Acoustic Characterization of Axial Flow Left Ventricular Assist Device Operation *In Vitro* and *In Vivo*

Running Head: Left Ventricular Assist Device Acoustic Analysis

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Disclosures: Approval of the local institutional review board/Ethics committee was obtained for this study

There were no sources of financial support for this work

Drs. Bhat and Tatooles disclose occasional consultancy to Thoratec and HeartWare corporations. None of the other authors have conflicts of interest to report.

The use of left ventricular assist devices (LVADs), implantable pumps used to supplement cardiac output, has become an increasingly common and effective treatment for advanced heart failure. Although modern continuous flow LVADs improve quality of life and survival over medical management of heart failure, device malfunction remains a common concern. Improved non-invasive methods for assessment of LVAD function are needed to detect device complications. An electronic stethoscope was used to record sounds from the HeartMate II axial flow pump *in vitro* and *in vivo*. The data were then uploaded to a computer and analyzed using two types of acoustic analysis software. LVAD acoustics were quantified and were related to pump speed, acoustic environment, and inflow and outflow graft patency. Peak frequency values measured *in vivo* were found to correlate strongly with both predicted values and *in vitro* measurements (r>0.999). Plots of the area under the acoustic spectrum curve, obtained by integrating over 50 Hz increments, showed strong correlations between *in vivo* and *in vitro* measurements (r>0.966). Device thrombosis was found to be associated with reduced LVAD acoustic amplitude in two patients who underwent surgical device exchange.

Condensed Abstract: A novel method of isolating and quantifying the acoustic signature produced by left ventricular assist devices was developed. Spectral analysis revealed harmonic peaks whose frequency matched expected values based on device impeller speed. Analysis of spectral tracings and area under the curve of spectral slices suggested an acoustic pattern associated with thrombosis.

1. Introduction:

The current methods of evaluating left ventricular assist device (LVAD) function are limited. Echocardiography is often utilized to assess left ventricular unloading, inflow velocities, and mitral valve function. Altered device power requirements, patient fluid status, and end organ function are common indirect clinical indicators of device function. In order to reduce surgical trauma during implantation, post-operative complications, and hemolysis during normal use, LVADs are designed to be both small in size and non-disruptive to blood flow.[1] Consequently, most manufacturers do not include direct hemodynamic monitoring equipment in implantable pumps. Furthermore, common medical imaging modalities are of limited use in visualizing pump complications like thrombus. Use of all types of magnetic resonance imaging is precluded due to metallic components within the pump. X-ray and CT typically cannot visualize clots within the radio-opaque pump housing, and echocardiography is limited by physical constraints within the chest, pump housing, and inflow and outflow grafts.[2,3] Cardiologists often rely on laboratory data and limited pump diagnostics like calculated flow, pulsatility, and power to diagnose pump thrombus and/or nonspecific clinical indicators including stroke, embolism, and signs of decreased system perfusion.[3,4,5] Consequently, there is a clinical need for a non-invasive method of characterizing pump functionality[6]. Mansy et al. demonstrated the utility of using electronic stethoscopes and post-processing of acoustic data in detecting changes in amplitude and spectral energy distribution following obstruction of blood flow in hemodialysis grafts[7]. Noting that acoustic measurement has been shown to be a sensitive diagnostic in the human chest, we made use of similar

methodology in the characterization of LVAD operation and investigated acoustic differences between functional and thrombosed pumps.[8]

2. Materials and Methods:

This study utilized a two-tiered approach in the analysis of LVAD acoustics. Clinical data and acoustics were collected from patients supported by functioning HeartMate II LVADs, while a mock-circulatory apparatus was built to allow controlled investigation of the effects of pressure, device speed, viscosity, and artificial stenosis on device acoustics. Modal analysis was performed *in vitro* to determine whether the structural resonance of the HeartMate II coincided with frequencies generated by typical operation.

2.1 Data Acquisition

Acoustic data were collected using a 3M Littmann 3200 electronic stethoscope (St. Paul, MN, USA). Recordings were made for 20 seconds. During the acquisition process, the stethoscope used a high-pass filter of 20 Hz and a low-pass filter of 2000 Hz. Data were uploaded to a personal computer using Zargis StethAssist software (Freehold, NJ, USA) and converted to .WAV files for further analysis. Visualization and data extraction were performed using both The Cornell Lab of Ornithology BioAcoustics Laboratory Raven Pro 1.5 (build 11) acoustic analysis software (Ithaca, NY, USA), and custom software developed in Matlab (Version 8.4, Mathworks, Natick, MA, USA)[9]. Spectrographic analysis was performed for each recording by plotting acoustic data as function of time, frequency, and amplitude. [10] A Hanning Window function with sample rate of 4 kHz and frequency grid

spacing of 0.488 Hz was used to generate spectrogram slices. The Hanning window is a common processing function which reduced the disruptive effect of amplitude discontinuities in the truncated time history of the signal used for spectral calculations. The sample rate and frequency spacing were set by the software running the electronic stethoscope measurements. Their values must conform to Nyquist sampling theory, which links the sample rate and time window length to the frequency span and frequency spacing**.** Automated peak detection was used to determine harmonic frequency and amplitude.[9,11] The Matlab software implemented the following steps:

i) Return sample rate of data and encode data in file;

ii) Determine the two-sided power spectral density with 50% overlap and Hanning windowing;

iii) Generate spectral slices (graphical representation of sample as a plot of signal amplitude versus frequency) with respect to frequency and harmonic order; and

iv) Calculate the area under the spectral slices in 50 Hz increments.

2.2 Statistical Analysis

Amplitude, frequency, and area under the curve data were gathered. Means, standard deviations, and counts were calculated. The correlation coefficients between peak frequency values and the definite integrals of spectrographic slices were calculated as area under the curve (AUC). Pearson's tests were used to determine correlations; an *r*-value > 0.90 was taken to indicate strong correlation. All statistical operations were performed in SPSS version 20 (IBM, Chicago, IL)

2.3 In Vitro Model

A mock-circulation *in vitro* model was developed and built (Figure 1). A HeartMate II LVAD (Thoratec, Pleasanton, CA, USA) was embedded in EcoFlex (Smooth-On Inc, Easton, PA, USA), a gel with acoustic and viscoelastic properties similar to that of soft biological tissue. The LVAD was suspended within a polypropylene reservoir with volume 1800 mL. EcoFlex, a polyorganosiloxane epoxy with density 1.03 g/mL and Young's modulus of elasticity 57 kPa, was prepared by mixing parts 1A and 1B in a 1:1 ratio by volume and was poured into the reservoir, filling it.[12-13] The gel was de-aired in a vacuum chamber (5305-1212, Thermo Scientific Nalgene, Rochester, NY) for 5 minutes, then allowed to cure at room temperature. The polypropylene reservoir was removed once the gel had cured. The gel elastic modulus was measured using an indentation test as described in references and was noted to be comparable to biological soft tissue.[14] The LVAD was positioned such that the entirety of the pump housing was contained within the gel and the driveline, inflow cannula, and outflow cannula remained unobstructed and accessible. To the outflow cannula was attached 1.27 cm inner diameter flexible vinyl tubing with length 157 cm. Suspended above the pump and counterbalanced with a 2.27 kg weight to allow for height adjustment, this tubing drained into a PVC funnel to relieve downward negative pressure. The funnel emptied into a 2.84 L reservoir independently suspended and counterbalanced in an identical manner to the outflow tubing. Finally, flexible vinyl tubing drained the reservoir into the inflow cannula of the HeartMate II. The downward gravitational force created by the column of water in the outflow tubing provided simulation of arterial pressure load against which the LVAD worked. Similarly, the column of water above the

inflow cannula provided simulation of pressures generated by the left ventricle at the inflow cannula of the pump *in vivo*. The system was leak-free and was operated using both pure water and varying concentrations of a water/glycerin solution. The pump driveline was connected to a pocket controller, which, in turn, was connected to the Thoratec pump driver and monitor apparatus. Using markings on the gel to ensure consistent stethoscope placement, auscultation was conducted at the surface of the EcoFlex. To approximate anatomical recording of LVAD sounds at the surface of the skin, the device was positioned such that approximately 2 cm of EcoFlex gel separated the LVAD from the diaphragm of the stethoscope. Acoustics, flow, revolutions per minute (RPM), pulsatility index (a measure of change in flow over time), and power consumption data were recorded across a range of inflow pressures, outflow pressures, viscosities, pump speeds, and artificial stenosis. Pressures at the inflow cannula were altered by changing the height of the "left ventricular" reservoir, and consequently the height of the column of water flowing into the pump. The pressure at the outflow cannula, intended to simulate arterial resistance pressures against which the device must pump, was altered in an identical manner. Fluid viscosity was varied using consecutive 20 mL additions of pure glycerol (viscosity=934 cP at 25 °C). Viscosity was calculated using relative volumes of water to glycerol. Pump speed was changed using the Thoratec pump controller and monitor apparatus. The system was given one minute to equilibrate to changes before auscultation was performed. All experimental conditions for the pressure, speed, and viscosity trials may be found in Table 1. Finally, to simulate aberrant flow conditions produced by *in vivo* stenotic narrowing of graft vasculature, as in the formation of thrombus, arterial clamps were used to constrain the inflow tubing at 30 cm from the inflow cannula to approximately 80% occlusion.

2.4 Modal Analysis

Experimental modal analysis reveals the resonant frequencies and associated deflection patterns that exist in metallic and other solid structures with moderate to low material viscosity. If the structure is driven at or near one of its resonant frequencies, deflections can become extreme under low viscosity conditions. Thus, by performing a modal analysis we can determine if there are any resonant frequencies within the range of frequencies we expect the structure to be driven. Modal analysis was performed on a HeartMate II LVAD using a PCB Piezotronics ceramic piezoelectric accelerometer (model #352A10, sensitivity 10.40 mV/g, mass 0.7 g), a PCB Piezotronics model 086C01 modally tuned impulse hammer with force transducer (PCB Piezotronics, Depew, NY, USA), and an Agilent 35670A Dynamic Signal Analyzer (Agilent Technologies, Santa Clara, CA, USA). With the LVAD suspended by its driveline, the accelerometer was glued to a fixed point in the center of the LVAD using cyanoacrylate. Acceleration was measured radially with instrumented hammer taps at 10 points distributed circumferentially around the LVAD, 3 hammer taps per point to ensure repeatability, which was assessed by confirming near unity coherence between measurements in the frequency range of interest (0-2000 Hz).[15,16] Data were transferred to a personal computer and analyzed using custom Matlab software.

2.5 Measurements in Human Subjects

Ten HeartMate II patients with stable LVAD function, hemodynamics, and cardiac, pulmonary, and renal function were auscultated in the outpatient setting following a

consent process per an institutional review board approved protocol. Recordings were made at the surface of the skin or through minimal clothing while the patient was sitting up and while the patient's LVAD was connected to a pump monitor displaying instantaneous RPM, flow, pulsatility index, and power consumption information. Recordings were made at the mitral and tricuspid positions in each case. Pulse rate, blood pressure, and LVAD operation data were collected at the time of auscultation. Echocardiographic and laboratory data were collected at the closest incidence to the time of auscultation.

Two additional patients (henceforth referred to as Patients A and B), separate from the group of ten stable patients, were monitored before and after a pump exchange procedure for device thrombosis. Both patients had HeartMate II LVADs. Echocardiographic, laboratory, and hemodynamic data were collected before and after surgery. To investigate potential acoustic effects of thrombus, acoustic measurements were made before and after exchange in each patient.

3. Results:

Spectrographic analysis revealed the presence of pronounced banding structure with a regular low amplitude and high amplitude striping pattern in the spectrogram plot (graphical representation of frequency vs time) and distinct frequency peaks in the spectrogram slice (graphical representation of amplitude vs frequency). The frequency spectra of an implanted HeartMate II are shown in Figure 2a. Frequency bands occur at regular intervals and tend to decrease in amplitude as frequency increases. When plotted against harmonic order, rather than a frequency scale, it can be seen that these frequency peaks occur at harmonic intervals of the LVAD operational speed (Figure 2b). The

relationship between expected harmonic intervals, calculated via Equation 1 and the measured peak frequencies at each band was found to be consistent both *in vivo* and *in vitro*. This was demonstrated by strong correlation between measured and predicted peak frequency values (all $r > 0.999$).

$$H_\lambda = \frac{(n \times RPM)}{60} \qquad \text{Equation 1}$$

Equation 1: H_λ= expected harmonic frequency for a given pump speed, n=harmonic number, RPM=pump speed in revolutions per minute.

3.1 In Vitro Results

Frequency band localization analysis at LVAD speeds ranging from 7,000 RPM to 12,000 RPM indicated the linear relationship between LVAD speeds and harmonic frequency. Flow (liters per minute) and power consumption (watts) increased with LVAD speed, though pulsatility index was not affected. Additionally, LVAD speed-matched correlations were calculated between peak harmonic frequencies for each patient and their corresponding speed measured *in vitro*. All *r*-values were greater than 0.999.

While changes in inflow pressure, outflow pressure, and fluid viscosity affected flow rates and power consumption, no changes in peak harmonic frequency or amplitude occurred as these fluid properties were altered. Presumably, under these conditions the fluid flow path through the LVAD conduit remained normal and there was no significant departure from device operation typical of normal physiological use. Additionally, modal analysis revealed no inherent structural resonance at the frequencies measured by the

electronic stethoscope (0-2 kHz).[15] The lowest frequency flexural mode of resonant vibration of the LVAD occurred at 8.5 kHz, approximately 4.25 times higher than the LVAD frequencies we recorded, indicating that all acoustic signals measured in the range of 0-2000 Hz were generated by operation of the device, not by structural resonance.

3.2 Results In Human Subjects

A total of ten HeartMate II supported patients with mean age of 56.4 ± 12.2 years and BMI 28.3 ± 4.8 were auscultated in our outpatient clinic. These patients were known to be in stable condition and relatively free of complications at the time of auscultation. The average duration on LVAD was 549.5 ± 334.7 days and LVAD, lung, and kidney function were noted to be normal. Echocardiography revealed 3 patients (30%) with mild mitral regurgitation, 3 patients (30%) with mild aortic insufficiency, 6 patients (60%) with mild tricuspid regurgitation, 2 patients (20%) with mild pulmonic insufficiency, and no patients with mitral or tricuspid valve replacements (Table 2). Additionally, hemodynamic and laboratory values did not suggest the presence of hemolysis or thrombus in any of the pumps.

Spectrogram slices for each of the 10 patients are shown in Figure 2b and spectrographic analysis revealed that pump acoustics *in vivo* are very similar to pump acoustics *in vitro*. LVAD speed, power consumption, flow, and patient blood pressures at the time of recording are indicated in Table 2. Occasionally, short frequency ranges and individual harmonics exhibited lower signal to noise ratio (SNR) and obfuscated peaks in *in vivo* recordings compared to in *in vitro* recordings. Despite signal artifacts, which may be a result of a considerably more complex acoustic environment *in vivo*, peak harmonic

frequencies occurred within a very small range of the expected values calculated by Equation 1 (r-values between predicted and measured harmonic frequencies > 0.999 for all patients). This was an expected result but indicates that minimal frequency distortion occurred during acoustic transmission through the human chest or the gel model used *in vitro*.

The location of the pump harmonics in these ten patients again correlated well with expected values and with measured *in vitro* values for equivalent speeds (r>0.999 for all). In six of the ten patients average amplitudes across all twelve recorded harmonics were significantly less than those measured *in vitro* at equivalent pump speeds.

Using custom Matlab software, areas under the spectral curve (AUC) were measured for each patient's spectrogram slice in 50 Hz segments over the 2000 Hz spectrum. Comparison of *in vivo* AUC segments and *in vitro* AUC segments at each patient's corresponding speed showed strong correlations in all incidences (r>0.966 for all AUC segments) (Figure 3).

3.3 Device Dysfunction

The AUC was compared for acoustic samples taken during normal *in vitro* pump function and while the inflow graft was occluded to 80%. Although statistical differences in AUC were non-significant, the spectral slices shown in Figure 4 indicate that the two samples are closely related in behavior, but with unique amplitude values. Previous work has shown that diameter changes of less than 20% in hemodialysis grafts are detectable using a surface sensor. The presence of a stenosis is expected to increase vessel resistance and reduce fluid velocity through the LVAD, reducing vascular sounds (6). Presumably the

reduction in amplitude in the occluded measurement in our study is a result of impaired pump function, specifically, reduced flow through the LVAD circuit. Identical analysis for the patients who underwent pump exchange for thrombosis revealed a similar trend, suggesting that our *in vitro* simulation of pump dysfunction is a good representation of acoustic changes caused by thrombus or impaired flow in live patients (Figures 5,6).

Acoustic changes resulting from device thrombosis were investigated in Patients A and B. Patient A presented with lactate dehydrogenase (LDH) levels of 4530 U/L, plasma free hemoglobin levels of 11.1 mg/dL, and elevations in pump power to approximately 12 W. Patient B presented with LDH levels of 1201 U/L, increasing heart failure symptoms, and continued LVAD alarms. Surgical LVAD exchange was deemed necessary in both patients.

Bronchoscopic exploration of the explanted LVADs revealed a thrombus at the inflow stator bearing, upstream of the impeller in Patient A and within the device inflow cannula and pump housing in Patient B. Comparison of spectra from the clotted and non-clotted pumps for both patients are shown in Figures 5 and 6. In both cases, the presence of thrombus is associated with appreciable reduction in spectral energy over the sample frequency range. When frequency is normalized to harmonic order by adjusting for device RPM, curve morphology is largely preserved, despite reduction in amplitude.

4. Discussion

Although heart transplantation remains the most effective treatment of advanced heart failure refractory to medical therapy, due to donor shortages, LVADs have become a popular and established method to restore patient functionality and quality of life.[17-19]

However, there is need for non-invasive evaluation of pump function to predict complications such as thrombus. In 2005 Mansy et al. published a means of detecting vascular patency in hemodialysis grafts using an electronic stethoscope with custom Matlab software for acoustic analysis.[7] Using this system the group was able to establish correlation between acoustic power and the degree of stenosis. In 2003 Tanishiro et al. showed that arterial sound can be used to detect malrotation in centrifugal LVADs in an *in vitro* setup, and in 2007 Slaughter et al. showed that acoustic changes predicted impending device malfunction in the pulsatile HeartMate XVE.[20-21] Recently Hubbert et al. showed significant differences in HeartMate II acoustics when inflow and outflow tubing were subject to artificial stenosis and when artificial clots were passed through the pump, and Kaufmann et al. showed that thrombus formation in HVAD pumps was associated with telltale changes in acoustic spectra.[22,23] Similar data collection techniques were used in all studies, though particular equipment differed. It should be noted that Kaufmann *et al*. focused data analysis on the frequency range 0-600 Hz and that the Hubbert group assessed acoustic signatures from 0 to nearly 22 kHz. Both groups analyzed changes in acoustic amplitude resulting from device malfunction (thrombosis or simulated thrombosis). To our knowledge this study is the first to pair clinical and laboratory investigation of HeartMate II acoustics, and is the first to compare pre- and post-explantation spectra for patients with confirmed HeartMate II thrombosis who underwent surgical exchange.

Our results indicate that acoustic analysis is an accurate means of detecting both the location of peak harmonic frequencies and the behavior of a spectrographic slice as measured by AUC segments. The *in vitro* and *in vivo* data show strong correlations with

expected values and with each other. This suggests that neither the thoracic nor experimental acoustic environments cause frequency shifts in the measured ranges. However, both amplitude and AUC were lower *in vivo* than *in vitro* for all patients (as shown for Patient 7 in Figure 3). This is likely due to amplitude attenuation in the chest where the acoustic environment is considerably more complex than the gel phantom used *in vitro*; transmission across muscle, bone, fibrous tissue, and fluid may reduce the magnitude of acoustic waves. Analysis of the spectrogram shown in Figure 2a indicates that acoustics generated by the HeartMate II are not changed significantly during the cardiac cycle. The independence of HeartMate II acoustics from changes in pressure is supported by our observation that device acoustics were not significantly altered *in vitro* by changes in system pressures. Further, cardiac sounds, including those of valve closure, generally occur at frequencies less than 200 Hz and are largely distinct from those associated with LVAD operation.

The strong correlation between the measured peak harmonic frequencies is an expected result, and indicates this methodology is a sensitive means of detecting device rotational speed. However, analysis of 50 Hz AUC segments provides greater quantitative insight into how the spectral slice is behaving. We suggest the areas between frequency peaks may be related to LVAD function, including flow through the device, and that calculation of AUC segments allows for quantification across all measured frequencies. The strong correlations between *in vitro* and *in vivo* AUC segments suggest that this too is a powerful means of quantifying LVAD acoustics. Further, the mirroring of *in vitro* and *in vivo* spectral slice curves shown in Figure 3 suggests that certain characteristics of the spectral slice are preserved in both laboratory and clinical measurements.

The data presented in Figures 5 and 6 support this conclusion, and suggest that LVAD auscultation may be an effective means of detecting acoustic changes caused by the presence of pump thrombus *in vivo*. When the inflow graft was occluded *in vitro*, a trend of curve mirroring with reduction in amplitude was observed, as shown in Figure 4. This supports the findings of Hubbert et al. who detected a similar pattern when ball valves were used to occlude the inflow and outflow conduits.[22] The similarities between these *in vitro* changes due to partial occlusion, and the effect of thrombus *in vivo* may be related to the location of the thrombus at the inflow stator of the pump, upstream of the impeller in Patient A and within the inflow tract and device housing in Patient B. We suggest that in the cases of partial occlusion *in vitro* and thrombosis *in vivo*, a reduction in LVAD amplitude compared to baseline measurements is related to reduced flow through the device. Notably, this trend was observed clinically in both patients with device thrombosis and may represent an early, non-invasive marker for impending device failure. This study analyzed only two patients with confirmed LVAD thrombosis. Continued study with larger sample sizes is required to determine whether reduction in amplitude may be used as a diagnostic of LVAD thrombus.

At this time we cannot explain some of the characteristics common in many acoustic samples such as a strong attenuation at approximately 700 Hz. However, the consistently strong third harmonic amplitude is likely due to the fact that the pump impeller has three blades, causing fluctuations in flow at three times the rotation frequency of the pump. Modal analysis did not reveal any inherent resonances in the device housing, leading to the conclusion that all acoustic behavior measured in the sample range 0-2000 Hz is resultant to LVAD operation.

5. Conclusion

Acoustic sampling and analysis is a sensitive and accurate method of detecting the presence, location, and individual amplitude of LVAD peak harmonic frequencies and AUC in spectrogram slices. Our methodology allows for characterization of pump function and may represent an important means for non-invasive detection of LVAD thrombosis. We are currently using this methodology to study the relationship of these acoustic parameters to pump complications, patient hemodynamics, and patient cardiac physiology.

Acknowledgements

We thank the Sejal Modi CCP, the nurses of the Advocate Christ VAD clinic, and the members of the UIC acoustics and vibrations laboratory.

Author Contributions

Gardner Yost: Concept/design, data collection, data analysis/interpretation, drafting, revision, statistics
Dr. Royston: Concept/design, data interpretation, revision of article, approval of article
Dr. Bhat: Concept/design, data interpretation, revision of article, approval of article
Dr. Tatooles: Approval of article

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Figure & Table Legends

Figure 1: *In Vitro* Apparatus- A) power supply B) controller C) HeartMate II LVAD D) "arterial resistance" outflow tubing E) "left ventricular" reservoir and inflow tubing F) stethoscope placement site

Figure 2a: Spectrogram- spectrogram (top) and spectrogram slice (bottom) for Patient 1. Range: 0-2 kHz.

Figure 2b: Spectrogram slice- spectrogram slices for patients 1-10 plotted against harmonic order.

Figure 3: Spectral analysis- comparison for Patient 4 and corresponding *in vitro* speed.

Figure 4: Spectral analysis- comparison for baseline vs. partially occluded LVAD *in vitro.*

Figure 5: Spectral analysis- comparison of acoustic samples from thrombosed and properly functioning LVADs. Samples were taken prior to and after surgical exchange for thrombus in Patient A.

Figure 6: Spectral analysis- comparison of acoustic samples from thrombosed and properly functioning LVADs. Samples were taken prior to and after surgical exchange for thrombus in Patient B.

Table 1: Experimental conditions for *in vitro* trials. Viscosity, speed, outflow pressure, and inflow pressure were varied individually to assess impact of fluid conditions on LVAD acoustics.

Table 2: Baseline demographics for patients 1-10. Abbreviations- Days to Ausc= number of days between implant and auscultation, RPM=device revolutions per minute at time of auscultation, PI= device pulsatility index at time of auscultation, Sys BP= Systolic Blood Pressure, Dia BP= Diastolic Blood Pressure, RVDd= Right Ventricular Dimension in Diastole, LVDd= Left Ventricular Dimension in Diastole, Pulm. Sys. Pressure= Pulmonary Systolic Blood pressure, Plasma free Hb= plasma free hemoglobin, LDH= lactate dehydrogenase, INR= International normalized ratio, ICM=ischemic cardiomyopathy, NICM=non-ischemic cardiomyopathy, AA= African American.