VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2011, Vol. 18, No. 3, pp. 270–276

ISSN 1897–5593

Skin microcirculation and echocardiographic and biochemical indices of left ventricular dysfunction in non-diabetic patients with heart failure

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Abstract

Background: *We sought to noninvasively investigate skin microcirculation and to assess the relation between parameters of microcirculation and echocardiographic and biochemical parameters of left ventricular (LV) function in non-diabetic patients with heart failure (HF).*

Methods and Results: *We measured skin microcirculation with laser Doppler flowmetry (LDF) at basal conditions (MFb), after warming to 44 degrees Centigrade (MF44) and after occlusion (AUC, PF%). Blood was sampled for NT-proBNP. We obtained information on patients' medical history and medication status. The mean (SD) age of 100 patients (43 women) was 68.2 ± 11.5 years. LV ejection fraction (LVEF) averaged 34.9 ± 13.3%, LV end-diastolic diameter (LVEDD) 6.0 ± 0.9 cm, NT-proBNP 4,582.6 ± 6,339.7 pg/mL. The parameters of microcirculation averaged: MFb 6.2 ± 4.7 perfusion units (PU), PF% 716.0 ± 437.8%, AUC 794 ± 706.1 PU/s, and MF44 77.9 ± 40.2 PU. NT-proBNP correlated negatively with LVEF ($p \leq 0.0001$) and positively with LVEDD ($p = 0.003$). MFb was positively correlated with LVEF ($r = 0.24$, $p = 0.03$), and MF44 was negatively correlated with LVEDD ($r = 0.22$, $p = 0.02$). The relations remained significant after adjustments for sex, age, and use of medication. We observed no relation between NT-proBNP and microcirculatory derangement.*

Conclusions: *LDF-derived parameters of skin microcirculation are related to echocardiographic, but not biochemical, indices of HF.* (Cardiol J 2011; 18, 3: 270–276)

Key words: heart failure, microcirculation, ejection fraction

Introduction

Microcirculation is one of the major players in the pathophysiology of heart failure (HF). Data from small-scale studies (mainly employing video-capillaroscopy) has shown a relation between degree of derangement in microcirculatory function and indices of left ventricular performance. However, many of these studies included diabetic patients, a fact which could have influenced the results.

Heart failure involves alterations in the structure and function of the cutaneous, skeletomuscular and coronary microcirculatory vessels. Dysfunction of peripheral circulation is a common feature of hemodynamic derangement in patients with HF. Hemodynamic changes in microcirculatory blood flow influence the redistribution of the output of a failing heart. An impaired vasomotor reaction of microcirculatory vessels occurs as a result of inflammation, dysfunction and apoptosis of endothelial cells [1].

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Received: 12.11.2010 Accepted: 20.11.2010

Moreover, not only vasomotor, which is endothelium dependent, but also endothelium-independent, reactions are impaired in HF. Abnormal peripheral blood flow causes progressive ischemia and malnutrition of tissues and organs, which may be involved with the progression of the disease.

The aim of our study was to assess skin microcirculation using laser Doppler flowmetry (LDF), and to establish whether a relation exists between microcirculatory parameters and important indices describing left ventricular (LV) function, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and the prescribed medication in patients treated for HF.

In a relatively large group (and one which excluded patients with diabetes mellitus), we show that impairment in skin microcirculation parallels impairment in left ventricular function, but is not cross-sectionally related to the level of NT-proBNP.

Methods

We diagnosed HF based on the criteria set out by the European Society of Cardiology [2]. Each patient was interviewed to obtain information on the symptoms and signs of HF. We graded the severity of HF using the New York Heart Association (NYHA) classification. We also obtained information regarding the cause of hospitalization, any co-morbidity (coronary artery disease — CAD, myocardial infarction — MI, hypertension, hypercholesterolemia), smoking status, alcohol intake, family history of cardiovascular disease, and medication use. In the framework of physical examination we collected anthropometric data. Sitting conventional blood pressure (BP) was measured twice in standard conditions, in accordance with current recommendations [3]. A standard transthoracic echocardiogram was performed using GE Vivid 4. We sampled blood to assess NT-proBNP levels. Forearm skin microcirculatory blood flow was measured in all subjects using LDF (Perimed, Sweden). LDF is based on the Doppler phenomenon, using light with a wavelength of 780 nm. Measurements of the cutaneous microcirculation were obtained with the probe fixed at the forearm, with the patient in the supine position. Microcirculatory measurements included three-minute determination of flow under basal conditions, followed by three-minute forearm ischemia elicited by arm occlusion using a conventional sphygmomanometer cuff at a pressure 50 mm Hg higher than the patient's systolic BP (SBP) at the beginning of the assessment. Next, cutaneous blood flow was measured during a three-minute post-occlusive procedure (hyperemic reaction). The probe temperature was then increased to 44 degrees Centigrade, and the flow was measured for eight minutes. The following indices were obtained: mean blood flux under basal conditions (MFb) expressed in perfusion units (PU); area under the curve (AUC) of flow recorded after three-minute arm occlusion during hyperemic reaction; peak flow during hyperemic reaction measured as a percentage increase in comparison to basal flow (PF%), and mean cutaneous blood flow at the temperature of 44 degrees Centigrade (MF44). All indices were measured considering the biological zero, which is a signal received during forearm ischemia.

Microcirculatory flow was measured in the hospitalized patients after stabilization of their clinical status i.e. when they were free of symptoms of decompensation (dyspnea, tachycardia, peripheral edema) on the day of the microcirculatory assessment. Any patients who required intravenous diuretics or intravenous inotropic agents, or who had fever, disseminated cancer or diabetes mellitus, were excluded from the study.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Statistical analysis

The database management and the statistical analysis were performed using SAS 9.2 version and JMP 5.1 Academic Edition. Means were compared using Student's *t*-test and the analysis of variance (ANOVA), the proportions using the χ^2 test. Whenever the distribution of the variables departed significantly from the normal distribution, logarithmic transformation was used. In cases where, even after the transformation, distributions were not normal, the nonparametric Wilcoxon test was used to compare two groups, and the Kruskal-Wallis test for comparisons across more than two groups. The relation between parameters of skin microcirculation and factors putatively influencing them was assessed first using correlation analysis, and subsequently using regression with stepwise selection of explanatory variables.

Results

The average age ± SD of the 100 patients included in the study was 68.2 ± 11.5 years, and 57% of them were male. Systolic and diastolic BP averaged 135.1 ± 21.9 and 80.0 ± 10.9 mm Hg, respectively. Women were significantly older (72.4 ± 10.5 *vs* 65.0 ± 11.3, $p < 0.01$, respectively), had lower

Table 1. Group characteristics — laboratory and echocardiography parameters.

Laboratory parameters	Women	Men
Erythrocytes [$10^6/\mu$L]	4.63 ± 5.11	4.57 ± 5.62
Glucose [mmol/L]	5.20 ± 0.64	5.20 ± 0.75
Creatinin [μmol/L]	84.14 ± 24.42	99.89 ± 28.64**
Total cholesterol [mmol/L]	5.19 ± 0.97	4.63 ± 1.05**
NT-proBNP [pg/mL]	4079.92 ± 5846.41	4952.97 ± 6706.79
Left atrium [cm]	4.93 ± 0.83	5.01 ± 0.67
LVEDD [cm]	5.49 ± 0.91	6.39 ± 1.02***
LVEF (%)	40.25 ± 16.32	30.91 ± 11.11***
E/A	1.08 ± 0.70	1.11 ± 0.80
Vp [cm/s]	49.98 ± 22.51	43.73 ± 21.03

Level of significance: ***p < 0.001, **p < 0.01, *p < 0.05; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction

Table 2. Group characteristics — microcirculatory parameters.

Microcirculatory parameters	Women		Men	
	Mean ± SD	Median	Mean ± SD	Median
MFb	6.3 ± 4.9	4.78	6.2 ± 4.6	4.83
PF%	781.2 ± 552.3	654.2	666.8 ± 323.2	636.8
AUC	959.9 ± 920.5	611.6	669.5 ± 457.6	593.4
MF44	90.3 ± 47.3	58.7	68.31 ± 3**	75.6

Level of significance ***p < 0.001, **p < 0.01, *p < 0.05; MFb — mean flow in basal conditions; PF% — peak flow in hyperemic reaction; AUC — area under the curve of hyperemic reaction; MF44 — mean flow in 44 degrees Centigrade

body weight (65.9 ± 13.2 *vs* 78.7 ± 14.4, p < 0.001, respectively), were shorter (157.9 ± 5.9 *vs* 171.5 ± ± 7.3, p < 0.001, respectively) and had a lower waist to hip ratio (0.89 ± 0.09 *vs* 0.99 ± 0.07, p < 0.001, respectively). Men had lower SBP (141.2 ± 24.0 *vs* 130.5 ± 19.1, p < 0.05, respectively) and heart rate (82.0 ± 15.7 *vs* 75.0 ± 14.9, p < 0.01, respectively). Forty one per cent of patients were hospitalized for exacerbations of chronic HF, 21% were hospitalized for MI, and 12% for pulmonary edema. Patients in NYHA class II accounted for 34% of the group, while those in the third and fourth classes represented 61% and 5%, respectively. Twenty eight per cent of patients had HF and atrial fibrillation, 87% CAD, 68% history of MI, and 88% hypertension. Eighty eight per cent of the analyzed group had LV systolic dysfunction, whereas 12% had HF with preserved systolic function. Most patients (87%) were treated with angiotensin-converting enzyme inhibitors (ACEI). Beta-blockers were administered to 75% of patients, diuretics to 81%, and acetylsalicylic acid (ASA) to 76% patients. Of the 75 patients who were receiving beta-blockers, 24 received carvedilol. The laboratory and echocardiographic parameters are set out in Table 1.

Microcirculatory parameters averaged as follows: MFb 6.2 ± 4.7 PU, PF% 716.0 ± 437.8, AUC 794.0 ± 706.2 PU/s, MF44 77.9 ± 40.2 PU. Apart from MF44, there were no sex-related differences in measures of skin microcirculation (Table 2). When compared to patients with LV ejection fraction (LVEF) < 45%, 12 patients with preserved systolic function had higher MFb, and MF44 (all p < 0.01), but did not differ with respect to levels of PF% and AUC (Table 3). Sixty seven patients with LV end-diastolic diameter (LVEDD) ≥ 5.6 cm, when compared to patients without LV dilation had lower AUC (p < 0.01) and MF44 (p < 0.001) (Table 4).

The median (range) concentration of NT-proBNP was 2,727.0 (125 – > 35,000) pg/mL. No relation was found between the parameters of microcirculatory blood flow and concentration of NT-proBNP.

Table 3. Differences in microvascular parameters between patients with and without preserved left ventricle (LV) systolic function.

Parameter	Preserved LV systolic function n = 12 (EF > 45%)		LV systolic dysfunction n = 88 (EF ≤ 45%)	
	Mean ± SD	Median	Mean ± SD	Median
MFb	8.7 ± 3.6	8.0	5.9 ± 4.8**	4.5
PF%	631.9 ± 433.9	533.3	727.5 ± 439.6	672.9
AUC	635.6 ± 331.9	644.9	815.5 ± 741.3	610.9
MF44	99.6 ± 36.0	85.4	74.9 ± 40.0**	64.8

Levels of significance: ***p < 0.001, **p < 0.01, *p < 0.05; abbreviations as in Table 2

Table 4. Differences in microvascular parameters between patients with and without left ventricular enlargement.

Parameter	LVEDD < 5.6 cm (n = 32)		LVEDD ≥ 5.6 cm (n = 67)	
	Mean ± SD	Median	Mean ± SD	Median
MFb	7.0 ± 5.4	4.9	5.9 ± 4.4	4.4
PF%	753.8 ± 384.0	680.9	700.8 ± 465.6	652.5
AUC	1032.5 ± 867.8	790.7	684.1 ± 594.4**	481.8
MF44	98.6 ± 40.0	88.3	67.8 ± 36.8***	56.9

Levels of significance: ***p < 0.001, **p < 0.01, *p < 0.05; abbreviations as in Tables 1 and 2

The relation between microcirculatory parameters and echocardiographic indices was analyzed using the linear regression approach. A significant positive relation was found between the mean flow in basal condition and LVEF, and a significant negative relation was found between the mean flow in the temperature of 44 degrees Centigrade and LV diastolic diameter (Figs. 1, 2). This was further confirmed in the multivariate analyses where we adjusted for sex, age, use of beta-blockers, ACEI, statins, ASA and nitrates.

Intake of drugs and parameters of skin microcirculation

In the above models, both in men and women separately and in the entire group, after adjustment for other confounders (including EF or LVEDD), intake of ACEI was positively associated with MF44 (all $p < 0.008$), and the use of beta-blockers was positively associated with MFb (all $p < 0.002$).

In the sensitivity analysis, we repeated our models excluding patients receiving carvedilol. In these models, the use of beta-blockers other than carvedilol was negatively related with MFb (all $p < 0.03$).

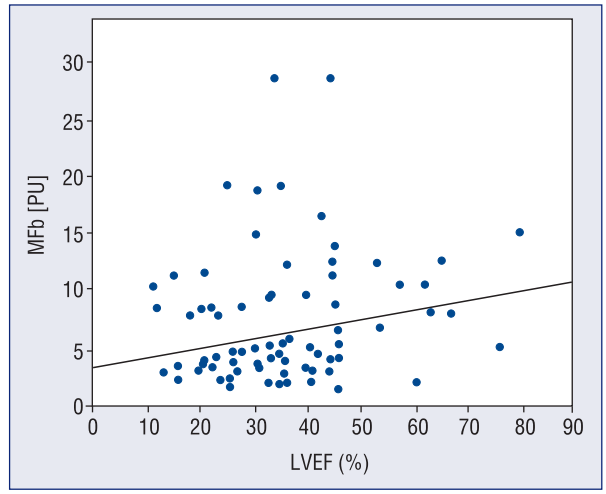

Figure 1. Relation between mean flow in basal conditions (MFb) and left ventricular ejection fraction (LVEF) (r = 0.24, p = 0.03).

Discussion

We demonstrated a relation between impaired skin microcirculation as assessed with LDF and

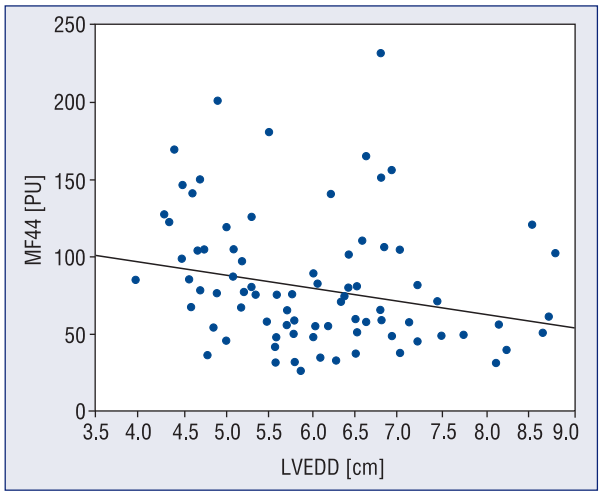

Figure 2. Relation between flow in 44 degrees Centigrade (MF44) and left ventricular end-diastolic diameter (LVEDD) ($r = 0.22$, $p = 0.02$).

echocardiographic indices of HF. However, we were unable to demonstrate such a relation for biochemical (NT-proBNP) markers of circulatory decompensation. In our analyses, we showed that intake of ACEI (when adjusted for indices of LV structure and systolic function) is associated with higher microcirculatory flow at 44 degrees Centigrade, and that in corresponding analyses the use of beta-blockers is associated with higher microcirculatory flow under basal conditions, when patients receiving carvedilol are included. The analysis of indices of microcirculatory function in patients with congestive HF demonstrated that LV enlargement, which characterizes the remodeled heart and the process of left ventricle adaptation, was directly related to microcirculatory functional impairment, both under basal conditions and at increased temperature. Also, reduction of EF was accompanied by microcirculatory flow deterioration. Thus, we found that microcirculatory blood flow under basal conditions was lower in hospitalized patients with EF < 45%. This was confirmed by a decrease of flow at 44 degrees Centigrade. In a group with LV dilatation, flow at 44 degrees Centigrade was lower, and furthermore we found that the area under the curve of hyperemic reaction was significantly smaller in individuals with LVEDD > 5.6 cm. This was largely confirmed after adjusting for sex, age and medications.

A number of studies have investigated the relation between skin microcirculation and LV performance. Duprez et al. [4], using computer-assisted videocapilaroscopy, showed that, in patients with HF, cutaneous microcirculation correlated with echocardiographic indices in a similar manner to our findings. Duprez et al. [4] found that the capillary blood flow velocity was positively correlated with LVEF and negatively correlated with LV end-systolic and end-diastolic diameter.

Houben et al. [5] showed that patients with severe HF had a lower density of microcirculatory vessels, reduced vasodilatatory reserve and abnormalities in microcirculatory morphology. In the group with HF mostly due to CAD, the percentage of abnormal conjunctival arterioles was negatively related with LVEF. A similar relation was noted when the authors considered abnormal morphology of capillaries [5]. The ability of microcirculatory vessels to relax is impaired in patients with HF due to dilated cardiomyopathy, as compared to healthy controls [6]. No relationship was detected between vasodilatation of microcirculation or stage of microangiopathy and either LVEF, NYHA class, or the duration of HF. However, that study included a relatively small group of patients [6].

Dilated cardiomyopathy can serve as a model for HF devoid of atherosclerotic background. Still, some reports show similar impairment of microcirculation in patients with cardiomyopathy and CAD and in patients with dilatative cardiomyopathy [7]. In our study, impairment of basal flow was associated with LV diastolic dysfunction. To the best of our knowledge, there have been no analyses of microcirculatory blood flow and its relation to left ventricle diastolic function in patients with HF.

We found no relation between levels of NT-proBNP and parameters of microcirculatory blood flow. Many factors could influence the levels of natriuretic peptide in the analyzed population, for instance advanced age, renal insufficiency, gender, atrial fibrillation, hypertension, acute coronary syndrome as a reason for admission to hospital, and ongoing, often intensive, treatment for HF. Moreover, NT-proBNP is produced by cardiomiocytes which represent only one third of the myocardium, while there are many more cells involved in the process of progression of HF. These are cells of the immune system and inflammation that are important in the regulation of peripheral blood flow, hypoxia and malnutrition of tissues and organs [8]. Therefore, markers of endothelial dysfunction, cytokines, products of monocyte and macrophage activation, or heat shock proteins probably could have been better markers of microcirculatory flow regulation than natriuretic peptides. One study showed no relation between the markers of endo-

thelial activation and BNP levels in patients with HF [9]. Andersson et al. [10] studied microcirculatory reaction to vasodilatatory factors, both endothelium-dependent and independent, and heat. The authors performed microcirculatory assessment using LDF, and found no relation between BNP levels and the vasodilatatory capacity of skin microcirculatory vessels.

Pharmacological treatment including drugs acting on the renin-angiotensin-aldosterone system, statins, ASA and beta-blockers may influence microcirculation via both endothelium dependent and independent mechanisms [11]. Therefore, we adjusted our analyses for the possible effect of drugs. Likewise, we assessed the microcirculatory function exclusively in stable patients, who did not require intravenous furosemide.

The group of patients we investigated differed from other analyses with respect to important characteristics. When compared to other studies, our patients were younger, but at the same time their overall condition was poorer. They had more advanced HF, more advanced CAD, and more often presented with a history of MI and hypertension. Another substantial difference was that by definition we excluded diabetic patients in whom we would expect overlap of diabetes-related factors interfering with microcirculation. This may have resulted in under-representation in our group of patients with renal insufficiency or other common complications of diabetes mellitus.

Our study needs to be considered in the context of its limitations. Our sample was relatively small. We also selectively excluded patients with diabetes mellitus. However, the exclusion of diabetic subjects resulted in a higher homogeneity of microcirculatory derangement in our patients. In our study, we assessed skin microcirculation using LDF. The major advantage of LDF rests with its noninvasiveness and that it permits assessment of the dynamic reactivity of the microcirculation in response to thermal and metabolic stimuli of vasodilatation (heat and hyperemia) [12].

The question is: why do patients with impaired LVEF and dilated left ventricle have impaired microcirculation? Perhaps the answer is that it reflects the endothelial dysfunction in patients with HF that promotes microcirculatory deterioration. Indeed, LDF is considered a method of assessment of endothelial function of skin microcirculatory vessels [13]. Several studies have shown an improvement in endothelial function and microcirculation after heart transplantation [14, 15] or with pharmacological treatment [16–18], mainly with ACEI [19] or statins [20, 21].

Conclusions

In the context of the presented data, and the reports described above, it seems that microcirculatory function assessed with LDF could be used as a prognostic factor in patients with HF, possibly irrespective of its cause. This hypothesis could be proven in carefully designed, prospective studies of large and homogenous groups of patients.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

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