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## **Title**

Time-synchronization of interventional cardiovascular magnetic resonance data using a biomechanical model for pressure-volume loop analysis

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### **Ethics approval and consent to participate**

The data collections for single-ventricle patients were performed under the ethical approvals of the Institutional Review Boards of UT Southwestern Medical Center Dallas (STU 032017-061). The data collections for rTOF patients were performed under the ethical approvals of the Institutional Review Boards of UT Southwestern Medical Center Dallas (STU-2020-0023) and UT Austin (IRB 2020-06-0128). The IRBs waived the need for a consent to use the anonymized retrospective data.

### **Running title**

Synchronization of pressure-volume data

## Introduction

Pressure-volume loops (*PV* loops) provide a meaningful insights into myocardial energetics (1, 2). Pressure-volume (*P-V*) data is often acquired by different modalities and subject to time-synchronization errors yielding skewed shapes of *PV* diagrams (Figure 1 (A)). A temporal dyssynchrony could be associated with cardiac magnetic resonance imaging (MRI) acquisition and reconstruction techniques: the temporal resolution of the scanner, the type of ECG trigger / gating (prospective vs. retrospective), averaging over cardiac cycles, and detection of R-peak from a wide QRS complex (3). In addition, some delays could arise from the inertia effect of the fluid-filled catheter that varies depending on the catheter type and size (4).

A complete synchronization of the *P-V* signals is possible when using an intraventricular conductance catheter. In other settings, a manual delineation of the isovolumic phases may be performed. However, such an approach can be suboptimal, e.g. in patients with valvular regurgitation due to the absence of clear isovolumic phases. We aim to develop a time-synchronization technique that is independent of the data acquisition methods or patients' pathophysiology by using patient-specific biomechanical model derived waveforms to detect *P-V* offsets in the measured data. Our previous pilot study demonstrated the potential of such an approach on *P-V* data acquired sequentially (volumetric data during cardiac MRI followed by pressure data during cardiac catheterization) without valvular regurgitation (3). In the present study we aim to extend the method for simultaneously acquired *P-V* data (i.e. during interventional cardiac MRI) and for patients with pulmonary regurgitation (i.e. right ventricles of patients with repaired tetralogy of Fallot, rTOF).

## Methods

## 2.1 Data

Datasets from two groups of patients were included in the study. The first group contained 10 patients with single-ventricle physiology undergoing interventional cardiac MRI within the pre-Fontan assessment.  $P$ - $V$  were acquired simultaneously at baseline and immediately after fluid administration providing 24  $P$ - $V$  datasets. Fluid boluses were administered either as a single 5 ml/kg bolus or as two 2.5 ml/kg boluses. A highly-accelerated prospective ECG-triggered cine bSSFP sequence (kt-BLAST factor 5, partial Fourier 0.625, slice thickness 10 mm, spatial resolution 2.4 x 2.4 x 10 mm) was used. Another group contained patients with rTOF with 17 left and 20 right ventricular  $P$ - $V$  datasets (rTOF-LV and rTOF-RV, respectively). A retrospective ECG-gated cine bSSFP sequence (SENSE 2, spatial resolution 2 x 2 x 10 mm) was used. Catheter pressures were sequentially acquired during pulmonary valve replacement therapy. Temporal resolution was ~30 ms in both groups and all acquisitions. A motion tracking algorithm (5) was used to obtain time-vs.-volume signals from cardiac MRI.

## 2.2. Biomechanical heart model

We employed a biomechanical heart model of a single heart cavity where the geometry and kinematics of the ventricle are represented by sphere (6) with constitutive mechanical laws describing active (contractile) and passive (viscoelastic) behavior of the myocardium. To model a cardiac cycle in patient-specific manner model parameters were tuned such that simulated waveforms corresponded to the maximum and minimum pressure and volume for a given patient (see e.g. (7)).

## 2.3 Time synchronization

The model was used as a template for temporal synchronization of original  $P$ - $V$  data. We assumed that synchronicity of simulated  $P$ - $V$  traces is given by the biophysical and physiological formulation of the model. We minimized the distance

between data and model waveforms (Figure 1 (B)) to detect the corresponding time offsets for  $t_{offset}^{pressure}$  and  $t_{offset}^{volume}$ .

$$\min_{t_{offset}} \int_0^{t_{end}} (f(t) - g(t - t_{offset}))^2 dt, \quad (1)$$

where  $f(t)$  and  $g(t)$  are the simulated and original ventricular pressure or volume, respectively;  $t_{end}$  is the end of the cardiac cycle in the original data. Total  $P$ - $V$  time offset was given by:

$$t_{offset}^{P-V} = abs(t_{offset}^{pressure} - t_{offset}^{volume}). \quad (2)$$

$PV$  loops were constructed for original and time-synchronized (t-syn) data. Quantitative evaluation of t-syn traces was derived from time-varying elastance (TVE). TVE (8), defined as  $E(t) = P(t)/V(t)$ , was computed from original and t-syn data, where  $P(t)$  and  $V(t)$  are ventricular pressures and volumes, respectively. According to TVE the isovolumic phase could be described as (9, 10):

$$\max(dP/dt) = \max(dE/dt) * EDV, \quad (3)$$

where  $\max(dP/dt)$  and  $\max(dE/dt)$  are maximum time derivatives of ventricular pressure and elastance, respectively, end-diastolic volume ( $EDV$ ) is assumed to be constant during isovolumic contraction. We confronted  $\max(dE/dt)$  derived from original and t-syn data ( $\max(E_{orig}/dt)$  and  $\max(E_{t-syn}/dt)$ , respectively) with respect to the  $\max(dP/dt)$  of the original pressure waveforms via linear regression analysis. Note that  $\max(dP/dt)$  does not change with time-synchronization.

Finally, the original, t-syn and model-derived values of maximum TVE (i.e.  $E_{max} = \max[P(t)/V(t)]$ ), and stroke work (i.e. area encompassed within the  $PV$  loop) were computed for each patient and statistically compared with Wilcoxon signed rank test at  $p < 0.05$ .

## Results

Figure 1 (D-F) shows t-syn *PV* loops for selected patients from all groups. The slope coefficients of linear regressions models (Coef) of  $\max(dE_{orig}/dt)$  vs.  $\max(dE_{t-syn}/dt)$  in single-ventricle patients were 1.279 vs. 1.040; in rTOF LVs 1.795 vs. 1.126; and in rTOF RVs 1.615 vs. 1.180 (Figure 2).

Mean ( $\pm$  SD) model-derived *P-V* offsets of single-ventricle patients were 0.059 ( $\pm$  0.022) s; of rTOF-LVs and rTOF-RVs 0.110 ( $\pm$  0.039) s and 0.116 ( $\pm$  0.032) s, respectively.

T-syn vs. original  $E_{max}$  ( $p=0.000$ ) and stroke work ( $p=0.000$ ) were significantly lower in all patients. The difference for model-derived vs. time-synchronized (1)  $E_{max}$  was not significant in all three groups ( $p>0.050$  in all patients), (2) stroke work was not significant for single-ventricle and rTOF LV ( $p>0.050$  in both groups) and significant for rTOF RV patients ( $p=0.000$ ), Figure 3.

## Discussion

We developed a biomechanical model-assisted time-synchronization technique for clinical *P-V* data. Time-synchronization qualitatively improves the shapes of *PV* loops in all patients. Quantitative improvement of t-syn data was demonstrated via stronger TVE relationship during isovolumic phase. In addition to that t-syn values of  $E_{max}$  and stroke work were significantly different from the non-synchronized ones. Therefore, time-synchronization of *P-V* data is crucial to derive meaningful values for ventricular energetics.

This model can replace noisy data traces, thus overcoming errors associated with data acquisition and/or processing protocols (e.g. missing part of the cardiac cycle, noise in the data, or non-physiological over-/undershoot in pressure measurements).

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## **List of abbreviations**

MRI	magnetic resonance imaging
ECG	electrocardiogram
LV	left ventricle
P-V	pressure-volume
QRS	QRS complex
rTOF	repaired tetralogy of Fallot
RV	right ventricle
TVE	time-varying elastance

## **Declarations**

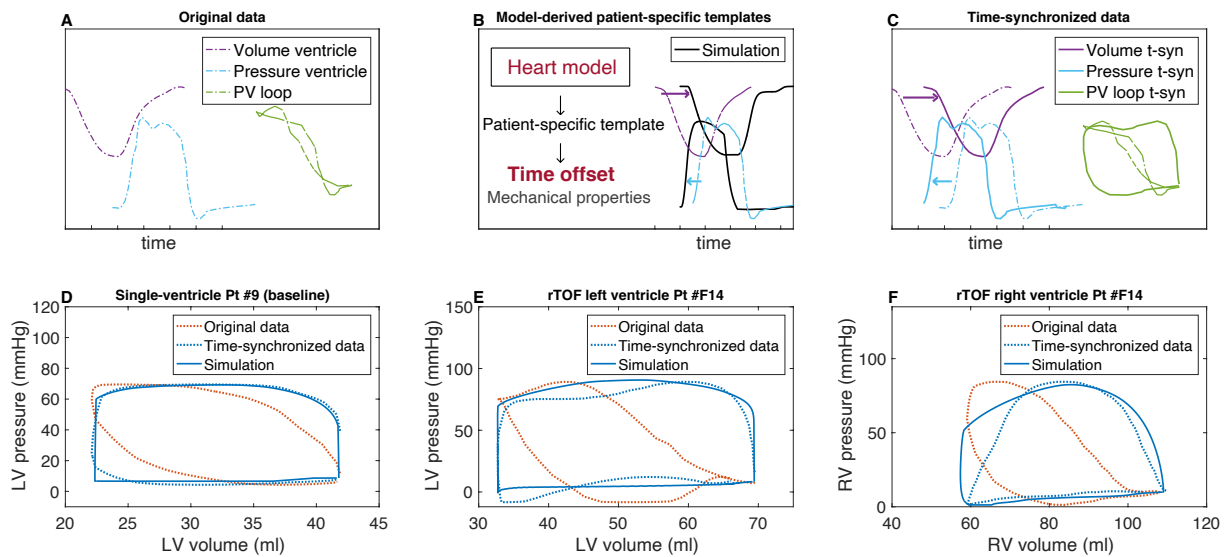
### **Availability of data and materials**

The datasets used in this study are available from the corresponding author on reasonable request.

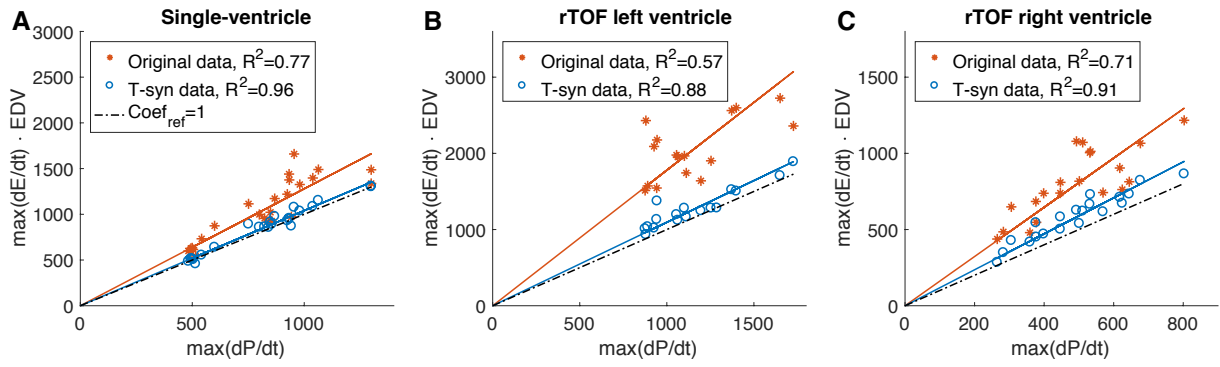
### **Competing interests**

The authors declare that they have no competing interests.

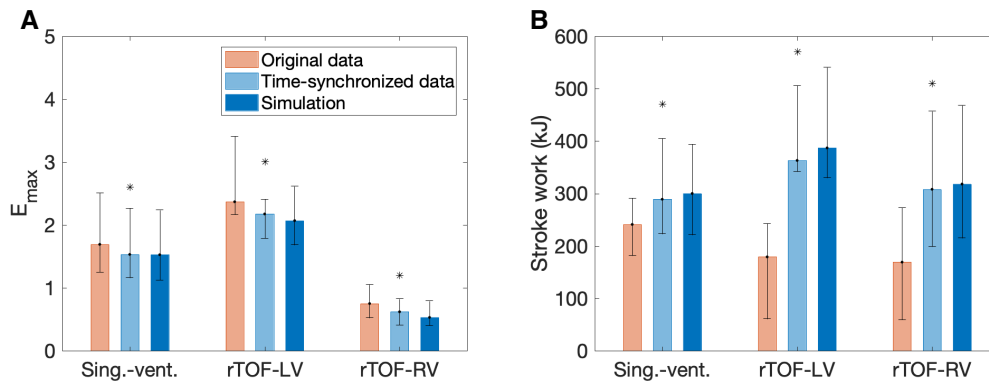
## Figures



**Figure 1:** Model-assisted time-synchronization of clinical pressure-volume data. A: Distorted pressure-volume loop (PV loop) due to the time offset between the acquired pressure and volume data illustrated on rTOF left ventricle Pt #AF24 from our study. B: Detection of the time offset by using patient-specific biomechanical model, simulating synchronous pressure and volume waveforms. C: Corrected PV loop (solid line) reconstructed from the time-synchronized (t-syn) data D: Pressure-volume loops for single-ventricle patient #9 at baseline (cine MRI is prospectively ECG-triggered). E-F: Pressure-volume loops for rTOF patient left and right ventricles (rTOF-LV and -RV, respectively), rTOF-RV Pt #F14 contains 11% and 30% of tricuspid and pulmonary regurgitation, respectively.



**Figure 2.** Linear regression models for original and time-synchronized (t-syn) data for single-ventricle patients (A), rTOF left ventricle (rTOF-LV) (B), and rTOF right ventricle (rTOF-RV) (C). Dotted black line is a reference linear model with slope ( $\text{Coef}_{\text{ref}}$ ) equal to 1.  $R^2$ : coefficients of determination of linear regression models.



**Figure 3.** Boxplot of original and time-synchronized indices of myocardial function in each patient group. A: maximum values of time-varying elastance ( $E_{max}$ ). B: stroke work (area encompassed within the pressure-volume loop). Bars correspond to the medians, upper and lower error bars are 75<sup>th</sup> and 25<sup>th</sup> percentiles, respectively. Asterisks show significant difference of time-synchronized data with respect to the original at  $p < 0.05$ . rTOF-LV/-RV: repaired tetralogy of Fallot left/right ventricle patients, respectively.