Modulation of pulmonary arterial input impedance during transition from inspiration to expiration

P. Castiglioni, R. Tommasini, M. Morpurgo, and M. Di Rienzo. Modulation of pulmonary arterial input impedance during transition from inspiration to expiration. J. Appl. Physiol. 83(6): 2123–2130, 1997.—We investigated whether respiration influences pulmonary arterial input impedance during transition from inspiration to expiration in five anesthetized, spontaneously breathing dogs. Impedance (Z) was separately assessed for heart beats occurring in inspiration, in expiration, and during the transition from inspiration to expiration (transitional beat). Transitional beats were scored by the ratio between the fraction of beats falling in expiration and the total beat duration [expiratory fraction (Efr)] to quantify their position within the transition. In transitional beats, input resistance linearly increased with Efr; Z modulus at the heart-rate frequency (fHR) decreased up to 50% for Efr = 50%; Z phase at fHR was greater than in inspiration for Efr < 40% and lower for Efr > 50%. Unlike blood flow velocity, mean value and first harmonic of pulmonary arterial pressure were correlated to Efr and paralleled the changes of input resistance and Z at fHR. This indicates that respiration influences Z through modifications in arterial pressure. The evidence of important respiratory influences on Z function may help the pathophysiological interpretation of dysfunctions of the right heart pumping action, such as the so-called cor pulmonale.

pulmonary circulation; pulmonary blood pressure; pulmonary blood flow; intrathoracic pressure

THE PULMONARY ARTERIAL input impedance (Z), defined as the ratio between the oscillations in blood pressure and blood flow at the entrance of the pulmonary circulation, is a quantitative coupling index between the right ventricle (RV) and the pulmonary vascular bed in the frequency domain (12). Because of the low values of pulmonary arterial pressure (PAP), the pulmonary input Z should be influenced by the changes in intrathoracic pressure associated with breathing. Surprisingly, the available literature does not report any significant difference between the average Z values of heart beats occurring during the inspiratory and expiratory phases of respiration, both at rest (3, 11) and during exercise (8). These studies, however, have not considered the pulmonary Z during the transition between inspiration (I) and expiration (E), namely, during the fraction of respiratory cycle characterized by marked changes in intrathoracic pressure.

In the present study, we focused on this unexplored issue by evaluating the pulmonary arterial input Z during the transition from I to E in spontaneously breathing dogs. To interpret the results obtained by the above analysis, we also separately investigated the influences of respiration on blood pressure and blood flow, i.e., on the individual determinants of the input Z.

METHODS

Animal preparation, data acquisition, and beat classification. The experiments were performed on five mongrel dogs. Anesthesia was induced by pentobarbital sodium (an initial bolus of 25–30 mg/kg iv followed by 0.07 mg·kg⁻¹·min⁻¹ infusion). Dogs were studied while they were in the right lateral position on a surgical table. They were intubated and then breathed spontaneously throughout the experiments.

PAP and blood-flow velocity (FV) were obtained via a high-fidelity Mikro-Tip catheter (SVPC-684A, 8 Fr; Millar Instruments) with pressure and velocity sensors at the same location. The catheter was advanced into the main pulmonary artery via the right jugular vein. Use of the integrated catheter avoided the surgical opening of the thorax for the implantation of a perivascular flowmeter, thus simplifying the experimental setup. It should be noted that with this approach blood flow is expressed in terms of FV (in cm/s) and that the derived parameters are velocity-derived input resistance (Rv) and Z. Nichols and O’Rourke (12) discussed in detail the differences between use of FV or use of flow-volume in expressing the Z modulus. According to these authors, use of flow volume has the benefit of familiarity and leads to Z moduli expressed in the same units of the hydraulic resistance. Nevertheless, these authors recommend the use of FV and point out that expressing Z modulus in terms of FV has a number of advantages, in particular when comparisons are made between animals or when comparisons are made in the same artery under different circumstances in which the artery dilates or constricts.

In two dogs, intrapleural pressure (IPP) was also determined by means of a catheter inserted into the pleural space through the fifth or sixth intercostal spaces. Airflow was measured with a heated mesh-screen pneumotachograph. All signals were sampled at 200 Hz and digitized through an analog-to-digital converter (HP 6942A). The average duration of each recording was 80.8 s.

The PAP and FV tracings were partitioned into individual waves, each referring to a single cardiac cycle. The onset of each systolic upstroke was identified on the PAP record and taken as the reference point for the partitioning. The duration of each cardiac cycle (heart interval) was obtained by measuring the time interval between consecutive reference points, and the instantaneous heart rate (fHR) was computed as the reciprocal of the heart interval. The airflow signal was subdivided into individual respiratory cycles. Each cycle was defined by a sequence of I, E, and postexpiration. I and E were identified by the onset of a positive and a negative airflow respectively; postexpiration was identified by the period of zero flow between E and I.

Each pair of simultaneous PAP and FV waves (hereafter this pair will be termed “beat”) was classified according to the respiratory phase during which it occurred. This led to three categories of beats: 1) inspiratory beats, which included all

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beats occurring entirely in I; 2) expiratory beats, which included all beats occurring entirely in E; and 3) transitional beats, which included the beats occurring during the transition from I to E. Moreover, for each transitional beat we computed the expiratory fraction (Efr), defined as the percent ratio between the fraction of time spent by the beat in E and the total heart beat duration (Fig. 1). This was done to quantify the position of the transitional beats within the transition. By definition, Efr ranges between 0 and 100%. All subsequent analyses were performed separately for each category of beats, the I beats being taken as the reference condition.

Beat-by-beat estimation of Z. The preliminary step to estimate the input Z is the computation of the Fourier coefficients for each pair of PAP and FV waves. The Fourier coefficients of a single wave are mathematically defined as the coefficients of a periodic signal composed of infinite replicas of the original wave (see Ref. 10 for details). The possible occurrence of differences between start and end values of a single wave produces discontinuities in the periodic signal and may affect the accuracy of the estimation of Fourier coefficients because of the phenomenon known as aliasing. Before computing the Fourier estimates, we made a preliminary exploration of whether the characteristics of pressure and flow signals were compatible with the requirements of the Fourier analysis. The actual influence of aliasing on the spectral results was evaluated and was shown to be negligible on the first five harmonics of PAP and FV waves, namely on all the harmonics we considered in this study (see details in APPENDIX A).

On the basis of this favorable validation, we computed the Fourier coefficients ($A_k$, $B_k$) for each pair of PAP and FV wave. Equations B9 and B10 in APPENDIX B show the mathematical expression of $A_k$ and $B_k$. From the Fourier coefficients, modulus $M_k$ and phase $\phi_k$ of the $k$th harmonic were calculated for each wave by the formulas $M_k = (A_k^2 + B_k^2)^{1/2}$ and $\phi_k = \arctan(B_k/A_k)$, with $k = 1...5$. The input Z modulus, $|Z(f)|$, was computed at $f = 0$ Hz as the ratio between PAP and FV mean values and at multiple frequencies of the instantaneous heart rate ($f = k \times f_{HR}$) as the ratio between the modulus of PAP and FV at the $k$th harmonic. Because Z was evaluated as the ratio between pressure and FV (instead of flow volume), it was expressed in dynes per second per cubic centimeters. The input Z phase, $\phi(Z(f))$, was computed at the same frequencies ($f = k \times f_{HR}$) as the difference between the phases of PAP and FV $k$th harmonics (10).

Subsequently, four parameters were derived from each estimated impedance curve $Z(f)$: the modulus of $Z(f)$ at $f = 0$ Hz (in short called input resistance (RI)); modulus and phase of $Z$ at the frequency of the instantaneous heart rate, $|Z(\text{f}_{HR})|$ and $\phi(\text{f}_{HR})$, respectively; and the characteristic Z modulus ($Z_c$), estimated by averaging the Z modulus between 2 and 12 Hz, as suggested by Bergel and Milnor (1). For each respiratory cycle, the differences between the estimates of the above four parameters in the transitional beat and in the inspiratory beat (the reference) were computed. The differences $\Delta R = |Z(\text{f}_{HR})|$, and $\Delta \phi = \phi(\text{f}_{HR}) - \phi(\text{f}_{HR})$, were then normalized with respect to the value in I to minimize variability between animals. Results of these four parameters were shown as a function of Efr.

Heart rate, pressure, and flow during the transition. To facilitate the interpretation of the results stemming from the analysis of Z, we also evaluated the effects of the transition from I to E on three factors that influence the Z estimation: heart rate, PAP, and FV.

The separate behavior of PAP and FV during the transition from I to E was also investigated to clarify the individual contribution of each variable on the results obtained from the Z analysis. To this aim, we considered the mean value and modulus and phase at the first harmonic of PAP and FV. Modulations of these parameters were separately quantified during transition by following the same procedure used for the assessment of Z changes.

RESULTS

Beat-by-beat estimation of Z. Figure 2 illustrates $Z(f)$ for I, E, and transitional beats in a typical animal (dog 4). Values at each harmonic are given as means ± SD. The Z modulus and phase were similar in I and in E. The only exception was the modulus at $0$ Hz ($R_I$), which was higher in E than in I. During the transition from I to E, when the transitional beats were considered as a whole (i.e., without taking into account Efr), the Z of the first harmonic was characterized by a marked reduction of the modulus and by a large variability of the Z phase. At higher frequencies, the Z phase was reduced with respect to both I and E, whereas the Z modulus was virtually unchanged.

The results of the analysis on transitional beats for the whole group of animals are depicted in Figs. 3 and 4 as a function of Efr. $R$ progressively increased for augmenting Efr values, whereas $Z(\text{f}_{HR})$ progressively decreased for Efr ranging from 0 to 50%, and thereafter symmetrically increased for Efr between 50 and 100%. At Efr values of $\sim 50\%$, $Z(\text{f}_{HR})$ was reduced to about one-half of the reference value on average. In no animal was this reduction less than $-30\%$. The phase $\phi(Z(\text{f}_{HR}))$ was positive with respect to the reference for $E_{fr} < 40\%$ and became negative for $E_{fr} > 50\%$. In reference to the $Z_c$, we did not find any clear dependence between $Z_c$ and $E_{fr}$ (Fig. 4).
Moreover, in the whole group of dogs, similar to the results obtained in the representative dog of Fig. 2, the Z phase of the transitional beats at harmonics 1, 2, 3, 4, and 5 was lower than in I for Efr between 10 and 90%, whereas the Z modulus was not influenced by Efr (data not shown). Because Zc was estimated as the average Z between 2 and 12 Hz, the latter finding also explains the lack of any dependence of Zc in relation to Efr.

Heart rate, pressure, and flow during the transition. Variations of the fHR that occurred in transitional beats with respect to inspiratory beats are plotted vs. Efr in Fig. 5. In all animals, fHR was stable throughout the transition from I to E, and this result excludes the possibility that the observed changes in Z(fHR) might be due to changes in fHR.

Results of the separate analysis on PAP and FV waves are illustrated in Fig. 6. Figure 6 shows the relationship between the mean value and Efr, and between the first harmonic modulus and phase and Efr. From a comparison of these data with the results of Fig. 3, it is apparent that the behaviors of mean value, modulus, and phase of PAP during transition parallel the behaviors of Rl and of Z modulus and phase at fHR. In contrast, no evident modulation was observed for the FV-derived parameters as function of Efr, apart from a slight downward linear trend in the mean value. In the analysis of harmonics 1, 2, 3, 4, and 5, we found a decrease of PAP phase for Efr ranging between 10 and 90%, and no changes for PAP moduli, FV moduli, and FV phases (data not shown in Fig. 6).

**DISCUSSION**

A new procedure was developed for the beat-by-beat analysis of pulmonary arterial input Z as a function of the respiratory cycle. This allowed us to investigate...
specifically the changes of Z(f) during the transition from I to E.

Through application of our procedure, we observed that the transitional beats are characterized by a large variability in Z modulus and phase at the frequency of the heart rate, Z(fHR). This variability was proven not to be caused by changes of the fHR, but rather by changes in the Z function \([Z(f)]\). These changes strictly depend on the onset time of the beat during the I-E transition. Specifically, the modulus of Z(fHR) displays a symmetrical pattern, which is characterized by a progressive drop from its reference value for Efr ranging from 0 to 50% and by an opposite progressive increase for Efr ranging from 50 to 100%. This has not been previously reported in literature. In particular, Murgo and Westerhof (11) measured PAP and FV in humans to compare input Z in I and E, but they classified transitional beats into one of the two phases of respiration according to where peak systolic FV occurred. They reached the conclusion that there was no difference between I and E in the overall Z spectrum. In a more recent study (3), our group investigated the influences of respiration on Z(f) by computing input Z in dogs during I, E, and postexpiration. Only beats completely occurring in a single respiratory phase were considered in that study. Significant differences were found between postexpiration and the other two respiratory phases but not between I and E, apart from a greater Rl in E. In view of the symmetric nature of the relationship between 0 and Efr, it is now evident why in both these studies no change in Z modulus was detected between I and E.

Concerning the determinants of Z changes, our results indicate that the changes in Z(f) are due almost entirely to changes in PAP, whereas during the transition from I to E the modifications of mean FV are negligible. It seems reasonable to ascribe the PAP changes and the concomitant changes in Z(f) to the rapid and substantial compression of the intrathoracic gases occurring between the end of I and the start of E, which are in turn reflected by an increase in IPP. To obtain an experimental support to this hypothesis, we also computed in two dogs the input Z from the pulmonary blood pressure “purified” from the influences of changes in IPP (Fig. 7). The purified intravascular pressure was obtained by computing the transmural pressure, namely PAP-IPP, on the assumption that the increase of IPP at the start of E induces an identical change in PAP. This assumption is in line with previous observations indicating that during the ventilatory cycle pulmonary intravascular pressure and IPP undergo similar changes (4). Figure 8 shows Rl and Z(fHR) obtained from PAP and from PAP-IPP in the two dogs. The removal of the influences of IPP from PAP resulted in the abolition of the modulation of Z(fHR) and in changes in the linear relation existing between Efr and Rl. These findings suggest that IPP exerts a major role in the genesis of Z changes.

On this basis, it remains to be explained how IPP may produce the specific pattern observed in Z during the transition from I to E. A possible explanation...
follows. The increase in IPP occurring during the transition superimposes on the first harmonic of the purified PAP wave a sinusoidal component with the same frequency but a different phase. The difference between phases produces a lowering in the first harmonic modulus of PAP that is more pronounced when the two components have opposite phases, i.e., when the transition from I to E occurs in the middle of the transitional beat ($E_{fr} = 50\%$). A first support of this reasoning is given by the experimental data of Fig. 9, which shows PAP, IPP, and transmural pressure of three transitional beats, along with their respective first harmonic components, for $E_{fr} = 25, 51,$ and $80\%$. The maximal reduction of the PAP modulus occurs for $E_{fr} = 51\%$, namely when the first harmonic components of IPP and transmural pressure are in counterphase.

Moreover, we theoretically verified whether the increase in IPP occurring during the transition from I to E was sufficient to explain the observed patterns in the mean value and first harmonic of PAP. This was achieved by developing the mathematical model described in Appendix B. The results of the simulation actually confirm that the IPP increase induced by the transition from I to E and the time of occurrence of this increase within the transitional beat (quantified by $E_{fr}$) may account for all the changes observed in the mean value and in the first harmonic modulus and phase of the PAP wave.

As for the biological relevance of our findings, we should consider that in the pulmonary circulation the pulsatile component of pressure and flow is an important determinant of the RV afterload. Thus variations of $Z(f_{HR})$ may substantially affect the RV work. The observed changes of $Z(f_{HR})$ are therefore likely to influence the RV dynamics. Actually, alterations of RV systolic time intervals during the transition from I to E have been previously reported by our group (14), and the present findings suggest that $Z(f_{HR})$ modulations...
may be one of the factors responsible for these alterations.

The potential clinical implications of the assessment of RV afterload through Z(f) have been recently illustrated in several papers. For instance, it has been suggested that changes in Z(f) may quantitate the afterload increase that characterizes the so-called chronic cor pulmonale (5) and that Z(f) is a more sensitive indicator of vascular alterations than pulmonary vascular resistance for the assessment of pulmonary function of donor lungs before transplantation (2). Kussmaul et al. (7) showed that the ventriculo-arterial coupling is importantly affected by pharmacological vasodilatation of pulmonary vessels in congestive heart failure and that the pulsatile properties of the pulmonary circulation must be taken into account to understand the effects of vasodilatation on cardiac output. More recently (4), pulmonary input Z has been used to evaluate the efficacy of nitric oxide administration and that of surgical interventions in the treatment and evaluation of chronic pulmonary hypertension. During the respiratory cycle, while shifting from I to E, the impairment in the RV afterload which characterizes pulmonary diseases may be further enhanced by alterations in the geometrical and mechanical characteristics of the proximal pulmonary arteries, as suggested for chronic cor pulmonale (9).

Moreover, the evaluation of the pulmonary input Z during respiration may be important for quantifying the milking-action effect, produced by the cyclical changes of lung volume due to respiration, on the blood circulation (5). This milking action is particularly important in the Fontan procedure when the RV is markedly hypoplastic.

In all these instances, the quantification of the ventriculo-arterial coupling, as obtained by the estimation of the Z(f) during the respiratory cycle and, in particular, during the I-E transition, where we showed that important Z changes occur, may be of great clinical relevance.

APPENDIX A

Transitional Beats and Aliasing

The PAP and FV waveforms in the pulmonary circulation are influenced by the respiratory movements, and this may result in differences between the start and the end values of any single wave. When individual waveforms have to be analyzed by the Fourier series (as in the present study), a discrepancy between the onset and end of the waveform introduces a discontinuity that adds high-frequency components into the spectrum of the single waveform. Spectral components possibly added at frequencies higher than half the sampling rate are shifted toward lower frequencies and introduce distortion in the estimates. This error, known as “aliasing,” can be avoided only by selecting a sufficiently high sampling rate (higher than two times the maximum frequency content of the signal). Because the discontinuity between starting and ending values results in an infinite number of harmonics, a residual aliasing error is unavoidable. Thus we quantified the practical influences of aliasing on our estimates of the Fourier components.

The analysis was performed in two steps. First, we computed the differences between starting and ending (head-tail) values of PAP and FV waves of each transitional beat. This was done to quantify the discontinuities actually occurred in our experimental data. Results are shown in Fig. 10 where the head-tail differences (dPAP and dFV) are expressed as a percentage of the wave amplitude for PAP and FV. The PAP differences are close to 0% (almost no head-tail difference) for Efr < 0, increase in a parabolic fashion reaching a maximum (~80%) for Efr = 50%, and progressively return to 0% when Efr approaches 100%. No appreciable head-tail difference was found in the FV waves at any value of Efr, thus excluding the possibility that aliasing may significantly affect the Fourier components of FV. On the basis of this finding, we continued the analysis by considering the effects of aliasing on PAP only.

In the second step of the analysis, we generated a simulated signal by summing 1) a real PAP wave characterized by the same initial and final values (this condition guarantees that the estimated Fourier components are not affected by aliasing) and 2) a sawtooth function f(t) that models possible head-tail discontinuities. This function was selected because its Fourier series is known in an analytic form (12); thus it is not affected by aliasing introduced by the estimation procedure. In particular, with W the amplitude and T the duration of the real PAP wave and dPAP defined as the head-tail difference of the simulated signal normalized by the wave amplitude W, then the saw-tooth function is given by the formula

\[ f(t) = \frac{W d_{PAP}}{2} \left[ t - nT \right] / T \quad nT \leq t \leq (n + 1)T \]  

(A1)

The expression of \( f(t) \) in terms of Fourier series is

\[ f(t) = \frac{W d_{PAP}}{2} - \sum_{k=1}^{\infty} \frac{W d_{PAP}}{\pi k} \sin \frac{2\pi k t}{T} \]  

(A2)

In our simulation, \( P = 0.4 \) s, \( W = 23.2 \) mmHg, and \( d_{PAP} \) was set equal to 100%, this value being greater than the maximum normalized head-tail difference occurred in the whole set of transitional beats (Fig. 10).

It should be noted that the signal has an infinite number of harmonics produced by the discontinuities at \( t = nT \) (see Eq. A1). When the simulated signal is sampled at 200 Hz (i.e., at the same sampling frequency used in this study) components >100 Hz in \( f(t) \) are shifted toward a lower frequency band and cause aliasing.
Because the Fourier coefficients of \( f(t) \) are available in an analytic form and those of the real PAP wave can be estimated without aliasing, the true Fourier coefficients of the simulated signal are known. Therefore, we evaluated the effects of aliasing by comparing the theoretical Fourier coefficients of the simulated signal with those affected by aliasing that are estimated by the procedure used in our study.

The results, shown in Table 1, point out that, even considering discontinuities larger than those actually occurring in experimental data, the aliasing error in the estimation of the modulus of the first harmonic is only 5%. This indicates that reliable Fourier coefficients can be computed also in transitional beats characterized by major head-tail discontinuities in the PAP wave.

**APPENDIX B**

**A Mathematical Model of the IPP Influence on PAP at the Start of Expiration**

In the text, we hypothesized that the changes in PAP during transitional beats might be due to the fast rise in IPP. In this **APPENDIX**, we show by means of a mathematical model that an increase of IPP resulting from the I to E transition is sufficient to explain the patterns observed in mean value and first harmonic of the PAP wave.

Let us define PAP\( ^p(t) \), with \( 0 \leq t \leq T \), the PAP waveform corresponding to a beat of duration \( T \) entirely occurring during I, and PAP\( ^{IE}(t) \) the waveform corresponding to a transitional beat (assumed of the same duration \( T \)). Moreover, let IPP\( ^p(t) \) be the increase of IPP during the transitional beat. Because of the fast pressure rise occurring in IPP at the start of expiration, let us schematize IPP\( ^p(t) \) with the following stepwise function

\[
\text{IPP}^p(t) = \begin{cases} 0; & 0 \leq t \leq t_1 \\ H; & t_1 < t \leq T \end{cases}
\]

where \( H \) is the rise of IPP after the compression of intrathoracic gases at the start of expiration and \( t_1 \) is the instant of the transition from I to E. From the definition of the Efr (see Fig. 1),\( t_1 \) is related to Efr according to the formula

\[
t_1 = (1 - Efr)T
\]

In our model, we assume that the P W of the transitional beat, PAP\( ^{IE}(t) \), is given by the sum of the W during I [PAP\( ^p(t) \)] and the variation in intrapleural pressure IPP\( ^p(t) \), namely

\[
\text{PAP}^{IE}(t) = \text{PAP}^p(t) + \text{IPP}^p(t)
\]

By considering the Fourier series of PAP\( ^{IE}, \text{PAP}^p \), and IPP\( ^p \), and Eq. B3, we obtain the following equations that link mean value and first harmonic modulus and phase of the PAP\( ^{IE} \) waveform to the corresponding Fourier coefficients of PAP\( ^p \) and IPP\( ^p \):

\[
\text{PAP}_{0}^{IE} = \text{PAP}_{0}^p + \text{IPP}_{0}^p
\]

\[
\text{PAP}_{1}^{IE} \cos \left( \frac{2\pi}{T} t - \phi_{1}^{IE} \right) = \text{PAP}_{1}^p \cos \left( \frac{2\pi}{T} t - \phi_{1}^{p} \right) + \text{IPP}_{1}^p \cos \left( \frac{2\pi}{T} t - \phi_{1}^{pp} \right)
\]

By definition of Fourier coefficients, we have

\[
\text{IPP}_{0}^p = \frac{1}{T} \int_{0}^{T} \text{IPP}^p(t) dt
\]

\[
\text{IPP}_{1}^p = \sqrt{A_1^2 + B_1^2}
\]

\[
\phi_{1}^{pp} = \arctan \left( \frac{B_1}{A_1} \right)
\]

with

\[
A_k = \frac{2}{T} \int_{0}^{T} \text{IPP}^p(t) \cos \left( \frac{2\pi}{T} t \right) dt
\]

\[
B_k = \frac{2}{T} \int_{0}^{T} \text{IPP}^p(t) \sin \left( \frac{2\pi}{T} t \right) dt
\]

Hence, by considering Eqs. B1–B2, we obtain IPP\( _0^p, \text{IPP}_1^p \), and \( \phi_{1}^{pp} \) as a function of the Efr

\[
\text{IPP}_{0}(Efr) = H \times Efr
\]

\[
\text{IPP}_{1}(Efr) = \frac{H}{\pi} \sqrt{2(1 - \cos [2\pi(1 - Efr)])}
\]

\[
\phi_{1}^{pp}(Efr) = \arctan \left( \frac{1 - \cos [2\pi(1 - Efr)]}{\sin [2\pi(1 - Efr)]} \right)
\]

![Graph](image-url)
Finally, by using Eqs. B11-B13 in Eqs. B4-B5, through trigonometric identities we have

$$PAP_0^{IE}(E_{fr}) = PAP_0^I + H \times E_{fr}$$  \hspace{1cm} (B14)

$$\phi_1^{IE}(E_{fr}) = \arctan \left( \frac{PAP_1^I \sin (\phi_1^I) + IPP_1^I \sin [\phi_1^{PP'}(E_{fr})]}{PAP_1^I \cos (\phi_1^I) + IPP_1^I \cos [\phi_1^{PP'}(E_{fr})]} \right)$$  \hspace{1cm} (B15)

$$PAP_1^{IE}(E_{fr}) = \frac{PAP_1^I \cos (\phi_1^I) + IPP_1^I \cos [\phi_1^{PP'}(E_{fr})]}{\cos [\phi_1^{IE}(E_{fr})]}$$  \hspace{1cm} (B16)

In this way, we obtain a description of the mean value and first harmonic phase and modulus of PAP in terms of changes in IPP and as a function of the $E_{fr}$.

$PAP_0^{IE}$, $\phi_1^{IE}$, and $PAP_1^{IE}$, as given by Eqs. B14–B16, were computed for $E_{fr}$ values ranging from 0 to 100% to verify the ability of this model to describe the patterns observed in our results. The values of the pressure parameters in I and the increase of IPP during transition from I to E, as required to solve the equations, were derived from the segment of experimental data illustrated in Fig. 7 (dog 2). In particular, $PAP_0^I$ was set equal to 29 mmHg, $PAP_1^I$ to 9 mmHg, $\phi_1^I$ to $-2.15$ rad, and $H$ to 9.8 mmHg. Figure 11 shows the results of the simulation superimposed on the experimental results obtained from dog 2. It is evident that the model can faithfully reproduce 1) the linear trend in the mean value of $PAP_1^{IE}$ for increasing values of $E_{fr}$; 2) the large reduction of the $PAP_1^{IE}$ first harmonic for $E_{fr}$ close to 50%; and 3) the sigmoidal shape of the shift between $PAP_1^{IE}$ and $PAP_1^I$ phases that characterize experimental data. Similarities between simulation and biological data corroborate the validity of the model and provide a mathematical support to the hypothesis that most of the changes observed in PAP are actually caused by the fast rise in IPP occurring during the transition from I to E.

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