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Comparison between Serum Aldosterone Levels in Class I-II and Class III-IV Functional Heart Failure Patients

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Abstract

BACKGROUND: Aldosterone plays a role in the initation and development of heart failure (HF). During congestive HF, the initial reduction in cardiac output stimulates the renin-angiotensin-aldosterone system, which in turn exerts additional stress on the heart.

AIM: This research was aimed to explore the comparison of aldosterone levels between Class I-II functional HF and Class III-IV HF to optimize therapy in cases of HF.

METHODS: The study design is an observational study with a cross-sectional approach. This study was conducted at the Department of Internal Medicine Dr. Moh Hoesin Hospital in Palembang, Indonesia. All patients diagnosed with functional III-IV function HF disease based on symptoms clinical, physical, and electrocardiography (ECG) examination and history of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blocker (ARB) treatment are willing to join the research by signing informed consent.

RESULTS: There is no confounding variable that has a significantly different effect on the group I-II and III-IV functional HF groups. Aldosterone levels also did not show a significant difference between the group New York Heart Association (NYHA) I-II active HF group and the NYHA Class III-IV functional HF group ($p = 0.445$).

CONCLUSION: Serum aldosterone levels in patients with Class I-II functional HF and those with Class III-IV functional HF who consumed ACEIs or ARBs were not significantly different.

Introduction

The prevalence of heart failure (HF) in developed countries is around 1–2% of the entire population. The incidence increases with age, with an increase of 20/1000 individuals at the age of 65–69 years and more than 80/1000 individuals beyond 85 years old [1]. Patients with HF often require hospitalization because of worsening symptoms. More than 1 million patients are treated for HF each year. Reports show that the average rate of rehospitalization in the 1st month is around 25%, and the average rate of rehospitalization in 3 months and 1 year is 30 and 50% [1], [2], [3]. Pharmacological therapy is a significant component of HF management, which includes angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin II-receptor blockers (ARB), β-blockers, digoxin, diuretics, and aldosterone antagonists. Hydralazine and nitrate can also be given in some cases. ACEIs and β blockers have become standard therapy in all patients with systolic HF, with aldosterone antagonists and hydralazines/nitrates, which are only recommended in individual patients [4], [5].

Aldosterone is a mineralocorticoid that is synthesized by the adrenal, cardiac, and vascular glands and provides pleiotropic effects on these organs. The role of aldosterone in the pathophysiology of cardiovascular disease has long been known. Aldosterone is a neurohormonal part of the renin-angiotensin-aldosterone system (RAAS) component that is responsible for the regulation of blood pressure, peripheral resistance, fluid, and electrolyte regulation. Aldosterone also plays a role in the occurrence of heart muscle fibrosis directly through mineralocorticoid receptors. Increased synthesis of aldosterone is stimulated mainly by angiotensin II (AT2) through the angiotensin-1 (AT1) receptor in the adrenal gland glomerulus zone cells. It is also encouraged by the hormone adrenocorticotropic hormone, potassium ions (hyperkalemia), endothelin, prolactin, vasopressin, catecholamines, acetylcholine, prostaglandins, and nitric oxide [5]. In HF, aldosterone plays a role in the initiation and development of its disease. During congestive HF, the initial reduction in cardiac output stimulates neurohormonal compensatory systems, such as the sympathetic nervous system and RAAS, which in turn exerts additional stress on the heart muscle. From several studies found a decrease in AT2 levels with ACEIs, ARBs, or a combination. Still, both are not enough to inhibit aldosterone production; this is known as "aldosterone escape." A study showed that 24% of patients taking ACEIs had elevated serum aldosterone levels. The cause of a secondary

increase in plasma aldosterone levels in patients who have received ACE blockers is unclear, but it may be an "escape phenomenon" of ACE blockers. Alternative pathways from the formation of AT2 can encourage increased production of AT2 so that there remains an increase in aldosterone levels after the enzyme conversion is inhibited. The initial treatment strategy focuses on reducing AT2 by administering ACE inhibitors because it is suspected that ACEIs can suppress the production of AT2 and aldosterone. However, several studies have shown that ACEIs and AT1 blockers only temporarily reduce aldosterone levels. There are several hypotheses that an increase in aldosterone levels results from the non-ACE pathway and the activation of the ACE-2 [6], [7], [8], [9], [10].

There are no specific studies on the comparison of serum aldosterone levels in patients with Class I-II functional HF with Class III-IV functional HF who consume ACEIs/ARBs. This study seeks to explore the comparison of aldosterone levels between Class I-II functional HF and Class III-IV HF to optimize therapy in cases of HF.

Methods

The design of this study is a quantitative observational study with a cross-sectional approach. This study was conducted at the Department of Internal Medicine Dr. Moh Hoesin Hospital in Palembang, Indonesia, where the study sample was all patients with HF in the Department of Internal Medicine who met the inclusion and exclusion criteria. The inclusion criteria were all patients diagnosed with outpatient functional I-II functional HF based on clinical symptoms, physical examination, and electrocardiography (ECG), as well as the history of consuming ACEIs/ARB. All patients are willing to join the research by signing informed consent. Exclusion criteria are patients with chronic kidney failure, patients suffering from primary hyperaldosteronism or thyroid disease or liver disease, patients undergoing treatment with anti-aldosterone/spironolactone, patients with myocardial infarction, and patients with chronic obstructive pulmonary disease and cor pulmonale.

A total of 32 subjects were included in this study using the consecutive sampling technique. Submission of subjects was conducted from December 1, 2019 to December 31, 2019. The ethics committee approved this study of the Faculty of Medicine of Universitas Sriwijaya with registration number 278/kptfkunsri-rsmh/2019.

The independent variable in this study is serum aldosterone levels, with the dependent variable being functional HF Class I-II and III-IV who consume ACEIs/ARB. HF, according to the New York Heart Association (NYHA), a functional class is divided into four categories based on complaints of occurrence of shortness of breath. Class I, there were no complaints of shortness of breath even with substantial activities. Class II, if there are complaints of shortness of breath when doing rather strenuous activities such as climbing stairs or walking 100 m. Class III, if there are complaints of shortness of breath when doing light activities or daily activities such as sweeping the house, bathing, and wearing clothes. Class IV, if there are complaints of tightness at rest or lying on their backs, the patient needs a pillow to raise his head. While confounding variables are body mass index (BMI), age, sex, hypertension, kidney disease, impaired liver function, hyperkalemia, hypernatremia, smoking, and dyslipidemia.

Data management and analysis are performed using the SPSS version 22.0 for Windows program. The results are described in the form of narratives, tabulations, diagrams, or pictures. Bivariate analysis was performed as a comparative analysis of serum aldosterone levels between Class I-II functional HF and Class II-IV functional HF using an unpaired t-test. Analysis to control for confounding variables uses a logistic regression test.

Results

Table 1 shows the baseline status and laboratory characteristics of the study subjects. The majority of subjects are male, age more than 55 years, the majority of high school and college-educated with the majority of labor and entrepreneurial work. The majority of participants smoke, with the etiology of most of the HF being due to hypertensive heart disease (HHD) and the prevalence of dyslipidemia and having a BMI of more than 24.9 kg/m^2. The majority of the subjects' blood pressure is also high.

Table 2 shows that there is no confounding variable that has a significantly different effect on the Group I-II and III-IV functional HF groups. Aldosterone levels also did not show a significant difference between the group NYHA I-II functional HF group and the NYHA Class III-IV functional HF group.

Discussion

ACEI drugs work by inhibiting the activity of ACE in converting AT1 to AT2 and inhibiting the degradation of bradykinin, with the result of reducing peripheral resistance and ultimately lowering blood pressure. In this study, aldosterone levels remained high in both groups despite the use of ACEIs or ARBs [11], [12], [13], [14], [15]. However, suppression of ANG-II production and serum aldosterone secretion

Table 1: Baseline characteristics

Characteristics	n (32)	%	Mean	p
Gender				
Male	19	59.4		
Female	13	40.6		
Age (years)* Age group (years)				
<55 years	14	43.8	56.75 ± 11.30	0.790**
>55 years	18	56.3		
Education				
Primary school	2	6.3		
Junior high school	11	34.4		
Senior high school	13	40.6		
University	6	18.8		
Occupation				
Laborer	8	24.9		
Entrepreneur	13	40.6		
Private employee	3	9.4		
Civil servant	2	6.3		
Housewives	6	18.8		
Smoking				
Yes	18	56.3		
No	14	43.7		
HF etiology				
Hypertensive heart disease	22	68.8		
Coronary arterial disease	9	28.1		
Others	1	3.1		
Medication				
ACEI	15	46.9		
ARB	17	53.1		
BMI				
<24.9 kg/m^2	24	75.0		
>24.9 kg/m^2	8	25.0		
Blood pressure				
Systolic*				
Median	Minimum	Maximum	144.06 ± 24.8	0.248
Diastolic*				
90	60	150		0.001
Laboratory variable	Value		p-value	
	Mean	Median		
Total cholesterol (mg/dl)	224.25 ± 42.49		0.76	
HDL (mg/dL)		44.00 (18.00–84.00)	0.03*	
LDL (mg/dL)		128.50 (68.00–230.00)	0.02*	
Triglycerides (mg/dL)	156.15 ± 32.28		0.27	
Potassium (mEq/L)		3.70 (2.80–5.40)	0.03*	
Sodium (mEq/L)	139.50 ± 3.48		0.48*	
Aldosterone serum (ng/dL)		6.11 (2.03–25.70)	0.02*	

HF: Heart failure, BMI: Body mass index, ACEI: Angiotensin-converting-enzyme inhibitor, ARB: Angiotensin II-receptor blockers, *The Shapiro-Wilk test obtained normal data distribution (p>0.05) rated mean and SD. Suppose an abnormal distribution is obtained (p<0.05), the median and range (minimum-maximum) are used. Categorical variables are presented in n (%). Numeric variables are normally distributed in the mean ± standard deviations. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, **p-values for age variables in all patient

Table 2: Relationships between variables with HF

Variables	NYHA Class I-II		NYHA Class III-IV		p
Gender	n	%	n	%	
Male	7	43.8	11	68.8	0.14*
Female	9	56.3	5	31.3	
Age					
<55 years	10	62.5	4	25	0.45*
>55 years	6	37.5	12	75	
Medication					
ACEI	8	50	7	43.8	0.72*
ARB	8	50	9	56.3	
HF etiology					
HHD	13	81.3	9	56.3	0.69**
CAD	3	18.8	6	37.5	
Others	0	0	1	6.3	
Dyslipidemia					
Yes	14	87.5	10	62.5	0.22***
No	2	12.5	6	37.5	
Smoking					
Yes	7	43.8	11	68.8	0.15*
No	9	56.3	5	31.3	
Aldosterone variable	Functional Class I-II (n=16)		Functional Class III-IV (n=16)		p-value
Aldosterone level	8.06 ± 3.92		5.31 (2.03–25.70)		0.445[#]

HF: Heart failure, NYHA: New York heart association, ACEI: Angiotensin-converting-enzyme inhibitor, ARB: Angiotensin II-receptor blockers, *Chi-square test, significant if p<0.05, **Kolmogorov–Smirnov test, ***Fisher's test, [#]Mann–Whitney.

by ACEIs and ARBs cannot be sustained even with long-term treatment.

At the beginning of treatment, ACEIs or ARBs can indeed eliminate most Ang-II from the serum, but in long-term treatment, Ang-II levels will appear and be re-measured. This situation is called "Ang-II reactivation" and this is associated with a poor prognosis. This is due to ACEIs and ARBs unable to inhibit the production of Ang-II produced by other pathways, namely non-renin and non-ACE lines. The continued formation of Ang-II means that it will also continue to stimulate aldosterone secretion. This phenomenon is considered as one of the fixed mechanisms of cardiovascular complications [16], [17], [18], [19], [20], [21], [22]. ACEIs are not able to suppress ACE activity and serum aldosterone secretion in the long term; this may be due to increased serum potassium levels. It has been explained that potassium levels previously, together with AT2 synergistically stimulate serum aldosterone production [23]. The above phenomena might occur in patient with Class I-II and Class III-IV functional HV who have consumed ACEIs or ARBs in this study. The use of ACE with ARB in the long term was unable to suppress Ang-II activity, and aldosterone secretion might be related to changes in the responsive mechanisms of various receptors involved with RAAS itself.

The results of this study are in line with a survey conducted by Kobayashi *et al*. in 2020, which stated that aldosterone did not play a role in clinical improvement of HF patients, improved therapeutic response, and had no effect on improving patient outcomes with HF [24]. This study is one of the researches that compared the aldosterone levels of patients with HF categories NYHA I-II and NYHA III-IV in an Asian population. The limitation of this study is the limited number of research samples.

Conclusion

Serum aldosterone levels in patients with Class I-II functional HF and those with Class III-IV functional HF who consumed ACEIs or ARBs were not significantly different.

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