

Early detection of subclinical organ damage in patients with risk factors – an ongoing journey

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Abstract

Despite the evolution of preventive therapies, cardiovascular morbidity and mortality remain high among patients with risk factors (RF) for atherosclerosis. We aimed to evaluate cardiac and vascular function parameters in patients with RF for atherosclerosis without overt vascular disease and the additional influence of diabetes on these parameters.

Fifty-six subjects (60 ± 8 years, 42 women) with RF for atherosclerosis without overt cardio-, cerebro- or peripheral artery disease were studied. Left ventricular (LV) ejection fraction, determined through standard 2D echocardiography (2DEF), and left ventricular 2D longitudinal strain (2DLS), determined through speckle tracking echocardiography, were used as markers of cardiac dysfunction. We determined the left and right ankle-brachial index (L-ABI and R-ABI, respectively) and cardiac ankle index (L-CAVI and R-CAVI, respectively), using dedicated equipment (VaSera VS-1500 Fukuda-Denshi, Japan) as markers of vascular dysfunction. The results of patients with diabetes mellitus (DM) (20 pts) were compared to those of patients without diabetes mellitus (non-DM) (36 pts).

Mean values of 2DEF and 2DLS were in normal limits in all patients, without significant differences between diabetic and nondiabetic (2DLS of -19.6 ± 3.1 in DM vs. $-20.3 \pm 2.9\%$ in non-DM, $p=NS$). Also, vascular function parameters were similar in both study groups (R-ABI of 1.04 ± 0.09 in DM vs. 1.06 ± 0.08 in non-DM, $p=NS$, and R-CAVI of 7.6 ± 1.1 in DM vs. 8.5 ± 1.5 in non DM, $p=NS$).

Cardiac and vascular function parameters that are currently used do not signal early organ damage even when measured in asymptomatic patients, suggesting that more subtle imaging or biological detection methods should be used in populations with RF for atherosclerosis.

Keywords: Atherosclerosis, diabetes, cardiac and vascular function, subclinical organ damage.

Introduction

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Cardiovascular diseases are the leading cause of death worldwide, including the European Union (EU). The World Health Organization estimates that 17.9 million people die from cardiovascular

diseases (CVDs) annually (31% of all deaths). Over 75% of CVD deaths are in low and middle-income countries. More than 85% of CVD deaths are due to heart attacks and stroke [1].

According to EUROSTAT, 1.68 million deaths were resulting from diseases of the circulatory system in the EU in 2016, which was equivalent to 37.1 % of all deaths - considerably higher than the second most prevalent cause of death, cancer (25.8 %) [2]. In 2017, in Romania, from a total of 150.379 deaths, 58% were caused by heart and vascular disease. Next to the Baltic States and Bulgaria, Romania occupies a leading role in cardiovascular morbidity and mortality in Europe, in opposition to Denmark and France, where less than one-quarter of all deaths are of cardiovascular cause. The number of in-patients with diseases of the circulatory system discharged from hospitals across the EU was 10.4 million in 2018 [2].

Most cardiovascular diseases can be prevented by addressing behavioral risk factors (such as tobacco use, unhealthy diet, obesity, and physical inactivity) using population-wide strategies.

Individuals with documented cardiovascular disease or at cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidemia) need early detection and management using counseling and adequate treatment. Individuals with diabetes mellitus are an especially sensitive category of patients due to the known impact of diabetes on all vascular territories.

Many risk assessment systems are available, have been comprehensively reviewed, and are used by most guidelines. Ideally, risk charts should be based on country-specific cohort data, which are unfortunately not available for many countries. Besides risk scores, the guidelines recommend several other biological markers (such as microalbuminuria) and non-invasive imaging techniques (such as ultrasound and coronary angiotomography) in order to complete and modify the calculated cardiovascular risk. Different cardiac ultrasound and vascular function parameters are feasible and could be efficient tools in the early detection of subclinical atherosclerosis and cardiovascular disease [3-5].

In this context, our study aimed to assess cardiac and vascular function parameters in patients with risk factors for atherosclerosis (smoking, arterial hypertension, dyslipidemia, diabetes mellitus), without overt vascular disease, and to evaluate the additional influence of diabetes on these parameters.

Material and Methods

Study population

Fifty-six subjects with risk factors for atherosclerosis (current or former smokers, arterial hypertension,

dyslipidemia, diabetes mellitus), without overt cardio-, cerebro- or peripheral artery disease, were enrolled. The study was approved by the Local Ethics Committee, and all patients signed the informed consent form.

The inclusion criteria were:

- Age between 18 and 75 years;
- Known/newly diagnosed arterial hypertension according to current European guidelines [5], with/without treatment;
- Known/newly diagnosed dyslipidemia according to current European guidelines [4], with/without treatment;
- Known/newly diagnosed diabetes mellitus according to the 2006/2011 World Health Organization and 2019 American Diabetes Association recommendations with/without treatment;
- Patients in sinus rhythm;
- Ability to understand the nature and aim of the study and to sign the informed consent.

The exclusion criteria were:

- History of acute coronary syndromes (ST-Segment Elevation Myocardial Infarction - STEMI, non-ST-Segment Elevation Myocardial Infarction - NSTEMI, unstable angina);
- Chronic coronary syndromes or atherosclerotic lesions with an indication for revascularization according to current European guidelines [6];
- History of stroke or cerebral atherosclerotic lesions with an indication for revascularization according to current European guidelines [7];
- Symptomatic peripheral artery disease (Fontaine II-IV) or peripheral artery atherosclerotic lesions with an indication for revascularization according to current European guidelines [7];
- Left ventricular (LV) systolic dysfunction (LVEF <40%);
- Hemodynamically significant valvulopathies (\geq grade III);
- Hypertrophic cardiomyopathy;
- Pericarditis;
- Pulmonary hypertension documented through right heart catheterism or high echocardiographic probability, according to current European guidelines [8];
- History of malignancy or any significant systemic disease;
- Chronic renal disease > stage III KDOQI;
- Pregnancy;
- A suboptimal acoustic window.

All the patients included in the study were evaluated by clinical examination and medical history; 12 leads ECG; 2D standard and 2D speckle tracking echocardiography (STE); left and right ankle-brachial index (L-ABI and R-ABI, respectively) and car-

ac ankle index (L-CAVI and R-CAVI, respectively), using dedicated equipment (VaSera VS-1500 Fukuda-Denshi, Japan) and blood sample.

Clinical examination and medical history

All patients had a complete clinical exam. Height, weight, body mass index (BMI) and body surface area (BSA), waist and hip circumferences, blood pressure, and heart rate were measured. All relevant medical history and prior cardiovascular/ non-cardiovascular medication were recorded.

Echocardiography

We used a VIVID E9 ultrasound machine (GE Healthcare, Horten, Norway), with simultaneous ECG recordings. Standard echocardiographic views were recorded at more than 40 frames/seconds and digitally archived for the off-line analysis using a dedicated software (EchoPac BT011 and BT013 versions).

Conventional echocardiography was used for the assessment of the cardiac structure and function, according to the current guidelines [9].

Left ventricular systolic function

It was evaluated through LVEF, measured from the 4- and 2-chamber views using a biplane method of disks summation (Simpson method).

2D Speckle tracking echocardiography was used in order to calculate the percent of deformation for all cardiac chambers, according to the current recommendations [10]. After optimizing the frame rate, we manually traced the endocardial borders at the end-systole; LV peak systolic global longitudinal strain (GLS) was automatically calculated as the average of 18 segments from the 4-, 2- and 3-chamber views during one cardiac cycle marked between the aortic valve opening (AVO) and aortic valve closure (AVC).

Data about our laboratory reproducibility and repeatability of the echocardiographic and arterial function parameters were reported elsewhere [11-13].

Arterial stiffness

It was evaluated using the cardio-ankle vascular index (CAVI) and the ankle-brachial index, determined by an automatic vascular screening system (Fukuda Denshi VaSera VS-1500). CAVI is a vascu-

lar health parameter derived from the β index, validated in the last 5 years, which reflects arterial stiffness from the ascendant aorta to the distal arteries of the lower limbs, without being influenced by blood pressure values at the measurement moment. The measurement of CAVI requires the placement of ECG electrodes on both wrists, a microphone for phonocardiogram on the sternum, and four blood pressure cuffs on all limbs. The upper arm and ankle pulse wave, as well as blood pressure and ankle-brachial index, are determined concomitantly.

The reproducibility of CAVI has been reported as “good”, with intra- and interobserver reproducibility around 3% [14].

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc. Chicago, Illinois). The results are expressed as mean ± standard deviation (SD) or percentages (%). Descriptive analysis was used to describe the baseline characteristics of the study population. The independent-T test was used to compare parametric variables between diabetic and non-diabetic patients. A p-value < 0.05 was considered statistically significant.

Results

Study population

Baseline characteristics of the study population are shown in Table 1. Forty-two patients were female (31 in the non-DM and 11 in the DM group), and the mean age was 60±8 years (59.9 ± 8.9 yrs in the non-DM and 59.2 ± 9.2 in the DM group). The mean interval since the first diagnosis was 6.2 ± 5.5 years for arterial hypertension, 7.1 ± 6.7 years for diabetes mellitus, and 5.1 ± 5.1 years for dyslipidemia. Body mass index (BMI) was above normal in both study groups, with values suggesting overweight in the non-DM group and grade I obesity in the DM group. Blood pressure values were at the normal threshold for the whole study group, with higher values in the DM subgroup, significantly higher than the target value of 130/80 mm Hg. Heart rate was normal in both groups, with slightly higher values for DM patients. The prevalence of cardiovascular (CV) risk factors was distributed as follows: 36.6% current or former smokers, 69.6% arterial hypertension, 67.9% dyslipidemia, 35.7% DM, and 26.7% patients with more than two risk factors. 57% of patients were already taking active CV medication (antiplatelets, antihypertensives, statins, or antidiabetics). In the DM group, 35% of patients were taking oral antidiabetics, and 10% had differ-

ent schemes of insulin. The distribution of cardiovascular medication is presented in Table 1.

Mean values of fasting blood glucose and glycated hemoglobin were normal in the study population, showing, as expected, higher values in DM patients. Also, total cholesterol, HDL-C, and triglycerides were normal in the study group, with a mean LDL-C of 120 mg/dl. Regarding distribution between non-DM and DM patients, DM patients had lower values of total cholesterol, HDL-C, and LDL-C, with higher values of triglycerides.

Conventional echocardiographic data are listed in Table 2. Patients had normal heart structure, without significant valvulopathies. There were no statistically significant differences between the two groups, and the values obtained were in the normal range.

Regarding left ventricular function parameters, LVEF was normal in the study population, with-

out statistically significant differences between DM and non-DM patients. Also, the global longitudinal strain was normal, with slightly higher values in the non-DM group (Table 3, Figure 1).

Concerning arterial stiffness parameters, left and right CAVI values were in the normal range in the study group, with lower values in the DM group compared to non-diabetic patients ($p=NS$). ABI was normal in the whole cohort, as well as in the two subgroups (Table 3, Figure 2).

Discussion

Current cardiovascular prevention guidelines recommend the routine assessment of total cardio-

Table 1. Baseline characteristics of the study population.

Variable	All subjects (N=56)	Non-DM subjects (N=36)	DM subjects (N=20)
BMI (kg/m ²)	30.2 ± 5.5	28.7 ± 4.9	33.2 ± 5.5
BSA (m ²)	1.9 ± 0.2	2.2 ± 1.9	2.0 ± 0.3
CV risk factors:	69.6% (39 pts)	72.2 % (26 pts)	65% (13 pts)
- HT	35.7% (20 pts)	-	-
- DM	67.9% (38 pts)	69.4% (25 pts)	65% (13 pts)
- Hyperlipidemia	36.6 % (21 pts)	33.3 % (12 pts)	45% (9 pts)
- Smoking	14% (8 pts)	11% (4 pts)	20% (4 pts)
Medications (yes):	50% (28 pts)	56% (20 pts)	40% (8 pts)
- Antiplatelets	21% (12 pts)	12.5% (7 pts)	25% (5 pts)
- ACEI	29% (16 pts)	30.5% (11 pts)	25% (5 pts)
- Sartans	52% (29 pts)	55.5% (20 pts)	45% (9 pts)
- CCB	57% (32 pts)	55.5% (20 pts)	60% (12 pts)
- Beta-blockers	46% (26 pts)	44 % (16 pts)	50% (10 pts)
- Statins	12.5% (7 pts)	-	35% (7 pts)
- Diuretics	3.5% (2 pts)	-	10% (2 pts)
Fasting blood glucose	114.0 ± 30.9	107 ± 24	130 ± 38
Glycated hemoglobin (%)	6.2 ± 0.7	5.9 ± 0.4	6.7 ± 0.8
Total cholesterol (mg/dl)	185 ± 46	193 ± 50	164 ± 23
LDL-C (mg/dl)	120 ± 50	131 ± 53	90 ± 20
HDL-C (mg/dl)	51 ± 12	53 ± 12	46 ± 13
Triglycerides (mg/dl)	117 ± 55	103 ± 37	151 ± 77
Systolic BP (mmHg)	143 ± 17	141 ± 15	147 ± 20
Diastolic BP (mmHg)	88 ± 10	86 ± 10	93 ± 10
HR (bpm)	67 ± 11	65 ± 12	71 ± 10

ACEI: Angiotensin-converting-enzyme inhibitors; BMI: Body mass index; BP: blood pressure; BSA: body surface area; CCB - Calcium channel blockers; CV: cardiovascular; DM: Diabetes mellitus; HDL: high-density lipoprotein; HR: heart rate; HT: Hypertension; LDL: low-density lipoprotein.

Table 2. Standard echocardiographic parameters.

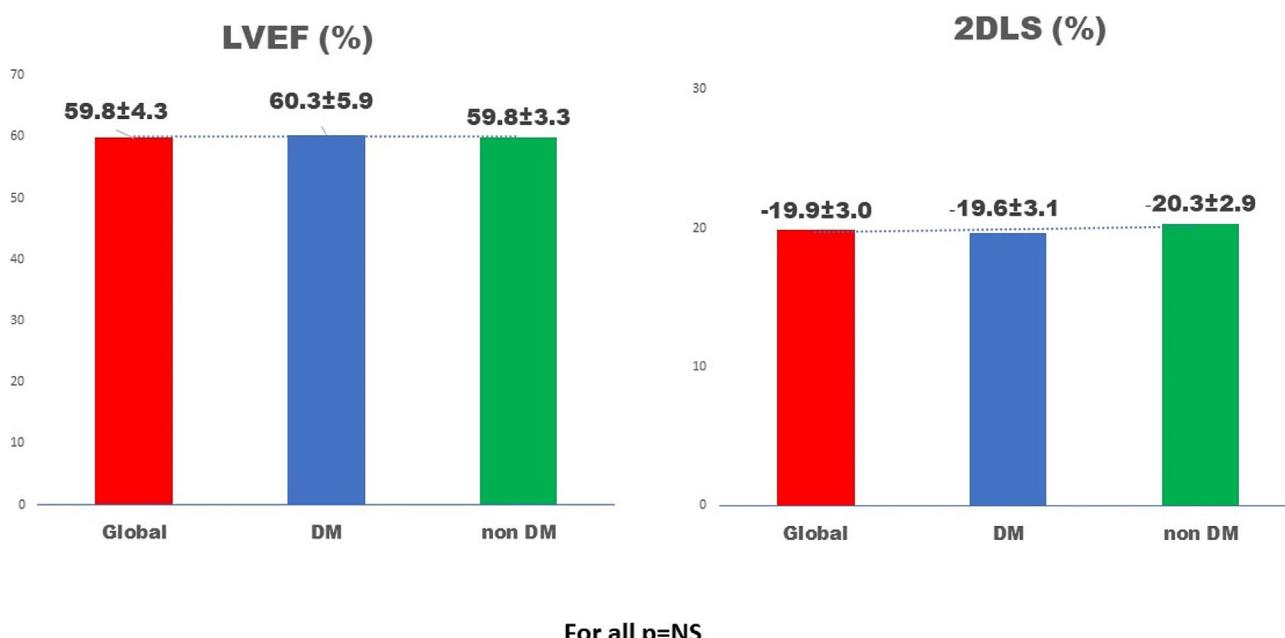
Parameter	All subjects (N=56)	Non-DM subjects (N=36)	DM subjects (N=20)
LVEDD (mm)	42.3 ± 4.1	43.2 ± 4.2	41.2 ± 4.2
LV septum (mm)	12.2 ± 1.6	12.6 ± 1.5	11.4 ± 1.7
LV posterior wall (mm)	11.0 ± 1.2	11.1 ± 1.1	11.0 ± 1.4
LA diameter	37 ± 3.2	37.5 ± 2.8	36.7 ± 3.7
LA volume (ml)	72.3 ± 16.4	77.5 ± 18.4	63.6 ± 6.6
Aortic annulus (mm)	20.7 ± 1.4	20.5 ± 1.4	21.3 ± 1.2
RV diameter (mm)	33.2 ± 3.7	34.1 ± 4.5	31.6 ± 1.4
RA diameter (mm)	36.4 ± 4.01	36.0 ± 4.9	37.0 ± 2.2

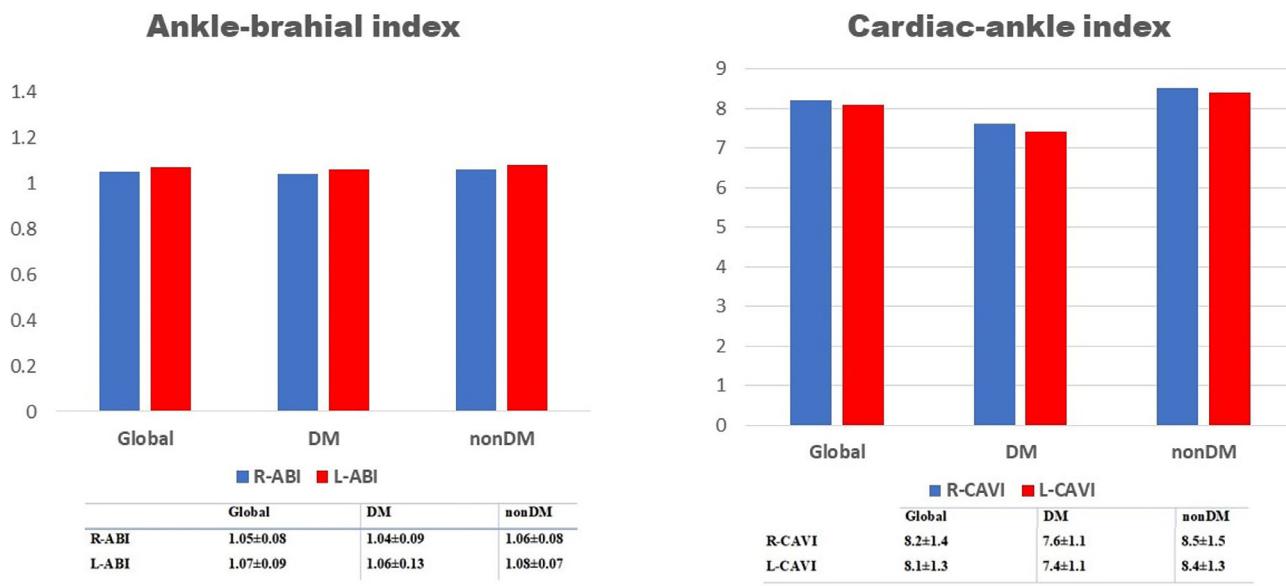
LA: Left atrium; LV: left ventricle; LVEDD: Left ventricular end-diastolic diameter; RA: Right atrium; RV: right ventricle.

Table 3. Left ventricle function and vascular function parameters.

Parameter	All subjects (N=56)	Non-DM subjects (N=36)	DM subjects (N=20)	P-value
LVEF (%)	59.9 ± 4.3	59.8 ± 3.2	60.6 ± 5.9	NS
Global longitudinal strain (%)	-19.9 ± 3.0	-20.3 ± 2.9	-19.6 ± 3.1	NS
Left CAVI	8.1 ± 1.4	8.4 ± 1.3	7.4 ± 1.1	NS
Right CAVI	8.2 ± 1.4	8.5 ± 1.5	7.6 ± 1.1	NS
Left ABI	1.07 ± 0.09	1.08 ± 0.7	1.06 ± 0.13	NS
Right ABI	1.05 ± 0.08	1.06 ± 0.08	1.04 ± 0.09	NS

ABI: ankle-brachial pressure index; CAVI: cardio-ankle vascular index; LVEF: left ventricular ejection fraction; NS: not significant.

**Figure 1.** Left ventricular systolic parameters in the studied groups.



For all p=NS

Figure 2. Arterial stiffness parameters in the studied groups.

vascular risk, as prevention actions for atherosclerosis should be directly proportional to the level of risk [15].

The quantification of cardiovascular risk in asymptomatic patients can be estimated clinically through several risk scores, of which the most agreed in Europe is the Systematic Coronary Risk Evaluation (SCORE) risk [4]. The SCORE risk assessment is derived from a large dataset of prospective European studies and predicts fatal atherosclerotic cardiovascular events over a ten year period. This risk estimation is based on the following risk factors: gender, age, smoking, systolic blood pressure and total cholesterol. The threshold for high risk based on fatal cardiovascular events is defined as “higher than 5%”. The SCORE model has been calibrated according to each European country’s mortality statistics. Countries with a CVD mortality rate of $\geq 150/100,000$ or more are considered to be at high-risk. There are low-risk, high-risk (including Romania), and very high-risk charts [16].

Persons with a history of cardiovascular events, type 1 or type 2 DM, chronic kidney disease (CKD), or cumulative high levels of individual risk factors should be considered form the start at high or very-high total CV risk and should receive active management of all risk factors [4].

There are asymptomatic patients with higher total CV risk than determined through the SCORE charts, patients who need a reclassification of risk and cardiovascular prevention according to the reclassification. These are socially deprived or individuals with psychosocial stress and unhealthy lifestyle, or with associated pathologies (obesity, chronic immune-mediated inflammatory diseases, treatment

for HIV infection, obstructive sleep apnea, non-alcoholic fatty liver disease). Also, in asymptomatic persons, abnormal markers of subclinical atherosclerotic vascular damage (such as albuminuria, atherosclerotic plaques at carotid or femoral ultrasonography, coronary artery calcium (CAC) score above 100 Agatston units, an ankle-brachial index (ABI) <0.9 or >1.40 or a carotid-femoral pulse wave velocity >10 m/s) may improve risk classification [4].

Standard echocardiography is more sensitive than electrocardiography in diagnosing left ventricular hypertrophy (LVH) as a marker of subclinical organ damage. Although current guidelines do not recommend echocardiography as a tool for CV reclassification [4, 15], there are several studies that confirm the fact that cardiac abnormalities detected by echocardiography have additional predictive power for cardiovascular risk [17, 18]. Left ventricular ejection fraction (LVEF) is the most widely used parameter for assessing cardiac function and is a predictor of outcomes. However, it has some limitations, such as a decrease only in advanced stages of heart disease, poor reliability in patients with LV hypertrophy and extensive myocardial dysfunction, and moderate inter-observer and intra-observer variability [19].

Speckle tracking echocardiography permits assessment of longitudinal, radial, and circumferential myocardial strain independent of the angle of insonation of the ultrasound beam. The longitudinal strain is probably the most frequent type of strain used to characterize LV systolic function in clinical practice [20]. Nowadays, strain imaging is recommended for identifying sub-clinical LV dysfunction in cardiomyopathies and as a routine

measurement in patients undergoing chemotherapy to detect a reduction in LV function prior to a fall in LVEF. It may also be used to diagnose myocardial ischemia [21].

There are several parameters that measure arterial stiffness. Having strong evidence about the prognostic value and correlations with cardiovascular risk factors, carotid-femoral pulse wave velocity is a reference standard measure of arterial stiffness and is included in the current guidelines as a marker of subclinical organ damage [5]. However, measurement of carotid-femoral pulse wave velocity is uncomfortable for the patient and operator dependent. Therefore it is used very little in clinical practice and more for research applications [22].

The cardio-ankle vascular index (CAVI) is a new parameter of arterial stiffness derived from the cardio-ankle pulse wave velocity and acknowledged in the 2015 American Heart Association Scientific Statement for Improving and Standardizing Vascular Research [22, 23]. CAVI reflects the stiffness of the entire aorta (including the ascending segment) and the femoral, popliteal, and tibial arteries and measures the increase in arterial stiffness occurring from end-diastole to end-systole [24]. A significant association between carotid-femoral pulse wave velocity (PWV) and CAVI has been reported [25]. CAVI is not dependent on blood pressure at the time of measurement compared to PWV [24], and its reproducibility of CAVI is good [14, 26].

A recent meta-analysis including nine prospective studies (5214 patients) and 17 cross-sectional studies (7309 patients), enrolling high cardiovascular disease risk populations in Asia has documented significantly higher values of CAVI in those with cardiovascular disease, with a modest association between CAVI and incident cardiovascular risk [22].

Our study is the pilot to a more complex research project, which aims to identify and validate extracellular vesicles as new markers of subclinical atherosclerosis, as well as to correlate these new biomarkers with already validated and used parameters of cardiac and vascular function [27]. We recruited patients with risk factors for atherosclerosis without overt vascular disease, in whom we collected blood samples for extracellular vesicles, and we also assessed cardiac and vascular function, comparing diabetic to non-diabetic patients.

We expected to find normal values of LVEF and ABI due to the fact that our study group did not have any history of vascular events or documented cardiac and vascular disease. On the other hand, we expected to find abnormal or borderline values for parameters of subclinical cardiac and vascular dysfunction, such as longitudinal strain or CAVI, which are already documented as potential tools for evaluating early heart and vessel affection [22, 28]. However, this did not happen, all cardiac ultrasound and vascular function parameters having normal mean values.

Also, we expected a significant supplementary impact of diabetes (most important RF for atherosclerotic disease and cardiac dysfunction) [29] on the studied parameters, which we failed to demonstrate in our study group.

Potential explanations for our results are:

- Good control of risk factors in the study population (most patients were treated, with satisfactory values for treatment targets);
- Diabetes was well controlled and with short evolution, not having time to induce significant vascular dysfunction;
- Currently used parameters of cardiac and vascular dysfunction are not sensitive enough to be useful in the early stages of cardiac and vascular disease.

The most important limitation of our research is, in our opinion, the small study population. However, enrollment is going on, and we expect to present the full results of our project by the end of next year.

Conclusion

Many of the currently used parameters of cardiac and vascular function do not signal early organ damage even when measured in asymptomatic patients, suggesting that more subtle imaging or biological detection methods should be researched and implemented in populations with risk factors for atherosclerosis.

Conflict of Interest

The author confirms that there are no conflicts of interest.

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