Dr. N. Nanda

Emeritus Editor-in-Chief

Echocardiography: A Journal of Cardiovascular Ultrasound and Allied Techniques

Dear Dr. Nanda,

Please consider our manuscript, entitled "Association of Left and Right Atrial Volume Indices with Outcome and Survival Time post-Cardiac Arrest" for possible publication in the *Echocardiography: A Journal of Cardiovascular Ultrasound and Allied Techniques*. The utility of the TTE measurements, LAVI and RAVI, have been explored in multiple instances including cardiogenic shock, pulmonary hypertension, atrial fibrillation, and myocardial infarction. Cardiac arrest is prominent topic of research in the field of cardiology and there has been significant interest in determining any markers or circumstances to help predict mortality and survival time if an arrest were to occur or if ROSC were to be achieved. While left atrial diameter has been a topic of discussion in relation to outcomes post-cardiac arrest, the research investigating the prognostic impact of left and right atrial volume indices in relation to cardiac arrest events has been lacking. This original manuscript discusses novel parameters using two-dimensional Doppler echocardiography that are associated with survival time post-cardiac arrest in hospitalized patients.

Regarding authorship, each of the co-authors contributed in a substantial and meaningful way to the creation of this manuscript. Sami Ibrahim, Matthew Miller, Olivia Blazek, Jarred Strickling, Robert Wharton, Paras Patel, and Comfort Elumogo participated in data collection, interpretation, and analysis, drafting and revision of the manuscript, and approval of the finalized version. Kenneth Bilchick participated in data interpretation and analysis. Sula Mazimba and Kenneth Bilchick critically reviewed the manuscript. Sula Mazimba participated in conception and design, revision of content, and final approval.

The attached manuscript constitutes an original article, has not been published, and is not being considered for publication elsewhere, in whole or in part, in any language. All authors have participated in the creation of this manuscript, and approve of its publication. We ensure complete accountability for this work should questions arise regarding its accuracy or integrity. There exists no conflict of interest from any of the co-authors. I thank you for your time to review this manuscript and look forward to any comments/constructive feedback from you all.

Sincerely,

Sami Ibrahim, MD

Increased Left and Right Atrial Volume Indices are Associated with Decreased Survival Times post-Cardiac Arrest

Sami H. Ibrahim, MD[1], Matthew S. Miller, MD[1], Olivia J. Blazek, MD[1], Jarred E. Strickling, MD[1], Comfort Elumogo, MD[1], Robert C. Wharton, MS4[1], Paras Patel, MD[2], Kenneth C. Bilchick, MD[2], Sula Mazimba, MD, MPH[2]

[1]Department of Medicine, University of Virginia Health System, Charlottesville, Virginia.

[2]Division of Cardiovascular Medicine, University of Virginia Health System, Charlottesville, Virginia.

Sami H. Ibrahim - shi5vs@virginia.edu, Matthew S. Miller – msm3rb@viriginia.edu, Olivia J. Blazek – ojb8k@virginia.edu, Jarred E. Strickling – js9yp@virginia.edu, Comfort Elumogo – coe9r@virginia.edu, Robert C. Wharton – rcw4bc@hscmail.mcc.virginia.edu, Paras Patel - PRP3A@hscmail.mcc.virginia.edu, Kenneth C. Bilchick – kcb7@virginia.edu, Sula Mazimba – sm8sd@virginia.edu

Address for Correspondence
Sula Mazimba, MD. MPH

Assistant Professor
University of Virginia
Cardiovascular Medicine
PO Box 800158
Charlottesville, VA 22908-0158
Phone: 434-982-4247
Sm8sd@hscmail.mcc.virginia.edu

Increased Left and Right Atrial Volume Indices are Associated with Decreased Survival Times post-Cardiac Arrest

Objectives: To investigate the clinical significance of left and right atrial volume indices in hospitalized post-cardiac arrest patients

Introduction: Left and right atrial volume indices (LAVI and RAVI) are markers of cardiac remodeling. LAVI and RAVI are associated with worse outcomes in other cardiac conditions. This study aimed to determine the association of LAVI and RAVI with survival time post-cardiac arrest.

Hypothesis: Atrial volumes will be associated with survival time post cardiac arrest.

Methods: This was a single academic center, retrospective study of patients with a cardiac arrest event during index hospitalization from 2014-2018. LAVI was calculated using a biplane Simpson's method, while RAVI was calculated using a single plane summation in the 4-chamber view. Patients were further stratified into either having a Vfib/pulseless VT (pVT) event or a PEA arrest/asystole event. Survival time was measured in days from event to death date. Kaplan-Meier plots were used to evaluate differences in survival time for patients based on mean LAVI and RAVI.

Results: Of 305 patients studied (64 +/- 14 years, 37% female (112 out of 305)), 162 had a reliable LAVI measurement with a mean of 34.1 mL/m2 (SD=15.8) and163 had a reliable RAVI measurement with a mean of 25.1 mL/m2 (SD=15.5). In patients who had sustained VFib/pVT, those with reduced LAVI (p=0.045) and RAVI (p=0.041) values below the mean had significantly improved survival time. No association was found in PEA/asystole. KM plots of patient survival for both LAVI and RAVI compared to mean are presented in figures 1a and 1b.

Conclusion: Among patients presenting with a Vifb/pVT arrest, increased LAVI and RAVI were associated with decreased survival time.

Key Words: Cardiac arrest, Left atrial volume index, Right atrial volume index, Outcomes, Survival Time, Ventricular fibrillation

Condensed abstract:
In patients who were post-Vfib/pVT arrest, increasing LAVI and RAVI values are associated with decreased survival time. These findings highlight the utility of using LAVI and RAVI as prognostic markers for those presenting with shockable rhythms, such as ventricular fibrillation/pulseless ventricular tachycardia, as well as their role in identifying the underlying pathophysiology that may increase mortality after achieving ROSC.

Abbreviations:

EF – Ejection Fraction

GLS – Global Longitudinal Strain

HF – Heart Failure

LA – Left atrium

LAD – Left Atrial Diameter

LAVI – Left Atrial Volume Index

LVEF – Left Ventricular Ejection Fraction

MI – Myocardial infarction

PEA – Pulseless Electrical Activity

pVT – Pulseless Ventricular Tachycardia

RA – Right atrium

RAVI – Right Atrial Volume Index

ROSC – Return of Spontaneous Circulation

RV – Right ventricle

TTE – Transthoracic Echocardiography

Vfib – Ventricular Fibrillation

Introduction:

Left and right atrial volume indices (LAVI and RAVI), measurements calculated on transthoracic echocardiography (TTE), are indicators of cardiac remodeling from a variety of pathologic etiologies [1]. Historically, atrial diameters were more frequently studied than volume indices. Left atrial diameter (LAD) in particular has been studied in the context of multiple disease states with close correlations to poor outcomes [2]. Specifically, increases in left atrial diameter have been associated with an increased incidence of atrial fibrillation [3], stroke [4], and myocardial infarctions [5]. The LAD was applied enough to help shape certain guidelines for practicing physicians up until 2005 [6]. However, it became apparent that the asymmetry of left atrial dilation causes an inaccurate estimation of true atrial size when only measuring the LAD [7]. This led to the emergence of the LAVI as a more accurate predictor of true atrial size, reflected in more recent guidelines from the American Society of Echocardiography which recommend the use of left atrial volumes in clinical practice [6]. Over the last decade the LAVI has continued to show associations (generally with higher sensitivity than those of the LAD) with a broad array of outcomes including all-cause mortality [8], atrial fibrillation and cardioembolic stroke [9], and morbidity and mortality in heart failure with preserved ejection fraction [10].

Historically, the RAVI has received limited attention due to the technical difficulties in its assessment. However, advances in echocardiography have led to enhanced utility as measurements have become more accurate [11]. For example, the RAVI has been shown to be an independent predictor of adverse events in heart failure with reduced ejection fraction [12], [13], and an increased RAVI to LAVI ratio has been associated with decreased survival in pulmonary hypertension patients [14].

Several echocardiographic variables have shown associations with cardiac arrest. Left ventricular ejection fraction [15], left ventricular hypertrophy [16], mitral annular calcification, and more relevant to the present study, left atrial diameter, have all been shown to have associations with sudden cardiac death [17]. Current indications for ICD placement revolve heavily around left ventricular ejection fraction [18], but there is data to suggest that as many as half of patients who experience out of hospital cardiac arrest have an ejection fraction greater than 50% [19]. This emphasizes the importance of identifying additional risk factors that may predict not only the incidence of cardiac arrest, but also predict poor outcomes and decreased survival time following a cardiac arrest event. With left atrial diameter previously shown to have association with sudden cardiac death and having data to support the LAVI as a more accurate and sensitive predictor of adverse cardiac events in general, LAVI should be explored as a risk factor for poorer outcomes following cardiac arrest. Further, RAVI has also emerged as a useful predictor of poor outcomes in multiple cardiac conditions. In this sense, the association of RAVI with survival following cardiac arrest warrant further exploration given the central role of 2-dimensional transthoracic echocardiography (TTE) as a first line diagnostic imaging of choice in critically ill patient. We hypothesized that increased LAVI and RAVI would be associated with both decreased rates of successful cardiac resuscitation following arrest, as well as with decreased survival time following resuscitation.

Methods:

Study Design and Patient Cohort

We retrospectively identified 305 consecutive patients who experienced a cardiac arrest during hospitalization at University of Virginia Health System between 2014 and 2018. Baseline patient demographics and clinical follow-up data were abstracted and analyzed retrospectively from the electronic medical records system. Clinical characteristics of patients included demographics, comorbid conditions, hospital length of stay, TTE, etiology of cardiac arrest, and date of death. Patients were included in the study only if they had a TTE with adequate images for the calculation of LAVI/RAVI within the 12 months of presentation. Patients with cardiac arrest were stratified into shockable rhythms (defined as pulseless ventricular tachycardia or ventricular fibrillation) versus unshockable rhythms (defined as asystole or PEA). The primary outcome was all cause mortality. Survival time was measured in days and calculated by subtracting the date of death from the date of event. This retrospective analysis of clinically acquired data was approved by the institutional review board of the University of Virginia, and consent was waived due to the retrospective nature of the study.

Echocardiography

All patients included in the study underwent 2D TTE within one year prior to cardiac arrest. Images were obtained by experienced echosonographers utilizing standard echocardiographic views: parasternal, apical, and subcostal. By using both the 4- and 2- chamber views LAVI was calculated with the biplanar Simpson method. RAVI was measured in the 4- chamber view using single plane disc summation. Left ventricular global longitudinal strain (LV GLS) was measured with a 2-dimensional speckle tracking analysis on apical 2-, 3-, and 4- chamber views using commercially available software. Right ventricular fractional area of change (RV FAC) was measured using apical four chamber images at end-diastolic and end-systolic cycles. All images were taken using Phillips IE33, Epiq 7CV or GE Vivid E9 ultrasound systems. Studies were analyzed and processed using Enterprise imaging (Agfa Healthcare N.V., Mortsel, Belgium). Offline echocardiographic analysis was performed by 4 investigators.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentages. Analyses of comparisons in continuous variables were performed using t tests or Wilcoxon test depending on normality. Patients were stratified by whether their cardiac arrest was due to a shockable or unshockable rhythm as described above. Analyses of differences in categorical variables between RAVI/LAVI groups were performed using Chi-square tests. Multivariable Cox proportional hazards regression and multivariable logistic regression were used to model associations of multiple independent variables of interest with survival following cardiac arrest. Univariate and multivariate logistic regressions were used to evaluate the associations of RAVI, LAVI, left ventricular ejection (LVEF), and left ventricular global longitudinal strain (GLS) with survival. Kaplan-Meier plots were then used to evaluate the differences in survival time for patients with LAVI and RAVI measurements above and below each of their respective mean values. Bland-Altman plots were used to assess the intra-observer agreeability for the RAVI and LAVI measurements. An alpha value of < 0.05 was used for statistical significance. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

Results:

Baseline characteristics

Our data set included 305 patients with 162 (53.1%) of those having reliable LAVI measurements and 163 (53.4%) of those having reliable RAVI measurements. The baseline characteristics of these patients are shown in table 1a and table 1b and are stratified into LAVI and RAVI measurements above and below their respective mean values. Table 1a shows the baseline characteristics of those with reliable LAVI measurements stratified into above and below their measured mean value. Patients with LAVI above the mean were more likely to have congestive heart failure, atrial flutter/fibrillation, chronic kidney disease and pulmonary hypertension. Table 1b shows the baseline characteristics of those with reliable RAVI measurements stratified into above and below their measured mean value. Patients with RAVI above the mean were similarly more likely to have congestive heart failure, atrial flutter/fibrillation, chronic kidney disease and pulmonary hypertension.

Association of LAVI with clinical outcomes

In our data set, 162 patients had adequate acoustic windows to accurately calculate the LAVI. The mean LAVI was 34.1 mL/m^2 with a standard deviation of 15.8mL/m^2. Based on the Cox proportional hazard regression (CPH) model, LAVI did not modify the survival time when looking at all event types (LAVI+any arrest, p=NS). However, LAVI had a statistically significant association with all cause mortality in patients who experienced Vfib/pVT (N=55) in hospital as demonstrated in Table 2 (p=0.0449 and HR=1.024). The relationship between LAVI and survival times after a VFib/pVT event is shown in the Kaplan Meier plot in Figure 1a. Patients with a LAVI less than the mean value have better survival after VFib/pVT arrest (log-rank 5.4847, p=0.0192) compared to those with LAVI greater than the mean.

Association with RAVI and clinical outcomes

In our data set, 163 patients had usable windows to accurately calculate the RAVI. The mean RAVI was 25.1 mL/m^2 with a standard deviation of 15.5mL/m^2. Based on CPH model RAVI did not modify the survival time when looking at all event types (RAVI+any arrest, p=NS). However RAVI showed a statistically significant association with all cause mortality in patients who experienced Vfib/pVT (N=51) in hospital as demonstrated in Table 2 (p=0.0409 and HR=1.027). The relationship between RAVI and survival times after a VFib/pVT event is shown in the Kaplan Meier plot in Figure 1b. Patients with a RAVI less than the mean had a trend for better survival after VFib/pVT arrest (log-rank 2.4978, p=0.1140) compared to those with RAVI greater than the mean.

Association of Left ventricular ejection fraction /Global Longitudinal Strain and clinical outcomes

The mean LVEF of 158 patients was 38.7% (SD 17.4%). The GLS mean of 146 patients was -9.8 (SD 6.2). Based upon the CPH model demonstrated in Table 2, neither LVEF nor GLS modify the survival time after being stratified with a Vfib/pVT arrest (p= 0.4028 and 0.9191 respectively).

Intra-observer Variability Analysis:

The intra-observer variability was shown using a Bland Altman plot. The intra-class correlation coefficient for LAVI was 0.994, $p<0.001$ while for RAVI was 0.995, $p<0.001$ as shown in Figure 2a and 2b, respectively, illustrating remarkable similarities between observers for LAVI and RAVI.

Discussion:

The present study evaluated the relationship between LAVI/RAVI with survival time among patients with in-hospital cardiac arrest. We found that patients with LAVI >34mL/m^2 and RAVI > 25mL/m^2 had worse outcomes even after adjustment for key characteristics. These findings highlight the important implications of atrial structural remodeling in the risk stratification of patients with in-hospital cardiac arrest.

Prior studies have evaluated the role of LAVI and RAVI in the prognostication of patients with congestive heart failure, cardiomyopathies, myocardial infarction, pulmonary hypertension, atrial fibrillation, and valvular heart disease. To our knowledge, this is the first study evaluating the clinical implications of LAVI and RAVI as prognostic markers among in-hospital cardiac arrest [20]. These results demonstrate a significant association between left and right atrial volume indices and survival time among hospitalized patients post-Vfib/pulseless VT events. Our primary endpoint was all-cause mortality in which both increased LAVI and RAVI values were significantly associated with increased mortality. More precisely, LAVI and RAVI values above their respective mean values were shown to portend decreased survival time in this patient cohort. The impact of atrial volume indices on survival was significant regardless of the type of primary etiology of the cardiac arrest (PEA/asystole vs. Vfib/pulseless VT), What is intriguing is the fact that LAVI and RAVI play an even greater role in predicting the survival time and clinical outcome of post-Vfib/pulseless VT events than ejection fraction

(EF) and global longitudinal strain (GLS) do as shown in Table 2. When plotting EF and GLS values in a similar manner with the same patient cohort, there was no significant association of these parameters with survival time or mortality, despite further stratification into PEA/asystole events and Vfib/pulseless VT events. This has been demonstrated in other studies as well, where an LVEF>40% on post-arrest TTEs was not a predictor of increased survivability [21].

In-hospital cardiac arrest events have been shown to carry a high mortality rate, however, there is limited evidence in the prognostication of these patients once return of spontaneous circulation (ROSC) is achieved. Risk stratification of patients with cardiac arrest is challenging with multiple scores using multivariable parameters that may be difficult to use [22]. LAVI and RAVI are novel indices that represent atrial remodeling and pressure-volume interactions of within the heart. Elevated atrial volumes may signal a multitude of pathologies including pressure overload, volume overload, impaired compliance, and conduction abnormalities. These clinical factors in isolation or in combination may influence mortality and impair cardiac recovery after a cardiac arrest event [23]. In a recent study, patients with worsened diastolic dysfunction had an increased risk of arrhythmic death and resuscitated cardiac arrest, regardless of ejection fraction [24]. In patients with preserved ejection fraction, LAVI is a powerful barometer of the severity of left ventricular diastolic impairment and is associated with adverse outcomes [25]. Furthermore, LAVI in patients with heart failure with reduced ejection fraction also portends adverse outcomes and may be a response to multiple stimuli (mitral valve disease, arterial hypertension, and any condition increasing the LV filling pressures) [26]. RAVI, on the other hand, often reflects RA dilation and can also be a surrogate marker for RV dysfunction and RV dilation. Unlike LVEF, RV dysfunction and RV dilation are significant prognostic markers for worse outcomes and decreased survival time post-arrest compared to those with normal RV function [27]. While the RV function was measured post-arrest in those studies, it is reasonable to infer a similar predictive value in those with pre-arrest RV dysfunction as well, independent of LV systolic function. Mechanisms behind why RV dysfunction plays a greater role than LVEF in post-arrest prognostication have been postulated as well and go beyond the analytical scope of this study [27]. Furthermore, as the RA becomes stretched with dilation due to a prolonged pressure overload, this may, in fact, lead to bowing of the interatrial septum into the left atrial space and impose additional left-sided pathophysiology [14]. To summarize, LAVI and RAVI are indices measured by TTE that incorporate a number of hemodynamic variables to indicate potential pathophysiology in the pressure-volume interactions of the heart. Identifying post-arrest patients with known elevated indices and therefore significantly decreased survival time will further aid with prognostication as well as propagate potential management pathways to offset the cardiac pathophysiology at hand.

Limitations

There are several important limitations to this study, first being that this was a single-center study. Our sample size was also limited by the number of patients who had reliable echocardiographic images with adequate quality for the measurement of RA/LA volumes. 2D Echo is a widely available and useful tool for the measurement of chamber dimensions and function [28]. However, 3D Echo is considered to be more reliable than the 2D Echo, given the absence of an orthogonal plane and reliance on geometric assumptions of atrial chambers in the 2D Echo [29]. Furthermore, our study was a retrospective cohort study, which is inherently biased with misclassification as well as a potential absence of data that could reveal confounding factors. These intrinsic biases were minimized and taken into account with the analysis and discussion of our findings.

Conclusion:

LAVI and RAVI are easily assessed TTE measurements that have been utilized as prognostic markers in various cardiac disease states. In hospitalized patients who present post-Vfib/pVT cardiac arrest, increasing LAVI and RAVI values are significantly associated with decreased survival time and increased mortality. Knowing that increased LV diastolic dysfunction and RV dilation/dysfunction already play a role in the prognostication of this patient population, the increased mortality can be explained by the pathophysiology implied with these elevated indices. These findings suggest further investigation into the use of LAVI and RAVI as prognostic indicators in more heterogeneous groups at multiple centers for validation.

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Clinical Competencies: Systems-Based Practice, Practice-Based Learning

Translational Outlook: This study focuses on echocardiographic findings in patients who were hospitalized between 2014-2018 and had a cardiac arrest during their hospital course. Patients require a pre-arrest (within one year) echocardiogram. Not all patients who met these initial criteria had TTE images of good enough quality to produce reliable LAVI and RAVI values, which resulted in the exclusion of a significant number of patients. In order to include a larger cohort for future studies, it will be important to consistently capture TTE images with good quality in the 2-chamber and 4-chamber views so these indices can be measured reliably. A prospective, multi-center study would help further determine the significance of these findings.

Table 1a: LAVI Baseline Demographic and Clinical Characteristics Stratified by Mean LAVI.

Characteristics	Below LAVI mean* (n=90)	Above LAVI mean* (n=79)	p-value
Age	63 +/- 13.0	66.5 +/- 12.9	0.08
Female gender	33 (36.7)	31 (39.2)	0.73
BMI	30.3 +/- 7.4	28.3 +/- 6.2	0.07
HTN	60 (66.7)	55 (69.6)	0.68
Coronary artery disease	32 (35.6)	38 (48.1)	0.10
Congestive heart failure	40 (44.4)	63 (79.7)	<0.001
Diabetes mellitus	38 (42.2)	38 (48.1)	0.44
Atrial fibrillation/flutter	26 (28.9)	42 (53.1)	<0.001
Tobacco abuse	56 (62.2)	47 (59.5)	0.72
Pulmonary hypertension	19 (21.1)	27 (34.2)	0.06
Chronic kidney disease	29 (32.2)	42 (53.1)	0.01
COPD	20 (22.2)	19 (24.0)	0.78

Values are presented as a mean +/- standard deviation or n (%). *LAVI mean is 34.1mL/m^2.

Table 1b: RAVI Baseline Demographic and Clinical Characteristics Stratified by Mean RAVI.

Characteristics	Below RAVI mean* (n=106)	Above RAVI mean* (n=61)	p-value
Age	62.4 +/- 13.4	67.9 +/- 12.1	0.58
Female gender	41 (38.7)	21 (34.4)	1.00
BMI	29.7 +/- 6.6	28.4 +/- 6.2	0.21
HTN	69 (65.1)	46 (75.4)	0.17
Coronary artery disease	43 (40.6)	29 (47.5)	0.38
Congestive heart failure	54 (50.9)	47 (77.0)	<0.001
Diabetes mellitus	45 (42.5)	29 (47.5)	0.52
Atrial fibrillation/flutter	32 (30.2)	33 (54.1)	<0.001
Tobacco abuse	62 (58.5)	35 (57.3)	0.89
Pulmonary hypertension	23 (21.7)	25 (41.0)	0.01
Chronic kidney disease	37 (34.9)	33 (54.1)	0.02
COPD	19 (17.9)	16 (26.2)	0.20

Values are presented as a mean +/- standard deviation or n (%). *RAVI mean is 25.1mL/m^2.

Table 2: CPH model for VFib/pVT interaction with various echo parameters

Parameters	Parameter estimate ($\boldsymbol{\beta}$ coefficient)	Standard error	Chi-squared	p-value	Hazard ratio
Any arrest + RAVI (N=163)	-0.00594	0.00684	0.7541	0.3852	0.994
Any arrest + LAVI (N=162)	-0.00608	0.00724	0.7051	0.4011	0.994
Vfib/pVT + RAVI (N=51)	0.02623	0.01283	4.1815	0.0409	1.027
Vfib/pVT + LAVI (N=55)	0.02334	0.01164	4.0235	0.0449	1.024
Vfib/pVT + LVEF	-0.01111	0.01328	0.7000	0.4028	0.989
Vfib/pVT + GLS	0.00354	0.03486	0.0103	0.9191	1.004

Figure 1a: Relationship of Survival with LAVI (stratified into values above and below the mean value). "Highlavi" refers to LAVI values above mean value. Survival time measured in days.

Legend: The purpose of this figure is to illustrate the difference in survival time when stratified by the mean LAVI value in our patient cohort. This Kaplan Meier curve was used to assess the variance in survival probability for those above and below the mean. There is a significant difference in outcomes when stratified by the mean LAVI value.

Figure 1b: Relationship of Survival with RAVI (stratified into values above and below the mean value). "Highravi" refers to RAVI values above mean value. Survival time measured in days.

Legend: The purpose of this figure is to illustrate the difference in survival time when stratified by the mean RAVI value in our patient cohort. This Kaplan Meier curve was used to assess the variance in survival probability for those above and below the mean. There is a significant difference in outcomes when stratified by the mean RAVI value.

Figure 2a: Bland-Altman plot for intra-observer variability with LAVI.

Legend: The figure represents the intraclass correlation coefficient of LAVI measurements. The purpose of this figure is to demonstrate the consistency of the measurements made by the two independent observers.

Figure 2b: Bland-Altman plot for intra-observer variability with RAVI.

Legend: The figure represents the intraclass correlation coefficient of RAVI measurements. The purpose of this figure is to demonstrate the consistency of the measurements made by the two independent observers.

Figure 1a: Survival after Vfib/pVT arrest by LAVI values

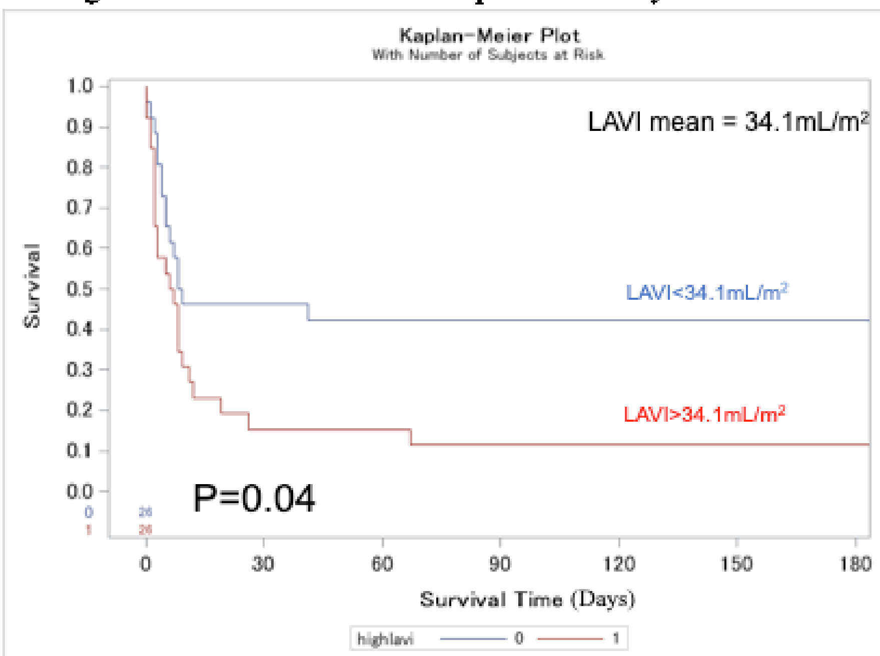

Figure 1b: Survival after Vfib/pVT arrest by RAVI values

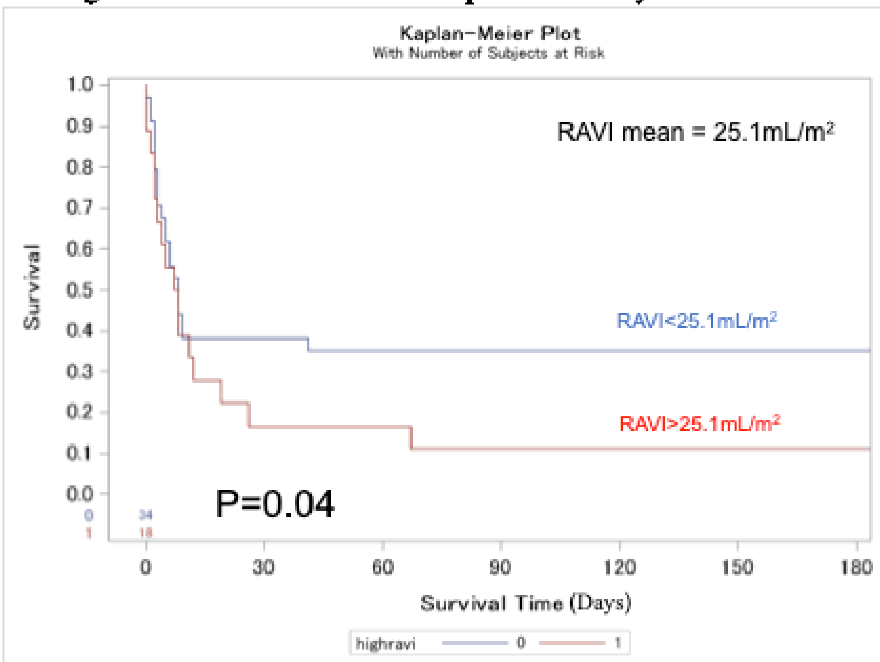

Figure 2a: Bland-Altman Plot for intra-observer variability with LAVI

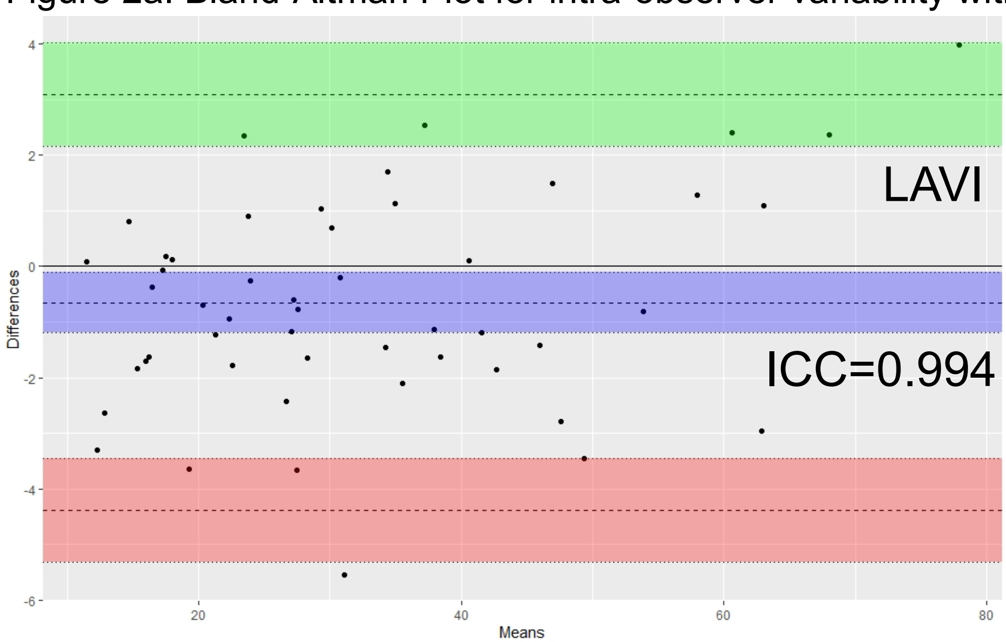

Figure 2b: Bland-Altman Plot for intra-observer variability with RAVI