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Original Article

Endothelial function evaluation in idiopathic vs. ischemic dilated cardiomyopathy

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Abstract: Aims: In the latest years an emerging interest has risen towards the role of endothelial dysfunction (ED) in the pathogenesis of heart failure (HF) since the very first steps of the disease. Since the prevalent etiology of HF is ischemic cardiomyopathy (ICM), it is still not clear whether the connection with ED is linked to HF itself or to atherosclerosis. The aim is to determine the presence of ED in subjects with idiopathic dilated cardiomyopathy (IDCM) compared to ICM. Methods: In this observational study 107 patients were enrolled, 65 of them suffering from IDCM and 42 from ICM. ED was assessed as peripheral arterial tonometry by means of EndoPAT device. The Reactive Hyperaemia Index (RHI) was calculated, ED being established with RHI values ≤1.67 and normal endothelial function >2.00 (grey area between 1.67 and 2.00). Results: ED, expressed both as RHI ≤1.67 and RHI ≤2.00, showed a similar prevalence in the two groups. However, they differed as regards sex, dyslipidemia and statin use. Conclusion: Endothelial function, evaluated through peripheral artery tonometry, seems equally compromised in patients with IDCM and ICM.

Keywords: HF, endothelial dysfunction, ischemic cardiomyopathy, dilated cardiomyopathy, EndoPAT

Introduction

Despite many recent improvements in therapy, heart failure (HF) still has high mortality and morbidity rates [1], and new therapeutic targets and prognostic factors are still being researched. In the latest years an emerging interest has risen towards the role of endothelial dysfunction (ED) in the pathogenesis of HF. Chronic exposure to cardiovascular risk factors and the harmful circulating stimuli asso-ciated with these conditions overwhelms the defense mechanisms of the vascular endothelium, hence compromising its integrity and ultimately initiating ED. ED is commonly associated with reduced nitric oxide (NO) bioavailability, and hence an inability of the endothelium to initiate vasodilation in response to vasodilatory stimuli such as acetylcholine or shear stress. It represents an initial reversible step in the development of atherogenesis, and for this reason, early clinical identification of ED may become an important tool in the prevention or reversal of progression to atherosclerosis and IHD. ED comprises a loss of balance between endothelial-derived vasodilatory and vasoconstrictory factors, where the pro-vasoconstrictory state becomes dominant, leading to progressive pathophysiological changes. These changes appear as sequentially occurring responses in endothelial cells, also referred to by some as the endothelial activation-dysfunction-injury triad. Collectively, these endothelial changes exhibit pro-inflammatory, pro-oxidant, proliferative, pro-coagulation and pro-vascular adhesion features [2]. Its presence in patients with chronic HF was shown in peripheral and coronary arteries, related to an increase in morbidity and mortality. The prevalent etiology of HF is ischemic cardiomyopathy (ICM) [6], but it is still not clear whether the connection with ED is linked to HF itself or to atherosclerosis. Vice versa, idiopathic dilated cardiomyopathy (IDCM) represents the third cause of HF and one of the main causes of heart transplant [7]. Some studies claim ED might even last after a heart

transplant. While the precise mechanisms that cause abnormal vaso-motor function in heart failure have not been elucidated, decreased bioavailability of nitric oxide is likely to play an important role in impaired endothelium-dependent vasodilation. High tissue and circulating levels of angiotensin II for patients with heart failure may promote superoxide radical formation, resulting in increased degradation of nitric oxide. Improvement of endothelial function after cardiac transplantation in nonischemic cardiomyopathy patients might, therefore, be related to decreased activation of the renin-angiotensin system. However, after heart transplant, for patients with a history of ischemic heart disease, the presence of systemic atherosclerosis may lead to persistent endothelial dysfunction in spite of improved hemodynamic and neurohormonal conditions [3]. ED in coronary arteries has also been reported in patients with acute HF [4]. The link between atherosclerosis and ED has been widely explained. the most clearly defined and well-understood early precursor of atherosclerosis is ED. In fact, ED can be regarded as the primum movens of atherosclerotic disease. The healthy, intact endothelium is a highly selectively permeable barrier and does not promote leukocyte adhesion and invasion, or platelet aggregation and adhesion. However, as the endothelium progresses to a dysfunctional state, vascular homeostasis becomes impaired, leading to reduced anti-oxidant, anti-inflammatory and anti-thrombotic properties (due to reduced NO bioavailability), enhanced endothelial permeability (barrier dysfunction), upregulated pro-inflammatory cytokine levels, and expression of adhesion molecules such as VCAM-1 and ICAM-1, which facilitate leukocyte adhesion to the endothelium. Leukocyte adhesion represents one of the first steps in the initiation of atherosclerosis [5].

This study aims to evaluate ED, using peripheral artery tonometry, in a population of patients with IDCM compared with patients with ICM, seeking a possible relationship with ED, regardless of atherosclerosis.

Methods

Study design

In this observational study, prior written informed consent, 107 patients were enrolled, 65 of them suffering from idiopathic dilated cardiomyopathy and 42 from ischemic cardiomyopathy. Of them, 79 (74%) were men, 28 (26%) were women. The study was carried out in the Cardiology Department of Spedali Civili di Brescia, Italy, it was approved by the local Ethical Committee (NP 3996, 21st January 2019) and was conducted in compliance with the Declaration of Helsinki. The presence of dilated cardiomyopathy or ischemic cardiomyopathy was assessed consulting the electronical archives and assuring that every patient had underwent at least one echocardiographic examination and a coronary angiography to exclude coronary artery disease.

Demographic, clinical, and therapeutic data were extracted from the hospital's electronic archives.

Inclusion criteria for patients with IDCM were Caucasian ethnicity, age >18 years old, dilated cardiomyopathy with unknown etiology and undamaged coronary arteries. Exclusion criteria were non-Caucasian ethnicity, age <18 years old, ischemic or congenital cardiomyopathy, relatives with dilated cardiomyopathy.

Inclusion criteria for ischemic patients were Caucasian ethnicity, age >18 years old, presence of coronary artery disease (CAD). Exclusion criteria were non-Caucasian ethnicity, age <18 years old, unstable CAD or acute myocardial infarction in the previous 3 months.

During the office evaluations every patient was subjected to peripheral artery tonometry (PAT), preceded by brachial blood pressure measurement, performed using aneroid sphygmomanometer. The patient was let at rest for 5 minutes before the measurement, and subsequently blood pressure was measured on the left arm. The left arm was chosen as "control arm" for EndoPAT examination, according to Itamar Medical Ltd. product usage guidelines. The data were recorded from July 2018 to December 2018.

Peripheral arterial tonometry

Endothelial function was evaluated using EndoPAT 2000 device, produced by Itamar Medical Ltd (Israel). EndoPAT 2000 allows a non-invasive measurement of tone variations in peripheral arteries in basal conditions and during

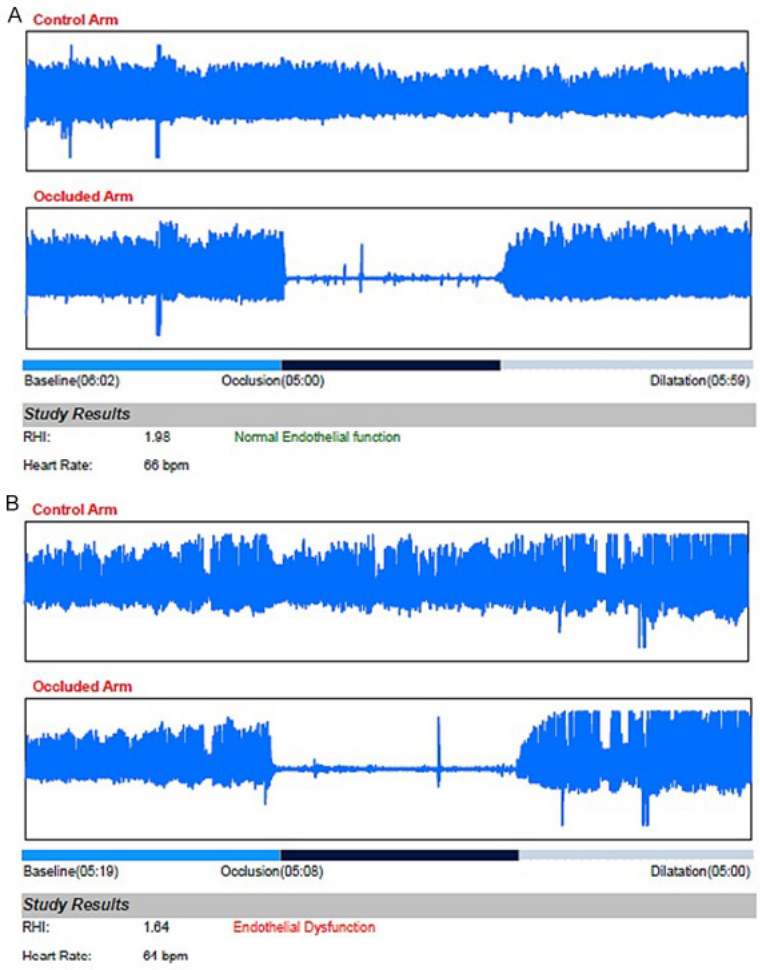

Figure 1. A. Normal endothelial function. B. Endothelial dysfunction.

reactive hyperaemia (RH). This evaluation is called peripheral artery tonometry. The device is connected to two single use probes, created for the distal phalanges of the second finger. They are composed of a rigid external structure internally lined with a system of inflatable neoprene membranes, able to produce a pressure of 70 mmHg. This pressure is needed to avoid venous stasis, which could produce a reflected venous-arteriolar constriction, to avoid blood backflow which could alter the calculation, to amplify volume variations and to limits artefacts related to finger movements. A cable allows a link with a PC with a software that can elaborate automatically all the data transmitted by the device, thus making the exam completely operator-independent. The patients were in supine position in a silent room with stable temperature to reduce vascular tone variability. On the study arm (right arm) a sphygmomanometer was positioned. The probes were placed on the distal phalanx of the second finger in both hands. During the first 5 minutes, basal signal registration was done. Subsequently, the sphygmomanometer cuff was quickly inflated at least 50 mmHg beyond the subject's systolic arterial blood pressure, preferably at 200 mmHg, determining downstream ischemia. The ischemia was maintained for 5 minutes, time needed to get the maximum response [8]. After 5 minutes the sphygmomanometer was quickly deflated causing a significant shear stress with reactive hyperaemia. Registration was then continued for another 5 minutes. At the end of the registration all data were sent to the software, which started to calculate the Reactive Hyperaemia Index (RHI). The software processed the tracks obtained by EndoPAT probes and calculated RHI as the ratio between the average amplitude of the PAT signal over a one-minute time interval, starting 1.5 minutes after ischemia, divided by the average signal amplitude of a period of 3.5 minutes before cuff inflation. The ratio was normalized for patient weight and height and for blood pressure measurement of the left arm. The software is also programmed to communicate the endothelial condition (normal endothelial function or ED), dysfunction being established with RHI values ≤1.67 [**Figure 1A** and **1B**]. These values were selected since they show the endothelial inadequacy to produce vasodilating factors, related to a higher risk to face cardiovascular adverse events [9, 10]. On the other hand, there are some cases in literature in which RHI value ≤2.00 was considered pathological. Therefore, in this study ED was expressed in two forms: related to RHI ≤1.67 and to RHI ≤2.00. The main advantage of the EndoPAT device consists in being a simple and completely operator-independent instru-

Table 1. Clinical and demographic characteristics of the study population

Characteristics	IDCM (n=65)	ICM (n=42)	p
Age (years)	65±12	68±8	0.121
Male sex	41 (63%)	38 (91%)	0.002
Height (cm)	168±9	168±5	0.981
Weight (kg)	78±18	82±19	0.279
Body mass index (kg/m^2)	26±7	29±6	0.050
Systolic blood pressure (mmHg)	122±16	118±17	0.319
Diastolic blood pressure (mmHg)	75±10	72±7	0.058
Heart rate (bpm)	68±11	64±9	0.998
Hypertension	36 (55%)	30 (71%)	0.108
Dyslipidaemia	35 (54%)	38 (91%)	<0.001
Chronic kidney disease	13 (20%)	16 (38%)	0.047
Atrial fibrillation	14 (21%)	14 (33%)	0.186
Diabetes mellitus	21 (32%)	18 (43%)	0.307
End-systolic volume (mL)	174±43	180±43	0.670
End-diastolic volume (mL)	119±34	123±40	0.697
Ejection fraction (%)	33±9	31±6	0.256

Table 2. Chronic therapy of the study population

Therapy	IDCM (n=65)	ICM (n=42)	p
Furosemide	53 (81%)	40 (95%)	0.045
ACEi or ARB	57 (88%)	38 (90%)	0.761
Beta-blockers	63 (97%)	36 (86%)	0.055
MRA	49 (75%)	34 (81%)	0.636
Ivabradine	15 (23%)	10 (24%)	1.000
Statins	35 (53%)	36 (86%)	0.001
Pacemaker	6 (9%)	2 (5%)	0.477
ICD	31 (48%)	34 (81%)	0.001
CRT-P/D	32 (49%)	16 (38%)	0.321

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; ICD, implantable cardioverter defibrillator; CRT-P/D, cardiac resynchronization therapy-pacemaker/defibrillator.

ment, which ensures high reproducibility with minimum operator-related interferences.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) after normality testing through Q-Q plots graphics. Categorical variables were expressed as frequency (n) and sample percentage. Welch's t-test was used for independent samples to analyze the difference between the means of continuous variables. The difference between proportions was studied using χ^2 test. To exclude possible bias, we evaluated non-parametric relationship (Spearman's) between ED and the different variables in the two groups. The statistical analysis was performed using IBM SPSS Statistic for Windows Software. Statistical significance was set at a *p*-value <0.05 with a two-tailed test.

Results

Population characteristics

The study included a population of 107 patients. Demographic and clinical characteristics are shown in **Table 1**. Most of them, such as age, weight, height, were balanced in the two groups, while a higher prevalence of men in the ICM population was found (90.5% vs. 63.1%; P=0.002). The population also show comparable ejection fraction, heart rate and blood pressure between the IDCM group and the ICM group. Likewise, some of the main comorbidities and risk factors, such as arterial hypertension and diabetes, were present in a similar percentage of cases. As expected, dyslipidemia was found mostly in the ICM population (90.5% vs. 53.8%; P≤0.001). Ischaemic cardiomiopathy population had higher body mass index, diastolic blood pressure, cholesterol and creatinine levels compared with idiomatic dilated cardiomyopathy population.

Therapy influencing endothelial function was also considered [**Table 2**]. The two groups were assuming similar drugs, except for statins, which were more prescribed in the ICM population (85.7% vs. 53.8%; P=0.001).

Endothelial dysfunction

ED, expressed as RHI value ≤1.67 and RHI ≤2.00, showed a similar prevalence in the two groups [**Table 3**].

Considering that the two groups strongly differed in three relevant variables, namely sex, dyslipidemia and statin use, the relationship between these variables and ED was then evaluated, in order to exclude confusing values. No relationship between the evaluated vari-

Table 3. Prevalence of endothelial dysfunction in the two groups

Endothelial dysfunction	IDCM (n=65)	ICM (n=42)	p
RHI ≤1.67	40 (71%)	36 (86%)	0.145
RHI ≤2.00	57 (88%)	36 (86%)	0.767

RHI, reactive hyperemia index.

Table 4. Correlation between variables significantly different in **Table 1** and RHI value

Variables	RHI ≤1.67		RHI ≤2.00	
	Rho	p	Rho	p
Male sex	-0.045	0.659	-0.004	0.971
Dyslipidaemia	0.112	0.273	0.074	0.474
Statin use	0.165	0.105	0.140	0.172

RHI, reactive hyperemia index.

ables and ED was found [**Table 4**]. Male participants were 77.3%. They contributed to the ED population vs. normal endothelial function respectively for 78.4% vs. 73.9% (P=0.776) and 77.4% vs. 76.9% (P=1.000) for RHI values of ≤1.67 and ≤2.00. Patients with dyslipidemia were part of the ED group in 73.0% cases. They contributed to the ED population vs. normal endothelial function respectively for 73.0% vs. 60.9% (P=0.303) and 71.4% vs. 56.5% (P=0.521) for RHI values of ≤1.67 and ≤2.00. Finally, patients on statin therapy were the majority (70.1% vs. 29.9%). They contributed to the ED population vs. normal endothelial function respectively for 74.3% vs. 56.5% (P=0.122) and 72.6% vs. 53.8% (P=0.199) for RHI values of ≤1.67 and ≤2.00.

Discussion

The aim of this study was to identify the prevalence of ED in patients with IDCM, defining a link between this specific cardiac pathology and endothelial function. Results revealed a clear relationship between ED and IDCM. The comparison with ICM patients supports these results, showing similar prevalence of altered endothelial cell function. In the study emerges a close connection between HF and ED. This connection is independent from HF etiology. The pathophysiological basis for ED in HF appears to be increased oxidative stress and chronic inflammation. Among the most important mechanisms a reduced nitric oxide production (NO) must be considered, with possible genetic polymorphism on endothelial NO synthase (eNOS), NO oxidative inactivation, the increasing plasmatic concentration of eNOS endogenous inhibitor, such as asymmetric dimethylarginine (ADMA) and higher oxidized LDL in plasma [11]. Endothelial cells produce many factors implicated in cardiovascular system homeostasis, with opposite actions. In physiological conditions, production of protective factors with vasodilating and antithrombotic effect is prevalent compared to damaging factors production. In contrast, in case of altered endothelial function the result turns towards reduced vasodilation and a proinflammatory and prothrombotic state [12]. Thus, ED is thought to have a key role in HF development, taking part to the onset and progression of myocardial damage. In fact, it contributes to excessive systemic vasoconstriction and to the consequent afterload increase. It was furthermore highlighted how altered endothelial function is crucial in vasomotor dysregulation of coronary circulation. The reduction in endothelial-dependent vasodilation damages myocardial perfusion, reduces coronary flow and worsens ventricular function [13]. It is thus shown how in HF a vicious circle starts, in which HF causes the onset of ED, and the latter determines a worsening of HF. However, it is still not clear whether the well-known relationship between HF and ED is always valid, despite the etiology.

In our study no difference was found in ED prevalence between IDCM and ICM. Previous researches in this field produced discordant results. Treasure et al. observed that endothelial-dependent vasodilation is compromised in coronary microvasculature of patients with IDCM [14]. A study conducted by Kubo et al. also showed attenuated endothelial-dependent vasodilation in HF patients with non-ischemic etiology [15]. Both studies support the obtained results, but the tests performed in such studies are difficult to execute as practical routine, because of their invasiveness. Conversely, in our research endothelial function evaluation was performed through a non-invasive method.

One study conducted with a non-invasive method, evaluation of flow-mediated dilatation (FMD), produced results contrasting with ours [16]. However, the examined sample was very small, including only 11 ICM and 12 IDCM. Shah et al. found endothelial anomalies only in patients with ICM. Equally, in a study conduct-

ed by Klonsinska et al. endothelial-dependent vasodilation was lower in patients with ICM than in non-ischemic patients [17]. The disparity in the results obtained with FMD method and our research, which uses peripheral artery tonometry, might be explained by the method itself. In fact, peripheral artery tonometry is more reproducible and operator-independent, while FMD, even if widely validated, is strongly operator-dependent [18].

From this study also comes to light that a narrower or larger RHI values cut-off (respectively 1.67 and 2.00) does not determine significant differences in the prevalence of ED in the examined populations. According to literature, this result shows that an RHI value ≤2.00 is a reliable marker for ED [19]. The prevalence of ED in the IDCM sample is higher than in the ICM group, if RHI ≤2.00 cut-off is considered. This supports this work's hypothesis, stating that IDCM has an important relationship with ED. It must be underlined how altered endothelial function, found in both groups, might be linked to many cardiovascular risk factors implied in ED onset, such as diabetes and arterial hypertension. However, these risk factors were equally present in both groups.

At the end, endothelial function, evaluated through peripheral artery tonometry, seems equally compromised in patients with IDCM and patients with ICM, for both RHI cut-off of ≤1.67 and ≤2.00.

The study has several limitations. First, a small sample and the monocentric design. In addition, the population was representative of a single ethnicity. A potential limit of the present study could reside in the sample unevenness for sex, dyslipidemia, and statin, which can strongly influence ED. To exclude biases derived from this unevenness, the variables were singularly evaluated in relation to RHI and no connection was found. Thus, we can affirm that these elements are not confusing variables. Treatments are a significant limit in any endothelial function study. Some drugs, such as ACE-inhibitors, can influence endothelial function. Anyway, for ethical reasons, it is not possible to study HF patients without any ongoing treatment. Nonetheless, these treatments should not be able to condition this study's results, because their use is comparable in both groups. At most, therapies might determine a global improvement in endothelial function in both groups, causing higher RHI values, without altering ED prevalence.

We can conclude that our research fits the literature. Independent of etiology, HF leads to ED. Our results are in contrast with some works based on a very small population, in which there can be several confounders. Bigger and multicentre studies are needed to confirm our results.

Disclosure of conflict of interest

None.

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References

[1] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH and van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891-975.

[2] Prasad A, Higano ST, Al Suwaidi J, Holmes DR, Mathew V, Pumper G, Lennon JR and Lerman A. Abnormal coronary microvascular endothelial function in humans with asymptomatic left ventricular dysfunction. Am Heart J 2003; 146: 549-554.

[3] Patel AR, Kuvin JT, Pandian NG, Smith JJ, Udelson JE, Mendelsohn ME, Konstam MA and Karas RH. Heart failure etiology affects peripheral vascular endothelial function after cardiac transplantation. J Am Coll Cardiol 2001; 37: 195-200.

[4] Mathier MA, Rose GA, Fifer MA, Myamoto MI, Dinsmore RE, Castano HH, Dec WG, Palacios FI and Semigran MJ. Coronary endothelial dysfunction in patients with acute-onset idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1998; 32: 216-224.

[5] Mudau M, Genis A, Lochner A and Strijdom H. Endothelial dysfunction: the early predictor of atherosclerosis. Cardiovasc J Afr 2012; 23: 222-231.
[6] Ho KK, Pinsky JL, Kannel WB and Levy D. The epidemiology of heart failure: the framingham study. J Am Coll Cardiol 1993; 22: 6A-13A.
[7] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman EC and Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006; 113: 1807-1816.
[8] Faizi AK, Kornmo DW and Agewall S. Evaluation of endothelial function using finger plethysmography. Clin Physiol Funct Imaging 2009; 29: 372-375.
[9] Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Kuvin JT and Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol 2004; 44: 2137-2141.
[10] Kitta Y, Obata JE, Nakamura T, Hirano M, Kodama Y, Fujioka D, Saito Y, Kawabata K, Sano K, Kobayashi T, Yano T, Nakamura K and Kugiyama K. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol 2009; 53: 323-330.
[11] Alem MM. Endothelial dysfunction in chronic heart failure: assessment, findings, significance, and potential therapeutic targets. Int J Mol Sci 2019; 20: 3198.
[12] Premer C, Kanelidis AJ, Hare JM and Schulman IH. Rethinking endothelial dysfunction as a crucial target in fighting heart failure. Mayo Clin Proc Innov Qual Outcomes 2019; 3: 1-13.
[13] Giannitsi S, Bougiakli M, Bechlioulis A and Naka K. Endothelial dysfunction and heart failure: a review of the existing bibliography with emphasis on flow mediated dilation. JRSM Cardiovasc Dis 2019; 8: 2048004019843047.
[14] 14. Treasure CB, Vita JA, Cox DA, Fish RD, Gordon JB, Mudge GH, Colucci WS, Sutton MG, Selwyn AP, Alexander RW and Ganz P. Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. Circulation 1990; 81: 772-779.
[15] Kubo SH, Rector TS, Bank AJ, Williams RE and Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. Circulation 1991; 84: 1589-1596.
[16] Shah A, Gkaliagkousi E, Ritter JM and Ferro A. Endothelial function and arterial compliance are not impaired in subjects with heart failure of non-ischemic origin. J Card Fail 2010; 16: 114-120.
[17] Klosinska M, Rudzinski T, Grzelak P, Stefanczyk L, Drozdz J and Krzeminska-Pakula M. Endothelium-dependent and -independent vasodilation is more attenuated in ischaemic than in non-ischaemic heart failure. Eur J Heart Fail 2009; 11: 765-770.
[18] Caputo A and Trimarco B. Donatori dell'ossido nitrico e metodi di valutazione della funzione endoteliale. Cardiologia Ambulatoriale 2018; 3: 192-195.
[19] Moerland M, Kales AJ, Schrier L, van Dongen MG, Bradnock D and Burggraaf J. Evaluation of the EndoPAT as a tool to assess endothelial function. Int J Vasc Med 2012; 2012: 904141.