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1 Simultaneous pressure-volume measurements using optical sensors and MRI  
2 for left ventricle function assessment during animal experiment

3 Dima Abi-Abdallah Rodriguez<sup>a,b\*</sup>, Emmanuel Durand<sup>a,b</sup>, Ludovic de Rochefort<sup>a,b</sup>, Younes Boudjemline<sup>c,d</sup>  
4 and Elie Mousseaux<sup>c,e</sup>

5 <sup>a</sup>*Univ Paris-Sud, IR4M, UMR8081, Orsay, France*

6 <sup>b</sup>*CNRS, IR4M, UMR8081, Orsay, France*

7 <sup>c</sup>*Univ Paris 05, France*

8 <sup>d</sup>*Hôpital Necker-Enfants malades, AP HP, Paris, France*

9 <sup>e</sup>*INSERM, U678, Paris, France*

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10 \*Corresponding author email : [dima.rodriguez@u-psud.fr](mailto:dima.rodriguez@u-psud.fr)

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12 **Abstract**

13 Simultaneous pressure and volume measurements enable the extraction of valuable parameters for left  
14 ventricle function assessment. Cardiac MR has proven to be the most accurate method for volume estima-  
15 tion. Nonetheless, measuring pressure simultaneously during MRI acquisitions remains a challenge given  
16 the magnetic nature of the widely used pressure transducers. In this study we show the feasibility of si-  
17 multaneous *in vivo* pressure-volume acquisitions with MRI using optical pressure sensors. Pressure-volume  
18 loops were calculated while inducing three inotropic states in a sheep and functional indices were extracted,  
19 using single beat loops, to characterize systolic and diastolic performance. Functional indices evolved as  
20 expected in response to positive inotropic stimuli. The end-systolic elastance, representing the contractility  
21 index, the diastolic myocardium compliance, and the cardiac work efficiency all increased when inducing  
22 inotropic state enhancement. The association of MRI and optical pressure sensors within the left ventri-  
23 cle successfully enabled pressure-volume loop analysis after having respective data simultaneously recorded  
24 during the experimentation without the need to move the animal between each inotropic state.

## 1. Introduction

The evaluation of the left ventricle (LV) performance is of high importance in physiologic investigation and clinical practice. The diastolic LV function can be assessed by evaluating relaxation properties and myocardium stiffness during the filling process. As for the systolic LV performance, it is governed by three principal factors, preload, afterload and the contractile or inotropic state of the myocardium. The first two determinants can be relatively easily measured or evaluated, but assessing contractile state is far more difficult. Any index intended to reflect contractility must be load-independent.

Common studies evaluate contractility using left ventricular stroke volume (SV), ejection fraction (EF) and cardiac output (CO). Though intuitive and simple, these parameters are load-dependent and consequently represent poor contractility indices. For instance, they are not good indicators of heart failure and cardiac dysfunction Maeder and Kaye [26], Gaddam and Oparil [11]. Other studies rely on pressure measurements alone to assess the LV performance. They evaluate, for example, the maximum rate of pressure change ( $dP/dt_{max}$ ) which is known to be sensitive to inotropic state and thus correlates with cardiac contractility. Nonetheless, its load-dependence Grossman et al. [15], Kass et al. [19], Mason et al. [27] makes it a weak contractility indicator. The peak decline of pressure ( $dP/dt_{min}$ ), on the other hand, can quantify isovolumic relaxation, but it cannot be qualified as an intrinsic relaxation index since it is preload-dependent Cohn et al. [6] as well as afterload-dependent Weiss et al. [47]. A widely used parameter for the relaxation quantification is the time constant  $\tau$  which characterizes the pressure decay during isovolumic relaxation. Despite being preload-independent Varma et al. [46],  $\tau$  cannot be considered an ideal index because of its afterload dependence.

No perfect assessment index can be obtained from volume or pressure alone. Indeed, volume or pressure measurements on their own are not sufficient to characterize the systolic performance, they cannot solely define contractility and cardiac response to inotropic agents. Simultaneous pressure and volume measurements are necessary to provide valuable functional parameters. Pressure indices can thus be coupled with volume information to negate load dependence. For example, rather than considering  $dP/dt_{max}$ , the relationship of this value to end diastolic volume (EDV) can be computed by varying preload conditions. This relationship is linear and its slope provides a preload-independent contractility index Little [24]. The relaxation constant  $\tau$  can also be evaluated over a range of afterloads and plotted against EDV Zile and

53 Brutsaert [49].

54 In addition, a wide variety of indices that can be quantified by analyzing pressure-volume (PV) loops  
55 have been proposed to characterize the left ventricle systolic and diastolic performance. For instance a  
56 straightforward characterization of the myocardium stiffness can be obtained from the slope of the pressure-  
57 volume relationship during diastole. Furthermore, a measurement of the ventricular elastance when the  
58 contractile forces in the ventricle are at their peak, constitutes a good indicator of the ventricular contractility  
59 and systolic function. Known as end-systolic elastance  $E_{es}$ , it is independent of preload, afterload and heart  
60 rate Brinke et al. [3], Suga [40]. The arterial system, as afterload, can also be assessed from the PV loop,  
61 and, like the ventricle chamber, it can be characterized by its elastance  $E_a$ . Studies have shown the  
62 importance of  $E_a$  as a descriptor of the vascular load and its impact on cardiac performance Hayashida  
63 et al. [16], Kelly et al. [20], indicating that the ratio  $E_a/E_{es}$  quantifies the coupling between the ventricle  
64 and arterial system and governs ventriculoarterial matching. Additionally, PV loop area analysis can provide  
65 an evaluation of mechanical energies of a ventricular beat and an assessment of the LV efficiency.

66 To measure the ventricle volume, the conductance catheter technique has been used extensively, it is  
67 based on the electrical conductance of the blood contained in the cavity. This technique, nonetheless, is  
68 based on geometric assumptions, needs volume-dependent calibration and is limited by the non-linearity of  
69 the conductance-volume relation when large volume changes are involved Danton et al. [7]. Furthermore,  
70 it relies on Ohm's law which might not be fully appropriate due to the non-uniformity of the composition  
71 of ventricle and blood, and uses correction parameters that are error prone due to ventricle geometry and  
72 wall thickness changes during contraction Jacoby et al. [17]. Volume assessment using cine cardiac MR are  
73 proven to yield a more accurate and reliable estimate Jacoby et al. [17], Winter et al. [48]. For PV loop  
74 construction, simultaneous volume and pressure measurements are necessary, but given the magnetic nature  
75 of standard pressure sensors, this is problematic during MRI. The pressure signal would be contaminated  
76 by the MR environment and the presence of the sensor would produce artifacts on the image.

77 In this paper we present a feasibility study for simultaneous pressure measurements using optical sensors  
78 during MRI to produce valid indices for the assessment of LV function. *In vivo* measurements on one sheep  
79 were performed and pressure-volume loops were derived by combining MRI-estimated ventricular volumes  
80 with simultaneous on-site pressure measurements for various inotropic states. PV loops were analyzed and

81 functional parameters were computed to evaluate the response to inotropic agents.

## 82 **2. Methods**

### 83 *2.1. Experimental Protocol*

#### 84 *Animal preparation*

85 Two female sheep were used in this study. An intervention on the first sheep was performed to compare  
86 the optical pressure sensor measurements against the Millar standard probes. A subsequent intervention on  
87 another sheep allowed simultaneous pressure and volume measurements. The ewes were placed in a sitting  
88 position to induce reflex akinesia then anesthetized with a slow injection of 1 g of diluted thiopental. Tracheal  
89 tube was inserted and forced ventilation was started with a concentration of 1.5-2% isoflurane to maintain  
90 anesthesia. To prevent clotting, acetylsalicylic acid (0.5 g) and heparin (3000 IU) were injected intravenously.  
91 The carotid artery was catheterized and a vascular dilator was inserted under X-ray monitoring. The animals  
92 received humane care in compliance with the standards of the European Convention on Animal Care. The  
93 study was approved by a local institutional ethics committee (INRA, Paris, France). Qualified personnel  
94 supervised the procedures and adequate anesthesia was used to minimize unnecessary pain.

#### 95 *In vivo pressure measurements*

96 An optical pressure sensor probe (model OPP-M, Opsens, Quebec, Canada) based on the white-light  
97 polarization interferometry technique was used. The probe tip, 0.4 mm in diameter and 0.5 mm in length,  
98 attached to a 10 m long optical fiber directly transduces pressure into an optical signal which is then  
99 sampled at 1kHz. This device is fully MRI compatible, and immune to radiofrequency effects. The sensor  
100 is linear, with a total error of 2 mmHg and a temperature sensitivity of 0.2 mmHg/°C. Furthermore, each  
101 probe has two specific constant calibration factors. The nude fiber was sheathed into a non-magnetic 4F  
102 catheter (C4F100D, Balt extrusion, Montmorency, France) 1 m in length. The sensor was positioned 5 mm  
103 before the catheter tip, facing a slot that had been manually cut in the catheter wall to ensure pressure  
104 transmission. The fiber was then glued into the catheter through another slot 5 mm above. A null point  
105 was set prior to inserting the sensor inside the sheep by zeroing the measurement at atmospheric pressure.

106 The validation of the optical probe against a reference pressure transducer (Millar, Houston, USA) was  
107 performed during an aortic intervention that served wider purposes than those stated in the present paper.  
108 During the intervention, the mounted optical probe and the Millar sensor were inserted simultaneously

109 through the dilator up to the aorta of a 56kg ewe. Pressure was recorded *in vivo* outside the magnet for  
110 about 5 minutes including 20 seconds during which ventilation was stopped to acquire a stable signal with  
111 no respiration modulation.

#### 112 *Simultaneous in vivo pressure and volume measurements*

113 Pressure measurements with the optical probes were conducted simultaneously with MRI acquisitions in  
114 another female sheep (60 kg). After four acquisitions at a baseline condition (heart rate ranging between 78  
115 and 83 bpm), the sheep was infused dobutamine at a rate of 5  $\mu\text{g}/\text{kg}/\text{min}$ . Heart rate increased to 145-150  
116 bpm and three acquisitions were performed. Dobutamine rate was then decreased to 2.5  $\mu\text{g}/\text{kg}/\text{min}$  (heart  
117 rate decreased to 125-131 bpm) and a last acquisition was performed before waking the animal up. The  
118 whole MR procedure lasted 2 hours and 20 minutes.

#### 119 *MRI acquisitions*

120 Cardiac imaging was performed with a 1.5 T MR scanner (Philips Medical Systems, Achieva) with a  
121 5-element SENSE cardiac array coil and ECG triggering. After calibration and scouting sequences, true  
122 FISP gated cine images ("balanced TFE") were acquired in 12 sequential 8-mm short-axis slices (2 mm  
123 interslice gap) from the apex to the atrial-ventricular ring, for 30 cardiac phases (TE/TR= 1.7ms/3.4ms,  
124 flip angle of  $60^\circ$ , field of view= $320 \times 240 \text{ mm}^2$ , matrix= $256 \times 192$ , voxel size 1.25mm, echo train length  
125 of 10, readout bandwidth 1042 Hz). Mechanical ventilation was continued during the MRI acquisition  
126 procedures without respiratory synchronization. Other sequences were also acquired for other purposes, not  
127 mentioned here.

#### 128 *2.2. Offline Pressure-Volume loop calculation*

129 For each slice, the LV was delineated semi-automatically and its area was computed then multiplied  
130 by the slice thickness to derive an elementary volume. These slice volumes were then added up to define  
131 the total LV volume. This was performed for all cardiac phases, and an LV volume evolution in time was  
132 obtained. During each of the imaging sessions the ventricular pressure was recorded continuously. Since we  
133 only have one volume curve reflecting a somewhat average volume evolution during the image acquisition,  
134 an average pressure cycle was derived for the loop computation. Figure 1 summarizes the cycle calculation.  
135 To delimit a heart cycle, pressure peaks were considered to be the end points of a pressure period. By

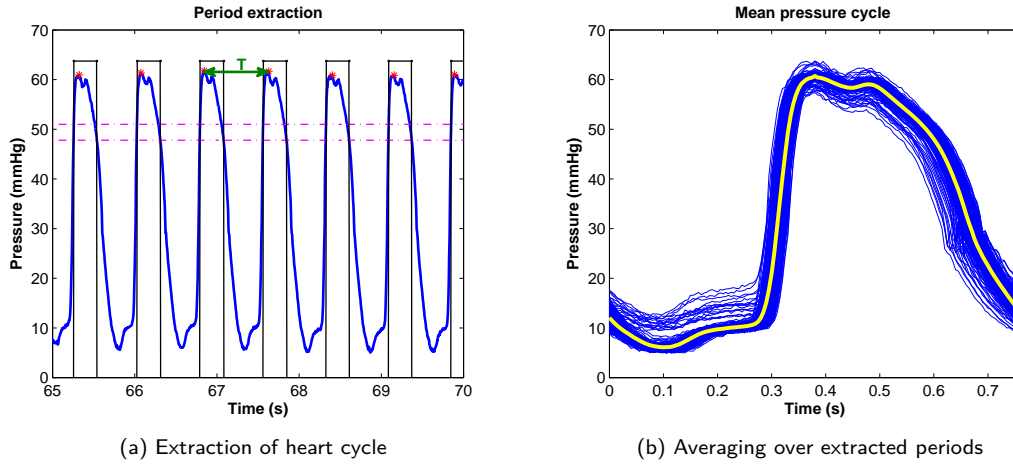


Figure 1: Mean pressure cycle computation

Local maxima were first identified at times  $t_{peak,i}$ , then individual periods  $T_i$  were computed as being the times separating two consecutive peaks, finally pressure cycles were extracted between  $t_{peak,i} - \frac{T_i}{2}$  and  $t_{peak,i} + \frac{T_i}{2}$ . A mean pressure curve was thus obtained by averaging all cycles.

136 applying a double threshold on the pressure signal, we delimited individual windows each containing a  
 137 pressure peak. Afterward the local maximum was identified inside each window, thus defining a cycle end  
 138 point. Once all peaks were determined, individual periods  $T_i$  were computed, and cycles were extracted  
 139 between  $t_{peak,i} - \frac{T_i}{2}$  and  $t_{peak,i} + \frac{T_i}{2}$ . These cycles were then averaged to yield a mean pressure curve.  
 140 The volume and pressure curves were then associated by assuming that maximum volume is attained with  
 141 maximum  $\frac{dP}{dt}$  Mason et al. [27].

### 142 2.3. Pressure-Volume Analysis

143 Selected indices were estimated using the PV loop in order to evaluate systolic and diastolic functions  
 144 as well as mechanical efficiency during the three inotropic states. The end-systolic elastance was evaluated  
 145 as a contractility index and the myocardium compliance was estimated during diastole to characterize the  
 146 filling process. The effective arterial elastance, representing the afterload, was also evaluated to assess  
 147 ventriculoarterial coupling.

148 *End-systolic elastance as contractility index*

149 The end-systolic elastance  $E_{es}$  index is given by the slope of the end-systolic pressure-volume relationship  
150 (ESPVR). The ESPVR is defined as the line connecting the end-systolic points of a series of PV loops  
151 with different ventricular filling volumes. It is approximated as linear in the physiological range and is  
152 characterized by its slope, and a volume intercept  $V_0$ , a theoretical volume for which no pressure is developed  
153 Grossman et al. [14], Mehmehl et al. [28], Suga et al. [41].

154 To obtain the ESPVR several PV loops are usually measured while gradually decreasing preload, using  
155 a balloon occlusion of the vena cava, for example. The invasive nature of this procedure, limiting clinical  
156 applications, has motivated several authors to propose methods for computing the ESPVR from a single  
157 PV loop. Takeuchi *et al.* Takeuchi et al. [44] simulated end-systolic isovolumic pressure by cosine fitting  
158 of the pressure curve, as done by Sunagawa *et al.* Sunagawa et al. [43], to locate a theoretical maximum  
159 pressure  $P_{iso}$  that would be attained if ejection did not take place. The  $E_{es}$  is then computed as the slope  
160 of the line connecting the point defined by  $(EDV, P_{iso})$  to the end-systolic point on the PV loop. Other  
161 authors relied on a time-varying elastance model to derive  $E_{es}$  Senzaki et al. [36], Shishido et al. [37], Chen  
162 et al. [5]. Recently Brinke *et al.* Brinke et al. [3] using Takeuchi's technique with a modified fitting scheme  
163 (fifth order polynomial instead of a cosine), showed that a good estimation of intercept volumes can be  
164 achieved.

165 In this study we estimated the ESPVR following the method proposed by Brinke *et al.* Brinke et al. [3].  
166 We computed a maximum isovolumic pressure  $P_{iso}$  by using a fifth order polynomial fitting scheme to fit  
167 the left ventricle pressure curve. We started after end diastole and excluded from the fitting the pressure  
168 data points that lie after  $dP/dt_{max}$  and before  $dP/dt_{min}$  and those after the point where  $dP/dt$  increased  
169 above 10% of  $dP/dt_{min}$ .

170 *LV compliance during the filling phase*

171 The pressure-volume relationship during diastole, known as the end-diastolic pressure-volume relation-  
172 ship (EDPVR), is generally exponential and depends on the elastic properties of the myocardium, the wall  
173 thickness and the ventricle's equilibrium volume  $V_0$  Glantz and Kernoff [12] which is the intercept of the  
174 EDPVR with the volume axis. At any given instant of the EDPVR, the ventricle's stiffness modulus  $E = \frac{\partial P}{\partial V}$   
175 is given by the slope of the tangent to the curve at that point. We can also think in terms of compliance



176 and compute  $C = \frac{\partial V}{\partial P}$  as the slope reciprocal. The EDPVR is independent of the contractility state. When  
 177 the inotropic state is enhanced (or decreased), the diastolic filling portion of the PV loop remains on this  
 178 curve while sliding towards the left (or the right) Dickstein et al. [9], Thomas and Weyman [45]. This  
 179 of course leads to compliance alterations in response to inotropic changes. In this study the EDPVR was  
 180 fitted by  $P = \alpha (e^{\beta(V-V_0)} - 1)$ , and the compliance was computed using the slope of the EDPVR during  
 181 the slow filling phase, where viscous forces might be ignored, thus reflecting purely elastic properties of the  
 182 ventricle. This phase is defined as the portion of diastole lying between the point where pressure starts  
 183 increasing slowly while the volume continues to increase, and the point where pressure starts increasing  
 184 rapidly while volume remains somewhat constant.

### 185 *Effective Arterial Elastance*

186 The arterial elastance is determined by the pressure in the ventricle at end systole, and by the amount  
 187 of blood that the ventricle ejected into the arterial system such as  $E_a = ESP/SV$ , where ESP denotes the  
 188 end-systolic pressure. It can be represented on the PV loop diagram as the line connecting the end systolic  
 189 coordinates and the end-diastolic volume point on the volume axis.

### 190 *Cardiac work efficiency*

191 The efficiency of energy transfer from the ventricle to the arterial system, called cardiac work efficiency  
 192 (CWE), is given as the ratio of the stroke work to the total mechanical energy,  $CWE = SW/PVA$ . The  
 193 total mechanical energy of a ventricular beat known as the pressure volume area (PVA) is equal to the sum  
 194 of potential energy and stroke work,  $PVA = PE + SW$ , Suga [40]. The stroke work (SW) is given by the  
 195 area inside the PV loop, and the potential energy (PE) is represented by the area of the triangle between  
 196 the point of end systole on the PV loop,  $V_0$  and the end-systolic volume (ESV) intercept on the EDPVR.  
 197 CWE is reciprocally related to  $\frac{E_a}{E_{es}}$  Kameyama et al. [18], it increases with contractility enhancement, and  
 198 decreases with afterload increase Nozawa et al. [30].

## 199 **3. Results**

### 200 *3.1. In vivo pressure measurements validation*

201 Figure 2 shows two 20 second extracts of the recorded pressure signals in the aorta outside the MRI, one  
 202 while the ventilation was off and another, almost 2 minutes later during normal ventilation. The Opens

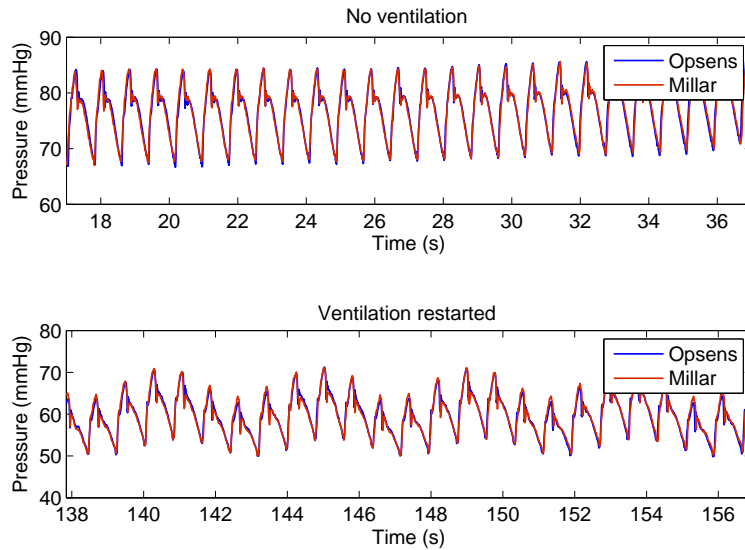


Figure 2: OpSens and Millar pressure signals

Extracts of pressure signals recorded simultaneously using OpSens and Millar are represented during a time period where the ventilation had been stopped, and later when the ventilation had been restarted. The OpSens offset was corrected so that the mean error would be null.

203 offset was corrected such that the mean error would be zero. Figure 3 shows the extracted average cycles  
 204 of both OpSens and Millar with no ventilation. Pressure measured with the optical transducer agrees well  
 205 with the standard Millar sensor.

### 206 3.2. MRI acquisitions and PV loops calculations

207 As shown in figure 4 the images were not affected by the presence of the pressure sensors, however some  
 208 artifacts due to breathing motion can be noted. Pressure-volume loops were computed for all measurements  
 209 covering three contractility states, figure 5 shows an example of the computed pressure and volume curves  
 210 for a baseline state. Overall we obtained 8 PV loops : 4 for baseline, 1 with dobutamine 2.5, and 3 with  
 211 dobutamine 5.

### 212 3.3. Baseline measurements

213 The computed mean baseline parameters were compared to values obtained in other studies dealing  
 214 with sheep Charan et al. [4], Lee et al. [23], Bauer et al. [2], Ratcliffe et al. [33], Pilla et al. [32], Segers

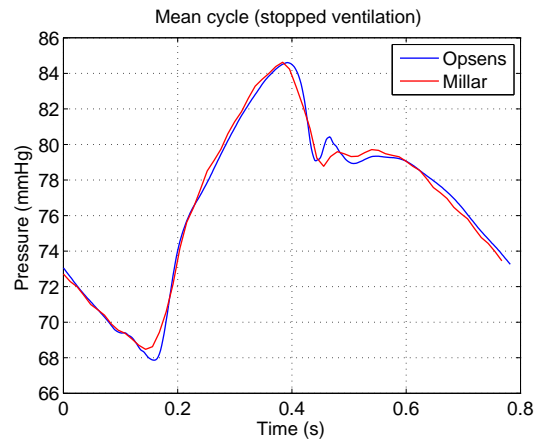


Figure 3: Opsens and Millar average pressure cycles  
 The mean pressure cycles of Opsens and Millar extracted during the period when the ventilation was stopped.

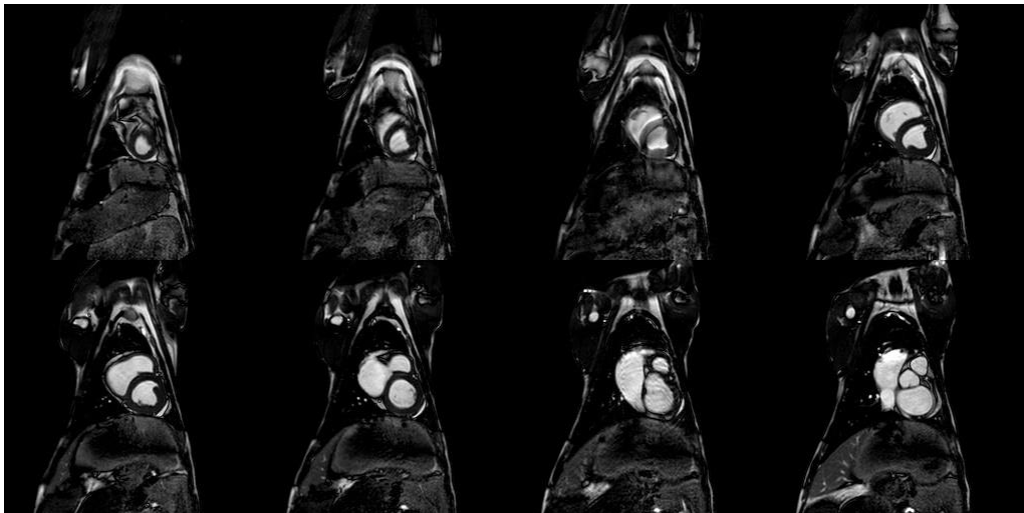


Figure 4: Left ventricle short axis slices acquired with MRI at end systole  
 MRI images used for LV volume estimation were not affected by the optical sensors but show some breathing motion artifacts.

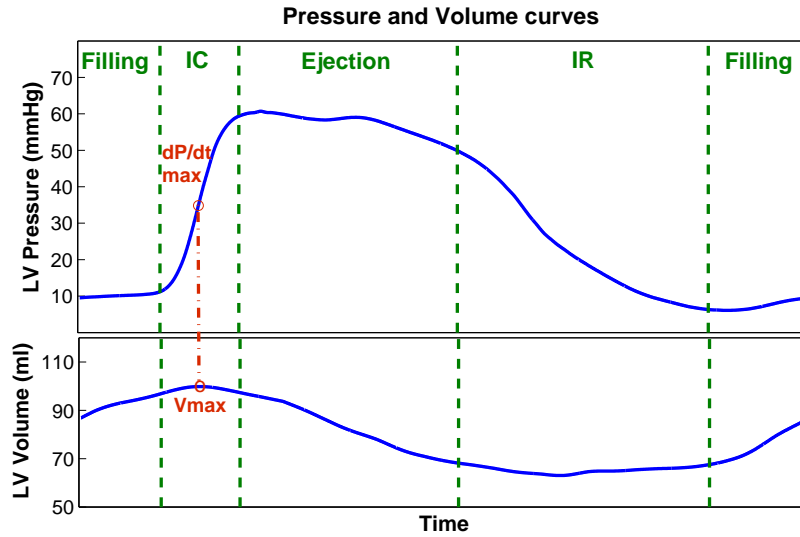


Figure 5: Associated LV pressure and volume curves

Measured volume and average pressure cycle during baseline state. To produce the PV loop, the curves were matched so that maximum volume would coincide with the maximum first derivative of pressure.

215 et al. [35] in order to situate our calculations with respect to usual parameter values. These values are  
 216 given in table 1 , shown as (mean value  $\pm$  standard deviation)

### 217 3.4. Contractility states comparison

218 Figure 6 shows the experimental time-line and heart rate evolution throughout the consecutive states.  
 219 The instantaneous frequencies were computed, over the pressure recordings, as the inverse of the time  
 220 interval separating two pressure peaks, as shown in figure 1a. Heart rate (HR) increases gradually after  
 221 the dobutamine administration starts, it stabilizes then decreases when the dobutamine rate is diminished.  
 222 An HR increase can be observed as we go from one rate to another, as the remaining dobutamine might  
 223 have been injected rapidly when flushing the tubes for the next infusion. Of course, functional changes  
 224 in response to the inotropic agents, go beyond the obvious HR variation. Not only did the pressure cycle  
 225 period vary, but its shape was drastically altered. Figure 7 shows mean pressure cycles, each representing  
 226 an inotropic state.

227 Pressure volume loop analysis was performed for all 8 measurements. The obtained parameter values are  
 228 given in table 2. Compared to baseline,  $E_{es}$  increased significantly with positive inotropic stimuli. Figure

	Present Study	Charan et al. [4]	Lee et al. [23]	Bauer et al. [2]	Ratcliffe et al. [33]	Pilla et al. [32]	Segers et al. [35]
Weight (kg)	70	72.50	35± 5		41.62 ± 0.45		40.00 ± 5.00
HR(bpm)	79.28 ± 2.79	97±5	85 ±21	109 ± 15	102.10 ± 14.50	97.60 ± 9.73	81
CWE(%)	76.26 ± 4.23					60.80 ± 12	
EDV(ml)	95.22 ± 3.82					60	79.00
ESP(mmHg)	48.04 ± 3.58			87 ± 34	100.30 ±12.80		
ESV(ml)	68.55 ± 2.49					36.15 ± 9.78	
P <sub>max</sub> (mmHg)	59.46 ± 1.53				102.30 ± 12		
V <sub>0</sub> (ml)	38.49 ± 3.36				-27.69	-24.80 ± 20.10	-36.00
SV(ml)	26.67 ± 1.84				24.60 ± 4.80	20.20 ± 8.76	49.00 ± 6.00
EF(%)	27.99 ± 1.16			60 ± 9	57.60 ± 3.50	35	
EDP(mmHg)	10.88 ± 0.87	7 ± 1.60	7.30	9 ± 3	13.80 ± 5.20	5.25 ± 1.86	
C(ml/mmHg)	6.23 ± 0.47		2.94		1.70 ± 0.65		
CO(l/min)	2.11 ± 0.11	4 ± 0.40		2 ± 0.30	2.45 ± 0.24	2.03 ± 0.71	
E <sub>es</sub> (mmHg/ml)	1.62 ± 0.19		0.46	2.71 ± 0.35	2.52 ± 0.27	3.40	1.37
SW(mmHg.ml)	1574.27 ± 183.24					1400	
$\frac{dp}{dt}_{max}$ (mmHg/s)	1020.64 ± 20.24	1902 ± 267		1346 ± 478		1492 ± 235	
$\frac{dp}{dt}_{min}$ (mmHg/s)	-347.02 ± 20.26					-1813 ± 359	
PVA(mmHg.ml)	2066.15 ± 238.61		2558			3400	
PE(mmHg.ml)	491.89 ± 107.13					1024 ± 345	

Table 1: Comparison of PV loop extracted parameters with respect to the literature

229 8 shows an example of PV loops representing the three states (baseline measurement n°4, dobutamine  
230 2.5, dobutamine 5 measurement n°2) , as well their corresponding end-systolic elastances. Moreover, the  
231 cardiac work efficiency was enhanced by dobutamine administration. As expected, the diastolic compliance  
232 increased with inotropic enhancement. As contractility is increased, the PV loops shift to the left on the  
233 EDPVR, thus going towards lower slopes (i.e. stiffness).

#### 234 4. Discussion

235 MRI is considered to be the gold standard for absolute cardiac volume measurements. Obtaining PV  
236 loops requires simultaneously recording pressure during the MRI sessions. Pattynama *et al.* Pattynama et al.  
237 [31] used a Millar micromanometer to achieve such measurements, and argued that because it is made  
238 from brass the obtained pressure signals were not significantly altered, however, some image artifacts were  
239 observed. Schmitt *et al.* Schmitt et al. [34] and Kuehne *et al.* Kuehne et al. [22] used liquid filled catheters  
240 to measure ventricular pressure down a 1m pressure line. The impedance of the transmission line reduces  
241 pressure amplitudes, and constitutes a low pass filter that attenuates high frequency components. A pressure  
242 sensor placed inside the ventricle would provide a more accurate representation of the actual LV pressure.  
243 The use of optical sensors in this study enabled pressure measurements directly in the ventricle without any  
244 interaction with the MRI acquisition.

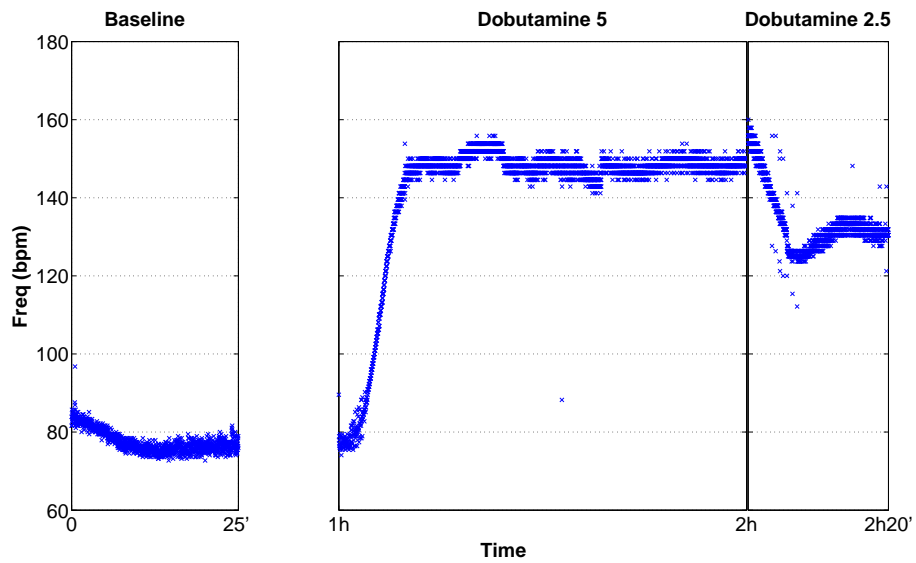


Figure 6: Heart rate evolution throughout the experiment  
Heart rate evolution vs the experimental time-line throughout the three consecutive inotropic states.

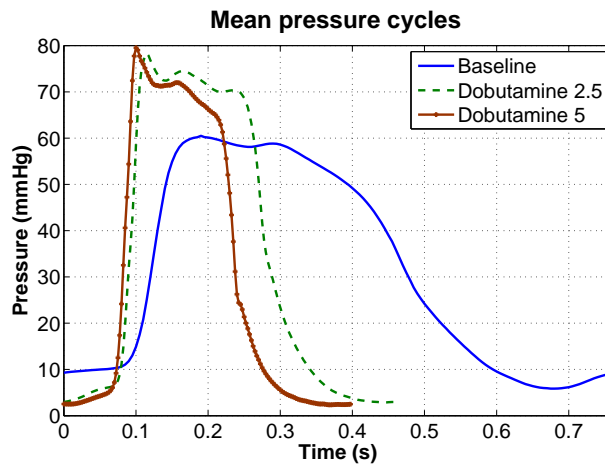


Figure 7: Mean pressure cycles for the three inotropic states  
Extracted average cycles for baseline, dobutamine 2.5 $\mu\text{g}/\text{kg}/\text{min}$  and dobutamine 5 $\mu\text{g}/\text{kg}/\text{min}$ . The shape and duration of the pressure cycle is altered in response to positive inotropic stimuli.

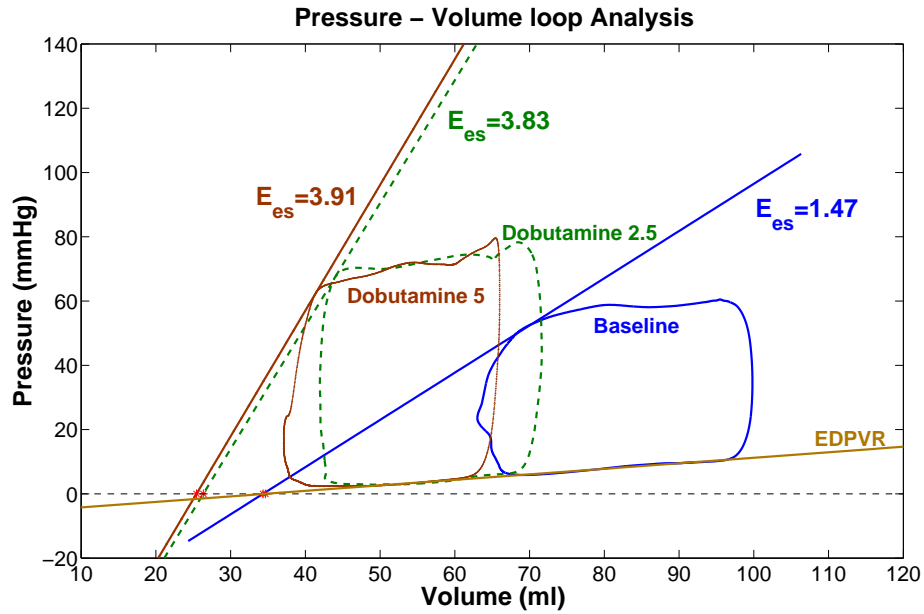


Figure 8: End-systolic elastance for the three contractility states PV loops obtained during baseline, dobutamine 2.5 $\mu\text{g}/\text{kg}/\text{min}$  and dobutamine 5 $\mu\text{g}/\text{kg}/\text{min}$ . For each loop ESPVR is represented and the value of its slope  $E_{es}$  is given in mmHg/ml .

	Baseline	Dobutamine 2.5	Dobutamine 5
HR (bpm)	78.28 $\pm$ 2.79	129.77	150.99 $\pm$ 0
SV (mL)	26.67 $\pm$ 1.84	25.39	20.59 $\pm$ 1.40
EF (%)	27.99 $\pm$ 1.16	36.66	33.14 $\pm$ 2.88
$P_{max}$ (mmHg)	59.46 $\pm$ 1.53	78.31	77.64 $\pm$ 2.52
C (mL/mmHg)	6.23 $\pm$ 0.47	6.88	8.55 $\pm$ 3.35
$E_{es}$ (mmHg/mL)	1.62 $\pm$ 0.19	3.83	4.21 $\pm$ 0.26
$V_0$ (mL)	38.49 $\pm$ 3.36	26.35	28.26 $\pm$ 6.59
$\frac{dP}{dt}_{max}$ (mmHg/s)	1020.64 $\pm$ 20.24	3370.92	3556.28 $\pm$ 232.13
$\frac{dP}{dt}_{min}$ (mmHg/s)	-347.02 $\pm$ 20.26	-1860.39	-2342.00 $\pm$ 428.75
SW (mmHg.mL)	1574.27 $\pm$ 183.24	1939.42	1548.46 $\pm$ 229.35
CWE (%)	76.26 $\pm$ 4.23	80.91	88.38 $\pm$ 3.24
$E_a$ (mmHg/mL)	1.81 $\pm$ 0.18	2.64	2.74 $\pm$ 0.37
$E_a/E_{es}$	1.12 $\pm$ 0.11	0.69	0.65 $\pm$ 0.10

Table 2: Functional indices extracted from the PV loops of the three inotropic states

#### 245 4.1. Volume measurements

246 Unlike the conductance catheter technique, PV loop calculation using MRI imposes the use of an  
247 average pressure cycle vs average volume instead of instantaneous pressure vs instantaneous volume. Thus,  
248 the PV loop here reflects a global performance cycle and does not take into account an exact punctual  
249 correspondence between individual volume and a pressure measurements. Moreover the time synchronization  
250 between the volume and pressure cycle in this study was done based on bibliographic data, a more accurate  
251 match could be achieved by using the pressure signal to trigger the image acquisition and thus synchronize  
252 both waveforms.

253 Due to the lack of real-time volume recordings, it was impossible to obtain a series of load varying PV  
254 loops using MRI because a steady state over several cycles is needed in order to compute a volume. For  
255 the same reason, the assessment of contractility transit states is not possible using MRI. This remains, for  
256 now, an advantage in favor of the conductance technique, however, future advances in MRI may enable the  
257 overcoming of this limitation.

#### 258 4.2. Pressure measurements

259 Even though the dynamics of the pressure measurements performed here were shown to be accurate,  
260 these optical pressure sensors present an offset that drifts throughout the experiment, thus introducing an  
261 unknown pressure shift between measurements. This variable drift can exceed 2 mmHg/hour. To be able to  
262 compare the obtained loops and the extracted parameters, a correction was necessary to bring the pressure  
263 cycles to a common reference. To eliminate these relative offsets we relied on theoretical fact that the  
264 filling parts of all measured PV loops should lie on the same EDPVR. Hence, we computed that relation for  
265 one of the baseline loops (we arbitrarily chose the fourth) and then shifted the pressure cycles of the rest  
266 of the loops so that they would be supported by the estimated EDPVR. Of course this does not eliminate  
267 the “absolute” pressure offset that is added to the reference pressure measurement, but at least all loops  
268 had that same offset and could be compared. An attempt to estimate and correct the absolute offset was  
269 made by considering the EDPVR and ESPVR intersection point. Theoretically these relationships should  
270 have the same zero axis intercept. Thus, we could assume that the absolute offset would be eliminated  
271 by shifting the reference baseline loop so that EDPVR and ESPVR intersect at zero pressure. Of course  
272 the same shift would afterward be applied to the rest of the loops. This procedure would, however, not



273 guarantee the elimination of the real offset. In fact it greatly depends on the ESPVR estimation, which  
274 itself is not very precise given that it is computed from a single beat. Besides given the instability of ESPVR  
275 and the equilibrium volume  $V_0$  and their variability between repeated measurements Spratt et al. [38], the  
276 chosen loop probably does not reflect the real  $V_0$ .

277 To sum up, the presented pressures here might not actually reflect the real ones, but present a residual  
278 offset that introduces errors in the calculations of some parameters, such as  $V_0$ ,  $PE$ , and  $E_a$ . Other  
279 parameters such as  $E_{es}$ ,  $C$ , and  $SW$ , are independent of the pressure offset and thus can be assumed  
280 accurate even if there's an unknown shift of the PV loop. Regardless of whether the offset is substantial  
281 or not, comparison between the considered contractility states remains valid, since the relative offsets are  
282 corrected and the absolute shift applies equally to all states. Further studies will focus on modeling the  
283 sensors behavior to enable measurement correction.

#### 284 4.3. Baseline PV loops indices

285 When comparing baseline measurements with other authors works we found that some parameters such  
286 as  $E_{es}$  agree well with the literature range. Others, like the compliance and  $V_0$ , differ significantly from  
287 what is obtained by other authors. These differences can be explained by the fact that the sheep studied  
288 by those authors are much smaller (weighting around 40 kg) than the one used in our experiments (60 kg).  
289 Since the diastolic compliance decreases with the chamber size Diamond et al. [8], Forrester et al. [10],  
290 smaller animals with smaller hearts have less compliant ventricles. Moreover, smaller volumes mean that  
291 the PV loops are shifted to the left, thus the ESPVR axis intercept is also shifted to the left, thus explaining  
292 the smaller  $V_0$ .

#### 293 4.4. Response to inotropic stimuli

294 Both end systolic elastance and diastolic compliance increased significantly in response to positive  
295 inotropic stimuli. Increasing the dobutamine concentration did not enhance the stroke work (the SV  
296 decreased with an insignificant increase in maximum pressure), it did however somewhat enhance the  
297 cardiac work efficiency. The SW varies very slightly with afterload but is very sensitive to preload Kass  
298 et al. [19], and thus the study of the relationship between the EDV and the SW would be more suitable.  
299 This relationship is called the preload recruitable stroke work (PRSW). It is a linear relationship Glower

300 et al. [13] which slope reflects the inotropic state. It was also shown to be insensitive to afterload over  
301 the physiological range, and thus qualifies as a contractility index, although it might depend on cardiac  
302 geometry and heart rate Glower et al. [13]. Nonetheless, the PRSW is less sensitive to inotropic changes  
303 than  $E_{es}$  and  $dP/dt_{max}$  vs  $EDV$  Little et al. [25]. Since preload conditions variations were not performed  
304 during this feasibility study, it was not possible to derive such relationships which rely on multiple PV loops.  
305 A method to estimate the slope of PRSW from a single beat was proposed by Mohanraj *et al.* Mohanraj  
306 and Feneley [29], however their method did not exclude prior preload variation experiments. For their  
307 estimations they computed an empirical constant from a set of VCO experiments, which they used for the  
308 slope estimation of another group of the same species.

309 The ESPVR axis intercept  $V_0$  varies slightly among states but not distinctly enough to be attributed to  
310 contractility changes. This volume should be independent of the inotropic state Suga et al. [41], all ESPVR  
311 and EDPVR should meet at the same axis intercept. Positive inotropic interventions would increase  $E_{es}$   
312 and shift the ESPVR to the left, while depressors of the cardiac function would decrease  $E_{es}$  shifting  
313 ESPVR to the right, nevertheless the volume axis intercept  $V_0$  would not significantly change Spratt et al.  
314 [38], Dickstein et al. [9]. The changes observed here account for the instability of  $V_0$  Spratt et al. [38] as  
315 well as measurement and estimation errors. Note that the  $V_0$  range here is affected by the pressure offset  
316 and its correction.

317 The effective arterial elastance  $E_a$  increases with inotropic enhancement as end systolic pressure (ESP)  
318 is increased. The ventriculoarterial coupling index  $E_a/E_{es}$  decreases when contractility increases. Studies  
319 have shown that  $\frac{E_a}{E_{es}} = 0.5$  ensures maximal CWE Starling [39], Asanoi et al. [1]. On the other hand,  
320 given that the energy transfer from one elastic chamber to another is maximal when they both have the  
321 same elastance Sunagawa et al. [42], maximal SW would occur when  $E_a = E_{es}$ . It has been shown that  
322 the normal heart at rest operates at neither maximal CWE nor maximal SW, but in fact finds an optimal  
323 working point between the two, which is actually closer to maximal efficiency Starling [39], Asanoi et al. [1].  
324 In our baseline measurements,  $E_a/E_{es}$  is close to 1, indicating that the ventricle is working near maximal  
325 SW. With dobutamine, this index is approximately 0.6, thus the heart is functioning around the optimal  
326 working point between maximal SW and maximal CWE, while remaining closer to maximal efficiency.

#### 327 4.5. Valid contractility index

328 The results obtained here showed that parameters computed using volume alone might not correctly  
329 reflect LV contractility. In fact, the stroke volume measurements confirmed that it is not a good contractility  
330 index. Despite the contractility enhancement, because of its load dependence, the stroke volume of the  
331 dobutamine loop is smaller than that of baseline. Since the preload (EDV) decreased, so has the SV. The  
332 same can be argued for the ejection fraction which did not reflect the inotropic increase induced by the  
333 dobutamine augmentation.

334 On the other hand,  $dP/dt_{max}$  often used as a contractility index based on pressure measurements alone,  
335 behaved as expected in this study and did increase with inotropic stimuli. Even though this index is more  
336 sensitive to inotropic changes than  $E_{es}$ , it depends on heart rate, and is still preload-dependent. Even when  
337 considering  $dP/dt_{max}$  vs  $EDV$  to negate the preload effect, it was shown that  $E_{es}$  remains a better index.  
338 Kass *et al.* found that in the presence of both preload and afterload alterations,  $E_{es}$  was relatively less  
339 affected than  $dP/dt_{max}$  vs  $EDV$ . So, despite the  $E_{es}$  lesser sensitivity to inotropic change, its minimal  
340 dependence on both types of load alterations, coupled with its adequate characterization of contractility,  
341 make it somewhat more advantageous than  $dP/dt_{max}$  vs  $EDV$  Kass *et al.* [19].

342 The accuracy and load independence of  $E_{es}$  is however questionable when obtained using single-beat  
343 estimation methods which rely on load-dependent elements such as  $dP/dt$  and end-diastolic volume. Sin-  
344 cepreload has not been changed during this study and only single beat methods were used, it would be  
345 more valid to view the estimated  $E_{es}$  as a load-dependent approximation of the load-independent elas-  
346 tance Kjorstad *et al.* [21]. Even though these methods might underestimate  $E_{es}$  and do not agree closely  
347 with the vena cava occlusion (VCO) technique estimation, they are still reasonable approaches given their  
348 experimental advantages Brinke *et al.* [3].

#### 349 5. Conclusion

350 By analyzing the ventricular PV loop, several functional parameters can be extracted and used to assess  
351 the LV performance. In this study we showed the feasibility of PV loop computation using simultaneous  
352 MRI volume estimation and direct pressure measurements with optical sensors on a sheep in three inotropic  
353 states. The optical nature of the pressure sensors ensured the absence of pressure signal contamination as

354 well as image artifacts. Functional parameters were extracted and compared to the values reported in the  
355 literature showing good agreement. Contractility indices such as end diastolic elastance, were possible to  
356 estimate despite the pressure sensors offset problem. Following up on this feasibility investigation, a more  
357 comprehensive study including several animals will be carried out.

#### 358 **List of abbreviations**

359 CO Cardiac Output

360 CWE Cardiac Work Efficiency

361 EDPVR End-Diastolic Pressure-Volume Relationship

362 EDV End Diastolic Volume

363 EF Ejection Fraction

364 ESP End Systolic Pressure

365 ESPVR End-Systolic Pressure-Volume Relationship

366 ESV End-Systolic Volume

367 HR Heart Rate

368 IC Isovolumic Contraction

369 IR Isovolumic Relaxation

370 LV Left Ventricle

371 MRI Magnetic Resonance Imaging

372 PE Potential Energy

373 PV Pressure-Volume

374 PVA Pressure Volume Area

375 SV Stroke Volume

376 SW Stroke Work

377 VCO Vena Cava Occlusion

### 378 **Competing interests**

379 The authors declare that they have no competing interest.

### 380 **Declarations on funding and ethical approval**

381 There was no funding for this research. This study did not involve any human subjects.

### 382 **Authors contributions**

383 DAR: participated in data acquisition, performed data processing, analysis and interpretation, and  
384 drafted the manuscript. ED: participated in the conception of the study, performed critical revision of  
385 the manuscript, and participated in data acquisition. LdR: participated in data acquisition. YB: partici-  
386 pated in animal preparation and data acquisition. EM: participated in the conception of the study, and  
387 animal preparation. All authors read and approved the final manuscript

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