Reactive hyperemia is associated with adverse clinical outcomes in heart failure

Nicola J. Paine, PhD,[a] Alan L. Hinderliter, MD,[b] James A. Blumenthal, PhD,[a] Kirkwood F. Adams, Jr., MD,[b] Carla A. Sueta, MD,[b] Patricia P. Chang, MD,[b] Christopher M. O'Connor, MD,[a] and Andrew Sherwood, PhD[a]
Durham and Chapel Hill, NC

Introduction Impaired endothelial function, as assessed by brachial artery flow-mediated dilation (FMD), is an established risk factor for cardiovascular events. FMD is impaired in heart failure (HF) patients, but less is known about hyperemic brachial artery flow. We investigated the relationship between FMD and hyperemic flow with adverse clinical outcomes in HF patients.

Methods Brachial artery FMD and hyperemic flow were assessed in 156 patients (70.5 % Male; 45.5% Caucasian; mean age (± SD) = 56.2 (±12.4) years) with HF and reduced left ventricular ejection fraction (LVEF). Cox proportional hazard models were used to assess the potential explanatory association of FMD and hyperemic flow with the composite outcome of death or cardiovascular hospitalization over a median 5-year follow-up period.

Results Both FMD and hyperemic flow were negatively correlated with age, but unrelated to sex, race, body mass index, LVEF or N-terminal pro-B-Type natriuretic peptide (NT-ProBNP). Reduced hyperemic flow, but not FMD, was associated with an increased risk of death or cardiac hospitalization after controlling for traditional risk factors.

Conclusion The association of reduced hyperemic flow with increased risk of adverse clinical outcomes suggests that micro-vascular function may be an important prognostic marker in patients with HF. (Am Heart J 2016;178:108-14.)

Nearly 6 million Americans suffer from heart failure (HF)[1] with a 46% increase projected by 2030.[2] Both the instability of symptoms and deterioration of patients' clinical status can lead to hospitalization for HF, which is estimated to result in an annual cost of $31 billion.[1] The vascular endothelium plays an important role in the regulation of vascular tone, coagulation, cell adhesion, and cell proliferation, and endothelial dysfunction is a predictor of atherosclerotic events.[3-5] Flow-mediated dilation (FMD) of the brachial artery is a useful non-invasive measure of endothelial function that is considered broadly reflective of the endothelial health of the entire arterial system, including the coronary arteries.[6]

Endothelial dysfunction is linked to a wide range of cardiovascular risk factors[7-9] and is a predictor of cardiovascular events, independent of other traditional risk factors.[4,10,11] Endothelial dysfunction is evident in HF patients,[12-14] and previous studies have suggested that impaired FMD is predictive of cardiac death and hospitalization.[12,13,15] The stimulus for the FMD response is increased shear stress, which is evoked by transient forearm occlusion giving rise to hyperemic flow through the brachial artery. There is some evidence that cardiovascular risk is related to hyperemic velocity,[14,16] with some studies noting that the hyperemic response to forearm ischemia is a better predictor of adverse cardiovascular outcomes than FMD.[17,18]

Although comparatively few studies have examined the relationship between FMD and clinical events in patients with HF, they have shown that impaired FMD is associated with worse clinical outcomes.[12,13,15,19,20] However, none of these studies assessed the potential role of hyperemic flow as an independent predictor of adverse outcomes. Therefore, we evaluated whether FMD and reactive hyperemia were associated with risk of death or cardiac hospitalization in patients with HF, in a secondary analysis from a previously reported study.[21]

Material and methods

Participants

Participants were recruited from a series of patients seen at the heart failure clinics at Duke University Medical

From the [a]Duke University Medical Center, Durham, NC, and [b]University of North Carolina at Chapel Hill, Chapel Hill, NC.
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Reprint requests: Andrew Sherwood, PhD, Box 3119, Duke University Medical Center, Durham, NC 27710.
E-mail: sherw002@mc.duke.edu
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Center and the University of North Carolina at Chapel Hill, from January 2000 through December 2002. Approximately 500 patients that met our eligibility criteria (see below) were approached; 219 of these patients consented to participate and were enrolled; for 204 of these participants we obtained a plasma NT-proBNP value necessary to control for HF disease severity in our analyses, as reported in our original paper.[21] From this main sample, 156 of these participants were NOT taking nitrates and were included in the current analyses; no participants were lost to clinical follow-up which included 156 of the participants comprising the current sample (N = 156). Inclusion criteria were: New York Heart Association class II-III HF; chronic HF of at least 3-months duration; and left ventricular ejection fraction (LVEF) of 40% or less as assessed by echocardiography, radionuclide imaging, or left ventriculography within 6 months of study enrollment. Exclusion criteria were uncontrolled hypertension (blood pressure (BP) > 180/105 mm Hg); myocardial infarction or coronary revascularization procedure in the past 3 months; HF due to correctable cause or condition, such as uncorrected primary valvular disease, uncorrected thyroid heart disease, or persistent tachyarrhythmia; pacemaker dependence; use of mechanical assist devices; life limiting or complicated illness including cancer, renal dysfunction, hepatic dysfunction, dementia, and nitrate use. Patients who were pregnant, had atrial fibrillation, reported alcohol or drug abuse within 12 months, or were unable to comply with the assessment procedure or to provide informed consent were excluded. The study complies with the Declaration of Helskinki and was approved locally by the Institutional Review Board at Duke University Medical Center, where all assessments were performed. Written informed consent was obtained from all participants before their participation.

Assessments

Clinical status and medications. Heart failure diagnosis, etiology, comorbidities and health behaviors (smoking, alcohol use) were assessed by questionnaires and medical record review. Medication use was documented by participants showing research staff all their current medications. Blood samples for NT-proBNP analysis were taken, stored and analyzed in line with standard procedures and with the associated coefficients as described elsewhere.[22]

Blood pressure. BP was assessed using a Suntech 4240 blood pressure monitor, with measurements of systolic (SBP) and diastolic (DBP) BP acquired during the final 5 minutes of a 30 minute period of quiet relaxation in a seated posture.

Endothelial function. All participants completed the FMD assessment protocol in the morning, following an overnight fast. Prescribed medications were taken as normal, except for low dose aspirin which participants took with a breakfast provided following the FMD assessment protocol. While others advise that if possible, vasoactive medications should be withheld prior to FMD assessment,[23] the maintenance of the medication regimen in this study allows us to ascertain the predictive value of FMD and reactive hyperemia on outcomes, when taking these daily medication regimens, leading us to more generalizable data relevant to our population. Vascular imaging was performed by a single sonographer using an Acuson Aspen ultrasound platform equipped with an Acuson L10 (7-10 MHz) linear array transducer, following guidelines described elsewhere.[23] After the participant had rested for 10 min in the supine posture, longitudinal B-mode images of the brachial artery, in the region 4 to 6 cm proximal to the antecubital fossa, were acquired. Images were then captured during the first 120 seconds of reactive hyperemia achieved by inflation of a pneumatic occlusion cuff located around the forearm to supra-systolic pressure (~200 mm Hg) for 5 minutes. Gated end-diastolic images of the artery were stored and arterial diameters were measured as the distance between the proximal and distal arterial wall intima-media interfaces using PC-based software (Brachial Analyzer - Version 5.0, Medical Imaging Applications LLC, Iowa City, Iowa). Peak FMD response was assessed from 10 to 120 seconds post-deflation of the cuff, with peak arterial diameter quantified using polynomial curve fitting. FMD was expressed as percent increase in arterial diameter (maximum arterial diameter − baseline arterial diameter/baseline arterial diameter × 100).[23] Because the percent change index may result in bias towards greater vasodilation in smaller arteries,[23] baseline arterial diameter was used as a covariate in all analyses. Pulsed Doppler flow signals in the brachial artery were recorded at baseline and for up to 15 seconds after cuff release. The velocity-time integral for baseline and reactive hyperemia was based upon the mean of triplicate pulsed-Doppler flow tracings recorded at each of these phases. Hyperemic velocity was derived by dividing the velocity-time integral by the inter-beat interval, and hyperemic flow was calculated from hyperemic velocity and brachial artery cross-sectional area. All ultrasound image analyses were performed blinded to participants' identities. In our previous work, we have demonstrated excellent reproducibility of the FMD measure (r = 0.81) between participants.[24]

Follow-up of vital status and hospitalizations. The medical records of participants were reviewed annually, on the anniversary of their baseline assessments, over a median of 5 years (with a range of 4 to 7 years); no participants were lost to follow-up. Each year, patients also were contacted by mail and asked to indicate whether they had been hospitalized during the previous 12 months and provided consent for retrieval of their hospitalization records. The primary end point was defined as the time to cardiovascular hospitalization or