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Original Article

Diagnostic Test for Estimation of Plasma Volume on Assessment of Congestive Status in Acute Heart Failure Patients at Saiful Anwar General Hospital

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ABSTRACT

Background: Heart failure is a health issue with high mortality and morbidity rates globally, including in Indonesia. Congestion is the main symptom of acute heart failure. B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) are well-known markers to confirm the condition. Plasma volume estimation (ePVS) is one of the procedures currently being developed to assess a patient's congestive status at a lower cost.
Objective: This study aims to evaluate the sensitivity and specificity value of ePVS to assess the congestive status in acute heart failure patients
Methods: This is a descriptive observational research with a cross-sectional study method that included all patients with dyspneu that come to emergency room between May 2018-February 2023. Baseline characteristics, medication history, and echocardiography were also included in the statistical analysis. We used univariate and bivariate analysis to assess the effect of each variable on the patient's congestive condition. A diagnostic test of plasma volume estimation was carried out using Receiver Operating Characteristics (ROC) Analysis compared to NT pro-BNP as a diagnostic tool of congestive in acute heart failure based on guideline. Plasma volume estimation calculated using Strauss-Duarte formula.
Result: A total of 506 subjects with dyspnea at ER Dr. Saiful Anwar Malang Hospital, who met the inclusion and exclusion criteria. The mean age was older in congestive patients with 51.3% being male. Patients with congestive conditions have a lower ejection fraction with a higher estimated right atrial pressure from echocardiography. The estimation plasma volume status was also higher in congestive conditions (4.90 vs 3.5). The ePVS from ROC analysis has a good diagnostic value at the reduced and mildly reduced EF.
Conclusion: The estimation of plasma volume status has a good sensitivity and specificity value to assess congestive status in patients with acute heart failure who are fluid-overloaded.

1. Introduction

In developed as well as industrialized nations including Indonesia, heart failure is a severe health issue with high mortality and morbidity rates.[1] Its prevalence is steadily increasing, with more than 26 million people worldwide suffering from this condition.[2] Acute cardiac failure is more common in persons between the ages of 70 and 73 in diverse nations. In Indonesia, on the other hand, heart failure patients are relatively younger with a more severe clinical appearance.[3,4] Acute heart failure also has a fairly high mortality rate, both during hospitalization and after discharge, with a significant rehospitalization rate.[5] The prevalence of heart failure in Indonesia reaches 0.3% based on Basic Health Research data in 2017.[6]

Overall, acute heart failure is an emergency condition that requires immediate treatment because it can threaten the patient's life.[7] The incidence of acute heart failure is influenced by various factors such as acute myocardial dysfunction due to ischemia, inflammation, drug use, nutritional disorders, endocrine disease, or exposure to toxins.[8] Other causes can come from worsening heart failure conditions caused by a lack of education about treatment, arrhythmias, infections, anemia, and other factors.[9] The many classifications used to identify heart failure can help in assessing the risk of complications and providing appropriate therapy to patients in emergency conditions.[10]

Congestion is one of the most common signs of acute heart failure and the main reason patients are hospitalized.[1] Congestion during hospitalization and before discharge has a significant value in the

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prognosis of mortality and rehospitalization.[11] Further tests that need to be done to confirm the patient's condition can be done by electrocardiography (ECG), chest X-ray, cardiac catheterization, and examination of biomarkers B-type natriuretic peptides (BNP) and N-terminal prohormone B-type natriuretic peptides (NT-proBNP).[12] In addition, several other assessments that are non-invasive at this time can also be performed to assess congestive status in patients such as the estimation of plasma volume status and hemodynamic index.[13] Plasma volume estimation is one of the methods for measuring plasma volume based on the Strauss-Duarte formula : ePVS = 100-hematocrit (%) / hemoglobin (g/dL).[14]

2. Material and Methods

This is a descriptive observational study with a cross-sectional study method. This study is part of the National ICCU Registry's multicenter research using registry data sources. The participants in this research were dyspnea patients who were admitted at Dr. Saiful Anwar Malang in the period of May 2019-February 2022. Selection of subjects based on inclusion and exclusion criteria. The exclusion criteria were acute coronary syndrome, Emergency hypertension, Cardiac arrest, Stenotic heart valve disease (moderate-severe aortic and/or mitral stenosis), Patients with mechanical or bioprosthetic valves, Heart failure with CRRT (Continuous renal replacement therapy), Moderate-severe hypoalbuminemia, CKD undergoing routine hemodialysis or CAPD, Septic Condition, Obesity, Pulmonary Embolism, Congenital Heart Disease, Anemia / receiving blood transfusions and Use of mechanical ventilation. We divided them into two groups with congestive heart failure and non-congestive heart failure based on NT-pro BNP values. Estimation of plasma volume was calculated based on the Strauss-Duarte formula, as mentioned above. The subgroup analysis was performed based on EF.

2.1. Sample

In this study, the required sample size was adjusted from the required sample size formula for diagnostic test research, namely using the Lemeshow formula.[15] The estimated proportion used is the prevalence of heart disease in East Java based on the 2018 Basic Health Research (Riskesdas) study. Based on the formula above, the minimum number of subjects needed is 506 people. The technique for taking subjects is non-random sampling using consecutive sampling techniques. Independent and dependent variables are assessed simultaneously. The independent variables assessed were NT-proBNP and plasma volume status. Then, the dependent variable in this study is congestive conditions in acute heart failure. Baseline characteristics, history of medication, and echocardiography result was also included in statistical analysis.

2.2. Statistical analysis

Overall data analysis was carried out with the SPSS program. The analysis carried out was univariate analysis which aimed to determine the characteristics of the subject. Univariate analysis in this study consisted of the mean value, standard deviation, and prevalence to assess the basic characteristics of the research subjects. The basic characteristics of this study include age, gender, and BMI. The prevalence of comorbidities in the study subjects included a history of stroke, hypertension, diabetes mellitus, acute myocardial infarction, and medical history.

The analysis was then continued with bivariate analysis, which was preceded by a normality test using the Kolmogorov-Smirnof test. Categorical variables such as gender and medical history will be analyzed for their effect on acute heart failure with the Chi-Square test. Multivariate analysis with logistic regression aims to assess the relationship between variables on congestive status. Diagnostic test using Receiver Operating Characteristics (ROC) Analysis, to calculate the Area Under the Curve (AUC) for the eVPS value and determine the best cut-off value in identifying congestive heart failure. Results with $p<0.05$ were considered statistically significant.

3. Result

Patients with congestive heart failure (51.5%) and patients without congestive heart failure (51.3.3%) were both predominately male at baseline, and there was no significant different between the two groups. Patients with congestive cardiac failure had been identified to be 56 years older (40-71) than non-congestive heart failure patients. The BMI values of the two groups had very slight differences and no statistically significant differences were found.

Table 1. Baseline Characteristic

Variable	Congestive Heart Failure		P Value
	No (n=95)	Yes (n=411)	
Gender, f (%)			
Male	49 (51.5%)	211(51.3%)	0.141
Female	46 (48.4%)	200 (48.6%)	
Age (year), median (min-max)	53 (38–69)	56 (40-71)	0.087
IMT, median (min-max)	24.4 (17.6 – 69.20)	24.2 (13.9 – 37.50)	0.094

Statistical analysis of the relationship between the characteristics of co-morbidities and congestive heart failure where out of 11 types of comorbidities without a significant association (Table 2).

From the results of the echocardiography bivariate test, it was found that patient with congestive has a lower EF. From multivariate analysis the Ejection Fraction had a significant effect on the incidence of congestive heart failure ($p=0.015$; OR 0.937 (0.890 – 0.987)). OR<1 means that the higher the ejection fraction inhibits the possibility of congestive heart failure. Then eRAP (normal) also had a significant effect on the incidence of congestive heart failure ($p=0.000$; OR 680.461 (91.978 – 5034.087)). OR> 1 means that patients with normal eRAP have an increased chance of developing congestive heart failure compared to low eRAP. Thus eRAP (high) also had a significant effect on the incidence of congestive heart failure ($p=0.001$; OR 45.376 (5.259 – 391.536)). OR> 1 means that patients with high eRAP have an increased chance of developing congestive heart failure compared to low eRAP.

The ePVS results in patients with congestive heart failure had a higher value of 4.90 (4.20 – 27.90) and were significant compared to patients without congestive heart failure ($p=0.000$). From the multivariate results, ePVS had a significant effect on the incidence of congestive heart failure ($p=0.000$; OR 41.347 (18.273 – 93.559) with OR > 1, meaning that the higher the hematocrit value, the higher the chance of congestive heart failure.

Receiver Operating Characteristics (ROC) analysis is used to calculate the Area Under the Curve (AUC) for the eVPS value and determine the best cut-off value in identifying congestive heart failure. Results with $p<0.05$ were considered statistically significant.

Table 2. Comorbidities Characteristic

Comorbidities	Congestive Heart Failure		P value
	No (n=95)	Yes (n=411)	
Ischemic Heart Disease, f (%)			
No	64 (76.4%)	238 (57.9%)	0.115[a]
Yes	31 (32.6%)	173 (42.1%)	
Hypertensive Heart Disease, f (%)			
No	68 (71.6%)	271 (65.9%)	0.351[a]
Yes	27 (28.4%)	140 (34.1%)	
Atrial Fibrillation, f (%)			
No	86 (90.5%)	367 (89.3%)	0.867[a]
Yes	9 (9.5%)	44 (10.7%)	
Smoker/Ex-smoker, f (%)			
No	55 (57.8%)	199 (48.4%)	**0**.141[a]
Yes	40 (42.1%)	212 (51.6%)	
Hipertension, f (%)			
No	47 (49.5%)	194 (47.2%)	0.775[a]
Yes	48 (50.5%)	217 (52.8%)	
Diabetes Mellitus, f (%)			
No	77 (81.1%)	281 (68.4%)	**0**.120[a]
Yes	18 (18.9%)	130 (31.6%)	
Dyslipidemia, f (%)			
No	83 (87.4%)	374 (91.0%)	0.376[a]
Yes	12 (12.6%)	37 (9.0%)	
Cerebrovascular Disease			
No	85 (89.5%)	376 (91.5%)	0.574[a]
Yes	10 (10.5%)	35 (8.5%)	
Chronic Kidney Disease, f (%)			
No	95 (100%)	398 (86.8%)	0.141[b]
Yes	0 (0%)	13 (3.25)	
COPD, f (%)			
No	92 (96.8%)	402 (97.8%)	0.478[b]
Yes	3 (3.25)	9 (2.25)	
Pneumonia , f (%)			
No	23 (24.2%)	269 (65.4%)	0.061[b]
Yes	72 (75.7%)	142 (34.5%)	

*COPD : Chronic Obstructive Pulmonary Disease

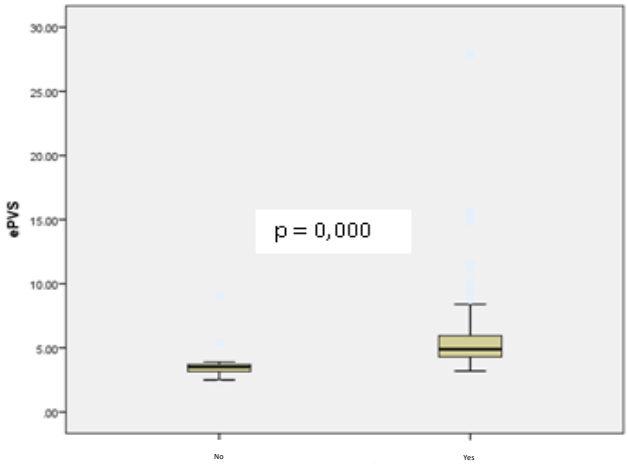
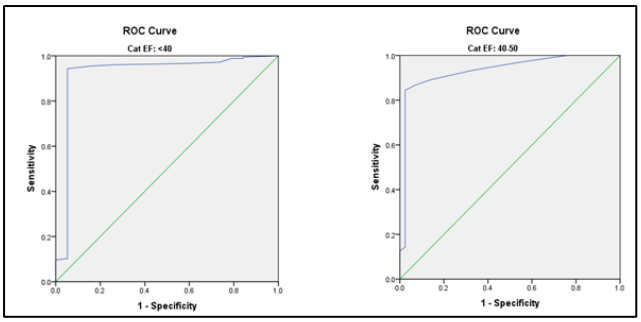


Figure 1. Multivate Analysis of ePVS in congestive heart failure

From subgroup analysis, we found that there was a strong positive correlation (r : 0.651) between reduced EF (EF <40%) with the NT-proBNP. There was no significant correlation between preserved EF (EF >50%) with the NT pro BNP. AUC results The ePVS value in identifying congestive heart failure was 93.4% (95% CI 92.9%-98.0%) with p=0.000. The AUC value obtained is in the very good category (> 90%) and is statistically significant. Furthermore, the determination of the cutoff point with the greatest specificity and the greatest sensitivity above 50% was carried out, using the coordinates of the curve table and obtained a cut-off of 4.90 with a sensitivity of 92.3%, a specificity of 91.7% at reduced EF.



4. Discussion

Women are more likely to develop symptoms of heart failure with preserved ejection fraction (HFpEF) later in life and to have fewer cases of ischemic myocardial disease (which is more common in males and associated to a lower ejection fraction) than men.[16] The vast majority of our congestive heart failure patients are male but non significant.[17] In addition, several studies have shown that the negative effect of CHF on quality of life is even more pronounced and severe in women than in males. This is likely attributable to both the presence of CHF and a greater degree of comorbidity associated with advanced age.[18,19] Obesity is linked to several cardiovascular diseases, one of which is heart failure. Because it does not take into account fat distribution—information that is important in assessing cardiovascular risk—BMI is an unreliable indicator of obesity severity. The Framingham Heart Study found that a continuous rise in body mass index of 1 kg/m2 was associated with a 5% and 7% greater risk of illness in men and women, respectively.[20] There is a correlation between obesity and HFpEF, and patients with HFpEF are more likely to be overweight than those with HFrEF, with a prevalence of 85% vs 45%, respectively. Numerous confounding variables might make it difficult to draw conclusions about the association between HFrEF and obesity.[17]

Congestion, characterized by dyspnea, orthopnea, and edema owing to high LV filling pressure, is the primary cause of hospitalization in patients with heart failure.[21] Further renin-angiotensin-aldosterone system (RAAS) and sympathetic activation, ventricular geometric alterations, pulmonary hypertension, and other end-organ hypoperfusion are all ways in which congestion may contribute to the development of heart failure.[22] Given the difficulties in accurately evaluating volume status by clinical examination, several different biomarkers and other innovative approaches have been developed to aid clinicians in quantifying congestion.[23] For quite some time, natriuretic peptides have served as the gold standard for volume status biomarkers. Combining it with bioimpedance methods to help direct emergency room care in cases of severe, sudden cardiac failure has also been the focus of some research.[24] Hemoconcentration (which occurs later in hospitalization despite deteriorating renal function) has been linked to a better outcome in investigations of patients with acute heart failure. After administering tracer molecules, normal dilutional analysis may be used to calculate plasma volume (PV), the intravascular part of the extracellular fluid volume.[14,25] However, the Strauss method may be used to predict percentage changes in PV (rather than absolute values) using serial concurrent hemoglobin and hematocrit concentrations. The data we have show that PV changes have major consequences for heart failure treatment in the clinic.[26] Patients with stable HF on standard medication show a reduction in PV size, while edematous participants show PV enlargement prior to treatment. Lower baseline ePVS was related with better outcomes in the previous trial, which used the Strauss formula to evaluate congestion severity in symptomatic patients.[27] Fluid overload was defined as an ePVS at baseline more than 5.5%, according to the cohort study, which was also associated with an elevated risk of hospitalization and death due to heart failure.[26,28]

Before clinical congestion occurs, it is crucial to evaluate hemodynamic congestion.[11] So, it is believed that congestion may be evaluated better if plasma volume can be estimated.[29] Congestion biomarkers have also been demonstrated to correlate with estimated plasma volume (ePVS), which is calculated from hemoglobin and hematocrit.[30] Our findings, similar to those of previous research, demonstrate that ePVS is related to various congestion biomarkers such as NT-pro BNP, IVC diameter, and echocardiographic estimates of RA pressure.[31] Our results also demonstrated that the ejection fraction was decreased in patients with congestive heart failure. Our analysis shows that ePVS has high sensitivity and specificity for determining congestive state at the reduced EF.

Limitations

The current research has a number of flaws. We should start with the fact that this was a retrospective study conducted at a single institution and does not give enough weight to sample size. The second limitation is that we did not monitor or account for fluctuations in plasma volume status, and instead relied only on initial measurements taken during the first twelve hours of admission. Third, we have not taken into account changes in medical parameters or post-discharge therapy since we have accessed this research utilizing just data on hospitalization. Therefore, studies that look into the future with a bigger sample size are required. Although this study has certain limitations, it does provide fresh light on how patients' plasma volume status affects their acute heart failure.

5. Conclusion

The most prominent clinical manifestation of acute heart failure is congestive. Although NT pro-BNP and other echocardiographic measurements have limitations, such as high costs and the necessity for an echocardiografer, they are useful for evaluating congestion or higher plasma volume. The estimated plasma volume status using a formula was an easy and inexpensive technique to evaluate congestive heart failure especially in reduced EF.

6. Declaration

6.1 Ethics Approval and Consent to participate

The subjects in this study are humans, so ethical rules must be followed. This research has passed the ethical due diligence, approved based on the Certificate of Ethical Eligibility No. 400/258/K.3/302/2021 issued by the Health Research Ethics Committee at Dr. Saiful Anwar Malang.

6.2. Consent for publication

Not applicable.

6.3 Availibility of data and materials

Data used in our study were presented in the main text.

6.4 Competing interests

Not applicable.

6.5 Funding Source

Not applicable.

6.6 Authors contributions

Idea/concept: OSP. Design: OSP. Control/supervision: IP, TA, MSR, NK. Data collection/processing: OSP, IP. Analysis/interpretation: OSP, IP. Literature review: OSP, IP. Writing the article: OSP. Critical review: IP, TA, MSR, NK. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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References

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–726. 10.1093/eurheartj/ehab368

2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016;13(6):368–78. 10.1038/nrcardio.2016.25

3. Ural D, Çavuşoğlu Y, Eren M, et al. Akut kalp yetersizliği tanı ve tedavisi. Anatol J Cardiol 2015;15(11):860–89. 10.5152/AnatolJCardiol.2015.6567

4. Greenberg BH. Heart failure epidemic. Curr Cardiol Rep 2002;4(3):185. 10.1007/s11886-002-0048-y

5. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail 2020;22(8):1342–56. 10.1002/ejhf.1858

6. Kemenkes RI. Situasi kesehatan jantung. Pus data dan Inf Kementeri Kesehat RI 2014;3. http://www.depkes.go.id/download.php?file=download/pusdatin/infodatin/infodatin-jantung.pdf. 10.1017/CBO9781107415324.004

7. Tsukada YT, Katoh YK, Seino Y. Home-based management in patients with chronic heart failure. Nippon rinsho Japanese J Clin Med 2007;65 Suppl 5:323–8.

8. Tubaro M, Vranckx P, Price S. Oxford Medicine Online The ESC Textbook of Intensive and Acute Cardiovascular Care. 2016. 10.1093/med/9780199687039.001.0001

9. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J 2008;29(19):2388–442. 10.1093/eurheartj/ehn309

10. Cerlinskaite K, Javanainen T, Cinotti R, Mebazaa A. Acute heart failure management. Korean Circ J 2018;48(6):463–80. 10.4070/kcj.2018.0125

11. Strobeck JE, Feldschuh J, Miller WL. Heart Failure Outcomes With Volume-Guided Management. JACC Hear Fail 2018;6(11):940–8. 10.1016/j.jchf.2018.06.017

12. Gaggin HK, Januzzi JL. Biomarkers and diagnostics in heart failure. Biochim Biophys Acta - Mol Basis Dis 2013;1832(12):2442–50. http://dx.doi.org/10.1016/j.bbadis.2012.12.014. 10.1016/j.bbadis.2012.12.014

13. Sakka SG. Hemodynamic monitoring in the critically ill patient - current status and perspective. Front Med 2015;2(AUG):1–6. 10.3389/fmed.2015.00044

14. Kobayashi M, Girerd N, Duarte K, et al. Estimated plasma volume status in heart failure: clinical implications and future directions. Clin Res Cardiol 2021;110(8):1159–72. 10.1007/s00392-020-01794-8

15. Chadha VK. Sample size determination in health studies. 2006;55–62.

16. Sciomer S, Moscucci F, Salvioni E, et al. Role of gender, age and BMI in prognosis of heart failure. Eur J Prev Cardiol 2020;27(2_suppl):46–51. 10.1177/2047487320961980

17. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41(10):1797–804. http://dx.doi.org/10.1016/S0735-1097(03)00309-7. 10.1016/S0735-1097(03)00309-7

18. Kocabaş U, Sinan ÜY, Aruğaslan E, et al. Clinical characteristics and in-hospital outcomes of acute decompensated heart failure patients with and without atrial fibrillation. Anatol J Cardiol 2020;23(5):260–7. 10.14744/AnatolJCardiol.2020.94884

19. Crousillat DR, Ibrahim NE. Sex Differences in the Management of Advanced Heart Failure. Curr Treat Options Cardiovasc Med 2018;20(11). 10.1007/s11936-018-0687-y

20. Zafrir B, Salman N, Crespo-Leiro MG, et al. Body surface area as a prognostic marker in chronic heart failure patients: results from the Heart Failure Registry of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2016;18(7):859–68. 10.1002/ejhf.551

21. Mentz RJ, Kjeldsen K, Rossi GP, et al. Decongestion in acute heart failure. Eur J Heart Fail 2014;16(5):471–82. 10.1002/ejhf.74

22. Miller WL. Fluid volume overload and congestion in heart failure. Circ Hear Fail 2016;9(8):1–9. 10.1161/CIRCHEARTFAILURE.115.002922

23. Nadar SK, Shaikh MM. Biomarkers in Routine Heart Failure Clinical Care. Card Fail Rev 2019;5(1):50–6. 10.15420/cfr.2018.27.2

24. Ibrahim NE, Gaggin HK, Konstam MA, Januzzi JL. Established and emerging roles of biomarkers in heart failure clinical trials. Circ Hear Fail 2016;9(9):1–10. 10.1161/CIRCHEARTFAILURE.115.002528

25. Roumelioti M-E, Glew RH, Khitan ZJ, et al. Fluid balance concepts in medicine: Principles and practice. World J Nephrol 2018;7(1):1–28. 10.5527/wjn.v7.i1.1

26. Kobayashi M, Girerd N, Duarte K, Preud'homme G, Pitt B, Rossignol P. Prognostic impact of plasma volume estimated from hemoglobin and hematocrit in heart failure with preserved ejection fraction. Clin Res Cardiol 2020;109(11):1392–401. https://doi.org/10.1007/s00392-020-01639-4. 10.1007/s00392-020-01639-4

27. Martens P, Nijst P, Dupont M, Mullens W. The Optimal Plasma Volume Status in Heart Failure in Relation to Clinical Outcome. J Card Fail 2019;25(4):240–8. https://doi.org/10.1016/j.cardfail.2018.11.019. 10.1016/j.cardfail.2018.11.019

28. Duarte K, Monnez JM, Albuisson E, Pitt B, Zannad F, Rossignol P. Prognostic Value of Estimated Plasma Volume in Heart Failure. JACC Hear Fail 2015;3(11):886–93. 10.1016/j.jchf.2015.06.014

29. Zile MR, Bennett TD, St. John Sutton M, et al. Transition from chronic compensated to acute d compensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118(14):1433–41. 10.1161/CIRCULATIONAHA.108.783910

30. Knudsen NN, Kjærulff TM, Ward LC, Sæbye D, Holst C, Heitmann BL. Body water distribution and risk of cardiovascular morbidity and mortality in a healthy population: A prospective cohort study. PLoS One 2014;9(2):1–7. 10.1371/journal.pone.0087466

31. McKie PM, Burnett JC. NT-proBNP: The Gold Standard Biomarker in Heart Failure. J Am Coll Cardiol 2016;68(22):2437–9. 10.1016/j.jacc.2016.10.001