Clinical Investigations

Vascular and Microvascular Endothelial Function in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Background: Assessment of vascular endothelial function lacks consistency, and microvascular endothelial function has been only partly assessed in heart failure with preserved ejection fraction (HFpEF).

Methods: The study population consisted of 90 patients: 45 had well documented HFpEF, and 45 had hypertension and no history or evidence of heart failure. Patients with hypertension but no heart failure were matched with HFpEF patients for age, sex, and diabetes. They served as control subjects. All patients underwent 2-dimensional Doppler echocardiography and vascular function measurements, including assessment of arterial wave reflections and arterial stiffness, brachial artery flow-mediated dilation (FMD), and forearm cutaneous blood flow with the use of a laser Doppler flow probe at rest and after release of arterial occlusion for 5 minutes.

Results: Brachial artery FMD was lower in HFpEF than in control subjects (median (IQR) 3.6 (0.4-7.4) vs 7.2 (3.2-17.2)%, $P = .001$). Forearm cutaneous blood flow at rest was similar in HFpEF and control subjects ($P = .68$). After release of arterial occlusion, forearm cutaneous peak blood flow was lower in HFpEF than in control subjects ($P = .03$). Estimated aortic systolic and mean blood pressures were similar in HFpEF and control subjects, whereas pulse pressure and pressure augmentation were greater in HFPEF than in control subjects (both $P < .05$).

Conclusion: Compared with hypertensive control subjects, patients with HFpEF had a depressed endothelial function in the forearm vasculature and microvasculature. (*J Cardiac Fail 2016;22:3−11*)

Key Words: Heart failure with preserved ejection fraction, vascular function, microcirculation, arterial stiffness, echocardiography.

Symptoms in patients with heart failure with preserved ejection fraction (HFpEF) are related to the severity of left ventricular (LV) diastolic dysfunction which in turn results from vascular alterations.[1,2] Aortic stiffness and vascular endothelial function are the vascular alterations that have received the most attention in the syndrome of HFpEF. Aortic stiffening is consistently greater in HFpEF patients than in patients without HFpEF despite the presence of similar comorbid conditions.[3−5] Vascular endothelial function was reported to be impaired in the digital microvasculature and preserved in a large conduit vessel in HFpEF.[6−9] Vascular endothelial function is known to be impaired in heart failure with reduced ejection fraction and in conditions that are commonly associated with HFpEF, such as diabetes, hypertension, and obesity.[10−12] Therefore, the present investigation was prospectively

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undertaken to provide an assessment of vascular and microvascular endothelial function in HFpEF. Patients with well documented HFpEF and patients with hypertension and similar comorbid conditions to those with HFpEF but without history or evidence of heart failure underwent a thorough evaluation of endothelial function in the forearm vasculature and microvasculature.

Methods

Study Population

Patients with HFpEF were identified during a hospitalization for symptomatic deterioration that improved with loop diuretic therapy. Within the 1st hour of hospitalization, all patients underwent a 2-dimensional (2D) Doppler echocardiographic examination and had a left ventricular ejection fraction (LVEF) of ≥50% and echocardiography-derived criteria of LV diastolic dysfunction.[13,14] They all met Framingham criteria for heart failure and had evidence of venous pulmonary congestion on chest X-rays. Patients with atrioventricular or sinoatrial conduction defects, atrial fibrillation or flutter, pacemakers, prosthetic heart valves, acute coronary syndromes, restrictive or hypertrophic cardiomyopathy, pericardial constriction, end-stage kidney disease, pulmonary arterial hypertension, congenital heart diseases, nephrotic syndrome, cor pulmonale or other cause of isolated right ventricular failure, liver cirrhosis, or high-output heart failure were ineligible for the study, as were patients with clinical or laboratory evidence of myocardial ischemia on stress echocardiography or thallium study or with a history of myocardial infarction or peripheral arterial disease. History of coronary artery disease was not an exclusion criteria. Patients were studied 6−8 weeks after the index hospitalization, when they were stable and had returned to their baseline functional capacity. Control subjects were recruited among ambulatory patients who were receiving care in our outpatient facility for hypertension. None of them had a history or evidence of heart failure. Sedentary patients receiving care for hypertension and no history or evidence of heart failure were matched for age, sex, and diabetic status to HFpEF patients. Diabetes was defined by a fasting blood glucose level of >126 mg/dL on 2 occasions or by the patient currently receiving oral hypoglycemic medication or insulin. Hypercholesterolemia was considered if the patient was on a cholesterol-lowering medication or, in the absence of treatment, a low-density lipoprotein cholesterol level of >160 mg/dL. Patients with HFpEF and control subjects were recruited in parallel. They all signed informed consents that had been approved by our Institutional Review Board.

Vascular Assessment

Brachial Artery Flow-Mediated Dilation. Flow-mediated vasodilation (FMD) was measured in the response of the brachial artery after peak reactive hyperemia.[15] A broadband 14-MHz ultrasonic transducer (M12 L probe; General Electrics, Horton, Norway) connected to a General Electrics Vivid 7 ultrasound system was used to measure brachial artery diameter at baseline and 90 seconds after release of a cuff inflated around the arm to 50 mm Hg above systolic blood pressure (SBP) for 5 minutes. Patients were studied ≥8 hours after their last meal in a quiet temperature-controlled room (22°C) after 30 minutes of rest in the supine position. All FMD images were obtained by the same experienced investigator (S.M.) according to current guidelines.[15] The transducer was positioned above the antecubital fossa to visualize the vessel at its largest diameter with the vessel walls parallel in the 2D sector image and the blood pressure cuff placed below. All images were digitally recorded on DVDs for later blinded analysis. Off-line analysis was performed at the end of the study on a dedicated EchoPAC workstation (General Electrics) by a reader who was blinded to all aspects of patient history (including participant group [HFpEF vs control]). With the use of electrocardiographic gating, the mean arterial diameter was calculated from 3 cardiac cycles incident with the R-wave. FMD was expressed as the percentage increase in brachial artery diameter (media-adventitial interface to media-adventitial interface) with reactive hyperemia: FMD = ([peak brachial artery diameter after cuff deflation − diameter at rest]/diameter at rest) × 100.

Forearm Cutaneous Blood Flow at Rest and After Arterial Occlusion. Forearm cutaneous blood flow was measured at rest and during reactive hyperemia by means of laser Doppler flowmetry (LDF; Periflux PF4; Perimed, Stockholm, Sweden) as previously described.[16] Laser Doppler flowmetry does not directly measure cutaneous blood flow but provides an index of cutaneous perfusion, quantified as the product of average red blood cell velocity and their concentration. The laser light penetrates the cutaneous tissue and is partially backscattered by red blood cells. According to the Fizeau-Döppler principle, the frequency of the backscattered light is changed in proportion to the velocity of the red blood cells. The frequency shifts are converted into a voltage signal that is proportional to the number and velocity of the illuminated red blood cells. Cutaneous blood flow was measured at rest and during reactive hyperemia during the same maneuver as for FMD, and values were expressed in perfusion units (PU). The laser Doppler signal was continuously registered on a computer (Perisoft software; Perimed). The LDF probe was consistently held on the thenar region and remained placed at the exact same location before and during the reactive hyperemia maneuver.[16] As with FMD measurements, room temperature was carefully maintained at 22°C during forearm cutaneous blood flow measurements; reactive hyperemia was produced by arresting forearm blood flow with a pneumatic cuff inflated to a pressure of 50 mm Hg above the SBP for 5 minutes. The signal obtained during complete arterial occlusion was taken as the biologic zero for cutaneous blood flow measurements before and during reactive hyperemia. Resting flow was taken as the average of a 5-minute stable LDF recording. Peak flow was defined as the highest flow signal after release of arterial occlusion. On each curve after release of arterial occlusion, the slope of the best-fit line traced with the use of linear regression associated with the upward portion of the blood flow rise (1st 3 seconds: slope 1; 2nd half: slope 2) was determined (Fig. 1).

The power spectral density (PSD) of the LDF signal was measured with the use of the basic fast Fourier transform algorithm. The small arteries of the microcirculation present rhythmic and spontaneous variations of their diameter called, by convention, vasomotion and characterized by frequency and amplitude. The spectra of frequencies and amplitudes contained in the LDF signal were obtained at rest and after release of arterial occlusion with the use of the basic fast Fourier transform algorithm to identify the amplitude of the signal divided into 5 subintervals: 0.01−0.02 Hz (endothelial function), 0.02−0.06 Hz (sympathetic activity), 0.06−0.2 Hz (vascular myogenic activity), 0.2−0.6 Hz (respiratory activity), and 0.6−1.6 Hz (heart activity).

Arterial Stiffness. Assessment of arterial stiffness was performed noninvasively with the use of the commercially available Sphygmocor system (Atcor Medical, Sydney, Australia).