SclencePG
Science Publishing Group

Research Article

No Difference in Systolic Dysfunction from Left Ventricular Pressure-Volume Loop's Area and Stroke Work Between Chronic Late Load vs. Early Systolic LV Load in Porcine Model

Popevska Sofija[*]

Imaging and Dynamics, Department of Cardiovascular Sciences, Medical faculty, Katholieke Universitet Leuven, Leuven, Belgium

Abstract

Background: in increased LV afterload as in hypertension, early systolic LV dysfunction (SD) in late compares to early peak systolic LV load for P-V area, stroke work, potential energy with effective LV work (EW) is not being defined (aortic stenosis, arterial hypertension or coarctation of the aorta) in LVH remodeling. *Objectives:* to assess in porcine model how LV stroke work, PVA and EW are related to LVH remodeling in developing early SD with HF, between 4th vs 8th week in chronic LL compares to EL. It is suggested that reduced proximal thoracic or asc. aortic compliance results with myocardial ischemia. However, difference for LV O_2 demand and effective LV work in different LV afterload is not understood in early development systolic HF. *Methods:* in fourteen domestic male pigs (28±3 kg) with moderate descending aortic banding having chronic late LV load (LL=8) or ascending aortic stenosis with early systolic LV load (EL=6) SD was assessed, from PVA, in invasive LV pressure-volume loops' measurements, at 4th vs. 8th week, to assess LV maximal ESPVR, with Millar 5Fr P-V pig-tailed conductance catheter. LV stroke work, and pressure-volume area PVA, reflecting the maximal LV O_2 demand were assessed in chronic LL compares to EL from nonlinear regression analysis of maximal LV end-systolic stiffness, in special software. For variance analysis, two-way repeated measures ANOVA was performed, with normality assessment. Results are means±(SEM) or medians for significant p<0.05. *Results:* LV PVA was not different, in LL compared to EL at 4th vs. 8th week. LV stroke work with effective works were not different and potential energy, neither were changed between 4th vs. 8th week. No difference was found in different LV afterload, in both indexed and absolute LVO$_2$ demand, in LL vs. EL at 4th or 8th week. Indexed PVA parameters with LV stroke work, effective work and potential energy were not different or changed in LL compares to EL between 4th vs. 8th weeks, normalized per body surface-area (in m^2). *Conclusion:* Both absolute and indexed LV stroke work, potential LV energy, PVA with EW and maximum LV O_2 demand are not different in LL compares to EL at 4th vs. 8th week of LVH remodeling, indicating no difference in early SD development in increased late vs. early LV afterload.

[*]Corresponding author: popevskasofija@hotmail.com (Popevska Sofija)

1. Introduction

LVH in increased LV load is risk for early systolic HF. In increased LV afterload, as found in arterial hypertension, coarctation or aortic stenosis, relative effects of chronic late compared to early afterload on LV potential energy, stroke work and pressure-volume loop's area, a parameter for LV O_2 demand with effective LV work are not defined in terms of earlier development systolic LV dysfunction (SD) with HF [1, 2, 6, 12, 15, 18, 22].

Diastolic LV function can deteriorate when the potential LV energy has been converted and used to generate wasted LV work, thus presenting inefficient contractions. This eventually results in development of earlier SD.

ACE inhibition increases LV O_2 consumption, reduces O_2 demand and improves LV stiffness, from stroke work with effective work, and novel antihypertensive treatments, with dapagliflozines [3]. This is important for adequate treatments of HTA and AS patients, having increased LV load.

LV pressure-volume loop's area is relevant for assessing diastolic LV dysfunction, in different cardiovascular conditions in early SD. This includes the LV contractility in afterload associated hypertrophy, as well as the LV myocardium O_2 consumption. It has been of relevance to assess SD, in LVH remodeling [1, 4, 5, 7-15]. Chronic LL has been found to result with increased LV O_2 demand and early development of SD. However, when compared to EL there are studies showing that acute or chronic early LV load is related to early developing diastolic LV dysfunction and could be important as LL, resulting with SD [1, 13, 16].

LV pressure-volume loop's area represents the overall energy stored and released during mechanical contractions and is being considered to be a parameter for LV O_2 consumption [2, 8, 12, 15]. This is important to determine LV functional capacity and reduce tolerance to increased LV load. Difference in LV pressure-volume area can be used to assess the LV mechanic work with O_2 demand in the development of insufficient systolic and diastolic LV function. In the presence of different LV loading, resulting from chronic early and late LV load, PVA, stroke work and EW with potential energy have not been assessed previously. This is needed in order to differentiate functional abnormalities early, including LV O_2 demand in LL and EL for early assessment of presence of diastolic and systolic LV dysfunction [2, 20-23].

In order to assess energetic depth present within chronic LL vs. EL in early SD, the aim was to investigate whether defects in LV O_2 demand and stroke work are present in the 4th vs. 8th week period in the LV pressure-volume loop's area. The hypothesis tested whether difference with imbalance between LV stroke work with PE and PV loop area for absolute O_2 demand are related to difference in load, comparing nonpulsatile with pulsatile LV afterload in porcine heart.

Increased LV pressure-volume loop's area and stroke work are being described in arterial hypertension in the presence of LVH remodeling compared to normal left ventricles and in aortic stenosis in presence of symptoms, having reduced systolic LV function, as well as in chronic HF [10, 16, 19-24]. However, a relative difference in LV pressure-volume loop's area has not been assessed in association with the SD for difference in systolic LV load and its relation to normalized PVA per body surface area BSA (m³) and LVH remodeling (per 100 grams of LV mass) at 4th vs 8th week.

2. Methods

In fourteen domestic male pigs (28±3.4 kg) that underwent randomly either descending thoracic (n=8) or ascending aortic stenosis (n=6) during 8 weeks, LV invasive P-V loops' were obtained during LV preload reduction, with inflating balloon catheter in inferior vena cava (figure 1).

After sedation with intramuscular Telazol (Zoletil 100, 8mg/kg) and Xylazine M 2% (2.5mg/kg) for endotracheal intubation, anesthesia was induced intravenously (Propofol bolus dose 3 mg/kg). It was continued with intravenous combination of Propofol (10 mg/kg/h) and Fentanyl (18 µg/kg/h).

Mechanical ventilation maintained inspiratory 50% SaO_2 (Drager ventilator), with tidal volume 9-10 ml/kg; fr.16/min This kept arterial SaO_2 between 98-100 % and CO_2 under 35%. Intravenous NaCl 0.9% infusion (5-10 ml/kg/h) maintained a normal range of heart rate and blood pressure.

Following preparation with dissection of the common carotid artery and external jugular vein, with enoxaparin, administered intravenously for clot prevention (100 IU/kg), serial LV pressure-volume loops were obtained during afterload and preload reduction. This was recorded digitally in LabChart 7 (AD Instruments, Houston, Texas, USA, KU Leuven), having mechanical ventilation preserved and suspended transitionally, during preload reduction. For LV load reduction, inflating 10Fr balloon catheters was positioned in the inferior vena cava above the diaphragm, using guidewire.

The P-V catheter was calibrated at atmospheric pressure and we used manometer calibration within LabChart 7. LV volumes were assessed from cine cMRI LV volumes' that were used. LV pressure-volume loops' measurements were performed (Millar 5Fr pig-tailed conductance catheter) in the 4th vs. 8th weeks of surgical creation of moderate aortic stenosis. LV maximal end-systolic elastance was calculated, using special software and was used to assess the pressure-volume loop's plane, from single nonlinear regression assessment (figure 2). LV stroke work and pressure-volume area with effective work were analyzed, as parameters of systolic LV dysfunction, with maximum LV O_2 demand in different LV afterloads (late vs. early systolic LV load) between 4th vs. 8th week.
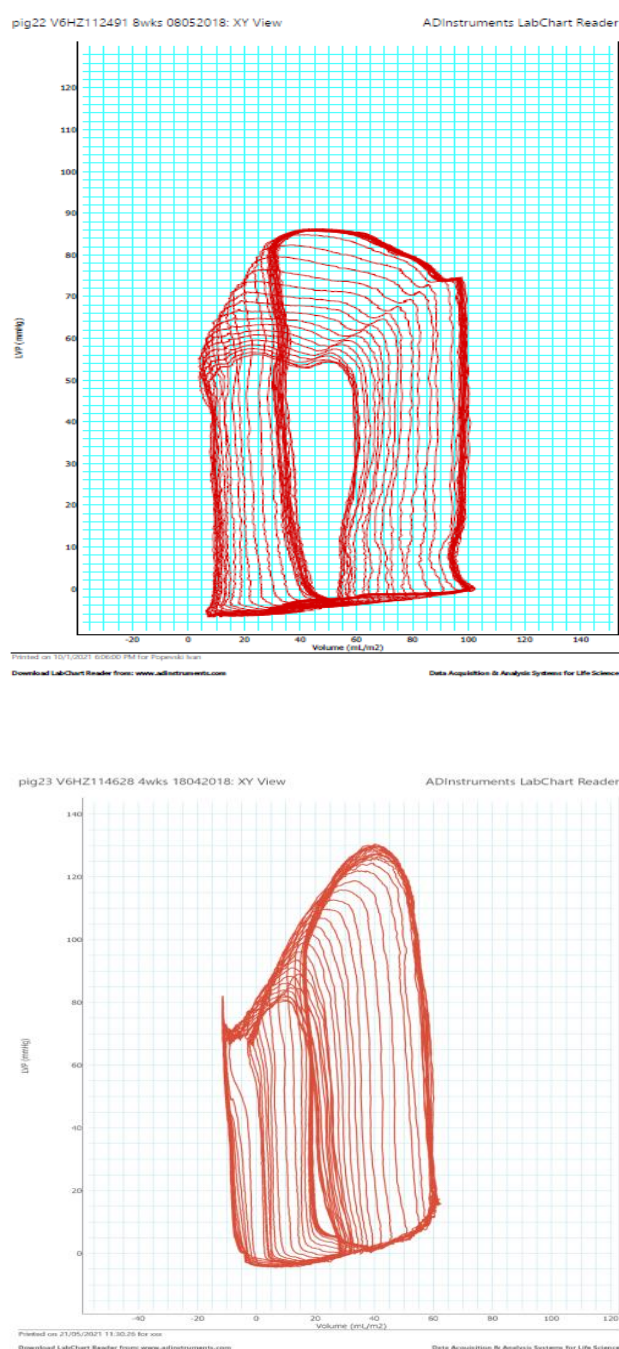
***Figure 1**. Presents LV P-V loops at maximal LV load reduction, with LV PVA in LL (up) vs. EL (down figure) in the 8th week.*

LV stroke work and pressure-volume loop's area were assessed, from the systolic part from the P-V loop and the LV O_2 demand in absolute and relative volumes, indexed per BSA and LV mass in different LV afterloads (late vs. early systolic LV load), so to characterize the LV work with O_2 demand, for SD assessment.

Stroke work and its index (SWI) were calculated as LV stroke volume (index) × end-systolic LV pressure. Maximal ESLVP was measured from the LV PV loop of single heart beat [2, 3].

LV pressure-volume loops` area (PVA), an index of O_2 demand LVO_2, was calculated as SW and SWI + potential energy, being defined as: end-systolic LV pressure from the loop × (end-systolic volume (index) −Ves0)/2), having Ves0 be the volume-axis intercept of the nonlinear end-systolic pressure-volume relationship fit [6, 23]. Maximum LV O_2 demand was assessed from the pressure-volume area and per heart beat, being presented in Joules.

Theoretical LV potential energy for LV volumes at end-systolic pressure of 100 mmHg (Ves100) from the non-linear ESPVR regression was calculated from the LV P-V loops' measurements in the 4th vs. 8th weeks.

CMRI measured end-systolic and end-diastolic LV volumes' analysis was performed with software for cMRI images assessment (K.U. Leuven, CardioViewer). Left ventricular ESPVR and PVA parameters were further indexed, being assessed from LV volumes indexed per BSA (m^2) and 100 grams of LV mass, that was measured from cine cMRIs.

For statistical analysis of variance in R studio, two-way repeated measures ANOVA with post hoc Tukey test were used, having $p < 0.05$ considered as significant level. In addition, $p < 0.1$ was consider for the *post hoc* analysis, with Levene normality test assessment. Analysis of the variance of aligned nonlinear transformation of the data was performed, as a nonparametric test.

Results are presented as means±SEM or medians with an interquartile range in the 4th vs. 8th week between chronic late and early loaded groups.

3. Results

The LV pressure-volume loop's area being assessed in LL compares to EL in the 4th vs. 8th weeks of banding, with potential energy (PE), LVO_2 demands, LV stroke work, and effective work (EW) in absolute and relative values in terms of BSA are presented in detail in table 1.

Normalization in terms of LV mass showed similar results when compare to BSA indexing of the nonlinear ESPVR curve.

Stroke work was not different or changed between 4th vs. 8th week (figure 3). LV PVA, with maximum LV O_2 demand, was also not different between groups, although being higher in LL compares to EL in the 8th week. This was calculated using the nonlinear regression analysis of ESPVR (figure 4).

Indexed LV stroke work for BSA (m^2) and per 100 grams of LV mass were not different between LL and EL group. LV PVA was not different neither was changed significantly between groups, when indexed for m^2 BSA and per 100 grams of LV mass.

The potential LV energy in linear ESPVR (PE) was different. It trended to be associated with the LV systolic loading sequence, being higher in the LL compared with the EL group in the 8th week (interaction p=0.07). This was not found in PVA regression assessed, from maximum LV afterload in indexed LV volumes per m^2 BSA at 4th vs. 8th week.
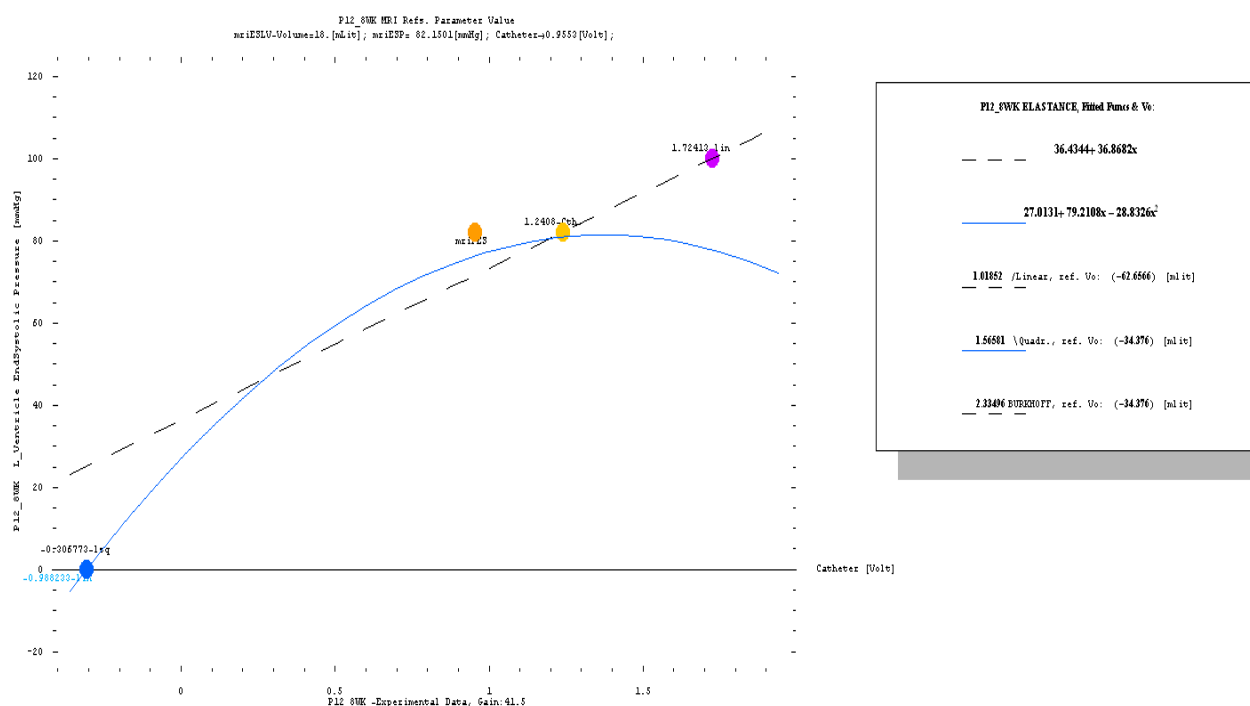
Figure 2. *Presents the software for nonlinear ESPVR assessment for PVA analysis in asc. banding (Pig12_8th week) with EL. It was performed, for nonlinear and linear regression, using absolute LV volumes. These were compared. The nonlinear ESPVR assessment of LV elastance with VA coupling is being discussed in other research article (unpublished data with results).*

Table 1. *Presenting LV PVA parameters, from ESPVR assessment using absolute and indexed LV volumes per BSA in m².*

LV_PVA parameters	LL (n=8) 4th week	EL (n=6) 4th week	LL (n=8) 8th week	EL (n=6) 8th week	p group
SW (mmHg·mL)	5152±868	4209±600	6908±1287	5029±1097	0.5
SWi (mmHg·mL/m²)	5072±669	4081±415	5797±833	3596±291	0.3
PE (mmHg·mL)	2589 (1341-4580)	2085 (1051-3278)	3686 (3368-5180)	1613 (1251-2691)	0.5
PEi mmHg·mL/m²	2734±567	3612±1367	3161 (1963-4251)	1698±351	0.6
PE100 (mmxHg·mL)	1008±337	446±205	802±488	177±443	0.3
PVA (mmHg·mL)	7817±1587	6527±1102	10482±1609	5389±583	0.5
PVAi (mmHg·mL/m²)	7806±949	7693±1660	9527 (7015-10821)	5294±513	0.7
LVO$_2$ (J/min)	1.1±0.2	0.86±0.16	1.5±0.2	0.9±0.2	0.5
LVO$_2$i (J/min/m²)	1.04±0.1	1 ±0.2	1.2 (0.92-1.44)	0.7±0.07	0.7
LVO$_2$I (J/beat/m²)	0.013±0.002	0.014±0.003	0.014 (0.01-0.185)	0.01±0.0013	0.8
EW	0.69±0.04	0.65±0.03	0.63±0.03	0.74±0.05	0.39
EWi	0.66±0.05	0.6±0.07	0.6 (0.55-0.74)	0.7±0.05	0.96

TABLE legends: SW –stroke work, PE potential energy, PVA for PV area, EW for effective work. LVO$_2$ for nonlinear analysis of LV O$_2$ demand, (LVO$_2$=PVA*1, $33*10^{-4}$ Nozawa et al -reff. list), † for p<0.05 in two-way repeated measurement ANOVA for group difference; ¶ for significant interaction effect; $ for significant change between 4th vs. 8th week.
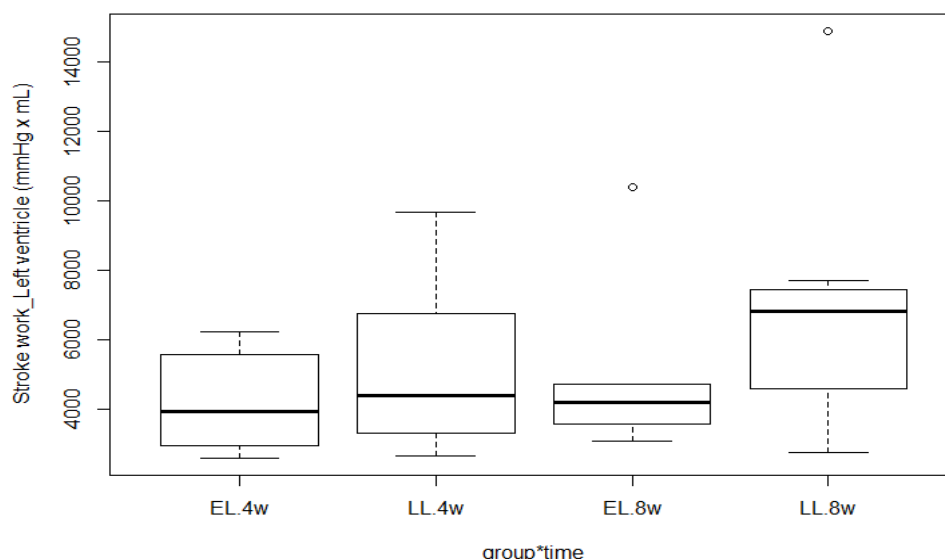
Figure 3. Presents the LV stroke work in LL vs. EL group - no significant difference was found between the groups or change at 4th & 8th week.
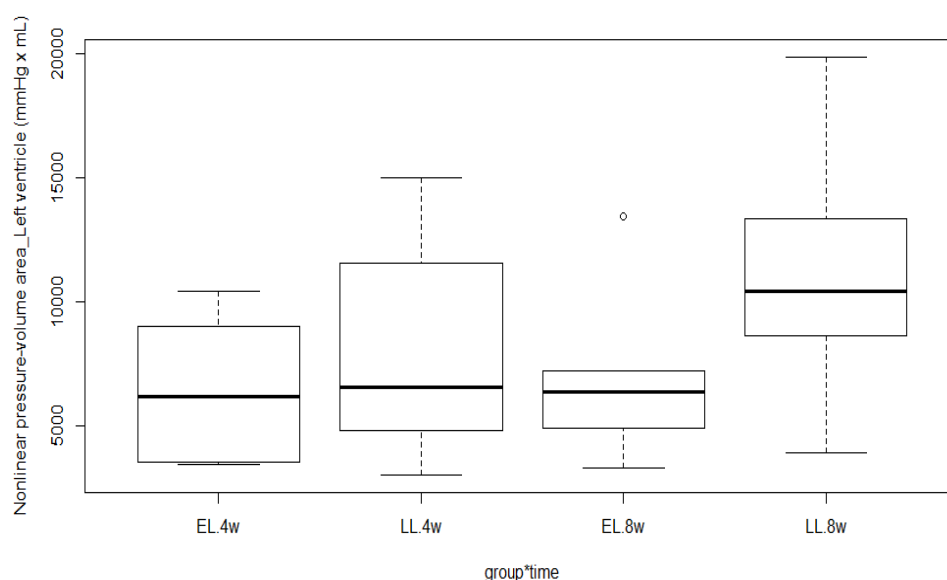

Figure 4. Left ventricular pressure-volume area was calculated using the nonlinear ESPVR regression method, in LL and EL presents no significant difference at 4th or 8th week.

Nonlinear ESPVR analysis did not present difference in the nonlinear potential LV energy (PEb) in LL compares to EL, neither change from the systolic LV load between 4th vs. 8th week (figure 5). This was also found when ESPVR was assessed from indexed LV volumes per BSA and per 100 grams of LV mass. The theoretical LV potential energy for ventricular volume at 100 mmHg end-systolic LV pressure was not different significantly, when being assessed from nonlinear regression method. It was higher in LL compared to EL in hypertrophic LV remodeling presented per 100 grams of LV mass in the 8th week (post hoc p=0.036).

LV O_2 demand was not different, though being higher in LL at 8th week (LVO$_2$b in LL 4 weeks 0.013±0.003 and 8 weeks 0.018±0.002 J/beat *vs.* EL 4weeks 0.011±0.003 and 8 week 0.01±0.0015 J/beat p=0.04 group). There were no differences for indexed LV O_2 demand between LL and EL group in the 4th vs. 8th week.

LV PVA was not different between LL and EL indexed per BSA, and when assessed in 100gr LV mass for LVH remodeling. Effective LV work was also not different neither changed, being reduced in LL compared to the EL group between 4th vs. 8th week (figure 6).

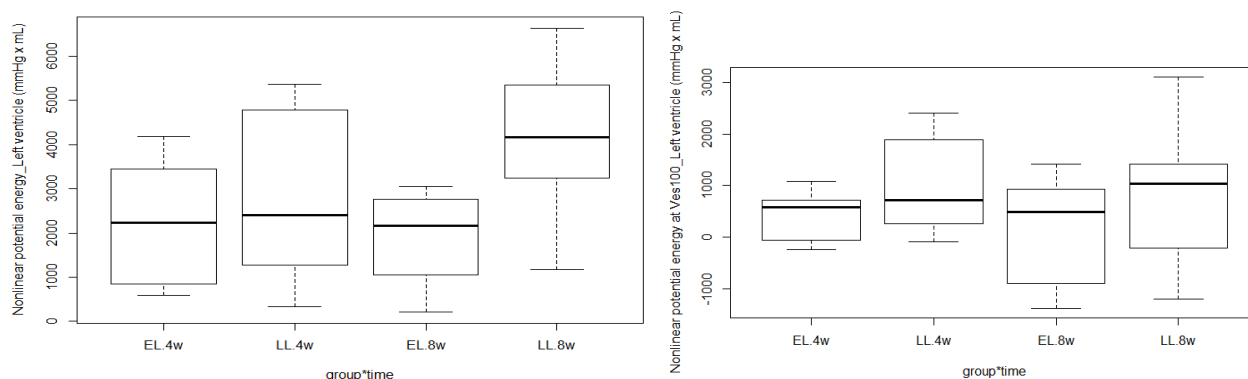This was result from difference in LV afterload.

50

Figure 5. *Showing no difference for LV ventricular potential energy, calculated using the nonlinear regression method in the 8th week. Nonlinear potential energy at Ves100 was not different in LL compares to EL between 4th vs. 8th week.*
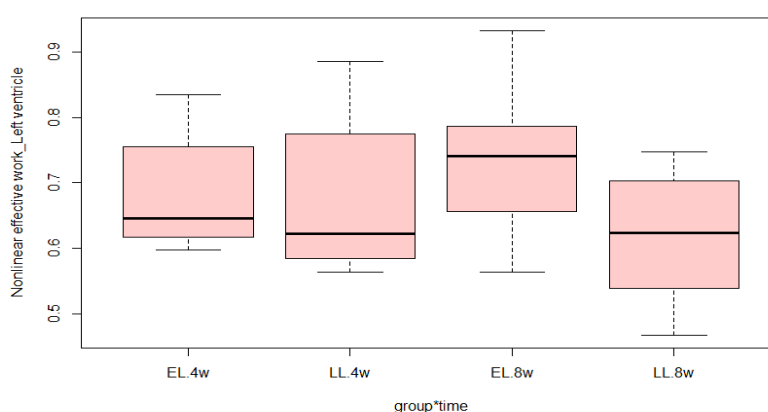

Figure 6. *Effective LV work assessed, using the nonlinear regression method for ESPVR assessment, is not different in different systolic LV load comparing LL with EL in the 4th vs. 8th week.*

4. Discussion

This study that assessed in LVH, both relative and absolute LV SW with maximum O_2 demand from the pressure-volume loop's area, with EW, showed no differences in LV potential energy or absolute LV O_2 demand and systolic dysfunction, as well as from normalized effective LV work, having no changes in chronic LL and EL between 4th vs. 8th week. Differences were present, being found previously in LL vs. EL [13, 19, 21, 22]. Furthermore, indexing PVA parameters did not find difference, being relevant and related to EL and LL group in the 4th or 8th week. These relevant findings show no difference in SD from LV nonlinear pressure-volume loop's area assessment when maximal end-systolic LV elastance is used to calculate the O_2 demand in LL and EL. It further indicates no difference in increased LV O_2 demand between chronic LL and EL in the 8th week.

Increased LV O_2 demands and reduced EW are related to the increased afterload, in earlier developmental reduction in contractile LV function, as found in LL compared to EL group, with further developing earlier chronic systolic in diastolic LV dysfunction and decompensated stage of LVH remodeling [10,

22]. However, the most important finding of this study is that in EL vs LL there is no difference in stroke work and effective work at 4th and 8th week, in PVA plane assessment in SD, being present.

In this porcine model of chronic LL to compare with EL, there was no difference in LV mass, being calculated from cMRI, except in RWT in the 8th week, presenting with thicker concentric LVH in EL (DB 0.45 vs. AB 0.67 p=0.003) [17, 18]. Concentric LVH remodeling in arterial hypertension or AS is related to reduced mechanical myocardial work compared to eccentric LVH remodeling, resulting from differences present in LV stroke work and reduced O_2 extraction, within increased demand having worsen SD [10, 19]. In this study, difference present in LVH remodeling for the LV relative wall thickness did not present difference in effective LV work between groups in the 4th or 8th week and when being indexed, also per LV mass.

In previous report, assessing the PVA in increased LV afterload for early SD showed increased PVA with reduced effective LV work [13, 21]. This is related to reduced O_2 extraction level in higher LV working state and increased LV load [22-25].

In increased LV afterload, the LV hypertrophy and development of SD has been related to imbalance between the

intraventricular coupling, the LV working range and energy potentials, resulting with increased LVO_2 demands at rest.

These relative findings indicate indexed PVA parameters of the end-systolic pressure-volume relation for BSA and per 100 grams LV mass, as parameters for LV O_2 demand are not different, in LL vs. EL group in the 4th vs. 8th week. This did not change in LL or EL.

The coupling between the LV contractility and the LV afterload have been extensively evaluated in previous studies showing that, in physiologic condition, there is an adaptation to differences for the peak in LV afterload [2, 5, 8, 13, 15]. However, ability to tolerate stress in the intraventricular coupling assessed through the pressure-volume loop's area analysis is not precisely defined in chronic LL and EL in developing systolic with diastolic LV dysfunction [1, 5, 19, 21, 22].

Indexed LVO_2 demand was reported as not different between hypertrophic and normal LVs. However, it was different, when using absolute volumes, thereby indicating the impact of LV mass being present on basal resting O_2 demand [16]. This is somehow related to LV stroke work in HTA [25]. Further, imbalances in LV mechanical effective work have been associated with the presence of LVH, being present in arterial hypertension [21].

Ventricular contractility and myocardial O_2 consumption are coupled closely in the ventricles and the heart, being heart rate dependent, in both physiological and pathological conditions [8, 9, 12]. However, in diastolic LV dysfunction and in HF there is an inadequate response to stress and resting state in heart rate that can have an impact on the resting LV working state. These relative changes may present earlier affection of LV O_2 demand, being increased at rest and worsen with stress earlier before systolic LV function would present its fall in effective end-systolic LV elastance.

Further metabolic changes of the LV myocardium are earlier LV changes in its shape and structure, changes that have not been analyzed in vivo for the non–working related LV myocardium [21]. It was showed that non-indexed myocardial O_2 consumption is greater in LVH and has been related to the extent of the LV mass, correlating inversely with mechanical myocardial efficiency in several reports [16, 21-23]. Shift of contractility in the PVA plane may case linear parallel shift in basal non-work related myocardial O_2 consumed for 100 grams in LV mass in situ, where ESPVR may become more or less linear in presence of LVH remodeling [5, 6].

In TNNT2 cardiomyopathy or in HTA and AS, systolic LV dysfunction in LVH remodeling, having positive genotype with phenotype negative feature presenting absent LV hypertrophic remodeling in the progression towards HF with contractile dysfunction has increased LV O_2 consumption with reduced mechanical myocardial efficiency [19, 20, 22, 25]. However, presence of LVH is important for reduced ability to tolerate exercise or stress, being result of SD [1, 21, 24].

There are different phenotypes of metabolic changes of the LV myocardium that are related to the phase of the hypertrophic ventricular remodeling when being assessed that is also related to the NYHA class and EF [10, 14, 21, 22].

In this report, it was shown that absolute LV O_2 demand and LV potential energy with stroke work are not different or affected in LL and EL and are different compares to ventricular arrhythmia occurrence group. LV stroke work was not different between these two groups, being higher in LL compares with EL. These differences were not significant in the 8th week and when PVA parameters were indexed per 100 grams of LV mass or BSA. However, difference was found in LV nonlinear PE for 100 mmHg end-systolic pressures when indexed per 100 grams LV mass.

Comparing LL to EL it was showed that the LV working range and limited LV ESPVR are different, being less in EL group when volumes for end-systolic pressure of 100 mmHg has been generated in both absolute or normalized PVA per 100 grams of LV mass. This is seen from the differences created in LV afterload that is relevant to understand why LVH remodeling with systolic dysfunction and insufficient filling can result especially from LL and in the 8th week for EL. The most important finding of this study shows that PVA, as parameter of maximal LV O_2 demand during rest is not different between LL and EL with LV stroke work and effective work in the progression towards systolic HF, assessing metabolic remodeling. In previous findings it was showed how reduced aortic compliance, as well as presence of LVH in AS are related to increased MVO_2 consumption with demand of more that 30-50% compared from rest state. In HTA however, LVO_2 demand at peak exercise is reduced compares to controls, indicating reduced exercise capacity, due to higher heart rate and reduced vasodilator reserve with response to stress [22-25].

This novel and relevant finding indicates no difference present in LV stroke work and PVA earlier on between chronic LL and EL in the 4th vs. 8th week. There were no differences related with the LV hypertrophy developed, that was not different between LL and EL group or when normalized per BSA in the 4th vs. 8th week. These findings show that these are no differences being related to that associate with maximal absolute LV O_2 demand, at rest in EL and LL in the 4th and 8th week. LV potential energy, being stored during systole, was not different in this analysis, except for the nonlinear potential energy for Ves100 indexed for BSA, as for LV mass.

It was showed that presence of negative external LV work is related to the adaptive physiologic response of the ventricle [11]. This was present in EL in this porcine model, indicating early SD in increased LV afterload. By comparison, in LL there was higher LV stroke work, presenting a more positive LV effective work for both Ves0 and Ves100, thus indicating that the ventricle is deteriorating by failing to generate negative effective stroke work. The novelty introduced in this study brings the value of intraventricular coupling, being assessed through the PVA, as relevant for differences in systolic LV loading, as found in the presence of arterial hypertension, coarctation or aortic stenosis in the development of

earlier LV insufficient pump function, resulting from dysfunction of LV filling. Furthermore, the increased absolute LVO_2 demand in LL compared to EL can imply on the pathophysiologic background for developing earlier systolic or/and diastolic LV dysfunction, in LL or EL, being assessed previously [17]. This can be found in relation to ventricular arrhythmia occurrence. In this study LVEF was not different between groups in the 8th week and there was no difference in PVA and LV O_2 demand, as well as in normalized PVA parameters in the 8th week, except in PE for PES100. This was showed that can be assessed, from nonlinear regression assessment of ELV, indicating of early increased PE needed to complete LV relaxation in LL competed to EL, where is incomplete. *This is indirect parameter that may show reduced exercise capacity with increased resting LVO_2 demand, as relevant for different LV afterload, result of arterial hypertension.*

In the presence of aortic valve stenosis, reduced myocardial effective work with stroke work, and their blunt or reduced reserves at rest have been associated with presence of chronic systolic HF and higher NYHA functional class, suggesting on need of O_2 supplement in this condition [10]. Though values of myocardial O_2 demand and stroke work are compared on individual bases, these present findings in this porcine model are representative for human pathophysiology, having thus comparable ventricular volumes, in moderate descending thoracic vs. ascending aortic stenosis resulting for differences in LV systolic load (timing and LVESP). Difference in pathology makes these different diseases different to compare and to assess nonpulsatile vs. pulsatile component of the LV afterload. This may be considered as range, in hypertension, (supracoronary) aortic stenosis and/or descending thoracic aorta stenosis associated with coarctation of the aorta being relevant for early SD. These several pathologic disease conditions promote the LVH remodeling processes, thereby affecting the ventricle with resulting changes of the LV with atrial shape, structure, and function, further leading towards development of LV relaxation abnormality and SD in increased load. This occurs within the hypertrophic and structurally changed ventricles, as a result of the afterload-related injury, promoting neurohormones and mechanical processes that affect the LV hypertrophic myocardium in terms of change in the metabolic substrate being used to complete LV relaxation.

In HF, mechanical myocardial efficiency is reduced with state of increased O_2 consumption by the LV myocardium, being reported in previous work [22, 23]. Contractile LV deterioration in cardiomyopathy is related to an increased myocardial O_2 consumption of the septum with reduced effective work. In this model, the aim was to assess early systolic in diastolic LV dysfunction, from the myocardial effective work with O_2 demand. Instead, the assessment of stroke LV work through the PVA analysis found no difference in LL vs. EL group in systolic dysfunction from portion of PVA in the 4th vs. 8th week, when using maximal ELV for calculation

of the PVA and maximum LV O_2 demand. LV stroke work reduced in EL compares to LL at 8th week, showing that SD is more severe in EL vs. LL.

LV work with pressure-volume area calculation, from the pressure-volume loops, was performed based on maximum single end-systolic LV pressure measurement in normal heat beat to calculate the LV pressure-volume loop's area, having the highest value from the pressure-volume measurement analyzed. The values were compared to multiples beats assessment that did not show difference. This method used for interpreting the invasive assessment of LV mechanical coupling, for assessing the diastolic and systolic function with their interaction are measurements of the LV work and efficiency, so to assess early SD and HF development. This kind of data interpretation is preferred in terms of better independent LV functional and energetic assessment for avoiding other relevant cardiovascular conditions that can affect the interpretation of the pressure-volume loop's hysteresis when assessing the LV work and energetic potential with systolic-diastolic functional coupling in the PVA plane assessment.

In conclusion, absolute LV potential energy at Pes0, and LVO_2 demand are not different, as well as, stroke work and PVA with effective work in a model comparing LL and EL. Indexed LV PVA parameters for m² and per 100 grams of LV mass are not different between 4th vs. 8th week in LL compares to EL. This is cause for the development of earlier diastolic with systolic dysfunction in chronic LV afterload increase. This study found that LL is important for early systolic LV dysfunction, as well as EL having diastolic LV dysfunction.

Limitation of this study is the use of porcine model and need to compare these findings to previous dogs model that do not have the same anatomy and hemodynamic to be compared, as human. The baseline with resting basal LV O_2 demand have not been measured and calculated, limiting the present assessment.

Clinical perspective: in hypertensive model having increased LV load, LV stroke work with PVA and EW are not different, and PE with maximum LVO_2 demand at rest, during load reduction in LVH remodeling for early SD between 4th vs. 8th week. In HTA/AS model having LL and EL, nonlinear PVA parameters indicate that chronic LL compares to EL are both important for early development SD and HF, but earlier in EL. Difference found for PE100 indicates on relaxation changes in relation to intraventricular coupling relation, in assessment of early SD development in LL and EL.

Central message: No difference in SD is found presenting with LV SW with PVA and EW that are not different in nonlinear ESPVR regression, between LL and EL in the 4th vs. 8th week. Normalizing PVA for BSA in m² or per LV mass did not show different or was related to changes with differences in PE, when assessing early HF with SD, from P-V assessment of LV stroke work with maximum LV O_2 demand and EW, between 4th vs. 8th week in concentric LVH remodeling.

Abbreviations

LV	Left Ventricle
PE	Potential LV Energy
PVA	Pressure-Volume Loop's Area
LVO_2	Nonlinear Left Ventricular O_2 Demand

Disclosures

None.

Acknowledgments

POPEVSKI Ivan MSc.

Funding

K. U. Leuven, Belgium between August 2016-2019.

Author Contributions

Dr. Popevska S. is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Lam YY, Kaya MG, Li W, Gatzoulis MA, et al. Effect of Chronic Afterload Increase on Left Ventricular Myocardial Function in Patients With Congenital Left-Sided Obstructive Lesions Am J Cardiol 2007; 99: 1582–1587.

[2] Nozawa T, Yashumura Y, Futaka S, Tanaka N, Igarashi Y, et al. Relation between oxygen consumption and pressure-volume area of in situ dog heart. Am J Physiol 1987; 253: H31-H40.

[3] Loke KE, Messina EJ, Shesely EG. Et al. Potential role of eNOS in the therapeutic control of myocardial oxygen consumption by ACE inhibitors and amlodipine. Cardiovascular research 2001; 49(1), 86-93. https://doi.org/10.1016/S0008-6363(00)00196-6

[4] Suga H, Hayashi T, Shirahata M. Ventricular systolic pressure-volume area as predictor of cardiac oxygen consumption. Am J Physiol. 1981 Jan; 240(1): H39-44. https://doi.org/10.1152/ajpheart.1981.240.1.H39

[5] Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. The American Journal of Physiology, 1986; 250(6): R1021–R1027.

[6] Burkhoff D, Yue DT, Oikawa RY, Franz MR, Schaefer J, Sagawa K. Influence of ventricular contractility on non-work-related myocardial oxygen consumption. Heart and Vessels, 1987; 3: 66–72.

[7] Suga H, Hisano R, Goto Y, Yamada O, Igarashi Y. Effect of positive inotropic agents on the relation between oxygen consumption and systolic pressure volume area in canine left ventricle. Circulation Research, 1983; 32(3): 306–318.

[8] Suga BH, Sagawa K. Instantaneous Pressure-Volume Relationships and Their Ratio in the Excised, Supported Canine Left Ventricle. Circulation Research, 1974; 35: 117–126.

[9] Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res. 1973; 32(3): 314-322. https://doi.org/10.1161/01.res.32.3.314

[10] Hansson NH, Sörensen J, Harms HJ, Kim WY, Nielsen R, Tolbod LP, et al. Myocardial Oxygen Consumption and Efficiency in Aortic Valve Stenosis Patients With and Without Heart Failure. J Am Heart Assoc. 2017 Feb 6; 6(2): e004810. https://doi.org/10.1161/JAHA.116.004810

[11] Suga H, Goto Y, Yasumura Y, Nozawa T, Futaki S, Tanaka N, Uenishi M. Oxygen-saving effect of negative work in dog left ventricle. American Journal of Physiology-Heart and Circulatory Physiology, 1988; 254(1), H34–H44. https://doi.org/10.1152/ajpheart.1988.254.1.H34

[12] Suga H, Hisano R, Hirata S, Hayashi T, Yamada O, Ninomiya I. Heart rate-independent energetics and systolic pressure-volume area in dog heart. Am J Physiol. 1983 Feb; 244(2): H206-14. https://doi.org/10.1152/ajpheart.1983.244.2.H206

[13] Nozawa T, Yasumura Y, Futaki S, Tanaka N, Uenishi M, Suga H. Efficiency of energy transfer from pressure-volume area to external mechanical work increases with contractile state and decreases with afterload in the left ventricle of the anesthetized closed-chest dog. Circulation, 1988; 77(5), 1116–1124. https://doi.org/10.1161/01.cir.77.5.1116

[14] Peterzan MA, Lygate CA, Neubauer S, Rider O. Metabolic remodeling in hypertrophied and failing myocardium: a review. American Journal of Physiology. Heart and Circulatory Physiology, 2017; https://doi.org/10.1152/ajpheart.00731.2016

[15] Starling MR, Mancini GB, Montgomery DG, Gross MD. Relation between maximum time-varying elastance pressure-volume areas and myocardial oxygen consumption in dogs. Circulation 1991; Jan; 98(1): 304-14. https://doi.org/10.1161/01.cir.83.1.304

[16] Izzi G, Zile MR, Gaasch WH. Myocardial Oxygen Consumption and the Left Ventricular Pressure-Volume Area in Normal and Hypertrophic Canine Hearts. Circulation 1991; 84: 1384-1392.

[17] Popevska S., et al. Adverse left ventricular hypertrophy in descending thoracic vs. ascending aorta banding in novel porcine model. cMRI study. Presented abstract ESC 2019 poster presented in Paris France, published in European Heart Journal (2019), 40 Supplement, 911.

[18] Popevska S et al. Different left ventricular remodeling between descending thoracic vs. ascending aorta banding in porcine model. Abstract presentation ESCVS 2019 Groningen NL. published in Journal of Cardiovascular Surgery 2019; Vol 60, Suppl. 1 to No3.: 401, 56.

[19] Akinboboye OO, Chou RL, Bergmann SR. Myocardial blood flow and efficiency in concentric and eccentric left ventricular hypertrophy. American Journal of Hypertension, 2004; 17(5), 433–438. https://doi.org/10.1016/j.amjhyper.2004.02.006

[20] Parbhudayal R, Harms H, Mchels M, Van Rossum AC, Germans T, Van der Velden J. Increased myocardial oxygen consumption precedes contractile dysfunction in hypertrophic cardiomyopathy caused by pathogenic TNNT2 gene variants. J Am Heart Assoc. 2020; 9: e015316. https://doi.org/10.1161/JAHA.119.015316

[21] Laine H, Katoh C, Luotolahti M, Yki-Järvinen H, Kantola I, Jula A, et al. Myocardial oxygen consumption is unchanged but efficiency is reduced in patients with essential hypertension and left ventricular hypertrophy. Circulation. 1999; 100: 2425–2430. https://doi.org/10.1161/01.cir.100.24.2425

[22] Abou Ezzeddine OF, Kemp BJ, Borlaug BA et al, Myocardial Energetics in Heart Failure. Circ Heart Fail. 2019; 12: e006240. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006240

[23] Bombardini T, Costantino MF, Sicari R, Ciampi Q, Pratali L, Picano E. End-Systolic Elastance and Ventricular-Arterial Coupling Reserve Predict Cardiac Events in Patients with Negative Stress Echocardiography. BioMed Research International, 2013, 1–14. https://doi.org/10.1155/2013/235194

[24] Kelly RP, Tunin R, Kass DA. Effect of Reduced Aortic Compliance on Cardiac Efficiency and Contractile Function of In Situ Canine Left Ventricle. Circ 1992; 71: 490–502.

[25] Bachte R, Zheng Dai X. Myocardial oxygen consumption during exercise in the presence of left ventricular hypertrophy secondary to supravalvular aortic stenosis. JACC 1990; 5(15): 1157-64.