



# INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

## CORRELATION BETWEEN VENTRICULAR ACTIVATION TIME FROM 12-LEAD ECG AND LEFT VENTRICULAR SYSTOLIC FUNCTION IN PATIENTS DIAGNOSED WITH HYPERTENSION

Hery D. Putra<sup>1</sup>, Abdullah Afif Siregar<sup>2</sup>, Nizam Z. Akbar<sup>2</sup>, Anggia C. Lubis<sup>2</sup>, T. Bob Haykal<sup>2</sup>, Harris Hasan<sup>2</sup>

<sup>1</sup>Resident of Department of Cardiology, Faculty of Medicine, Sumatera Utara University

<sup>2</sup>Department of Cardiology, Faculty of Medicine, Sumatera Utara University

DOI: 10.5281/zenodo.3734255

**Keywords:** ventricular activation time; left ventricular ejection fraction; diastolic heart failure; systolic heart failure.

### Abstract

**Background:** Hypertension is a cardiovascular risk factor which could lead pressure overload in left ventricle then causing diastolic and systolic dysfunction. Echocardiography has important role to assess heart structure and function in hypertensive patients, still the myocardial changes actually has occurred before remodelling of left ventricle. Electrical changes of the heart would develop first, which ventricular activation time (VAT) duration from ECG increased in left ventricular hypertrophy. This condition is closely related to course of hypertensive disease. The aim of this study is to investigate correlation between VAT and left ventricular ejection fraction in hypertensive patients.

**Method:** Data were collected from 60 consecutive patients with hypertension whom visiting policlinic in Cardiac Centre Haji Adam Malik General Hospital Medan. Data of VAT (Q-T interval) from ECG and left ventricular ejection fraction (LVEF) from echocardiography were collected and analyzed. Then the duration of VAT and LVEF changed were assessed. Statistical analysis was performed using correlation and comparative test, including scatter-plot graphic.

**Result:** Among 60 hypertensive patients as total subject, divided to 30 subjects with diastolic heart failure and 30 subjects with systolic heart failure. Mean of VAT duration from total subject was 42 milliseconds and mean of LVEF was 45.71%, while mean of LVEF in diastolic heart failure group was 56% and mean of LVEF in systolic heart failure group was 35.43%. Spearman correlation test was used to assess relationship between VAT and LVEF, the result showed there was reverse correlation with  $p < 0.001$  and had strong correlation with coefficient  $r = -0.789$ . Then Mann-Whitney comparative test was performed to compare VAT between diastolic heart failure group and systolic heart failure group, the result showed statistically significant difference between 2 groups.

**Conclusions:** VAT duration from ECG in hypertensive patients and LVEF have reverse correlation, which means the increasing of VAT duration related to the decreasing of LVEF. Besides, there is a significant difference of VAT duration of hypertensive patients between diastolic heart failure and systolic heart failure with mean cut-off value is 44.68 milliseconds.

### Introduction

The increasing prevalence of hypertension every year is a major problem in both developed and developing countries. It is estimated that in 2025 the percentage of hypertensive patients will increase by 24% in developed countries. Whereas in developing countries the percentage of people with hypertension increases much higher at around 80%.<sup>1</sup> Indonesia is an example of a developing country with a high prevalence of hypertension. The average prevalence of hypertension throughout Indonesia is 29.8%.<sup>2</sup>

Recommendation from recent guideline of heart failure management highlighted the importance of echocardiography to assess heart structure and function alteration. But actually, myocardium had been changed before the damage occurred. Alteration of heart's electrical activity occurred first, which ventricular activation time (VAT) increased in left ventricular hypertrophy even no changed in left ventricular mass. VAT represented myocardial excitation time to transmit electrical conduction from bundle of His to Purkinje fibres, which had



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE &amp; MANAGEMENT

correlation with diastolic dysfunction and natural history of hypertension. VAT is measured from the beginning of QRS complex to peak of R wave on ECG (QR interval).<sup>3</sup>

Prolonged hypertension would fall into heart failure condition. Heart structural changed which dominated by pressure overload will cause diastolic dysfunction and left ventricular hypertrophy, manifested as heart failure with preserved ejection fraction (HFpEF). End stage of hypertensive heart disease marked by pressure and volume overload and lead to dilated cardiomyopathy, manifested as heart failure with reduced ejection fraction (HFrEF).<sup>4</sup>

A study conducted by Boles *et al.* showed that VAT from ECG of hypertensive patients was increased and had strong correlation with diastolic dysfunction from echocardiography, with cut-off normal value was 35 – 40 milliseconds.<sup>3</sup> Based on that consideration, this study aims to further investigate the correlation between VAT from ECG and left ventricular systolic function from echocardiography in patients with hypertension.

### Methods

This study design is a correlative cross-sectional study with consecutive sampling technique, which ECG data and left ventricular systolic function data from echocardiography of hypertensive patients were collected in Heart Centre Polyclinic of Haji Adam Malik General Hospital Medan. Sample data had been carried out from July 2019 until December 2019. The inclusion criteria were subjects with BP  $\geq$  140/90 or patients with normal blood pressure but routinely taking hypertension medication. The exclusion criteria were patients with arrhythmia, heart valve abnormalities due to rheumatic heart disease, severe functional disorders of the mitral or aortic valve, congenital heart disease, pericardial abnormalities, patients who could not lie on their backs, and poor echo window.

Patients who met the inclusion criteria were then conducted anamnesis and physical examination to obtain clinical baseline data and patient's history, then electrocardiographic examination with a speed of 50 mm/s and a scale of 20 mm/mV. VAT was measured as length or duration from the beginning of Q wave to peak of R wave on a 12-lead ECG, but might be represented only by lead V6 measurement. Measurements were made manually using a 150 mm Krisbow vernier caliper micrometer (KW0600352) and a magnifying glass. Measurement results are reported in milliseconds units. The patient then performed an echocardiographic examination, data such as left ventricular ejection fraction and a complete LV study, left ventricular diastolic function as assessed by the ratio E/A and E/e' were recorded. Then the patients were divided into 2 groups: diastolic heart failure (HFpEF) and systolic heart failure (HFrEF).

Data was presented by frequency distribution and percentage for categorical data while numerical data is presented by displaying the mean (average)  $\pm$  standard deviation and median (middle value) with minimum - maximum values. The correlation between VAT and LVEF would be assessed by Pearson or Spearman test, and the data distribution would be displayed with scatter-plot diagram. Thus, the comparison of VAT between HFpEF group and HFrEF group would be assessed by independent T-test or Mann-Whitney test. Statistical data analysis used SPSS software version 23, and p value  $<$ 0.05 was said to be statistically significant.

### Results

This study was performed by collecting data from outpatient diagnosed with hypertension in in Heart Centre Polyclinic of Haji Adam Malik General Hospital Medan, and total 60 patients were enrolled in this study after inclusion and exclusion criteria were fulfilled. Data from study population showed the baseline characteristic that consist of clinical characteristic; ECG result; laboratory result; patient routine medications; and echocardiography result (*table 1, table 2, table 3*).

The average of population age in this study was 57.5 years-old, dominated with male gender 43 patients (71.7%). Mean of body mass index was 24.68 kg/m<sup>2</sup>. Mean of systolic and diastolic blood pressure were 141 mmHg and 84 mmHg. Meanwhile the average of patients duration having hypertension was 7.45 years. ECG data revealed that the average of QRS complex duration and VAT duration was 83 milliseconds and 42 milliseconds. The pattern of left ventricular hypertrophy from ECG in this study dominated with strain pattern or



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE &amp; MANAGEMENT

pressure type (46.7%). While the morphology of P wave ECG mostly showed P mitral pattern (56.7%) which related to enlargement of left atrium. From laboratory results, there were increasing of HbA1c level (6.89%) and LDL value (111 mg/dL).

Table 1. Baseline characteristic of study population

Variable	Mean	n (%)
Age (years)	57.50 ± 9.30	
Gender		
Male		43 (71.7%)
Female		17 (28.3%)
Systolic blood pressure (mmHg)	141.40 ± 14.55	
Diastolic blood pressure (mmHg)	84.46 ± 9.69	
Duration of hypertension (years)	7.45 ± 3.43	
<b>ECG results</b>		
QRS duration (milliseconds)	83 ± 21.49	
VAT duration (milliseconds)	42 ± 11.13	
Left ventricular hypertrophy (strain pattern)		
Yes		28 (46.7%)
No		32 (53.3%)
Left ventricular hypertrophy (Sokolow-Lyon criteria)		
Yes		25 (41.7%)
No		35 (58.3%)
P wave morphology		
Normal		26 (43.3%)
P mitral (LAE)		34 (56.7%)
<b>Laboratory results</b>		
Creatinine	1.08 ± 0.24	
HbA1c	6.89 ± 1.22	
Total cholesterol	181.06 ± 33.01	
HDL level	55.53 ± 13.85	
LDL level	111.06 ± 27.67	

Antihypertensive therapy from renin-angiotensin inhibitor group that used in this study was dominated with angiotensin receptor blocker (58.3%) than ACE-inhibitor (41.7%). ARB therapy consisted of Valsartan (28.6%), Candesartan (51.4%), and Telmisartan (20%). Meanwhile ACE-inhibitor therapy consisted of Captopril (44%) and Ramipril (56%). Beta-blockers therapy was given 90% of population in this study, which were Bisoprolol (75%) and Carvedilol (15%). The others antihypertensive that included in this study were Furosemide (66.7%), Calcium Channel Blocker (40%), and Spironolactone (25%).

Table 2. Analysis of antihypertensive therapy

Antihypertensive drugs	n (%)
Renin-angiotensin inhibitors	
ACE-inhibitors	25 (41.7%)
Captopril	11 (44%)
Ramipril	14 (56%)
ARB	35 (58.3%)
Valsartan	10 (28.6)
Candesartan	18 (51.4%)
Telmisartan	7 (20%)



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE &amp; MANAGEMENT

$\beta$ -blockers		
Not given		6 (10%)
Bisoprolol		45 (75%)
Carvedilol		9 (15%)
Diuretics (Furosemide)		
Yes		40 (66.7%)
No		20 (33.3%)
Calcium Channel Blocker		
Yes		24 (40%)
No		36 (60%)
Aldosterone antagonist (Spironolactone)		
Yes		15 (25%)
No		45 (75%)

Echocardiography data of population in this study revealed that mean of LVEF was 45%, which further categorized as HFpEF (mean EF = 56%) and HFrEF (mean EF = 35%). Heart chamber morphology were distinguished as normal left ventricle (5%); concentric LVH (45%); and eccentric LVH (50%). Based on diastolic function, study population was grouped as normal diastolic function (10%); diastolic dysfunction relaxation type (53.3%); diastolic dysfunction pseudonormal type (26.7%); and diastolic dysfunction restriction type (10%). Data of left ventricular morphology of population study was represented by the average thickness of interventricular septum wall and left ventricular posterior wall, which were 12.95 mm and 12.97 mm consecutively. After that, Spearman correlation test was performed to assess relationship between VAT and left ventricular thickness, the result showed that there was a significant correlation between VAT and interventricular septum wall thickness ( $p < 0.005$ ;  $r = 0.93$ ) as shown on *table 4*.

*Table 3. Analysis of echocardiography data*

Variable	Mean	n (%)
Left ventricular ejection fraction (%)	45.71 $\pm$ 11.91	
HFpEF	56 $\pm$ 7.91	
HFrEF	35.43 $\pm$ 2.71	
Diastolic function (E/A)	1.11 $\pm$ 0.53	
Diastolic function (E/e')	11.02 $\pm$ 4.41	
Interventricular septum wall thickness/ IVSd (milimeter)	12.95 (11 – 16)	
Left ventricular posterior wall thickness / LVPWd (milimeter)	12.97 (11 – 16)	
Left ventricular chamber		
Normal		3 (5%)
Concentric hypertrophy		27 (45%)
Eccentric hypertrophy		30 (50%)
Diastolic dysfunction		
Normal		6 (10%)
Grade I (relaxation)		32 (53.3%)
Grade II (pseudonormal)		16 (26.7%)
Grade III (restrictive)		6 (10%)



INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Table 4. VAT dan left ventricular wall thickness correlation

	Ventricular Activation Time (VAT)
Interventricular septum wall thickness	r = 0.93 p = 0.012* n = 60
Left ventricular posterior wall thickness	p = 0.128* n = 60

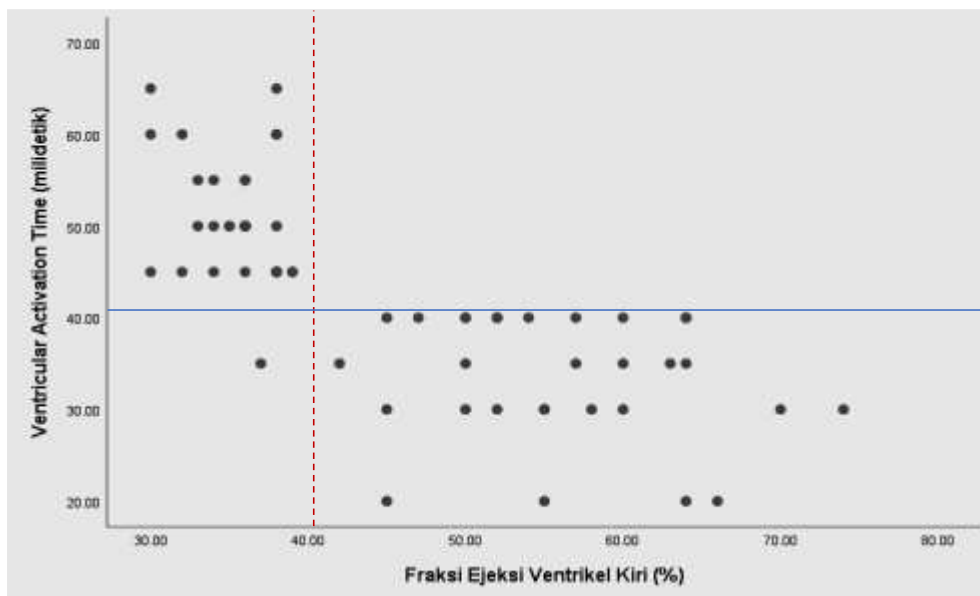
\*Spearman test

Distribution of VAT and LVEF were assessed with scatter-plot diagram (picture 1). Thus, statistical analysis was performed to assess correlation between VAT and LVEF which represented left ventricular function. Spearman correlation test showed that there was inverse correlation between VAT and LVEF (p <0.05; r = -0.789), which means increasing of VAT would decrease LVEF (table 5).

Table 5. VAT and LVEF correlation

	Left Ventricular Ejection Fraction (%)
Ventricular Activation Time (milliseconds)	r = - 0.798 p < 0.001* n = 60

\*Spearman test



Picture 1. Scatter-plot diagram of VAT dan LVEF distribution

To investigate the mean difference VAT duration between diastolic heart failure and systolic heart failure, the comparative test using Mann-Whitney test was performed on HFpEF group and HFrEF group. The result showed that there was a statistically significant difference between VAT in HFpEF group and in HFrEF group (p <0.05), with cut-off of VAT duration between two groups was 44.68 milliseconds (table 6).

Table 6. Comparison of VAT duration based on heart failure groups

	Mean Rank	p value*
VAT in HFpEF (n = 30)	16.32	< 0.001
VAT in HFrEF (n = 30)	44.68	

\*Mann-Whitney test



## Discussion

Alteration or heart dysfunction caused by hypertension is marked by left ventricular hypertrophy, which ECG examination is quite sufficient to establish the diagnosis. Meanwhile, echocardiography is most accurate to assess left ventricular geometry (concentric or eccentric hypertrophy) and function.<sup>5</sup> The increasing of intrinsicoid deflection time or ventricular activation time (VAT) on ECG indicates alteration of myocardial function and could be used as predictor of heart failure.<sup>6</sup>

Based on baseline characteristic in this study, the average of patients age was 57.5 years-old and mean of hypertension duration was 7.45 years. Previous study had similar results, which showed the incident of hypertension commonly found in patients with 50 years-old or more of age. It is because increasing of blood pressure by aging has close correlation with alteration of arterial vasculature which lead to blood vessel stiffness.<sup>7</sup> In a study conducted by Tackling *et al.*, patients duration or length of time from firstly diagnosed hypertension to heart failure condition was approximately 14.1 years in average.<sup>8</sup>

In this study, the average of QRS complex duration from study population ECG was within normal range 83 miliseconds, with mean VAT duration was increased 42 miliseconds. Boles *et al* in a study concluded that VAT represented myocardial excitation duration to transmit electrical conduction from bundle of His to Purkinje fibres, with normal value 35 – 40 miliseconds.<sup>3</sup> So that, VAT duration was above the normal value which showed lengthening myocardial excitation time in hypertensive patients.

Based on pathophysiology mechanism, the increasing of intrinsicoid deflection or VAT is a secondary effect of heart electrical conduction deceleration because of myocardial mass increasing. Some of mechanism which related to deceleration of impulse conduction and arrhythmogenicity are myocardial thickness and changing of interstitial collagen structure. In a study conducted about ECG in hypertensive patients with left ventricular hypertrophy, there was an increasing of VAT duration related to decreasing of LVEF and sudden cardiac death.<sup>9</sup> Myocardial thickness, especially on interventricular septum where bundle of his laid on, will cause lengthening of left ventricular conduction and excitation. It is consistent with this study which revealed that there was statistical correlation between VAT and interventricular septum thickness ( $p = 0.01$ ).

The primary end-point of this study is to investigate correlation between VAT from ECG and LVEF from echocardiography in hypertensive patients. Spearman correlation test was performed, the result showed inverse correlation between VAT and LVEF with  $p$  value  $<0.001$  and strong coefficient correlation power ( $r = -0.789$ ), which mean the increasing of VAT on ECG would decrease LVEF of population study. Next, to make the result more precise, we assessed comparison of VAT between HFpEF group and HFrEF group. Mann-Whitney comparative test was performed to compare VAT between 2 groups, the results showed there was statistically significant difference between VAT in HFpEF group and VAT in HFrEF group ( $p <0.001$ ), which representing that the average of VAT duration in HFrEF group was higher than HFpEF group. So, the increasing of VAT duration is related to possibility of systolic heart failure event with reduced LVEF, which cut-off point of VAT in HFrEF was 44.68 miliseconds.

A study that conducted by O'Neal *et al* which comparing ECG pattern in patients with HFpEF and HFrEF. The results revealed that ECG pattern related to HFrEF were: increasing of QRS complex duration; deceleration of intrinsicoid deflection which manifested VAT prolongation; left axis deviation; QT interval prolongation; left ventricular hypertrophy; and left bundle branch block. Meanwhile, ECG pattern related to HFpEF were: increasing of resting heart rate and abnormal P wave. After statistical analysis was performed, the significant ECG pattern to differ HFrEF and HFpEF were VAT prolongation and QT interval prolongation.<sup>10</sup> That result is parallel with our study where VAT duration was longer in HFrEF group than HFpEF group, so that VAT could be used as predictor of LVEF in patients diagnosed with hypertension.

## Conclusion

VAT duration from ECG in hypertensive patients and LVEF have reverse correlation, which means the increasing of VAT duration related to the decreasing of LVEF. Besides, there is a significant difference of VAT duration of hypertensive patients between diastolic heart failure and systolic heart failure with mean cut-off



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

value is 44.68 milliseconds. Therefore, as a simple screening tool which widely available, the duration of VAT from ECG has ability to detect systolic dysfunction marked by decreasing of LVEF from echocardiography in patients diagnosed with hypertension.

### References

- [1] Kearny JB, Davis BR, Cutler J, et al. 1997. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension: SHEP Cooperative Research Group. *JAMA*. 278:212–216.
- [2] Sundoro T. In :Riset Kesehatan Dasar (RISKESDAS / *Basic Health Research*). 2008. National Report. Badan Penelitian dan Pengembangan Kesehatan, Departemen Kesehatan R.I(*Indonesian Health Department*). 134-135.
- [3] Boles U., Abdollah H., Al-Ghabra W., et al. 2015. Ventricular activation time as a marker for diastolic dysfunction. *Biomarker in Cardiovascular Disease*. DOI 10.1007/978-94-007-7741-5\_45-1
- [4] Messerli F.H., Rimoldi S.F., Bangalore S. 2017. The transition from hypertension to heart failure: contemporary update. *JACC: Heart Failure*. Vol. 5 No. 8
- [5] Khatib O.M.N, El-Guindy M.S. 2005, WHO Clinical Guidelines For The Management of Hypertension. *EMRO Technical Publication Series*. Vol. 29
- [6] O'Neal W.T., Qureshi W.T., Nazarian S., et al. 2016. Electrocardiographic Time to Intrinsicoid Deflection and Heart Failure: The Multi-Ethnic Study of Atherosclerosis. *Clin Cardiol*. 39(9): 531-536
- [7] Pinto, Elisabete. 2007. Blood Pressure and Ageing. *Postgrad Med J*. 83: 109-114. DOI: 10.1136/pgmj.2006.048371
- [8] Tackling G., Borhade M.B. 2019. Hypertensive Heart Disease. *StatPearlsPublisihing*. PMID: 30969622
- [9] Darouian N., Narayan K., Aro A.L., et al. 2016. Delayed Intrinsicoid Deflection of the QRS Complex is Associated with Sudden Cardiac Death. *Heart Rhythm*. Vol 13(4): 927-932
- [10] O'Neal W.T, Mazur M., Bertoni A.G., et al. 2017. Electrocardiographic predictors of heart failure with reduced versus preserved ejection fraction: The multi-ethnic study of atherosclerosis. *J Am Heart Assoc*. DOI: 10.1161/JAHA.117.006023.