

Detection of Subclinical Left Ventricular Systolic dysfunction by 2D Speckle Tracking Echocardiography in Patients with Peripheral Artery Disease

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ABSTRACT

Background: peripheral arterial disease (PAD) is estimated to affect 202 million people worldwide, with prevalence that is increasing over time. PAD represents a local manifestation of systemic atherosclerosis and portends a 2-6 fold increase in both cardiovascular and cerebrovascular events with an annual mortality rate of 4-6%^(1,2).

Aim of the Work: the aim of this work was to detect left ventricular subclinical dysfunction using 2-dimensional speckle-tracking echocardiography (2D-STE) in patients with peripheral arterial disease.

Patients and Methods: the ethical approval was obtained from the hospital Ethical Research Committee and each patient entering the study signed an informed consent. In a case-control study, 30 patients included were diagnosed with peripheral arterial disease and 20 control. They were recruited from Vascular department at Al-Hussein and Bab El-She'riya University Hospitals during the period from June 2018 to November 2018.

Results: there was moderately strong significant correlation between ABI and left ventricle 2d speckle tracking echocardiography (2D-STE) (GLS% (p=0.003, r=0.52), AP4% (p=0.001, r=0.57), AP3% (p=0.004, r=0.51) and AP2% (p=0.005, r=0.50)). This correlation was obvious according to limb affection (one limb vs. both limbs, GLS% p=0.025, AP4% p=0.038, AP3%=0.013 and AP2%=0.046) and severity (severe arterial disease vs. moderate arterial disease vs. some arterial disease subgroups GLS% p=0.003, AP4% p=0.001, AP3%=0.002 and AP2%=0.015). Also, there was moderately strong significant correlation of ABI with left ventricle systolic function (p=0.011, r=0.46) while other conventional echo parameters were of no significance with decline in ABI.

Conclusion: peripheral arterial disease patients had lower global and segmental longitudinal strain than the healthy subjects and this was more prominent either with severity or limb affection. This study showed that even there is correlation between decline ABI and left ventricular systolic function EF% but LV GLS offer a better economic way to detect subclinical dysfunction in asymptomatic patient.

Keywords: echocardiography, peripheral arterial disease, ankle brachial index and speckle tracking, global longitudinal strain.

INTRODUCTION

Peripheral arterial disease (PAD) represents a local manifestation of systemic atherosclerosis⁽²⁾ and portends a 2-6 fold increase in both cardiovascular and cerebrovascular events. The diagnosis is also associated with an annual mortality rate of 4-6%. In addition to causing lifestyle limiting claudication symptoms, uncontrolled disease can progress on to critical limb ischemia the end stage of PAD⁽¹⁾. The ankle-brachial index has been used as an important indicator for diagnosis of peripheral arterial disease, particularly in studies of elderly populations with a high incidence of clinically significant atherosclerotic disease. A low ABI is also associated with higher risk of cerebrovascular

disease, more severe coronary artery disease, improved prediction of acute coronary events, higher prevalence of atherosclerosis⁽³⁾.

Approximately 202 million people are affected with PAD worldwide, of whom almost 40 million are living in Europe. Eight to ten million Americans suffer from PAD with an overall prevalence 12% in the adult population⁽⁴⁾. Regarding the natural history, in a recent meta-analysis, most patients with Intermittent Claudication present increased 5-year cumulative CV-related morbidity of 13% vs. 5% in the reference population. Regarding the limb risk, at 5 years, 21% progress to Critical Limb Ischemia, of whom 4-27% have amputations⁽⁵⁾. Leg amputation due to

atherosclerotic PAD gives rise to an acute mortality rate of approximately 30% and a 5-year survival rate of less than 30%^(6,7).

Although the reason for this poor prognosis for patients with PAD is unknown, it may be explained that a higher prevalence of co-existent coronary artery disease (CAD) in patients with PAD has frequently been mentioned as the primary cause for this high mortality rate thus decreased attention to additional or associated cardiac findings that may contribute to this poor prognosis despite prospective studies that showed and suggested that a low ABI predicts all-cause mortality even in subgroups of patients without established CAD. This make sense as coronary arteries and peripheral arteries have different embryological origin⁽⁸⁻¹¹⁾. But limited data are available on the association between echocardiographic findings and PAD^(12,13).

The coexistence of CAD and PAD was described since 1960. Peripheral arterial disease. PAD whether symptomatic or asymptomatic, is a risk factor for non-fatal and fatal coronary disease and cerebrovascular events⁽¹⁴⁾. Not only CAD are frequent in patients with PAD, but also this is true for heart failure, atrial fibrillation and left ventricular hypertrophy^(2,15).

The development of heart failure represents a late event in the cardiovascular variety and is largely the result of the concerted influence of risk factors that mediate atherosclerosis. Risk factors for HF (i.e., atherosclerosis, smoking, hypertension, and diabetes) cluster in patients with PAD. The presence of PAD is associated with a nearly 2-fold increase in the prevalence of HF⁽¹⁶⁾. So, the new guidelines of ESC for PAD recommends not only, screening for heart failure in patients with symptomatic PAD should be considered but also screening for PAD may be considered in heart failure patients specially if is indicated for heart transplantation or a cardiac assist device, transcatheter aortic valve implantation or other structural interventions. Such coexistence may carry important prognostic and therapeutic implications and often needs a multidisciplinary approach⁽²⁾.

Echocardiography is the leading cardiac imaging technique in patients with suspected cardiac disease however; at rest it provides little information regarding the presence and extent of CAD⁽¹⁷⁾. Left ventricular (LV) function can be evaluated using directional components of

myocardial deformation or strain. Longitudinal LV strain (also referred to as global longitudinal strain, GLS) appears to be a sensitive measure of impaired LV systolic function⁽¹⁸⁾ and has been shown in several studies to be better than ejection fraction at predicting cardiovascular disease events and death⁽¹⁹⁻²¹⁾.

AIM OF THE WORK:

The aim of this work is to detect left ventricular subclinical dysfunction using 2-dimensional speckle-tracking echocardiography (2D-STE) in patient with peripheral arterial disease.

PATIENTS AND METHODS

The ethical approval was obtained from the hospital Ethical Research Committee and each patient entering the study signed an informed consent. In a case-control study, 30 patients diagnosed with peripheral arterial disease was included and 20 normal control. They were recruited from Vascular department at Al-Hussein and Bab El-She'riya University Hospitals during the period from June 2018 to November 2018. In this study we assessed the patients by conventional echocardiography and 2D speckle tracking echocardiography of left ventricle.

Case group (group A); case selection

- a) **Inclusion criteria:** Patients with documented peripheral arterial disease attending vascular surgery clinic diagnosed by $ABI \leq 0.9$.⁽²⁾
- b) **Exclusion criteria:** Documented IHD, patient with history of cardiac intervention (PCI or CABG), patients with moderate or severe valvular disease, patients with conduction abnormalities, pacemaker, ongoing arrhythmia and bundle branch block, patients with congenital heart disease, patients with reduced $EF \leq 50\%$ or cardiomyopathy, atrial fibrillation, end stage renal disease, poor echocardiographic window, and patient refusal.
- c) **Classification:** Patient group was classified according to limb affection into one limb affection and both limb affection. Also, it was classified according to ABI into some arterial disease (ABI 0.80 – 0.89), moderate arterial disease (ABI 0.5 – 0.79) and severe arterial disease (ABI < 0.5).⁽²⁾

Control group (group B): Twenty healthy individuals, age and sex matched, were used as a control group.

Methods:

- (1) Clinical evaluation: included full history taking, general and local examination.
- (2) Resting surface 12 ECG leads for analysis for any of exclusion criteria.
- (3) Transthoracic echocardiogram (TEE): Based on recommendations on the echocardiographic assessment of chamber quantification guidelines⁽²²⁾:
 - a) **Standard trans-thoracic echocardiographic study (TEE):** TEE was performed using S4-2 transducer 4-2 MHz with a commercially available ultrasound system (Affiniti 50; Philips, Andover, MA, USA) according to the standardized protocol. LV internal dimensions, LV end-diastolic dimensions, and end-systolic dimensions, LV EF by Biplane Simpson's method.
 - b) **2D strain imaging by speckle tracking (2D-STE):** 2D echocardiography images will be obtained from apical four, apical three and apical two chamber views. All images will be stored in cine-loop format from three consecutive beats. The frame rate for images was between 50 and 90 frames/s while analysis was performed off-line using commercially available software (Philips QLAB Advanced Quantification Software version 8.1).
- (4) Ankle brachial index: The blood pressure cuff is inflated proximal to the artery in question and measured by the Doppler probe (5-8 MHZ), the inflation continues until the pulse in the artery ceases then, pressure cuff was slowly deflated. When the artery's pulse is re-detected through the Doppler probe the pressure in the cuff at that moment indicates the systolic pressure of that artery. The pressures in each foot's posterior tibial artery and dorsalis pedis artery are measured with the same way then, ABI was calculated⁽²⁾. ABI is defined as the ratio of the systolic blood pressures of the 2 ankle arteries of that limb (either the dorsalis pedis or the tibial artery) and the systolic blood pressures of the upper limb. We used ABI average of both limbs as some other authors preferred⁽⁷⁾.

Statistical analysis:

Data were analyzed using the computer program SPSS (Statistical package for social science) version 20. Categorical variables were expressed as frequency and parentage. Chi-square test was used when comparing between Categorical variables. Continuous variables are reported as mean \pm SD (standard deviation) and compared by t test (2 groups comparisons) or ANOVA (>2 groups comparisons). P-value <0.05 was considered significant, P-value <0.001 was considered highly significant, while P-value >0.05 was considered insignificant.

RESULTS:

Among 50 participants in this study, 33 (66%) were male and 17 (34%) were female, 19 (38%) were smokers, 14 (28%) had diabetes mellitus, 11 (22%) had hypertension, 3 (6%) had family history mean age was 62.18 \pm 7.18 years. While among 30 participants in case group in terms of PAD severity, 13 (43%) had one limb affection, 17 (57%) had both limb affection, 4 (13%) had some arterial disease, 19 (63%) had moderate arterial disease and 7 (23%) had severe arterial disease.

Regarding to comparison between baseline characteristics between the case and the control groups, there was no statistically significant difference between patients and control as regard age (P-value = 0.26), gender (P-value =0.229), diabetes mellitus (P-value =0.118), hypertension (P-value =0.163), smoking (P-value =0.148), and family history (P-value =0.265).

Also, regarding to characteristics of study parameters mean of ABI average was 0.74 \pm 0.23, mean LV_EDD was 4.37 \pm 0.22, mean LV_ESD was 3.22 \pm 0.17, mean LV_EDV was 84.00 \pm 12.20, mean LV_ESV was 33.78 \pm 5.32, mean EF% was 59.54% \pm 4.89%, mean AP3% was -17.71 \pm -3.32, mean AP4% was -18.25 \pm -3.73, mean AP2% was -17.94 \pm -3.30 and mean GLS was -18.02 \pm -3.27.

There was statistically significant difference between patients and control as regard ABI (P-value < 0.0001), 2D-STE parameter (P-value < 0.0001) but there was no statistically significant difference between patients and control as regard other conventional echocardiography parameters (table 1).

There was statistically significance (P-value = 0.011) between left ventricle systolic function EF% and ABI average with a moderately strong negative correlation between both parameter (r = -0.46) (fig.2) and this

significance was more affected in severe arterial disease than moderate arterial disease than some arterial disease subgroups (P-value= 0.043) (table1).

Table 1: Shows study parameter in different groups

	Study groups			Limb affection subgroup			
	Patient	Control	P-Value	One Limb	Both Limb	P-Value	
	Mean±SD	Mean±SD		Mean±SD	Mean±SD		
Age	62.57±7.53	61.60±6.76	0.646	60.54±8.84	64.12±6.18	0.202	
Conventional Echo.	<i>LV_EDD</i>	4.34±0.26	4.41±0.15	0.238	4.33±0.27	4.35±0.25	0.846
	<i>LV_ESD</i>	3.19±0.16	3.27±0.18	0.128	3.14±0.14	3.23±0.16	0.109
	<i>LV_EDV</i>	82.44±13.92	86.35±8.85	0.271	81.85±14.46	82.88±13.92	0.845
	<i>LV_ESV</i>	32.80±4.82	35.25±5.80	0.111	31.15±1.16	34.06±5.02	0.102
	<i>EF%</i>	59.70±5.13	59.30±4.62	0.78	61.23±5.78	58.53±4.40	0.157
2D Speckle Echo.	<i>AP3%</i>	-15.54±-2.32	-20.98±-1.22	< 0.0001	-16.71±-2.01	-14.65±-2.19	0.013
	<i>AP4%</i>	-15.83±-2.67	-21.87±-1.43	< 0.0001	-16.98±-1.82	-14.96±-2.92	0.038
	<i>AP2%</i>	-15.94±-2.63	-20.93±-1.37	< 0.0001	-17.03±-2.25	-15.11±-2.28	0.046
	<i>GLS%</i>	-15.87±-2.25	-21.26±-1.23	< 0.0001	-16.90±-1.80	-15.08±-2.28	0.025
ABI average	0.59±0.15	0.98±0.08	< 0.0001	0.69±-0.13	0.51±0.11	< 0.0002	

LV_EDD left ventricular end-diastolic dimension, LV_ESD left ventricular end-systolic dimension, LV_EDV left ventricular end-diastolic volume, LV_ESV left ventricular end-systolic volume, EF% left ventricular ejection fraction, AP3% apical three view left ventricular strain, AP4% apical four view left ventricular strain, AP2% apical two view left ventricular strain, GLS % global longitudinal strain of left ventricle and ABI ankle brachial index.

Table 2 Characteristics of patients according to severity

		Some	Moderate	Severe	P- Value
		Mean±SD	Mean±SD	Mean±SD	
Age		55.50±11.09	62.47±6.60	66.86±5.18	0.05
Conventional Echo.	<i>LV_EDD</i>	4.45±0.13	4.26±0.28	4.48±0.11	0.096
	<i>LV_ESD</i>	3.11±0.07	3.17±0.15	3.31±0.14	0.045
	<i>LV_EDV</i>	87.93±7.80	78.39±15.43	90.29±6.95	0.105
	<i>LV_ESV</i>	30.00±2.16	32.00±1.59	36.57±4.76	0.04
	<i>EF%</i>	65.50±5.07	58.58±4.41	59.43±5.44	0.043
2D Speckle Echo.	<i>AP3%</i>	-18.05±-2.08	-15.81±-1.98	-13.37±-1.49	0.002
	<i>AP4%</i>	-18.45±-0.82	-16.26±-2.32	-13.17±-2.12	0.001
	<i>AP2%</i>	-18.93±-1.34	-15.92±-2.31	-14.31±-2.77	0.015
	<i>GLS%</i>	-18.48±-1.01	-15.99±-1.99	-14.04±-1.88	0.003
ABI Average		0.82±0.03	0.61±0.10	0.41±0.04	< 0.0001

LV_EDD left ventricular end-diastolic dimension, LV_ESD left ventricular end-systolic dimension, LV_EDV left ventricular end-diastolic volume, LV_ESV left ventricular end-systolic volume, EF% left ventricular ejection fraction, AP3% apical three view left ventricular strain, AP4% apical four view left ventricular strain, AP2% apical two view left ventricular strain, GLS % global longitudinal strain of left ventricle and ABI ankle brachial index.

While other conventional echocardiography parameters there was no statistically significance with neither ABI nor severity.

There was statistically significance between 2D-STE parameters including AP3%, (P-value = 0.004, r = 0.51), AP4% (P-value= 0.001, r = 0.57), AP2% (p-value = 0.005, r = 0.50) and GLS% (P-value= 0.003, r = 0.52) and ABI average with a moderately strong positive correlation between both parameters (fig.1).

In terms of severity of ABI decrease, this significance was more affected in both limbs affected subgroup (table 1) than one limb affected subgroup regarding 2D-STE parameters including AP3%, AP4%, AP2% and GLS% (P-value = 0.013, 0.038, 0.046 and 0.025 respectively). Also, this significance was more affected in severe arterial disease than moderate arterial disease than some arterial disease subgroups regarding 2D-STE parameters including AP3%, AP4%, AP2% and GLS% (P-value = 0.002, 0.001, 0.015 and 0.003 respectively) (table 2).

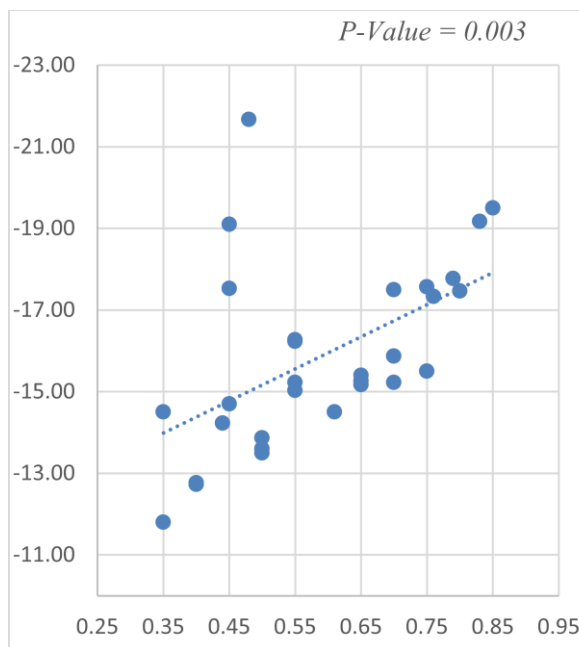


Fig.1. showing correlation between ABI and GLS%

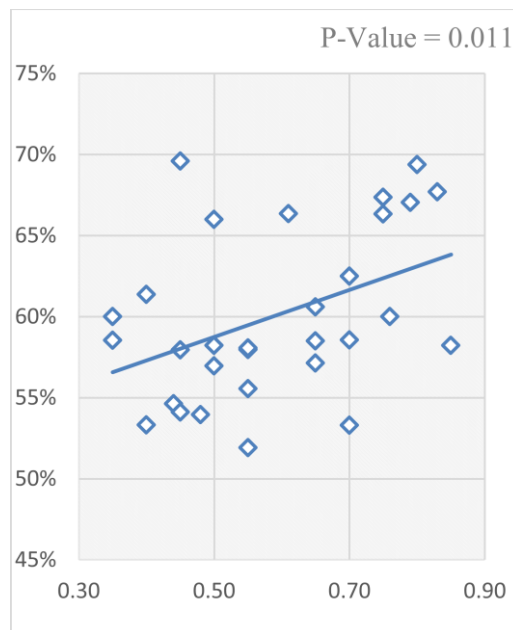


Fig.2. showing correlation between ABI and EF%

DISCUSSION

Overall, LV dysfunction and heart failure are more frequent in patients with PAD. One-third of patients with symptomatic PAD have reduced left ventricular (LV) ejection fraction (12,23) and at least twice as prevalent in patients with PAD as in the general population, matched for age and sex. (24,25) In a meta-analysis of 11,304 patients with PAD, Anand *et al.*, (26) found that the prevalence of heart failure in patients with PAD was 7.9%, which was greater than the 4.1% expected from NHANES data. Thus, the prevalence of PAD is nearly doubled in the setting of heart failure, and PAD is associated with greater functional impairment and worse prognosis. Despite the high prevalence and incidence of heart failure in patients with PAD, outcome data for this group are very limited. Evaluation of LV function in PAD may be of value for better risk stratification for future CV events and comprehensive management of patients' CV diseases (25). This is particularly important when an intermediate- or high-risk vascular intervention is planned (27).

Few previous studies have assessed the relation between LV systolic function and the ABI. Of 204 patients with symptomatic PAD, Ward *et al.*,⁽¹²⁾ found that decrease in LVEF was more common among patients with a low ABI than in those with a normal ABI. They found PAD to be an independent predictor of LV dysfunction. Thatipelli *et al.*,⁽²⁸⁾ studied 395 patients referred for dobutamine stress echocardiography and ABI determination and found ABI to be the stronger predictor of all-cause mortality and it was unrelated to the LV wall motion index.

Similar to, Rizvi *et al.*,⁽²⁴⁾ had concluded that ABI was independently associated with LVEF in community patients referred for ABI studies. Compared with subjects with a normal ABI, those with a low ABI had a lower LVEF and those with a high ABI had a higher LVEF. These findings were independent of the presence and severity of CAD. the relation between ABI and LVEF was independent of PAD symptom status. Also, it was found that in non-diabetic individuals those with a low ABI had a lower LVEF⁽²⁹⁾.

To our knowledge no previous study studied detection of subclinical LV dysfunction in peripheral arterial disease and effect of its severity. The main finding of this study that the global and segmental longitudinal strain was lower in peripheral arterial disease patients than in healthy one with lower strain in more lower ankle brachial index which denote subtle LV systolic dysfunction in peripheral arterial disease patient irrespective to risk factors as age, gender, hypertension, smoking or diabetes mellitus. Although, as far as we know the mechanism of heart failure in PAD is uncertain but it could be multi factorial. Co-existent CAD⁽³⁰⁾ or microangiopathy together with diabetes, smoking and other risk factors, inflammation all may be factors leading to the development of heart failure in PAD patients.

Also, elevated aortic stiffness increases left ventricular (LV) afterload and high pulse pressure impairs coronary blood flow, resulting in hypertension, LV hypertrophy, diastolic dysfunction and ultimately heart failure^(31,32). Importantly, skeletal muscle involvement and deconditioning in PAD may affect heart failure severity. On the other hand, functional limitation due to heart failure is likely to mask

symptoms of PAD, causing underestimation of the number of patients with both conditions⁽²⁾.

The study found that there is moderate positive correlation between the Ankle brachial index and LVEF (P-value = 0.011, r = 0.47). Similar to recent study by Nunez *et al.*,⁽³³⁾ in 2018 who studied the relation of the ankle brachial index to the left ventricular EF in 55 patients without CAD (normal coronary angiography, he found that ABI correlated with LVEF (r = 0.40, p = 0.002) and his median LVEF was lower in subjects with low ABI values compared to those with normal ABI values (33 vs. 61%; p = 0.001).

Although there have been many studies addressing ventricular-arterial coupling, this study is the first study addresses this point using speckle-tracking imaging with LV GLS as a marker of LV longitudinal function and ABI as arterial stiffness marker. This study showed the independent association between ABI as a predictor for arterial stiffness and Left Ventricular global longitudinal strain (LV GLS), suggesting a close interaction between arterial stiffness and LV long-axis function. This study showed that even there is correlation between decline ABI and left ventricular systolic function EF% but LV GLS offer a better way to detect subclinical dysfunction in asymptomatic patient.

This is indirectly consistent with another study that have been conducted on 248 subjects without structural heart problems, that used brachial-ankle pulse wave velocity (baPWV) another marker for arterial stiffness, that showed that there is a significant positive association with LV GLS and baPWV. (P = 0.001) and concluded that may be there is independent linear correlation between LV GLS measured by 2D speckle-tracking imaging and baPWV, supporting the concept that increased arterial stiffness impairs LV performance⁽³⁴⁾.

STUDY LIMITATIONS

Several potential limitations of this study should be considered. First, it had a relatively small number of patients. Second, regional, circumferential, radial strains were not evaluated in this study. Lastly, no functional testing to assess the severity of myocardial ischemia was performed.

CONCLUSION

Peripheral arterial disease patients had lower global and segmental longitudinal strain than the healthy subjects and this was more prominent either with severity or limb affection. This study showed that even there is correlation between decline ABI and left ventricular systolic function EF% but LV GLS offer a better economic way to detect subclinical dysfunction in asymptomatic patient. Further multicenter and prospective studies are required to confirm our findings.

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