Journal of Clinical and Experimental Cardiology

Mahfouz et al., J Clin Exp Cardiolog 2019, 10:9

Research Article Open Access

Blood Pressure Variability and Coronary Artery Remodeling Index in Patients with Coronary Artery Disease: An Intravascular Ultrasound Study

Ragab A Mahfouz*, Islam Galal, Moataz Elsanan and Mohamed Arab

Department of Cardiology, Zagazig University Hospital, Ash Sharqia Governorate 4451, Egypt

***Corresponding author:** Mahfouz RA, Department of Cardiology, Zagazig University Hospital, Ash Sharqia Governorate 44519, Egypt, Tel: +1006427671; E-mail: ragabaziza61@yahoo.com

Received: August 14, 2019; **Accepted:** August 30, 2019; **Published:** September 07, 2019

Abstract

Objective: We aimed to investigate the relation between Blood Pressure Variability (BPV) and coronary artery remodeling in patients with coronary artery disease coronary by intravascular ultrasound (IVUS).

Materials and methods: Coronary artery remodeling derived from IVUS was calculated in 109 patients with stable coronary artery disease (CAD), who were scheduled for percutaneous coronary intervention. The remodeling index was defined as the ratio of the external elastic membrane (EEM) area at the lesion site to the EEM area at the proximal reference site. Patients were stratified into 2 groups: group I included patients with positive remodeling (RI ≥ 1.05) (n=59), and group II included those with intermediate remodeling/negative remodeling (RI<1.05) (n=50). 24 hours ambulatory blood pressure parameters were obtained. In our study we calculate the weighted systolic blood pressure standard deviation-day and night (W-SD_{dn}) as the BPV index.

Results: Weighted-SD_{dn} and morning blood pressure surge (MBPS) were significantly higher in group I patients (PR) compared with group II (IR/NR) p<0.001. Remolding index was significantly correlated with TG/HDL-C and hs-CRP (p<0.01 and<0.05 respectively. TG/HDL-C was significantly correlated with BPV index (p<0.003). Multivariate analysis showed that weight-SD_{dn} and MBPS were the independent predicting positive remodeling in our cohort. ROC curve analysis showed that, the cut-off values of ≥ 13 mmHg and ≥ 45 mmHg for weighted SD_{dn} and MBPS were found to be the best cut-off values for predicting positive remodeling in patients with stable CAD

Conclusion: We suggest that blood pressure variability index (W-SD_{dn}) and MBPS are associated with positive coronary artery remodeling index independent of coronary artery disease risk factors in patients with stable CAD.

Keywords: Blood pressure variability; Remodeling index; Coronary artery IVUS

Introduction

A growing body of evidence that, Blood Pressure Variability (BPV), is suggested to be a marker of the alterations in cardiovascular regulatory mechanisms that could result in cardiovascular complications and target organ damage regardless the mean Blood Pressure (BP) level [1]. Coronary artery remodeling is changes in the External Elastic Membrane (EEM), usually occurred in response to atherosclerotic plaque accumulation. Positive remodeling (PR) refers to a larger EEM area at a lesion site than the adjacent reference site, and negative remodeling (NR) refers to a smaller EEM area than the adjacent reference site. Positive remodeling has an index>1.05, while negative remodeling has an index<0.95. Direct evidence of remodeling can only be demonstrated in serial studies showing changes in the EEM cross sectional area over time, since remodeling may also be encountered at the "normal-appearing" reference coronary segment [2]. Several studies have demonstrated that PR is more predominant in patients with Acute Coronary Syndrome (ACS) comparing to patients with stable angina pectoris [3-5]. Previous studies have reported that PR lesion has higher lipid contents and a macrophage count, both markers of plaque vulnerability [6]. Plaques exhibiting positive remodeling had more often thrombus and signs of rupture [7]. Conversely, plaques with negative remodeling have a stable phenotype, but they could be identified only in prospective observations and not in a unique IVUS observation. Nevertheless, the association between increased BPV and coronary artery lesion remodeling is not clear. Herein, we conducted the current study to explore the association between BPV and coronary artery remodeling by Intravascular Ultrasound (IVUS), in patients with stable coronary artery disease.

Materials and Methods

Our prospective study included 109 patients with stable coronary artery disease, who were prepared for percutaneous coronary intervention under IVUS control. We excluded patients with, valvular heart disease and inflammatory disease. Patients with poor images of IVUS and those with severe calci ication were also excluded.

24-Hour Ambulatory Blood Pressure Monitoring (ABPM)

All subjects underwent ABPM with the use of device (Mobil-O-Graph; IEM GmbH, Stolberg, Germany). The blood pressure readings were obtained at 30- and one hour intervals in the daytime and at nighttime, respectively. The relevant daytime and nighttime periods were defined as the time intervals, which ranged from 6 am to 10 pm and from 10 pm to 6 am. Any subject lacking ≥ 20% of the readings was excluded. In our study blood pressure variability was considered as

the weighted mean SD of both systolic and diastolic daytime and night blood pressure (W-SD). The Weighted systolic-SD_{dn} is the mean of day and night SD values of systolic blood pressure corrected for the number of hours included in each of these two periods, based on the following formula: SD_{dn}=([day SD × hours included in the daytime]+[night SD × hours included in the night time])/(hours included in daytime+nighttime) [8]. Morning Blood Pressure Surge (MBPS) was calculated as the difference between morning systolic blood pressure obtained after waking (averaged systolic blood pressure for 2 hours just after waking up) minus the lowest nocturnal systolic [9]. Participants who showed a nocturnal fall of ≥ 10% in SBP were considered dippers. Likewise, a patient whose nocturnal SBP fell by <10% or even rose was defined as a non-dipper.

IVUS imaging and analyses and definitions of remodeling

All coronary intravascular ultrasound studies were performed with the use of 20-MHz, 2.9 F IVUS system (Eagle Eye, Volcano Corp, Rancho Cordova, CA, USA). The IVUS catheter was advanced >10 mm beyond the lesion and automated pullback was performed to the aorto-ostial junction at a speed of 0.5 mm/s. For evaluation, the proximal reference site and the target lesion site were chosen. The target lesion was defined as the site with the smallest minimal lumen diameter. Whilst, the proximal reference segment was defined as the site with the least amount of plaque proximal to the target lesion without any intervening side branch.

The EEM area at the site of the target lesion was measured and compared with EEM area at the proximal reference site. After that, the coronary artery remodeling index was calculated as the ratio of EEM area at the target lesion site to the area at the proximal segment. In our study, the patterns of coronary artery remodeling were stratified into two groups; the first group with positive remodeling (PR), (Figure 1) and the second group included those with intermediate/negative (IR/NR), (Figure 2). Positive remodeling was considered, when the remodeling index>1.05, intermediate remodeling (a remodeling index between 0.95 and 1.05) and those with negative remodeling (a remodeling index<0.95) [5].

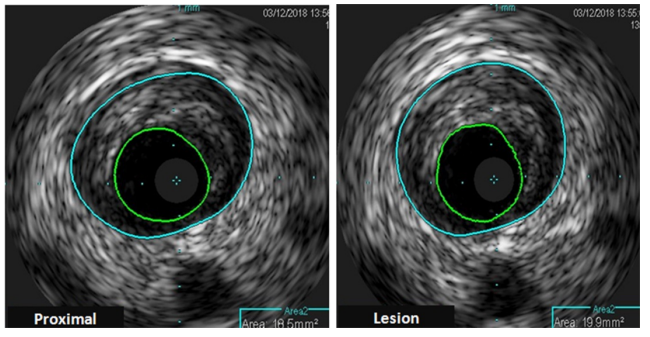

Figure 1: An example of positive remodeling. A patients with weighted SD_{dn}=14 mmHg. The remodeling was [1.08], an example of negative remodeling. A patients with weighted SD_{dn}=8 mmHg. The remodeling was [0.6].

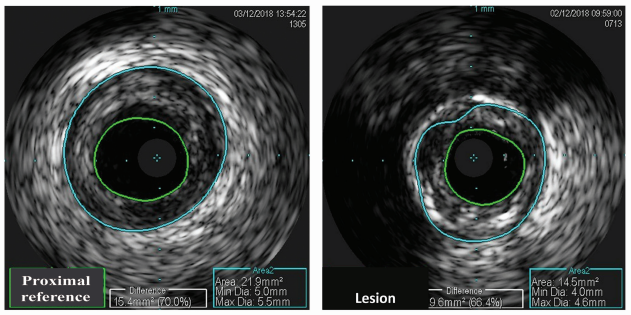

Figure 2: Correlation between weighted SD_{dn} and triglyceride to high density lipoprotein (TG/HDL-C) ratio. ROC shows that weighted SD_{dn} ≥ 13 mmHg is the best cut-off value for predicting positive remodeling. AUC=0.91, p<0.001.

Laboratory analysis

Blood samples were obtained before PCI for assessment of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride levels, blood glucose, high-sensitivity C-reaction protein (hs-CRP). TG/HDL-C ratio was also calculated.

Statistical analysis

Statistical analyses were performed with SPSS version 16.0 (SPSS Inc). Continuous and normally distributed data are presented as mean ± 1 SD and were compared by two-tailed unpaired t tests. Spearman correlation coefficient test was used for correlations analyses. Univariable and multivariable binary logistic regression models were performed to characterize predictors of positive remodeling. ROC curve analysis was performed to obtain the cutoff value of weighted systolic-SD_{dn}, with the highest sensitivity and specificity, of predicting positive remodeling in patients with patients coronary artery disease.

Results

Patients were stratified into two groups based on the remodeling pattern as positive remodeling group (PR, remodeling index>1.05), which included 59 patients and intermediate remodeling (IR, remodeling index ≤ 1.05 and ≥ 0.95)/negative remodeling (NR, remodeling index<0.95) which included 50 patients. Table 1 represents the demographic data of both groups. There were no significant differences among both groups as regards baseline characteristics except for TG/HDL-C (p<0.01) and hs-CRP (p<0.05).

	Positive remodeling n (59)	Intermediate/negative remodeling n (50)	p value

Age (y)	49.5 ± 11.5	48.9 ± 11.8	0.25
Women, No. (%)	17 (29)	15 (30)	0.22
BMI (Kg/m2)	26.1 ± 3.5	25.0 ± 3.1	0.13
Smoking n (%)	23 (39)	20 (40)	0.32
Diabetes mellitus, n (%)	26 (44)	25 (50)	0.45
Hypertension, n (%)	32 (54)	29 (58)	0.36
Office SBP, mmHg	127 ± 11	126 ± 12	0.85
Office DBP, mmHg	75 ± 8	73 ± 7	0.48
Total cholesterol (mg/dL)	185 ± 42	179 ± 45	0.62
Triglycerides (mg/dL)	159 ± 73	140 ± 65	0.06
HDL-C (mg/dL)	40 ± 8	45 ± 11	0.05
LDL-C (mg/dL)	107.8 ± 40.8	104.3 ± 37.4	0.55
TG/HDL-C ratio	3.9 ± 0.8	3.0 ± 0.5	<0.01
hs-CRP (mg/dl)	0.67 ± 1.41	0.31 ± 1.02	<0.01
Remodeling index	1.35 ± 0.12	0.89 ± 0.08	<0.001
Number of diseased vessels	59 (54%)	50 (46%)	0.07
Single vessel	27 (45.8)	23 (46)	0.51
Two vessels	20 (33.9)	18 (36)	0.45
Multi-vessels	12 (20.3)	9 (18)	0.42

Table 1: Baseline characteristics of the study cohorts according to the presence or absence of positive remodeling.

Table 1 depicts the ABPM data of patients in group I compared with those in group II. Weighted systolic-SD_{dn} was significantly higher in group I compared with group II ($p<0.001$). Furthermore, the weighted systolic day SD was higher in group I patients ($p<0.05$). Importantly, we found that group I patients had a significant exaggerated MBPS was compared with group II ($p<0.003$)

The relations between remodeling index and the tested variables are represented in Table 1. Our results showed that weighted systolic-SD_{dn} and MBPS were significantly correlated with remodeling index ($r=0.49$, and 0.45 respectively; $p<0.001$). TG/HDL-C ration had a significant correlation with remodeling index ($r=0.39$, $p<0.003$). Besides, TG/HDL-C ratio was significantly correlated with weighted SD_{dn} ($r=0.43$, $p<0.001$).

Correlation analysis showed significant correlations between remodeling index and the weighted systolic-SD_{dn} ($p<0.001$), MBPS ($p<0.001$), day SBP variability ($p<0.01$), nocturnal SBP variability ($p<0.01$), TG/HDL-C ($p<0.003$) and hs-C reactive protein ($p<0.05$).

Multivariate analysis showed that weighted systolic-SD_{dn} ($p<0.001$) and Morning surge ($p<0.001$), were the independent predictors of positive remodeling in subjects with stable CAD. With ROC carve analysis, we found that BPV index (weighted systolic-SD_{dn}) value ≥ 13 mm Hg had a sensitivity of 95% a specificity 83% for identification of patients with the positive remodeling. The area under the curve was 0.91 (95% CI, 0.85-0.97). Furthermore, MBPS value>45 mmHg was the optimal cut-off value for predicting positive remodeling with a sensitivity of 93% and a specificity of 81%. The area under curve=0.89(95% CI, 0.83-0.95).

Discussion

The current study provides an explicit evidence of a significant correlation between blood pressure variability and coronary artery remodeling in subjects with stable coronary artery disease. It implies that BPV index (weighted-SD_{dn}) and exaggerated MBPS are independent predictors of positive remodeling in patients with stable CAD. Our study provides additional interesting merits. First, weighted SD_{dn} index value ≥ 13 mmHg was the optimal cut-off value, to predict positive remodeling in subjects with stable CAD, second MBPS ≥ 45 mmHg was the best cut-off value to predict positive remodeling, third, TG/HDL-C ratio was significantly correlated with both blood variability index (weighted systolic-SD_{dn}) and remodeling index, finally, hs-C reactive protein was significantly higher in patients with positive remodeling and correlated with remodeling index.

Many investigators demonstrated that coronary artery lesions with positive remodeling are more biologically dynamic compared with intermediate or negatively remodeled lesions. Meanwhile, subjects, who have coronary lesion with positive remodeling are more prone to have vulnerable plaque [10,11].

Yet, the clear-cut morphological characteristics for plaque vulnerability, and precise management, which could improve or alter

features of coronary plaques vulnerability to be stable, are uncertain. Hence, early detection or prediction of vulnerable plaque before rupture is of great value for the prevention of disastrous clinical outcomes and can be a guide for an adjunctive therapy or early intervention.

Obviously, histopathological researches demonstrated that positive remodeling is associated with abundant of inflammatory cells infiltration, more pro-inflammatory cytokines, and enhanced protease activity [10,12].

IVUS have provided a good *in vivo* assessment of coronary plaque and demonstrated positive remodeling is correlated with the plaque volume and a larger necrotic core [13,14]. Hence, great plaque burden with positive remodeling determined by IVUS is related to plaque vulnerability and more atherosclerosis burden. For that, coronary remodeling evaluation might be a major risk predictor for plaque rupture.

Kikuya et al. [15] found an independent relation between short term blood pressure variability and increased risk of cardiovascular events in the general population. Furthermore, Cay et al. [16] found a significant correlation between increased short-term blood pressure variability and the risk of in-stent restenosis in normotensive subjects.

Weiss et al. [17] reported that the fourth quartile (BPV ≥ 17.95 mm Hg) was associated with adverse cardiovascular outcomes, when compared with the first quartile (BPV ≤ 10.56 mm Hg) in both normotensive and hypertensive individuals.

Previous experimental studies in animals showed that higher short-term blood pressure variability was associated with end-organ damage, even at a normal mean blood pressure, consistent with the evidence in humans [18,19].

Li Y et al. [20] found a significant relationship between within-visit diastolic blood pressure variability and the occurrence internal carotid artery plaque and increased intima-media thickness in normotensive subjects. Moreover, they reported that this relation was independent of the impact of mean blood pressure and heart rate on the carotid arteries.

Nagai et al. [21] found an independent relation between subclinical carotid atherosclerosis and visit-to-visit blood pressure fluctuations regardless average blood pressure.

In fact blood pressure variability is a multifaceted incident involving interactions among behavioral, environmental, humoral, and neural effects. The key mechanisms of blood pressure variability are functional impairment of both vascular endothelium and baroreceptor [22]. Moreover, great blood pressure variability might enhance stress on the coronary vasculatures and results in endothelial dysfunction. Consequently, blood pressure variability might have a significant impact on progression of coronary atherosclerotic process.

Another interesting issue, we found a significant higher TG/HDL-C ratio and hs-C reactive protein in subjects with positive remodeling. More so, TG/HDL-C and hs-C reactive protein were correlated with BPV in individuals with positive remodeling. Therefore, TG/HDL-C and hs-C reactive protein could be parts of the determinant links between increased BPV and positive remodeling in normotensive subjects with coronary artery disease.

Da luz et al. [23] demonstrated that TG/HDL-C was an indicator of coronary artery disease progression and is associated with the disease severity. Hence, this ratio is an easily non-invasive predictor of the presence and severity of CAD.

Rodríguez-Morán et al. [24] found a significant association between elevated TG: HDL-C ratios and pre-hypertension in both obese and non-obese children independent of family history of hypertension, insulin levels and HOMA-IR.

Kim et al. [25] demonstrated that high sensitive C-reactive protein was significantly associated with daytime and 24-hour systolic and diastolic BP variability. They concluded that high sensitive C-reactive protein levels were independently predicted by BPV, in spite of clinical confounders.

Implications

The detection of increase of blood pressure variability may predict the early vascular complications, and it could be as a mark of premature cardiovascular morbidity. So, not only keeping the blood pressure in a normal range but also decreasing the blood pressure variability might be of great value to prevent the early cardiovascular morbidity and adverse outcome.

Conclusion

The current study demonstrated blood pressure variability is an independent predictor of plaque vulnerability in patients with stable CAD. We found that BPV index (weighted systolic-SD_{dn}) ≥ 13 mmHg and MBPS ≥ 45 mmHg were the optimal cut-off value for predicting positive remodeling. Hence, we suggest that evaluation of blood pressure variability is important and provides a useful tool for risk stratification for patients with coronary artery disease.

Limitations

This is a single center study with a small number of patients, hence having the possibility of selection bias. No follow-up study was performed.

References

1. Parati G, Ochoa JE, Lombardi C, Bilo G (2015) Blood pressure variability: Assessment, predictive value, and potential as a therapeutic target. Curr Hypertens Rep 17: 537.
2. Palmer ND, Northridge D, Lessells A, McDicken WN, Fox KA (1999) In vitro analysis of coronary atheromatous lesions by intravascular ultrasound; Reproducibility and histological correlation of lesion morphology. Eur Heart J 20: 1701-1706.
3. Kaji S, Akasaka T, Hozumi T, Takagi T, Kawamoto T, et al. (2000) Compensatory enlargement of the coronary artery in acute myocardial infarction. Am J Cardiol 85: 1139-1141.
4. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, et al. (2000) Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: An intravascular ultrasound study. Circulation 101: 598-603.
5. Nakamura M, Nishikawa H, Mukai S, Setsuda M, Nakajima K, et al. (2001) Impact of coronary artery remodeling on clinical presentation of coronary artery disease: An intravascular ultrasound study. J Am Coll Cardiol 37: 63-69.
6. Varnava AM, Mills PG, Davies MJ (2002) Relationship between coronary artery remodeling and plaque vulnerability. Circulation 105: 939-943.
7. Gyongyosi M, Yang P, Hassan A, Weidinger F, Domanovits H, et al. (1999) Arterial remodelling of native human coronary arteries in patients

with unstable angina pectoris: a prospective intravascular ultrasound study. Heart 82: 68-74.

8. Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, et al. (2007) A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. J Hypertens 25: 2058-2066.
9. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, et al. (2003) Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. Circulation 107: 1401-1406.
10. Endo A, Hirayama H, Yoshida O, Arakawa T, Akima T, et al. (2001) Arterial remodeling influences the development of intimal hyperplasia after stent implantation. J Am Coll Cardiol 37: 70-75.
11. Pasterkamp G, Schoneveld AH, van der Wal AC, Haudenschild CC, Clarijs RJ, et al. (1998) Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: The remodeling paradox. J Am Coll Cardiol 32: 655-662.
12. Hong YJ, Jeong MH, Choi YH, Song JA, Ahmed K, et al. (2013) Positive remodeling is associated with vulnerable coronary plaque components regardless of clinical presentation: Virtual histology-intravascular ultrasound analysis. Int J Cardiol 167: 871-876.
13. Lee CS, Seo YH, Yang DJ, Kim KH, Park HW, et al. (2012) Positive vascular remodeling in culprit coronary lesion is associated with plaque composition: An intravascular ultrasound-virtual histology study. Korean Circ J 42: 747-752.
14. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, et al. (2011) A prospective natural-history study of coronary atherosclerosis. N Engl J Med 364: 226-235.
15. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, et al. (200) Prognostic significance of blood pressure and heart rate variabilities. Hypertension 36: 901-906.
16. Cay S, Cagirci G, Demir AD, Balbay Y, Erbay AR, et al. (2011) Ambulatory blood pressure variability is associated with restenosis after percutaneous coronary intervention in normotensive patients. Atherosclerosis 219: 951-957.
17. Weiss A, Beloosesky Y, Koren-Morag N, Grossman A (2017) Association between mortality and blood pressure variability in hypertensive and normotensive elders: A cohort study. J Clin Hypertens (Greenwich) 19: 753-756.
18. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, et al. (2010) Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 9: 469-480.
19. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, et al. (2010) Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 375: 895-905.
20. Li Y, Liu J, Wang W, Zhao D (2014) The association between within-visit blood pressure variability and carotid artery Atherosclerosis in general population. PLoS ONE 9: e97760.
21. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K (2011) Visit-to-visit blood pressure variations: New independent determinants for carotid artery measures in the elderly at high risk of cardiovascular disease. J Am Soc Hypertens 5: 184-192.
22. Parati G, Ochoa JE, Lombardi C, Salvi P, Bilo G (2013) Assessment and interpretation of blood pressure variability in a clinical setting. Blood Press 22: 345-354.
23. Da luz PL, Cesena FH, Favarato D, Cerqueira ES (2005) Comparison of serum lipid values in patients with coronary artery disease at<50, 50 to 59, 60 to 69, and>70 years of age. Am J Cardiol 96:1640-1643
24. Rodríguez-Morán M, Guerrero-Romero F, Aradillas-García C (2012) Atherogenic indices and prehypertension in obese and non-obese children. Diab Vasc Dis Res 10: 17-24.
25. Kim KI, Lee JH, Chang HJ, Cho YS, Youn TJ, et al. (2008) Association between blood pressure variability and inflammatory marker in hypertensive patients. Circ J 72: 293-298.