ORIGINAL ARTICLE

PLAUSIBLE CONFOUNDING FACTORS INFLUENCING ASSOCIATION OF LEFT VENTRICULAR HYPERTROPHY WITH VENTRICULAR LATE POTENTIALS IN HYPERTENSIVE PATIENTS

Bushra Riaz, Sadia Mubarak*, Tallat Naureen, Sidra Hamid***, Mehvish Ashfaq†, Mahvash Khan††**

Department of Physiology, Pak International Medical College, Peshawar, *Islamabad Medical and Dental College, Islamabad, **Rawal Institute of Health Sciences, Islamabad, ***Rawalpindi Medical College, Rawalpindi, †HITEC-IMS, Taxila Cantt, ††Akhtar Saeed Medical College, Rawalpindi, Pakistan

Background: Ventricular late potentials (VLPs) are low amplitude, high frequency signals which are remarkable non-invasive electrocardiographic markers of myocardial tissue damage which can be used to identify ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy (LVH). There are significant confounding factors which affect the association of LVH with VLPs in hypertensive patients. Noteworthy among these are gender, age, body surface area (BSA) and smoking. This study was planned to observe the effect of these confounders on VLPs in hypertensive patients with LVH. **Methods:** The study was conducted in Department of Cardiac Electrophysiology, Armed Forces Institute of Cardiology, Rawalpindi from Nov 2019 to Nov 2020. This was a cohort retrospective study in which 64 patients with systemic arterial hypertension on the basis of LVH were divided into two equal groups. Patients meeting inclusion criteria were selected for Signal-Averaged ECG (SAECG). **Results:** Out of 64 patients, 49 (76.6%) were males and 15 (23.4%) were females. The overall mean age was 60±11.80 years. To rule out the effect of probable confounders (gender, age, BSA, and smoking) which predominantly affects VLPs in hypertensive patients with LVH, logistic regression was applied. Significance of association of LVH with VLPs increased from 0.01 to 0.03 reflecting that confounder, i.e., age, gender, BSA, and smoking were actually having a negative effect on association of VLPs with LVH. **Conclusion:** None of the confounders were associated with VLPs reflecting negative effect on association for the two variables of interest.

Keywords: Ventricular late potentials, VLPs, left ventricular hypertrophy, LVH, Signal averaged ECG

Pak J Physiol 2023;19(1):3–6

INTRODUCTION

Ventricular late potentials (VLPs) are high frequency electrical signals with low amplitude appearing in the terminal part of QRS complex that may spread up to variable length in ST segment.[1] They are the non-invasive electrocardiographic markers of myocardial tissue damage which can be used to identity ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy (LVH).[2] Systemic arterial hypertension and LVH are significant prognosticators of ventricular arrhythmias which are the leading cause of sudden cardiac death in these patients.[3] Knowledge about arrhythmias developing in patients with systemic arterial hypertension notably affects the prognosis and management of the disease. Pathophysiological mechanisms instigating the development of LVH involves systolic and diastolic pressure overload along with neurohormonal activation.[4] The LVH results in myocardial fibrosis which through gap junctions and ion channel remodelling evokes significant electrophysiological changes which lead to delayed conduction velocity.[5] This scarred myocardium becomes an ideal substrate for re-entry which can give rise to life threatening ventricular arrhythmia.[6] Studies have demonstrated potential links between hypertension, LVH and ventricular arrhythmias. VLPs detected through signal averaged ECG[7] are the most substantial non-invasive, practical and cost-effective electrocardiographic parameter to identify life threatening ventricular arrhythmias which may result in sudden cardiac death in these patients.[8]

Significant confounding factors have been discussed in literature which affect the association of LVH with VLPs in patients with systemic arterial hypertension.[9] The robust among these are age, gender, BSA, and smoking.[10] Limited literature is available showing composite effects of these confounders on VLPs in hypertensive patients with LVH. Published data suggests that age, male gender, increased BSA and chronic smoking infuriate VLPs thus confounding the effect of LVH.[11–14] It is critical to identify the plausible factors that masks the real impact of LVH in instigating VLPs in hypertensive patients. The present study was designed to look into this substantial deficient aspect that may affect the arrhythmic susceptibility in these patients.

MATERIAL AND METHODS

The project was formally approved by Ethical Review Committee after which it was piloted at Research

Laboratory of Physiology Department, Army Medical College, Rawalpindi in collaboration with Cardiac Electrophysiology Department of Armed Forces Institute of Cardiology. Written informed consent was also attained from the patients under study.

Sample size was calculated by using 'GS Power' software, version 3.1.9.2. Considering the values of effect size, alpha error and power (1-beta error) as 0.5, 0.05 and 0.85 respectively the minimum sample size was calculated to be 60. However, we used a sample of 64 patients (n=64) through non-probability purposive sampling. History and general physical examination was done and the patients having known cardiac diseases or diabetes mellitus were omitted. The selected participants were subjected to standard ECG and echocardiography to rule out bundle branch block, heart failure, acute or old myocardial infarction, cardiomyopathies and any other structural heart disease. Patients fulfilling the inclusion criteria were dividing into two groups. Group I included 32 hypertensive patients with LVH whereas group II recruited 32 hypertensive patients without LVH.

Selected patients were requested to visit Electrophysiology Department of AFIC for Holter monitoring. DMS 300-4L Holter recorders were used for recording signal averaged ECG. The recorded data was shifted to the computer. The whole data were manually edited by DMS CardioScan software[15] with extreme care using visual checks and correction of all QRS complexes. All erroneous beats were identified and edited from data. After editing, the Holter ECG data were analysed for time domain analysis of the cardiac signal. VLPs were spotted through scrutinizing filtered QRS complex which distinctively included signal averaged ECG filtered QRS complex duration more than 114 mS, the duration of the terminal part of the QRS complex with an amplitude below 40 μV greater than 38 mS and the root mean square voltage signal amplitude of the last 40 mS less than 20 μV. VLPs were considered positive if any two out of three criteria were fulfilled.[16,17]

Two D echocardiography was performed on Toshiba Power Vision 1754TS and Philips IE 33 machines. According to the American Society of Echocardiography the LVH was calculated as left ventricular mass index. The left ventricular mass index is the ratio of left ventricular mass to the BSA. Two D echocardiography was performed to measure three parameters, i.e., left ventricular internal dimension (LVIDd), posterior wall thickness (PWTd) and septal wall thickness (SWTd), all at the end of diastole and subsequently left ventricular (LV) mass was calculated by using the following formula.[6]

$$\text{LV mass} = 0.8 \times \{1.04[(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6\ \text{g}$$

Mosteller formula was used to calculate BSA of all the patients enrolled in the study[18]:

$$\text{BSA}\ (\text{m}^2) = (\text{Height (Cm)} \times \text{Weight (Kg)}/3600)^{1/2}$$

Left ventricular mass index was calculated by obtaining the ratio of left ventricular mass to the body surface area. Left ventricular hypertrophy was confirmed if the left ventricular mass index was greater than 134 g/m^2 for men and 110 g/m^2 for women.[19]

Data was analysed using SPSS-23. Mean±SD were calculated for numerical variables, whereas frequency and percentage were calculated for categorical variables. Logistic regression was applied to rule out the effect of probable confounders, i.e., age, gender, body surface area, and smoking on VLPs in hypertensive patients with LVH. Alpha value was kept at 0.05 at confidence level of 95%.

RESULTS

A total of 64 hypertension patients, 49 male and 15 female, were studied in the present study with mean age of 60±11.83 years (Range: 31–96 Years). The value of 'Nagelkerke R Square' generated by the regression model was 0.27 which was fairly good and illustrated that 27% variance in the outcome variable could be predicted jointly by the predictor variables. None of the confounders were associated with ventricular late potentials (p>0.05). However, significance of association of LVH with VLPs increased from 0.01 (block 1) to 0.03 (block 2) reflecting that confounders were actually having a negative effect on association of the two variables of interest. Same is evident from the value of unadjusted (crude) and adjusted odds ratios for association of LVH and VLPs. The value of unadjusted odds ratio (block 1) was 14.09 (95% confidence interval of 1.68–118.21) which dropped to the adjusted odds ratio (block 2) of 13.10 (95% confidence interval of 1.45–125.47) when confounding factors were also brought into the regression equation. Association between LVH and VLPs remained statistically significant even after controlling the confounding factors (p<0.05). (Table-1)

Table-1: Hierarchical logistic regression showing effect of left ventricular hypertrophy and confounding factors on ventricular late potentials

Variables		Beta coefficient (B)	Wald test	p	Exponent B (Odds ratio)	95% confidence interval
Left ventricular hypertrophy	Block 1	2.70	5.94	0.01*	14.09	1.68–118.21
	Block 2	2.61	5.24	0.03*	13.10	1.45–125.47
Age		0.02	0.30	0.58	1.02	0.95–1.09
Gender		0.74	0.43	0.51	2.10	0.23–19.06
Body surface area (m^2)		1.59	0.47	0.49	4.92	0.05–462.14
Smoking		0.02	0.001	0.98	1.02	0.17–6.10

*Significant

DISCUSSION

Association of VLPs with hypertension was revealed in our study after controlling the effect of confounders which predominantly include age, gender, body surface area, and smoking. VLPs were found significantly associated with hypertension and no association was revealed with age, gender, body surface area and smoking. Soliman *et al*[20] conducted a study on 8,164 patients with left ventricular systolic dysfunction, a significant risk factor for systemic arterial hypertension. They reported a significant association of VLPs with left ventricular systolic dysfunction. No association of VLPs was revealed with age, gender, smoking and body surface area in our study. Findings of Soliman *et al* matched with the results of our study as we also found a significant association of VLPs with systemic arterial hypertension after controlling the effect of confounders (p=0.03). This similarity might be attributed to the same signal averaged ECG criteria used for diagnosis of VLPs in both studies. The mean age of their patients was 54.15±5.3 years which was approximately similar to age of our patients (60±11.80 years). Most of the patients recruited in their study had BMI <30 Kg/m^2.

Bacharova *et al*[1] documented in their study that a significant correlation existed between LVH and VLPs. They further reported that demographic variables (age, gender, body surface area, and smoking) had no role in confounding LVH in regards to VLPs (p<0.001). We also report that LVH had significant association with VLPs (p=0.03), even after controlling the effect of confounders, i.e., age, gender, body surface area and smoking. This similarity might be due to the fact that LVH was diagnosed in both studies on the basis of left ventricular internal dimension, posterior wall thickness and septal wall thickness at the end of ventricular diastole. A study by Cuspidi *et al*[9] to differentiate the effects of age and gender on LVH concluded that ventricular remodelling prompting late potentials occurs more in females than males. They also confirmed that the gender difference despite of body indexation and hemodynamic variabilities to body size are directly correlated with instigating change in ventricular conduction.[9] Their finding is opposite to our result of no association of gender difference in left ventricular hypertrophy and dysfunction. This may be due to the race difference as they included Hispanic whites (59% females) while our study group was Pakistani Asian population. Moreover, difference in mean blood pressure seems to be a significant reason for discrepancy in results. Our participants had a mean blood pressure of 114 mmHg whereas that of Cuspidi *et al* was 121 mmHg. Degree of hypertension is related directly with increase in left ventricular mass and thus LVH; most patients enrolled in their study were female with chronic hypertension with an increased systolic stress. Thus, the chances of ventricular remodelling leading to late potentials increased in their study. In our study majority of the patients were male and were not chronic hypertensive having less risk of ventricle remodelling and thus VLPs.

A study conducted in 2019 by Caselli *et al* concluded that there is high prevalence of hypertension and LVH in athletes having increased BMI.[21] They compared normal blood pressure with increased in high endurance exercise athletes and found a significant difference in body mass index (p<0.001) and body surface area. There results differ with ours as we restricted the group of studies to reduce these cofounders to a minimal level.

Our finding of no effect of confounding factors on VLPs is contradicted by Lee *et al*.[22] They analyzed Korean athletes with normal sedentary controls for late potentials with signal averaged ECG. They reported that there are more late potentials in the athletes than in normal controls. The variation in the results may be due to the age group they collected were lower than (26±2.1) our control groups (60±11.83). Moreover, the increased prevalence of late potentials in their study might be due the reason that athletes heart had eccentric hypertrophy as compared to the concentric ones present in hypertensive patients.[23]

It seems that though the genesis of VLPs in hypertensive patients with LVH is multifaceted and many intricate processes are involved which might have blunted the effect of age, gender, body surface area and smoking despite variations in the apparently underlying mechanisms.

CONCLUSION

VLPs have a robust significant association with LVH even after controlling the effect of probable confounders. As multiple factors are involved in genesis of VLPs in hypertensive patients with LVH, this might have blunted the effect of age, gender, body surface area and smoking thus reflecting negative effect on association on the two variables of interest. VLPs assessment can be used as a non-invasive tool for risk stratification in these patients.

REFERENCES

1. Bacharova L. Missing link between molecular aspects of ventricular arrhythmias and QRS complex morphology in left ventricular hypertrophy. Int J Mol Sci 2019;21(1):48.
2. Raisi-Estabragh Z, McCracken C, Condurache D, Aung N, Vargas JD, Naderi H, *et al*. Left atrial structure and function are associated with cardiovascular outcomes independent of left ventricular measures: a UK Biobank CMR study. Eur Heart J Cardiovasc Imaging 2022;23(9):1191–200.
3. Nadarajah R, Patel P, Tayebjee MH. Is hypertensive left ventricular hypertrophy a cause of sustained ventricular arrhythmias in humans? J Hum Hypertens 2021;35(6):492–8.
4. Koracevic G, Stojanovic M, Lovic D, Zdravkovic M, Sakac D. Certain beta blockers (e.g., bisoprolol) may be reevaluated in hypertension guidelines for patients with left ventricular

hypertrophy to diminish the ventricular arrhythmic risk. J Hum Hypertens 2021;35(7):564–76.
5. Fomina IG, Dyakova TA. Left ventricular hypertrophy in arterial hypertension and arrhythmia risk. Cardiovasc Ther Prev 2022;5(8):83–9. [in Russian]
6. Yildiz M, Oktay AA, Stewart MH, Milani RV, Ventura HO, Lavie CJ. Left ventricular hypertrophy and hypertension. Prog Cardiovasc Dis 2020;63(1):10–21.
7. Banks L, Al-Mousawy S, Altaha MA, Konieczny KM, Osman W, Currie KD, *et al*. Cardiac remodeling in middle-aged endurance athletes: relation between signal-averaged electrocardiogram and LV mass. Am J Physiol Heart Circ Physiol 2021;320(1):H316–22.
8. Zorzi A, Vessella T, De Lazzari M, Cipriani A, Menegon V, Sarto G, *et al*. Screening young athletes for diseases at risk of sudden cardiac death: role of stress testing for ventricular arrhythmias. Eur J Prev Cardiol 2020;27(3):311–20.
9. Cuspidi C, Gherbesi E, Sala C, Tadic M. Sex, gender, and subclinical hypertensive organ damage —heart. J Hum Hypertens 2022:1–8. doi: 10.1038/s41371-022-00750-5.
10. Giamouzis G, Dimos A, Xanthopoulos A, Skoularigis J, Triposkiadis F. Left ventricular hypertrophy and sudden cardiac death. Heart Fail Rev 2022;27(2):711–24.
11. Oknińska M, Paterek A, Bierła J, Czarnowska E, Mączewski M, Mackiewicz UJB, *et al*. Effect of age and sex on the incidence of ventricular arrhythmia in a rat model of acute ischemia. Biomed Pharmacother 2021;142:111983.
12. LaBounty TM, Bach DS, Bossone E, Kolias TJJ. Indexing left ventricular wall thickness to body surface area improves prognostic value. J Echocardiography 2019;36(5):824–30.
13. Shivkumar K. Catheter ablation of ventricular arrhythmias. N Engl J Med 2019;380(16):1555–64.
14. Park J, Lee HJ, Kim SK, Yi JE, Shin DG, Lee JM, *et al*. Smoking aggravates ventricular arrhythmic events in non-ischemic dilated cardiomyopathy associated with a late gadolinium enhancement in cardiac MRI. Sci Rep 2018;8(1):15609.
15. Maretta M, Simurda M, Lesko N, Gbur M, Skorvanek M, Misikova S, *et al*. Excessive supraventricular activity and risk of atrial fibrillation in patients with cryptogenic ischaemic stroke. Neurol Neurochir Pol 2022;56(1):75–80.
16. Pearman CM, Lee D, Davies B, Khan H, Tadros R, Cadrin-Tourigny J, *et al*. Incremental value of the signal-averaged ECG for diagnosing arrhythmogenic cardiomyopathy. Heart Rhythm 2023;20(2):224–30.
17. Samesima N, God EG, Kruse JCL, Leal MG, Pinho C, França FFAC, *et al*. Brazilian Society of Cardiology Guidelines on the Analysis and Issuance of Electrocardiographic Reports. Arq Bras Cardiol 2022;119:638–80.
18. Mosteller RD. Simplified calculation of body-surface area. N Eng J Med 1987;317(17):1098. doi: 10.1056/NEJM198710223171717. PMID 3657876
19. Li X, Guo X, Chang Y, Zhang N, Sun Y. Analysis of alterations of serum inflammatory cytokines and fibrosis makers in patients with essential hypertension and left ventricular hypertrophy and the risk factors. Am J Transl Res 2022;14(6):4097–103.
20. Soliman EZ, Ambrosius WT, Cushman WC, Zhang ZM, Bates JT, Neyra JA, *et al*. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with hypertension: SPRINT (Systolic Blood Pressure Intervention Trial). Circulation 2017;136(5):440–50.
21. Caselli S, Serdoz A, Mango F, Lemme E, Vaquer Seguì A, Milan A, *et al*. High blood pressure response to exercise predicts future development of hypertension in young athletes. Eur Heart J 2019;40(1):62–8.
22. Lee JM, Chung H, Kim HO, Woo JS, Kim SJ, Kim W, *et al*. Ventricular late potentials measured by signal-averaged electrocardiogram in young professional soccer players. Int J Arrhythm 2021;22:3.
23. D'Ascenzi F, Fiorentini C, Anselmi F, Mondillo S. Left ventricular hypertrophy in athletes: How to differentiate between hypertensive heart disease and athlete's heart. Eur J Prev Cardiol 2020;28(10):1125–33.

Address for Correspondence:

Dr. Sidra Hamid, Assistant Professor, Department of Physiology, Rawalpindi Medical University, Rawalpindi, Pakistan. **Cell:** +92-331-5025147

Email: drsidraqaiser@gmail.com

Received: 7 Dec 2022 **Reviewed:** 8 Mar 2023 **Accepted:** 9 Mar 2023

Contribution of Authors

BR: Concept, study design, data analysis and interpretation, final write-up
SM: Concept, study design, data analysis and interpretation, literature review
TN: Draft of manuscript and critical revision of the text
SH: Data analysis and tabulation
MA: Literature review and revision of the text
MK: Draft of manuscript

Funding: None
Conflict of Interest: None