge. The optimal exponential weighting decay rate is estimated as part of the identification process. This technique approximately represents $h(t)$ with damped sinusoidal basis functions that reflect the dominant frequency content of $x(t)$. Hence, only a small number of basis functions (or weighted-principal components) are needed, thereby decreasing the number of parameters for estimation and thus the estimation error variance.

Once the unknowns are estimated, the component of the MAP fluctuations that can be predicted by the CO fluctuations ($y_p(t)$, i.e., “predicted MAP”) is computed as follows:

$$y_p(t) = \sum_{i=0}^{\hat{m}} \hat{h}(i) \cdot x(t-i) \quad (2)$$

where the hat symbol indicates estimate. The term $n(t)$ is then simply given as $y(t)-y_p(t)$.

2.4. Frequency Domain Analysis

Following system identification in the time domain, analysis in the frequency domain was carried out. More specifically, power spectra of the fluctuations in MAP ($y(t)$), CO ($x(t)$), predicted MAP ($y_p(t)$), and the non-CO related component of MAP fluctuations ($n(t)$) were estimated by AR analysis. The powers in the LF band (0.02–0.10 Hz) and HF band (0.10–0.40 Hz) in these spectra were computed consistent with previous work (O'Leary and Woodbury 1996). Finally, to quantify the ability of the CO fluctuations to predict the variability in MAP in the LF and HF bands, the ratios between the non-CO related component and measured MAP powers in the LF and HF bands were computed. Note that the non-CO component power plus the predicted MAP power is theoretically equal to the MAP power. (However, in practice, this equality may not be exactly achieved due to spectral estimation error). So, a zero power ratio would indicate that the CO fluctuations had perfectly predicted the MAP fluctuations, whereas a unity power ratio would denote that the CO fluctuations had no predictive value. Also note that the two power ratios are actually

equivalent to the *causal* coherence function (Porta *et al* 2002, Porta *et al* 2009) integrated over the LF and HF bands. The integration was done to arrive at numerical values that could be statistically compared as described below. The causal coherence function itself did not provide added insight here. A minor difference is in our definition of coherence. As just stated a power ratio value of zero (rather than unity) indicates a perfect causal relationship, whereas a power ratio value of unity (instead of zero) indicates no relationship.

2.5. Statistical Analysis

One or two sample t-tests to detect a difference or equivalence were used to compare the power ratios. Logarithmic transformation of the data was applied before performing the statistical tests to make them more normally distributed. A p-value < 0.05 was considered significant.

3. Results

The Table shows the LF powers in the MAP and CO oscillations (relative to the sum of their LF and HF powers) for each of the six dogs. The MAP fluctuations were larger in the LF band (LF MAP power of $63 \pm 11\%$), whereas the CO fluctuations showed a larger HF component (LF CO power of $37 \pm 12\%$). In dogs 2 and 3, the HF power in MAP was relatively small, so there was little to predict. As a result, these subjects were not considered for further analysis of the HF MAP oscillations. However, for this band, it was previously demonstrated that CO fluctuations explain most of the MAP variability (O'Leary and Woodbury 1996).

The Table also shows the MAP prediction results for each of the six dogs. The amount of LF power in MAP predicted or explained by the non-CO related component was 0.99 ± 0.04 , while the amount of HF MAP power explained by the non-CO component was 0.30 ± 0.04 . These two values were statistically different according to a two sample t-test ($p = 0.04$). Further, the former value was statistically equivalent to unity (or, more precisely, fell within an interval between 0.9 and 1.1) according to a one sample t-test for equivalence ($p = 0.03$). Hence, CO fluctuations were able to predict about 70% of the HF oscillations in MAP but could not predict any of the LF MAP oscillations. The non-CO component was LF dominant even in the presence of non-trivial HF MAP oscillations (LF non-CO component power of $78 \pm 2\%$).

Figures 1 and 2 provide examples of the fluctuations in MAP, predicted MAP, and the non-CO related component in both the time and frequency domains for dogs 1 and 2.

In the first example, the predicted and measured MAP fluctuations showed agreement in the HF band (i.e., respiratory frequency), while the noise term non-CO component and MAP fluctuations agreed more in the LF band (e.g., at about 65 and 100 seconds). In the second example, since HF MAP oscillations were not evident, the non-CO component and MAP fluctuations closely corresponded to each other throughout.

In sum, CO was the prevalent component in explaining the fast MAP oscillations (i.e., in the HF band) but was of little value in predicting the slow MAP oscillations (i.e., in the LF band).

4. Discussion

A number of investigators have provided important insights into the genesis of beat-to-beat oscillations in ABP. In the HF band, respiration causes HR variations via a neural coupling that then cause ABP fluctuations (Akselrod *et al* 1985). In the LF band, TPR fluctuations are

a source of ABP fluctuations, and CO variability buffers these fluctuations (Wang *et al* 1995, O'Leary and Woodbury 1996, Elstad *et al* 2011). The TPR fluctuations may actually be elicited by central mechanisms (Cevese *et al* 1995, Just *et al* 1995) rather than local mechanisms as hypothesized by Akselrod *et al*. (Akselrod *et al* 1985). CO could also be a source of LF ABP variability, for instance through a central oscillator that perturbs CO and, in turn, produces ABP oscillations. However, the question of whether CO fluctuations are actually another source of LF ABP variability during normal physiologic conditions has remained unanswered so far (Elstad *et al* 2011). Our main goal was to answer this question.

Our strategy was to employ a mathematical analysis to determine the extent to which the past values of CO fluctuations are able to predict the present value of ABP oscillations via a parameterized impulse response model. The greater the predictive capacity, the more important CO fluctuations are as a source of ABP variability. We chose to study animals rather than humans in order to obtain accurate measurements of both CO and ABP fluctuations via an aortic flow probe and intra-arterial catheter. We sought to predict fluctuations in MAP rather than systolic or diastolic ABP, because the unpredicted or non-CO related component could be interpreted more easily (i.e., largely due to TPR fluctuations) (O'Leary and Woodbury 1996). (Note that others have investigated the genesis of systolic and diastolic ABP variability but with the different goal of elucidating the complexity of closed-loop cardiovascular regulatory mechanisms (Aletti *et al* 2009, Aletti *et al* 2012). We represented the impulse response with only moving average parameters instead of both AR and moving average parameters so that the predicted MAP fluctuations and non-CO component would be uncorrelated and therefore easier to interpret. Finally, we used a weighted principal component regression technique to more reliably identify the impulse response (Xiao *et al* 2006, Chen and Mukkamala 2008).

Our mathematical analysis brought quantitative evidence to conclude that CO is not a significant source of LF oscillations in MAP in conscious dogs at rest. The evidence was specifically that CO fluctuations could not predict or explain 99% of the LF MAP power. On the other hand, our approach also showed that CO fluctuations are a significant source of HF oscillations in MAP by accounting for about 70% of these oscillations. Hence, as was already known, respiration induces CO fluctuations via HR and stroke volume changes and these fluctuations, in turn, cause HF MAP variability.

Our quantitative approach did not use inevitably imperfect estimates of beat-to-beat TPR fluctuations, as we previously showed pitfalls of such estimates (Mukkamala *et al* 2003). However, the non-CO related component of MAP fluctuations captures the oscillations in this variable. This component could also represent other sources that induce MAP variability directly (rather than indirectly via CO and TPR fluctuations). One example is respiratory-induced intrathoracic pressure variations, which directly causes MAP fluctuations due to conservation of volume in the intrathoracic arteries. However, respiratory-induced intrathoracic pressure variations have a larger impact on MAP fluctuations through a venous return/CO effect. Another example is central venous pressure fluctuations, which directly causes MAP fluctuations due to a backpressure effect. However, this source should be small due to the normalization of MAP variability by its means value. Further, both of these sources may be more significant in the HF band and could indeed account for at least some of the 30% of the HF MAP fluctuations that could not be explained by the CO fluctuations. Hence, TPR appears to be the dominant mediator of spontaneous LF MAP fluctuations, and CO fluctuations are only responsible for dampening these fluctuations likely through the baroreflex.

The findings here are consistent with previous work (O'Leary and Woodbury 1996, Elstad *et al* 2011) but also add important physiologic insight into the actual role of CO fluctuations

in the genesis of MAP variability. To our knowledge, no one had previously quantified the exact contribution of CO fluctuations to naturally occurring MAP oscillations.

Studies of Windkessel and other arterial models have shown that CO can predict ABP quite well. With this point of view, it may be difficult to reconcile that CO is not always a cause of ABP. However, these models were most often employed to represent the pulsatile (intra-beat) relationship for which CO is of primary importance. In studies of beat-to-beat variability, TPR and other fluctuations also significantly impact MAP fluctuations. Our results suggest that in the LF band, the non-CO component is dominant such that CO fluctuations are of little value in causing MAP fluctuations. However, in the HF band, CO fluctuations are more important such that they are a significant cause of the MAP fluctuations.

It is important to remark that the question of whether CO fluctuations are a significant source of spontaneous LF MAP oscillations or not may have only been possible to answer through a mathematical analysis study. However, all such studies are limited by the assumptions underlying the mathematical analysis. Limitations of this study due to the mathematical analysis and otherwise include the following.

Firstly, our analysis ignored potential nonlinear effects in the relationship between fluctuations in CO and MAP. That said, the linearity assumption has been shown repeatedly to be a good one for resting beat-to-beat variability, which is small (Xiao *et al* 2005). Secondly, our analysis surely yielded error in the model parameter estimates. However, a demonstrated system identification technique was used to mitigate the estimation error variance. Finally, our sample population was limited to four dogs in the analysis of the HF MAP oscillations, since not all of the subjects from our original population displayed significant MAP power in this band. When the relative HF power in the output signal (MAP) is very low, system identification will focus the fit of the input signal (CO) to the output signal in the LF band (i.e., where the power is concentrated). Such fitting would bias the interpretation of the results, as it would suggest a greater role of CO fluctuations as a source of slow MAP oscillations. For this reason, the two dogs that did not show enough HF power were excluded from the HF MAP oscillation analysis to avoid an incorrect physiological interpretation because of mathematical issues. While these limitations make our quantitative estimates on the contribution of CO fluctuations to the genesis of MAP fluctuations imperfect, they in all likelihood do not impact the major study conclusion that CO fluctuations are not a significant source of LF MAP oscillations during normal physiologic conditions in conscious dogs.

Acknowledgments

Grants

This work was supported by the Young Research Mobility Award of Regione Lombardia to support the corresponding author, the NIH Grants 1 R21 EB004444, HL095819 and RO1 HL55743, the National Science Foundation CAREER Grant 0643477, and the HeartCycle FP7-216695 grant of the European Union.

References

- Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science*. 1981; 213(4504):220–222. [PubMed: 6166045]
- Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am. J. Physiol.* 1985; 249:H867–H875. [PubMed: 4051021]

- Aletti F, Bassani T, Lucini D, Pagani M, Baselli G. Multivariate decomposition of arterial blood pressure variability for the assessment of arterial control of circulation. *IEEE Trans. Biomed. Eng.* 2009; 56:1781–1790. [PubMed: 19307165]
- Aletti F, Chen X, Sala-Mercado JA, Hammond RL, O'Leary DS, Cerutti S, Baselli G, Mukkamala R. Identification of sources of low frequency variability of arterial blood pressure: cardiac output acts as a buffer and not as a source. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2010; 2010:3460–3462. [PubMed: 21097024]
- Aletti F, Ferrario M, Xu D, Greaves DK, Shoemaker JK, Arbeille P, Baselli G, Hughson RL. Short-term variability of blood pressure: effects of lower-body negative pressure and long-duration bed rest. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2012; 303:R77–R85. [PubMed: 22552795]
- Baselli G, Cerutti S, Civardi S, Malliani A, Pagani M. Cardiovascular variability signals: towards the identification of a closed-loop model of the neural control mechanisms. *IEEE Trans. Biomed. Eng.* 1988; 35:1033–1046. [PubMed: 3220497]
- Baselli G, Cerutti S, Badilini F, Biancardi L, Porta A, Pagani M, Lombardi F, Rimoldi O, Furlan R, Malliani R. Model for the assessment of heart period and arterial pressure variability interactions and of respiration influences. *Med. Biomed. Eng. Comput.* 1994; 32:143–152.
- Cevese A, Grasso R, Poltronieri R, Schena F. Vascular resistance and arterial pressure low-frequency oscillations in the anesthetized dog. *Am. J. Physiol. Heart Circ. Physiol.* 1995; 268:H7–H16.
- Chen X, Mukkamala R. Selective quantification of the cardiac sympathetic and parasympathetic nervous system by multisignal analysis of cardiorespiratory variability. *Am. J. Physiol. Heart Circ. Physiol.* 2008; 294:H362–H371. [PubMed: 17993596]
- Elstad M, Walløe L, Chon KH, Toska K. Low-frequency fluctuations in heart rate, cardiac output and mean arterial pressure in humans: what are the physiological relationships? *J. Hypertens.* 2011; 29:1327–1336. [PubMed: 21558953]
- Julien C. The enigma of Mayer waves: Facts and models. *Cardiovasc. Res.* 2006; 70:12–21. [PubMed: 16360130]
- Just A, Wagner CD, Ehmke H, Kirchheim HR, Persson PB. On the origin of low-frequency blood pressure variability in the conscious dog. *J. Physiol.* 1995; 489:215–223. [PubMed: 8583405]
- Mukkamala R, Toska K, Cohen RJ. Noninvasive identification of the total peripheral resistance baroreflex. *Am. J. Physiol. Heart Circ. Physiol.* 2003; 84:H947–H959. [PubMed: 12433656]
- O'Leary DS, Woodbury DJ. Role of cardiac output in mediating arterial blood pressure oscillations. *Am. J. Physiol.* 1996; 271:R641–R646. [PubMed: 8853386]
- Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ. Res.* 1986; 59:178–193. [PubMed: 2874900]
- Porta A, Furlan R, Rimoldi O, Pagani M, Malliani A, van de Borne P. Quantifying the strength of the linear causal coupling in closed loop interacting cardiovascular variability signals. *Biol. Cybern.* 2002; 86:241–251. [PubMed: 12068789]
- Porta A, Aletti F, Vallais F, Baselli G. Multimodal signal processing for the analysis of cardiovascular variability. *Philos. Trans. A Math. Phys. Eng. Sci.* 2009; 367(1887):391–409. [PubMed: 18940775]
- Rimoldi O, Pierini S, Ferrari A, Cerutti S, Pagani M, Malliani A. Analysis of short-term oscillations of R-R and arterial pressure in conscious dogs. *Am. J. Physiol. Heart Circ. Physiol.* 1990; 258:H967–H976.
- Steiner C, Kovalik AT. A simple technique for production of chronic complete heart block in dogs. *J. Appl. Physiol.* 1968; 25:631–632. [PubMed: 5687372]
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur. Heart J.* 1996; 17:354–81. [PubMed: 8737210]
- Wang M, Evans J, Knapp C. Spectral patterns and frequency response characteristics of arterial pressure in heart paced dogs. *IEEE Trans. Biomed. Eng.* 1995; 42:708–717. [PubMed: 7622154]
- Wyss CR, Bennett TD, Scher AM. Beat-by-beat control of cardiac output in awake dogs with atrioventricular block. *Am. J. Physiol.* 1982; 242:H1118–H1121. [PubMed: 7091352]

- Xiao X, Mullen TJ, Mukkamala R. System identification: a multi-signal approach for probing neural cardiovascular regulation. *Physiol Meas.* 2005; 26:R41–R71. [PubMed: 15798289]
- Xiao X, Mukkamala R, Cohen RJ. A weighted-principal component regression method for the identification of physiologic systems. *IEEE Trans. Biomed. Eng.* 2006; 53:1521–1530. [PubMed: 16916086]

Figure 1.

Normalized, beat-to-beat fluctuations in mean arterial pressure (MAP), MAP predicted by cardiac output (CO) fluctuations (predicted MAP), and the non-CO term representing the component of MAP variations that could not be predicted by the CO fluctuations in the time (upper plot) and frequency (lower plot) domains for dog 1.

Figure 2.

Normalized, beat-to-beat fluctuations in MAP, MAP predicted by CO fluctuations (predicted MAP), and the non-CO term representing the component of MAP variations that could not be predicted by the CO fluctuations in the time (upper plot) and frequency (lower plot) domains for dog 2.

Table 1

Spectral analysis and mean arterial pressure (MAP) prediction results for all the dogs.

Dog	LF MAP [%]	LF CO [%]	LF non-CO [%]	LF non-CO / LF MAP [unit-less]	HF non-CO / HF MAP [unit-less]
1	42	6	66	0.94	0.36
2	89	73	/	0.99	/
3	90	64	/	0.97	/
4	73	52	83	0.90	0.50
5	62	14	86	0.98	0.25
6	19	16	77	1.17	0.08
Mean $\pm$ SE	63 $\pm$ 11	37 $\pm$ 12	78 $\pm$ 2	0.99 $\pm$ 0.04 [†]	0.30 $\pm$ 0.04 [*]

LF is low frequency (0.02–0.10 Hz); CO, cardiac output; non-CO, component of MAP fluctuations that cannot be predicted by CO fluctuations; and HF, high frequency (0.10–0.40 Hz).

[†] denotes that LF non-CO / LF MAP is statistically equivalent to unity ($p = 0.03$).

^{*} denotes that LF non-CO / LF MAP is statistically different from HF non-CO / HF MAP ($p = 0.04$).