Analysis of Calcium and Phsophate in Patiens with Heart Failure

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Abstract

Heart failure is a clinical syndrome caused by abnormalities in the structure or function of the heart in the myocardium, causing ventricular filling or cardiac output. Calcium and phosphate are metabolic markers that have been linked to the development of the cardiovascular disease. Increased levels of phosphate in patients cause increased production of FGF-23 which induces activation of calcineurin signaling in cardiomyocytes and triggers cardiac hypertrophy. Calcium plays an important role in connecting membrane stimulation with contractions in the myocardium. This study uses a cross-sectional method. Examination of calcium and phosphate levels using serum samples was taken on 57 heart failure patients treated at the Integrated Heart Center Dr. Wahidin Sudirohusodo during the period May to August 2019. Data were analyzed statistically by the Kolmogorov Smirnov test and the Independent T-test.This study showed a significant difference between the calcium levels of the ejection fraction group <50% with a median of 4.67 mg / dL and the ejection fraction group> 50% with a median of 6.06 mg / dL (p <0.01). There was a significant difference between the phosphate levels of the ejection fraction group <50% with a median of 3.62 mg / dL and the ejection fraction group> 50% with a median of 3.04 mg / dL (p = 0.04). It was concluded that calcium levels arehigher in heart failure patients with ejection fraction> 50% & phosphate levels lower in heart failure patients with ejection fraction> 50%.

***Keywords**: Calcium, phosphate, ejection fraction, heart failure*

Introduction

Heart failure is a clinical syndrome caused by structural and functional defects in the myocardium that causes impaired ventricular filling or cardiac output.[1] According to the American College of Cardiology (ACC) and the American Heart Association (AHA), heart failure with a decreased ejection fraction is defined as an ejection fraction ≤40%, whereas heart failure with maintained ejection fraction is defined as an ejection fraction ≥50%.[2]Data from the Atherosclerosis Risk in Communities Study has shown that around 915,000 new cases of heart failure occur annually in the United States. The incidence rate increases with the age of patients of both sexes. Data from the Framingham Heart Study has shown that the annual rate of new heart failure per 1000 people/year is 9.2 for white men aged 65 to 74 years, 22.3 for white men aged 75 to 84 years, and 43.0 for white men ≥85 years.[3]Higher thresholds for case definition, greater severity of the disease, and limited availability of evidence-based therapy can explain this higher death rate in developing countries.[4]

Heart failure is a multisystem disorder in which there is interference with the heart, skeletal muscle and kidney function, stimulation of the sympathetic nervous system and complex neurohormonal changes. In systolic dysfunction, there is a disruption in the left ventricle which causes a decrease in cardiac output. This results in activation of the neurohormonal compensation mechanism, the Renin-Angiotensin-Aldosterone system (RAA system) as well as vasopressin and natriuretic peptide levels that aim to improve the cardiac environment so that cardiac activity can be maintained.[5,6]

Calcium plays an important role in connecting membrane stimulation with contractions in the myocardium. Damaged calcium homeostasis in heart failure can occur due to pathological changes in the expression, and activity of calcium homeostatic binding proteins, ion channels and enzymes. Calcium also plays

an important role in the excitation and contraction of cell membranes, called Excitation-Contraction Coupling (ECC). Cardiac contraction depends on increasing transient concentrations of cytosolic calcium to activate the formation of cross-bridges between the myofilament proteins which ultimately leads to the development of pressure in the heart chambers and provides energy for blood pumps. Cardiomyocytes wrapped in myofibrils are enveloped in tissue storing calcium sarcoplasmic reticulum and mitochondria. The research of Adeniran et al concluded that with calcium disruption and ion channel remodeling in the ejection fraction, the duration of the potential action of ventricular cells becomes prolonged, along with an increase in diastolic calcium concentration.[7]

Increased phosphate levels in patients with heart failure result in increased production of FGF-23, which induces activation of calcineurin signaling in cardiomyocytes, promoting cardiac hypertrophy.[8] Increased phosphate load has been associated with valvular heart disease, with hypertrophic left ventricles, and especially with vascular calcification.[9] Research conducted by Lutsey et al high phosphate concentrations to be associated with an increased risk of heart failure, atrial fibrillation, and a worse prognosis among patients. Framingham's research and post hoc analysis from Cholesterol and Recurrent Events clinical trials have found a positive relationship between serum phosphorus risk and heart failure.[8]

Research on the analysis of calcium and phosphate levels in heart failure patients is still ongoing and continues to be developed. Based in there backgrounds, we were interested in conducting research on the analysis of calcium and phosphate levels in heart failure patients.

Method

This study is a cross-sectional analytic study, analyzing calcium and phosphate levels in patients with heart failure based on ejection fraction. The study was conducted from May to August 2019 at the Clinical Pathology Laboratory of Dr. Wahidin Sudirohusodo Hospital Makassar. The study sample was all patients diagnosed with heart failure by the cardiologist. All subjects were tested for serum calcium and phosphatelevels in. In conducting this research, every action was carried out with the permission and knowledge of patients who were used as research samples through an informed consent sheet and was declared to have met the ethical requirements to be carried out by the Health Research Ethics Commission (KEPK) Faculty of Medicine, Hasanuddin University-UNHAS State University Hospital (RSPTN UH) -RSUP Dr. Wahidin Sudirohusodo Makassar.

Data were analyzed statistically by the Independent T-test is used to assess the difference between calcium levels of heart failure with ejection fraction <50% and ejection fraction> 50% and phosphate levels of heart failure with ejection fraction <50% and ejection fraction> 50%. Hypothesis test results are significant if $p \leq 0.05$.

Results

The study samples obtained were 57 heart failure patients who met the inclusion criteria. The characteristics of study samples can be seen in Table 1 that shows male subjects were more than female. Most study subjects were found in the 40-64 year group.

Table 1. Sample characteristics

Characteristics	n (%)	Mean ± SD	Median (Min-Max)
Gender Male Female	39 (68.4) 18 (31.6)		
Age (year)		52.87±12.06	
Calcium		5.47 ± 1.61	5.66 (2.54-9.23)
Phosphate		4.05 ± 1.90	2.65(1.99–7.60)

Table 2 showed ejection fraction group <50% with mean calcium level 4.72 mg / dL ± 1.06 and ejection fraction group> 50% with mean calcium level 6.41 mg / dL ± 1.62. The results of the statistical analysis in table 2 show that there are significant differences between these two groups with a value of p = 0.00 (p <0.01).

Table 2.The difference between calcium in heart failure based on ejection fraction

Ejection Faction	calcium levels (mg/dL)		P
	Mean ± SD	Median (min-max)	
< 50 %	4.72 ± 1,06	4.67 (2.54 – 6.44)	*0.000
> 50 %	6.41 ± 1.62	6.06 (3.10 – 9.23)	

*Independent T test

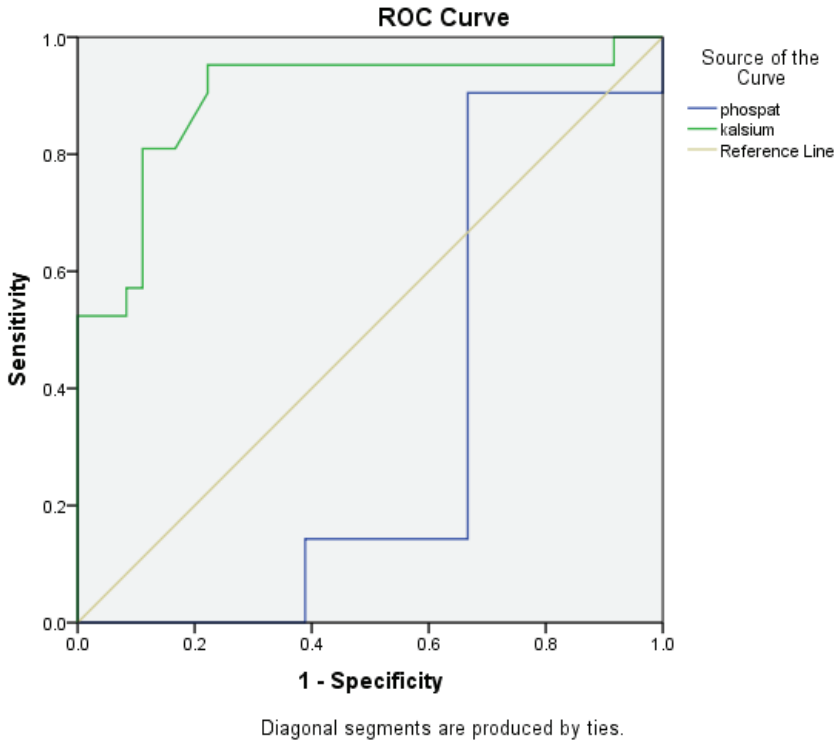
Table 3 shows the ejection fraction group <50% with mean phosphate level of 3.80 ± 1.79 and the ejection fraction group> 50% with a mean phosphate level of 3.44 ± 1.07. Statistical analysis showed that there were significant differences between the two groups with p <0.05.

Table 3. The difference between phosphate in heart failure is based on the ejection fraction

Ejection Faction	Phosphate levels (mg/dL)		P
	Mean ± SD	Median (min-max)	
< 50 %	3.80 ± 1.79	3.62 (1.49-7.60)	*0.047
> 50 %	3.44 ± 1.07	3.04 (1.99-6.30)	

*Independent T test

Pictures 1 shows statistical analysis based on ROC curves shows there is a cutoff in calcium levels in heart failure patients based on ejection fractionis 5.7 mg / dL with ROC = 0.046 (0.011-0.197) with a sensitivity of 87% and a specificity of 76.5%. Pictures 1 shows statistical analysis based on ROC curves shows there is a cutoff in phospate levels in heart failure patients based on ejection fractionis 2.5 mg / dL with ROC = 0.314 (0.077-1.285) with a sensitivity of 87% and a specificity of 32.4%.



Pictures 1. Receiver operating characteristic (ROC) calcium dan phospat levels in heart failure patients based on ejection fraction

Discussion

In this study, subjects were mainly male (68.4%) with a mean age of the subjects 52.8 years. Epidemiological data show that the incidence of heart failure is higher in men than women and the risk increases with age.[10] This study is in line with research conducted by The Netherlands' Rotterdam which found that the majority of heart failure that was obtained was male (33%) compared to women (29%) and the average age of 55 years.[11] In old age and male sex are risk factors associated with atherosclerosis and the occurrence of SCS that cannot be modified.[12]

The results of this study indicate calcium levels in heart failure patients (5.47 ± 1.61 mg / dL). One study reported a patient with hypocalcemia (23%) in heart failure patients (Rozentryt et al., 2015). Other studies have shown calcium levels in heart failure patients to be around 32% with hypocalcemia.[13]

The dysregulation of calcium homeostatic mechanisms are common in heart failure. There have been many studies in patients treated in intensive care units (including those with acute heart failure) showing a high prevalence of hypocalcemia and its association with a poor prognosis. Calcium is an important element for ventricular systolic and diastolic function. During the active process of depolarizing the myocardial membrane, there is a rapid flow of calcium ions through the active membrane calcium channels and the subsequent release of calcium ions from the sarcoplasmic reticulum. Then calcium binds to the troponin-tropomyosin complex, supporting myocardial contraction and fusion of actin-myosin. Relaxation occurs when calcium ions are actively pumped back into the sarcoplasmic reticulum, tropomyosin continues in its shape and myosin returns and releases actin. [14,15]

This study also showed a significant association of calcium levels between the heart failure group and the ejection fraction <50% with> 50%. At the determination of the cut point in calcium in heart failure patients based on ejection fractionis 5.7 mg / dL with ROC = 0.046 (0.011-0.197) with a sensitivity of 87% and a specificity of 76.5%. This is in line with research by Wang et al, 2015 found that low calcium levels are one of the factors that influence the low left ventricular ejection fraction. In another study conducted by Grandi et al, stated that there was a significant correlation between calcium and phosphate levels with a value of p <0.0001.[16] This

is certainly related to calcium phosphate metabolism which is influenced by various factors including the role of parathyroid hormone and vitamin D levels.

The results of this study indicate phosphate levels in heart failure patients (4.05 ± 1.90 mg / dL). Another large-scale study with 977 heart failure patients showed an independent relationship between serum phosphate levels even in the normal range with the severity of disease and prognosis in patients with heart failure. [17]

Hypophosphatemia can cause heart failure. ATP synthesis in muscle cells is decreased in hypophosphatemic patients, indicating that intramyocellular phosphate regulates ATP synthesis. Myocardial and inorganic phosphate keratin phosphate concentrations are significantly reduced during periods of phosphate depletion along with mitochondrial and myofibrillar keratin phosphate kinase activities, which have an important role in contractility of the heart muscle. Stroke volume is increased by administration of phosphate independently of the Frank-Starling effect in patients with severe hypophosphatemia, indicating an increase in myocardial contractility.[18]

Phosphate levels in this study were found to be within normal limits in the heart failure group with ejection fractions <50% and> 50%. At the determination of the cut point in calciumin heart failure patients based on ejection fractionis 2.5 mg / dL with ROC = 0.314 (0.077-1.285) with a sensitivity of 87% and a specificity of 32.4%. A cross-sectional study found high serum phosphate levels were associated with an increase in left ventricular mass and enlarged left ventricular internal dimensions that affected the ejection fraction.

The group with normal phosphate levels was found as many as 26 people. From all research subjects, the mean phosphate value was 4.05. These results are in line with the research of Kamiyama et al, who reported a normal phosphate level of 3.3 mg / dL in heart failure patients. Recent research shows that high serum phosphate levels, even in the normal range, can contribute to an increased risk of cardiovascular diseases such as myocardial infarction and heart failure.[19] Several factors that can affect phosphate levels include diabetic status, albumin levels, smoking history, parathyroid hormone activity, vitamin D levels, history of using beta-blockers, in addition to genetic polymorphism variations that affect FGF-23 production.[20]

This study had some limitations. This study is a cross-sectional study with one-time sampling so it does not see changes in phosphate and calcium levels due to the therapeutic effect and other than that in this study other factors that could affect phosphate and calcium levels were not excluded.

Conclusion and Suggestion

This study concluded that there were differences in phosphate and calcium levels between heart failure patients with ejection fraction < 50% and > 50%. There are significant differences in calcium and phosphate levels in heart failure based on ejection fraction.We recommend further studywith the better distribution of samples in each group, considering therapy received by the patientsand control other risk factors that affect phosphate and calcium levels. We also recommend further study that measures phosphate and calcium levels serially at the beginning and at the end of treatment.

Ethical Clearance: The study was approved by the Health Research Ethics Commission (KEPK) Faculty of Medicine, Hasanuddin University-UNHAS State University Hospital (RSPTN UH) -RSUP Dr. Wahidin Sudirohusodo Makassar Indonesia.

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Conflict of Interest: The authors declare that they have no conflict interest

References

1. Cooperstein, N. Coronary Artery Disease Diagnosis and Management Coronary artery Cardiovascular Risk reduction Prevention, Primary Care Clinics in Office Practice.Elsevier Inc.2018; 45(1) : 45–61.
2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol*. 2016;13(6):368–378. doi:10.1038/nrcardio.2016.25
3. Thomas S, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in the elderly. *Heart Fail Clin*. 2007;3(4):381–387. doi:10.1016/j.hfc.2007.07.004
4. Diastutik D. Proporsi karakteristik penyakit jantung koroner pada perokok aktif berdasarkan karakteristik merokok (*Characteristic Proportion of CHD for Active Smoker by Smoking Characteristic*). Jurnal berkala Epidemiologi. 2016;4(3): 326–337

5. Jackson G, Gibbs CR, Davies MK, Lip GY. ABC of heart failure. Pathophysiology. *BMJ*. 2000;320(7228):167–170. doi:10.1136/bmj.320.7228.167
6. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol*. 2017;14(1):30–38. doi:10.1038/nrcardio.2016.163
7. Kendrick J, Kestenbaum B, Chonchol M. Phosphate and cardiovascular disease. *Adv Chronic Kidney Dis*. 2011;18(2):113–119. doi:10.1053/j.ackd.2010.12.003
8. Lutsey PL, Alonso A, Michos ED, et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2014;100(3):756–764. doi:10.3945/ajcn.114.085167
9. Heine, G. H., Nangaku, M. and Fliser, D. Calcium and phosphate impact cardiovascular risk. *European Heart Journal*. 2013;34(15):1112–1121.
10. Mbakwem A, Aina F, Amadi C. *Expert Opinion*-Depression in Patients with Heart Failure: Is Enough Being Done?. *Card Fail Rev*. 2016;2(2):110–112. doi:10.15420/cfr.2016:21:1
11. Dunlay SM, Pereira NL, Kushwaha SS. Contemporary strategies in the diagnosis and management of heart failure. *Mayo Clin Proc*. 2014;89(5):662–676. doi:10.1016/j.mayocp.2014.01.004
12. Mirza Aj, Taha AY, Khdir BR. Risk factors for acute coronary syndrome in patients below the age of 40 years. *The Egyptian Heart Journal*.2018;70(4):233-235.
13. Jensen ASC, Polcwiartek C, Sogard P., et al. The Assocoiation Between Serum Calcium Levels and Short-Term Mortality in Patients with Chronic Heart Failure. *The American Journal of Medicine*. 2019;132(2):200-208.e1.
14. Parepa I, Mazilu L, Suceveanu A, Voinea C, Tica I. HYPOCALCEMIC CARDIOMYOPATHY - A RARE HEART FAILURE ETIOLOGY IN ADULT. *Acta Endocrinol (Buchar)*. 2019;-5(1):107–112. doi:10.4183/aeb.2019.107.
15. Rozentryt P, Niedziela JT, Hudzik B, Doehner W, Jankowska EA, Nowak J, et al. Abnormal Serum Calcium Levels are Associated with clinical response to maximization of heart failure therapy. *Pol Arch med Wewn.* 2015;125(1-2):54-64.
16. Lucock MD, Martin C, Boyd L, et al. Response to "calcium, phosphate and the risk of cardiovascular events and all-cause mortality in a population with stable coronary heart disease." *Heart*. 2012;99(5):349-350. doi:10.1136/heartjnl-2012-302480
17. Ess M, Heitmar-Wietzorrek K, Frick M., et al. Serum phosphate and long-term outcome among patients with stable heart failure. *Journal of Cardiac Failure*. 2013; 19(1):25-30. doi: 10.1016/j.cardfail.2012.11.008.
18. Christopoulou, E.C., Filippatos, T.D., Megapanou, E. et al. Phospahte Imbalance in Patients with Heart Failure. *Heart Fail Rev*.2017;22: 349. https://doi.org/10.1007/s10741-017-9615-6.
19. Kamiyama Y, Suzuki H, Yamada S, Kaneshiro T, Takeishi Y. Serum phosphate levels reflect responses to cardiac resynchronization therapy in chronic heart failure patients. *J Arrhythm*. 2015;31(1):38–42. doi:10.1016/j.joa.2014.06.006.
20. Palmer SC, Teixeira-Pinto A, Saglimbene V, et al. Association of drug effects on serum parathyroid hormone, phosphorus, and calcium levels with mortality in CKD: A meta-analysis. *Am J Kidney Dis*. 2015;66(6):962-971. doi:10.1053/j.ajkd.2015.03.036