In vivo pressure-volume loops and chamber stiffness estimation using real-time 3D echocardiography and left ventricular catheterization – application to post-heart transplant patients

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Abstract. *In vivo* pressure-volume loops (PVLs) are the gold standard measurement to assess ventricular function. We developed a pipeline to integrate hemodynamic measurements with real-time three-dimensional (3D) echocardiographic data to construct *in vivo* PVLs for 25 post-heart transplant patients. We then evaluated left ventricular diastolic function for these patients by calculating chamber stiffness from a cubic polynomial fit of the diastolic pressure-volume relationships (PVR). We examined the ability of a well-established mathematical (Klotz) model to predict the patient-specific diastolic PVRs. We found that beat-to-beat variation in hemodynamic measurement was typical for this group of patients, which resulted in mean ± standard deviation end-diastolic chamber stiffness estimates of 0.75 ± 0.40 mmHg/ml. The cubic polynomial fits of the individual diastolic PVRs resulted in much smaller errors (0.25 ± 0.01 mmHg) compared to those associated with the Klotz predicted diastolic PVRs (4.0 ± 0.27 mmHg), which provided a poor representation of the *in vivo* diastolic PVRs. The proposed framework enables the temporal alignment between hemodynamic and 3D imaging data to produce *in vivo* PVLs that can be used not only to quantify global ventricular function, but also to estimate mechanical properties of the myocardium.

Keywords: In vivo pressure-volume loop, real-time 3D echocardiography, catheterization, chamber stiffness, heart transplant

1 Introduction

Historically, analyses of the left ventricular (LV) pressure-volume loops (PVLs) have been considered the gold standard for assessment of cardiac function under both *in vivo* and *ex vivo* conditions [1]. PVLs reflect the most direct relationship between pressure and volume inside the LV and allow the derivation of other mechanical properties of the heart, such as chamber stiffness and end-systolic elastance [1]. Methods for measuring PVLs can be broadly categorized as: 1) simultaneous measurements of pressure and volume via a micromanometric conductance catheter [2]; and 2) image-based methods that combine catheterization measurements with cardiac geometric data derived from imaging, such as cardiac magnetic resonance (CMR) imaging or echocardiographic (echo) imaging [3, 4]. While conductance catheters allow for synchronized acquisitions of pressure and volume measurements, the accuracy of LV volume measurement remains limited and often involves a calibration against other types of imaging techniques such as ventriculography [5]. The advancement of non-invasive cardiac imaging has improved the accuracy and accessibility of LV volume quantification. However, accurate temporal registration between LV pressure and volume is not well developed. We have previously described a piecewise linear temporal scaling method based on cardiac events, identified on both invasive pressure traces and cine CMR images [3]. Time delays between catheterization and CMR can lead to discrepancies in haemodynamic states between the two data acquisitions. Real-time 3D-echocardiography (RT3DE) has evolved to a readily available and cost-effective modality for rapid LV assessment. Furthermore, scanner portability enables imaging to be performed immediately after catheterization, thereby minimizing time-dependent hemodynamic variability.

While chamber stiffness is straightforward to calculate, it is also load- and geometry-dependent, making it challenging to discern diastolic dysfunction at the myocardial tissue level. On the other hand, intrinsic myocardial tissue stiffness can only be estimated using inverse finite element modeling techniques. Personalized finite element modeling of ventricular mechanics generally requires patient-specific measurements of heart anatomy and motion across the cardiac cycle, hemodynamic loading conditions, and microstructural information. Estimation of the passive myocardial tissue stiffness can then be made by matching the model-predicted diastolic PVR with subject-specific PVR and/or global and regional deformations derived from imaging data. Although the diastolic PVR provides information about LV filling characteristics, personalized measurements of the PVR are not routinely available. Instead, an algebraic mathematical model, known as the Klotz curve [6], has been adopted in many studies to predict an individualized PVR based on a single set of pressure and volume estimates [7, 8]. However, to the authors' knowledge, there are no published reports that have compared the Klotz-predicted diastolic PVR with catheterization measurements.

In the present study, we propose a framework for temporally registering invasive LV and aortic pressures (LVP and AOP) acquired during left heart catheterization with RT3DE images to generate *in vivo* PVLs in a group of heart transplant (HTx) patients.

We estimated chamber stiffness from the diastolic pressure-volume relationships (PVRs) for each patient and examined the subject-specific variability. Lastly, we investigated the predictive power of the Klotz model for the HTx patient cohort to examine its suitability to estimate an individualized single-beat diastolic PVRs.

2 Methods

Orthotopic heart transplantation patients (HTx) attending for routine coronary assessment were recruited for invasive hemodynamic measurement and RT3DE imaging. Ethical approval for the present study was granted by the Health and Disability Ethics Committee of New Zealand (17/NTB/46), and written informed consent was obtained from each participant. 49 post-HTx patients were prospectively enrolled and 25 cases were selected for analysis based on satisfactory apical echocardiographic windows for 3D geometric modelling and adequate hemodynamic data quality.

2.1 In vivo data collection

LV catheterization. A fluid-filled pigtail catheter (Impulse by Boston Scientific, Marlborough MA) was advanced into the LV through the aortic valve via radial access under X-ray guidance. Four continuous multi-cycle recordings (i.e., over 9-15 heartbeats) of LV cavity pressure were obtained using the Mac-Lab Hemodynamic Recording System (GE Healthcare, Chicago, IL, USA). The catheter was then withdrawn from the LV into the aorta, where AOPs were recorded for a similar period as the LVPs at the root of the aorta and aortic arch. An electrocardiogram (ECG) was simultaneously recorded during the entire procedure at a sample rate of 240 Hz.

RT3DE imaging. Within an hour of catheterization, single-beat transthoracic RT3DE volumetric imaging of the LV was performed using a Siemens ACUSON SC2000 Ultrasound System with a 4Z1c transducer (Siemens Medical Solutions, CA, USA) from the apical window in a left lateral decubitus position. Imaging parameters were optimized for each patient to maximize the temporal resolution while maintaining an adequate spatial resolution (reconstructed to 1 mm^3 isotropic voxels in Cartesian space) for geometric analysis. This resulted in between 15-41 imaging frames per cardiac cycle across the study population.

2.2 Data analysis

Hemodynamic analysis. A piecewise linear temporal scaling method based on cardiac events of CMR images [3] was extended to handle RT3DSE. LVPs and AOPs were processed using an in-house analysis tool written in Matlab R2020b (MathWorks Inc., Natick, MA, USA). Noise was removed interactively using a Fourier transform with a participant-specific low-pass filter with frequencies ranging from 10.3 Hz to 20 Hz. Breathing artifacts, which manifested as low-frequency shifts of the LVP traces across

the cardiac cycles, were corrected with a high-pass filter with cut-off frequencies ranging up to 0.83 Hz. The difference in cut-off frequencies to remove breathing artifacts was mainly due to variations in patients' breathing motion. R-peaks were identified on the ECG traces and used to isolate the LVP and AOP traces from individual cycles. For the analyses, the following exclusion criteria were used: 1) no arrhythmia; 2) no visible pressure overshoot (e.g. air bubbles in the catheter can cause a positive LVP overshoot during ejection, and a LVP undershoot during relaxation [9]); and 3) acceptable noise.

For temporal alignment with RT3DE imaging data, we identified five cardiac events in the pressure traces (Fig. 1a) based on characteristics described in Table 1. Although identification of end-diastole (ED) and end-systole (ES) is well described in the literature, methods for identifying end of isovolumic contraction (eIVC), end of isovolumic relaxation (eIVR), and diastasis (DS) are sparsely discussed. DS is often assumed to correspond to the minimum LVP by commercial hemodynamic analysis software. However, neither pressure nor volume changes substantially at diastasis, thus the minimum pressure may not necessarily be the diastatic pressure, as rapid recoil during IVR can cause a significant drop of LVP due to a suction effect.

Geometric modeling. Semi-automatic analysis of RT3DE volumetric imaging data was performed offline using EchoBuildR 3.5.1 prototype software (Siemens Medical Solutions, CA, USA) [10, 11]. In our imaging protocol, RT3DE from 4 cardiac cycles were typically acquired, but only the cycle with the best imaging quality was used for geometric modeling. Geometric LV models were manually constructed at ED and ES, followed by automatic tracking across intermediary frames to estimate LV volume and mass over the entire cardiac cycle. Image frames corresponding to the same five cardiac events identified for hemodynamic analysis were manually identified for each RT3DE dataset (Fig. 1b) using the methods described in Table 1.

Table 1. Characteristics of key cardiac events in LVP trace and RT3DE.

Cardiac event	Pressure trace	RT3DE
End-diastole (**ED**)	Rapid change in LVP slope occurs (maximum rate of change of acceleration)	R peak of the ECG and closure of the mitral valve
End of isovolumic contraction (**eIVC**)	LVP equal to minimum AOP, beyond which aortic valve opens	Sudden LV and/or opening of the aortic valve
End-systole (**ES**)	LVP equal to the AOP at dicrotic notch	Maximal LV contraction and/or aortic valve closure
End of isovolumic relaxation (**eIVR**)	Maximum change of rate of LVP (peak d^2P/dt^2)	Instance prior to the opening of the mitral valve
Diastasis (**DS**)	Inflection point of the LVP trace ($d^2P/dt^2=0$)	Plateau in volume curve or partial mitral valve closure

In vivo PVL generation. After identifying cardiac events, the individual pressure traces were divided into five segments: DS to ED, ED to eIVC, eIVC to ES, ES to eIVR, and eIVR to DS. Each segment of each loop was temporally scaled to match the duration of the respective echo segment and sampled at the echo imaging time points,

which had coarser temporal resolution compared to the hemodynamic measurements, This resulted in multiple pressure values for each echo frame due to beat-to-beat variation in LVP. The temporally aligned pressure values were further averaged to find the beat-averaged LV PVL (Fig. 1c). The number of cycles used for beat averaging ranged between 5 to 14 cycles.

In vivo diastolic PVRs. To analyze diastolic PVRs, we isolated the portion of the PVL between DS and ED for each cardiac cycle. Quantification of chamber stiffness can be made by fitting a function to the diastolic PVRs, then evaluating the slope (dP/dV) of the fitted curve at LVEDV. A range of equations (e.g. exponential, polynomial, power laws) is summarized in [1], among which a mono-exponential with an offset is commonly adopted in the field. However, when we fitted the diastolic PVRs using the mono-exponential equation, we found that the fitted curves did not adequately represent the underlying data particularly at ED, which led to inaccurate estimation of the slope of the curve at LVEDV, and hence chamber stiffness. Instead, we fitted the diastolic PVRs using a cubic polynomial and obtained much more accurate fits to the data.

Next, we normalized the diastolic PVRs using maximum and minimum pressure and volume to examine whether the normalized curves conformed to one single relationship as proposed in [6]. Using the coefficients (A and B) published in their study, we estimated model-predicted diastolic PVRs using subject-specific EDV and EDP as input for the algorithm. To examine the accuracy of the Klotz model-predicted diastolic PVRs, we evaluated LV pressures at the LV cavity volumes estimated from RT3DE between DS and ED, and then calculated the root-mean-squared error (RMSE) between Klotz predicted LV pressures and the corresponding *in vivo* measurements.

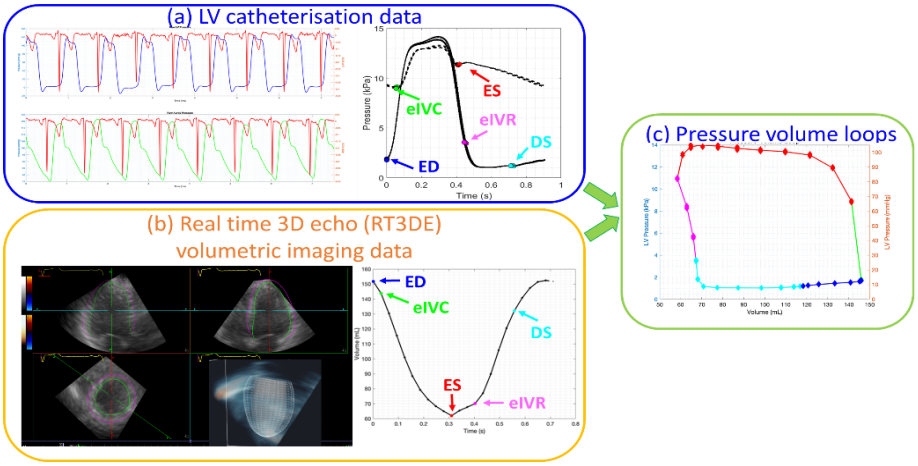

Fig. 1. Patient-specific input data for generation of *in vivo* pressure-volume loops.

3 Results

3.1 Demographics and functional indices

A summary of patient demographics and functional indices is shown in Table 2. The mean age was 54 years (± 8) and 7 (28%) were women. The mean LV ejection fraction (EF) was 58 ± 6% while only two patients had an EF below 50%, indicating majority of these patients have preserved EF.

Table 2. Patient demographics and LV functional indices (EF = ejection fraction).

Index (mean ± S.D.)	Male (*n* = 18)	Female (*n* = 7)	**Total (*n* = 25)**
Age (years)	54 ± 7	55 ± 9	54 ± 8
Height (cm)	178 ± 9	165 ± 3	174 ± 10
Weight (kg)	83 ± 11	69 ± 13	79 ± 13
Body surface area (m^2)	2.02 ± 0.17	1.77 ± 0.17	1.95 ± 0.20
EF (%)	56 ± 5	63 ± 3	58 ± 6

3.2 *In vivo* LV PVLs and diastolic function

Multiple *in vivo* PVLs were constructed for each patient based on the number of selected cardiac cycles for hemodynamic analysis and a beat-averaged PVL (Fig. 2a) was also generated for each of the 25 post-HTx patients. With the exception of one case, the beat-averaged PVLs exhibited classically representative shape with distinct isovolumic contraction and isovolumic relaxation phases. Of the 25 patients, 2 patients showed a significantly higher LVESP than the others, while 6 patients had LVEDPs greater than 15 mmHg (2 kPa), indicating potential diastolic dysfunction.

The individual diastolic PVRs for all patients are shown in Fig. 2b, with beat-to-beat variation observed in most patients. For some cases, the variation manifested as an offset in LVP, whereas changes in the diastolic PVR slope were observed in other cases. The mean chamber stiffness across all patients was 0.75 ± 0.40 mmHg/ml (interquartile range (IQR): [0.51 0.86] mmHg/ml) and the mean beat-to-beat variation in chamber stiffness across all patients was 0.12 ± 0.06 mmHg/ml (IQR: [0.08 0.13] mmHg/ml), which were calculated using the chamber stiffness standard deviations across each set of cycles recorded for each participant.

3.3 Klotz prediction of diastolic PVR

The Klotz predicted diastolic PVRs for one representative case are shown in Fig. 2c along with the *in vivo* measurements. By definition, all Klotz predicted diastolic PVRs matched LVEDV and LVEDP, but the predicted LV pressures at other LV volumes were less accurate. The normalized diastolic PVRs for all 25 patients (Fig. 2d) did not conform to one single relationship as suggested in [6]. The nonlinearity of the diastolic PVRs differed across the HTx cohort. The average RMSE between *in vivo* diastolic

PVRs and those predicted by the Klotz model was 4.0 ± 0.27 mmHg (IQR: [2.6 5.8] mmHg). In comparison, the average RMSE for the cubic polynomial fit was only 0.25 ± 0.01 mmHg (IQR: [0.13 0.28] mmHg).

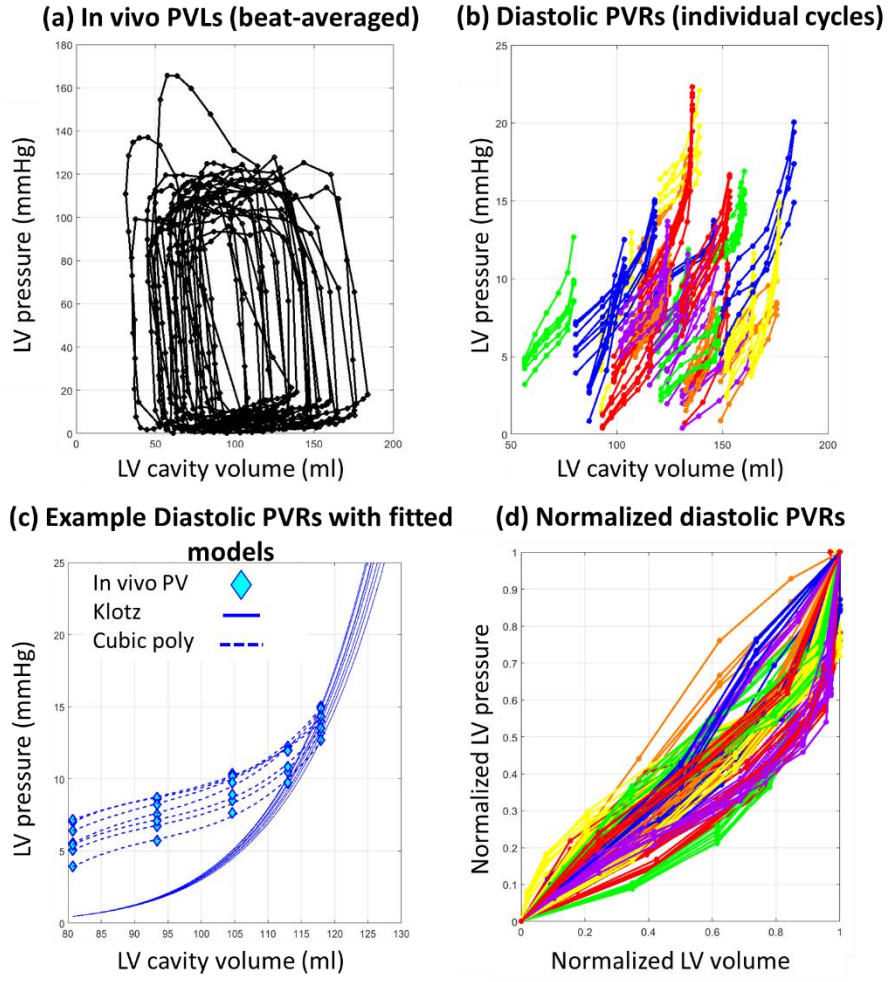

Fig. 2. a) Beat-averaged *in vivo* pressure-volume loops (PVLs) for all 25 post-HTx patients. b) Individual diastolic pressure-volume relationships (PVRs). c) Raw diastolic PVRs (diamonds) overlaid with cubic polynomial and Klotz fitted diastolic PVRs. d) Normalized diastolic PVRs.

4 Discussion

In the present study, a framework was developed to construct subject-specific PVLs using *in vivo* hemodynamic measurements and RT3DE data from the same subject,

acquired within an hour of left heart catheterization. We proposed an algorithm to identify key cardiac events from the LVP and AOP traces as well as from the LV cavity volume-time curve quantified from RT3DE. Recognizing that a uniform temporal scaling based on the R-R interval difference was insufficient to align the pressure and volume data temporally, we implemented temporal scaling for each of the five cardiac phases individually. This scheme resulted in excellent *in vivo* PVLs with well-preserved isovolumic phases for the group of 25 HTx patients in comparison to previous studies [4, 5]. The constructed *in vivo* PVLs represent an efficient diagnostic tool for clinicians to gauge LV function for patients undergoing catheterization. It not only allows calculation of chamber stiffness, but it also enables estimation of indices that reflect cardiac energetics, such as stroke work and cardiac work, which are difficult to calculate without PVLs. For patients with cardiac interventions such as heart/lung transplantation, it is also a useful tool to monitor a patient's response to surgery.

Chamber stiffness is used widely to characterize ventricular diastolic function, and can be calculated directly from the diastolic PVR. It has been considered as an important indicator of diastolic dysfunction, which manifests as restrictive filling for HTx patients. In the present study, the chamber stiffness estimated for the HTx patients (0.75 ± 0.40 mmHg/ml) was larger than that reported for groups of control subjects with normal LV function (0.16 ± 0.11 mmHg/ml [2]; 0.09 [IQR:0.07,0.12] mmHg/ml [5]), and for patients with heart failure with preserved LV ejection fraction (0.24 [IQR:0.16,0.37] mmHg/ml) [5]. It is worth noting that the chamber stiffness derived in the present study was based on single beat diastolic PVRs, while the aforementioned studies transiently reduced the preload to measure EDPVRs, which may partially explain the differences in chamber stiffness estimates.

Direct measurement of LVP is not routinely accessible due to the invasive nature of the procedure. Consequently, several studies have used the Klotz model to estimate the diastolic PVR on a per-subject basis for the purpose of estimating myocardial tissue stiffness [7, 8]. Based on the *in vivo* diastolic PVRs in the present study, we found that the shape of the normalized diastolic PVRs was very different among the patients as opposed to a single relationship reported in [6]. The RMSE in the Klotz predicted diastolic PVRs ranged between 2.6 mmHg (25% quartile) and 5.8 mmHg (75% quartile), illustrating its inability to predict *in vivo* diastolic PVR accurately. These errors are comparable to the RMSE (2.79 ± 0.21 mmHg) previously reported in heart failure patients in [12], which showed poor prediction at low pressures (e.g. <10 mmHg). Such inaccuracies in the prediction of the diastolic PVR may confound estimates of passive myocardial stiffness.

The beat-to-beat variation observed in these patients is mostly due to the variability in hemodynamic measurements over several cardiac cycles because the volume estimate was derived from a single cardiac cycle. While this approach did not provide concurrent pressure and volume measurements, the volume measurement obtained from RT3DS is much more accurate. The quantification of beat-to-beat variation and reproducibility of volume from RT3DE was beyond the scope of the present study. However, previous experiments have demonstrated that RT3DE is able to provide low test-retest variation and high reproducibility of LV volumes [13, 14]. In addition, we ensured that the cavity volume used for generation of *in vivo* PVLs was derived from the cardiac

cycle with the best imaging quality. Nevertheless, this framework can be readily extended to construct a family of *in vivo* PVLs based on multi-cycle pressure and volume data.

5 Conclusion

We proposed a framework to construct patient-specific *in vivo* PVLs from hemodynamic measurements obtained during left heart catheterization and cavity volume quantified from RT3DE using a temporal alignment scheme based on cardiac events. Application to patients post heart transplantation revealed beat-to-beat variation of hemodynamic state. Normalized diastolic PVRs showed varying degrees of nonlinearity among the patients, suggesting that the use of a simple algebraic mathematical model for the prediction of subject-specific diastolic PVR is insufficient.

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References

1. Burkhoff, D., Mirsky, I., Suga, H.: Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. American Journal of Physiology-Heart and Circulatory Physiology 289, H501-H512 (2005)
2. Zhang, W., Kovács, S.J.: The diastatic pressure-volume relationship is not the same as the end-diastolic pressure-volume relationship. American Journal of Physiology-Heart and Circulatory Physiology 294, H2750-H2760 (2008)
3. Wang, Z.J., Wang, V.Y., Bradley, C.P., Nash, M.P., Young, A.A., Cao, J.J.: Left Ventricular Diastolic Myocardial Stiffness and End-Diastolic Myofibre Stress in Human Heart Failure Using Personalised Biomechanical Analysis. Journal of Cardiovascular Translational Research 11, 346-356 (2018)
4. Chowdhury, S.M., Butts, R.J., Hlavacek, A.M., Taylor, C.L., Chessa, K.S., Bandisode, V.M., Shirali, G.S., Nutting, A., Baker, G.H.: Echocardiographic Detection of Increased Ventricular Diastolic Stiffness in Pediatric Heart Transplant Recipients: A Pilot Study. Journal of the American Society of Echocardiography 31, 342-348.e341 (2018)
5. Westermann, D., Kasner, M., Steendijk, P., Spillmann, F., Riad, A., Weitmann, K., Hoffmann, W., Poller, W., Pauschinger, M., Schultheiss, H.-P., Tschöpe, C.: Role of Left Ventricular Stiffness in Heart Failure With Normal Ejection Fraction. Circulation 117, 2051-2060 (2008)

6. Klotz, S., Hay, I., Dickstein, M.L., Yi, G.-H., Wang, J., Maurer, M.S., Kass, D.A., Burkhoff, D.: Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. American Journal of Physiology-Heart and Circulatory Physiology 291, H403-H412 (2006)
7. Rumindo, G.K., Ohayon, J., Croisille, P., Clarysse, P.: In vivo estimation of normal left ventricular stiffness and contractility based on routine cine MR acquisition. Medical Engineering & Physics 85, 16-26 (2020)
8. Genet, M., Lee, L.C., Nguyen, R., Haraldsson, H., Acevedo-Bolton, G., Zhang, Z., Ge, L., Ordovas, K., Kozerke, S., Guccione, J.M.: Distribution of normal human left ventricular myofiber stress at end diastole and end systole: a target for in silico design of heart failure treatments. Journal of Applied Physiology 117, 142-152 (2014)
9. de Vecchi, A., Clough, R.E., Gaddum, N.R., Rutten, M.C.M., Lamata, P., Schaeffter, T., Nordsletten, D.A., Smith, N.P.: Catheter-induced errors in pressure measurements in vessels: an in-vitro and numerical study. IEEE Trans Biomed Eng 61, 1844-1850 (2014)
10. Zheng, Y., Barbu, A., Georgescu, B., Scheuering, M., Comaniciu, D.: Four-chamber heart modeling and automatic segmentation for 3-D cardiac CT volumes using marginal space learning and steerable features. IEEE transactions on medical imaging 27, 1668-1681 (2008)
11. Lin, Y., Georgescu, B., Yefeng, Z., Meer, P., Comaniciu, D.: 3D ultrasound tracking of the left ventricle using one-step forward prediction and data fusion of collaborative trackers. In: 2008 IEEE Conference on Computer Vision and Pattern Recognition, pp. 1-8. (Year)
12. ten Brinke, E.A., Burkhoff, D., Klautz, R.J., Tschöpe, C., Schalij, M.J., Bax, J.J., van der Wall, E.E., Dion, R.A., Steendijk, P.: Single-beat estimation of the left ventricular end-diastolic pressure–volume relationship in patients with heart failure. Heart 96, 213-219 (2010)
13. Thavendiranathan, P., Liu, S., Verhaert, D., Calleja, A., Nitinunu, A., Van Houten, T., De Michelis, N., Simonetti, O., Rajagopalan, S., Ryan, T., Vannan, M.A.: Feasibility, Accuracy, and Reproducibility of Real-Time Full-Volume 3D Transthoracic Echocardiography to Measure LV Volumes and Systolic Function: A Fully Automated Endocardial Contouring Algorithm in Sinus Rhythm and Atrial Fibrillation. JACC: Cardiovascular Imaging 5, 239-251 (2012)
14. Jenkins, C., Bricknell, K., Hanekom, L., Marwick, T.H.: Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. Journal of the American College of Cardiology 44, 878-886 (2004)