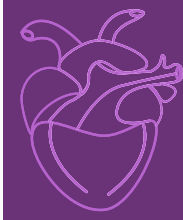
NONINVASIVE MEASUREMENT OF LEFT VENTRICULAR CONTRACTILITY IN SMALL ANIMALS



WHITE PAPER ON MYOCARDIAL CONTRACTILITY

Contractility is the intrinsic strength of the myocardium or cardiac muscle and often called left ventricular (LV) contractility. LV contractility, measured by either (a) the pressure-volume loops or (b) the maximum of first derivative of LV pressure (+dLVP/dtmax or simply +dP/dtmax), is considered to be the gold standard measurement of contractility. Because, the use of pressure or pressure-volume catheters is invasive in humans or animals, it was always desirable to develop noninvasive indices of cardiac contractility. With the rapid growth of use of small animals in cardiovascular research, this issue has become particularly important in the determination of cardiac contractility in animals such as mice, rats, and similar sized animals, as invasive LV pressure measurements in these animals are only done as terminal experiments. Therefore, the ability to reliably measure LV contractility noninvasively allows researchers to pursue longitudinal studies while greatly reducing the numbers of animals used in such studies.

Ever since the sixties, researchers have attempted to develop noninvasive indices of cardiac contractility in humans and in animal models. Several methods were developed and reported, with many of them based around aortic flow or aortic flow velocity. For the sake of completeness, the invasive methods and the noninvasive methods previously reported are described briefly followed by the results and discussion of the validation of our noninvasive method with simultaneous invasive method in mice at baseline and with the administration of positive and negative ionotropic agents.

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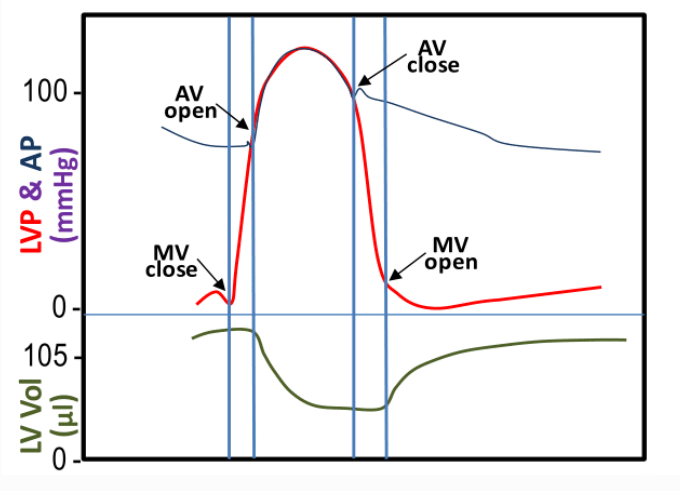
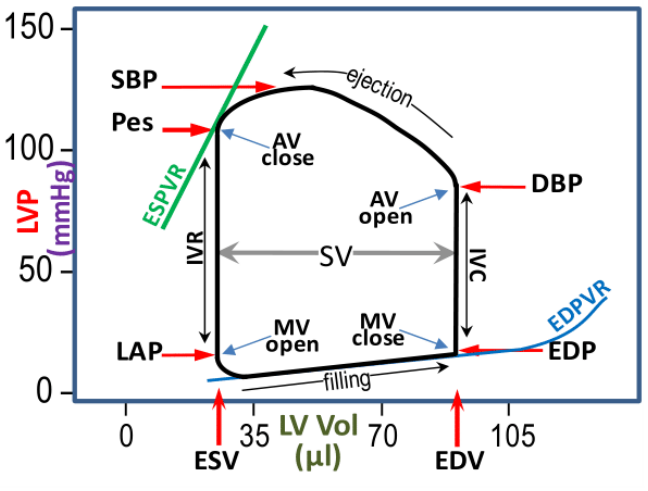
INVASIVE MEASUREMENTS OF LV CONTRACTILITY

LV Pressure-Volume Loops:

The pressure-volume loop is obtained by plotting the simultaneously measured instantaneous values of ventricular pressure versus ventricular volume in a given cardiac cycle. The PV-loop is considered to comprehensively describe of cardiac function as one can extract several parameters (EDV, ESV, SBP, DBP, ESP, EDP, LAP, & SV=ESV-EDV) that can be used to describe the overall cardiac function. Cardiac or myocardial contractility mainly refers to the contractile state of each cardiac cell independent of preload or afterload conditions. The load independent contractility of the heart is determined by occluding the inferior vena cava to generate a sequence of PV loops. Changes in contractility are associated with changes in LV pressure and volume and the relative changes in both usually fall on a linear systolic pressure volume relationship (ESPVR). Thus, the slope of the ESPVR line represents cardiac contractility. The slope of ESPVR increases with positive ionotropic agents (dobutamine, digoxin, etc) and decreases with negative ionotropic agents (propranolol, norepinephrine, etc) [1].





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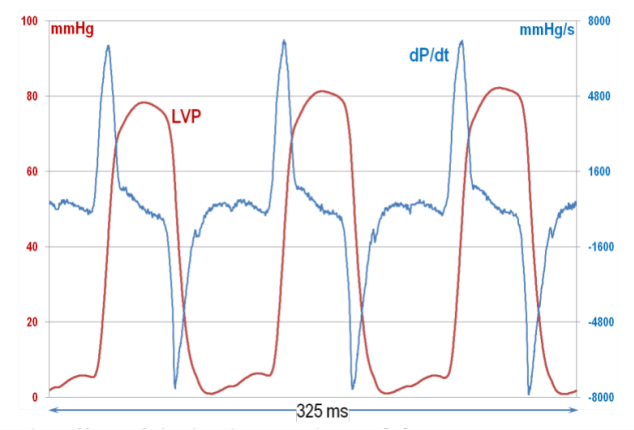
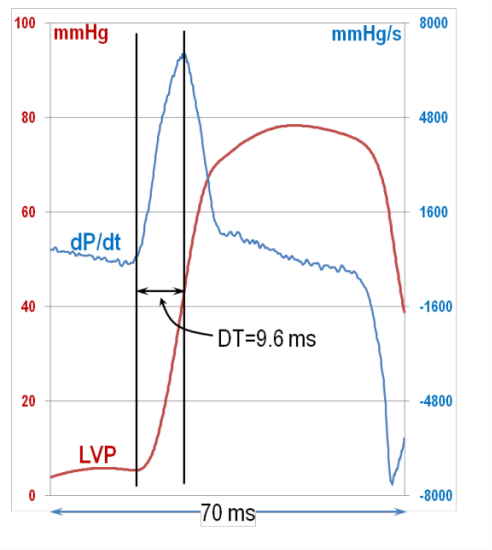
LV Pressure and dP/dtmax:

Another method of measuring LV contractility is by taking the first derivative of invasive obtained LV pressure and determining the maximal change of pressure during the isovolumic contraction phase (dP/dt max) and is considered to represent LV global contractility. The greater the contractile force exerted, the greater is the rate of increase in left ventricular pressure. However, LV dP/dtmax can be affected by preload, afterload, influenced, heart rate and myocardial hypertrophy. So, for a given subject the measured baseline dP/dtmax can be varied by the administration of positive and negative ionotropic agents to study cardiac contractility over a larger range with the assumption that preload and afterload conditions are kept constant. Additionally, LV dP/dtmax can be divided by instantaneous LV pressure to minimize the effect of the loading conditions [1]



DT - Time from Onset of LVP to dP/dtmax:

A simpler way of determining preload independent method of LV contractility in dogs was described by Adler et al. [2]. They reported that the time (DT) from onset of LVP to either dP/dtmax or (dP/dt)/P is indicative of only time-dependent aspects of contraction, independent of preload, while dP/dtmax by itself depends on both preload and the time-dependent aspects of contraction. They also report DT is independent of afterload as long as dP/dtmax occurs before aortic valve opening, and that DT was inversely and linearly related to heart rate. The study was based on measurements made at baseline and after the administration of dobutamine and propranolol [2].



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INVASIVE MEASUREMENTS OF LV CONTRACTILITY

Aortic flow/flow velocity and acceleration measurements: Majority of the studies that have validated noninvasive methods of LV contractility used aortic flow, flow velocity and/or aortic acceleration as these measures were obtained noninvasively or with implanted sensors. The use of aortic velocity and acceleration as noninvasive indices of global myocardial contractility has been reported in humans [3-6], dogs [7-9], sheep [10] and rats [11,12]. The devices used to measure aortic flow or flow velocity range from pulsed Doppler [10], continuous wave Doppler [5,7,9], electromagnetic flowmeter [3,8,11,12], and MRI [6].

Human Studies:

Rushmer [3] defined initial ventricular impulse (I) as the product of force (F) and time (t) to describe the dynamics of ventricular ejection, which is the net force acting over the time from the beginning of ejection to the attainment of peak aortic flow velocity. This net force is due the initial rapid increase in LVP as determined by its rate of change and the rate of blood flowing into the aorta during the initial phase of ejection. Kolettis et al [4] reported that the ratios of stroke volume to peak aortic velocity and stroke volume to maximal acceleration were significantly squared/ time to peak (V2 /T) to LV dP/dtmax and reported that V2 /T had the best correlation (dP/dtmax = 74.2 (V2 /T) + 847; r=0.77, p<0.001). Tasu et al. [6] reported significant correlation between LV dP/dtmax and aortic flow velocity (AFV) (dP/dtmax= 9.22 AFV + 567 mmHg/s, r = 0.59, p = 0.05) and maximal aortic flow acceleration (FVacc) (dP/dtmax= 0.63FVacc + 678 mmHg/s, r = 0.74, p = 0.015) measured by MRI

Dog Studies:

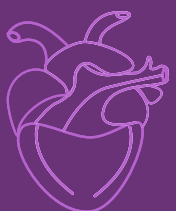
Wallmeyer et al. [7] reported significant changes in the Doppler measured peak aortic velocity ($p<0.01$) and mean acceleration ($p<0.05$) in response to ionotropic agents. The heart rate was maintained by pacing while nitroglycerine was used to alter preload conditions. Peak aortic velocity correlation well with peak aortic flow ($r=0.96$), peak acceleration of aortic flow0.95), +dP/dtmax ($r=$ ($r=0.92$). Doppler measured mean aortic acceleration was also reported to be well correlated +dP/dtmax despite being subjected to inter-observer variability. Harada et al. [8], showed that maximum acceleration of aortic blood flow when multiplied with pulse wave velocity (c) and the density of blood (ρ), highly correlates with +dP/dtmax (ρc Maxdu/dt = 1.01 MaxdP/dt - 2, $r=0.97$). Sagar et al. [9] reported that peak aortic velocity was well correlated with peak aortic blood flow ($r=0.94$) and peak acceleration of aortic velocity correlated well with the acceleration of blood flow ($r=0.92$). All the noninvasive parameters were reported to be well correlated with invasive +dP/dtmax.

Sheep Study:

Bauer et al. [10] compared mean aortic acceleration obtained from aortic blood velocity, which was measured by pulsed Doppler, to maximal elastance of LV (Em) which was measured by conductance catheter. Various loading conditions were used to validate the noninvasive indices. Mean aortic acceleration was reported to have a strong correlation with maximal LV elastance (LV(Em) = 3.84V/T + 1.87, $r=0.85$, $p<0.001$).

Rat Studies:

In rats, acceleration of aortic flow aortic flow (dF/dt) was compared to +dP/dtmax at baseline and after administration of ionotropic agents and agents affecting afterload. The results of this study as reported by de Wildt and Sangster [11] showed that dF/dt max can be used to replace the noninvasive contractility index in rats, as long as the afterload conditions are accounted for. Dowell & Houdi [12] evaluated peak aortic flow velocity as an index of LV contractility in conscious rats at baseline and under various ionotropic conditions. They found that peak aortic velocity in the conscious rats was almost double to that in anesthetized rats, but responses to ionotropic agents was very similar. This confirmed the possibility of using peak aortic velocity to estimate myocardial contractility in the instrumented conscious rat.



OTHER NONINVASIVE STUDIES

Cardiac Force-Frequency Relationship:

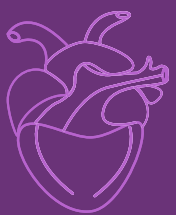
The Bowditch effect is defined as the ability of the myocardium to increase its force of contraction in response to increased heart rate and is known as the cardiac force-frequency relationship (FFR) [13]. Gemignani et al. [14] has validated the method of cardiac FFR against invasive LV pressure measurement in pacing induced heart failure model of minipig as a noninvasive alternative to the measurement of myocardial contractility. The vibrations generated cardiac contraction during isovolumic phase were measured with an accelerometer placed on the chest of the minipig and compared with LV dP/dt, both at baseline and after administration of dobutamine. The authors reported that FFR showed a high correlation between invasive and noninvasive assessment and thus would be useful in estimating contractile function at various stages of pacing induced heart failure.

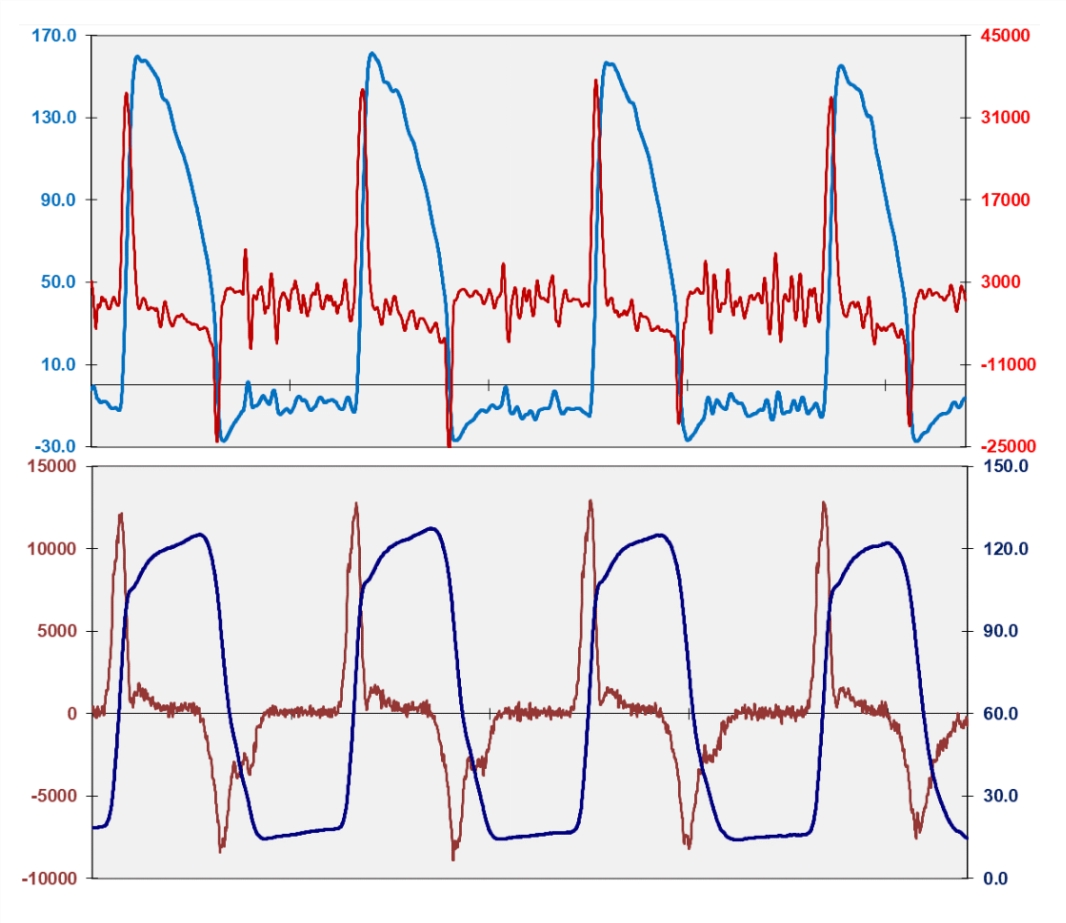
VALIDATION OF NONINVASIVE DOPPLER BASED LV CONTRACTILITY IN MICE

Almost all of the studies reported were done mainly in humans and large animals with a few studies reported on rats. Of all the studies reported here, the noninvasive measurement of aortic acceleration in dogs was reported to have high correlation to +dP/dtmax. We undertook this study to determine the noninvasive Doppler derived indices of peak and mean aortic acceleration of aortic flow velocity in lieu of +dP/dtmax to assess LV contractility in mice.

Methodology:

We measured aortic blood flow velocity noninvasively using Doppler flow velocity system, with simultaneous invasive LV pressure measurement in anesthetized mice. Peak aortic velocity waveforms were analyzed to obtain peak acceleration (dV/dtmax) and mean acceleration (peak velocity/time to peak). LV pressure waveform was analyzed to obtain +dP/dtmax. Measurements were made at baseline and after administration of dobutamine (1.5µg/g) and esmolol (5µg/g) in 10 normal mice (5 males & 5 females, aged 5-6 months).

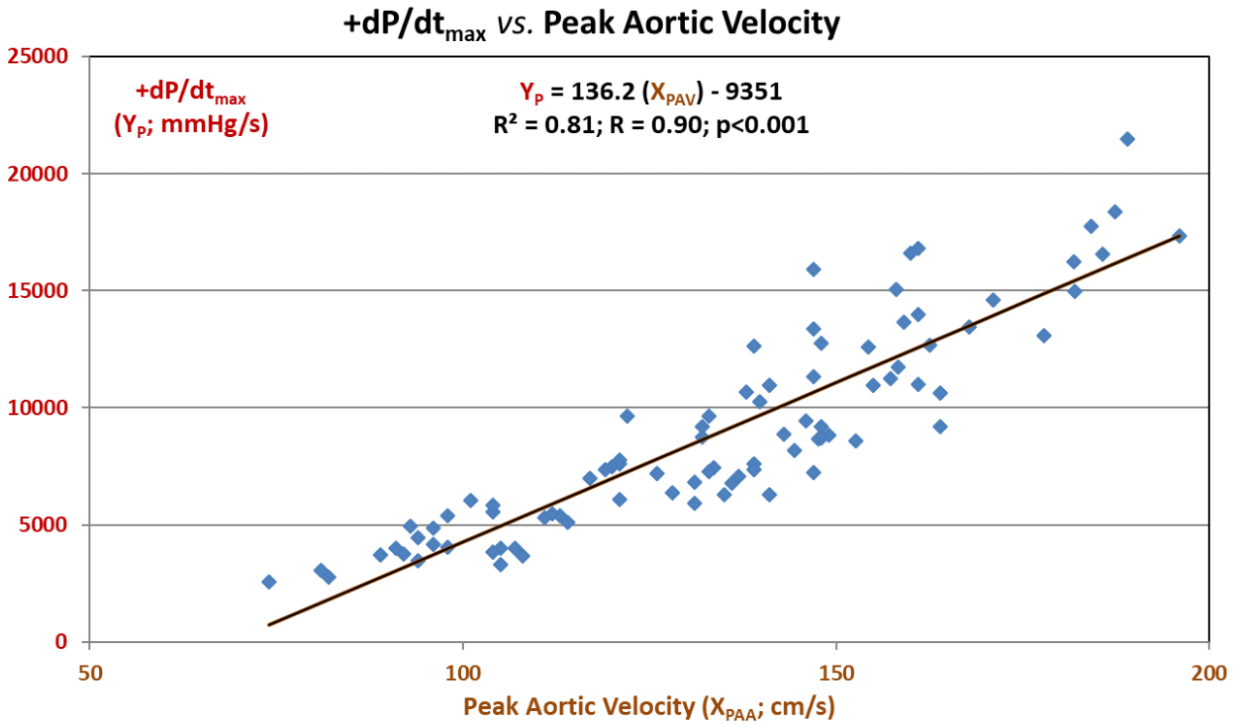




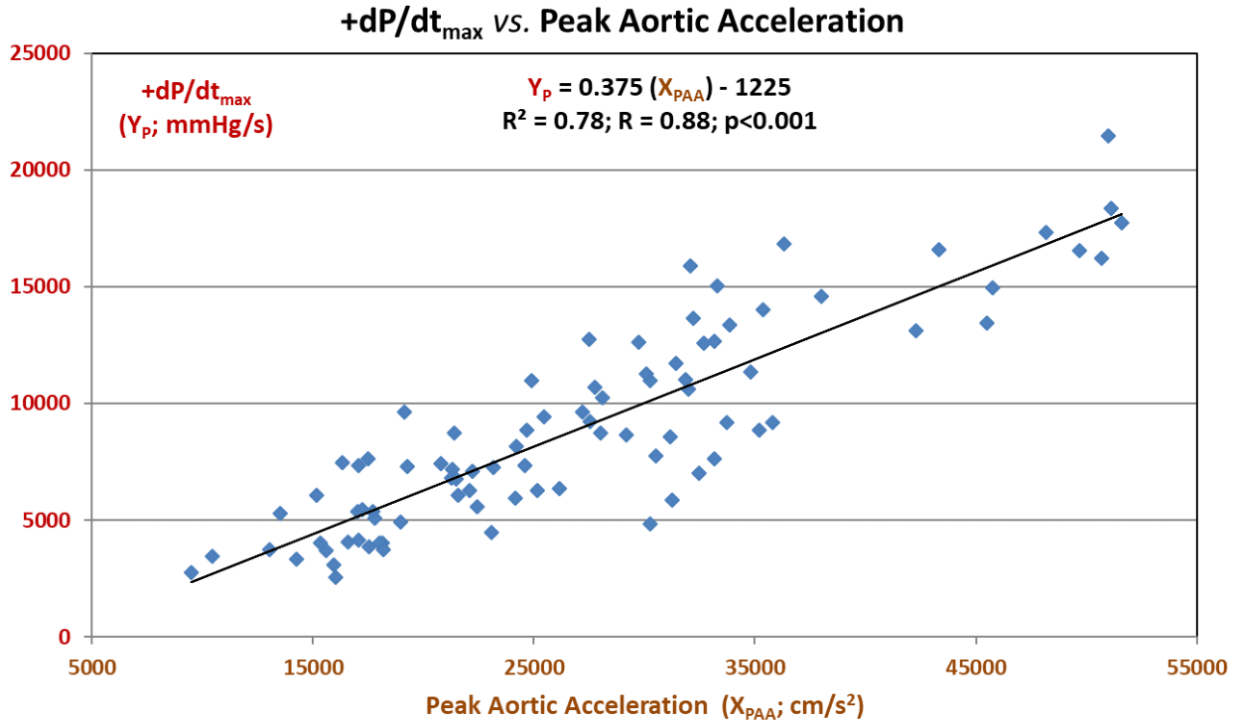
Results :

Peak aortic velocity and peak and mean aortic accelerations were compared to +dP/dtmax calculated from simultaneously measured LV pressure at baseline and after administration of dobutamine and esmolol. Measured heart rates ranged from 387-701 bpm, and 87 data points from 10 animals were used in the regression analysis. The following equations show the estimated linear relationships of the non-invasive parameters to the invasively derived +dP/dtmax.

Peak Aortic Velocity versus +dP/dtmax:



Peak Aortic Acceleration versus +dP/dtmax:



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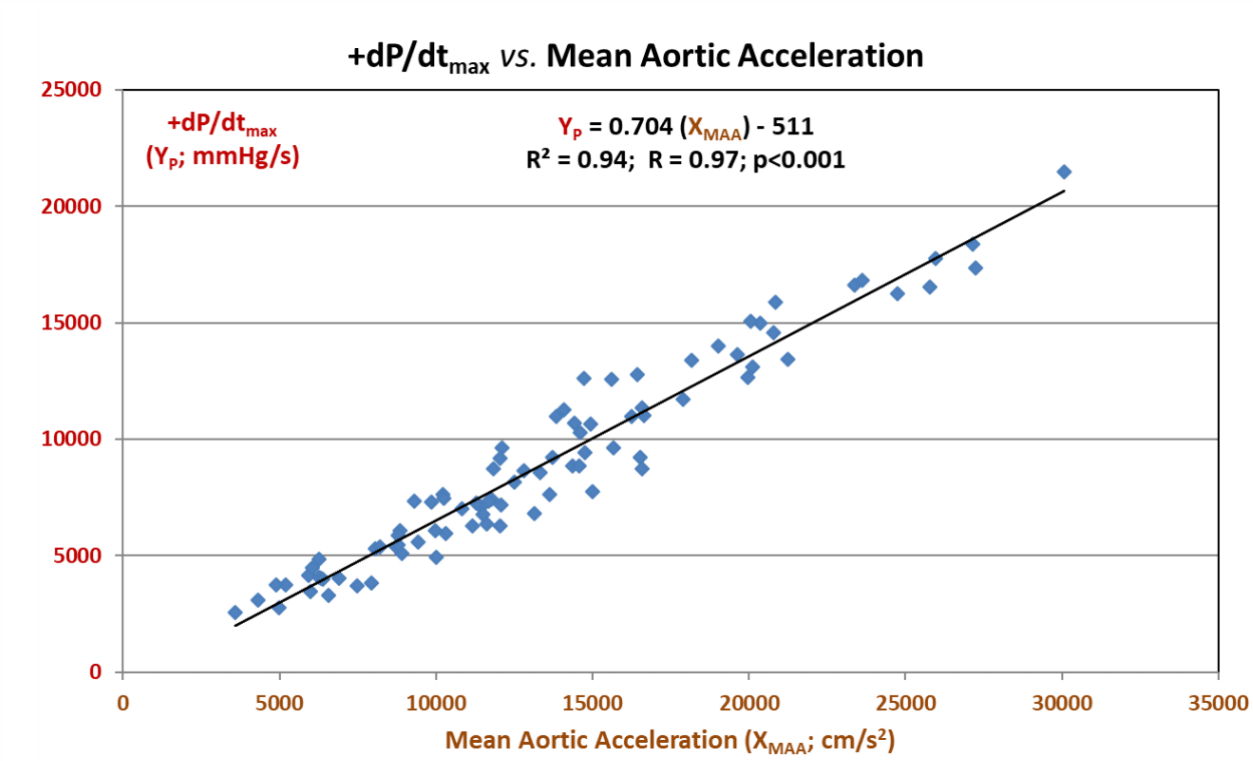
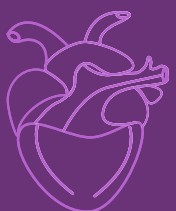
Mean Aortic Acceleration versus +dP/dtmax:



Conclusions and Future Directions:

The results show high correlation between the noninvasive Doppler measurements of peak aortic velocity (XPAV) and peak (XPAA) or mean (XMAA) aortic acceleration versus invasively measured +dp/dtmax (YP). While mean aortic acceleration was highly correlated with +dP/dtmax, our findings show that all the above noninvasive indices may be used as surrogates for invasive measurement of myocardial contractility index. We are currently examining the relationships between echocardiography parameters as well and will make our findings available soon. Additionally, we will also be evaluating the conditions of physical changes in preload and afterload by acute occlusion of inferior vena cava and abdominal aorta, respectively. The measurements obtained under all conditions will be compared using the hallmark Bland-Altman test to determine the agreement between two measurement methods.



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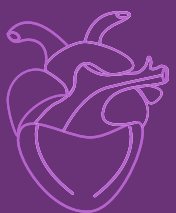

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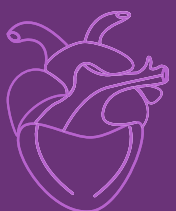

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