Non-invasive testing to determine cardiac or non-cardiac etiology of dyspnea in the ED

A Thesis submitted to the University of Arizona College of Medicine - Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Abstract:

Objectives: There were two main objectives of this study. The first was to determine the diagnostic threshold of hemodynamic values derived from impedance cardiography (ICG) and whether these thresholds are sex specific in determining the etiology of shortness of breath (dyspnea) in patients presenting to the emergency department (ED). The second was to compare ICG hemodynamic values with the results of bedside cardiothoracic ultrasonography and B-type natriuretic peptide (BNP) levels in patients with dyspnea in the ED.

Methods: A prospective cohort of 50 adult patients presenting to the Maricopa Medical Center ED with dyspnea were evaluated using ICG, bedside cardiothoracic ultrasound, and BNP to determine the etiology of their complaint. The final etiology was determined through review of the treating practitioner's final diagnosis and evaluation of the data available from the patient's ED visit. Cardiac and non-cardiac groups were then compared to determine the accuracy, sensitivity, and specificity of ICG, bedside cardiothoracic ultrasound and BNP in identifying the etiology of their complaint.

Results: BNP at a threshold of 164 pg/mL proved to be the most accurate with a sensitivity of 84.21%, a specificity of 79.17% and an area under the curve (AUC) of 0.8684 when plotted on a receiver operating characteristics (ROC) curve. Right ventricle diameter during systole was the most accurate bedside ultrasound parameter; at a threshold of 1.71 cm it showed a sensitivity of 77.78%, a specificity of 60.00% and an AUC of 0.7489. Heather index (HI) was the most accurate ICG parameter; at a threshold of 9.2 Ohm/sec^2 it showed a sensitivity of 72.41%, a specificity of 85.00%, and an AUC of 0.8405. Only HI showed a significant difference between male and female patients. HI in females at a threshold of 10.4 Ohm/sec^2 was 87.50% sensitive and 87.50% specific with an AUC of 0.9297. In males a HI threshold of 6.9 Ohm/sec^2 was 69.23% sensitive and 66.67% specific with an AUC of 0.7564.

Conclusion: Bedside cardiac ultrasound was technically challenging and the least accurate modality. ICG demonstrated some sex specific thresholds and while an easy to use modality, it was slightly less accurate than BNP which proved to be a simple and accurate modality for determining a cardiac or non-cardiac etiology of dyspnea.

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Introduction/Significance:

Dyspnea, or shortness of breath, is a common presenting complaint among patients in the emergency department (ED). Dyspnea can be the result of various etiologies and requires rapid interpretation and intervention by the ED team. Impedance cardiography (ICG) is a rapid and non-invasive technology that has been validated[1-6] and shown to aid ED practitioners in narrowing down the cause of dyspnea to a cardiac or non-cardiac derived etiology.[7-11] Previous studies have shown that hemodynamic values are difficult to predict based on clinical presentation[2] and that ICG derived hemodynamic values can improve the accuracy of ED diagnosis[9] and that ED staff can quickly learn how to use this technology accurately.[12]

During ICG monitoring, four dual sensors are placed on the neck and thorax. A current is then passed between the electrodes to measure the impedance between the electrodes. Impedance is the inverse of conductivity; therefore, if the electrodes are placed on a surface with high conductance such as a fluid filled cavity, then the impedance would be low. Using this concept, algorithms have been developed that utilize the impedance through the thoracic cavity to measure real-time changes in the blood flow through the aorta and inferior vena cava to determine hemodynamic parameters such as cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), and contractility. ICG data can be collected in 3-5 minutes, making it a rapid, non-invasive method to calculate hemodynamic parameters that were traditionally obtained via thermodilatution.[13] Thermodilution, the gold standard in determining hemodynamic parameters, is an invasive, expensive test that involves placing a catheter into the pulmonary artery, which is usually only performed in an intensive care setting and carries risk to the patient and the team performing the procedure.

In a review of the most current literature, there are discrepancies between studies reporting the diagnostic threshold values that should be utilized in ICG derived hemodynamic values.[7-11] It has been demonstrated that ICG is not affected by obesity,[14] but it is uncertain at this time if ICG derived hemodynamic values vary by sex.[10] This study attempted to examine these previously reported values as well as determine if the reported discrepancies can be attributed to differences by sex.

As part of this study, B-type natriuretic peptide (BNP) levels were checked on all patients who were enrolled. Both ICG derived hemodynamics and BNP levels have been shown to be independently effective,[7-11, 15-17] but they have not both been shown to be effective when compared head to head in a single study.[18, 19] BNP is a hormone released from the ventricles of the heart in response to dilation as seen in heart failure. BNP levels can be measured in the blood in approximately 15 minutes and is fairly inexpensive. In one study BNP levels were shown to be 91% accurate at distinguishing heart failure from pulmonary disease in patients who presented to the ED with dyspnea.[15] Unfortunately, while BNP levels may be a good screening tool in the ED[18] they are subject to variability. Studies have shown that serial BNP levels do not correlate with treatment induced hemodynamic changes.[20] Other studies have indicated that BNP levels are inversely associated with BMI which would require different diagnostic thresholds dependant on the patient's BMI in order to maintain high rates of sensitivity and specificity. At this time, neither age nor sex appears to have any significant effect on BNP levels.[22] In this study, BNP results were also compared to the hemodynamic data acquired from ICG analysis for each patient.

As a second part of this study, the results of bedside cardiothoracic ultrasound were compared to the results of ICG evaluation and BNP levels. Bedside focused cardiothoracic ultrasound is currently being integrated into the assessment and management of patients presenting to the ED with undifferentiated dyspnea. A focused cardiothoracic ultrasound can provide useful data concerning the patient's intravascular volume status, whether or not the patient has a decreased cardiac ejection fraction, if cardiac chamber dilation is present, whether the patient has pulmonary edema, an infiltrate, or evidence of a pleural effusion or pneumothorax contributing to their symptoms.

Having an inexpensive, rapid, reliable, and non-invasive method of determining the cause of dyspnea in the ED will help practitioners initiate the correct treatment sooner which should lead to improved patient outcomes and lower healthcare costs because unnecessary tests and treatments can be avoided. ICG technology has been shown to work, but how to interpret the information it provides is still debated. By gathering more data, establishing diagnostic thresholds and comparing those results with previous studies, we hope to help

practitioners better utilize this versatile technology to improve patient care. If we can establish sex specific diagnostic thresholds then this will help clarify some of the discrepancies in the scientific literature that are creating the debate about how to interpret ICG derived hemodynamic data. Furthermore, if we can demonstrate a clear advantage in terms of better sensitivity and specificity of ICG derived hemodynamic data over BNP levels in determining the etiology of dyspnea then we can eliminate redundancy from the ED work-up that results in wasted time and costs. By comparing the data derived from ICG versus that acquired with bedside cardiothoracic ultrasound, we can learn how to integrate both advanced technologies into the acute assessment and management of patients presenting with dyspnea to the ED and determine which would be the best test to utilize during the acute assessment of patients with a chief complaint of dyspnea.

Specific Aims:

1. Determine the diagnostic threshold for ICG derived hemodynamic values to differentiate between a cardiac and non-cardiac cause of dyspnea.
2. Determine if the ICG derived hemodynamic diagnostic threshold values are sex specific.
3. Compare ICG data to results of bedside cardiothoracic ultrasound.
4. Compare sensitivity/specificity of ICG versus cardiothoracic ultrasound verse BNP in determining cardiac vs. non-cardiac etiology of dyspnea.

Research Materials and Methods:

This prospective cohort study was conducted in the ED of Maricopa Medical Center in Phoenix, Arizona with approval from the Maricopa Integrated Health System Institutional Review Board. Non-pregnant patients, 18 years of age and older, capable of providing informed consent and presenting with a chief complaint of dyspnea were eligible to enroll in this study. Vulnerable patients (e.g. incarcerated patients, patients with a psychiatric complaint, etc.) were excluded from the study. Consent was obtained in both Spanish and English without coercion or monetary reward to patients. After consent, research staff obtained ICG data utilizing the Sonosite BioZ device (Bothell, WA) then conducted a focused bedside cardiothoracic ultrasound utilizing a Sonosite M-turbo (Bothell, WA). BNP levels were ordered on all patients who were enrolled in the study. All other blood tests and imaging studies were obtained per the discretion of the treating practitioner. As seen in other studies, the final diagnosis of cardiac or non-cardiac etiology of the patient's shortness of breath was determined through clinical gestalt by senior emergency medicine residents after retrospective review of the patient's electronic medical record. The patient's final diagnosis and results from the patient's ED evaluation were taken into account to determine whether the patient's final diagnosis was considered to be cardiac or non-cardiac in nature. ICG, ultrasound and BNP data was then separated by final diagnosis and comparisons were made between those patients with a cardiac etiology of dyspnea and those with a non-cardiac etiology for their dyspnea. Less than ten percent of patients approached for participation in this study declined to participate.

Results:

A total of 50 patients were enrolled in this study, 25 males and 25 females. The mean age of subjects was 55.1 ± 12.9 years. There were 20 subjects with a final diagnosis of cardiac etiology for their dyspnea, of which 8 were female. The mean age of subjects with a final diagnosis of cardiac etiology was 60.4 ± 12.2 years. The mean age for males with a cardiac etiology was 58.8 ± 13.4 years. The mean age for females with a cardiac etiology was 62.8 ± 10.5 years (Table 1).

There were 30 subjects with a final diagnosis of non-cardiac etiology, of these 17 were female. The mean age of subjects with a final diagnosis of non-cardiac etiology was 51.6 ± 12.4 years. The mean age for males with a non-cardiac etiology was 57.9 ± 10.9 years. The mean age for females with a non-cardiac etiology was 46.8 ± 11.5 years (Table 1).

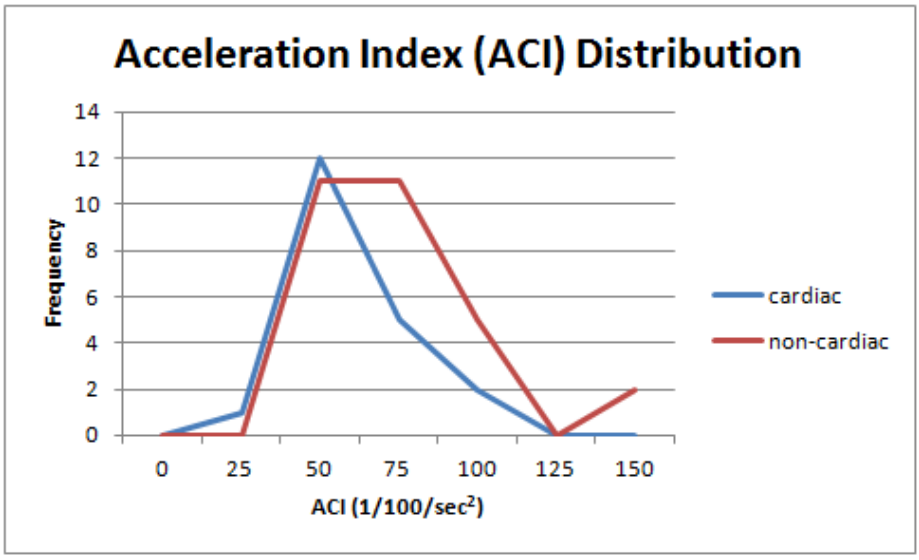
Table 1: Summary of Patient Demographics

Total subjects	50		
Mean age	55.1 ± 12.9 years		
Male subjects	25		
Female subjects	25		
Total cardiac	20	**Total non-cardiac**	30
Mean age	60.4 ± 12.2 years	Mean age	51.6 ± 12.4 years
Male subjects	12	Male subjects	13
Mean age of males	58.8 ± 13.4 years	Mean age of males	57.9 ± 10.9 years
Female subjects	8	Female subjects	17
Mean age of females	62.8 ± 10.5 years	Mean age of females	46.8 ± 11.5 years

Of the 50 subjects, some patients were excluded from subgroup analysis due to partially incomplete data collection. Those with incomplete data left the department prior to finishing their ED evaluation. One patient was excluded from ICG data analysis (n=49), seven were excluded from the ultrasound data analysis (n=43), and six were excluded from the BNP data analysis (n=44).

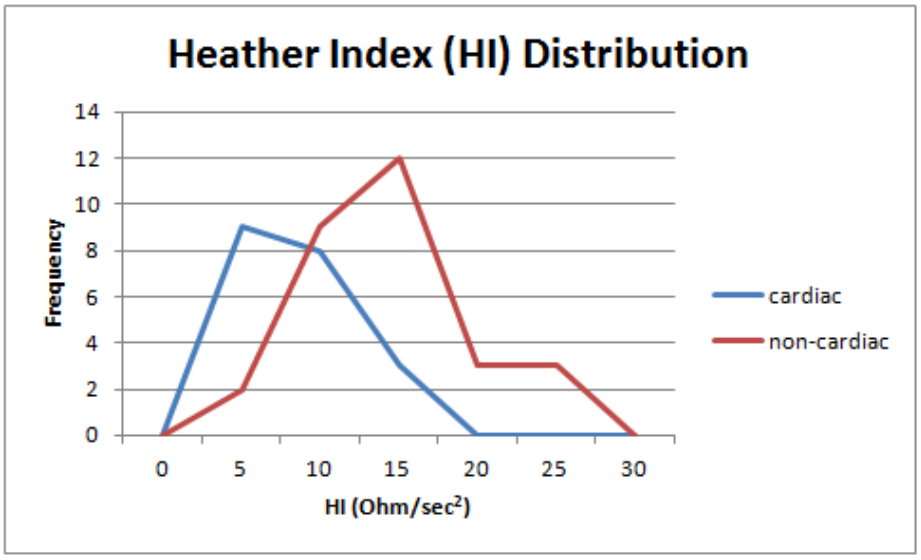
The distribution of all measured ICG and ultrasound parameters as well as BNP values were charted for all cardiac and non-cardiac patients. The distribution for each parameter was compared between the cardiac and non-cardiac patients to identify parameters that best differentiated cardiac from non-cardiac etiology. Using the student's T-test function of Microsoft Excel, significant differences were noted between the cardiac and non-cardiac patients for the following ICG parameters: cardiac index (CI), velocity index (VI), acceleration index (ACI), Heather index (HI), left cardiac work index (LCWI), systemic vascular resistance index (SVRI), and systemic vascular resistance (SVR). See figures 2-14.

Figure 2: Acceleration index distribution



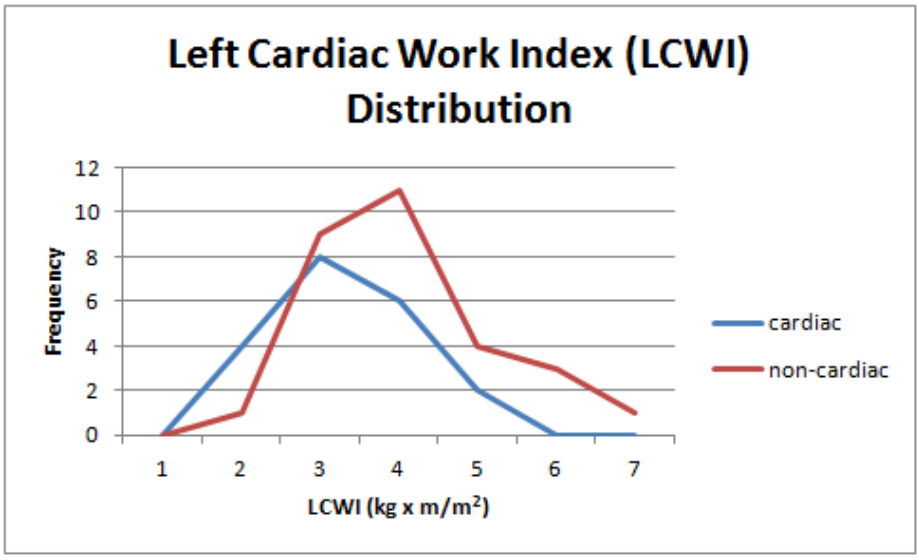
Acceleration index measures peak acceleration of blood flow in aorta during systole normalized to body surface area of the patient; low ACI correlates with decreased left ventricular function. Reference ranges for males were 70 - 150 1/100/sec^2 and for females 90 - 170 1/100/sec^2.

Figure 3: Heather index distribution



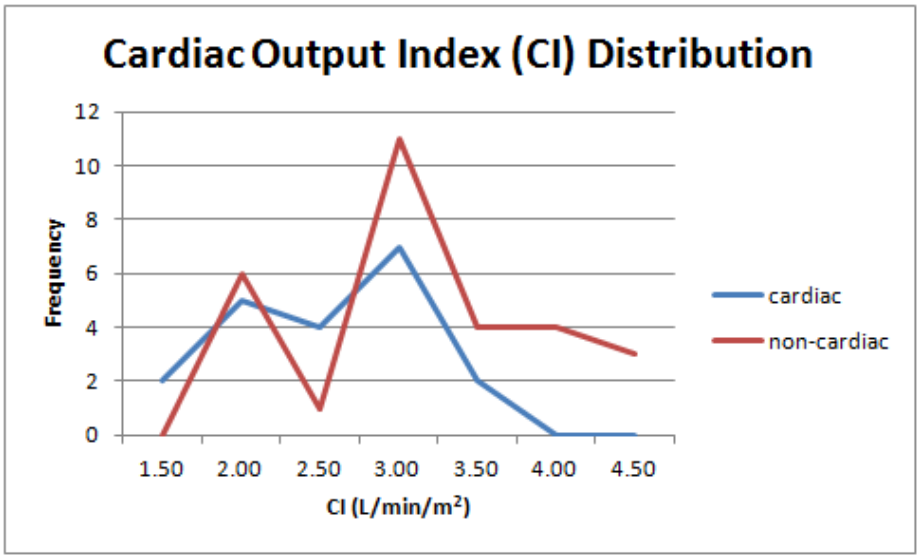
Heather index is a contractility indicator normalized to body surface area of the patient; low HI correlates with decreased left ventricular function. No reference range was available.

Figure 4: Left cardiac work index distribution



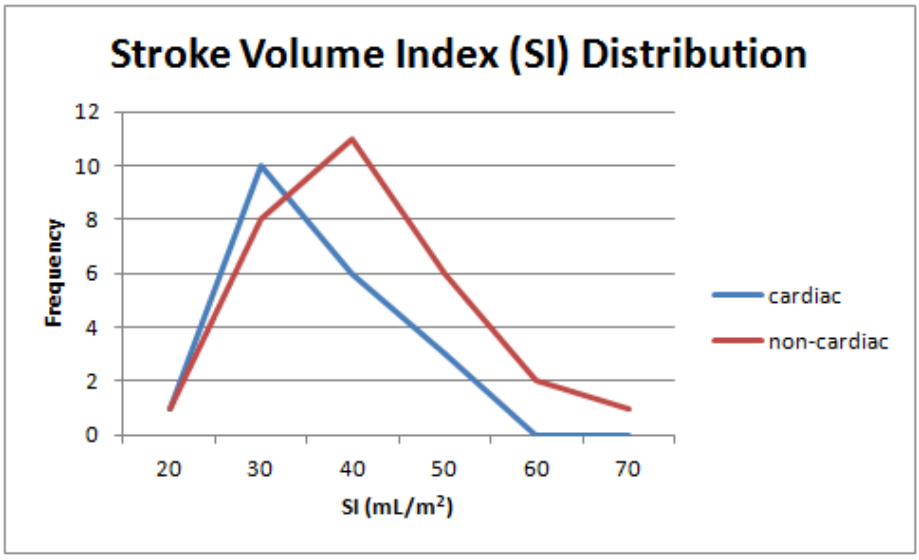
Left cardiac work index represents the work the heart must perform to pump blood each min or myocardial oxygen demand. A higher LCWI correlates with a lower angina threshold. Reference range was 3.0 – 5.5 kg x m / m^2.

Figure 5: Cardiac output index distribution



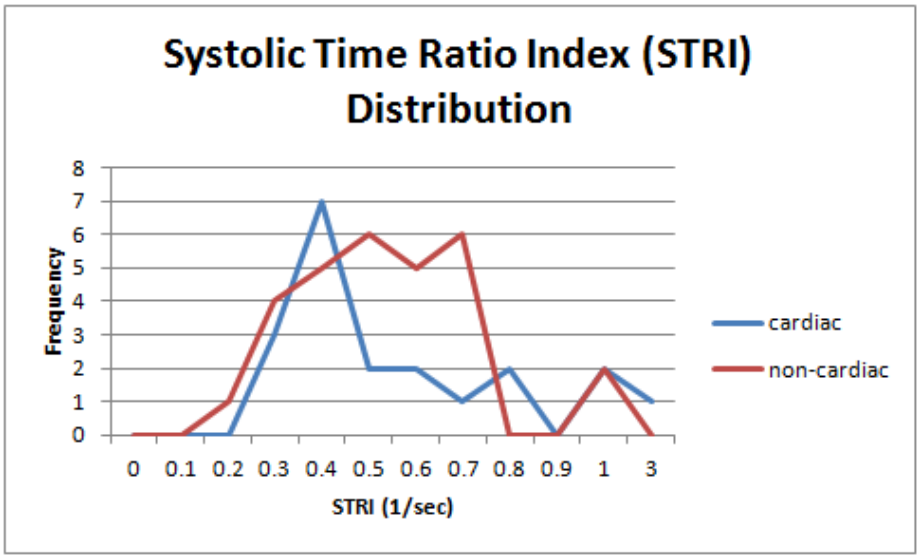
Cardiac output index is the amount of blood pumped by the heart per minute normalized to the body surface area of the patient; it is calculated by heart rate x stroke volume, low CI correlates with decreased left ventricular function and ejection fraction. Reference range was 2.5 – 4.2 L/min/m^2.

Figure 6: Stroke volume index distribution



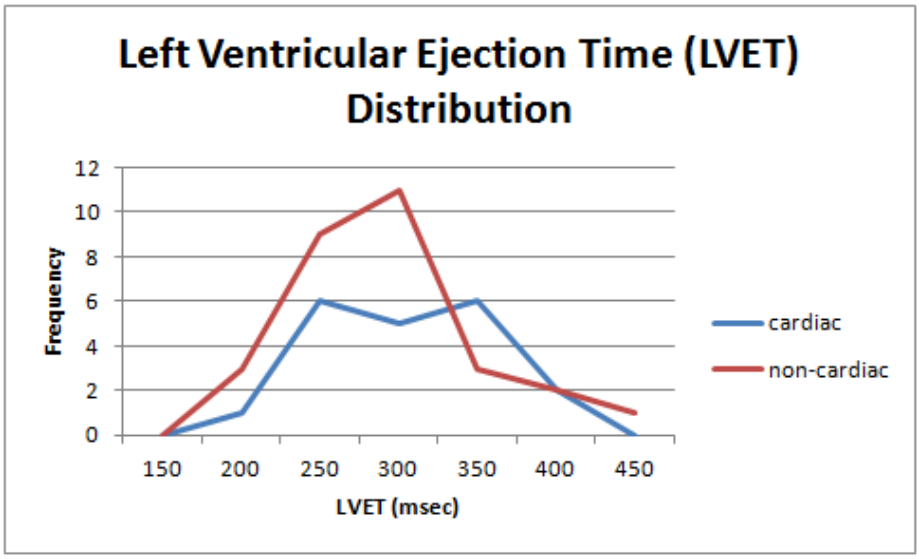
Stroke volume is the amount of blood pumped by the heart with each beat, normalized to the body surface area of the patient. SI can be affected by preload, afterload or contractility. Reference range was 35 – 65 mL/m^2.

Figure 7: Systolic time ratio index distribution



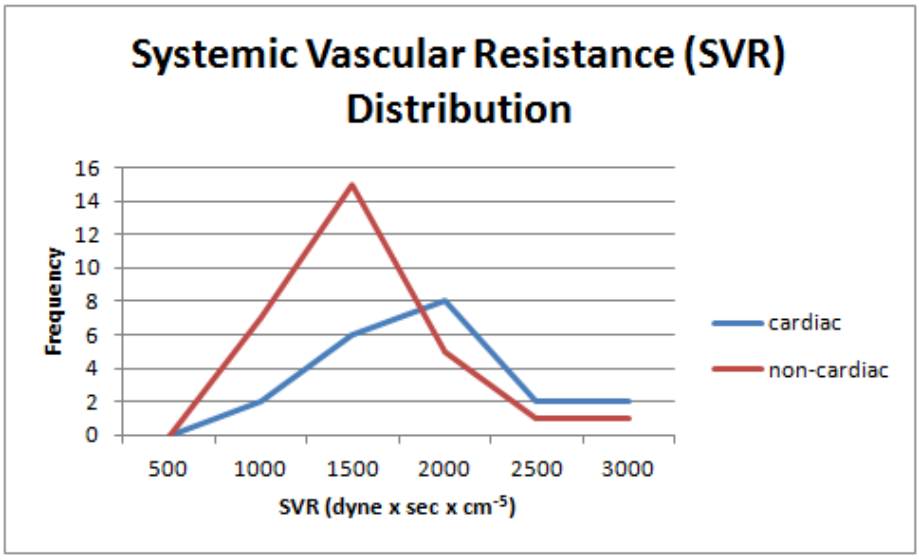
Systolic time ratio index is the ratio of electrical to mechanical systole normalized to the body surface area of the patient; high STRI correlates with decreased ejection fraction or a left bundle branch block, pacer, or a conduction delay. Reference range was 0.3 – 0.5 1/sec.

Figure 8: Left ventricular ejection time distribution



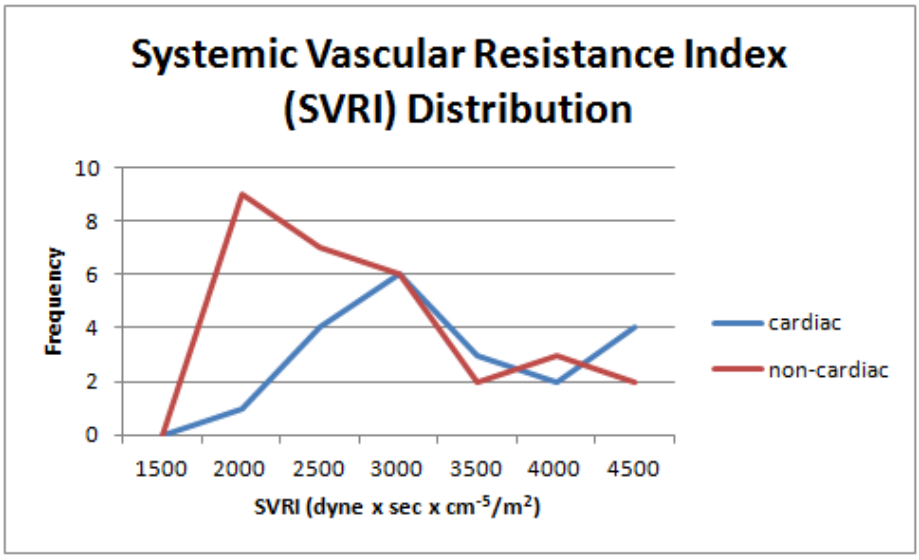
Left ventricular ejection time is the duration of mechanical systole; a high LVET correlates with decreased sustained ejection. Reference range unavailable as this value varies with heart rate.

Figure 9: Systemic vascular resistance distribution



Systemic vascular resistance is the force the left ventricle must overcome to eject blood into the aorta, it is an estimate of afterload. High SVR correlates with vasoconstriction. Reference range was 770 – 1500 dyne x sec x cm^{-5}.

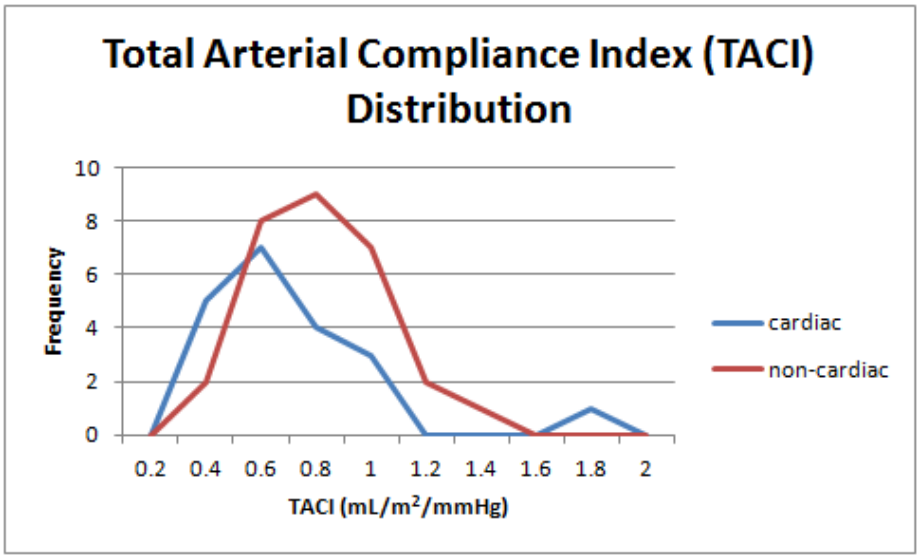
Figure 10: Systemic vascular resistance index distribution



Systemic vascular resistance index is the force the left ventricle must overcome to eject blood into the aorta normalized to the body surface area of the patient; it is an estimate of afterload. High SVRI correlates with vasoconstriction.

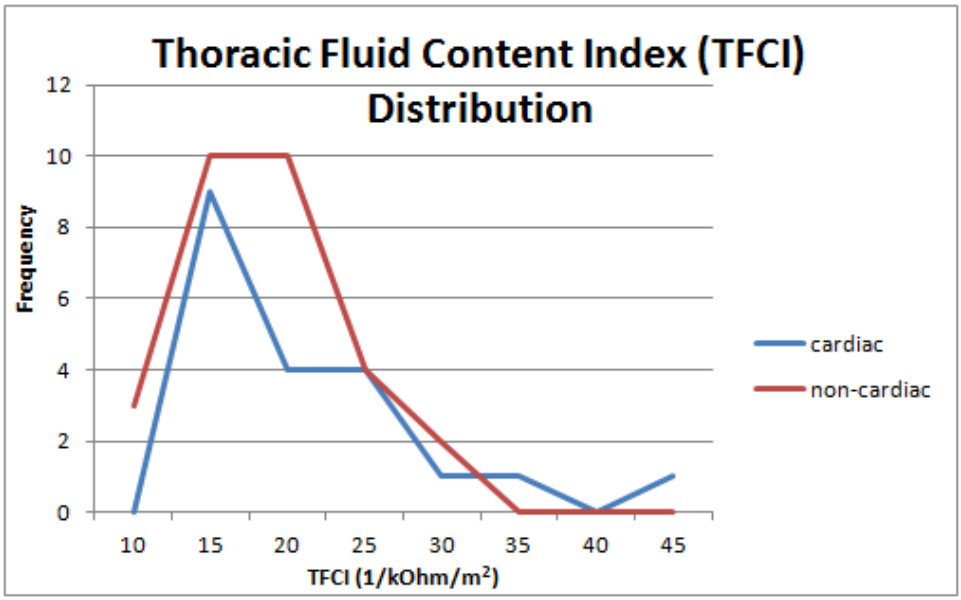
Reference range was 1680 – 2580 dyne x sec x cm^{-5}/m^2.

Figure 11: Total arterial compliance index distribution



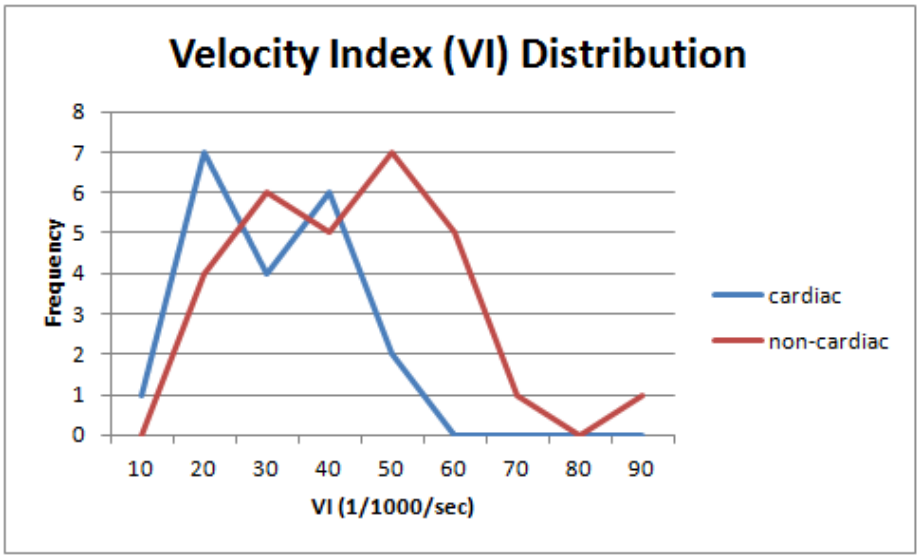
Total arterial compliance index is an indicator of peripheral arterial stiffness or compliance normalized to the body surface area of the patient. Low TACI correlates with increased arterial stiffness or, stated another way, decreased arterial compliance. Reference range was 8 -14 $mL/m^2/mmHg$.

Figure 12: Thoracic fluid content index distribution



Thoracic fluid content index is a measure of the impedance through the thorax normalized to the body surface area of the patient. A high TFCI correlates with increased thoracic fluid or a muscular body habitus; a low TFCI correlates with dehydration, old age, obesity or emphysema. Reference ranges for males were 30 – 50 1/kOhm/m^2 and for females 12 – 21 1/kOhm/m^2.

Figure 13: Velocity index distribution



Velocity index is the peak velocity of blood flow in aorta during systole normalized to the body surface area of the patient; it is decreased in obese patients. Low VI correlates with decreased left ventricular function. Reference range was 33- 65 1/1000/sec.

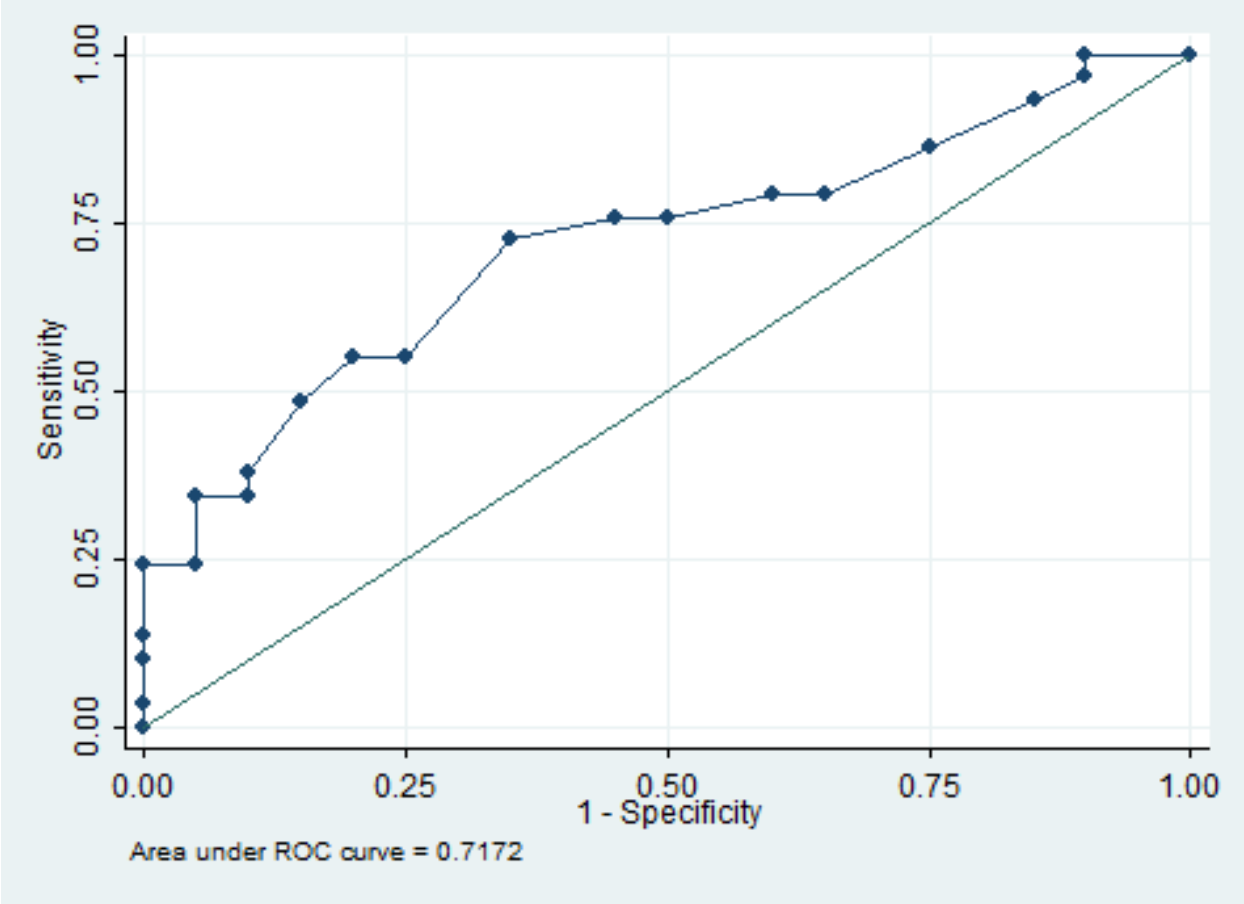
Table 14: Summary of significant ICG parameters

Parameter	Cardiac (n=20)	Non-cardiac (n=29)	P value
Cardiac Index* ($L/min/m^2$)	2.4 ± 0.6 Median 2.4	2.9 ± 0.8 Median 2.9	0.005
Velocity Index* (1/1000/sec)	26 ± 11 Median 25	40 ± 16 Median 40	0.001
Acceleration Index* ($1/100/sec^2$)	48 ± 19 Median 41	62 ± 27 Median 54	0.042
Heather Index* (Ohm/sec^2)	6.0 ± 3.0 Median 5.6	11.9 ± 5.4 Median 11	<0.001
Left cardiac work* index ($kg \times m/m^2$)	2.9 ± 0.8 Median 2.8	3.5 ± 1.2 Median 3.3	0.031
Systemic vascular resistance index* ($dyne \times sec \times cm^{-5}/m^2$)	3080 ± 770 Median 2970	2531 ± 767 Median 2182	0.018
Systemic vascular resistance* ($dyne \times sec \times cm^5$)	1644 ± 531 Median 1607	1328 ± 450 Median 1310	0.036

* mean ± 1 standard deviation

Receiver operating characteristic (ROC) curves were generated using STATA version 13 for the ICG parameters that demonstrated significant difference between the cardiac and non-cardiac patients. Using these ROC curves, giving equal weight to sensitivity and specificity, threshold values were established for distinguishing cardiac from non-cardiac etiology of shortness of breath. For CI the threshold was 2.7 L/min/m^2, for VI the threshold was 29 /1000/sec, for HI the threshold was 9.2 Ohms/sec^2, for LCWI the threshold was 3.1 kg x m/m^2, for ACI the threshold was 45 /100/sec^2, for SVRI the threshold was 2760 dyne x sec x cm^{-5}/m^2, and for SVR the threshold was 1577 dyne x sec x cm^{-5}. The area under the curve (AUC) of the various ROC curves was compared to establish the most accurate ICG parameter for distinguishing cardiac from non-cardiac etiology. The ROC with the greatest AUC, and therefore the most accurate at distinguishing cardiac from non-cardiac etiology was HI with an AUC of 0.8405. See figures 15-21.

Figure 15: ROC curve cardiac index



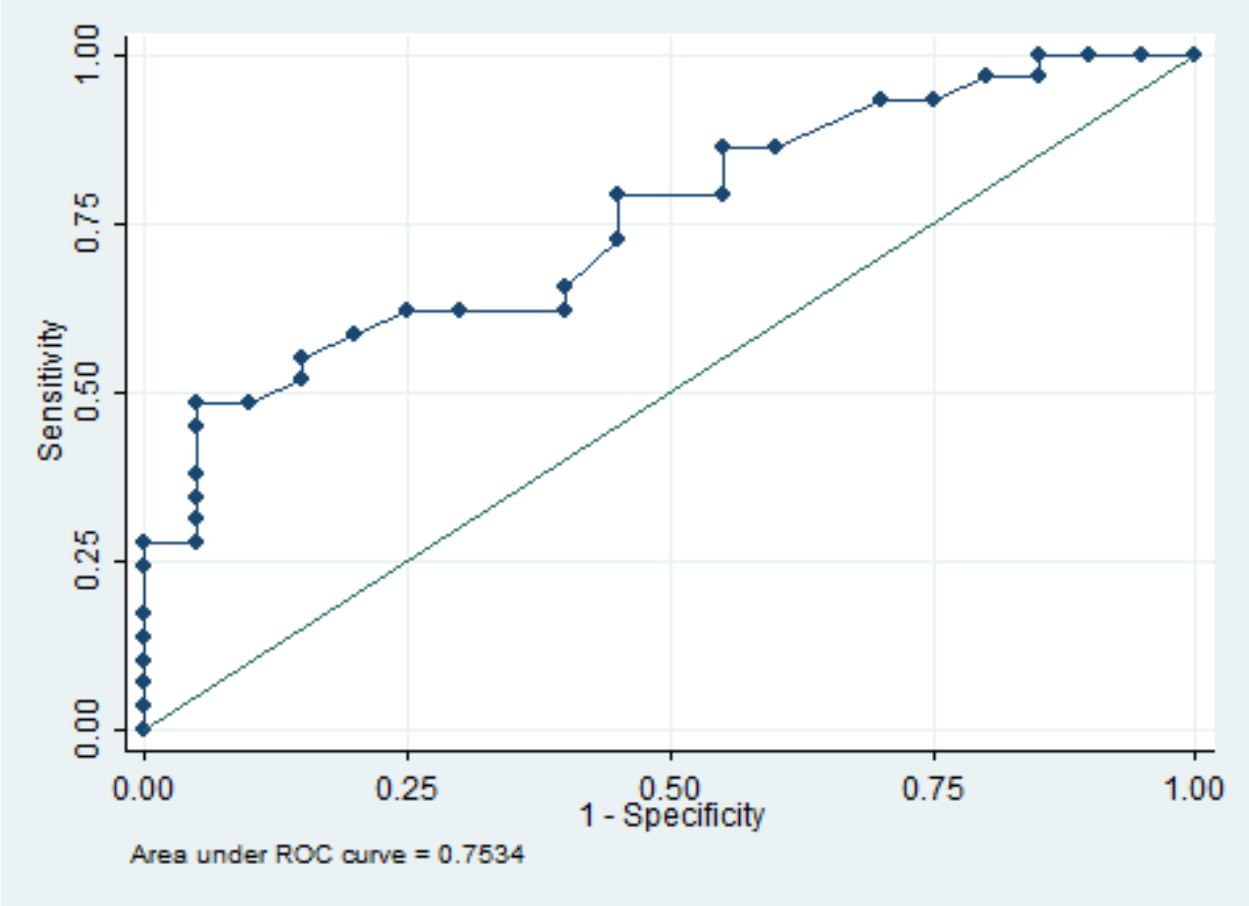
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Cardiac index	2.7 L/min/m^2	72.41	65.00	2.0690	0.4244	0.7172	0.56737 - 0.83416

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 16: ROC curve velocity index



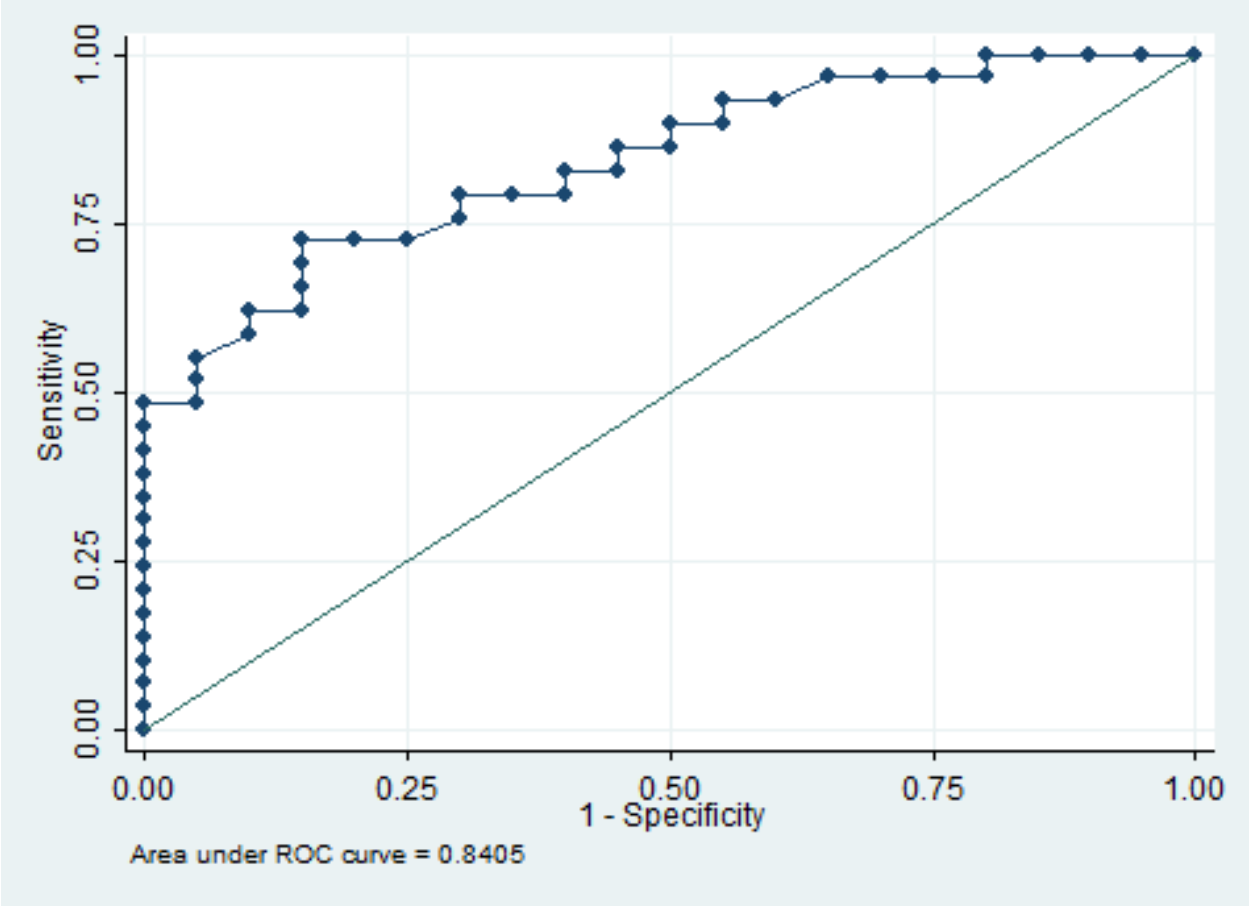
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Velocity index	29 1/1000/sec^2	79.31	55.00	1.7625	0.3762	0.7534	0.61130 – 0.86657

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 17: ROC curve heather index



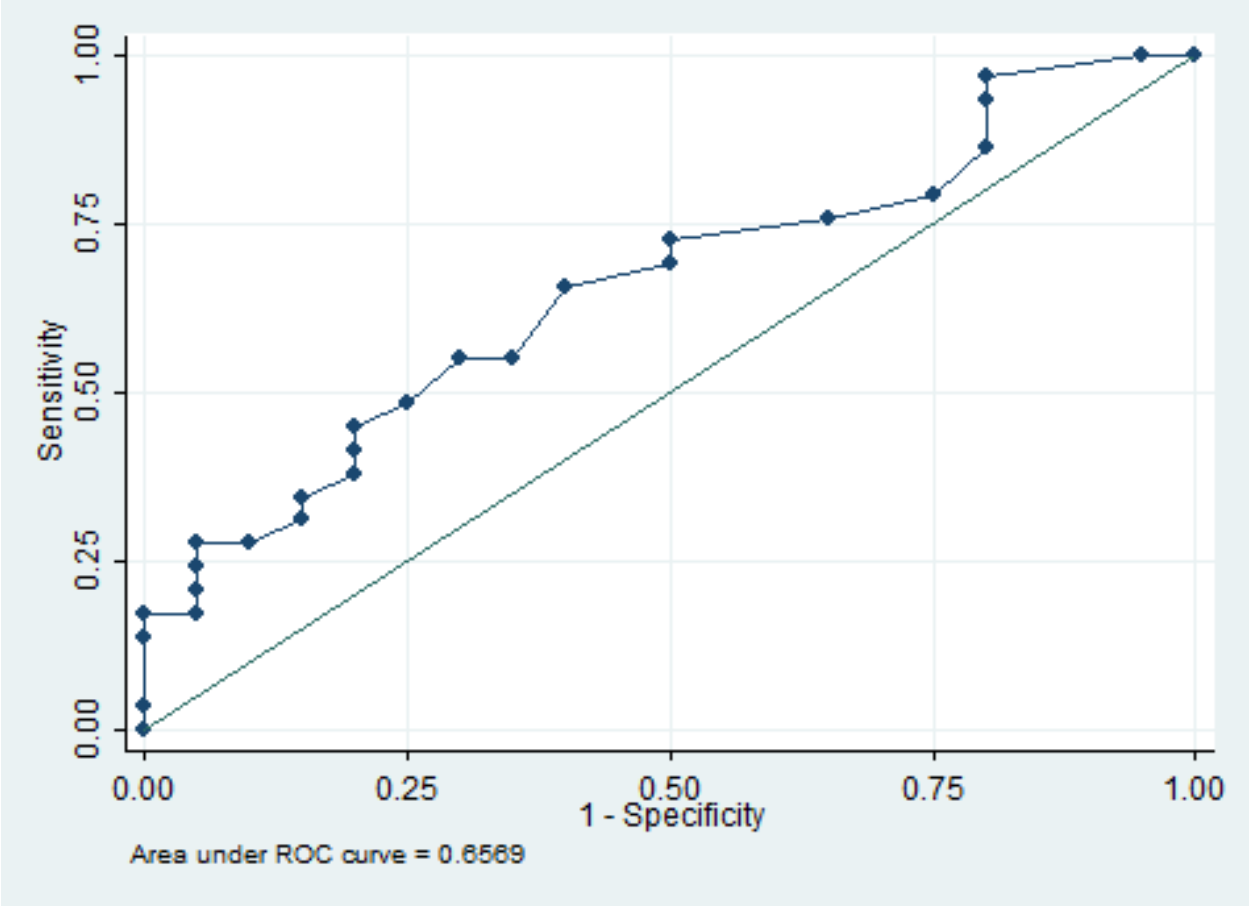
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Heather index	9.2 Ohm/sec^2	72.41	85.00	4.8276	0.3245	0.8405	0.70343 – 0.92678

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 18: ROC curve left cardiac work index



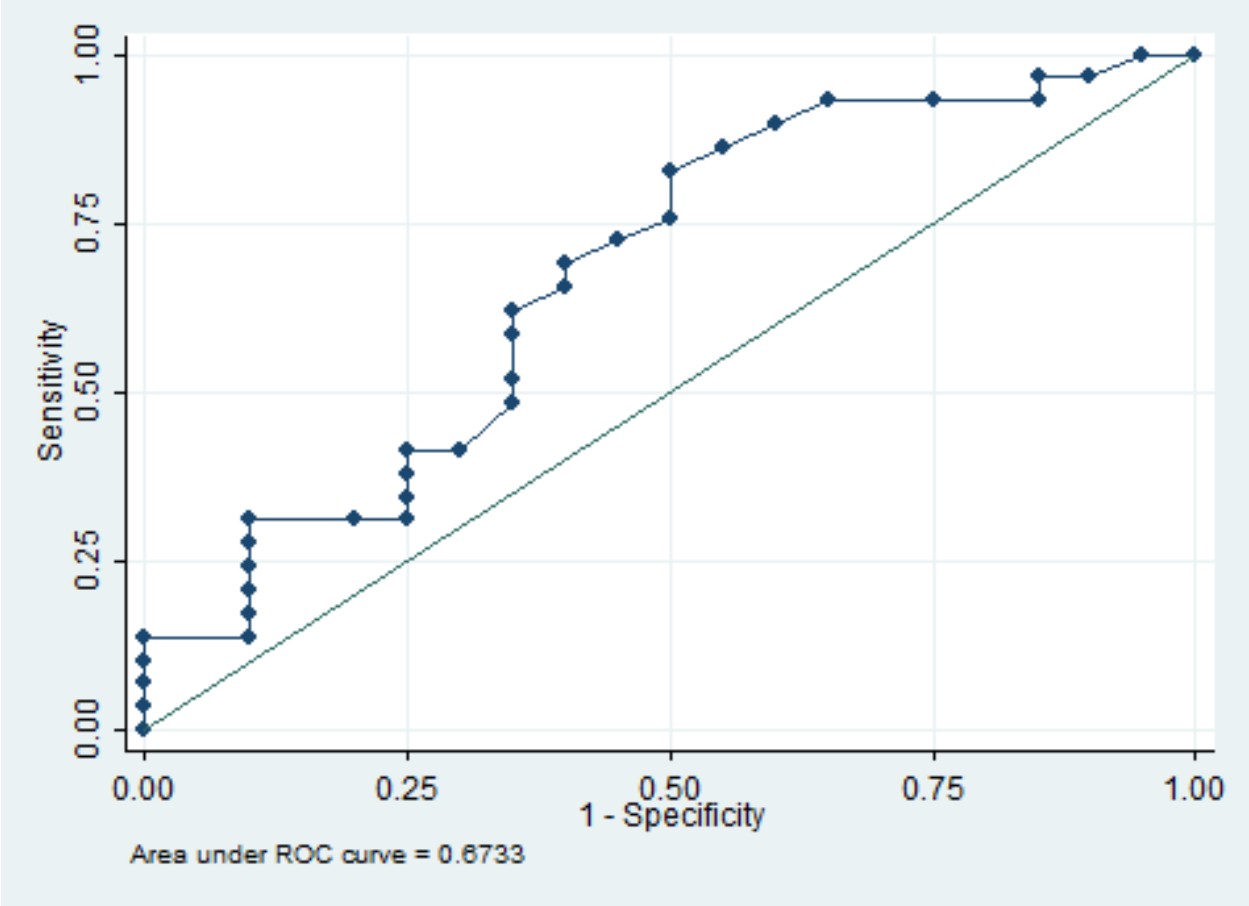
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
left cardiac work index	3.1 kg x m/m^2	65.52	60.00	1.6379	0.5747	0.6569	0.50361 – 0.78328

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 19: ROC curve acceleration index



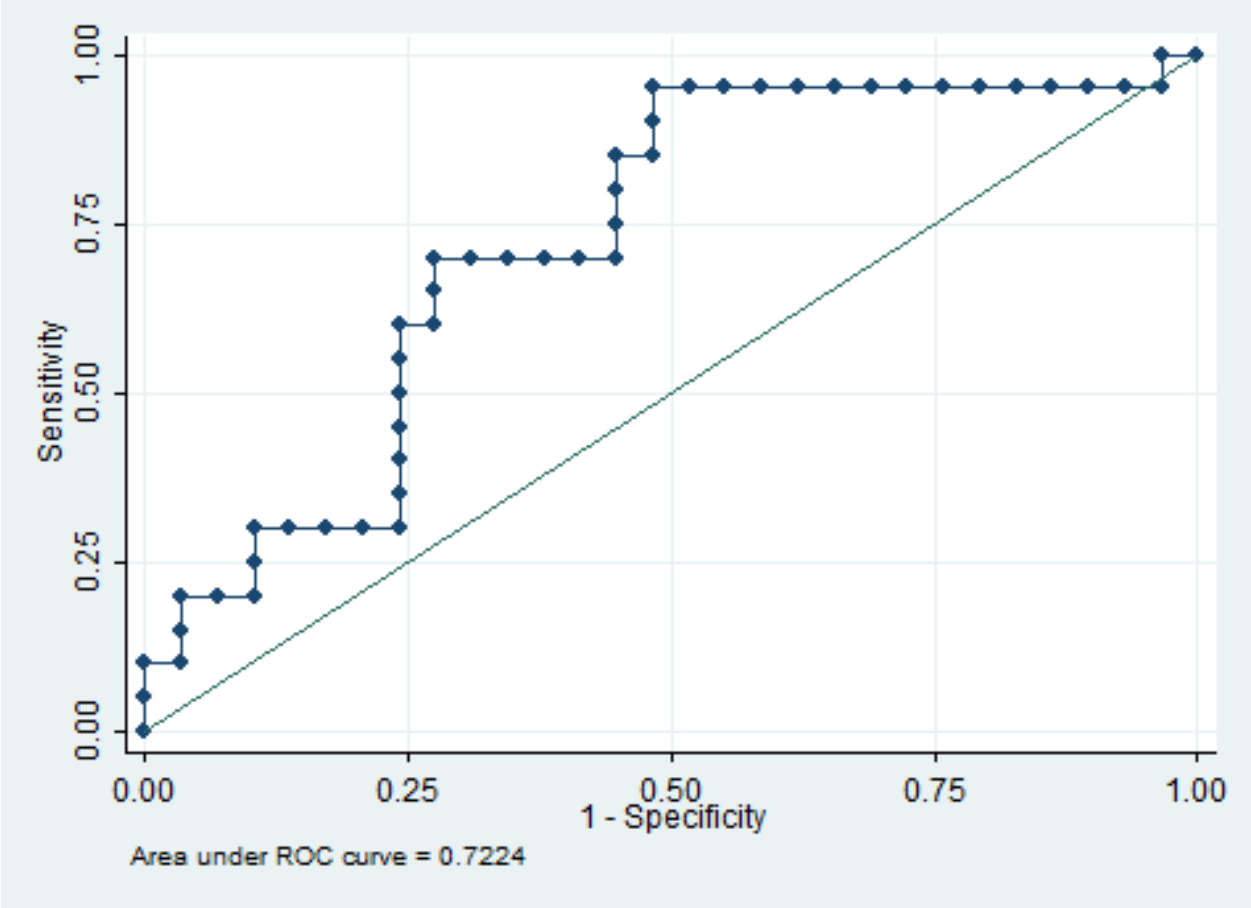
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
acceleration index	45 $1/100/sec^2$	68.97	60.00	1.7241	0.5172	0.6733	0.52460 - 0.80051

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 20: ROC curve systemic vascular resistance index



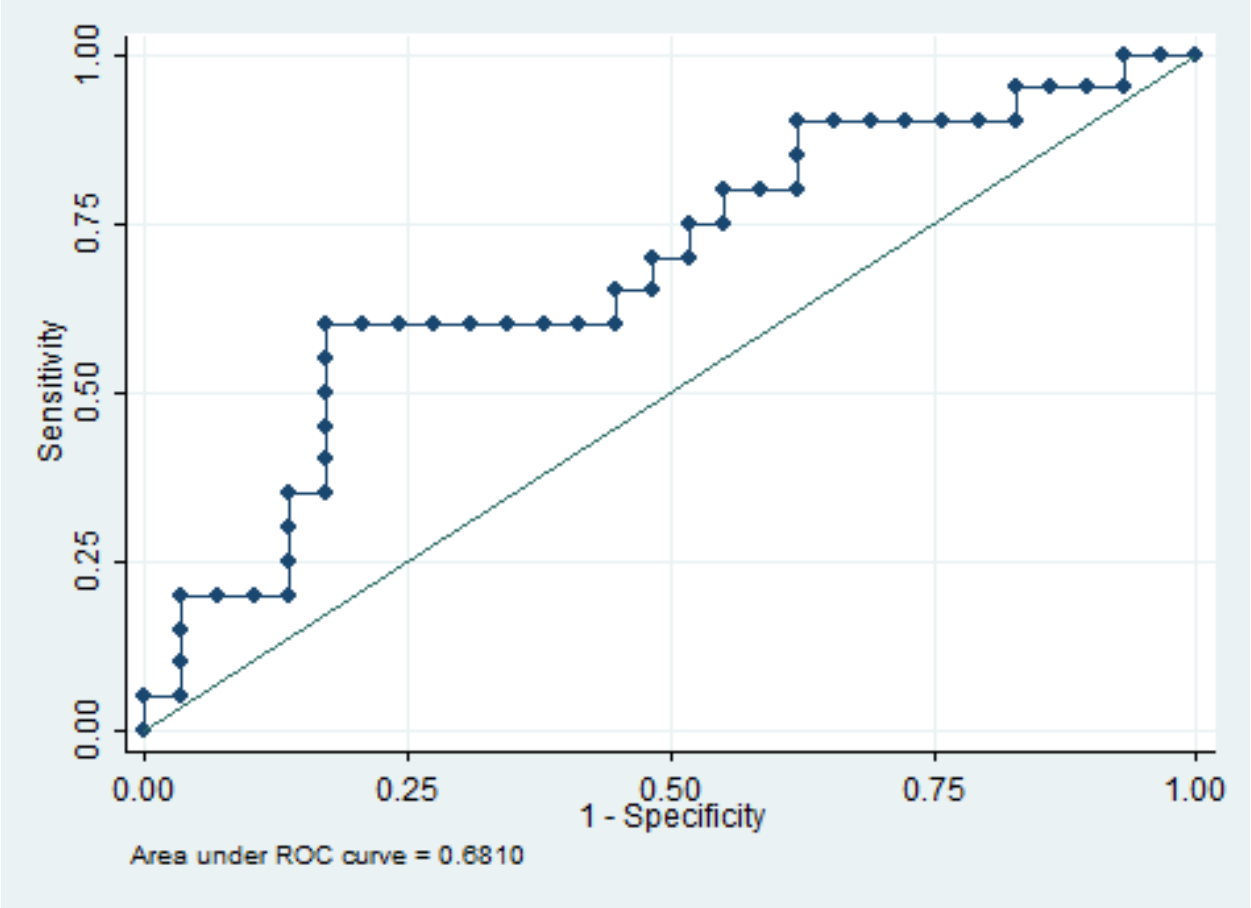
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
systemic vascular resistance index	2760 dyne x sec x cm^{-5}/m^2	70.00	72.41	2.5375	0.4143	0.7224	0.56737 - 0.83416

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 21: ROC curve systemic vascular resistance



Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
systemic vascular resistance	1577 dyne x sec x cm^{-5}	60.00	82.76	3.4800	0.4833	0.6810	0.52460 - 0.80051

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Once patients were stratified by their sex, significant differences were noted between the females with a cardiac etiology versus non-cardiac etiology for the following values: stroke index (SI), cardiac index (CI), velocity index (VI), acceleration index (ACI), left cardiac work index (LCWI), and heather index (HI). Significant differences were noted between the males with cardiac versus non-cardiac diagnoses for only heather index (HI). Only heather index (HI) was significantly different between male and female patients with a non-cardiac diagnosis. No significant differences were noted between males and females with cardiac reasons for their dyspnea. HI was the only ICG parameter to show significant differences between cardiac and non-cardiac patients in both sexes.

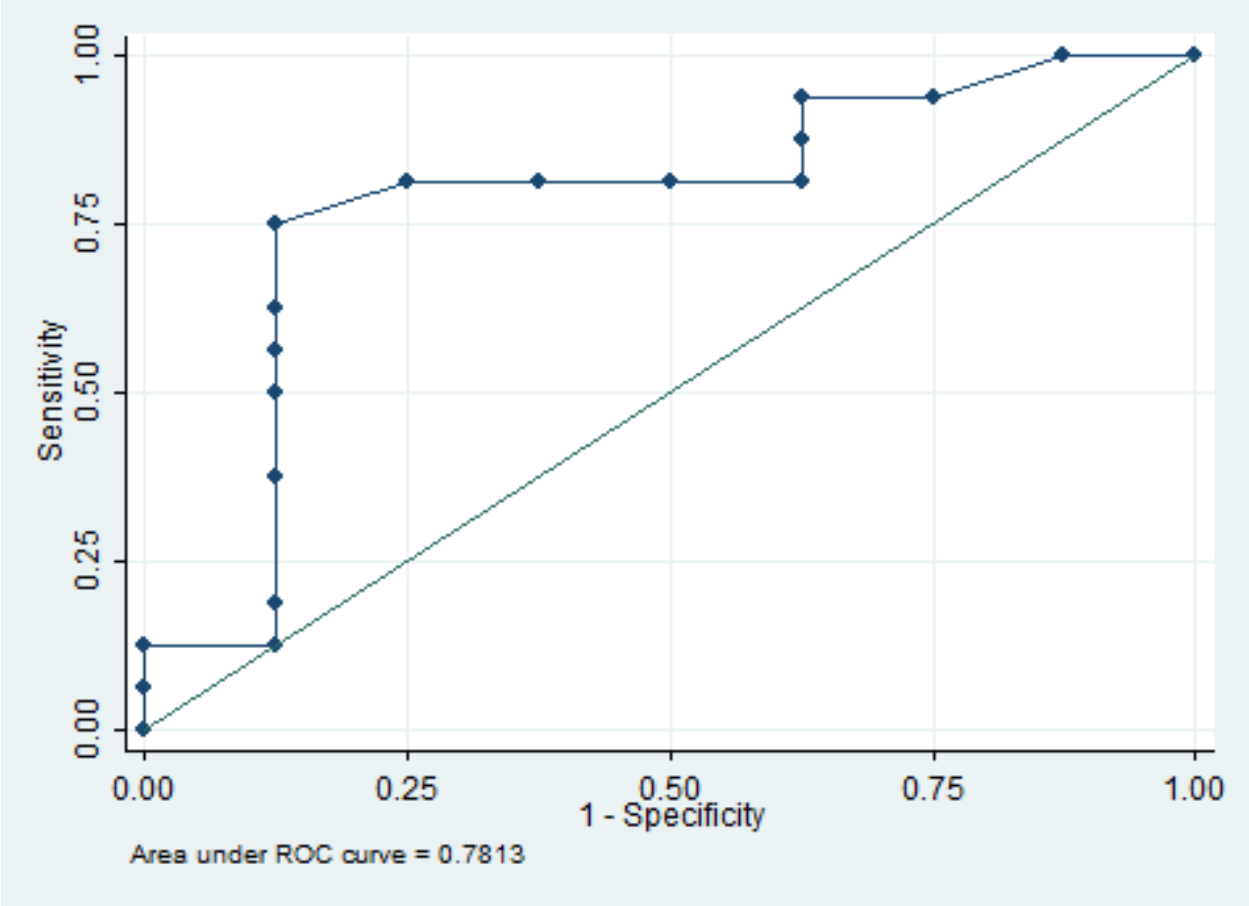
ROC curves of all significant ICG parameters grouped by sex were generated to determine if diagnostic thresholds were sex specific. Giving equal weight to sensitivity and specificity the SI threshold for females was 33 mL/m^2, the CI threshold for females was 2.7 $L/min/m^2$, the VI threshold for females was 23 /1000/sec, the ACI threshold for females was 41 $/100/sec^2$, the LCWI threshold for females was 3.1 kg x m/m^2, and the HI threshold for females was found to be 10.4 Ohm/sec^2. For males the HI threshold was found to be 6.9 Ohm/sec^2. However, HI was much more accurate for females with an AUC's of 0.9297 compared to an AUC of 0.7564 for males. See figures 22-29.

Table 22: Summary of significant ICG parameters by sex

Females			
Parameter	**Cardiac (n=8)**	**Non-cardiac (n=16)**	**P value**
Stroke index* (mL/m^2)	30 ± 8 Median 30	39 ± 11 Median 39	0.021
Cardiac index* ($L/min/m^2$)	2.3 ± 0.7 Median 2.2	3.1 ± 0.7 Median 3.1	0.013
Velocity index* (1/1000/sec)	25 ± 10 Median 21	41 ± 11 Median 44	0.003
Acceleration index* ($1/100/sec^2$)	47 ± 14 Median 40	61 ± 17 Median 56	0.034
Left cardiac work* index ($kg \times m/m^2$)	2.6 ± 0.8 Median 2.6	3.6 ± 1.1 Median 3.4	0.017
Heather index* (Ohm/sec^2)	6.5 ± 3.5 Median 6.4	14.4 ± 5.1 Median 13.3	<0.001
Males			
Parameter	**Cardiac (n=12)**	**Non-cardiac (n=13)**	**P value**
Heather index* (Ohm/sec^2)	5.6 ± 2.7 Median 5.2	8.9 ± 4.2 Median 7.9	0.026
Non-cardiac			
Parameter	**Female (n=16)**	**Male (n=13)**	**P value**
Heather index* (Ohm/sec^2)	14.4 ± 5.1 Median 13.3	8.9 ± 4.2 Median 7.9	0.004

* mean ± 1 standard deviation

Figure 23: ROC curve stroke index females



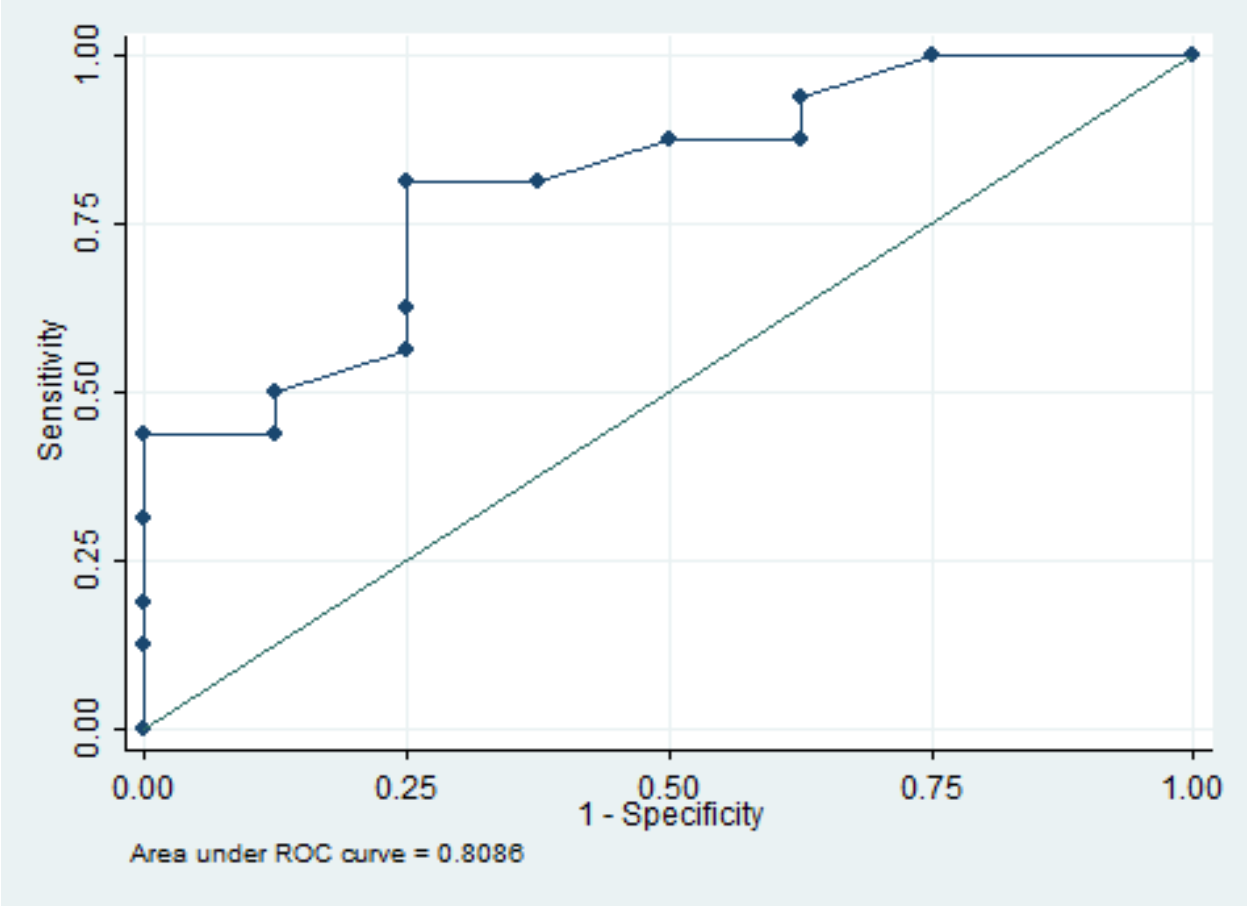
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Stroke Index (females)	33 mL/m^2	81.25	75.00	3.2500	0.2500	0.7813	0.57849 - 0.92868

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 24: ROC curve cardiac index females



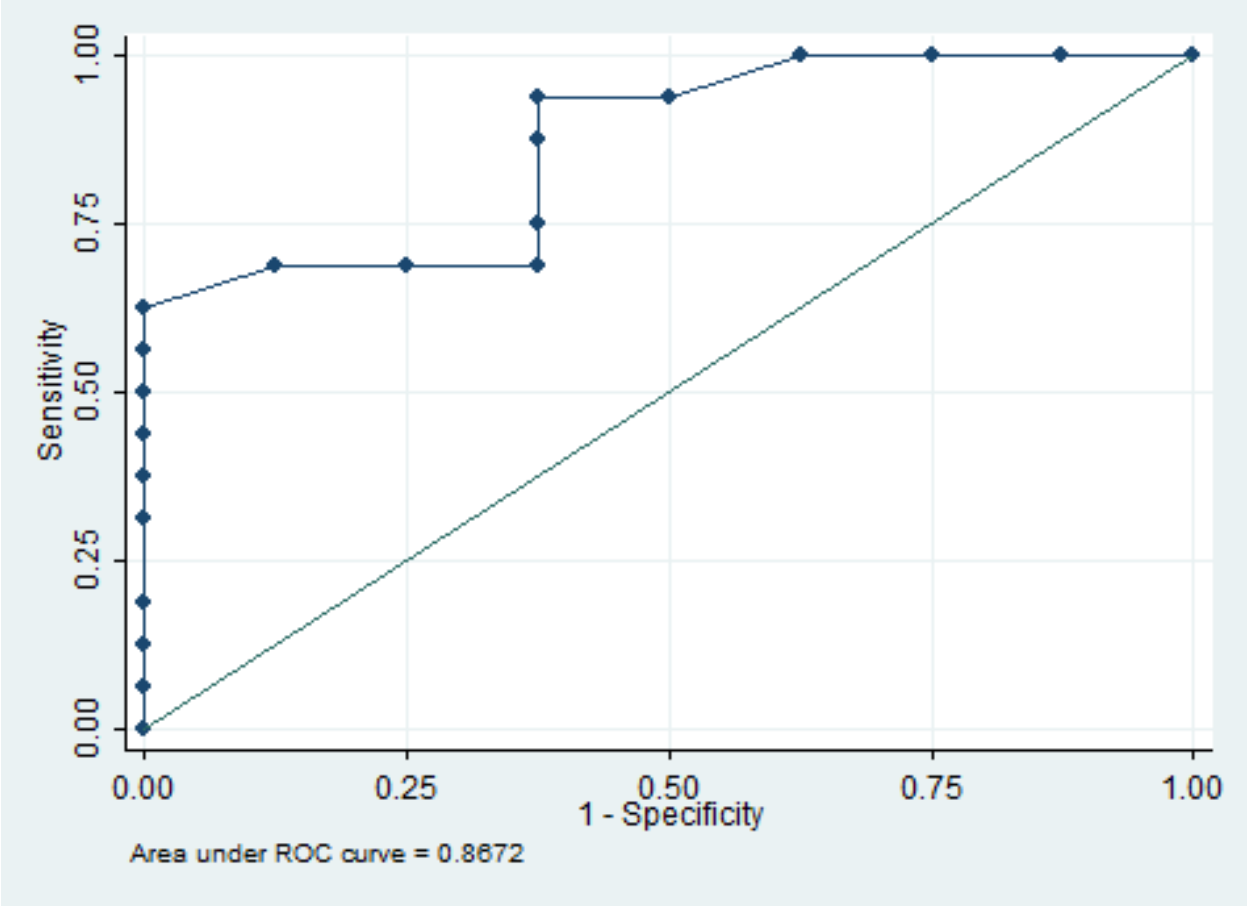
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Cardiac Index (females)	2.7 L/min/m^2	81.25	75.00	3.2500	0.2500	0.8086	0.57849 - 0.92868

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 25: ROC curve velocity index females



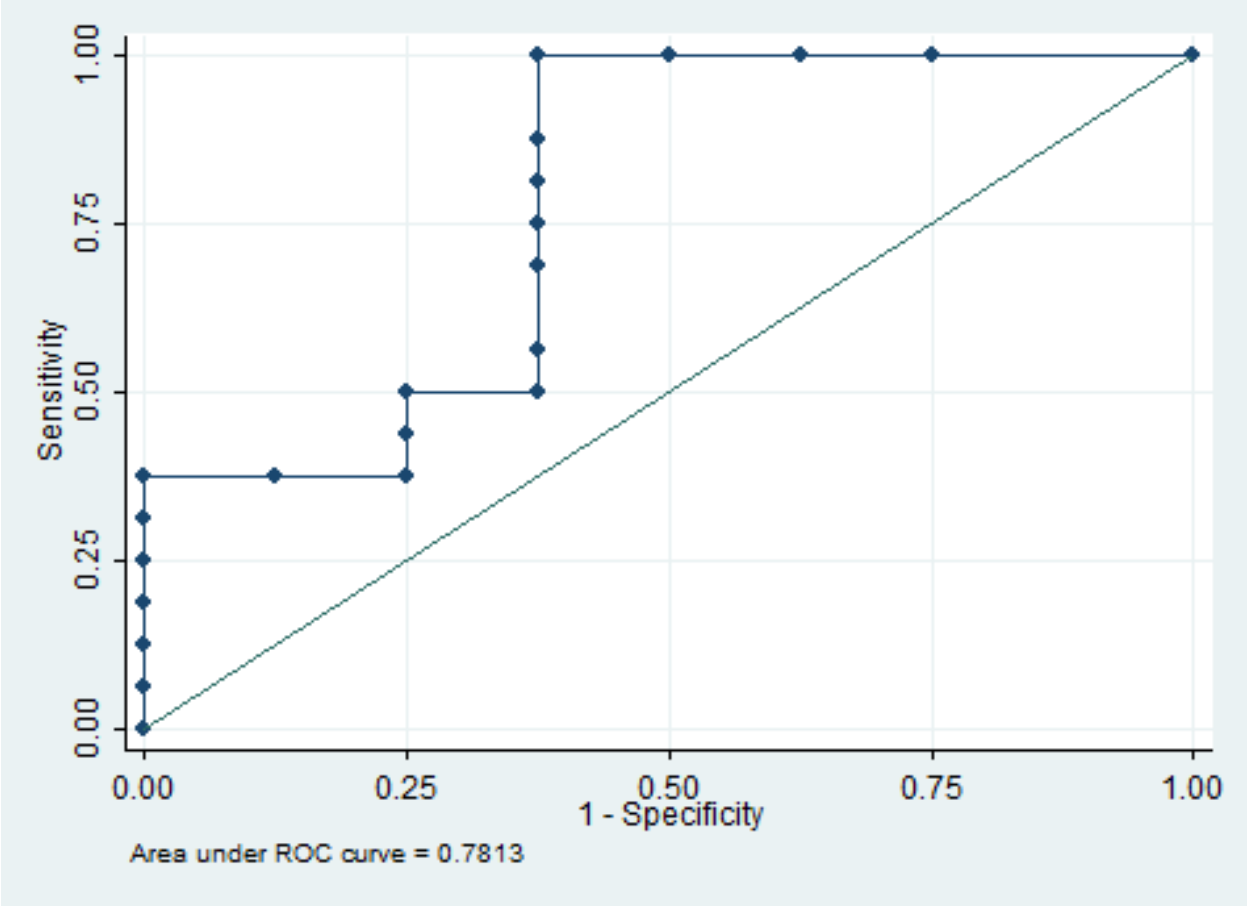
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Velocity Index (females)	23 1/1000/sec	93.75	62.50	2.5000	0.1000	0.8672	0.67639 - 0.97344

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 26: ROC curve acceleration index females



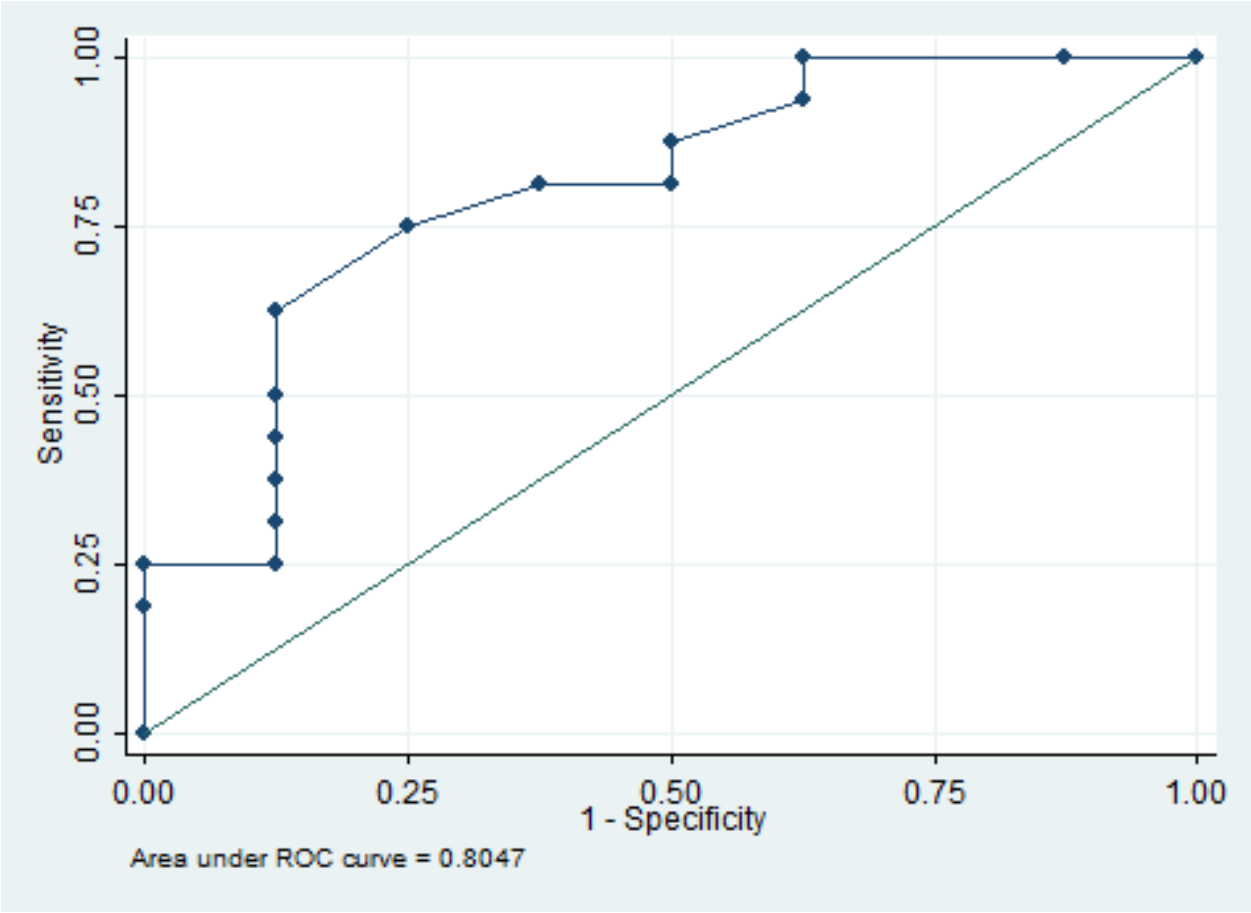
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Acceleration Index (females)	41 1/100/sec^2	100.00	62.50	2.6667	0.0000	0.7813	0.57849 - 0.92868

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 27: ROC curve left cardiac work index females



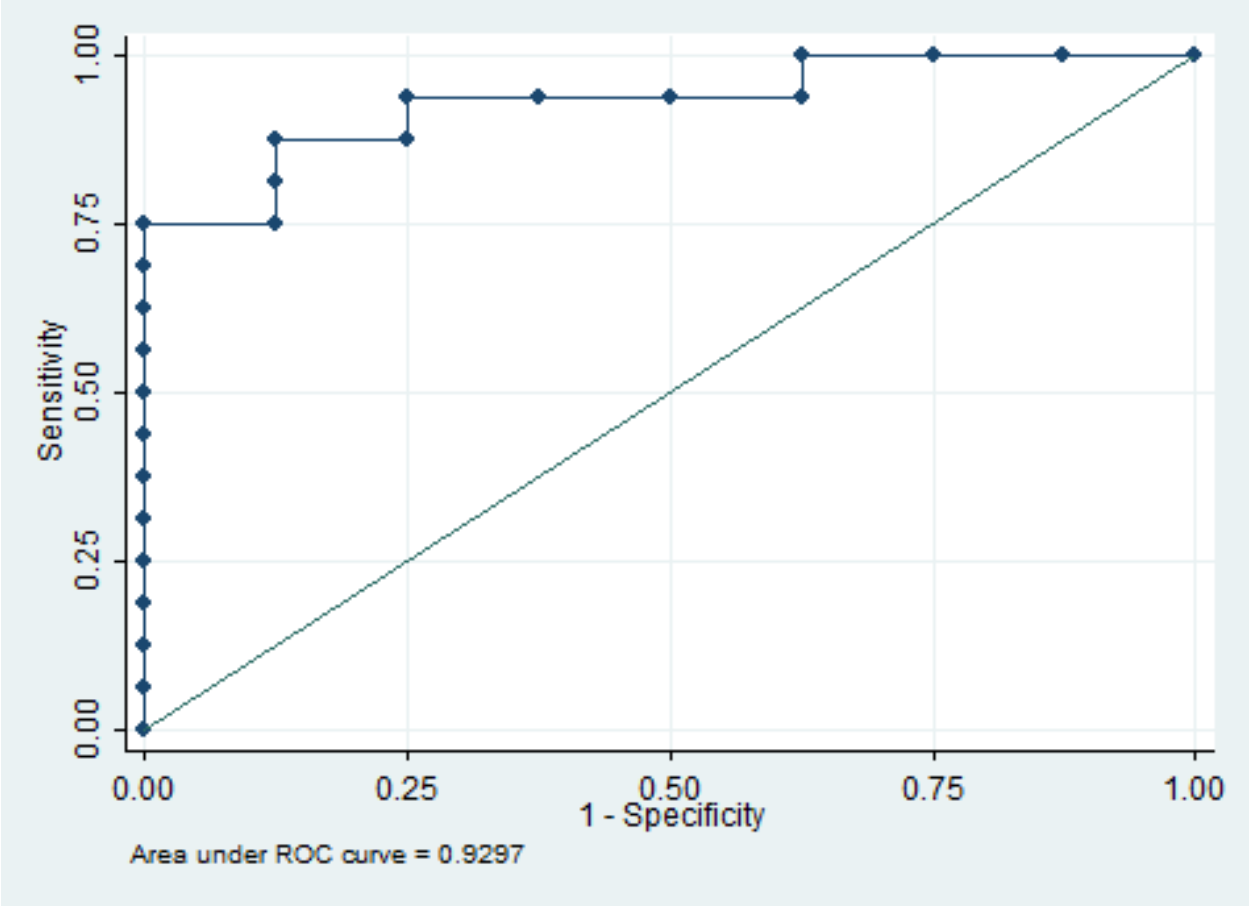
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Left cardiac work index (females)	3.1 kg x m/m^2	75.00	75.00	3.0000	0.3333	0.8047	0.57849 - 0.92868

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 28: ROC curve heather index females



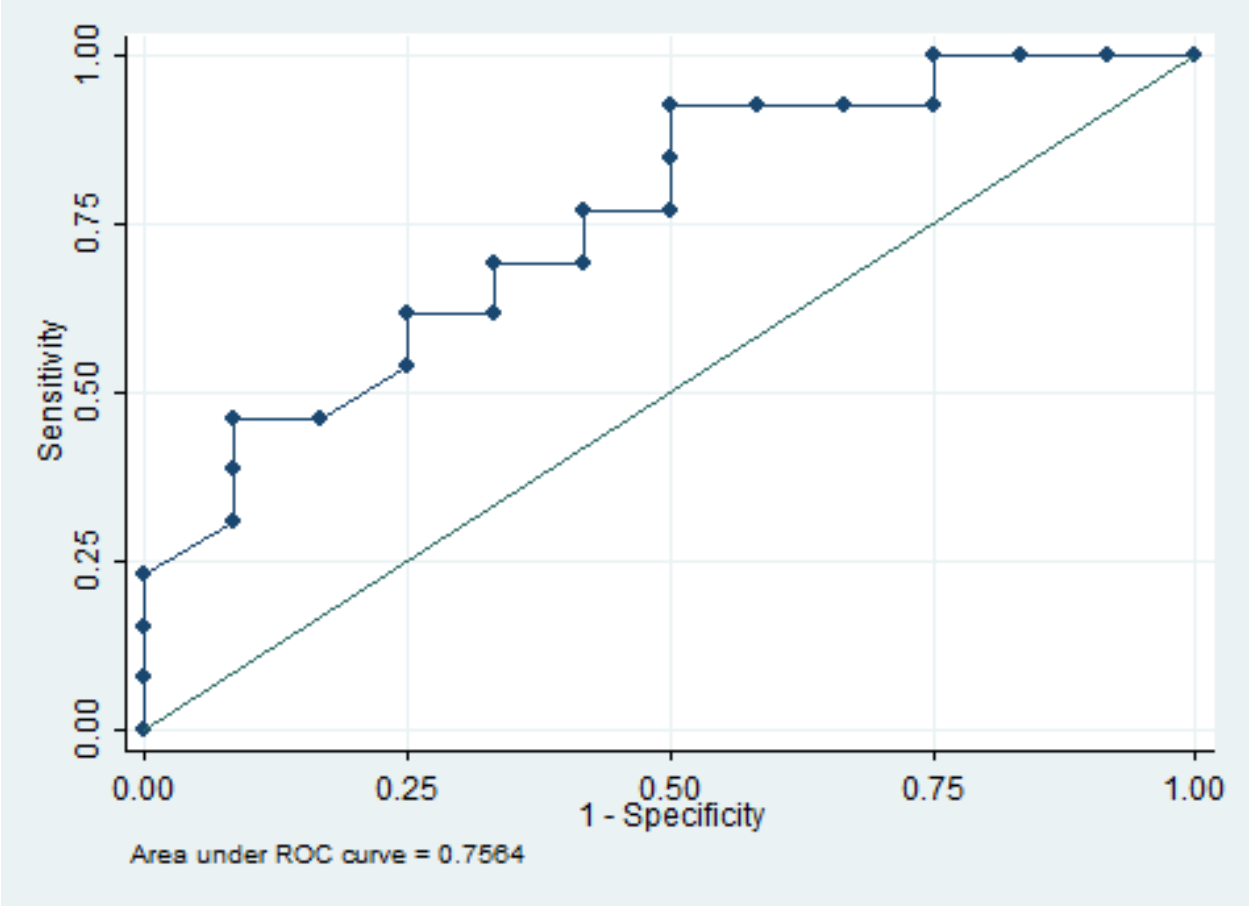
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Heather index (females)	10.4 Ohm/sec^2	87.50	87.50	7.0000	0.1429	0.9297	0.73003 - 0.98974

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 29: ROC curve heather index males



Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Heather index (males)	6.9 Ohm/sec^2	69.23	66.67	2.0769	0.4615	0.7564	0.54871 - 0.90644

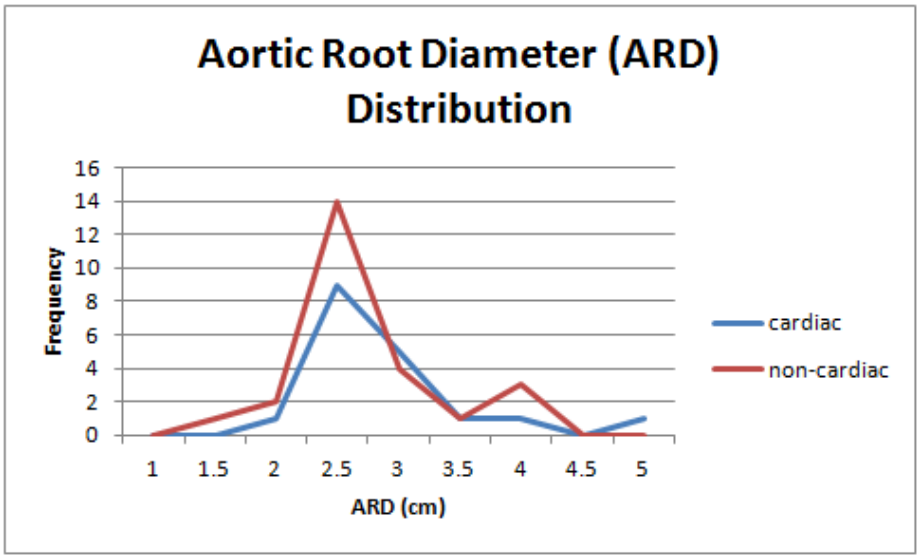
* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Significant differences were noted between cardiac and non-cardiac patients for the following ultrasound parameters: maximal inferior vena cava (IVC) diameter, right ventricle (RV) diameter both during systole and diastole, and left ventricle (LV) diameter both during systole and diastole. ROC curves were created to establish diagnostic thresholds for the various parameters, and sensitivity and specificity were weighted equally. The threshold for maximal IVC diameter was found to be 1.68 cm, for RV systolic diameter 1.71 cm, for RV diastolic diameter 3.07 cm, for LV systolic diameter 1.64 cm, and for LV diastolic diameter 3.34 cm. The AUC's were compared and it was found that RV systolic diameter had the largest AUC at 0.7489 and was therefore the most accurate ultrasound parameter at distinguishing cardiac from non-cardiac etiology. See figures 30-42.

Figure 30: Aortic root diameter distribution



Aortic root diameter is measured just distal to the aortic valve, labeled B in the image below.

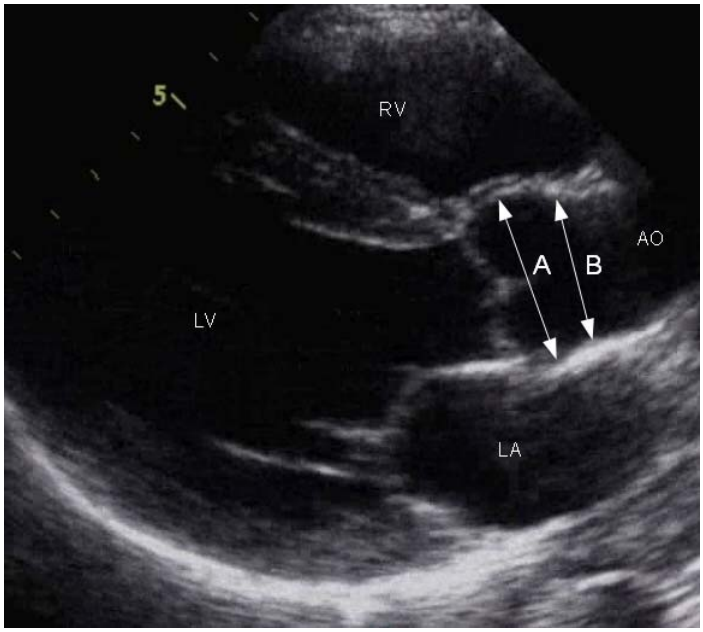
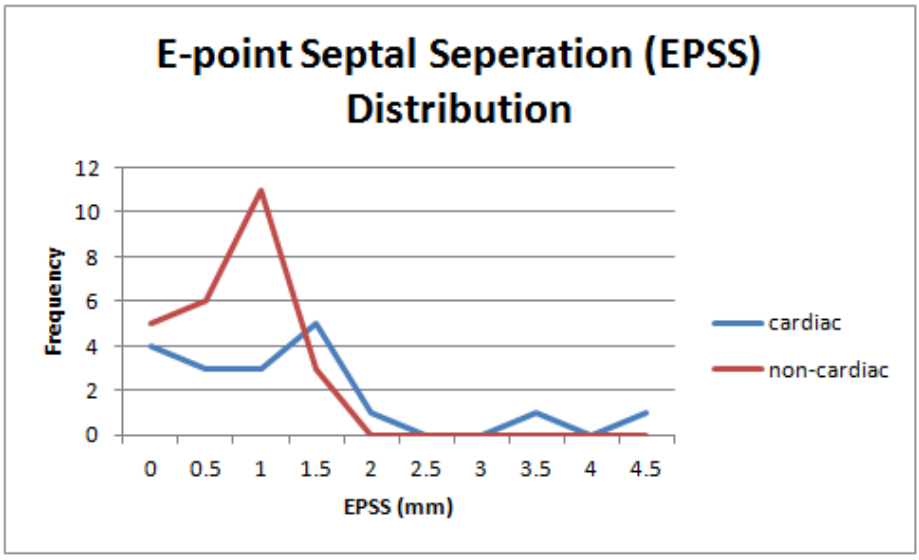


Figure 31: E-point septal separation distribution



E-point septal separation represents the distance from the anterior septal endocardium to the maximum early opening point of the anterior mitral leaflet during early diastole, it is the distance from A to A as seen in the M mode image below. It correlates with ejection fraction. Normal EPSS values are less than 6 mm; larger values correlate with decreased ejection fraction.

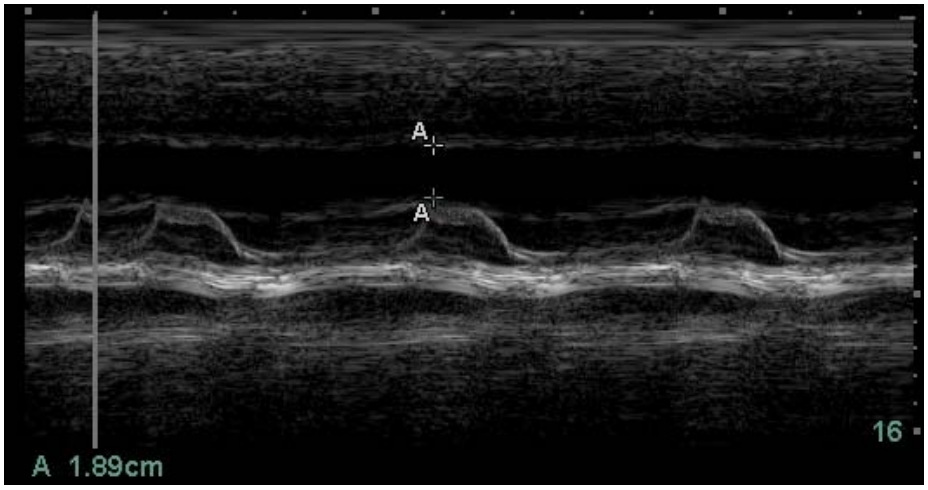


Figure 32: Distribution of maximal inferior vena cava diameter

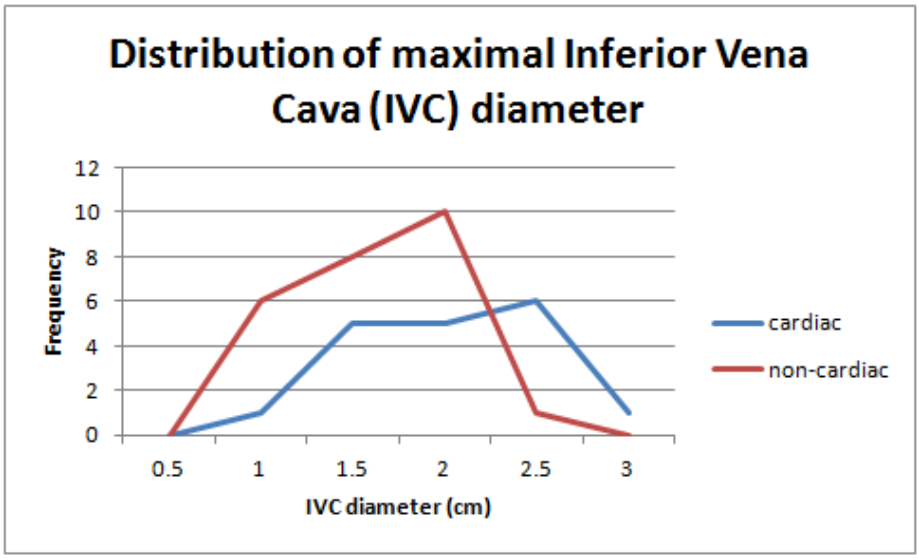
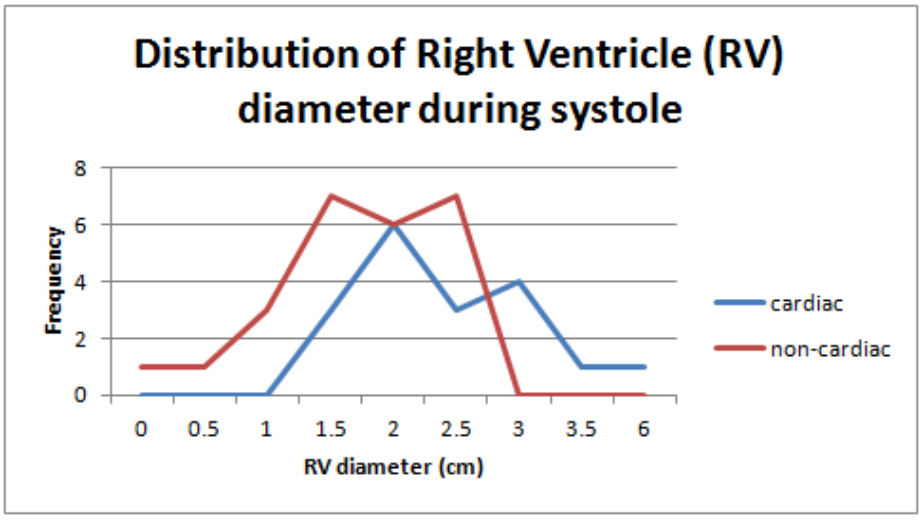


Figure 33: Distribution of right ventricle diameter during systole



The diameter of the right ventricle is measured as seen by line A in the image below. While the image below shows the heart during diastole, a similar approach is taken to measure when the diameter is smallest (systole). Increased right ventricular diameter correlates with decreased contractility.

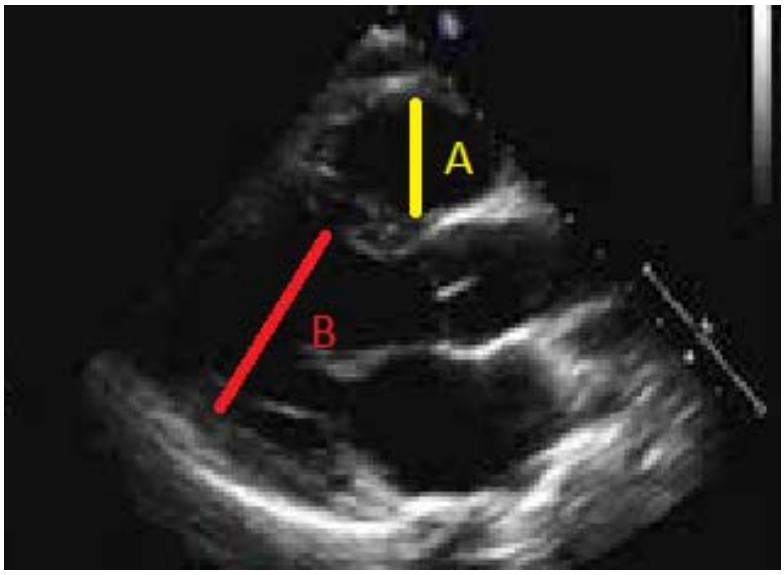
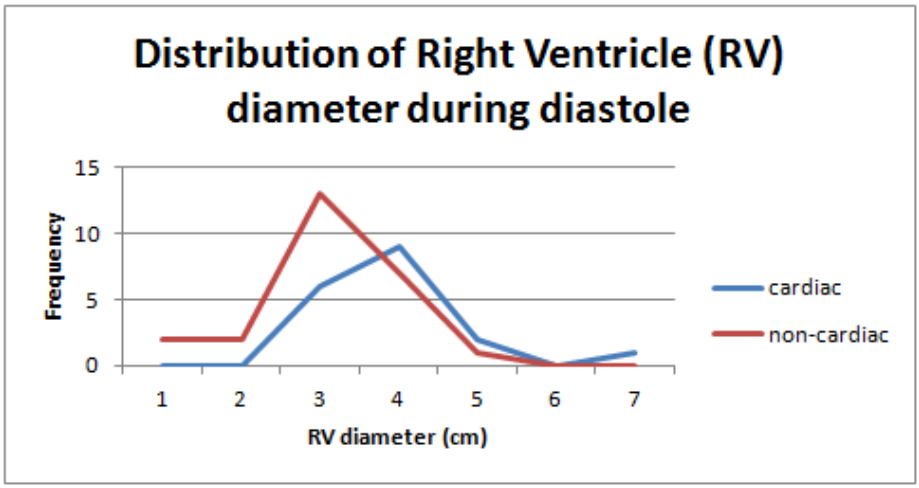


Figure 34: Distribution of right ventricle diameter during diastole



The diameter of the right ventricle during diastole is measured as seen by line A in the image below. Increased right ventricular diameter correlates with decreased contractility.

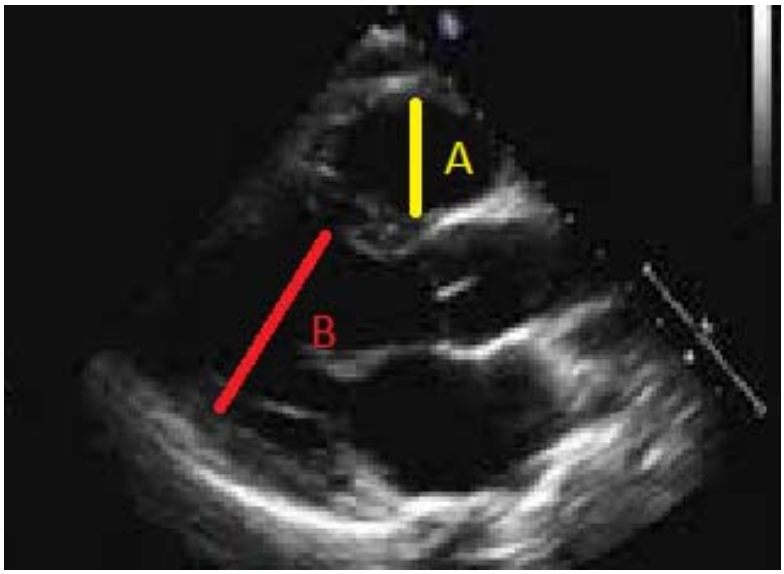
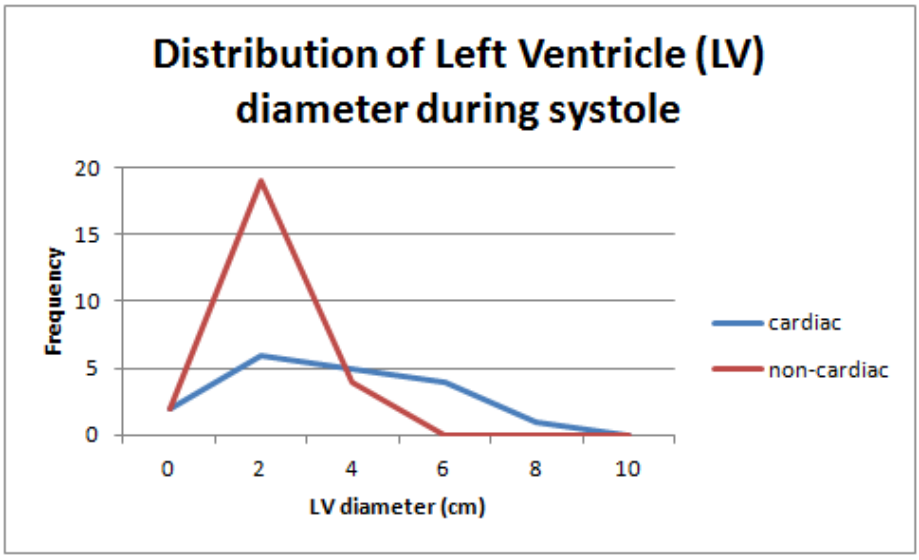


Figure 35: Distribution of left ventricle diameter during systole



The diameter of the left ventricle is measured as seen by line B in the image below. While the image below shows the heart during diastole, a similar approach is taken to measure when the diameter is smallest (systole). Increased left ventricular diameter correlates with decreased contractility.

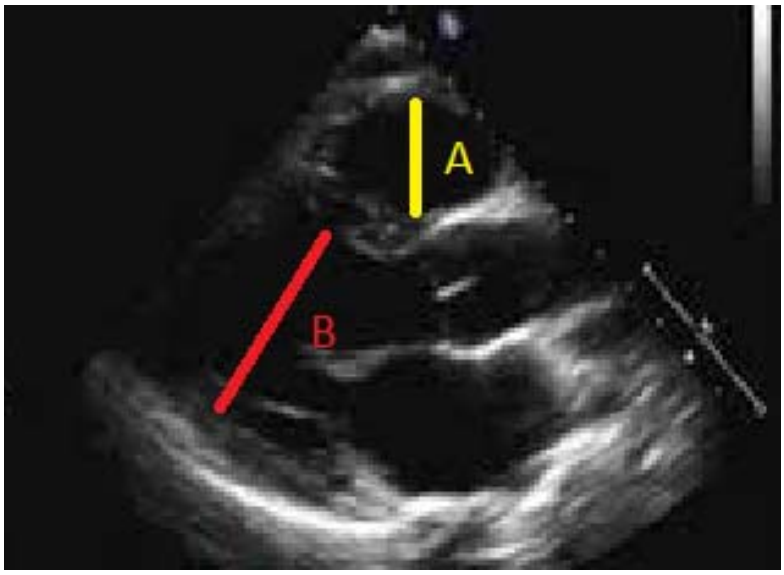
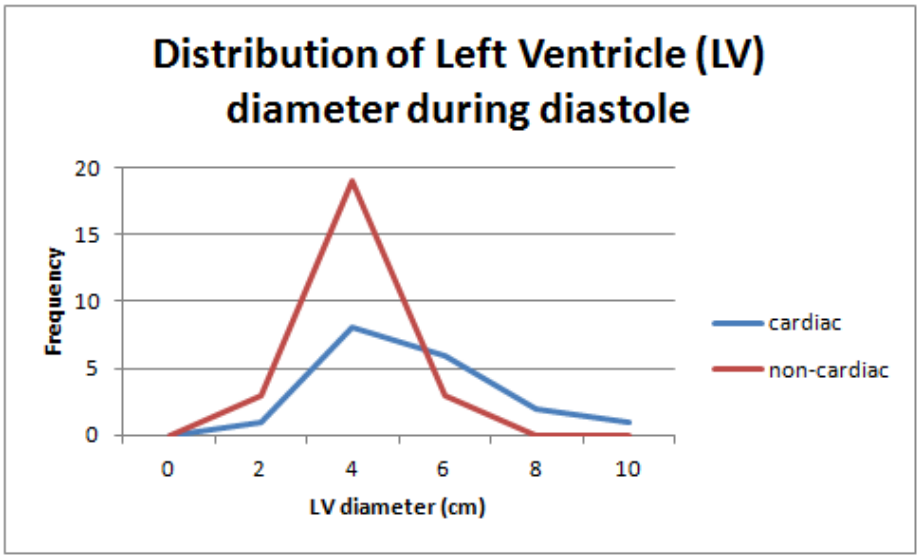


Figure 36: Distribution of left ventricle diameter during diastole



The diameter of the left ventricle during diastole is measured as seen by line B in the image below. Increased left ventricular diameter correlates with decreased contractility.

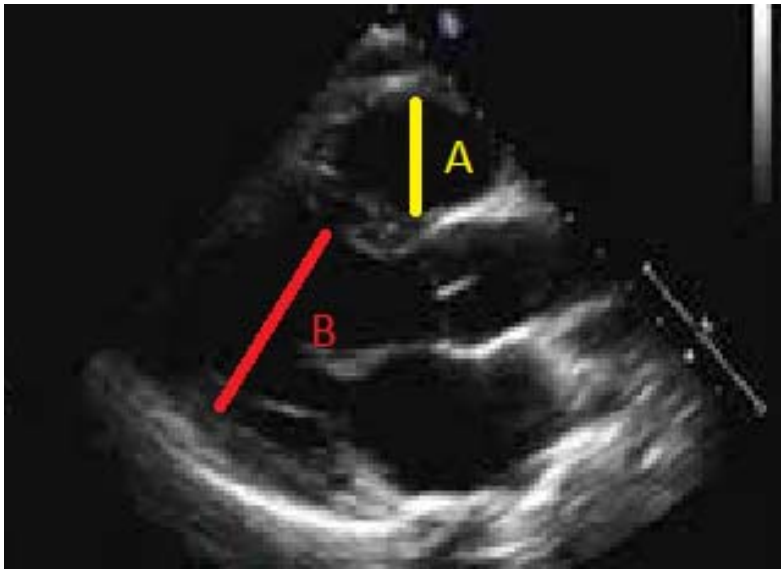
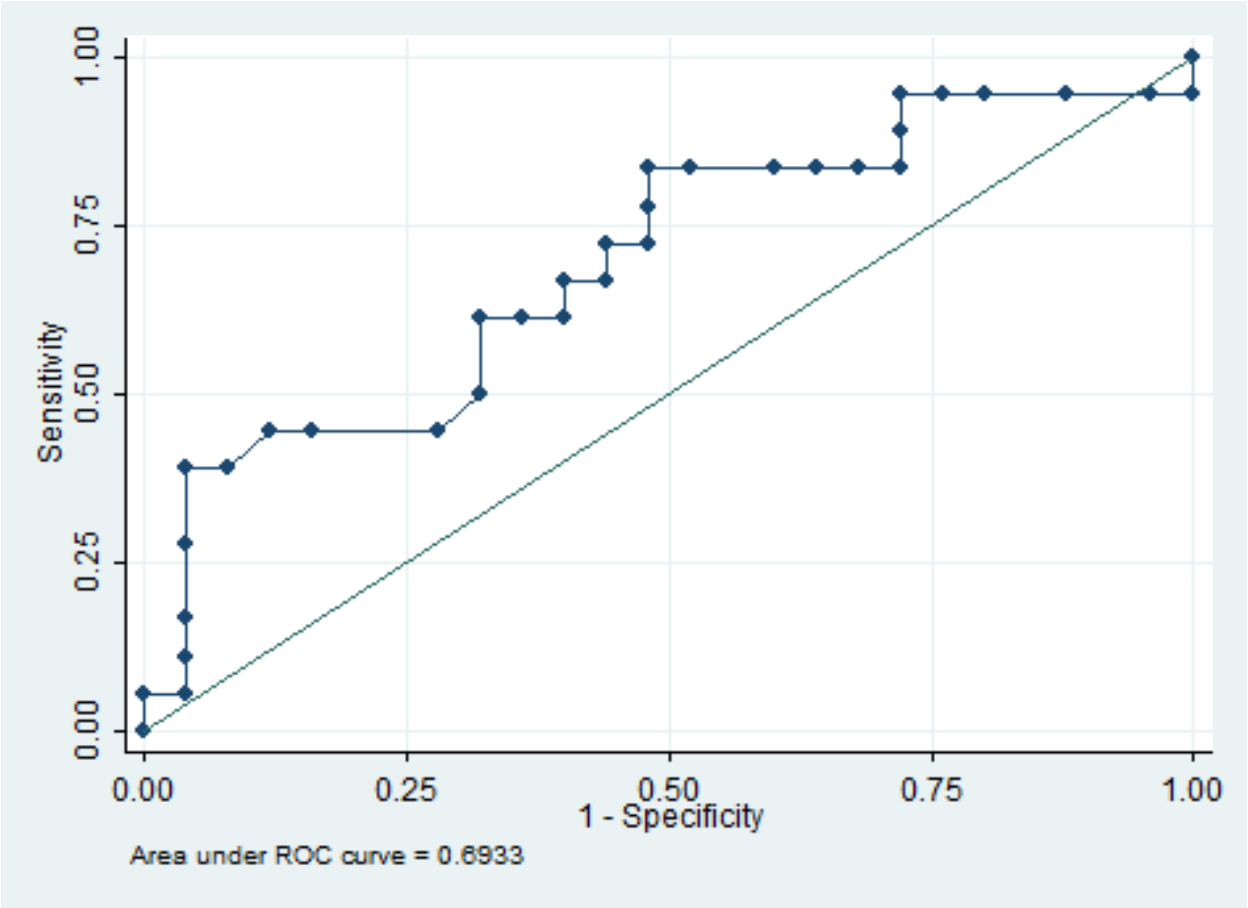


Table 37: Summary of significant ultrasound parameters

Parameter	Cardiac (n=18)	Non-cardiac (n=25)	P value
Maximal Inferior Vena Cava diameter* (cm)	1.76 ± 0.57 Median 1.70	1.41 ± 0.42 Median 1.26	0.037
Right Ventricle diameter during systole* (cm)	2.30 ± 1.07 Median 2.03	1.46 ± 0.65 Median 1.52	0.007
Right Ventricle diameter during diastole* (cm)	3.43 ± 1.07 Median 3.16	2.66 ± 0.88 Median 2.57	0.018
Left Ventricle diameter during systole* (cm)	2.95 ± 2.19 Median 2.58	1.42 ± 0.98 Median 1.27	0.011
Left Ventricle diameter during diastole* (cm)	4.30 ± 1.84 Median 4.10	3.00 ± 0.92 Median 2.89	0.011

* mean ± 1 standard deviation

Figure 38: ROC curve maximal inferior vena cava (IVC) diameter



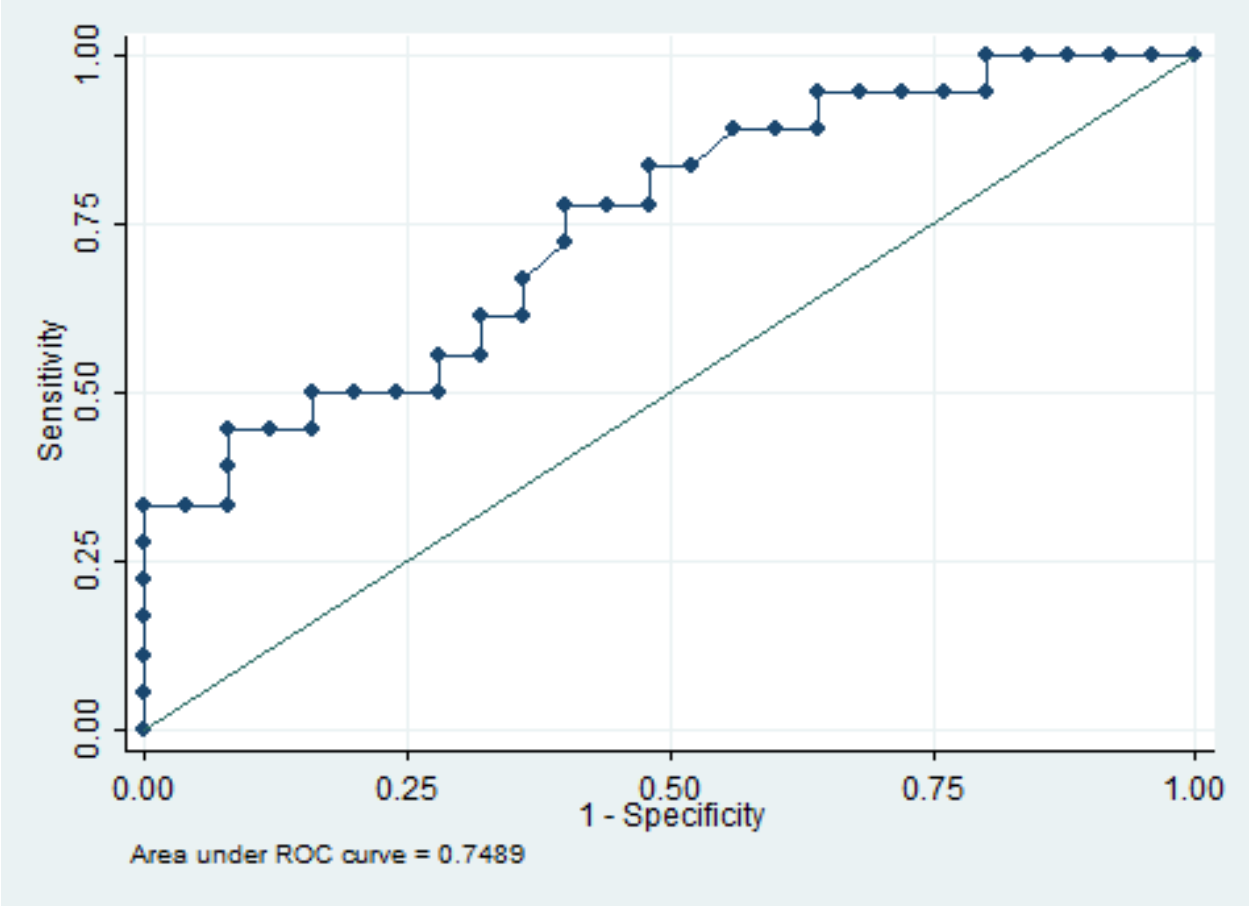
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Maximal IVC diameter	1.68 cm	61.11	68.00	1.9097	0.5719	0.6933	0.53875 - 0.82818

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 39: ROC curve right ventricle (RV) systolic diameter



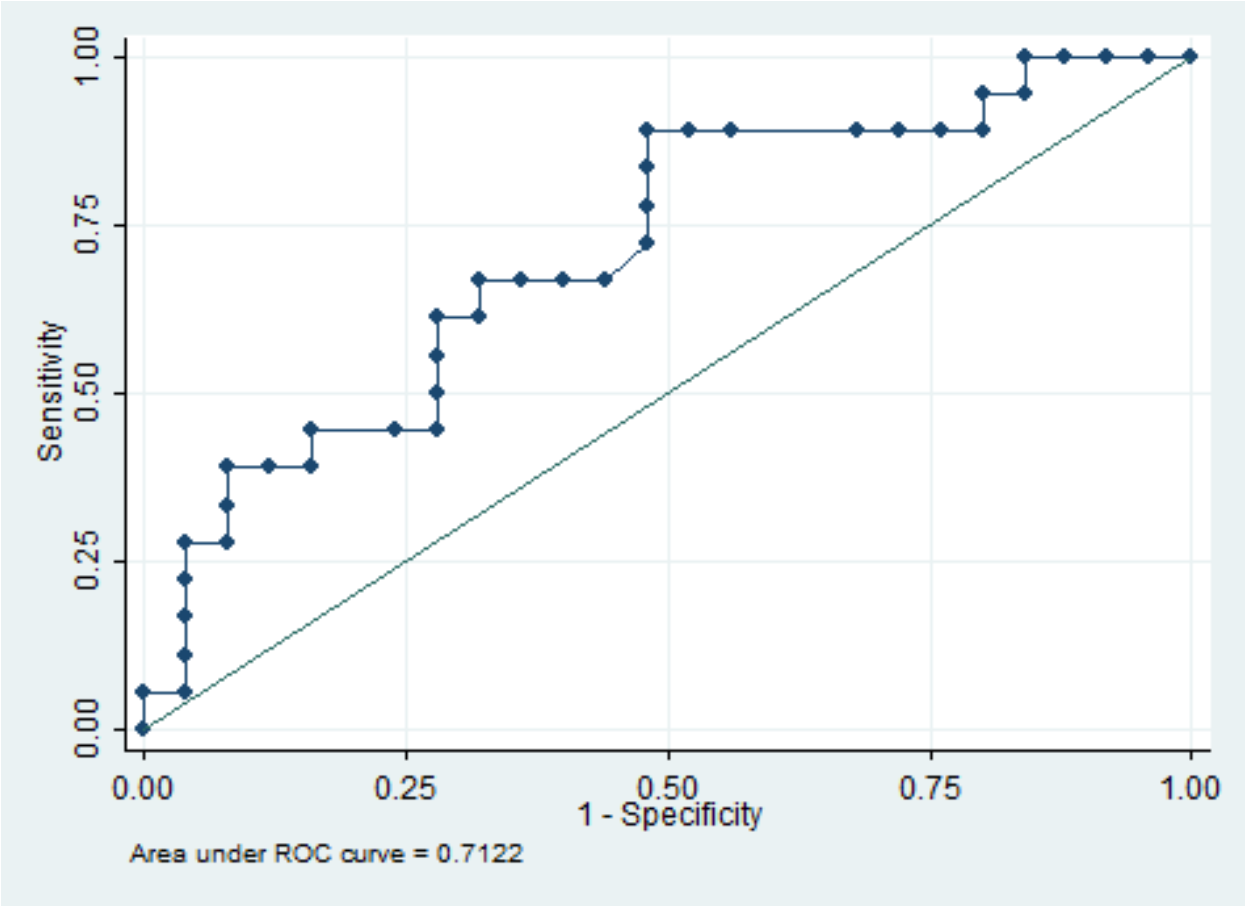
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
RV systolic diameter	1.71 cm	77.78	60.00	1.9444	0.3704	0.7489	0.58828 - 0.86481

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 40: ROC curve right ventricle (RV) diastolic diameter



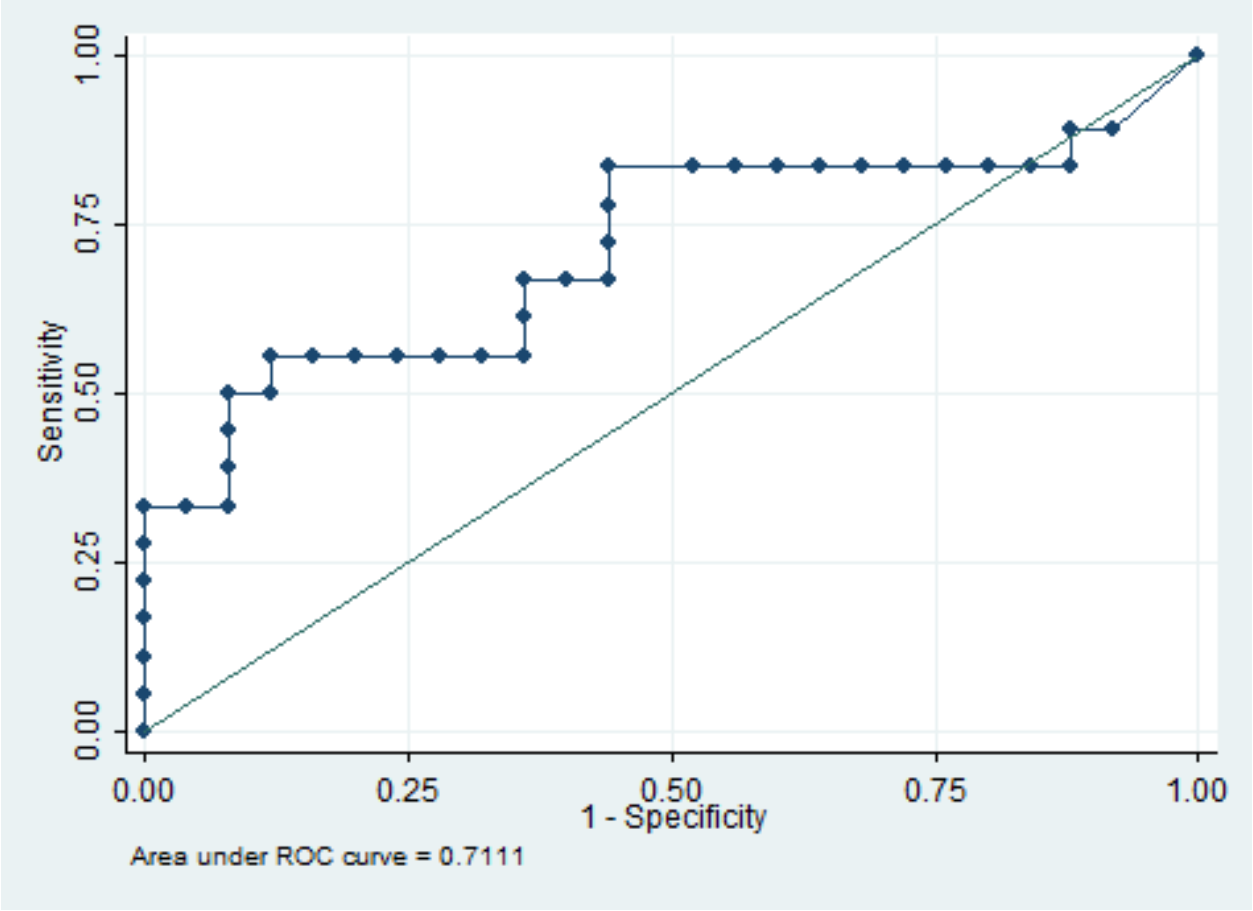
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
RV diastolic diameter	3.07 cm	66.67	68.00	2.0833	0.4902	0.7122	0.56331 - 0.84671

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 41: ROC curve left ventricle (LV) systolic diameter



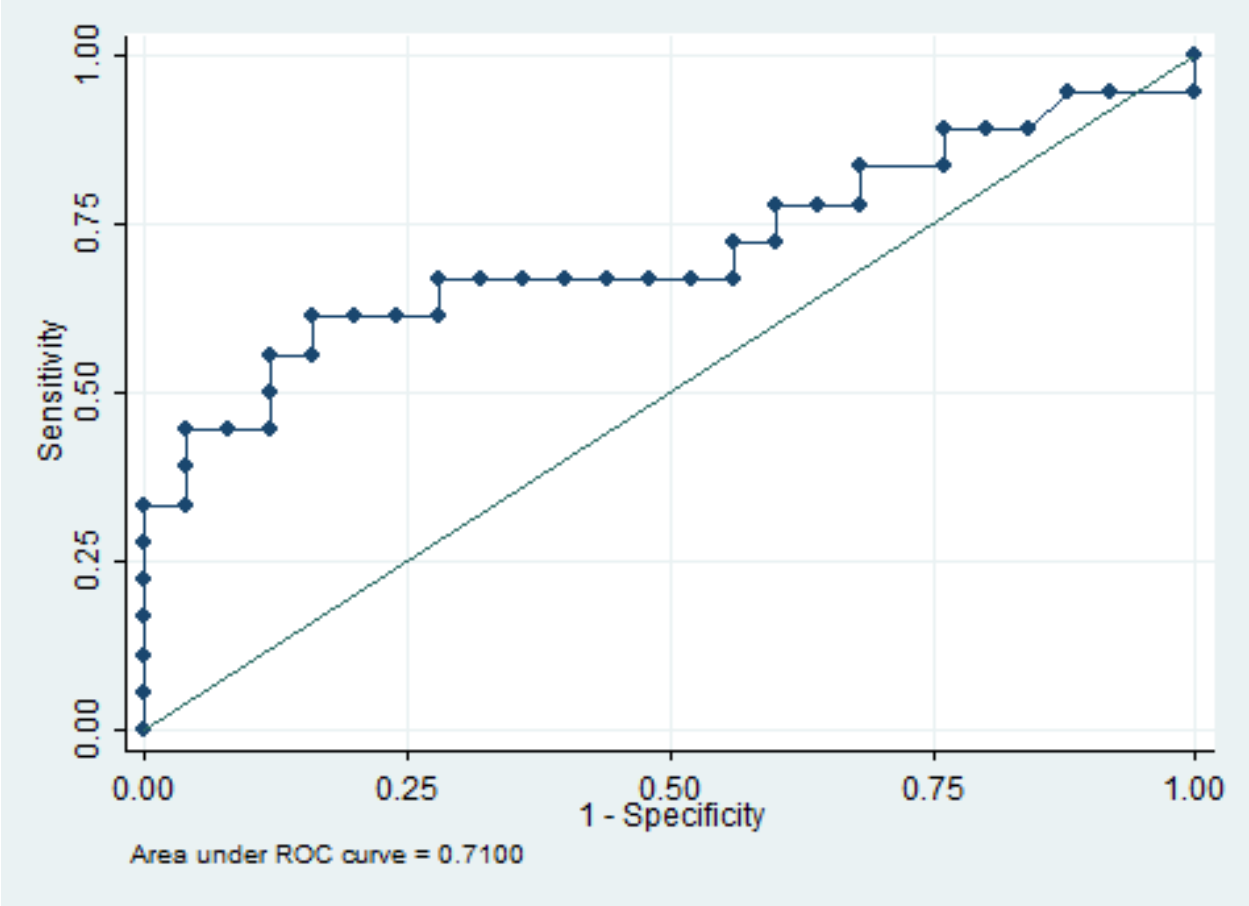
Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
LV systolic diameter	1.64 cm	66.67	64.00	1.8519	0.5208	0.7111	0.56331 - 0.84671

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Figure 42: ROC curve left ventricle (LV) diastolic diameter



Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
LV diastolic diameter	3.34 cm	66.67	72.00	2.3810	0.4630	0.7100	0.56331 - 0.84671

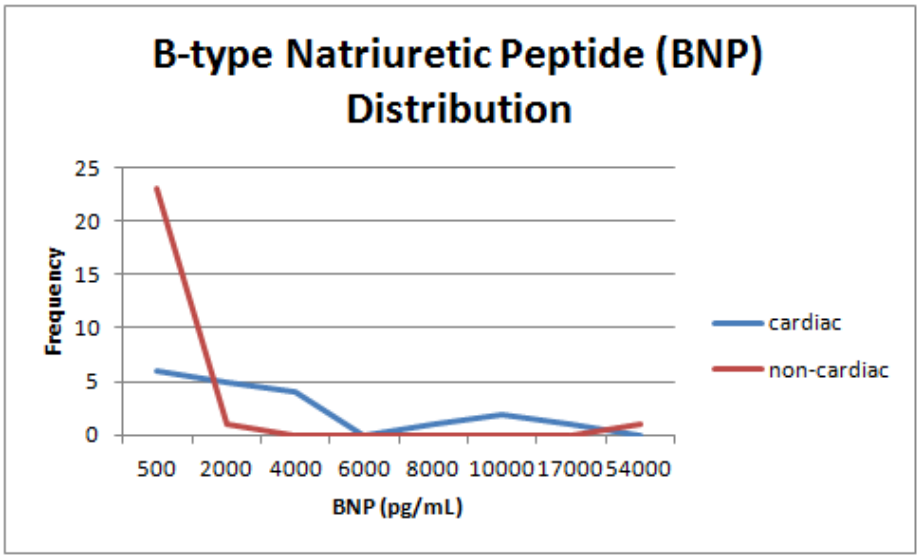
* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

Initially no significant differences were noted between BNP values for cardiac and non-cardiac patients. However, after removing one outlier from the non-cardiac group, significant differences were noted between the cardiac and non-cardiac patients. An ROC curve was created for BNP to establish a diagnostic threshold which was found to be 164 pg/mL with an AUC of 0.8684. See figures 43-45.

Figure 43: B-type natriuretic peptide distribution



BNP is peptide secreted by the ventricles when chronically overstretched, elevated BNP levels are correlated with congestive heart failure.

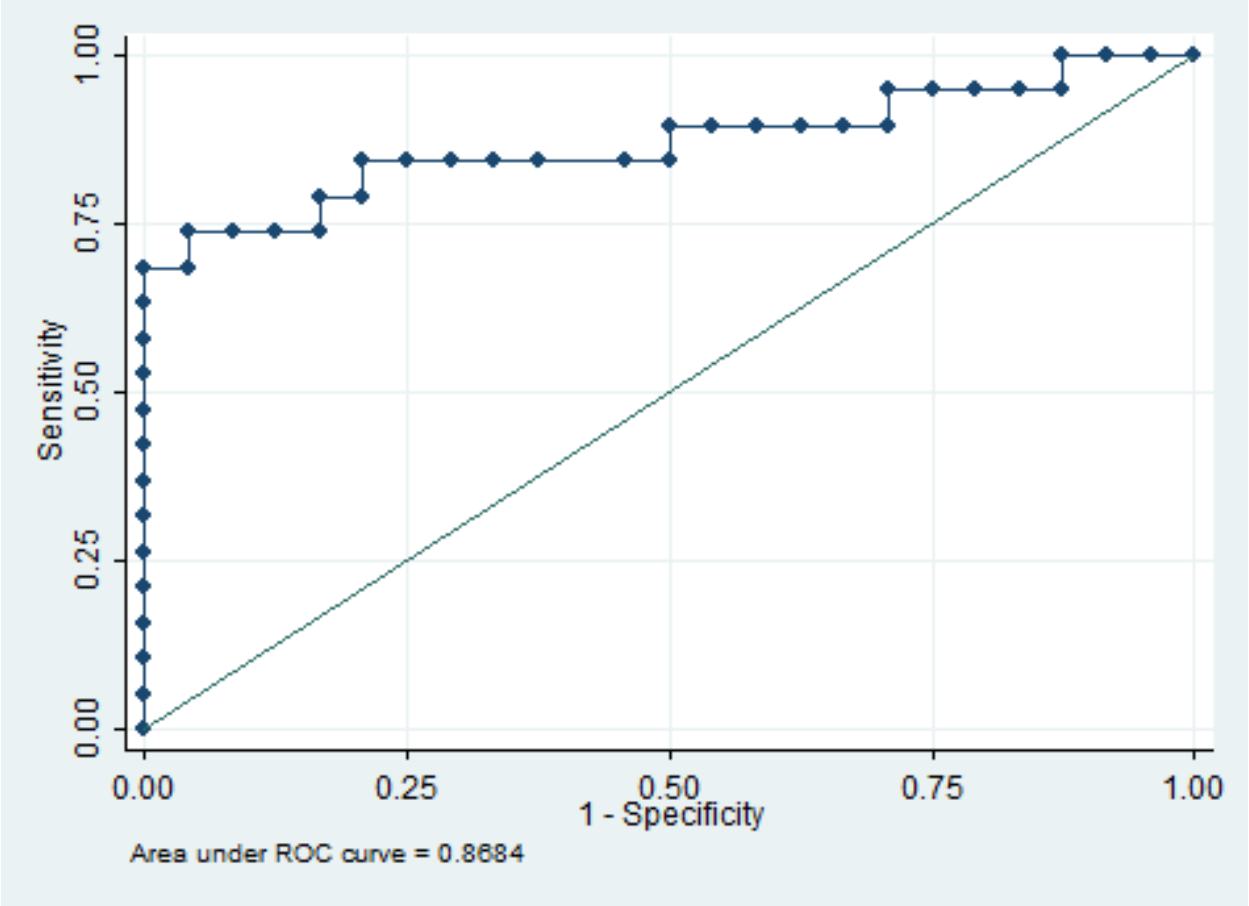
Table 44: Summary of significance of BNP with and without outlier

Parameter	**Cardiac (n=19)**	**Non-cardiac (n=25)**	**P value**
B-type natriuretic peptide* (pg/mL)	3129 ± 4447 Median 1150	2275 ± 10735 Median 85	0.722
Parameter	**Cardiac (n=19)**	**Non-cardiac (n=24)**	**P value**
B-type natriuretic peptide* (pg/mL)	3129 ± 4447 Median 1150	128 ± 135 Median 79	0.008

* mean ± 1 standard deviation

The outlier in this data set likely represented a patient with a history of congestive heart failure, but who presented to the emergency department for a respiratory issue such as pneumonia or chronic obstructive pulmonary disease exacerbation thus he would have an extremely elevated BNP (14,000+) but classified as non-cardiac.

Figure 45: ROC curve for BNP without outlier



Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
B-type natriuretic peptide	164 pg/mL	84.21	79.17	4.0421	0.1994	0.8684	0.72068 - 0.94702

* Positive Likelihood ratio

**Negative Likelihood ratio

***Area under the curve

After comparing all AUC's from the various modalities it was found that BNP had the greatest AUC and was therefore determined to be the most accurate of the three modalities utilized in this study at distinguishing cardiac from non-cardiac etiologies of dyspnea in patients presenting to the ED. See figure 46.

Table 46: Summary of ROC curves

Parameter	Threshold	Sensitivity (%)	Specificity (%)	+LR*	-LR**	AUC***	95% Confidence Interval
Cardiac index	2.7 $L/min/m^2$	72.41	65.00	2.0690	0.4244	0.7172	0.56737 - 0.83416
Velocity index	29 $1/1000/sec^2$	79.31	55.00	1.7625	0.3762	0.7534	0.61130 – 0.86657
acceleration index	45 $1/100/sec^2$	68.97	60.00	1.7241	0.5172	0.6733	0.52460 - 0.80051
Heather index	9.2 Ohm/sec^2	72.41	85.00	4.8276	0.3245	0.8405	0.70343 – 0.92678
left cardiac work index	3.1 $kg \times m/m^2$	65.52	60.00	1.6379	0.5747	0.6569	0.50361 – 0.78328
Systemic vascular resistance index	2760 dyne x sec x cm^{-5}/m^2	70.00	72.41	2.5375	0.4143	0.7224	0.56737 - 0.83416
Systemic vascular resistance	1577 dyne x sec x cm^{-5}	60.00	82.76	3.4800	0.4833	0.6810	0.52460 - 0.80051
Maximal inferior vena cava diameter	1.68 cm	61.11	68.00	1.9097	0.5719	0.6933	0.53875 - 0.82818
Right ventricle systolic diameter	1.71 cm	77.78	60.00	1.9444	0.3704	0.7489	0.58828 - 0.86481

Right ventricle diastolic diameter	3.07 cm	66.67	68.00	2.0833	0.4902	0.7122	0.56331 - 0.84671
Left ventricle systolic diameter	1.64 cm	66.67	64.00	1.8519	0.5208	0.7111	0.56331 - 0.84671
Left ventricle diastolic diameter	3.34 cm	66.67	72.00	2.3810	0.4630	0.7100	0.56331 - 0.84671
BNP	164 pg/mL	84.21	79.17	4.0421	0.1994	0.8684	0.72068 - 0.94702

Discussion:

From the results, we see that patients presenting with cardiac causes of dyspnea tended to be older compared to the non-cardiac group. By sorting the groups according to sex we see that the males in both groups were approximately the same age, with mean ages of 58.8 and 57.9 years in the cardiac and non-cardiac groups respectively. However, the females between groups showed a dramatic difference in mean age of 62.8 and 46.8 years for the cardiac and non-cardiac groups respectively. Perhaps this large age gap between the groups could be attributed to the effects of estrogen on cholesterol. Estrogen is cardioprotective in that it lowers LDL and raises HDL cholesterol in premenopausal women. The average age of menopause in the US is 51 years old, thus postmenopausal women in their 60's would be a decade removed from the protective effects of estrogen on the heart and therefore would be more likely to have a cardiac cause of dyspnea compared to their younger premenopausal counterparts in the non-cardiac group. Thus, when a patient presents to the ED with dyspnea, we may begin to utilize heuristic shortcuts to identifying the etiology based on the patient's age and sex. If it is a female in her 60's we would be more likely to suspect a cardiac etiology compared to a female in her 40's. However, in male patients, age does not help with pre-test probabilities of distinguishing a cardiac versus non-cardiac reason for dyspnea.

With regards to the ICG data collected, we began to see trends emerge as to which parameters may be useful in distinguishing cardiac from non-cardiac causes of dyspnea. HI, VI, CI and SVRI appeared to be the most promising; however, any conclusions must be tempered by the fact that the 95% confidence intervals were wide secondary to our small sample size. Our intention was to enroll 97 patients in this study, but patient enrollment had to be curtailed when the loan time expired on the ICG machine used in this study. The most promising ICG parameter from our research was HI. Using a threshold of 9.2 Ohm/sec/m^2 we achieved a sensitivity of 72% and a specificity of 85% with an AUC of 0.8405. Unfortunately this parameter has not been well established as I did not come across it in any other studies and there were no reference ranges for HI provided in the BioZ manual, where it was only described as a contractility indicator with a decreased value corresponding to decreased LV function.

Comparing our results to other studies which often found CI to be a good indicator, our experimental threshold of 2.7 L/min/m^2 for CI fell within the range of values used as thresholds in other studies. While the sensitivity and specificity were comparable to other studies that utilized the same gold standard, they were slightly lower in our results. Vorwerk,[10] with a comparable sample size of 51 patients, found a CI threshold of 3.2 L/min/m^2 had a sensitivity of 86.7% and a specificity of 88.9% with an AUC of 0.906, indicating a greater accuracy than obtained in our study. Of note, the male to female ratio was about the same; however, the mean age of patients in the Vorwerk study, 72.6 and 60.3 years in the cardiac and non-cardiac groups, were much higher than in our population. An older population could potentially have a more dramatic difference in cardiac function between the cardiac and non-cardiac groups than our younger sample. Springfield[7] did a similar study involving 38 ED patients with a similar ratio of male to female patients. However, that study also involved older patients with a mean age of 67.2 years compared to our 55.1 years. Using a CI threshold of 2.4 L/min/m^2 the Springfield study had a sensitivity of 92% and a specificity of 88%. Of note though, this study relied on an additional criteria in determining sensitivity and specificity. Besides the CI threshold of 2.4 L/min/m^2, patients with an STRI of >0.55 and a CI of <3.0 L/min/m^2 were also included in the cardiac group to yield the above mentioned sensitivity and specificity which may have enhanced the results. Again, that study achieved sensitivity and specificity values that were better than those obtained in this study. Whether these differences between studies can be attributed to age or random variation within a population would require larger sample sizes with subgroup analysis by age.

One of the objectives of this study was to determine if sex played a role in establishing diagnostic thresholds for ICG parameters. From the subgroup analysis of HI by sex we see that significant differences (p value of 0.004) exist between sexes in those with a non-cardiac etiology, with women averaging 5.5 Ohm/sec/m^2 higher HI than males. However, in the cardiac group no significant difference was noted in HI by sex. A possible explanation for this could be that cardiac dysfunction neutralizes any differences in hemodynamic parameters that may exist between healthy male and female hearts. To test this hypothesis healthy males and females could act as a control group to determine if HI truly varies by sex in healthy hearts and not just

as seen in our non-cardiac patients, the key being that non-cardiac patients in this study may or may not have had normal, healthy hearts. The data in our study does suggest that differences exist in HI based on sex and that establishing sex specific thresholds for distinguishing cardiac from non-cardiac etiologies improves the accuracy of the test. In our results we increased our sensitivity and specificity as well as the AUC in the female group by using a higher threshold of 10.4 Ohm/sec/m^2 and saw a decreased in sensitivity, specificity and AUC in the male population, even at the best possible threshold of 6.9 Ohm/sec/m^2. This implies that HI may be a tool for evaluating dyspnea that is more effective in females than in males. This is further substantiated by the fact that significant differences were seen between the cardiac and non-cardiac females in SI, CI, VI, ACI, and LCWI that were not seen in the male subgroups. It is therefore likely that the significant differences seen in CI, VI, ACI, and LCWI when comparing cardiac to non-cardiac without regards to sex are in large part due to the female portion of that population.

The data showed that HI, the most accurate ICG parameter, was more accurate at distinguishing cardiac from non-cardiac etiologies than the most accurate ultrasound parameter, which was RV systolic diameter. This is evidenced by the higher AUC of 0.8405 seen with HI compared to the AUC of 0.7489 AUC seen with RV systolic diameter. Part of the greater accuracy seen with ICG can likely be attributed to the greater technical challenges and inter-operator differences when using ultrasound to evaluate a patient. The ability to visualize the necessary structures on ultrasound is dependent not only on the skill of the operator, but also the body habitus of the patient. Conversely, ICG data collection requires minimal to no technical proficiency and is not affected by body habitus as shown by Brown.[14] Bedside cardiothoracic ultrasound, while being more technically challenging, is advantageous because of its versatility. With bedside ultrasound you have the ability to evaluate for pneumothorax, pulmonary edema, and pleural or pericardial effusions when evaluating patients with dyspnea in addition to obtaining an estimation of heart function. Actual diagnoses can be seen and made at the bedside using ultrasound, whereas numerical results are resulted and analyzed to make the final diagnosis when using ICG or BNP analysis.

When comparing ICG to BNP in this study we see that the results were very similar. The sensitivity and specificity of the best ICG parameter, HI, were 72.41% and 85% respectively with an AUC of 0.8405 while the sensitivity and specificity of BNP were 84.21% and 79.17% respectively with an AUC of 0.8684. BNP therefore was slightly more accurate based on the AUC; however, this AUC was obtained after having to remove one obvious outlier from the dataset which would have otherwise lowered the AUC to 0.8337. Seeing how similar these two tests are at distinguishing cardiac from non-cardiac causes of dyspnea, the logistics of obtaining the necessary data should be considered. BNP has the advantage of being a simple blood test that is almost universally available while ICG is more involved, as it requires a mobile device that is less common, requiring some setup time and greater patient cooperation.

Some limitations to this study, besides the aforementioned small sample size, are that it relied on retrospective chart review by ED practitioners as the gold standard for establishing the etiology as cardiac or non-cardiac. This seems to be the best method available at this time and has been commonly done in other studies as seen in a review of the literature on the topic.[7,10] However, studies[7,10,16] have shown this gold standard to only be 74-88% accurate. This poses a problem because we are establishing the accuracy of new modalities by incorporating the results of a process that is imperfect, thereby compounding inaccuracies. In this study our best markers demonstrated sensitivities and specificities in the 70's-80's which were essentially identical to the gold standard of retrospective chart review. Another factor that may have affected our study is that the BNP values were included in the patients' electronic medical records while the ICG and ultrasound data was stored separately. This may have artificially increased the accuracy of BNP in comparison to the other modalities because the practitioners performing the chart review could have been biased by the BNP value in determining if the etiology was cardiac or non-cardiac. If the BNP values weighed heavily in the classification of patients into cardiac or non-cardiac groups during the chart review then that would in essence be affecting the gold standard to which BNP would later be compared. If the gold standard did rely heavily on BNP that would cause the sensitivity and specificity of BNP to be artificially elevated.

Another confounding factor in our study was provider experience. Because accurate cardiothoracic ultrasonography requires significant skill and training, some of the results of the cardiothoracic scans performed could have been affected by the operators' skill level and expertise. All practitioners had undergone formal didactic and hands-on ultrasound training, but the number of scans completed and proficiency varied between those performing the scans for this study. In an effort to reduce intra-observer and provider variability, future studies would benefit by having one sonographer or practitioner dedicated to obtaining the ultrasound results for all patients enrolled.

Future Directions:

Some of the patients in this study population were evaluated with formal echocardiography. Using this same data set, comparisons could be made between bedside cardiac ultrasound measurements and formal echocardiography measurements to evaluate the accuracy and utility of bedside cardiac ultrasound. Another interesting study would be to determine how well the cardiac output as determined by ICG correlates with formal echocardiography as well as E point septal separation (EPSS). Studies have shown that EPSS correlates with cardiac output as determined by formal echocardiography, so it would be interesting to see how ICG estimates of cardiac output compare. As mentioned in the discussion, the role of sex on ICG values could be further clarified by obtaining control data from a sample of healthy male and females.

Conclusion:

This study showed that noninvasive testing such as ICG, bedside ultrasound or BNP can be an effective means of evaluating patients presenting to the ED with dyspnea. In determining a cardiac versus non-cardiac etiology of dyspnea, all three of these modalities demonstrated sensitivities and specificities that were comparable to the gold standard of clinical judgment. While ultrasound is a very versatile technology, it is the most technically challenging and yielded the lowest accuracy of the three methods being evaluated. ICG and BNP were very similar in accuracy, with BNP having the advantage of being more universally available and requiring no specialized equipment in the ED. In patients who require an immediate evaluation of their dyspnea at the bedside, cardiothoracic ultrasound or ICG analysis can be utilized to guide immediate resuscitation or treatment options. Both modalities provide faster results than waiting for BNP levels to be drawn and resulted. There are benefits to utilizing each of the three modalities evaluated in this study, and the extent and timing of their use should be dictated by the patient's condition and clinical presentation.

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