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Research Article

Shorten τ_1 in Chronic Early vs. Late Systolic LV Load for Systolic Dysfunction in Ascending vs. Descending Thoracic Aortic Stenosis

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Abstract

Background: Arterial hypertension (HTA) results with diastolic LV dysfunction (DD), important to develop systolic LV dysfunction and exercise intolerance with HF. Separating between chronic late (LL) to early LV load (EL) during systole, impaired LV relaxation is present earlier in chronic LL vs. EL, having early HF, as result of myocardial ischemia and systolic LV dysfunction in HTA. *Objective and Methods:* to assess early systolic in diastolic LV dysfunction from biexponential τ regression assessment, using single beat and mono-exponential regression analysis, with nonzero asymptote with special software in LL and EL, between 4th and 8th week in a porcine model. This assesses early HF and systolic LV pump dysfunction, from fast_τ (τ_1), for early systolic LV dysfunction, in LVH remodeling in moderate LV afterload increase. Fourteen domestic male pigs, underwent LV pressure measurements with conductance Millar 5F catheter having moderate ascending aortic banding (EL=6), and in descending thoracic aortic stenosis, as in hypertension (LL=8). τ_1 (τ_fast) and τ_2 (for τ_slow) component of bi-exponential τ analyzed LV dysfunction at 4th vs. 8th week. Under reduced LV load (m3), during ventilation preserved (m1) or suspended transitionally (m2), fast τ assess early systolic dysfunction in LL vs. EL. Associated murmurs were assessed to detect LV valves dysfunction. Data was compared statistically, using two-way repeated measurement ANOVA, after Leven normality test. Results are means ±SEM or medians (quartiles), for significant $p<0.05$. *Results:* mono-exponential τ was not different, neither changed in LL vs. EL at 4th and 8th week in m1, m2 or m3, that reduced in both groups with mechanical LV load reduction at 4th and 8th week ($p<0.05$). Prolonged bi-exponential asynchronous τ_2/τ_1 ratio in EL was different from LL at 8th week, resulted from LV afterload ($\tau_2\tau_1$ interaction $p<0.05$). τ_fast was different, being shorten in EL vs. LL at 4th and 8th week. Reduced bi-exponential $\tau_2\tau_1$ ratio in EL and increased in LL, with mechanical load reduction, improved LV ischemia with DD in EL at 4th and 8th week of moderate LV afterload increase, but did not respond in LL. There was predominant systolic murmur in EL and diastolic murmur in LL, pronounced with load reduction. *Conclusion:* Prolonged bi-exponential τ_1 in LL shows early systolic LV dysfunction within DD. LV ischemia and systolic with diastolic LV pump dysfunction in EL presents shorten fast_τ, being unresponsive to mechanical LV load reduction in LL.

Keywords

Afterload, τ, Relaxation, Systolic Dysfunction, Hypertension, Aortic Stenosis, Coarctation, Load Reduction

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1. Introduction

In HTA, associated differences in systolic LV pump dysfunction between pulsatile compares to non-pulsatile LV afterload, differentiate between chronic late load (LL) and early peak in LV afterload increase (EL), presenting with development earlier prolonged LV relaxation and early systolic dysfunction with HF in presence of chronic LL compares to EL [1, 2, 5, 9, 11, 12, 15, 16, 22, 25, 26]. However, afterload associated difference in developing early impaired LV relaxation are inconsistent between chronic LL vs. EL in developing systolic HF [3, 6, 7, 9, 22, 23]. Impaired LV relaxation with diastolic LV dysfunction has not been assessed precisely to define early developing diastolic LV dysfunction in LL compares to EL between 4^{th} vs. 8^{th} week (3, 5, 10, 13). It indicates early diastolic with systolic LV pump dysfunction in hypertension, aortic coarctation and/or aortic stenosis, being associated with developing adverse outcome. This has been related to increased myocardial ischemia in coronary artery disease CAD, being responsive to LV load reduction and sensitive to change in load [1, 5, 7, 30]. However, early development of LV diastolic dysfunction with impaired LV relaxation in relation to moderate systolic LV load, as an early phase parameter of diastolic dysfunction are inconsistent [3, 7, 22, 23, 30]. Both LL or EL affect LV relaxation rate, being prolonged or shortened, as result from difference between period of systole when contractile elements are imposed to increased LV load, the animal models used and experimental condition, if in situ or ex vivo. Still, active LV relaxation abnormality is related to systolic LV dysfunction, and is assessed most accurately from calculating LV relaxation time constant, known as isovolumic LV pressure decay constant in time (τ), using exponential regression. In the presence of systolic and/or diastolic LV dysfunction, LV pressure fall is assessed from LV pressure measurements, with conductance pig-tailed micromanometer catheter [30-33]. Noninvasive assessment has been described and used to assess accurately LV relaxation τ constant, using echocardiography in different cardiovascular conditions, and after MI [3, 9, 15, 23, 26]. It can early detect present diastolic LV dysfunction related to the presence of ischemia from several different methods being previously described, to assess τ [2, 11, 12, 20-35]. However, LV pressure fall during the isovolumic period is well assessed from an exponential regression method, especially in HF being able to assess earlier subclinical systolic HF and how these responses to reduced LV load [31]. Bi-exponential regression with zero asymptote of LV pressure fall has been used previously to detect asynchronous τ ratio. If increased, it is result of regional LV ischemia that was not different in LL compares to EL, in acute setting [12, 32]. This has been used to assess the presence of subclinical myocardial ischemia in CAD [31]. Prolonged LV active relaxation has been assessed previously in the presence of chronic LL compares to EL [3, 21] and still, early development of diastolic LV dysfunction between LL or EL in the progression towards systolic LV dysfunction is not defined precisely from previous studies assessing τ in different LV afterload [1, 3, 5, 6, 8-10, 13, 15, 20, 23]. The purpose of this study was: (1) to assess τ in representative porcine model of different (late vs. early) systolic LV load, in the stage B phase, having descending thoracic vs. moderate asc. aortic banding with stenosis, from mono-exponential and bi-exponential regression with nonzero asymptote, so to assess bi-exponential τ2τ1 ratio and τ1, using invasive LV pressure measurements in LL compares to EL, at 4^{th} vs. 8^{th} week. This is used to differentiate early development of systolic and diastolic LV dysfunction and [2] presence of associated murmurs with valves' dysfunction between LL and EL at 4^{th} vs. 8^{th} week. The hypothesis that chronic LL compares to EL group relates with early prolonged exponential τ with associated diastolic murmurs from valves' dysfunction was assessed, being tested in prospective experimental randomized study in a porcine model. The aim was to assess early associated development systolic with diastolic LV dysfunction in LL compares to EL group in porcine model. Further assessment of τ, during LV load reduction was used to differentiate early systolic HF and potential benefit from mechanical LV load reduction, as medical treatments to normalize impaired LV relaxation with valves dysfunction in LL compares to EL between 4^{th} vs. 8^{th} week of moderate aortic stenosis. In previous report, there were no differences in asynchronous LV relaxation between LL compares to EL in acute setting [12]. This was found to be important to assess early the extent of LV ischemia between segments, using τ assessment that is prolonged in presence of CAD [30].

2. Methods

Fourteen male domestic pigs (28±4 kg weight) were included in this study. It is being approved by the Local Ethical Committee of the Animalium, from the Katholieke Universiteit Leuven, in Leuven, Belgium. The animals were treated as humans, in accordance to the EU regulative for animal care and welfare in laboratory condition (2010/63/EU; 2006/3/EU ETS No.123 Article 5, 2008/0211/EU annex VIII). For sedation and anesthesia induction, intramuscular Telazol (Zoletil 100, 8mg/kg) and Xylazine M 2% (2.5mg/kg) were used, with Propofol bolus dose (3 mg/kg). Pigs were intubated and ventilated mechanically. The anesthesia was maintained with intravenous Propofol (10 mg/kg/h) and Fentanyl (15 μg/kg/h) during the invasive measurements. Mechanical ventilation (Drager ventilator), with tidal volume 9-10 ml/kg; fr.16/min, and inspiratory Sa O_2 at 50% kept arterial O_2 saturation between 98-100% and CO2 under 40%. Intravenous NaCl 0.9% infusion (5-10 ml/kg/h) maintained a normal range of heart rate and aortic pressure. SaO_2 and pCO_2 were written down at 30 minutes interval, until pigs fully recovered from anesthesia. Invasive LV pressure measurements were performed at 4^{th} vs. 8^{th} week of aortic banding, in the pigs having moderate

chronic LL from descending thoracic aorta banding (LL=8) and in ascending aortic stenosis for chronic early LV afterload increase (EL=6). For τ assessment, a 5Fr fluid-filled pig-tailed Millar high-fidelity catheter was used, being positioned in the LV apex. The catheter measurements were recorded digitally, at a sampling rate of 200 Hz in LabChart7, with synchronized ECG DII lead. Following the catheter calibration at zero pressure at room temperature and using a manometer calibrator in LabChart 7, LV pressure measurements were recorded for analysis during baseline, having respirations preserved (M1), mechanical ventilations suspended transitionally (M2), and during preload reduction (M3) (LabChart 7, AD Instruments, Houston, Texas, USA). Intravenous enoxaparin was used for cloths' prevention (100 IU/kg). 8Fr vascular access inserted in the common carotid artery, guide the micro conductance catheter to be positioned in the ascending aorta and LV apex for measurements acquisition. 10Fr plastic balloon catheter was used for mechanical LV preload reduction, being inserted with a guidewire, positioned in the IVC, above the diaphragm.

The LV relaxation time constant τ was assessed from single mono-exponential and bi-exponential regression analysis of isovolumic LV pressure fall with nonzero asymptote, using special software. LV pressure was measured in 1 msec interval, between LV dP/dt*min* and mitral valve opening pressure (set at 5 mmHg above presiding end-diastolic LVP at ECG R wave), using dedicated software (LabChart Reader8) [2, 27, 33].

Heart sounds and presence of LV valvular dysfunction with associated murmurs were analyzed in LabChart Reader 8 (AD Instruments), using band-pass filter that was applied to the LV pressure signal with the cut-off set between 25 and 50 Hz.

Statistical analysis was performed, using two-way repeated measures ANOVA and variance analysis of aligned rank transformed data, as non-parametric test, with post-hoc Tukey test and Levene normality test at $p<0.1$. Results presented are means±SEM or medians with inerquartiles' range, for significant level for $p<0.05$.

3. Results

The results of the mono-exponential with bi-exponential regression τ assessment, being measured at 4^{th} vs. 8^{th} week between LL vs. EL are presented in the table. Figure shows the regression assessment with change in LVP curve in LL compares to EL group at 4^{th} vs. 8^{th} week, in single beat assessment.

In M1, mono-exponential τ was not different or changed between LL and EL in the 4^{th} vs. 8^{th} week. Bi-exponential asynchronous τ2τ1 ratio was different that prolonged and became more asynchronous in EL compares to LL in the 8^{th} week. This was result from late vs. early LV systolic load in the 4^{th} vs. 8^{th} week (*interaction* p=0.04). τ1 (fast τ) being early shorten in EL, while prolonged in LL at 4^{th} vs. 8^{th} week showing systolic LV dysfunction in LL and EL group at 4^{th} and 8^{th} week. Slow τ (τ2) constant prolonged significantly in both groups at 8^{th} week, though earlier in presence of LL. Bi-exponential b regression constant of τ assessment was found to be increased and different in LL vs. EL group suggesting that in LL the active LV relaxation ends at higher LV pressures, being more convex and can indicate effect from difference in load, having increased pressures at the end of LV relaxation. In EL there was negative LV pressure developed at the end of the active LV relaxation, suggesting preserved LV filling. This was significant in terms of time and between groups in the 8^{th} week. This indicates on the relative difference in the b regression constant of LV τ assessment, related to LV load in response to increased LVP during active LV relaxation in LL compares to EL. These are causes of early systolic LV dysfunction. The exponential curve was shifted downwards in LL and upward in EL between 4^{th} vs. 8^{th} week. This indicated on early increased pressures at the point of start of LV relaxation in EL. Assessing the possible error in LV pressure at the beginning and in the end of LV relaxation there was uncertainty in the higher LV pressures that indicates begin of LV relaxation especially in the pigs that developed VAs in the 4^{th} vs. 8^{th} week. This indicates that diastolic LV dysfunction is related to the LV afterload, LVP in the beginning of LVP fall and also from valves dysfunction, as result from worsening progress of LV systolic dysfunction.

In M2, mono-exponential τ was not different as in M1 neither changed in LL or EL. Bi-exponential regression showed shorten early τ (τ_1) in EL that was different between groups, whilst prolonged in LL ($p=0.047$). Prolonged asynchronous bi-exponential $\tau_2\tau_1$ ratio in EL was different from LL at 8^{th} week (post hoc $p=0.014$ for τ_2/τ_1).

Mechanical LV load reduction (M3) that reduced mono-exponential _τ compares to baseline M2 and M1 in both groups at 4^{th} and 8^{th} week. It was not different in LL vs. EL or changed. It shows load dependent diastolic LV dysfunction that was reversible in EL and LL at 4^{th} or 8^{th}. This was different from M2 indicating that mono-exponential τ is responsive to change in LV load in LL and EL group at 4^{th} and 8^{th} week. In LL, bi-exponential asynchronous $\tau_2\tau_1$ ratio tended to increase and did not respond to reduction in LV load in EL in the 8^{th} week. Furthermore, early_τ (τ_1), late_τ (τ_2) and bi-exponential τ ratio were not different between groups or chanced, being reduced compares to M1, but not in LL ($p=0.23$). Delayed aortic valve closure and mitral valve opening was present in LL vs. EL, pronounced with reduction of load, resulting with systolic murmur in EL and diastolic murmur with delayed aortic valve closure in LL. This resulted from prolonged τ_2 although this was not different in LL compares to EL. These findings suggest presence of myocardial ischemia, relevant to the LV load that causes higher asynchronous LV relaxation within EL at 8^{th} week.

However, prolonged τ_1 and τ_2, as found in LL indicates incomplete LV relaxation that can be result of early reduced LV stiffness and diastolic LV dysfunction, while systolic HF in EL from shortened τ_1 and prolonged bi-exponential $\tau_2/\tau_{1\ ratio}$.

Load reduction can precipitate immediate increased asynchronous LV relaxation within LL. Further these relative

findings indicate on presence of systolic LV dysfunction in EL and LL group, based on different τ_1 constant, being reduced in EL at 8th week.

This indicates diastolic LV dysfunction within EL vs. LL at 8th week that improves with mechanical LV load reduction, but does not improve within LL, with mechanical LV preload reduction, as result of systolic dysfunction in diastolic LV dysfunction.

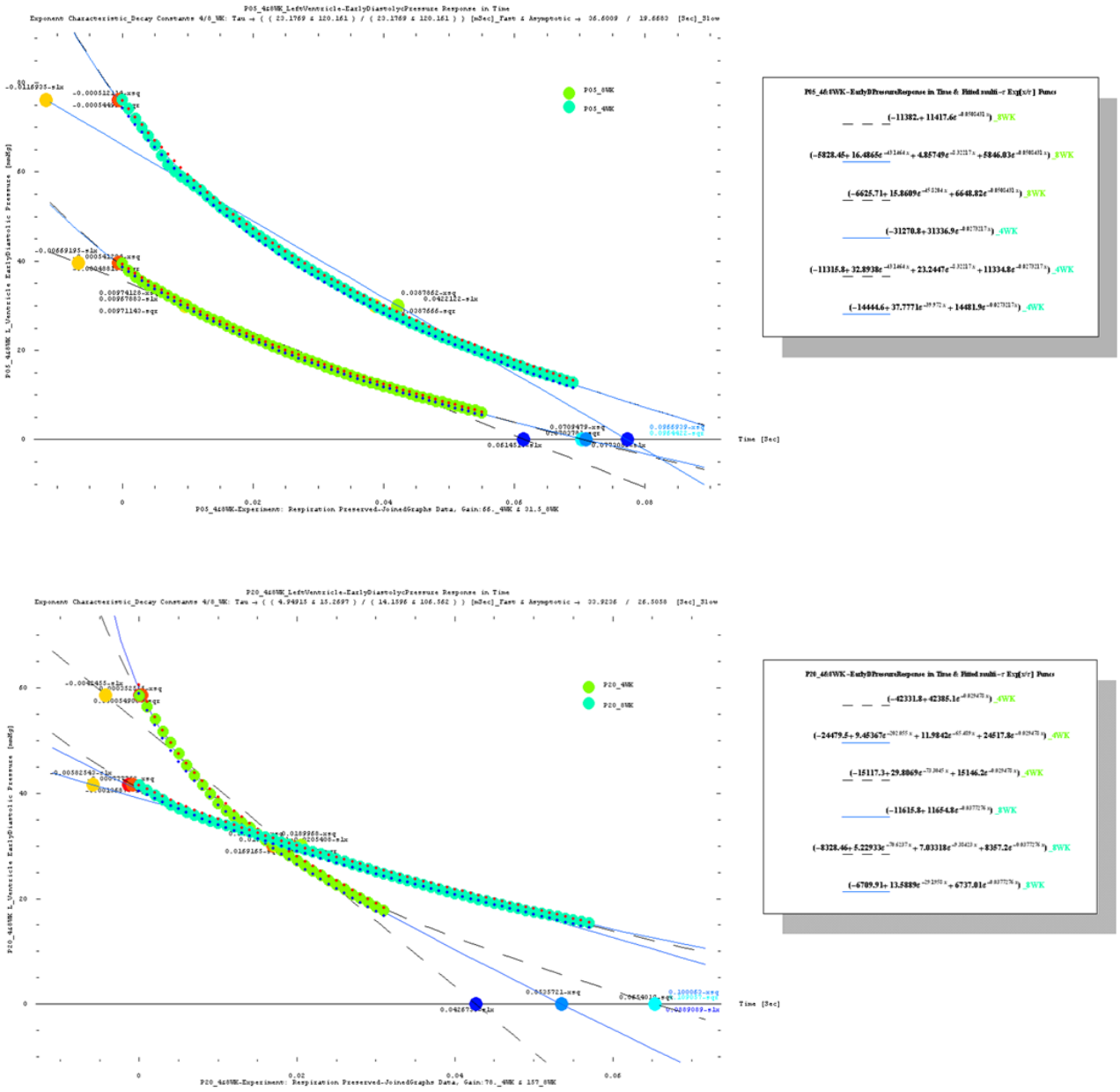

Figure 1. *Presenting LV mono-exponential with bi-exponential regression for τ calculation with nonzero asymptote, using special software in LL (upward) and EL (downward figure) at 4th vs. 8th week.*

4. Discussion

In this novel clinically relevant porcine model comparing chronic LL to EL, between 4th vs. 8th week of LVH remodeling, it was found that mono-exponential τ is not different between group, reduced in both groups with load reduction. However, prolonged bi-exponential asynchronous $\tau_2\tau_1$ ratio in EL that was different from LL at 8th week, being relevant to differentiate the chronic effect of LV afterload in LVH remodeling. Development of impaired LV relaxation and early development of systolic with diastolic LV dysfunction was found in LL and EL at 8th week.

Table 1. *Mono and bi-exponential τ assessment in LL compares to EL at 4th vs. 8th week of LVH remodeling.*

Group* interval	Exponential τ non-zero asymptote ms	Bi-exp b constant	Bi-exponential early τ(1) ms	Bi-exponential late τ(2) ms	Bi-exponential τ2/τ1 ratio
M1					
LL 4 weeks	33 ±3.4	36.4 ±3.3	20 ±2	66 (43.5-87)	3.3 (2.6-4.5)
LL 8 weeks	33 ±4 ^	30 ±4	27 ±4.5	79 (53-105.5)	3 (2-4)
EL 4 weeks	34 ±2.5	19 ±4	15.3 ±3	23 (20-24.5)	1.5 (1-2)
EL 8 weeks	33 ±4	12 ±2.5 ¶(& at 8 week)	15 ±2	60 (36-100) ¶	4.55 (2-7) * ¶
M2					
LL 4 weeks	31 (24-43)	27.5 ±3.5	18 ±3	65.5 ±6.5	4.24 ±0.6
LL 8 weeks	28 (26-30)	25.4 ±3	20±1.55	70 ±13	4 ±1
EL 4 weeks	35 (33-38)	26 ±5	11±2.4	63 ±13	6.4 ±1
EL 8 weeks	27 (26-29)	15.4 ±1	12 ±1 (&)	93.5 ±17	8 ±1 (&8w)
M3					
LL 4 weeks	23 ±3.55	11 ±2	19 ±4	55.5 ±10.4	4 (2-5)
LL 8 weeks	18 ±3	9 ±2	23.4 ±4.3	141 ±53.5	5(2-10.3)
EL 4 weeks	19 ±3.4	8 ±2.5	20 ±6	58 ±22	2 (2-3)
EL 8 weeks	16 ±1.5	4.5 ±2.2	17 ±4	48.5 ±8	3 (2-4.6)

Table legends: presenting LV τ assessment in M1, M2 vs. M3 - & for significant difference ($p<0.05$) between groups in LL compares to EL; ^ for ($p<0.1$ in LL vs. EL); * for significant interaction in LL compares to EL at 4th vs. 8th week; ¶indicating significant change in LL and EL group between 4th and 8th week.

The association present for between LV afterload and asynchronous $\tau_2\tau_1$ ratio was not found in measurements, during respirations off and volume reduction, though it was higher significantly in EL, indicating that an afterload-associated difference in asynchronous bi-exponential τ is preload with afterload related. Late vs. early LV systolic load can either prolong or shorten the rate of LV pressure fall, having LL relevant for early developing LV diastolic dysfunction in acute experimental setting, as being previousely described [5, 12]. In systolic LV dysfunction there is a load sensitive change in τ prolongation, being improved with mechanical LV load reduction [28]. EL resulted with greater asynchronous bi-exponential τ ratio, being different from LL at 8th week, but not in M3 something that has not been reported in terms of early development of systolic with diastolic LV dysfunction in response to mechanical LV load reduction. LV dysfunction develops in increased LV peak afterload that prolongs τ. LL has been related to prolonged τ and increased coronary blood flow, as result from increased end-systolic LV wall stress with O_2 demands [4]. Different heart rate does not have effect on τ, and in pathological condition as found in early HF that can cause increased O_2 demand. In this study reduced LVEF and prolonged timing of LL correlated with linear τ significantly that was not different, though this previous linear assessment of single normal beat did show that τ is earlier prolonged in LL, though not different from EL at 8th week.

It was reported previously that change in both end-systolic volumes and stroke volume, as in end-diastolic LV volume affect exponential τ, being significantly reduced in reduced timing of LV afterload and end-systolic LV volume [2, 5]. Also, reduced LV pressure at the beginning of isovolumic LV pressure fall shortens τ [3, 21]. In experimental conditions systolic fiber shortening and systolic LV dysfunction are factors affecting exponential τ, despite difference in LV volume or timing of systolic LV load [5]. Increased end-systolic LVP prolongs τ, as result of systolic LV dysfunction and is related to the interventricular interdependence [23, 24, 32]. It has been found in denervated ventricles that τ is prolonged in diastolic LV dysfunction, having SERCA2a reduced expression, presenting increased e'/a ratio in echocardiography. This can result from chronic use of cyclosporine. It is referred as early marker of diastolic LV pump dysfunction resulting, having reduced exercise capacities with response to stress and increased BNP concentration, with altered Ca_2+ handling [25, 34, 35]. Also, thyroid and reduced growth hormone abnormal levels can lead to development of diastolic LV dysfunction, having impaired LV relaxation. There was significant reduction in LV end-systolic volumes, but not LV stroke volume, being under 60ml/m^2 in both group. It was reduced in LL.

LVEF was not different at 8th week. Linear τ correlated positively with systolic LV dysfunction (negatively with LVdpdtmax) and negatively with native rest T1 time, measured from cMRI between LL vs. EL at 8th week. The extent of LV systolic dysfunction affects inversely the rate of LVP fall with difference in duration of LV systole being related to the type of systolic LV load and τ. Also LL and late timing of peak in LV afterload are related to change in linear, but not for exponential τ assessment. Late end-ejection increased stroke volumes that accelerated LVP fall [2]. The exponential regression provides the best assessment of LV relaxation, and can assess early systolic LV dysfunction that results with prolonged LV pressure fall and later mitral valve opening. This study showed early active LV diastolic dysfunction developed in relation to LV afterloading sequences, from mono-exponential, but not bi-exponential regression assessment of τ, further indicating on differences being present in time for developing systolic LV dysfunction with more asynchronous active LV relaxation early on in LL group in nonlinear assessment, being unresponsive to reduced LV load. These changes are present in EL, being more sensitive to changes of LV load that are being reversible in the presence of EL at 4th vs. 8th week. This prolonged asynchronous bi-exponential $\tau_2\tau_1$ ratio in EL that was different from LL, was showed to be relevant to determine the effects from the LV afterload sequence (LL or EL) in developing early impaired LV relaxation, being related to increased LV compliance that associated at 8th week. This association is relevant for and related with decreased diastolic microvascular coronary perfusion pressure, of the LV myocardium that occurs in this period of LV diastole. The presence of increased asynchronous LV relaxation has been related to presence of LV subclinical relevant myocardial ischemia.

In this porcine model, prolonged LV relaxation is considered as an early adverse both systolic and diastolic functional parameter that has impact on LV filling and with asynchronous bi-exponential τ, affecting the timing of aortic valve closure and mitral valve function in LL and EL. In a previous porcine model, impaired LV relaxation was not found, having τ reduced at 2nd and 4th mounts of aortic compressive banding compares to sham controls [10]. Acute LL prolonged τ, whiles shortened within EL in isolated ventricles, but did not have difference and increased bi-exponential asynchronous $\tau_2\tau_1$ ratio in LL compares to EL [2, 4, 6, 11, 12, 25, 29]. In diastolic LV dysfunction, afterload-associated early impaired LV relaxation in LL has prolonged active LV relaxation compares to EL in hypertensive patients and in subclinical systolic LV dysfunction [13, 15, 22]. It has been found that in congestive HF this can be improved with selective beta-blocker treatment that improves exercise capacity and diastolic dysfunction. Sarcoplasmic Ca_2+ concentration does not affect τ in physiologic conditions, but may affect its duration in pathological condition, as found in HF. In decompensate HF, τ is prolonged significantly, as a result of increased LV load, impaired Ca_2+ cycling and ATP state with reserves of the LV myocardium [28]. In this study exponential τ was not prolonged in EL, but instead fast τ shortened indicating systolic LV dysfunction. Its dependence on the difference in preload or LV afterload have been extensively evaluated, as in this study, having an increased nonlinearity, being reduced with LV load reduction in the presence of chronic systolic HF, as well as with noradrenalin [5]. The impact of Ca_2+, as well as the LV contractility have been described previously, having severe afterload sensitive increase in τ in presence of reduced systolic LV pump function. Diastolic and systolic LV dysfunction are closely coupled. This is being blunted or improved in response to increased Ca_2+ sensitivity, resulting with increased LV contractility. However, this does not affect τ that can reduce after norepinephrine that improves systolic LV dysfunction. The interaction between contractility and LV relaxation is more complex that being previously found [24]. This is well presented in bi-exponential assessment, having reduced τ_1 in LL, suggesting early systolic LV dysfunction. The extent of pressure fall is not regulated by Ca_2+ in the LVH remodeling that may affect and increase LV stiffness. This is affected from LV preload, being affected from the LV pressure at the beginning and end of LV relaxation period. LV afterload affects τ that can assess presence of early systolic dysfunction [32]. β_2-adrenergic receptors are also involved in isovolumic LV pressure fall in systolic LV dysfunction, improving LV filling duration and exercise capacity when adrenergic β1 receptors are being selectively blocked in ischemic cardiomyopathy. Assessing τ, using single mono-exponential regression, this study shows difference in bi-exponential asynchronous $\tau_2\tau_1$ ratio and fast τ component having early systolic LV dysfunction in LL compares to EL. This has been showed using non-invasive echocardiographic assessment, but not as in this invasive LV assessment of active diastolic LV dysfunction. Impaired coronary blood flow reserve are related to systolic dysfunction, impaired LV relaxation and diastolic dysfunction. Further, its calculation has been extended throughout non-invasive assessment in presence or absence of mitral valve regurgitation, measuring duration of LV isovolumic relaxation period, end-systolic and left atrial pressures, with echocardiography. The novelty of this study is that τ_1 is significantly shorten in EL, while prolonged in LL, and τ_2 being early prolonged in LL at 4th vs. 8th week. In EL it shortened at 8th week. In previous experimental report was found that prolongation of τ was dependent of LV systolic pressures and/or end-systolic pressure for moderate afterload increase, and the timing of LV afterload, but not being dependent on difference in LV end-diastolic or end-systolic volumes, as well as for elastic recoil [2, 5, 11-13, 17]. However, different LV systolic load causes τ prolongation in EL, being described previously in situ experiment [17]. In presence of chronic HF there is absolute increase in LV load that is relevant for prolonged τ. Increased aortic stiffness resulted with prolongation of τ, being result of increased LV load and maximum O_2 demand [13, 20]. In this study, there was difference in exponential τ in single beat LVP regression assessment in response

to LV load reduction. In this study τ was not different, although asynchronous bi-exponential τ ratio increased in EL and was different from LL at 8th week, associated with difference in LV systolic load. This is result of more concentric LVH remodeling in response to EL compares to LL at 8th week in the intact ventricle in this porcine model. No difference in τ was also found in the presence of greater hypertrophy, and also not found when having reduced mono-exponential τ in LL compared to EL after 4 weeks of aortic banding [6]. This relative LV response in hypertension that may results with diastolic LV pump dysfunction is characterized with variability of LV contractility, differences in LVH remodeling, prolongation of τ, and changes of the coronary flow reserve between different LV systolic load in HTA [4, 8, 10, 14, 18, 19, 22, 28]. Previous studies reported that reduced ascending aortic compliance results in prolongation of linear τ, having in chronic LL reduced coronary blood flow, prolonged τ, and greater LV fibrosis [6, 11, 14-20]. There is relevant myocardial ischemia being assessed, using cMRI in EL and LL in LV afterload increase [23, 24]. The presence of subclinical systolic dysfunction with silent myocardial ischemia and ventricular fibrosis with inadequate LV myocardial blood flow are surrogates that precipitate LV relaxation abnormality, as result of relevant subclinical LV ischemia with systolic dysfunction in early HF. Ventricular relaxation is a period more sensitive to assess early adverse changes in LV function, in afterload associated diastolic LV dysfunction that can identify early development of systolic dysfunction early on, being related to the change in LV contractility through assessing early tau τ_1 as for elastic recoil from bi-exponential τ assessment. In an acute LL compared with EL, occurrence of early inactivation may be related to reflex activation and increased post-systolic stretch that further shows how this affects the Ca_2+ handling of the LV myocardium. LV relaxation is regulated by LV afterload, usually improving after β adrenergic receptors agonists in systolic dysfunction, and HF. If reduced or unregulated, this may increase nonlinearity resulting with prolonged exponential τ that cannot be assessed from linear regression analysis of τ [30]. Mono with bi-exponential regression method with nonzero asymptote, using single beat of LV pressure to be assessed is preferred in terms of early detecting impaired LV relaxation in systolic and diastolic LV dysfunction in different LV load. This present study found a relevant relationship between prolonged asynchronous bi-exponential $\tau_2\tau_1$ ratio in the porcine model of moderate concentric LVH remodeling, having LL to compare with EL, as early parameter for LV active diastolic dysfunction in relation to chronic LL vs. EL where systolic LV dysfunction can be detected from fast τ. This is not found if assessed in linear or mono-exponential regression analysis. There is asynchrony in aortic and mitral valve function being present in LL compares with the EL group. Compares to previous studies describing differences in relaxation in relation to systolic LV load showed that with increased LV afterload τ is prolonged and is reduced with reduction of afterload and or preload in presence of HF. Porcine models are more clinical representative to model hypertension with difference in LV load that induces LV hypertrophic remodeling. When compares to the dog model, this porcine model is more representative to the human pathophysiology since having similar ventricles and coronary flow. Opening the pericardium in EL, compared to LL, occurred more often than was approximated before closing the thoracotomy, after being stabilized hemodynamically. This is not limiting effect for the τ assessment, as described previously [27]. In LV afterload increase as in hypertension, aortic stenosis and/or coarctation of the aorta between EL compares to LL there was prolonged asynchronous bi-exponential τ, at 8th week. This was compensated and occurred later on at 8th week and in LL it was present earlier at 4th week, in bi-exponential regression assessment.

In HTA, there is great benefit from exercise in terms of reducing the morbidity and mortality with improvement in diastolic LV dysfunction, as well as the premature development of systolic LV dysfunction and HF, by improving the exercise capacity and LV preload with afterload reserves. By normalizing LV afterload and exercise induced hypertensive response in HTA compares to sedentary lifestyle normotensive controls, HTA patients benefit more from moderate intense exercise, with greater improvements in overall survival with quality of life, with reduced progression of diastolic LV dysfunction, but not the sedentary normotensive group. Presence of systolic LV dysfunction, presenting reduced longitudinal myocardial stress with shortening is afterload dependent parameters that are sensitive to changes in LV load. Associated diastolic LV (dys)function is characterized by a functional difference being described in LL compares to EL [11]. This is relevant for associated difference found, being not described previously in bi-exponential assessment of asynchronous τ in this study at 4th and 8th week of LVH remodeling. Reduced myocardial and/or LV contractility affects τ in relation to difference in LV loading, as well as diastolic LV dysfunction in HF. This single beat τ calculation, showed early systolic and diastolic dysfunction in LL, but not in EL at 4th vs. 8th week. Single mono-exponential and bi-exponential regression assessment is method that can assess early systolic LV dysfunction in different LV systolic load that can also result with myocardial ischemia. This is needed as less invasive approach and should not be different compares to multiple beats LVP assessment. Single exponential regression with nonzero asymptote for assessing τ is preferred in different LV afterload, since it is a time constant that was showed in this study that is not different in m2 vs. m1. Also the beginning and ending of LVP fall are different in relation to LV afterload groups and may not be assessed accurately with the LnP linear regression assessment that cannot be compared with exponential pressure fall. The extent of asynchronous bi-exponential τ ratio was increased at 8th week in EL, improving with mechanical LV load reduction that significantly shortens τ. However, the effect of using general anesthesia, combining fentanyl and propofol may prolong muscle relaxa-

tion and affect probably the myocardium that was not assessed compares to using propofol only, in this porcine heart [31, 32]. This can affect τ in presence of LL where LV compliance is increased compares to EL. Exponential regression assessment of τ with nonzero asymptote is highly relevant in this porcine model for being able to further benefit from medical treatments to improve LV diastolic dysfunction and to make conclusions based on these data with results, compares to the previous small animal and dogs' models. Also, the method being used in this study is novel compares to the others that were using in their assessment of bi-exponential asynchronous τ ratio with zero asymptote [12, 32]. Increased LV afterload is important, that further suggests a reduced coronary perfusion that activates the neurohormonal cascade and release of a myocardial angiotensin. This can cause increased LV wall stress and also aggravates myocardial ischemia in the presence of LL vs. EL. Assessment of LV relaxation changes, as result from LV load reduction in LL and EL profile has not been assessed in invasive LV pressure measurements in patients, to be able to differentiate benefit from afterload and preload reduction treatment that can aggravate LV ischemia in LL compares to EL. In this study, invasive LV pressure measurements, being used to assess the τ constant, confirm the hypothesis tested showing that τ is not different in LL compares to EL, affecting $\tau_2\tau_1$ ratio in LL compared to EL in different fast τ, parameters of impaired LV relaxation and development of diastolic with systolic LV dysfunction as found in relevant ischemia. There was greater asynchronous $\tau_2\tau_1$ ratio in EL vs. LL in the 8^{th} week, responsive to reduced LV load, being result of thick concentric LVH remodeling at 8^{th} week. This suggests that myocardial ischemia is present earlier in the LL group in the 4^{th} week, and in EL group at the 8^{th} week having afterload and/or preload reduction aggravating LV subclinical ischemia in LL group. These results are indicating that this method being used is important to differentiate relative effects of chronic LL compares to EL on exponential τ, to be able to differentiate subclinical LV ischemia and systolic LV dysfunction with the possible benefits of reducing LV load with treatments. This suggests that treatments being use for preload and/or LV afterload reduction are needed in EL, since afterload reduction improved asynchronous LV $\tau_2\tau_1$ ratio compares to LL having it increased in the 4^{th} vs. 8^{th} week. This further suggests for the benefit from Ca_2+ antagonist and exercise in the subgroup of patients that present with chronic LL having increased asynchronous LV relaxation with reduction of preload and/or LV afterload and dapagliflozine. Further treatment with mechanical LV load reduction compares to ACE inhibitors, beta-blockers or calcium channel antagonists should be preferred to reduce asynchronous LV relaxation and load in EL, and to optimize hemodynamic profile and reduce systolic LV dysfunction in LL based on the chronic difference in the LV pressure waveform curve. In previous experiment the use of propofol and fentanyl did not prolong the rate of LV relaxation in small doses, as the once being used in this LV invasive assessment [29] In these experiments conducted in aortic banding, fentanyl may causes significant muscle relaxation, increasing the up-regulation of β adrenergic receptors that can have impact on LV relaxation, whilst increase the LV load by increasing systolic LV pressures, influencing the time constant of LV relaxation. Propofol may aggravate systolic LV dysfunction. Another relevant limitation is that this study was performed at normothermic condition that compares its result to previous experimental work performed in mild hypothermia that has been found to reduce τ.

5. Conclusion

This clinically relevant porcine model that was used in this study, has associated prolonged bi-exponential $\tau_2\tau_1$ ratio in EL different from LL at 8^{th} week, responsive to afterload with preload reduction in EL, but not in chronic LL at 4^{th} or 8^{th} week of LVH remodeling. In LL there is myocardial ischemia that worsens with reduction of LV load that further implies on the greater benefit from exercise for preserving and improving impaired LV relaxation, where antihypertensive and/or volume reduction treatment would do more harm, by aggravating myocardial ischemia with LV preload and/or afterload reduction compares to EL.

In this porcine model, mitral valve and aortic valve asynchronous function are present in both LL and EL, pronounced in volume reduction, having predominant systolic murmur in EL and diastolic murmur in LL that worsen with load reduction. These relative differences in relation to LV loading sequence indicate early hemodynamic LV relaxation changes in development of diastolic LV dysfunction with differences for presence of myocardial ischemia, as a response to LV diastolic dysfunction. This is developed earlier in LL in the disease progression towards systolic LV dysfunction and systolic HF in HTA.

6. Clinical Perspective

Shorten τ1 in EL compares to LL is indicating on early systolic LV dysfunction at 4^{th} and 8^{th} week. Monoexponential τ with nonzero asymptote is not different between late and early afterloaded group, with prolonged asynchronous bi-exponential $\tau_2\tau_1$ ratio present in EL compares to chronic LL at 8^{th} week, indicating myocardial ischemia and HF in EL at 8^{th} week. τ is reduced in LV load reduction in both groups, having improved bi-exponential asynchronous τ ratio in EL, but not in LL where it increases. These findings indicate the importance of different effects from mechanical LV load reduction treatments and exercise for peak LV afterload reduction on τ, from asynchronous $\tau_2\tau_1$ ratio, comparing chronic LL to EL between 4^{th} vs. 8^{th} week, to reduce LV ischemia and improve diastolic with systolic LV pump dysfunction in different LV systolic load in HTA.

Abbreviations

LV	Left Ventricle
τ	Tau Isovolumic LV Relaxation Time Constant

Author Contributions

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

Conflicts of Interest

The authors declare no conflicts of interest.

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