**Heart Failure and Cardiac Transplant**

# Flow-Mediated Vasodilation Predicts Outcome in Patients With Chronic Heart Failure

## Comparison With B-Type Natriuretic Peptide

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| **OBJECTIVES** | The aim of this study was to assess the predictive potency of impaired endothelium-dependent flow-mediated vasodilation (FMD) in patients with chronic heart failure (CHF). |
| **BACKGROUND** | Chronic heart failure is associated with reduced FMD; the prognostic impact of this observation is unknown. |
| **METHODS** | Seventy-five ambulatory CHF patients (United Network of Organ Sharing [UNOS] status 2) with a left ventricular ejection fraction (LVEF) ≤30%, despite optimized medical therapy (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, 100%; beta-blocker, 81%), were evaluated. Using high-resolution ultrasound, FMD of the brachial artery was assessed in addition to other neurohormonal, clinical, and hemodynamic variables. Age, gender, New York Heart Association (NYHA) functional class, LVEF, hemodynamic variables, B-type natriuretic peptide (BNP) levels, medical therapy, cardiovascular risk factors, and FMD were analyzed for prediction of the combined end point conversion to UNOS status 1 or death in a multivariate Cox model. |
| **RESULTS** | Up to three years, 21 patients (28%) converted to UNOS status 1, and 6 patients (8%) died. Univariate risk factors for the combined end point were log BNP (p = 0.0032), FMD (p = 0.0033), NYHA functional class (p = 0.0132), beta-blocker therapy (p = 0.0367), and mean blood pressure (p = 0.0406). In the multivariate analysis, only FMD (p = 0.0007), log BNP (p = 0.0032), and mean blood pressure (p = 0.0475) were independently related to the combined end point. In the Kaplan-Meier plot, significantly more patients with FMD <6.8% (median) reached the combined end point, as compared with patients with FMD >6.8% (p = 0.004). |
| **CONCLUSIONS** | In CHF, impaired FMD is a strong, independent predictor of conversion to UNOS status 1 or death. (J Am Coll Cardiol 2005;46:1011–8) © 2005 by the American College of Cardiology Foundation |

The vasodilatory, anti-inflammatory, and antithrombotic properties of the endothelium are markedly diminished by various injuries, including hypertension, hypercholesterolemia, smoking, and diabetes. This endothelial dysfunction

represents a key step in the development of atherosclerosis and is also involved in plaque progression. Several studies indicate that endothelial dysfunction, assessed as impaired endothelium-dependent flow-mediated vasodilation (FMD), predicts an increased rate of adverse cardiovascular events, including acute coronary syndromes, ischemic stroke, critical limb ischemia, coronary, carotid, and peripheral revascularization procedures, and cardiovascular deaths (1–8).

Traditional cardiovascular risk factors like hypertension, hypercholesterolemia, and obesity are associated with an increased risk of developing chronic heart failure (CHF)

and mortality in the general population. In patients with CHF, these risk factors are also related to outcome, but in the opposite direction, high systemic blood pressure, hypercholesterolemia, and obesity have been shown to indicate a better survival. Various mechanisms may contribute to this phenomenon (9).

Independent of the traditional cardiovascular risk factors, CHF itself causes endothelial dysfunction of both large conduit arteries and small resistance arteries (10). The specific mechanisms of impaired FMD in CHF include long-term decreased peripheral blood flow, cytokine activation, increased angiotensin-converting enzyme (ACE) activity, increased oxidative stress, and increased endothelin production (11,12). Long-term decreased peripheral blood flow, cytokine activation, and increased ACE activity are involved in the reduced synthesis and release of nitric oxide; the increased production of oxygen free radicals contributes to the inactivation of nitric oxide; and the increased endothelin production counteracts short-term vasodilation via nitric oxide by enhancing basal vascular tone (10,13). Each of these factors has an important prognostic impact in patients with CHF (14–18).

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Abbreviations and Acronyms
ACE   = angiotensin-converting enzyme
BNP   = B-type natriuretic peptide
CHF   = chronic heart failure
DCM   = dilated cardiomyopathy
FMD   = (endothelium-dependent) flow-mediated
        vasodilation
HTx   = heart transplantation
ICM   = ischemic cardiomyopathy
LVEF  = left ventricular ejection fraction
NMD   = nitroglycerin-mediated vasodilation
NYHA  = New York Heart Association
ROC   = receiver-operating characteristic
UNOS  = United Network for Organ Sharing
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Endothelial dysfunction may enhance the progression of CHF via peripheral and central effects. Increased arterial stiffness and reduced compliance increase ventricular afterload and left ventricular end-diastolic stress and enhance dilation and failure (19,20). Central effects of endothelial dysfunction include impaired function of the large epicardial coronary arteries, as well as the coronary microcirculation, which may cause or contribute to myocardial ischemia (10).

We hypothesized that in CHF patients with severe left ventricular systolic dysfunction despite optimized medical therapy, FMD differs between event-free survivors and patients reaching the combined end point conversion to United Network of Organ Sharing (UNOS) status 1 or death and that FMD is a predictor of these end points.

## METHODS

**Study protocol.** The recruitment of 75 ambulatory CHF patients (UNOS status 2—patients without inotropic or mechanical circulatory support and without mechanical ventilation [21]) was planned. Inclusion criteria were a left ventricular ejection fraction (LVEF) ≤30% assessed by radionuclide ventriculography within four weeks before study entry and optimized medical therapy. Patients with an acute myocardial infarction or coronary revascularization procedure within the last three months and patients with a severe valvular stenosis or severe primary regurgitation of the aortic or tricuspid valve were excluded from the study.

In eligible patients, a full clinical history was obtained and examination performed by a CHF specialist. Baseline demographic data, functional status, CHF medication, and cardiovascular risk factors were documented, and a 12-lead electrocardiogram was reviewed. Moreover, blood sampling was performed 2 h after routine morning medications, and ultrasound measurements of the brachial artery were performed 8 h after routine morning medications (and after an 8-h fast).

The study end points were conversion to UNOS status 1 (e.g., chronic inotropic support or implantation of a ventricular assist device [21]) or death. For patients who converted to UNOS status 1 and then died or underwent heart transplantation (HTx) within the observation period,

only the first event was considered in the analysis. The UNOS status 2 HTx was treated as a censored observation (these patients were counted as survivors and removed from follow-up "alive" at the time of HTx). The maximum follow-up time for a single patient was defined as three years; follow-up closure was scheduled 1.5 years after recruitment of the last patient. The study was approved by an institutional review committee, and all patients gave informed consent.

**Follow-up.** All patients had routine visits at our Heart Failure Center, as clinically indicated. In case of refractoriness to optimized medical treatment (ongoing New York Heart Association [NYHA] functional class IIIb/IV) and documented forward and backward failure (cardiac index <2.5 l/min/m², pulmonary capillary wedge pressure >20 mm Hg) and in the absence of contraindications, patients were considered HTx candidates. Patients were supported with positive inotropic agents or left ventricular assist devices when clinically indicated; the treating physicians were unaware of the FMD and B-type natriuretic peptide (BNP) levels.

At the follow-up closing date (April 30, 2003) or three years after inclusion into the study, the medical records of all patients were reviewed, and the outcome was assessed by telephone calls.

**Healthy subjects and control subjects.** Nineteen healthy young subjects and 14 age- and gender-matched subjects with several risk factors (for adequate comparison) but without systolic left ventricular dysfunction (excluded by echocardiography) or coronary artery disease (excluded by angiography) served as two control groups. The demographic and clinical characteristics of these two groups are given in Table 1.

**Laboratory tests.** Venous blood samples were obtained after 30 min of supine rest from an indwelling catheter. Test tubes were placed on ice and separated immediately. Plasma samples were stored at −70°C until analysis. The BNP level was measured using a commercially available fluorescence immunoassay (Triage BNP Test by Biosite Diagnostics Inc., San Diego, California).

**Assessment of FMD and nitroglycerin-mediated vasodilation (NMD).** Ultrasound measurements were performed according to the guidelines for the ultrasound assessment of FMD of the brachial artery (22). Using high-resolution ultrasound (Sonos 2500, Hewlett-Packard, Andover, Massachusetts) with a 7.5-MHz linear array transducer, diameter measurements of the right brachial artery were taken after supine rest for at least 10 min, after cuff deflation completing suprasystolic compression (50 mm Hg above systolic pressure) of the right upper arm for 5 min and after sublingual application of 0.8 mg nitroglycerin. A stereotactical arm was used for optimal transducer positioning on the brachial artery proximal of the bifurcation of the radial and ulnar arteries. The longitudinal image of the artery was recorded at baseline, continuously from 30 s before to 2 min after cuff deflation, and for 5 min after nitroglycerin admin-

**Table 1.** Characteristics of the Study Groups

| | Normal Subjects (n = 19) | Control Subjects (n = 14) | Survivors (n = 48) | UNOS-1/Death (n = 27) | p Value |
|---|---|---|---|---|---|
| Age, yrs | 31 ± 10*†‡ | 55 ± 9* | 55 ± 9† | 57 ± 7‡ | 0.0001 |
| Gender, M/F (%) | 16/3 (84/16) | 11/3 (79/21) | 43/5 (90/10) | 24/3 (89/11) | |
| BMI, kg/m² | 22.6 ± 2.3*†‡ | 26.8 ± 3.3* | 26.1 ± 3.8† | 26.0 ± 4.4‡ | 0.001 |
| Cholesterol, mg/dl | 188 ± 24 | 219 ± 49 | 206 ± 50 | 186 ± 57 | NS |
| LDL cholesterol, mg/dl | 111 ± 24* | 144 ± 31*§ | 118 ± 35 | 112 ± 34§ | 0.02 |
| HDL cholesterol, mg/dl | 54 ± 12† | 41 ± 18 | 41 ± 13† | 42 ± 14 | 0.04 |
| History of hypertension, n (%) | 0*†‡ | 8 (57)* | 32 (67)† | 18 (67)‡ | |
| Smokers, n (%) | 0*†‡ | 6 (43)* | 17 (35)† | 8 (30)‡ | |
| Diabetes mellitus, n (%) | 0*†‡ | 3 (21)* | 17 (35)† | 9 (33)‡ | |

*Normal subjects versus control: p = 0.0001 (age), p = 0.009 (BMI), p = 0.03 (LDL cholesterol), p = 0.001 (history of hypertension), p = 0.002 (smokers), p = 0.03 (diabetes mellitus). †Normal subjects versus survivors: p = 0.0001 (age), p = 0.001 (BMI), p = 0.03 (HDL cholesterol), p = 0.0001 (history of hypertension), p = 0.003 (smokers), p = 0.003 (diabetes mellitus). ‡Normal subjects versus patients who converted to UNOS status 1 or died: p = 0.0001 (age), p = 0.004 (BMI), p = 0.0001 (history of hypertension), p = 0.009 (smokers), p = 0.005 (diabetes mellitus). §Control subjects versus patients who converted to UNOS status 1 or died: p = 0.02 (LDL cholesterol).

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UNOS = United Network of Organ Sharing.

istration. Electrocardiographic gating was used during image acquisition to determine the diameter at the same time in the cardiac cycle. The baseline diameter and maximum FMD and NMD diameters were measured from one media-adventitia interface to the other. Vasodilation was then calculated as the percent change in diameter over the baseline value.

To verify that suprasystolic compression of the brachial artery produced an adequate increase in blood flow, flow velocity was measured at rest and within 15 s after cuff deflation. Despite using a stereotactical arm, the collapse of the brachial artery and a shift in soft tissue by the compression of the upper arm (22) sometimes required an optimization of the transducer position, which could have delayed the assessment of the hyperemic velocity after the optimal time point. Blood flow was calculated by multiplying the velocity-time integral by the heart rate and the vessel cross-sectional area (3.14 × [D2/4], where D indicates diameter). Reactive hyperemia was then calculated as the percent change in flow during hyperemia over the baseline value.

**Sample size and predefined observation period.** Sample size calculation for log-rank tests (23) was estimated based on the following assumptions: BNP, an excellent prognostic marker in CHF, showed a hazard ratio of 12 in patients with high compared with low BNP values (60% vs. 5% end point rate [24]). Because these data were acquired in the pre beta-blocker era, a 50% risk reduction by beta-blockers was taken into account. Assuming that FMD could be a strong but less powerful predictor than BNP, sample size calculation was performed using an expected hazard ratio of 3. From previous data (18), we deducted a 34% biennial event rate after adjustment for a 50% risk reduction due to beta-blocker therapy, yielding a ratio of survivors to non-survivors of 2:1 over the study period. The maximum follow-up time for a single patient was defined as three years. Follow-up closure was scheduled 1.5 years after recruitment of the last patient to ensure a minimum follow-up time of 1.5 years. Thus, assuming a recruitment period of one year, a mean follow-up time of two years, a

mean end point-free survival time of 20 months in the high event rate group (24), a hazard ratio of 3, and a ratio of survivors to non-survivors of 2:1, a test with an alpha of 0.05 and a power of 0.80 would require a total sample size of 72 patients. Including a safety margin for patients lost to follow-up, we aimed for the recruitment of 75 patients.

**Statistical analyses.** Continuous variables are expressed as the mean ± SD. Differences between groups were analyzed using one-factor analysis of variance followed by Tukey's studentized range test (if indicated) for continuous variables, and pairwise comparisons were performed by means of the Fisher exact test for categorical variables. Linear regression analysis was used to determine the relationship between FMD, BNP, and LVEF. A Cox proportional hazard regression analysis was performed to identify independent predictors of the combined end point. The model was built by introducing variables simultaneously or stepwise; the p value for entering and staying in the model was set at 0.05. Because BNP was not normally distributed, log values were used for analysis. Receiver-operating characteristic (ROC) analysis was calculated to assess the utility of FMD to distinguish between survivors and patients who reached the combined end point. The event-free survival between various patient groups was compared by Kaplan-Meier analysis. Differences were considered significant at p < 0.05.

## RESULTS

**Patients.** Seventy-five ambulatory patients (UNOS status 2) who had routine visits at our Heart Failure Center between January 1999 and December 2001 were entered into the study. Demographic and clinical data of all patients are given in Table 2. The etiology of the disease was verified by coronary angiography; patients without >75% stenosis of a major epicardial coronary artery were classified as having dilated cardiomyopathy (DCM).

**Clinical outcome.** After a mean observation period of 561 ± 344 days, 27 patients reached the combined end point conversion to UNOS status 1 or death. Of 21 patients who converted to UNOS status 1, 11 underwent urgent HTx, 8

**Table 2.** Characteristics of Chronic Heart Failure Patients According to Their Outcome

| | Survivors (n = 48) | UNOS-1/Death (n = 27) | p Value | All (n = 75) |
|---|---|---|---|---|
| Age, yrs | 55 ± 9 | 57 ± 7 | NS | 55 ± 8 |
| Gender, M/F (%) | 43/5 (90/10) | 24/3 (89/11) | NS | 67/8 (89/11) |
| Diagnosis, n (%) | | | NS | |
| DCM | 19 (40) | 16 (59) | | 35 (47) |
| ICM | 29 (60) | 11 (41) | | 40 (53) |
| LVEF, % | 21 ± 5 | 20 ± 6 | NS | 21 ± 5 |
| BNP, pg/ml | 264 ± 413 | 443 ± 372 | 0.05 | 328 ± 406 |
| Log BNP | 2.13 ± 0.52 | 2.43 ± 0.55 | 0.02 | 2.24 ± 0.55 |
| NYHA functional class, n (%) | | | 0.07 | |
| I | 9 (19) | 1 (4) | | 10 (13) |
| II | 12 (25) | 5 (19) | | 17 (23) |
| III | 24 (50) | 15 (56) | | 39 (52) |
| IV | 3 (6) | 6 (22) | | 9 (12) |
| Mean systemic blood pressure, mm Hg | 85 ± 13 | 81 ± 10 | NS | 83 ± 12 |
| Heart rate, beats/min | 68 ± 12 | 74 ± 13 | 0.02 | 70 ± 13 |
| Rhythm, n (%) | | | NS | |
| Sinus rhythm | 36 (75) | 17 (63) | | 53 (71) |
| Atrial fibrillation | 7 (15) | 7 (26) | | 14 (19) |
| Pacemaker | 5 (10) | 3 (11) | | 8 (10) |
| Neurohormonal antagonists | | | | |
| ACE inhibitor, n (%) | 47 (98) | 27 (100) | NS | 74 (99) |
| % of target dose | 152 ± 59 | 160 ± 52 | NS | 155 ± 56 |
| AT II receptor blocker, n (%) | 13 (27) | 4 (15) | NS | 17 (23) |
| Beta-blocker, n (%) | 43 (90) | 18 (67) | 0.01 | 61 (81) |
| % of target dose | 75 ± 42 | 63 ± 26 | NS | 71 ± 38 |
| Aldactone, n (%) | 20 (43) | 8 (30) | NS | 28 (37) |
| ICD, n (%) | 11 (23) | 2 (7) | NS | 13 (17) |

ACE = angiotensin-converting enzyme; AT = angiotensin; BNP = B-type natriuretic peptide; DCM = dilated cardiomyopathy; ICD = implantable cardioverter-defibrillator; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; UNOS = United Network of Organ Sharing.

died (6 due to progressive pump failure, 2 due to other reasons such as a thromboembolic complication after implantation of a left ventricular assist device and stroke), and 2 survived within the predefined observation period. Additionally, six patients died suddenly. Forty-eight patients survived event free until the end of the observation period (n = 42) or until elective HTx (n = 6). Differences between event-free survivors and patients who reached the combined end point are given in Table 2.

**Comparison of study groups.** Differences between gender-matched healthy subjects, control subjects, event-free survivors, and patients who reached the combined end point are given in Table 1.

**Vasodilation and blood flow response.** The results of the ultrasound measurements in the brachial artery are given in Table 3. The mean time to reach peak FMD was 69 ± 10 s. Vessel size and hyperemia were similar in the study groups; thus, it can be assumed that the stimulus for FMD was similar. However, FMD values were significantly impaired in CHF survivors (11.2 ± 7.4%, p = 0.02) and in patients who reached the combined end point (5.4 ± 5.1%, p = 0.0001), and they tended to be impaired in control subjects (10.8 ± 3.4%, p = 0.07) as compared with the healthy subjects (15.9 ± 4.1%). Moreover, FMD values were similar between the control subjects and CHF survivors (10.8 ± 3.4% vs. 11.2 ± 7.4%, p = NS), but differed between

**Table 3.** Results of Ultrasound Measurements in the Brachial Artery

| | Normal Subjects (n = 19) | Control Subjects (n = 14) | Survivors (n = 48) | UNOS-1/Death (n = 27) | p Value |
|---|---|---|---|---|---|
| Baseline diameter, mm | 4.5 ± 0.8 | 4.8 ± 0.8 | 4.9 ± 0.7 | 4.9 ± 0.8 | NS |
| Baseline flow, ml/min | 169 ± 102 | 144 ± 60 | 142 ± 79 | 139 ± 54 | NS |
| Hyperemia diameter, mm | 5.2 ± 1.0 | 5.3 ± 0.9 | 5.4 ± 0.7 | 5.2 ± 0.8 | NS |
| Hyperemia flow | 408 ± 202 | 410 ± 110 | 410 ± 333 | 484 ± 347 | NS |
| Hyperemia, % | 291 ± 215 | 302 ± 114 | 272 ± 138 | 339 ± 185 | NS |
| FMD, % | 15.9 ± 4.1*†‡ | 10.8 ± 3.4*§ | 11.2 ± 7.4†‖ | 5.4 ± 5.1§‖ | 0.0001 |
| NMD diameter, mm | 5.4 ± 1.1 | 5.5 ± 0.9 | 5.7 ± 0.6 | 5.5 ± 0.8 | NS |
| NMD, % | 19.8 ± 6.2‡ | 13.9 ± 4.7 | 15.4 ± 8.3 | 12.7 ± 5.1‡ | 0.008 |

*Normal subjects versus controls; p = 0.07 (FMD). †Normal subjects versus survivors; p = 0.02 (FMD). ‡Normal subjects versus patients who converted to UNOS status 1 or died; p = 0.0001 (FMD); p = 0.005 (NMD). §Controls versus patients who converted to UNOS status 1 or died; p = 0.04 (FMD). ‖Survivors versus patients who converted to UNOS status 1 or died; p = 0.001 (FMD).

FMD = flow-mediated vasodilation; NMD = nitroglycerin-mediated vasodilation; UNOS = United Network of Organ Sharing.

control subjects and CHF patients who reached the combined end point (10.8 ± 3.4% vs. 5.4 ± 5.1%, p = 0.04). As the main result of this study, FMD values were significantly impaired in CHF patients who reached the combined end point as compared with CHF survivors (5.4 ± 5.1% vs. 11.2 ± 7.4%, p = 0.001). None of the healthy subjects had FMD below the median FMD (6.8%) of the CHF patients (Fig. 1).

By comparing the endothelium-independent vasodilator capacity of the brachial artery, NMD values were similar between the control subjects (13.9 ± 4.7%), CHF survivors (15.4 ± 8.3%), and CHF patients who reached the combined end point (12.7 ± 5.1%). The NMD values of the healthy subjects (19.8 ± 6.2%) were slightly higher compared with the NMD values of the three groups, but a significant difference could only be detected between healthy subjects and CHF patients who reached the combined end point (19.8 ± 6.2% vs. 12.7 ± 5.1%, p = 0.005). In accordance, Schächinger et al. (1) demonstrated that impaired NMD of coronary arteries is also associated with a significantly higher incidence of cardiovascular events.

**Subanalysis of patients with DCM and patients with ischemic cardiomyopathy (ICM).** As listed in Table 2, 16 (46%) of 35 patients with DCM and 11 (28%) of 40 patients with ICM reached the combined end point. In accordance with the whole study population, FMD also differed in the subgroup of DCM patients (11.1 ± 7.7% vs. 5.6 ± 4.5%, p = 0.02) and in the subgroup of ICM patients (11.3 ± 7.4% vs. 5.1 ± 6.1%, p = 0.02) between event-free survivors and patients who reached the combined end point (Fig. 1).

**Relationship between FMD and NYHA functional class.** Flow-mediated dilation was significantly higher in patients in NYHA functional class I compared with class IV (Fig. 2). Interestingly, no correlation was found between FMD and BNP levels or between FMD and LVEF (≤30% in all patients) in a linear regression analysis.

**Univariate and multivariate predictors of the combined end point.** Univariate indicators for the combined end point were log BNP (p = 0.0032), FMD (p = 0.0033),
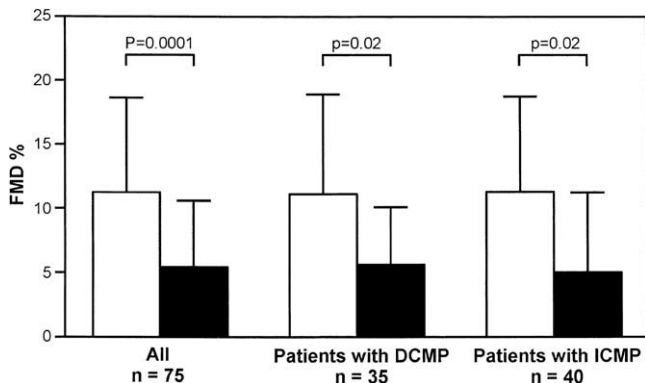


**Figure 1.** The mean endothelium-dependent flow-mediated vasodilation (FMD) of event-free survivors **(open bars)** compared with patients who converted to United Network for Organ Sharing status 1 or died **(solid bars)** in all chronic heart failure patients and in the subgroups of patients with dilated cardiomyopathy (DCMP) and ischemic cardiomyopathy (ICMP).
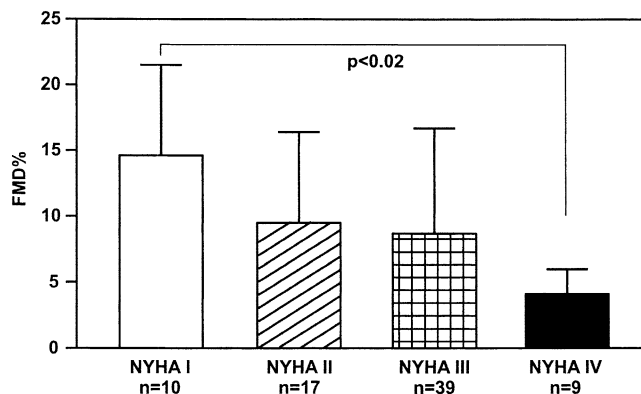


**Figure 2.** The mean endothelium-dependent flow-mediated vasodilation (FMD) of 10 patients in New York Heart Association (NYHA) functional class I, 17 in class II, 39 in class III, and 9 in class IV .

NYHA functional class (p = 0.0132), beta-blocker therapy (0.0367), and mean blood pressure (p = 0.0406) (Table 4). Introducing FMD and three univariate clinical predictors—NYHA functional class, beta-blocker therapy, and mean blood pressure—simultaneously in a multivariate model, FMD (chi-square = 5.1175, p = 0.0237) and mean blood pressure (chi-square = 4.0838, p = 0.0433) were the only independent predictors of the combined end point. When also introducing log BNP in this model, only log BNP (chi-square = 11.0171, p = 0.0009) and FMD (chi-square = 6.0157, p = 0.0142) were independent predictors. In accordance, in the multivariate stepwise regression analysis, only FMD (chi-square = 11.5363, p = 0.0007), log BNP (chi-square = 8.7129, p = 0.0032), and mean blood pressure (chi-square = 3.9289, p = 0.0475) were independently related to the combined end point (Table 4).

In order to identify a potential cutoff, another analysis was performed using the categorical variable FMD (below and above the median of 6.8%). Again, FMD was a strong univariate predictor (chi-square = 8.1911, p = 0.0042) and one of two independent predictors of the combined end point in the multivariate stepwise model (log BNP: chi-square = 8.7129, p = 0.0032; FMD: chi-square = 16.2788, p < 0.0001).

**Univariate predictors of sudden death, pump failure death, and conversion to UNOS status 1.** Analyzing event-free survivors and patients who died suddenly, univariate predictors of sudden death were log BNP (p = 0.02) and beta-blocker therapy (p = 0.02). By analyzing survivors and patients who died from pump failure, univariate predictors of pump failure death were log BNP (p = 0.006), FMD (p = 0.01), and NYHA functional class (p = 0.01). By analyzing survivors and patients who converted to UNOS status 1, univariate predictors of conversion to UNOS status 1 were FMD (p = 0.001), NYHA functional class (p = 0.002), log BNP (p = 0.02), and mean blood pressure (p = 0.03).

**ROC analysis.** The area under the ROC curve using FMD for discriminating patients who reached the combined end

**Table 4.** Univariate and Multivariate Predictors of Adverse Outcome

| | Univariate Analysis | | Multivariate Stepwise Analysis | |
|---|---|---|---|---|
| | Chi-Square | p Value | Chi-Square | p Value |
| Log BNP | 8.7129 | 0.0032 | 8.7129 | 0.0032 |
| FMD | 8.6369 | 0.0033 | 11.5363 | 0.0007 |
| NYHA functional class | 6.1407 | 0.0132 | | |
| Beta-blocker | 4.3642 | 0.0367 | | |
| Mean BP | 4.1943 | 0.0406 | 3.9289 | 0.0475 |
| Cholesterol | 3.5792 | 0.0585 | | |
| Age | 2.3351 | 0.1265 | | |
| Diagnosis | 2.1113 | 0.1462 | | |
| LDL | 1.0621 | 0.3027 | | |
| Smoking | 0.8671 | 0.3518 | | |
| BMI | 0.7944 | 0.3728 | | |
| LVEF | 0.5852 | 0.4443 | | |
| ACE inhibitors | 0.3688 | 0.5436 | | |
| Gender | 0.0692 | 0.7924 | | |
| HDL | 0.0013 | 0.9717 | | |
| Diabetes mellitus | 0.0001 | 0.9935 | | |

ACE = angiotensin-converting enzyme; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; FMD = flow-mediated vasodilation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

point from survivors was 0.76 (Fig. 3). The mean FMD of 6.8% in CHF patients had a sensitivity of 63% and a specificity of 67%.

**Kaplan-Meier survival estimation.** Using Kaplan-Meier analysis, event-free survival rates were significantly higher in patients with FMD >6.8% (median) compared with patients with FMD <6.8% (p = 0.004). Seven (19%) of 37 patients above, but 20 (53%) of 38 patients below this cutoff value converted to UNOS status 1 or died (Fig. 4).

**Combining FMD and BNP to a prognostic factor.** When stratifying patients according to the median of FMD and BNP levels and combining these stratifications to one factor (group A: FMD >6.8%, BNP <208 pg/ml [n = 17]; group B: FMD <6.8%, BNP <208 pg/ml [n = 21]; group C: FMD >6.8%, BNP >208 pg/ml [n = 20]; group D:

FMD <6.8%, BNP >208 pg/ml [n = 17]), this factor was the only independent predictor of the combined end point in the multivariate analysis (chi-square = 24.9390, p = 0.0001). No patient in group A, 7 patients in group B (33%), 7 patients in group C (35%), and 13 patients in group D (76%) reached the combined end point, resulting in a highly significant difference between groups (except between groups B and C) in the Kaplan-Meier analysis (Fig. 5).

## DISCUSSION

Flow-mediated dilation significantly differed between event-free survivors and patients who reached the combined end point conversion to UNOS status 1 or death in 75 CHF patients with LVEF ≤30% despite optimized medical therapy. Impaired FMD was a strong predictor of the combined end point in these patients, independent of BNP
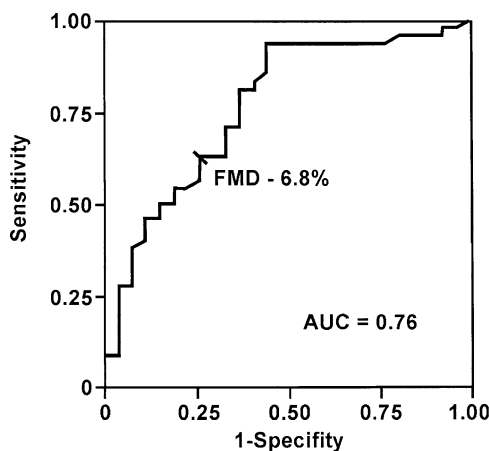


**Figure 3.** The receiver-operating characteristic curve illustrates the sensitivity and specificity of endothelium-dependent flow-mediated vasodilation (FMD) in discriminating patients who reached the combined end point from survivors (FMD 6.8%; sensitivity 63%, specificity 67%). The area under the curve (AUC) was 0.76.
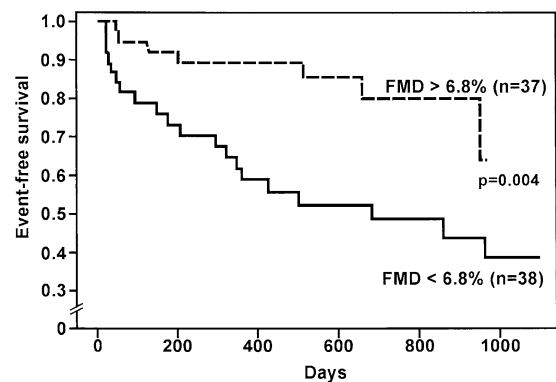


**Figure 4.** Kaplan-Meier analysis showing cumulative rates of event-free survival in 75 patients with chronic heart failure stratified into two groups according to the median of endothelium-dependent flow-mediated vasodilation (FMD). Patients with FMD >6.8% had a significantly better event-free survival compared with patients with FMD <6.8% (p = 0.004).
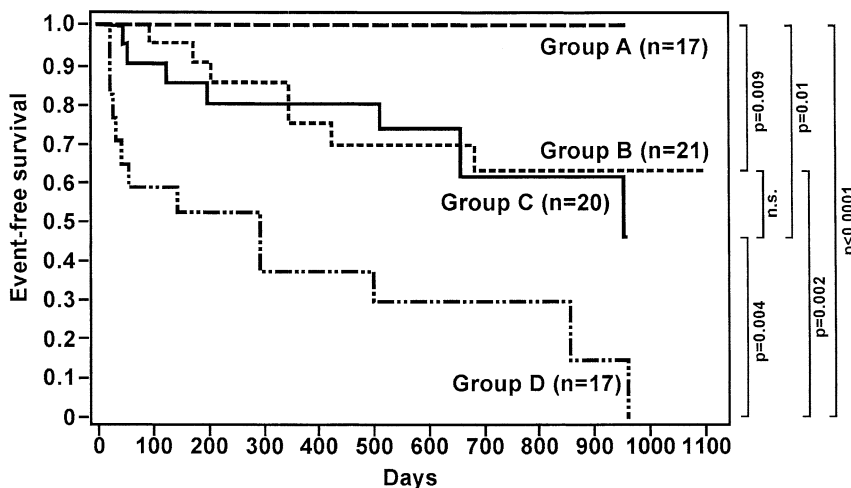
**Figure 5.** Kaplan-Meier analysis showing cumulative rates of event-free survival in 75 patients with chronic heart failure stratified into four groups according to their endothelium-dependent flow-mediated vasodilation (FMD) and B-type natriuretic peptide (BNP) levels—group A: FMD >6.8%, BNP <208 pg/ml; group B: FMD <6.8%, BNP <208 pg/ml; group C: FMD >6.8%, BNP >208 pg/ml; and group D: FMD <6.8%, BNP >208 pg/ml.

levels and various other clinical factors previously associated with a poor prognosis.

**Endothelial dysfunction as prognostic marker—previous studies.** In accordance with our findings, various other studies have already proved the prognostic potency of endothelial function to predict future adverse events (1–8). In some of these investigations, as well as in our study, the ultrasound evaluation of the brachial artery was used for assessment of FMD (6–8). The study population in these analyses included patients with hypertension (3), various cardiovascular risk factors (5), non-significant (2) or significant coronary artery disease (6), peripheral artery disease (7,8), a mixed patient population (1) or patients undergoing vascular surgery (4), and the study end points were clinical events resulting from atherosclerotic complications. Our patient population differs from those of previous studies because it consists exclusively of patients with severe systolic left ventricular dysfunction. Despite various cardiovascular risk factors, CHF patients are not at high risk of atherosclerotic complications but are at high risk of sudden cardiac death or clinical deterioration and death due to progressive pump failure (9). In the present study, we demonstrate that endothelial function predicts these CHF specific events, deterioration to UNOS status 1, or death.

The predictive impact of endothelial function in CHF patients is supported by several facts. First, the mechanisms contributing to impaired FMD in CHF, which include long-term decreased peripheral blood flow, cytokine activation, increased ACE activity, increased oxidative stress, and increased endothelin production, are per se strong predictors of adverse events in CHF (14–18). Second, impaired FMD may enhance the progression of CHF via an increase of ventricular afterload (19,20) and myocardial ischemia (10). Third, impaired FMD is causatively involved in the development of reduced functional capacity, an established prognostic marker in CHF (25–27). Rather than the extent of central hemodynamic disturbances and pulmonary abnor-

malities like increased death space ventilation, impaired skeletal muscle function represents the major determinant of exercise capacity (28). The histologic and biochemical abnormalities of the skeletal muscle in CHF are probably caused by reduced blood flow to the exercising muscle (10,28,29). Indeed, in CHF patients, the severity of impairment of endothelium-dependent vasodilation correlates with exercise capacity and functional class (30). Our findings are consistent with these reports, as FMD decreases with increasing functional class.

**BNP and FMD—two strong independent prognostic markers.** In several studies, BNP was demonstrated to be a strong independent predictor of adverse outcome in CHF (24,26,27,31). Our data support these findings but also show that, besides BNP, FMD is another strong independent prognostic marker in CHF patients. Moreover, when combining FMD and BNP levels as one factor, this factor was by far the strongest independent predictor of adverse outcome in the multivariate analysis. Considering the already described association between FMD and functional capacity, our data are in accordance with those of other groups. They demonstrate that BNP and peak oxygen consumption, a marker of functional capacity, are two strong independent predictors of outcome, and that the combination of both improves risk stratification in these patients (26,27).

**Prognostic power of FMD according to underlying heart disease.** Endothelium-mediated vasodilation is similarly impaired in patients with DCM and ICM (32); perhaps impairment is slightly more pronounced in ICM patients (32). Possible slight differences concerning the responsible mechanisms of reduced FMD in DCM and ICM are under discussion (32,33). Nevertheless, our data demonstrate that FMD differs similarly in ICM and DCM patients between event-free survivors and patients who died or converted to UNOS status 1.

**Study limitations.** A limitation of the study is the use of UNOS status 1 as a negative end point, as patients in UNOS status 1 have not died. Nevertheless, the expected survival experience of these patients without HTx is much closer to that of patients who have died than it is to patients who remain in UNOS status 2 (34). Indeed, 38% of our patients who converted to UNOS status 1 died and 52% underwent urgent HTx within the observation period.

Another limitation is the small sample size and multiple variables entered into the multivariate model. Therefore, the findings might be influenced by the confounding effects of measured or unmeasured risk factors.

**Conclusions.** In CHF, impaired FMD is a strong predictor of adverse outcome, independent of BNP levels and various other clinical factors previously associated with a poor prognosis. The predictive value of FMD may result from a summation of various factors that contribute to endothelial dysfunction and that have known prognostic importance. Moreover, the prognostic potency of FMD may also reflect its impact on the progression of the disease. Therefore, impaired FMD might be an important tool for the assessment of patients with CHF.

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