Endothelial Function and Arterial Compliance are not Impaired in Subjects With Heart Failure of Non-Ischemic Origin

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ABSTRACT

Background: Patients with heart failure and underlying ischemic heart disease (IHD) exhibit both endothelial dysfunction and increased arterial stiffness. We investigated whether this is also the case in heart failure of nonischemic etiology.

Methods and Results: Eleven patients with heart failure and IHD, 12 patients with heart failure from angiographically verified idiopathic nonischemic dilated cardiomyopathy (DCM), and 16 healthy subjects of similar age and sex were compared. Endothelium-dependent and independent function were evaluated by ultrasonic measurement of flow-mediated dilatation (FMD) and glyceryl trinitrate (GTN)-induced dilatation of the brachial artery respectively. Vascular compliance was assessed by carotid-femoral pulse wave velocity (PWV) and augmentation index (AIx). Heart failure severity was similar in IHD and DCM patients. FMD was impaired in the subjects with IHD as compared with control subjects (4.8 $\pm$ 0.3 vs. 8.0 $\pm$ 3.6 %, $P < .01$), but not in those with DCM. GTN-induced vasodilatation was not different in patients and controls. PWV was also increased in IHD patients compared with controls (12.1 $\pm$ 3.6 vs. 8.0 $\pm$ 1.6 m/s, $P < .01$), but not in DCM patients. AIx was similar in patients and controls.

Conclusion: Heart failure of nonischemic etiology is not associated with abnormalities of endothelium-mediated dilatation or of arterial compliance. The findings of our study now need to be confirmed in larger studies. (*J Cardiac Fail 2010;16:114–120*)

Key Words: Nitric oxide, vascular stiffness, cardiac dysfunction.

Heart failure is increasing in incidence and prevalence, and is associated with significant morbidity and mortality.[1,2] Coronary and peripheral artery endothelial dysfunction have been reported in patients with symptomatic heart failure and in patients with asymptomatic left ventricular dysfunction.[3–5] Moreover, endothelial dysfunction has been reported in both acute and chronic heart failure.[6,7] However, since the most prevalent etiology of heart failure is ischemic heart disease (IHD) caused by atheroma, which is itself strongly associated with endothelial dysfunction, it is not clear whether heart failure per se causes endothelial dysfunction in the absence of atheromatous coronary artery disease.

Endothelial dysfunction is associated with increased arterial stiffness,[8,9] which is characterized by increased pulse wave velocity (PWV) as well as an increase in augmentation index (AIx) as a result of earlier return of the reflected wave in the arterial tree. Heart failure has been reported to be associated with increased PWV[10,11] and elevated pulse pressure, another index of arterial stiffening, which has been associated with increased morbidity and mortality in patients with impaired left ventricular systolic function.[12–14]

We hypothesized that patients with heart failure would exhibit impairment of endothelium-dependent dilatation as well as an increase in arterial stiffness, and that this would be especially marked in patients with heart failure of ischemic origin. The aim of the present study was therefore to evaluate these parameters in patients with heart failure due to either IHD or to nonischemic dilated cardiomyopathy (DCM), as compared with healthy control subjects with no evidence of cardiovascular disease.

Methods

Subject Recruitment

Ethical approval for the study was granted by the Research Ethics Committee, King's College Hospital; all subjects gave

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Manuscript received May 11, 2009; revised manuscript received October 4, 2009; revised manuscript accepted October 8, 2009.

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A.S. was supported by a doctoral studentship from Pfizer plc; E.G. was supported by the Greek Foundation for State Scholarships.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2009.10.019

written informed consent. Twenty-three patients with heart failure were recruited consecutively from the Heart Failure Clinics at St. Thomas' and King's College Hospitals, London, UK. They were diagnosed with heart failure on clinical as well as echocardiographic criteria, and had a diagnosis either of underlying IHD or of DCM on the basis of results of coronary angiography as well as the absence of any other discernible cause of heart failure. In all cases, DCM was of unknown etiology, and no subject had a previous history of myocarditis. Sixteen control subjects of similar age, sex, and race were recruited from the database of healthy volunteers held by the Department of Clinical Pharmacology, St Thomas' Hospital. Controls were clinically healthy, as judged by history and physical examination, were not on any regular medications, and had not taken any medication in the 7 days before the study. All subjects attended in the morning after an overnight fast, and having refrained from caffeine-containing drinks and alcohol from the evening before. Any medications normally taken in the morning were omitted until after all study measurements were completed. All studies were undertaken in a warm, temperature-controlled room at the same time of day, by the same operator.

Measurement of Common Carotid Intima-media Thickness

Intima-media thickness (IMT) was measured in both common carotid arteries by high resolution B-mode ultrasound imaging, using a 7 MHz frequency linear transducer (Acuson Aspen, Siemens, Malvern, PA). The inner and outer walls of the right and left common carotid arteries were scanned longitudinally to obtain a clear image. Measurements were performed 1 cm proximal to the carotid bulb, on an R wave−triggered frozen longitudinal image of the wall.

Assessment of Endothelium-dependent and Independent Vasodilatation

Endothelium-dependent and independent responses were assessed from brachial artery flow−mediated dilatation (FMD) and glyceryl trinitrate (GTN)-induced dilatation respectively. The right brachial artery was imaged, 5 to 10 cm above the antecubital fossa, with a high-resolution ultrasound probe (Acuson Aspen, Siemens, Malvern, PA) held in a stereotactic clamp. Brachial artery FMD was induced by a 5-minute inflation of a pneumatic cuff placed around the forearm immediately below the medial epicondyle, with pressure 50 mm Hg higher than systolic blood pressure, followed by rapid deflation. The brachial artery was imaged longitudinally, and the spectral Doppler and an electrocardiogram R wave-triggered 2-dimensional image were recorded every 3 seconds throughout the 11-minute recording protocol and saved for analysis. The diameter of the brachial artery was measured using computer-assisted edge-detecting software (Brachial Tools, Iowa City, IA). After a 10-minute rest, 25 μg GTN was given sublingually and, after waiting for 3 minutes to achieve plateau response to the drug, brachial artery images were recorded for 1 minute. Both FMD and GTN responses were expressed as percentage change, calculated as follows:

$$\frac{(\text{Maximum brachial diameter} - \text{baseline brachial diameter}) \times 100\%}{\text{Baseline brachial diameter}}$$

Assessment of Arterial Stiffness

Arterial stiffness was assessed by pulse wave analysis (PWA) and also by measurement of carotid-femoral PWV. The technique of applanation tonometry was used, and the radial pressure-pulse waveform was acquired with a micromanometer probe (SPC-301, Millar Instruments, Houston, TX). Data were recorded directly onto a computer and analyzed with SphygmoCor software (SphygmoCor version 7.0, Moreton-in-Marsh, Gloucestershire, UK). The peripheral (radial) pressure waveform was used to estimate the central (aortic) pressure waveform with the transfer function in the SphygmoCor-PWA software, which also calculated central AIx (defined as the ratio of augmentation to central pulse pressure, and expressed as a percentage: AIx = (ΔP/PP) × 100%, where P is pressure and PP is pulse pressure). Brachial arterial blood pressure and heart rate were obtained with an oscillometric device (Omron 705 CP, Omron). PWV was measured from waveforms of the carotid and femoral arteries referenced to the R wave of the electrocardiogram with available software (SphygmoCor PWV-software, Atcor). Distance was measured over the body surface between the sternal notch and the femoral pulse in a direct line.

All measurements were performed 3 times and the mean of the 3 was used for further analysis. The measurements were repeated when the waveforms did not pass the automatic quality controls specified by the SphygmoCor software.

Statistical Analysis

All data were expressed as mean ± standard deviation, and were analyzed using GraphPad Prism 4 software. Data for continuous variables were confirmed to be normally distributed using the D'Agostino-Pearson test. These data were analyzed by analysis of variance, with Dunnett's posttest where significance was found to determine differences from control values. Noncontinuous variables were compared between the IHD and DCM groups by Mann-Whitney U test or χ^2 test as appropriate. In all cases, $P < .05$ (2-tailed) was considered significant. In preliminary experiments, we found that all vascular measurements had coefficients of variation <10%, when performed on different days within the same subjects by the same operators.

Results

Subject Characteristics

Subject characteristics are shown in Table 1. Patients with heart failure were on various medications, summarized in Table 2. Subjects with heart failure and healthy controls had similar age, sex, and ethnic distributions. Heart failure subjects had slightly higher pulse rate, urea, creatinine, and glycated hemoglobin than controls, as expected; they had lower total and low-density lipoprotein cholesterol levels, as well as lower triglycerides, than controls, which may be explained by the high prevalence of statin use in the heart failure (but not the control) group. Heart failure severity was similar in the IHD and DCM subgroups: the IHD group had 4, 4, and 3 patients in New York Heart Association (NYHA) Class I, II, and III, respectively, as compared with 4, 6, and 2 patients respectively in the DCM group, $P > .05$ between groups; moreover, left ventricular ejection fraction was 28 ± 9% in the IHD group and 25 ± 9% in the DCM group, $P > .05$.

Common Carotid IMT

Subjects with heart failure and IHD had higher IMT in both common carotid arteries than did controls; by contrast,