Flow-Mediated Dilation Normalization Predicts Outcome in Chronic Heart Failure Patients

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ABSTRACT

Background: Reduced flow-mediated dilation (FMD) is a known prognostic marker in heart failure (HF), but may be influenced by the brachial artery (BA) diameter. Aiming to adjust for this influence, we normalized FMD (nFMD) by the peak shear rate (PSR) and tested its prognostic power in HF patients.

Methods and Results: BA diameter, FMD, difference in hyperemic versus rest brachial flow velocity (FVD), PSR (FVD/BA), and nFMD (FMD/PSR × 1000) were assessed in 71 HF patients. At follow-up (mean 512 days), 19 HF (27%) reached the combined endpoint (4 heart transplantations [HTs], 1 left ventricle assist device implantation [LVAD], and 14 cardiac deaths [CDs]). With multivariate Cox regression analysis, New York Heart Association functional class ≥III (hazard ratio [HR] 9.36, 95% confidence interval [CI] 2.11−41.4; $P = .003$), digoxin use (HR 6.36, 95% CI 2.18−18.6; $P = .0010$), FMD (HR 0.703, 95% CI 0.547−0.904; $P = .006$), PSR (HR 1.01, 95% CI 1.005−1.022; $P = .001$), FVD (HR 1.04, 95% CI 1.00−1.06; $P = .02$), and nFMD (HR 0.535, 95% CI 0.39−0.74; $P = .0001$) were predictors of unfavorable outcome. Receiver operating characteristic curve for nFMD showed that patients with nFMD >5 seconds had significantly better event-free survival than patients with nFMD ≤5 seconds (log-rank test: $P < .0001$).

Conclusions: nFMD is a strong independent predictor of CD, HT, and LVAD in HF with left ventricular ejection fraction <40%. Patients with nFMD >5 seconds have a better prognosis than those with lower values. (*J Cardiac Fail 2013;19:260−267*)

Key Words: Endothelial function, flow-mediated dilation, shear rate, brachial artery, heart failure.

Flow-mediated dilation (FMD) of the brachial artery (BA) measured by the reactive hyperemia test under specific conditions[1] is commonly accepted to be a bioassay of in vivo endothelial function, particularly of the nitric oxide vasodilation effect on conduit arteries.[1,2] The noninvasive nature of the technique and growing evidence of reduced nitric oxide availability in many cardiovascular diseases[3] has prompted a marked increase in FMD research over the past few years.[4]

A reduced FMD has been identified as an independent predictor of cardiovascular events in peripheral vascular disease,[5,6] of adverse outcome in survivors of acute coronary syndrome without ST-segment elevation,[7] and of increased rehospitalization or death in both ischemic and nonischemic chronic heart failure (CHF).[8−11]

Recently, a wealth of physiologic evidence has emerged on the importance of normalizing the FMD of the BA during the hyperemia test to eliminate the influence of BA diameter on the FMD response; this would better reflect the endothelial function and allow greater comparability between studies.[1,12−18] But how best to normalize FMD, and whether it is feasible to consider a single measure of microvascular function as a predictor of vascular health, is still a field of debate[17−22]; moreover, little is known about the significance of normalizing FMD and of microvascular function measurement in CHF patients.

Therefore the present study aimed to evaluate the prognostic impact of FMD normalized by the peak shear rate

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(PSR) and the meaning of measures of vascular function correlated with PSR in CHF patients.

Methods

Study Population

From January 2006 to January 2009, 164 consecutive patients with diagnosed heart failure (HF) due to ischemic or idiopathic dilated cardiomyopathy referred to our HF units for inpatient cardiac rehabilitation were screened for inclusion in the study. Inclusion criteria were: New York Heart Association (NYHA) functional class ≥II, left ventricular ejection fraction (LVEF) <40%, and stable optimized medical therapy. Exclusion criteria were: acute myocardial infarction in the past 3 months, coronary revascularization and cardiac surgery in the past 3 months, valvular disease requiring surgery, severe ventricular arrhythmias, degree II or III atrioventricular block, pericarditis, severe renal dysfunction (ie, creatinine plasma levels >2.5 mg/dL), liver dysfunction (alanine/aspartate aminotransferase levels >1.5 times the upper normal limit), active inotropic or mechanical circulatory support, expected survival for noncardiac disease <1 year. After exclusion of ineligible subjects, 71 CHF patients formed the study population. The study was conducted in accordance with the Declaration of Helsinki, and our Institutional Ethical Committee approved the protocol. The purpose of the study was explained, and written informed consent obtained from each patient before inclusion.

Data Collection

Patients underwent high-resolution ultrasound assessment of brachial FMD with a Sonos 5500 device (Hewlett-Packard, Andover, Massachusetts) equipped with a 7.5-MHz linear array transducer following reactive hyperemia test guidelines.[12] Briefly, patients after fasting for 12 hours (including caffeine), not smoking for 24 hours, in washout from nitrate-derivative drugs for ≥24 hours, and after supine rest for 10 minutes in a quiet and warm room at stable temperature underwent left BA diameter and flow velocity assessment at baseline and after cuff deflation completing 5 minutes of suprasystolic compression (50 mm Hg above systolic pressure) of the left forearm distal to the site of FMD measurement. After 10 minutes to allow vessel recovery, while systolic blood pressure was >95 mm Hg, further scans of the BA were made before and 4 minutes after sublingual administration of nitroglycerin (NTG; 300 μg spray) to assess endothelium-independent vasodilation. The ultrasound probe was held in a stereotactic clamp with micrometer adjustment during the test for an optimal and stable positioning on the left BA. The longitudinal image of the artery was recorded for 3 cardiac cycles at baseline and 60 seconds after cuff deflation; electrocardiographic gating was used during image collection to determine the diameter at the same point in each cardiac cycle; in case of atrial fibrillation, an attempt was made to choose images with similar cycle lengths. BA diameter at baseline and 60 seconds after cuff deflation was measured (average of 3 measures synchronized with the R-wave peak on the electrocardiogram) from anterior to posterior media-adventitia interface. FMD was then calculated as the percentage change in diameter at 60 seconds after cuff deflation over the baseline value. Mean (velocity-time integral) flow velocity was measured at rest and 15 seconds after cuff deflation. PSR was computed as the difference in mean flow velocity (FVD) between hyperemic (15 seconds after cuff release) and baseline, divided by baseline BA diameter. As shown in Figure 1, normalized FMD (nFMD) was calculated by dividing FMD by the PSR, then multiplying by 1,000 for easier computation. Nitroglycerin (NTG)–induced vasodilation (NTG-D) was obtained as the percentage change in diameter at 4 minutes after NTG administration over the pre-NTG administration value. Intraobserver variability (coefficient of variation) for repeated measures of BA diameter before and after reactive hyperemia, tested in 20 patients, was, respectively, 2.3% and 2.6%, and interobserver variability was 6.5% and 7%, respectively; coefficient of variation for FMD measurement was 8%. Ultrasound studies were all performed by 2 sonographers (F.T.G., E.E.) blinded to patients' clinical status and therapy.

Follow-Up and Outcome Variables

Patients were followed by scheduled outpatient visits every 3 months or, in the case of new admission for worsening HF, through the hospital medical records. Follow-up of those who did not attend their scheduled appointments was obtained by telephone interview of the patient, patient's family, or primary care physician. The combined endpoint of this study was the occurrence of cardiac death, urgent heart transplantation (HT) or implantation of a left ventricle assistance device (LVAD). The "Adverse Events" group included patients who reached the combined endpoint at follow-up; the "No Adverse Events" group included the others. Follow-up ranged from 1 to 2 years (512 ± 208 days; Table 1).

Statistical Analysis

Continuous data are expressed as mean ± SD. Student *t* test for nonpaired values was used to compare the means of groups for quantitative variables. For qualitative variables, the χ^2 test with Yates correction, or Fisher exact test where appropriate, was used. The ability of each parameter to predict the occurrence of an event was determined with the use of univariable Cox proportional hazards regression analysis: Parameters that showed a significant association with the outcome ($P < .01$) underwent Cox multivariable analysis. The following diagnostic and verification steps for Cox models were performed after the multivariable fit: 1) The proportional hazards assumption of Cox models was verified by plotting smoothed scaled Schoenfeld residuals and searching for the interaction between the covariate and time; 2) linearity assumption for continuous variables was assessed graphically with the use of Martingale residuals; 3) goodness of fit was assessed analytically with the Grønnesby and Borgan method and graphically with Cox-Snell residual plots. The discrimination ability of the model was evaluated using Harrell C concordance index (which indicates the proportion of all usable subject pairs in which the predictions and outcomes are concordant; a value of 0.5 indicates no predictive discrimination, and a value of 1.0 indicates perfect separation of patients with different outcomes). Given the small number of events, we performed further validation and correction steps. Model validation was performed repeating the multivariable modeling procedure on data obtained from the original data sets with the use of random sampling with replacement (bootstrap). We estimated C-index optimism with 200 bootstrap samples, then subtracted the optimism value from model C-index to produce an Honest C estimate. The variables selected in the starting model had to be present in ≥50% of the bootstrapped selection results.[23] To improve calibration,[24] heuristic shrinkage was calculated to correct the estimates of the regression coefficients of the model for the total population. Survival rate was analyzed by the Kaplan-Meier method, and survival curves were compared by the log-rank test. All data were analyzed with the use of the