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PORCINE MODEL TO STUDY MECHANISMS OF EARLY FILLING IN THE LEFT VENTRICLE

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INTRODUCTION

During diastole the left ventricle (LV) fills with blood in two phases, late filling and early filling. Late filling, resulting in the mitral flow “A-wave”, is a result of the left atrial contraction. Early filling, manifest as the “E-wave”, is thought to be substantially due to diastolic suction (DS), a phenomenon where the LV aspirates blood and fills itself, independent of atrial activity. DS can be described as the result of the LV relaxing faster than it is able to fill, therefore pulling blood into itself [1]. Efficient filling of the ventricle is important in order for the heart to adjust to varying demands, such as when heart rate increases during exercise. However, before studying and understanding a diseased heart, we must first understand the mechanisms of filling in a healthy heart. The objective of this study is to first demonstrate that DS exists and to quantify the amount of DS under various experimental conditions.

METHODS

Experimental

The study was performed in 9 pigs (25 to 30 kg) as approved by the Animal Care Committee of the University of Calgary. A high-fidelity micro-catheter (Transonic Scisense Inc., London ON) was inserted through the left carotid artery into the LV. Aortic pressure was measured in the ascending aorta via a fluid-filled catheter. In 6 pigs, right atrial (RA) pressure was measured using a small fluid-filled catheter inserted through an internal jugular vein and advanced into the RA.

Cardiac MRI was used to acquire LV volume and mitral inflow velocity data. Specifically, a short-axis stack (SAX) of the LV along with 2-, 3- and 4-chamber long-axis (LAX) views provide the data for volume calculation using an in-house Matlab-based program (The Mathworks Inc., Natick, MA). Phase-contrast sequences were used to determine the mitral inflow velocity in a short-axis LV plane just below the mitral leaflets.

Data were acquired at baseline and during 4 interventions. Phenylephrine, a vasoconstrictor, was given to increase afterload, the pressure against which the LV must eject. The pigs were volume-loaded to increase preload, the end-diastolic volume. The rate of LV relaxation, denoted as tau (τ), was manipulated with the infusions of isoproterenol and metoprolol. Isoproterenol increases contractility, the strength of contraction, and decreases τ. Metoprolol decreases contractility and increases τ. These interventions were performed in a varied order.

After instrumentation, the pig was stabilized before baseline pressure and imaging data were acquired. Each experimental infusion would begin and ~20 minutes would be allowed for hemodynamic stabilization. Pressures and images were then acquired, as under baseline conditions. The infusion was then stopped and ~20 minutes was allowed to return to baseline conditions. Once stability was restored, another pressure was recorded and the next intervention would begin.

Analysis

Data were analyzed in Matlab. All pressure data were filtered at 30 Hz. Imaging data were filtered using a Gaussian 2-D image filter. No aliasing occurred during the filtering process. All data were resampled to 100 Hz in order to achieve a uniform sampling frequency across all interventions and all animals.

Two different methods were used to assess DS. First was the so-called Katz criterion [1], which focuses in the LV pressure-volume (PV) loop. V_{DS}, the amount of filling due to DS, is defined as the diastolic filling that occurs between mitral valve opening and the minimum in LV pressure (P_{LV}) (Fig. 1). The second method involves wave intensity analysis (WIA) [2]. WIA uses the P_{LV} and velocity (U) data to determine the presence and type of waves in the blood flow. This allows the filling pattern to be described in terms of a "push" (resulting from left atrial contraction) or a "pull" (resulting from suction of the LV).

According to WIA, DS is characterized by a backwards expansion wave (BEW) that decreases pressure and increases velocity. To quantify the BEW, the total area under the wave was calculated from the time of mitral valve opening until the completion of the E-wave.

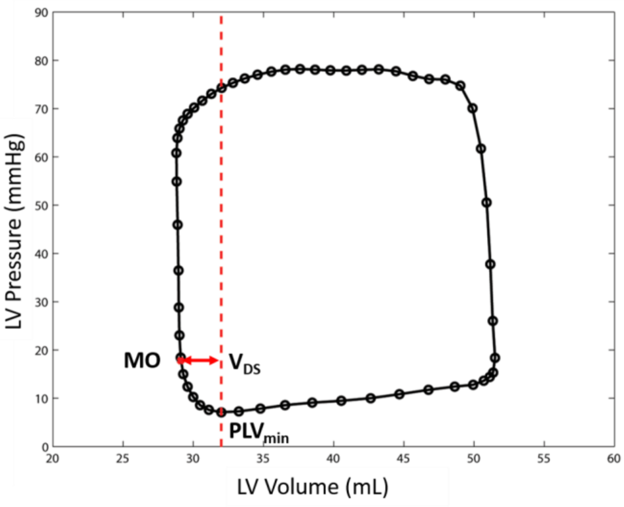

Figure 2: Typical PV loop showing mitral valve opening (MO) and minimum LV pressure (PLV_{min}). The volume of filling between MO and PLV_{min} is considered to be the amount of filling due to DS according to the Katz criterion (V_{DS}).

RESULTS

The Katz criterion was compared to end-systolic volume (ESV) in each animal (Figure 2). V_{DS} tended to increase as ESV decreased.

In Figure 3 normalized V_{DS} was plotted against normalized ESV, with data combined for all animals. This figure suggests that a vertical asymptote is approached, with V_{DS} becoming large when $ESV/ESV_B < 1$. When $ESV/ESV_B > 1$, normalized V_{DS} appears to approach a non-zero horizontal asymptote.

WIA results from each animal, compared to ESV, are presented in Figure 4. The relationship is not as strong as with V_{DS}; however, BEW still tends to increase as ESV decreases.

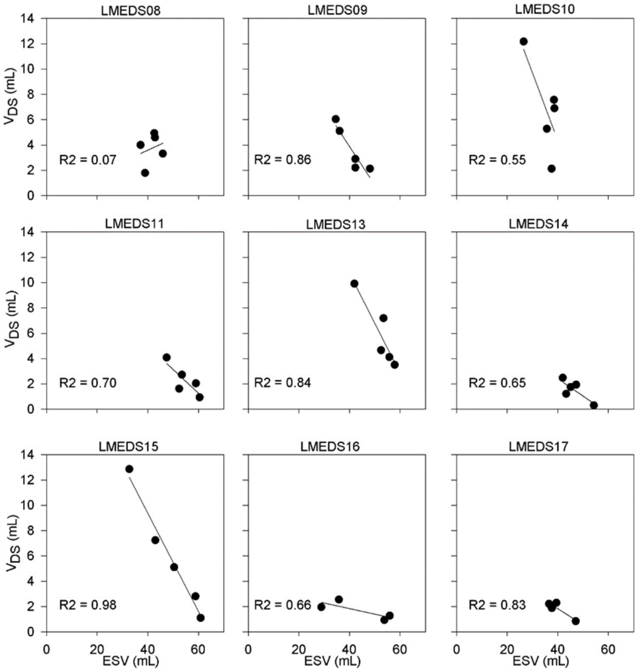

Figure 1: Katz criterion, V_{DS} vs ESV for each animal. For 8 of 9 animals there is a clear trend for V_{DS} to increase as ESV decreases.

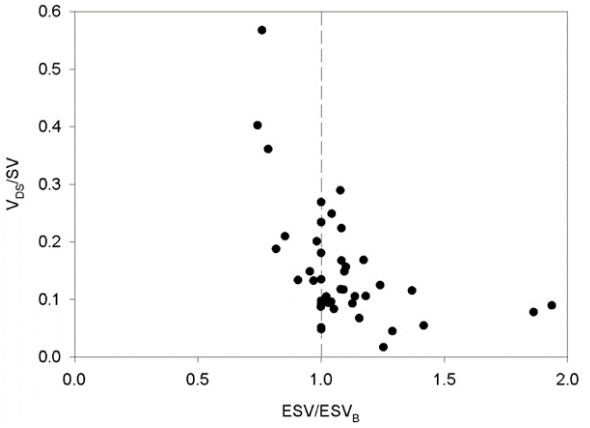

Figure 3: Katz criterion, V_{DS} normalized by stroke volume (SV) compared to ESV normalized by each animal's baseline ESV (ESV_B). The dashed line draws attention to ESV = ESV_B. Note that V_{DS}/SV appears to approach some horizontal asymptote when ESV>ESV_B and V_{DS}/SV is large when ESV<ESV_B.

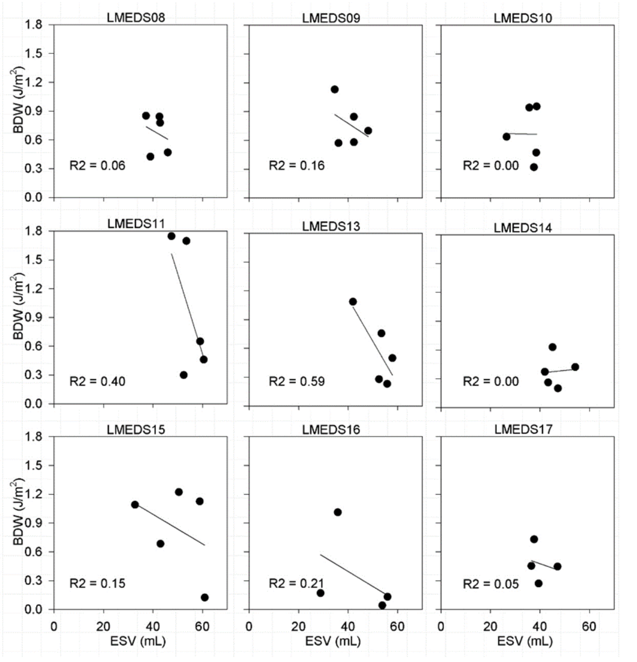

Figure 4: The energy under the BEW is shown compared to the ESV for each animal. The relationship between BEW and ESV here is not as obvious, however there is a suggestion that as ESV decreases there is more energy under the BEW.

DISCUSSION

Early filling (the bottom left portion of the PV loop, between MO and PLV_{min}, in Figure 1) is characterized by an increasing volume despite a decrease in pressure. This is counter-intuitive as when we think of most containers, when the volume increases the pressure also increases within the container (think of simply blowing up a balloon).

The Katz criterion, for quantifying DS based on how much filling occurs during the increasing volume-decreasing pressure period, suggest there is a strong relationship between DS and ESV. As ESV decreases, the volume of filling attributed to DS increases. A smaller volume at end-systole suggests that there is more recoil energy stored within the contracted LV, so after isovolumic relaxation, when the valve opens, the blood is able to rush into the LV from the atrium.

Similarly, comparing the normalized V_{DS} to ESV/ESV_B suggests that DS decreases as ESV becomes larger than baseline values and that DS is greatest when ESV is small. This is not a linear relationship, but V_{DS} appears to reach some horizontal, non-zero asymptote. Additionally, V_{DS} can be very large at any point when ESV < ESV_B.

The energy under the BEW represents the wave energy that accelerates the blood from the atrium into the LV. Where there is DS, the expectation would be that the BEW is larger, as suggested by the data in Figure 5. However, the argument is less convincing than for the Katz criterion. Nevertheless, in general, the data supports the developed theory, that a smaller ESV will increase DS as assessed by V_{DS} or the BEW.

LIMITATIONS

As a result of the experimental design, to measure both pressure and cardiac MRI signals, two different measurement systems had to be used. Therefore, in order to combine the recordings from each system, the temporal alignment was done manually based on optimizing the alignment of known physiological landmarks. Additionally, cardiac MRI sequences are an average of numerous heart beats, therefore the heart beat duration of the MRI data is not guaranteed to equal the heart beat duration of the recorded pressure data. In order to account for the uncertainty, WIA was calculated at both the optimal alignment and plus/minus t=0.01s.

Due to the limited temporal resolution of MRI, performing WIA (in particular) was challenging as it depends on the change in velocity.

Finally, there are some variations, in spite of the efforts to maintain the animal in a stable hemodynamic state throughout the experiment and within each intervention.

CONCLUSIONS

This study measured LV pressure, mitral velocity and LV volume in a porcine model and demonstrated that diastolic suction does exist under baseline conditions, as well as under different experimental interventions.

Using the Katz criterion, the amount of filling that occurs between mitral valve opening and minimum LV pressure (V_{DS}), it was demonstrated the DS can be quantified and tends to be related to ESV. As ESV decreases the amount of filling due to DS increases. When V_{DS} is compared to ESV normalized to baseline ESV, it appears that at volumes larger than baseline, filling due to DS is small (but non-zero). At volumes smaller than ESV, V_{DS} is large.

Using WIA to determine the total energy under the BEW after mitral valve opening, DS was again quantified. This measure of DS has a loose suggestion of a relationship with ESV, where a decreasing ESV would suggest an increase in the energy under the BEW.

Diastolic suction exists within a healthy left ventricle and is important in normal and efficient filling.

ACKNOWLEDGEMENTS

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