Estimation of right ventricular isovolumic pressure from a single ejecting beat in experimental pulmonary hypertension

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Abstract

Assessment of right ventricle (RV) pump function from end-systolic pressure-volume relationships (ESPVR) is hampered by the requirement of multiple-beats to be obtained through alterations in preload. Several single-beat (SB) methods have been proposed to calculate ESPVR, mostly based on estimation of maximum isovolumic pressure ($P_{\text{max}}$) using simplified isovolumic pressure waveforms. The purpose of this study was to determine the shape of the RV isovolumic pressure wave experimentally and to use this template to compute $P_{\text{max(SB)}}$ from ejecting beats. Isovolumic pressure curves were obtained by clamping the pulmonary artery in 3 control, 3 stable pulmonary hypertension (PH), and 2 progressive PH rats. PH was induced by monocrotaline (MCT) 40 and 60 mg/kg, respectively. Subsequently, these curves were normalized in amplitude and duration and averaged to obtain the standard isovolumic pressure wave shape. Then, this curve was used to estimate $P_{\text{max(SB)}}$ from ejecting RV pressure curves in 9 control, 7 stable PH and 8 progressive PH rats. $P_{\text{max(SB)}}$ values were compared to values obtained from multiple pressure-volume loops by vena cava occlusion [$P_{\text{max(VCO)}}$]. Three SB methods from literature were included for comparison. With our method close proportional relations were found between $P_{\text{max(SB)}}$ and $P_{\text{max(VCO)}}$ ($r^2=0.85$, $p<0.001$). The other methods had $r^2$ values of 0.82, 0.85 and 0.74; $p<0.001$; the first two methods showed increased bias for progressive PH. Our method not only predicts $P_{\text{max(SB)}}$ but also gives realistic isovolumic pressure curves close to experimental curves. In conclusion, we derived realistic isovolumic pressure waveforms, providing accurate estimates of $P_{\text{max}}$ over a wide range of RV contractility.

Keywords: maximum isovolumic pressure ■ contractility ■ pulmonary hypertension ■ right ventricle
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Introduction

The end-systolic pressure-volume relationship (ESPVR) of the left ventricle (LV) is a comprehensive index of LV pump function. This concept has also been validated to determine right ventricular (RV) pump function. The conventional assessment, however, is difficult since it requires measurement of pressure-volume loops at multiple loading conditions, usually obtained by alterations in cardiac preload. Alternatively, however, the ESPVR can be estimated from a single ejecting beat (thus, without the need of changes in preload), by combining the end-systolic pressure-volume point with the theoretical maximal isovolumic pressure ($P_{\text{max}}$) of that beat.

In 1980, Sunagawa et al. were the first to propose a method to estimate $P_{\text{max}}$ from a single LV pressure beat. They proposed that an isovolumic pressure curve could be modeled by an inverted cosine with offset, fitted through both isovolumic contraction and relaxation phases of an ejecting beat. $P_{\text{max}}$ was then taken as the maximum of this fitted cosine. This approach is based on three assumptions, namely that 1) an isovolumic pressure wave can be modeled as an inverted cosine wave, 2) the systolic duration of an isovolumic beat is similar to that of an ejecting beat, and 3) both the isovolumic contraction and relaxation phases can be used for fitting the cosine wave.

In experimental studies, however, some fundamental properties of an isovolumic pressure waveform have been reported, showing the limitations of the use of a single cosine wave. In particular, it has been shown that the duration of an isovolumic contraction is longer than that of an ejecting contraction and that the shape of the pressure curve is typically not symmetrical but skewed (unlike a cosine function).

Some researchers proposed alternative methods to estimate $P_{\text{max}}$. With the exception of Senzaki et al. and Shishido et al., all of these methods are based on simplified wave shapes of isovolumic pressure and all are fitted to both the isovolumic contraction and relaxation periods of pressure of ejecting contractions. Thus, all these methods assume a similar systolic duration of an ejecting and isovolumic pressure beat. These assumptions may be underlying to some of the problems that have been reported using the various single beat methods. Furthermore, most work is done for the LV and it is unknown how these methods perform on the RV, both in a normal and diseased state.

The purpose of this study was to derive a new, accurate and physiological based single-beat method to estimate $P_{\text{max}}$ in the RV. To reach this goal the RV isovolumic pressure wave shape was determined experimentally. Subsequently, this wave (after normalization) was used as the basis for computing the isovolumic pressure wave and $P_{\text{max}}$. Three single-beat methods from literature were included for comparison. Vena cava occlusion derived values of $P_{\text{max}}$ values were considered as a reference.
Methods

Experimental setup.
The institutional animal care and use committee at the VU University approved all experiments. In total, 24 male Wistar rats (weight 150–175 g; Harlan, Horst, the Netherlands) were included in this study.

Induction of PH
PH was induced by a single, subcutaneous bolus injection of monocrotaline (Sigma-Aldrich, Zwijndrecht, the Netherlands) dissolved in saline. Monocrotaline 40 mg/kg body mass was used to induce stable PH (n=7). A dose of 60 mg/kg monocrotaline was used to induce more progressive PH (n=8). Control rats were injected with saline only (n=9). Studies were performed 4 weeks after MCT treatment.

Invasive measurements
Conductance catheter measurements to obtain pressure-volume loops were performed under general anesthesia (isoflurane 2.0% in 1:1 O₂/air mix) and mechanical ventilation (micro ventilator, UNO, Zevenaar, the Netherlands). The conductance catheter (Millar Mikro-Tip® SPR-671, Millar Instruments, Houston, Texas, USA) was introduced into the RV through the RV wall and a tourniquet was placed around the inferior caval vein to enable temporary preload reductions. During a vena cava occlusion 10 to 20 pressure-volume loops were recorded.

Start and end of diastole and systole were determined using a method as previously described by Regen et al. Although the conductance signal in itself is non-calibrated, it was not converted to absolute volume as in the present study only the calibrated pressure signal is necessary for calculating \( P_{\text{max}} \).

Linearity of the conductance-volume relationship was tested by simultaneous measurement of flow at the ascending aorta using an ultrasonic transit-time flowprobe (MA2.5PSB, Transonic Systems Inc., Ithaca, New York, USA).

The normalized isovolumic pressure wave
In a subset of the rats (normal: n=3; MCT40: n=3; MCT60: n=2) isovolumic pressure beats were measured by occluding the pulmonary artery using a vascular mini-clamp. These beats were used to determine experimentally the shape of the isovolumic pressure curve. Because the clamping was performed manually, it was checked whether clamping was performed at end-diastole by comparing the length of the diastolic period just before
Estimation of isovolumic pressure from a single ejecting beat clamping with the same period of preceding beats. If this period did not match, the clamping was repeated after a steady state was reached again. The clamping procedure was considered acceptable when the pulmonary artery was clamped at end-diastole and no artifacts were present in the measured isovolumic pressure curves. In each rat, multiple beats were measured and averaged to obtain a single beat per rat.

In each rat, the acquired average isovolumic pressure waves were normalized both in amplitude and in time. For this normalization, end-diastolic pressure ($P_{\text{min}}$) was set at zero, maximum isovolumic pressure ($P_{\text{max}}$) was set equal to one, and the time of maximum pressure ($t_{\text{pmax}}$) was set at one. In case no complete cycle was measured the normalized curves were extrapolated to obtain a complete cycle. All normalized curves were averaged to obtain the standard isovolumic pressure wave shape, denoted as $P_{\text{iso,N}}(t_N)$ (Figure 1). This curve is used as a template to estimate isovolumic pressure.

Fourier series were used for efficient representation of the normalized isovolumic wave shape, for which we found that 6 Fourier terms (i.e. 13 Fourier coefficients) were sufficient to describe the shape accurately (Figure 1C and Table 1; see appendix for more detail).

**Estimation of isovolumic pressure**

Our single-beat method is based on $P_{\text{iso,N}}(t_N)$ to simulate a realistic RV isovolumic pressure wave, denoted as $P_{\text{iso,im}}(t)$. To this end, $P_{\text{iso,N}}(t_N)$ is fitted through the isovolumic contraction phase of an ejecting beat $P(t)$ measured in the RV, under the additional boundary condition that the minimum downslope of $P_{\text{iso,im}}(t)$ is equal to the minimum downslope of $P(t)$ (i.e. similar $dP/dt_{\text{min}}$ values in both waves).
To geth with $P_{iso,N}(t_N)$ (i.e. the known 13 Fourier coefficients of Table 1) four parameters are needed to estimate $P_{iso,sim}(t)$, namely minimum and maximum isovolumic pressure ($P_{min}$ and $P_{max}$), time to reach maximum isovolumic pressure ($t_{Pmax}$) and difference in onset time between $P_{iso,sim}(t)$ and $P(t)$ ($t_{0}$) (see also Appendix). All parameters need to be optimized such that the isovolumic contraction phase of $P(t)$ is best described by $P_{iso,sim}(t)$.

The isovolumic contraction phase was defined from the measured pressure at end-diastole until pressure exceeded 10% above the pressure at maximum $dP/dt$ ($dP/dt_{max}$; Figure 2A). The optimization was performed in a nonlinear least squares sense using the Levenberg-Marquardt algorithm. More detail about the construction of $P_{iso,sim}(t)$ from $P_{iso,N}(t_N)$ and the four parameters is provided in the Appendix. The condition of equal downslopes of isovolumic relaxation phase of $P_{iso,sim}(t)$ and $P(t)$ was implemented as follows. In the ejecting beat, pressure values were selected in the range ±20% of pressure at $dP/dt_{min}$. Subsequently, the same number of data points were selected above and below $dP/dt_{min}$ in $P_{iso,sim}(t)$. The $dP/dt$ values in these ranges were imposed to be equal in the non-linear least squares optimization.

To improve fitting stability, a constraint was applied to $t_{Pmax}$ by defining a lower and upper bound. This constraint was based on a previous finding of Regen et al. who observed a linear relation between the contraction period, defined as the beginning of contraction until the end of relaxation, of ejecting and isovolumic non-ejecting beats. In the present study, it was presumed that $t_{Pmax}$ is linearly related to contraction duration of an ejecting beat by the following relation: $t_{Pmax} = t_{dP/dt_{max}} + \beta (t_{dP/dt_{max}} - t_{dP/dt_{min}})$, in which contraction period was approximated as the period between $dP/dt_{max}$ and $dP/dt_{min}$, and...
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with $\beta$ a value between 0 and 1. We chose to approximate this contraction period in this way because it can easily be obtained from ejecting pressure curves and correlates closely with “true” contraction period, but which is much more sensitive to errors in exact estimation of the moment of start- and end-contraction. Experimentally, the value of $\beta$ was determined from isovolumic contractions, and estimates of $t_{\max(P_{\text{dP/dt}})}$ and $t_{\min(P_{\text{dP/dt}})}$ were obtained in the preceding ejecting beats. Subsequently, these values of $\beta$ were considered to be representative for all rats and were used to determine the initial condition and lower and upper bounds of $t_{\max(P_{\text{dP/dt}})}$ from ejecting beats only.

Data analysis

Estimated single-beat values ($P_{\text{max(SB)}}$) were compared with values computed from vena cava occlusion measurements ($P_{\text{max(VCO)}}$) considered as the reference values. $P_{\text{max(VCO)}}$ was determined from the end-systolic pressure volume relationship (ESPVR) that was extrapolated to end-diastolic volume of the beat used to derive the isovolumic beat (Figure 2B). Three other single-beat methods reported in the literature were compared (examples are shown in Figure 3). The first method is the original method introduced by Sunagawa et al., based on an inverted cosine wave fitted to both the isovolumic contraction and the isovolumic relaxation phase. The second method was proposed by Shih et al. who slightly modified the original approach by using half a sine wave instead of an inverted cosine that is fitted at a range ±20% of pressure at maximum $dP/dt_{\max}$ and ±20% of pressure at minimum $dP/dt_{\min}$. The third method was proposed by Kjørstad et al. who used a 5th order polynomial function instead of a cosine function. For each method, the coef-
icient of determination ($r^2$) and the root-mean square error (RMSE) was computed between $P_{\text{max}(SB)}$ and $P_{\text{max}(VCO)}$. In the subset of data with pulmonary artery occlusion measurements maximum values $P_{\text{max}(APO)}$ were also compared to $P_{\text{max}(VCO)}$. In addition to the maximal pressures ($P_{\text{max}}$), which is required to determine the ESPVR, we also calculated the mean isovolumic pressures ($P_{\text{mean}}$) for all approaches, as the latter values are required for constructing a pump-function graph. $P_{\text{mean}}$ is calculated from isovolumic pressure waves with diastolic pressures appended from the corresponding ejecting beat to cover a full cardiac cycle.

Results

RV systolic pressure obtained from the right heart catheterization measurements was elevated in MCT40 and MCT60 rats compared to control rats (41±9 and 69±14 versus 27±6 mmHg). Heart rate was modestly different between the rats (control: 252±28, MCT40: 248±27 and MCT60: 280±43 beats/min).

Figure 1A shows measured isovolumic pressure waves from the subgroup of rats (normal:...
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**Figure 5** - Examples of two dataset with large differences between P_{max}(APO) and P_{max}(VCO). The gray curves represent the last beat before preload is altered by VCO. The isovolumic pressure curves are experimentally obtained during APO.

**Figure 6** - Mean isovolumic pressure computed using the four evaluated single-beat methods in the different groups.
n=3; MCT40: n=2; MCT60: n=3), which were used to derive the average, normalized pressure waveform. Averages of at least two isovolumic pressure beats are plotted. In two animals only one isovolumic curve was available because of artifacts or clamping at other times than end-diastole. Figure 1B shows the same curves after normalization for both maximum amplitude and time moment to reach this maximum pressure (see methods). The thick line indicates the average of all normalized isovolumic waves \((P_{iso,N}(t_N))\). Figure 1C shows a reconstruction of \(P_{iso,N}(t_N)\) using 3 and 6 Fourier terms. Table 1 provides the 13 Fourier coefficients corresponding to the first 6 Fourier terms which form the basis for the reconstruction of \(P_{iso,sim}(t)\).

From the experimental isovolumic pressure curves, it was found that \(P_{max}\) was reached on average after 58% (range: 51-61%) of the contraction phase was finished (duration between maximum and minimum \(dP/dt\)). This finding (i.e. \(\beta=0.58\)) was used as an initial condition to estimate the moment of \(P_{max}\) from an ejecting beat.

Figure 4A-D shows scatterplots of \(P_{max(SB)}\) values obtained with the four single-beat methods and the reference values \(P_{max(VCO)}\), illustrating good correlations for all methods. The data are also presented in modified Bland-Altman plots. For these plots a modification was applied to compute the 95% limits of agreement, because the differences between \(P_{max(SB)}\) and \(P_{max(VCO)}\) are not well described by a mean value, and a regression line should be used instead.16 The figure indicates that the methods differ with respect to the systematic and random errors. The new method (A) indicates an overestimation of \(P_{max(VCO)}\) over the complete pressure range, while methods B and C especially have large errors in severe PH (MCT60). Figure 4E presents a scatterplot between \(P_{max(APO)}\) and \(P_{max(VCO)}\) as well as a modified Bland-Altman plot, indicating a significant bias. Figure 5 shows examples of two datasets with evident underestimation of \(P_{max(APO)}\) by \(P_{max(VCO)}\).

Figure 6 presents the mean isovolumic pressure of the estimated isovolumic pressure waves as calculated with the four single beat methods. The isovolumic pressure waves are appended with diastolic pressures from the corresponding ejecting beat to cover a full cardiac cycle. Using the single-beat method proposed here, the mean isovolumic pressure is significantly higher compared to the other methods.

Linearity of the conductance-volume relationship was tested in two MCT60 rats. A strong linear relationship was found between aortic stroke volume and conductance difference (measured at the moment of \(dP/dt_{max}\) and \(dP/dt_{min}\)) in beats that were used to calculate end-systolic pressure-volume relations \((r^2\text{ values of 0.91 and 0.96})\). However, complete occlusion of the caval vein resulted in a slight convex relation at very small volumes and corresponding beats were therefore avoided in the analysis.
Discussion

In this study we proposed a new method to estimate isovolumic (non-ejecting) pressure waves and its maximum $P_{\text{max}}$ from a single ejecting beat. The method is based on a realistic shape of a normalized isovolumic pressure curve and accounts for load-dependent ventricular contraction duration. The results were compared to $P_{\text{max}}$ values obtained from the extrapolated ESPVR in vena cava occlusion experiments ($P_{\text{max(VCO)}}$) in normal and pulmonary hypertension rats. We also derived mean isovolumic pressure, a quantity that can be used to derive the ventricular pump function graph$^{15,17}$. The accuracy of three other methods from literature was determined$^{3,8,9}$.

We demonstrated that estimates of maximum isovolumic pressure, $P_{\text{max(SB)}}$, using the new method had an excellent correlation with maximum isovolumic pressure derived from extrapolated vena cava occlusion data, $P_{\text{max(VCO)}}$ ($r^2 = 0.85$, $P < 0.001$). Good correlations between $P_{\text{max(SB)}}$ and $P_{\text{max(VCO)}}$ were also obtained using the methods from literature, but errors between $P_{\text{max(SB)}}$ and $P_{\text{max(VCO)}}$ differed between the methods and for disease severity. In normotensive rats, all methods estimated $P_{\text{max(SB)}}$ close to $P_{\text{max(VCO)}}$, but larger differences were observed in severe experimental PH (MCT60; figure 4 and 5). In particular, the original single-beat approach$^3$ resulted in relatively large underestimation of $P_{\text{max(SB)}}$ compared to $P_{\text{max(VCO)}}$. These findings are in correspondence with literature in which good reproducibility has been reported in normal left and right ventricles$^{3,10,18,19}$, but where problems have been reported in abnormal (left) ventricles$^8,11,12$.

All single-beat methods were validated against $P_{\text{max(VCO)}}$ instead of $P_{\text{max(APO)}}$. This was chosen based on the fact that measurements of $P_{\text{max(APO)}}$ are very sensitive to the exact moment of clamping (i.e. only small deviations from end-diastole result in considerable variation of $P_{\text{max(APO)}}$), and because the de facto standard way to obtain the ESPVR is through vena cava occlusion. However, in a subset of data we observed that measured $P_{\text{max(APO)}}$ was consistently higher than $P_{\text{max(VCO)}}$ (figure 3; figure 5 also illustrates two examples with a considerable discrepancy between $P_{\text{max(APO)}}$ and $P_{\text{max(VCO)}}$). An almost similar difference was observed between $P_{\text{max(SB)}}$, estimated using the new single-beat method, and $P_{\text{max(VCO)}}$ (Figure 3). Two of the other evaluated methods$^{3,8,9}$ underestimated $P_{\text{max(VCO)}}$ and thus also $P_{\text{max(APO)}}$ (Figure 3).

In 1899 it was recognized by Frank$^{20}$ that the ESPVR, obtained from ejecting frog ventricles under varying pre-load conditions, was quite different from the isovolumic relationship curve (the diagram to illustrate this was reproduced by Sagawa et al.$^{21}$ in figure 1-3). Similarly, in Baan et al.$^{22}$ showed in left ventricles of dogs that the type of loading intervention affects the ESPVR. In particular, they observed that aortic occlusion produced a steeper slope of the ESPVR compared to vena cava occlusions. These observations are in line with our findings of differences between $P_{\text{max(APO)}}$ and $P_{\text{max(VCO)}}$. 
Two assumptions are made in the original approach\(^3\) and may explain the varying success of its application: the systolic duration of an isovolumic beat was considered similar to an ejecting beat, and it was assumed that an isovolumic pressure wave could be approximated by a symmetric inverted cosine. In fact, true isovolumic beats are substantially longer in duration than ejecting beats and are typically skewed rather than symmetrical\(^{4-6}\), which is also apparent from the measured isovolumic (non-ejecting) contractions in our present study (figure 1). Although these assumptions do not accurately reflect physiology, errors in predicted \(P_{\text{max}}\) may not be always large. For example, if only the first assumption would be valid, \(P_{\text{max}}\) would be underestimated. In contrast, if only the shape of an isovolumic pressure wave would be different, \(P_{\text{max}}\) will be overestimated using a cosine. Thus, these errors act in opposite direction and tend to cancel each other\(^4\). This phenomenon appeared also in our data where a “wrong” fit does not necessarily lead to incorrect values of \(P_{\text{max}}\). In a disease state, however, one of these errors might dominate the other resulting in reduced accuracy of estimated \(P_{\text{max}}\). In particular, this might occur when the slopes of isovolumic contraction and of relaxation are very different\(^23\).

Kjørstad et al.\(^8\) proposed a modification of the original approach for improved curve fitting by using a 5\(^{\text{th}}\) order polynomial instead of a sine wave. Although this approach has not always been successfully applied\(^8,24\), recently, ten Brinke et al.\(^7\) reported promising results in the left ventricle for different types of cardiomyopathies. Also, in ten Brinke’s study\(^7\) the polynomial approach led to close relations between \(P_{\text{max(SB)}}\) compared to \(P_{\text{max(VCO)}}\) values.

A common disadvantage of the aforementioned single-beat methods is the assumption of a similar systolic duration of isovolumic and ejecting contractions. This assumption is especially problematic in case the complete isovolumic pressure curve is of interest instead of only \(P_{\text{max}}\). For example, to construct a pump function graph as an alternative of the ESPVR to characterize cardiac pump function\(^15,17\), mean isovolumic pressure should be computed from a complete isovolumic pressure curve. The mean pressure is underestimated considerably using the conventional single beat methods (Figure 6).

Regen et al.\(^4\) proposed a more realistic wave shape of an isovolumic pressure. From LV measurements in dogs it was observed that normalized isovolumic pressure waves – normalized by maximum pressure and total cycle duration – were remarkably consistent in shape and independent of heart rate and contractility. In this study, we normalized the isovolumic waves by the moment of \(P_{\text{max}}\) as we observed that the waves showed even smaller variation between each other. This observation also suggests that the time to reach \(P_{\text{max}}\) is linearly related to contraction duration. The average of these normalized waves was then fitted to the isovolumic contraction part of an ejecting pressure, under the condition of approximately similar slopes in the relaxation phase of the ejecting and
(simulated) isovolumic beats. This approach has the advantage that the duration of isovolumic and ejecting beats should not necessarily be the same. From a physiological point of view this approach is appealing because the isovolumic relaxation phase is affected by shortening deactivation resulting in different timings between ejecting and non-ejecting beats, and is also underlying to the differences in $P_{\text{max}(APO)}$ and $P_{\text{max}(VCO)}$.

A similarity in consistency of the isovolumic wave shape can be drawn with the normalized time-varying elastance curve that was presented by Senzaki et al.\textsuperscript{12} The authors derived this curve from multiple pressure-volume loops in humans and found that it was consistent among various cardiomyopathies. In case an isovolumic (non-ejecting) condition is assumed, the shape can be considered as an isovolumic pressure wave shape and favors the application of a normalized isovolumic pressure wave to estimate $P_{\text{max}}$. In future research, it should be validated whether the normalized isovolumic pressure is also valid in other (disease) conditions, and whether there are shape differences between mammals.

In conclusion, all methods were able to estimate maximum isovolumic pressure with reasonable accuracy. Differences between methods increased with more severe PH. Using our method, the bias in estimates of maximum isovolumic pressure was almost independent of the disease condition. In case the complete wave shape of isovolumic pressure and mean isovolumic pressure are required (e.g. for constructing a pump-function graph) our method is preferable.

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Appendix

We used Fourier series to describe the normalized isovolumic pressure waveform \( P_{iso,N}(t_N) \) from the beginning of contraction to the end of relaxation. The Fourier series in trigonometric form read:

\[
P_{iso,N}(t_N) = \frac{a_0}{2} + \sum_{n=1}^{N} \left( a_n \cos\left(\frac{2\pi n t_N}{T_N}\right) + b_n \sin\left(\frac{2\pi n t_N}{T_N}\right) \right)
\]

with \( a_n \) and \( b_n \) the Fourier coefficients, and \( T_N \) the period of the normalized isovolumic wave. We found that six harmonics \( (N=6) \) were sufficient to describe the normalized curve accurately (figure 1). The Fourier coefficients values are provided in Table 1, and \( T_N \) was found to be 2.658.

To obtain an expression of the simulated (non-normalized) isovolumic pressure curve \( P_{iso,sim}(t) \), the normalized wave shape was parameterized by minimum pressure \( (P_{min}) \), maximum pressure \( (P_{max}) \), offset time \( (t_0) \), and moment of \( P_{max} \) \( (t_{Pmax}) \). These parameters are used to scale and recombine the Fourier coefficients to construct \( P_{iso,sim}(t) \) by the following expression:

\[
P_{iso,sim}(t) = \frac{a_0}{2} \left( P_{max} - P_{min} \right) + P_{min} + \left( P_{max} - P_{min} \right) \sum_{n=1}^{N} \left( a_n \cos\left(\frac{2\pi n (t-t_0)}{t_{Pmax} \cdot T_N}\right) + b_n \sin\left(\frac{2\pi n (t-t_0)}{t_{Pmax} \cdot T_N}\right) \right)
\]

The parameters are optimized by fitting \( P_{iso,sim}(t) \) to an ejecting beat (see methods section).

References

Table 1 - Fourier coefficients to describe $P_{iso,N}(t)$ the normalized isovolumic pressure (see Appendix).

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