Endothelial progenitor cell at hospital admission: an important risk for impaired longitudinal Left ventricular strain among type 2 diabetic patients with acute myocardial infarction

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Abstract: Endothelial progenitor cells (EPCs), a subpopulation of adult stem cells, have emerged as critical to endothelial repair and vascular homeostasis. In response to tissue injury, their numbers significantly increase in patients with acute myocardial infarction (AMI). However, diabetic patients present impaired function and reduced numbers of circulating EPCs, but unfortunately the data addressing the correlation of EPCs level and left ventricular (LV) deformation in diabetic patients with acute AMI are scarce. **Objective:** To correlate LV longitudinal strain obtained by tissue Doppler imaging (TDI) or 2-D STE and EPCs level at hospital admission in type 2 diabetic patients with acute STEMI. **Methods:** We enrolled 30 patients with acute STEMI. 15 type 2 diabetic patients (mean age 58.1±6.9 years) were compared to 15 non-diabetic patients (mean age 57.5±9.5 years). All patients received thrombolytic therapy. A comprehensive 2D and Doppler echocardiography including TDI were obtained. Global LV longitudinal strain (GLS) was obtained by 2-D STE. Circulating EPCs (CD45dimCD34+KDR+cells) were evaluated using flow cytometry within the first 24 hours of hospital admission. **Results**: LV-GLS was significantly impaired in type 2 diabetic vs. non-diabetic patients (10.5±3.3% vs. 12.8±2.9%, $p<0.05$). EPCs level significantly decreased in diabetic vs. non-diabetic patients (3.1±0.7% vs. 8.3±2.3% CD45dimCD34+KDR+ cells count %, $p<0.0001$). A significant positive correlation was found between EPCs level and LV GLs by 2-D STE (r=0.436, p<0.05) in STEMI patients. Moreover, average peak LV systolic strain (Av.PSS) obtained by TDI was positively correlated with EPCs level (r=0.438, $p<0.05$). **Conclusion:** LV dysfunction evaluated by 2D-STE and TDI-derived strain was more prevalent among type 2 diabetic patients with acute ST segment elevation (STEMI). Circulating EPCs levels were strikingly reduced in the early phases of an AMI in diabetic patients that is likely to contribute to the deterioration in left ventricular function.

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Key words: Endothelial progenitor cells, acute myocardial infarction, speckle tracking echocardiography, type2 diabetes mellitus.

1. Introduction:

Physiological factors and conventional risk factors for atherosclerosis are associated with variations of the number and activity of endothelial progenitors and may be the bridge linking EPCs to common cardiovascular disorders such as coronary artery disease (CAD), myocardial infarction (MI) and heart failure[1]. Although the mechanisms whereby EPCs protect the cardiovascular system are still not fully understood, it has been extensively demonstrated that these bone marrow-derived cells contribute to endothelial repair and enhance vascularization[2] mediated by resident endothelial cells and/or promote angiogenesis[2]. The number of EPCs in peripheral circulation is generally low, and in normal physiological conditions, but they are mobilized from the bone marrow to the peripheral circulation in response to tissue injury, such as myocardial ischemia [3] which is considered the strongest stimulus for EPCs mobilization and it has been shown that their numbers significantly increase in patients with an AMI[4]. However, the function and numbers of circulating EPCs are significantly impaired in diabetic patients, reflecting a poor endogenous regenerative capacity that may contribute to the development of vascular complications and to the dismal prognosis associated with this prevalent disease [5].

2. Patients

A cross-sectional prospective study included 30 consecutive patients with acute ST elevation myocardial infarction (AMI) who were admitted to CCU of Al-Zahraa university hospital between November 2014 and June 2015.

The inclusion criteria were:

- Typical chest pain of at least 30 minutes' duration;

- Onset of symptoms < 12 h before hospital admission;
- new-onset ST-segment elevation >0.1 mV in 2 or more contiguous

peripheral leads and/or >0.2 mV in 2 or more contiguous precordial leads

— Evidence of myocardial injury or necrosis as indicated by elevated serum cardiac biomarkers, including creatine kinase –MB (CK-MB) and/or troponin I.

Several conditions may influence EPC kinetics and so, they had been excluded from the study:

— Prior coronary revascularization

— Cardiogenic shock on admission

— Severe heart failure (New York Heart Association class III or IV)

— Permanent atrial fibrillation

— renal insufficiency (creatinine> 2.0 mg/dl)

— Haemodynamically significant valvular or congenital heart disease

— Primary cardiomyopathy;

— Presence of features suggestive of an active inflammatory process on admission

— Therapy with steroids, immunosuppressive agents and non-steroidal anti-inflammatory drugs (excluding low doses of aspirin).

— Trauma or surgery (<1 month),

— Recent major bleeding requiring blood transfusion (<6 months)

— Patients with pacemakers, implantable cardioverter defibrillators

— Illicit drugs abuse

All patients received the standard therapy for the acute phase of STEMI that included thrombolytic therapy using streptokinase, acetylsalicylic acid (ASA), clopidogrel and low-molecular-weight heparin, according to usual hospital practice. Baseline demographic data, cardiovascular risk factors previous medications and ECG were recorded in all patients.

All patients provided written informed consent.

Methods

A**) Echocardiography**

Trans-thoracic echocardiography (TTE) was performed for all patients in both supine and left lateral position using VIVID S5 GE system with tissue Doppler imaging (TDI) capability. All cases were examined using multifrequency (2.5- 3.5 MH) Matrix probe M3S with simultaneous electrocardiographic recording to allow timing of flow.

Comprehensive trans-thoracic M-mode, 2Dimensional (2D), and Doppler were done in standard views (parasternal long axis, parasternal short axis, apical four and two chamber views) from all accessible windows to measure left ventricular (LV) dimensions and LV volumes.

The LV ejection fraction was calculated by a modified biplane Simpson's method from apical 4- and 2 chambers views.

Measurements of peak mitral annular velocities were obtained for four basal segments of LV (septal, lateral, inferior and anterior) using pulsed tissue Doppler echocardiography with the Doppler gate targeted at the junction of LV walls with the mitral annulus in four and two-chamber views. Average peak systolic mitral annular velocity (S') the markers of longitudinal LV systolic function, were obtained [6].

Diastolic LV function was assessed using pulsed Doppler echocardiography and pulsed tissue Doppler echocardiography by measurements of peak velocity transmitral flow in the early phase (E) and during atrial systole (A) to obtain the E/A ratio and the E/E' ratio, where E' is the average peak early diastolic mitral annular velocity.

LV longitudinal strain was assessed using TDI-derived strain from four LV sites (septal, lateral, inferior and anterior) in four and two-chamber views and averaged LV peak systolic strain (Av.PSS) was calculated. Also, LV longitudinal strain using 2D speckle-tracking analysis with QRS onset as the reference point, applying a commercially available LV strain software package to the left ventricle (EchoPAC version 110.1.2).Using dedicated software package (Automatic Function Imaging), images from the apical long, two and four chamber views were analyzed in a blinded manner. The LV was divided into 17 segments and automated measurements of segmental systolic longitudinal strain values then global LV longitudinal strain (LV-GLS) were calculated.

Blood sampling and laboratory analyses

Routine in-hospital laboratory analyses, performed in each case of acute STEMI in CCU included troponin I concentration 12 and 24 h after admission. Blood samples were collected to assess chemistry including fasting plasma glucose (FPG), HbA1c and total cholesterol, triglycerides, serum creatinine, blood urea, serum sodium, serum potassium and hematological parameters in all patients according to standard hospital practice.

Quantification of circulating EPCs by flow cytometry

For the identification and quantification of EPCs, flow cytometric analysis was performed within the first 24 h of CCU admission. One ml of whole blood was collected from a forearm vein into EDTA tubes, transported into the flow cytometry laboratory and processed within 1 to 2 hours of collection. Hence, 150 µl of whole blood were incubated with the following combination of anti-human monoclonal

antibodies: 10 µl of anti-CD45 conjugated with PC5, 10 µl of anti-KDR conjugated with phycoerythrin (PE) , 10 µl of anti-CD34 conjugated with fluorescein isothiocyanate (FITC) for 30 min , in the dark, then add 1 ml of diluted lysing solution (diluted 1:10 in distilled water), vortex the tubes immediately for one second and incubation of the tube was done again for 10 minutes in dark at room temperature. Centrifugation of the tube at low speed (1200-1500) was done for 5 minutes followed by aspiration of supernatant and resuspension of pellet in residual fluid. Two ml of phosphate buffer saline (PBS) were added to the tube, the suspension was centrifuged at low speed (1200-1500). The supernatant was discarded, and then 300-400 µ PBS was added to the residual suspension before flow cytometry acquisition. Monoclonal antibodies for CD34, CD45 and KDR were supplied by IMMUNOTECH SAS a Beckman coulter company (Marsseille, France).

Data acquisition and analysis were performed on cell quest program of the coulter EPICS XL flow cytometry. Human circulating EPCs were identified by a minimal antigenic profile that includes at least one marker of stemness/immaturity (CD34), plus at least one marker of endothelial commitment (KDR).CD45 staining was also performed to exclude leucocytes, as only the fraction of CD45dim cells harbors the "true" circulating EPCs. Then, CD45dimCD34+KDR+cells were quantified using cell quest software.

Statistical Analysis

Data were presented as mean ± standard deviation (SD) and analyzed by SPSS 16. Difference between two groups was compared by unpaired Student *t*-tests. $p< 0.05$ was considered statistically significant. Association of two sets of data was evaluated with Pearson and Spearman's test for correlation analysis.

3. Results

Patients enrolled to the study were divided into 2 subgroups according to the presence and absence of DM:

Group one: included 15 type 2 DM (T2DM) patients with mean age 58.1±6.9 years

Group two: included 15 non diabetic patients with mean age 57.5±9.5 years

- **Baseline clinical criteria:**

Table (1): demographic data across the studied groups

Variables	T2DM (n=15)	Non DM (n=15)
Age (years)	57.5±9.5	58.1±6.9
Male gender (number&%)	8 (53.3%)	11 (73.3%)
Hypertension (number)	10 (66.7%)	7 (46.7%)
Smoking (number)	6 (40%)	7 (46.7%)
Hyperlipidemia	12 (80%)	9 (60%)

There was no significant difference between both groups regarding the age or sex. There was a higher incidence of hypertension and hyperlipidemia in T2DM compared to non diabetic patients (Table 1).

- **Echocardiographic parameters and laboratory analysis:**

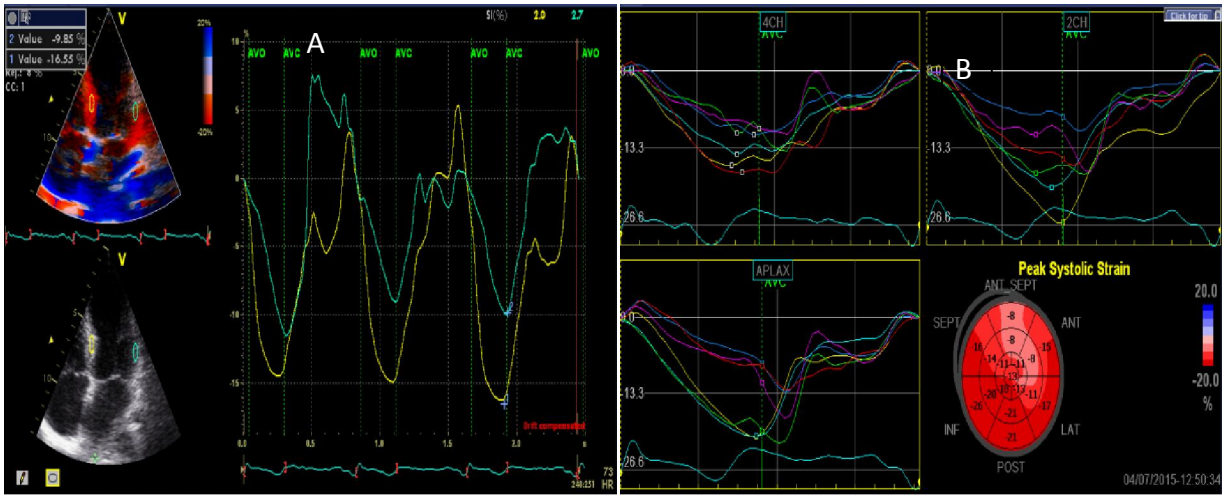
Table (2): comparison of echocardiographic parameters between T2DM and non diabetic patients

Echocardiographic parameters	T2DM n=15	Non DM n=15	*p* value
By M-mode:			
• LVEDD (mm)	56.1±8.7	52.9±7.2	NS
• LVESD (mm)	43.2±8.4	38.5±8.9	NS
• LVEF (%)	46.4±8.5	48.5±10.4	NS
By 2-D:			
• LVEDV.4 (mL)	133.8±32.8	115.2±35.5	NS
• LVESV.4 (mL)	77.3±18.3	63.9±24.3	NS
• LV EF.4 (%)	41.7±5.3	44.9±7	NS
• LVEDV.2 (mL)	122.4±19.1	119±29.4	NS
• LVESV.2 (mL)	70.7±14.4	67.7±24	NS
• LV EF.2 (%)	42.4±5.8	44.2±7.6	NS
• LV EF-biplane (%)	42±5	44.5±6.8	NS

Echocardiographic parameters	**T2DM n=15**	**Non DM n=15**	***p* value**
By Doppler:			
• E. vel (cm/sec)	68.5±13.4	68.2±13.4	NS
• A.vel (cm/sec)	70±25.4	71±22.6	NS
• E/A ratio	1.1±0.4	1.1±6.6	NS
By TDI:			
• Av. S_a (cm/sec)	4.5±1.1	4.9±1.9	NS
• Av.E_a (cm/sec)	4.4±1	5.2±1	<0.05
• Av.A_a (cm/sec)	6.1±1.6	6.3±2	NS
• E/Av.$E_a$ratio	16.3±4.6	13.4±2.9	<0.05
• Av.PSS (%)	13.5±2.2	16.3±3.1	<0.01
LV-GLS (%)	10.5±3.3	12.8±2.9	<0.05

LVEDD=left ventricular end diastolic dimension, LVESD=LV end systolic dimension, LV EF=LV ejection fraction, LVEDV.4=LV end diastolic volume by apical 4-chamber, LVESV.4=LV end systolic volume by apical 4 chamber, LV EF.4=LV EF by apical 4 chamber, LVEDV.2=LV end diastolic volume by apical 2- chamber, LVESV.2=LV end systolic volume by apical 2-chamber, LV EF.2=LV EF by apical 2 chamber, E. vel=early diastolic wave velocity, A.vel=late diastolic wave velocity, Av.S_a=average of systolicmitral annular wave velocity at 4 annular sites, Av.E_a=average of early mitral annular diastolic wave velocity at 4 annular sites, Av.A_a= average of late mitral annular diastolic wave velocity at 4 annular sites. Av.PSS=averaged peak systolic strain derived from TDI. LV-GLS=left ventricular global longitudinal strain derived from 2-D.

There was significantly lower Av.E_a velocity and higher E/Av.E_a in T2DM compared to non diabetic patients. Moreover, there was significantly reduced Av.PSS and LV-GLS in T2DM patients versus non diabetic patients despite that there were no significant difference between both groups regarding LV dimensions, volumes or LV EF evaluated by M-mode or bi-plane (Table 2) and (Figure 1).



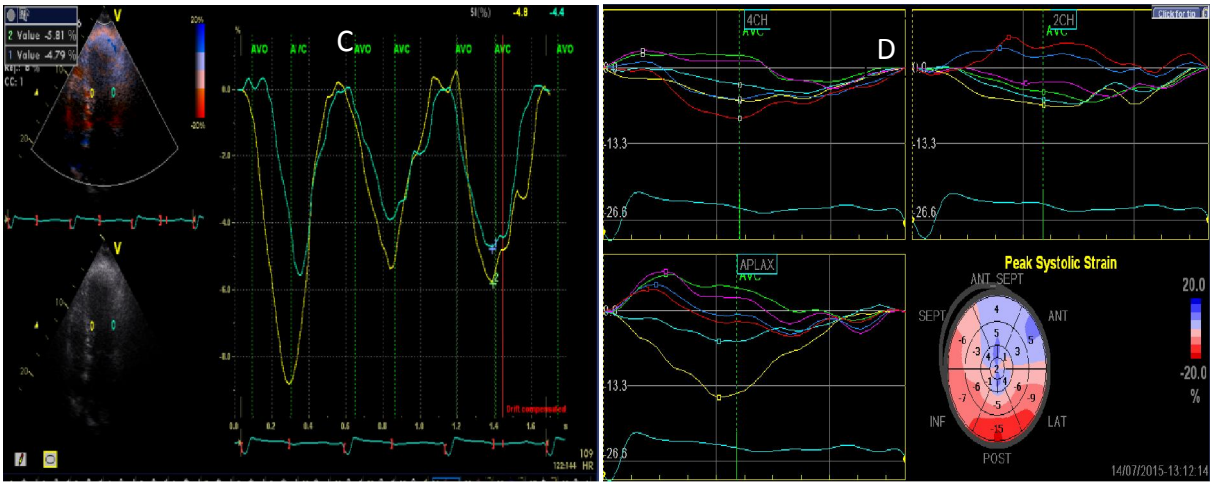


Figure (1): LV strain evaluated by TDI and 2-D speckle tracking in AMI (A, B) non-diabetic (C, D) T2DM patients

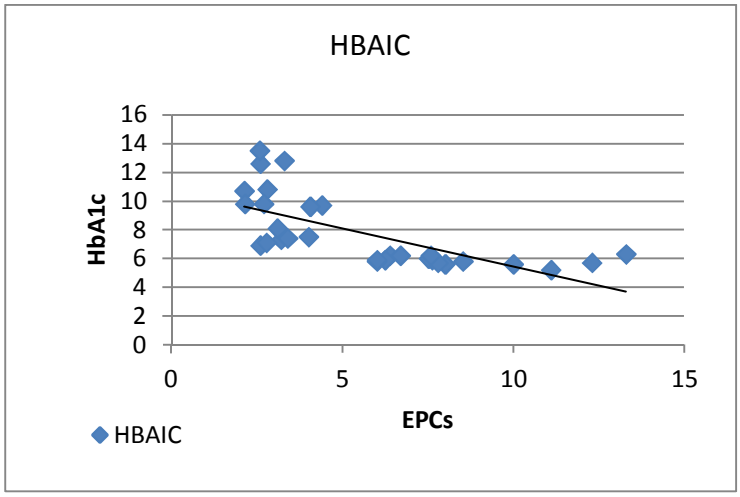
EPCs level significantly decreased in diabetic vs. non-diabetic patients meanwhile T2DM had higher levels of blood urea, serum creatinine, total cholesterol, triglyceride and HbA1c compared to non diabetic patients (table 3).

Table (3): comparison of laboratory investigations between T2DM and non diabetic patients

Variables	T2DM (n=15)	Non diabetic (n=15)	*p* value
Blood Urea (mg/dl)	59.6±37.1	31.±9.7	<0.01
Serum creatinine (mg/dl)	1.2±1	0.8±0.3	NS
Total cholesterol (mg/dl)	254.7±55	209.7±34.4	<0.01
Triglyceride (mg/dl)	176.9±31.1	141.4±31.3	<0.005
CD45dimCD34+KDR+ cells count (%)	3.1±0.7	8.3±2.3	<0.0001
HbA1c (%)	9.8±2.2	5.9±0.3	<0.0001

- **Correlation between EPCs and other laboratory investigation:**

There were significant negative correlation between the level of CD45dimCD34+KDR+ cells and HbA1c (r=-0.691, p<0.001), total cholesterol (r=-0.423, p<0.05) and triglycerides (r=-0.468, p<0.01) (Figure 2).



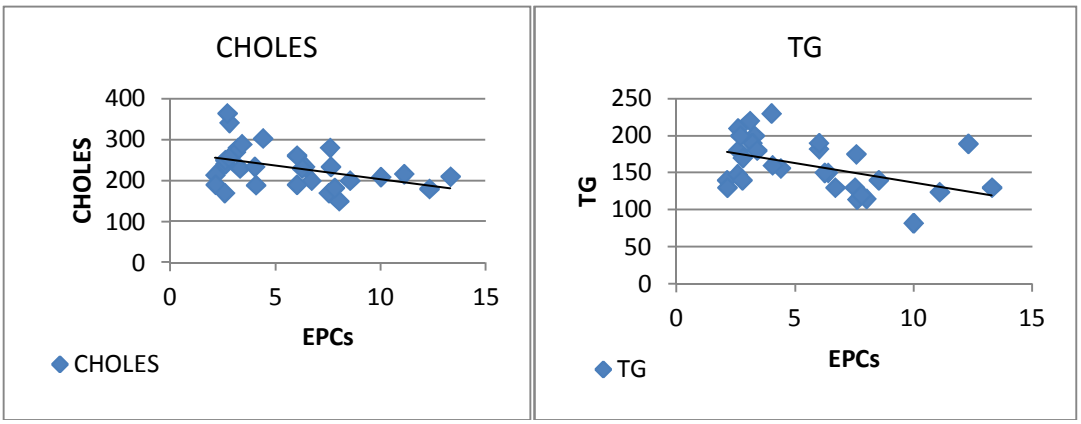


Figure (2): correlation between level of EPCs and other laboratory investigations

- **Correlation between EPCs level and different echocardiographic parameters:**

There were significant positive correlation between the level of CD45dimCD34+KDR+ cells and EF-biplane (r=0.443, r=0.05), Av.PPS (r=0.438, $p<0.01$) and LV-GLS (r=0.436, p<0.05) while there was significant negative correlation between circulating level of CD45dim CD34 + KDR+ cells and E/Av.E_a (r=-0.389, $p<0.05$) (figure 3).

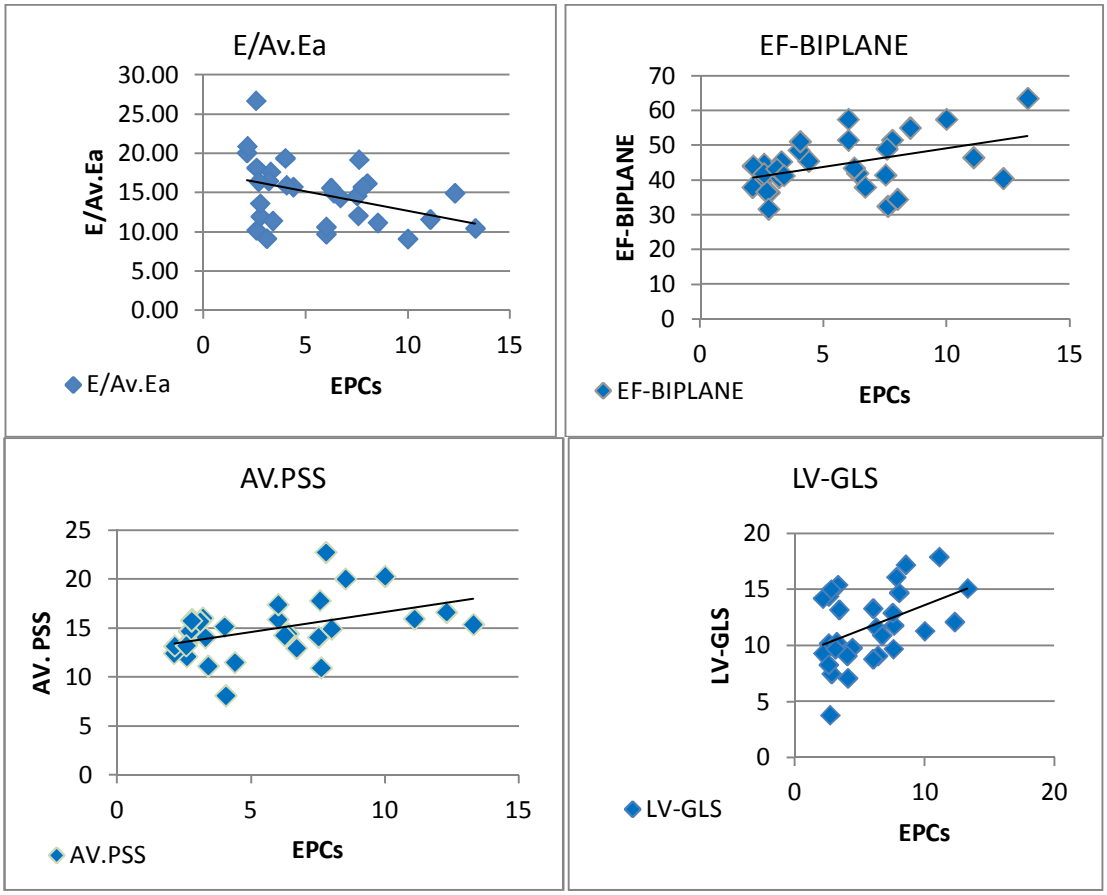


Fig. (3): correlation between circulating EPCs level and different echocardiographic parameters

4. Discussion

It has been shown that circulating EPCs increase immediately after the onset of an AMI, with a subsequent peak at day 5 and a rapid decline thereafter, normalizing within 2 months [7]. Circulating EPCs constitute a key endogenous repair mechanism

to counteract ongoing endothelial cell injury, replace dysfunctional endothelium, and enhance tissue repair after ischemic vascular injury [8]. Of note, depletion of circulating EPCs pool and impaired migratory activity of these progenitor cells have been shown to be predictive of future adverse cardiovascular events [9].

Type 2 diabetes mellitus (T2DM) is an independent predictor of adverse outcomes in patients with AMI [10]. After AMI, diabetic patients have a higher incidence of angina and heart failure, as well as increased mortality [11], which is in accordance with severe left ventricular remodeling and impaired cardiac function [12]. Endothelial dysfunction of blood vessels has been shown to contribute to vascular complications in T2DM patients [7].

In the current study, we primarily aimed at correlating LV longitudinal strain obtained by TDI or 2-D STE and circulating EPCs level in type 2 diabetic patients with acute STEMI at time of hospital admission.

We demonstrated that the level of circulating EPCS (CD45dimCD34+KDR+ cells sub-population) was significantly decreased in T2DM compared to non-diabetic patients presented by AMI.

Consistent with our result, **António *et al.*,**[13] evaluated EPCs level in diabetic and non-diabetic patients in the setting of AMI and confirmed that circulating EPCs levels were significantly reduced in the early phases of an AMI in diabetic patients as compared with non-diabetic patients (2.3 ± 0.9 Vs. 6.2 ± 3.0 CD45dim CD34 +KDR+ cells/106 WBC with $p<0.001$). They suggested that chronic hyperglycemia and not diabetes per se, is the responsible for impaired EPCs response of diabetic patients to myocardial ischemia **[13].**

Hyperglycemia significantly reduces endothelial nitric oxide synthase production by EPCs with a corresponding decline in nitric oxide bioavailability [14].

Sun et al., [7] observed that the circulating EPC levels were decreased in T2DM patients with AMI and that their peak level was delayed compared with that in non-diabetic patients and suggesting that beneficial effects of ischemic induced EPC mobilization are impaired in T2DM patients [15].

We correlated the level of circulating EPCs and LV function assessed by bi-plane EF and longitudinal strain obtained either by TDI or 2-D STE. We confirmed a significant positive correlation between EPCs level and LV longitudinal strain (both Av.PSS and LV-GLS). In addition, we found a significant positive correlation between EPCs level and LV diastolic function (assessed by E/Av.Ea).

Reduced EPCs numbers have been independently associated with impaired myocardial function in diabetic patients [16].

Wyderka et al., [17]reported that reduced mobilization of EPCs in acute phase of MI was associated with more significant impairment of LVEF and greater infarct.

Conversely **Massa et al.,** [4] showed no correlation between EPCs and LVEF in patients with AMI.

There is a paucity of data on such associations between LV function assessed by EPCs level and 2-D or longitudinal strain in the literatures and to the best of our knowledge, this is the first study evaluating the correlation between circulating EPCs level and LV function assessed by longitudinal stain.

In the present study, the level of circulating EPCs (CD45dimCD34+KDR+ cells) was negatively correlated with HbA1c, total cholesterol and triglyceride.

In the study by **António et al.,** [13] EPCs level was negatively correlated with HbA1c ($r = -0.371$, $p < 0.001$) that was in agreement with our result.

Hill et al.,[3] confirmed that EPC count had an inverse relationship with total cholesterollevel. Enhanced oxidative stress associated with dyslipidaemia may at least be partly involved in the dysregulation of EPC mobilization, maturation and survival. Hypercholesterolaemia may also directly affect the bone marrow, resulting in depletion or exhaustion of the bone marrow pool of endothelial progenitors, with a consequent limited supply of EPCs released into circulation [18].

Despite that acute STEMI patients in our study were reperfused medically using thrombolytic therapy as our hospital has no primary PCI capability, **Gaspardone *et al.,*** [19] concluded that the type of revascularization (ie, thrombolytic therapy or primary angioplasty) does not seem to affect EPC mobilization.

Limitations

The limitations of our study included 1) the widespread of laboratory variations in methodology used to quantify circulating EPCs, 2) exclusion criteria limited the enrollment of higher number of AMI patients in this study, resulting in a relatively small number of patients, 3) in addition to circulating EPC counts, EPC function may also contribute to cardiovascular repair, but function was not measured in this study.

Conclusion:

LV dysfunction evaluated by 2D-STE and TDI-derived strain was more prevalent among type 2 diabetic patients with acute STEMI. Circulating

EPCs levels were strikingly reduced in the early phases of an AMI in diabetic patients that is likely to contribute to the deterioration in left ventricular function.

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