Radial Artery Flow-Mediated Dilatation in Heart Failure Patients: Effects of Pharmacological and Nonpharmacological Treatment

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Abstract—Congestive heart failure (CHF) is associated with an impaired flow-mediated vasodilation that reflects an impaired endothelial function. Limited information is available, however, on whether and to what extent this impairment is improved by pharmacological or nonpharmacological treatment. We measured radial artery diameter and blood flow by an echo-tracking Doppler device both at baseline and after 4 minutes of hand ischemia, which increases diameter through NO secretion mediated by an increase in flow and shear stress. Data were collected from 44 CHF patients (New York Heart Association class I to III) under standard treatment (diuretic, digal, and enalapril, 20 mg/d), in whom CHF severity was assessed by a cardiopulmonary stress test, and from 16 age- and sex-matched controls. CHF patients were then randomized to maintain for (A) 2 months of standard treatment (n=11), (B) treatment with double the ACE inhibitor dose (n=11), (C) standard treatment with an angiotensin II antagonist (losartan, 50 mg/d; n=11), or (D) standard treatment with bicycle training for 30 minutes, 3 times a week (n=11). At baseline, radial artery diameter and flow were similar in CHF patients and controls; CHF patients had a modest although significant impairment in flow increase (36%) and a striking impairment (78%) in diameter increase following the 4 minutes of ischemia. After 2 months, baseline diameter and flow remained unaltered in the 4 groups. After the 4 minutes of ischemia, radial artery flow and diameter increased as before in the group under standard treatment (A), whereas in the other 3 groups, the increase was significantly (P<0.05) and, for diameter, markedly (B, 83%; C, 92%; and D, 95%) greater. The vasodilatation induced by trinitroglycerin was similar in CHF and control subjects and not affected by treatments. In CHF, radial artery shows a marked reduction in flow-mediated vasodilation, reflecting impairment of endothelial function. This impairment can be markedly improved by treatments that effectively block the renin-angiotensin system either at ACE or at ACE plus angiotensin receptor level. This is the case also with nonpharmacological treatment of CHF. (Hypertension. 2001;38:1451-1455.)

Key Words: flow-mediated dilation ■ endothelium ■ heart failure ■ angiotensin-converting enzyme inhibitors ■ receptor, angiotensin II ■ exercise

Endothelial dysfunction is believed to be an important pathophysiological feature of several cardiovascular diseases,1,2 and for this reason, the ability of endothelial cells to secrete substances with vasomotor effects in response to an appropriate stimulus has become a major issue in cardiovascular research.3-6 This ability can be tested by infusing in a brachial or coronary artery substances (eg, acetylcholine, methacholine, bradykinin) to stimulate endothelial secretion of NO and by measuring the resulting increase in forearm or coronary blood flow.1,2,7-9 It can also be tested, in a noninvasive fashion, by measuring the increase in radial artery diameter that follows a short-lasting ischemia of the hand, because this increase is due to a NO secretion triggered by an increase in blood flow velocity and shear stress.10

Conclusive evidence is available that in congestive heart failure, NO-dependent forearm or radial artery vasodilation is markedly reduced, and thus, this condition is characterized by a pronounced endothelial dysfunction.11-14 Limited information exists, however, as to whether this dysfunction is reversible with treatments of a pharmacological or nonpharmacological nature.15 In the present study, we have addressed these issues by measuring flow-mediated radial artery vasodilation in heart failure patients under standard therapy (ACE inhibitor, diuretics, and digal) in whom heart failure
severity was assessed by measuring peak oxygen consumption per unit time (V\text{O}_2) during a cardiopulmonary stress test. Measurements were repeated after 2 months during which patients (1) maintained the standard therapy, (2) doubled the dose of the ACE inhibitor, (3) associated the initial ACE inhibitor dose with an angiotensin (Ang) II receptor antagonist, or (4) added a physical training rehabilitation program to the standard therapy.

**Methods**

**Subjects**

We investigated a total of 60 subjects of either gender. Forty-four subjects (36 males; age, 61.0±1.5 years) were selected on a consecutive basis if they had (1) age <75 years; (2) chronic heart failure condition belonging to New York Heart Association class I (n=22), II (n=13), or III (n=8), with either an ischemic (n=30) or nonischemic (n=14) origin; (3) no major valvular abnormalities; (4) left ventricular ejection fraction always <40% (see below); (5) reported standard medical treatment (diuretic, digitalis, and enalapril at a dose of 20 mg daily) for ≥ 3 months; (6) no hemodynamically significant atherosclerotic carotid, femoral, or aortic lesions (echocor Doppler examination); (7) no chronic arrhythmias; and (8) no major disease besides heart failure and thus no chronic treatment with drugs other than those mentioned above. The remaining 16 subjects (14 males; age, 59.7±2.4 years) were age-matched normotensive healthy individuals who were used as controls. Five heart failure patients and 1 control were smokers. All subjects agreed to participate in the study after being informed of its nature and purpose. The protocol of the study was approved by the ethics committee of our hospital.

**Endothelial Function**

Radial artery diameter was measured by a B-M mode ultrasonic echo-tracking device that recorded the displacement of the radial artery over the cardiac cycle (WTS, Pie Medical). The device made use of a highly focalized transducer—which was stereotaxically positioned over the radial artery 2 to 4 cm above the wrist, direct contact with the skin being prevented by use of a gel as a medium—operating at a frequency of 7.5 MHz. With the subject supine and the arm immobile at the heart level, the transducer was oriented perpendicular to the longitudinal axis, based on the B mode image and the acoustic Doppler signal, so that its focal zone was located in the center of the artery and the backscattered echoes from both the anterior and the posterior walls could be clearly visualized and electronically digitized (via an analogic/digital fast transducer) to allow internal diameter variations to be derived at a 50 Hz with a resolution of 300 μm. Blood flow velocity was measured at the same site of the diameter measurement from Doppler spectra obtained by the same transducer at an angle of 40° to 60° from the principal axis of the artery. Blood flow was calculated as the product of peak systolic flow velocity and arterial diameter. Measurements were made before and immediately after a 4-minute inflation of a pediatric cuff placed around the wrist below the site of radial artery measurements. This is commonly employed to assess endothelial function because it has been demonstrated that the increase in radial artery diameter following a short-lasting hand ischemia is abolished by N\text{O}\text{3}-monomethyl-L-arginine administration, suggesting its dependence on a flow-mediated local increase in NO. Radial artery diameter and blood flow were additionally measured after sublingual administration of trinitroglycerin to obtain an increase in radial artery diameter mainly due to nonendothelial factors.

**Additional Evaluations**

During the week before the study, each subject underwent a standard echocardiograph color Doppler examination to obtain information on cardiac structure and function, ie, on left ventricular end diastolic diameter, left ventricular wall thickness, early and atrial transmittal flows, and left ventricular ejection fraction (Simpson formula). In addition, each heart failure patient underwent 2 cardiopulmonary stress tests (at a 10-week interval) with a cycloergometer ramp protocol (10 watt/min) using breath-by-breath V\text{O}_2 and CO\text{2} sampling for continuous gas analysis, averaging expiratory data over 15-second periods, and calculating the V\text{O}_2/\text{max} (%) during the test. Calculation was also made of the maximal exercise time, V\text{O}_2/\text{max} and maximal exercise time were obtained also after 2 months of therapy. In each subject, blood pressure was measured both by a mercury sphygmomanometer (taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively). Heart rate was derived from an ECG.

**Protocol and Data Analysis**

Each subject was asked to come to the outpatient clinic of the San Gerardo University Hospital in the morning following a 12-hour abstinence from alcohol, caffeine, and cigarette smoking. The study (which began 3 hours after a light meal) had the following protocol and sequence: (1) blood pressure was measured 3 times by mercury sphygmomanometer with the subject in the sitting position; (2) the subject was placed supine in a quiet room kept at constant temperature (21°C) and fitted with the radial artery echo-color-tracking device and the pediatric wrist cuff; (3) following a 15-minute interval, radial artery diameter and flow were measured for 15 minutes; (4) the pediatric wrist cuff was inflated at suprasystolic pressure for 4 minutes, and radial artery diameter and blood flow were recorded for 4 minutes after the release of the inflation; and (5) following a further 15-minute period, trinitroglycerin (300 μg) was administered sublingually, and arterial diameter was measured every 30 seconds for the following 5 minutes.

The above-mentioned measurements were obtained in the same fashion and sequence after 2 months, during which heart failure patients had been randomly assigned to (1) continuation of the previous standard therapy (11 patients); (2) modification of the previous therapy by increasing the dose of enalapril up to 40 mg daily (11 patients); (3) modification of the previous therapy by adding 50 mg losartan daily (11 patients); and (4) addition to the previous treatment of a physical training rehabilitative program, based on bicycling 30 minutes a day, 3 times a week. Treatment was continued for 2 months. Compliance to treatment was checked by pill counting or by attendance to rehabilitation sections. All vascular measurements were made by a single operator unaware of the experimental design and therapy assignment.

In each subject and for each study session, the 3 sphygmonometric blood pressure values were averaged. In the baseline condition, radial artery diastolic diameter and blood flow were obtained, by averaging, respectively, data from 5 periods of 6 seconds each (taken at 2-minute intervals) and 3 consecutive blood flow velocity values. The effect of the 4-minute ischemia on both variables was obtained by taking the peak radial artery diameter and blood flow values, respectively, after 180 and 30 seconds from the release of the wrist inflation. The effect of trinitroglycerin was obtained from the peak values seen during the 5 minutes following the drug administration. In our laboratory, intra- and intersession coefficient of variations for the measurements employed in the present study are as follows: baseline radial artery diameter, 2.5% and 2.8%; baseline radial artery blood flow values, 8.0% and 10.0%; radial artery diameter after the 4-minute ischemia, 3.5% and 4.2%; radial artery blood flow after the 4-minute ischemia, 3.0% and 5.0%; and radial artery diameter after trinitroglycerin administration, 2.0% and 3.0%. Results from individual subjects were averaged and shown as means±SE separately for the control group, the heart failure group as a whole, and the heart failure groups under different treatments. The statistical significance of the differences in mean values was assessed by 2-way ANOVA and by ANOVA for repeated measurements. The 2-tailed t test for paired and unpaired observations was used (with the Bonferroni correction for multiple comparisons) to locate the statistical significance of between-group differences. P<0.05 was taken as the level of statistical significance.
TABLE 1. Baseline Hemodynamic and Radial Artery Values in CHF Patients and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=16)</th>
<th>CHF Patients (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>139.0 ± 7.2</td>
<td>125.7 ± 2.9*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81.7 ± 1.9</td>
<td>76.7 ± 1.3*</td>
</tr>
<tr>
<td>HR, b/min</td>
<td>66.1 ± 2.2</td>
<td>72.8 ± 3.5</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>51.0 ± 2.4</td>
<td>67.1 ± 1.1**</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61.1 ± 3.9</td>
<td>32.8 ± 1.0**</td>
</tr>
<tr>
<td>E/A</td>
<td>0.9 ± 0.1</td>
<td>1.5 ± 0.2*</td>
</tr>
<tr>
<td>RADD, mm</td>
<td>2.6 ± 0.9</td>
<td>2.7 ± 0.8</td>
</tr>
<tr>
<td>RABF, mL/min</td>
<td>40.2 ± 6.3</td>
<td>30.1 ± 3.9</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEDD, left ventricle ejection fraction; E/A, early/late transmortal flow velocity; RADD, radial artery diastolic diameter; and RABF, radial artery blood flow. *P<0.05, **P<0.01 vs controls.

Results

Table 1 shows that compared with controls, heart failure patients had a lower systolic blood pressure, diastolic blood pressure, and left ventricular ejection fraction but a greater left ventricular end diastolic diameter and E/A (ratio between early and atrial transmortal peak flow). Heart rate, baseline radial artery diameter, and blood flow were not statistically different in the 2 groups. In contrast, as shown in Figure 1, the increase in radial artery diameter following the 4-minute ischemia was strikingly less in heart failure patients than in controls. The corresponding blood flow increase was also less in heart failure patients, but the difference was much less marked than that of arterial diameter. The increase in radial artery diameter induced by sublingual trinitroglycerin was similar in the 2 groups (+0.7 ± 0.2 mm versus +0.8 ± 0.15 mm, P=NS).

Table 2 shows the data obtained in the 4 groups that underwent different treatments for 2 months. Compared with the initial values, systolic and diastolic blood pressure, heart rate, left ventricular ejection fraction, left ventricular end diastolic diameter, and E/A never showed any significant change in any of the 4 different treatment groups. VO_{2max} was also never significantly different from baseline, whereas maximal exercise time was significantly, although modestly, increased in the 2 groups in which drug treatment was modified and in the group in which physical training was implemented. Baseline radial artery diameter and blood flow were also absolutely unchanged in all 4 groups. In comparison with data obtained during the first study, the increase in radial artery diameter and blood flow after the 4-minute ischemia remained unchanged in the group in which treatment was unchanged, but it showed a significant increase in the other 3 groups (Figure 2). The increase was a marked one for arterial diameter, the response of which to the short-lasting ischemia became ~2 times as large after treatment modification, regardless whether it consisted of the increase in the ACE inhibitor dose, the addition of the Ang II antagonist, or the implementation of physical training. The increase in radial artery diameter after sublingual trinitroglycerin was not significantly different from the first study in all groups (0.81 versus 0.75 mm in the group with unchanged treatment, 0.72 versus 0.69 mm in the group with the increased ACE inhibitor dose, 0.76 versus 0.73 mm in the group given losartan, and 0.84 versus 0.79 mm in the group in which physical training was implemented).

Discussion

Our study provides 3 major results. First, in patients with congestive heart failure, the increase in radial artery diameter observed at the release of a 4-minute ischemia of the hand was strikingly reduced, which confirms previous findings that this condition is characterized by a striking impairment of endothelial function. Second, the radial artery diameter response to short-lasting hand ischemia was markedly increased by 2 months of controlled treatment regimens, which shows that the endothelial dysfunction occurring in heart failure is largely and quickly reversible. Third, the increase in the radial artery response occurred to a similar extent in patients in whom treatment (1) included an ACE inhibitor administered at a high dose, (2) a lower ACE inhibitor dose was associated with the administration of an Ang II antagonist, and (3) standard drug treatment was combined with a physical exercise program. This provides evidence that an effective blockade of the renin-angiotensin system has a favorable effect on the impaired endothelial function typical of heart failure, regardless whether the blockade is effected at multiple sites of the renin-angiotensin axis or selectively at the ACE site only. It also provides evidence, however, that in heart failure, endothelial function can be favorably affected not only by drug treatment but also by nonpharmacological procedures that are now part of the management of this condition, such as physical training.

Compared with controls our heart failure patients showed (1) no significant reduction in baseline radial artery blood flow; (2) only a moderate impairment in the increase in flow induced by the 4-minute hand ischemia, with only a moderate improvement under controlled treatments; and (3) no impairment at all in the increase of radial artery dilatation induced by trinitroglycerin either before and during controlled treatments. Taken together, these observations suggest that in heart failure, the impairment in the radial artery diameter increases following short-lasting ischemia is not greatly accounted for by a reduction in shear stress due to a heart failure-dependent reduction in blood flow volume and velocity. Nor is it due to an intrinsic stiffness of the radial artery...
that curtails its ability to dilate in response to NO. The problem, in other words, is likely to resides at the endothelial cell level and consists of a reduced capacity to properly secrete or increase secretion of NO in response to physiological stimuli.1,2,9

The mechanisms responsible for the favorable effect of the 3 treatments tested on endothelial function are not clarified by our data. Evidence is available, however, that Ang II exerts a direct adverse influence on endothelial function,20 which offers a plausible explanation for the results obtained with drugs blocking the renin-angiotensin system. The protocol of our study did not allow us to determine whether a favorable effect on endothelial function already begins with low doses of an ACE inhibitor. It allowed us to demonstrate, however, that a clearcut benefit does occur with high ACE inhibitor doses or with interference with the renin-angiotensin system both at the ACE and at the angiotensin receptors site, possibly because this more effectively opposes the influence of the increased Ang II levels characterizing heart failure.

A reduction in the adverse effect of Ang II on endothelial function may also explain the favorable effect of physical training, because physical training improves the sensitivity of cardiopulmonary reflexes,21 which restrain renal secretion of renin.22 Other factors are likely to play a role under this circumstance, however. For example, Drexler et al23 have observed an improvement in radial artery vasodilation caused by endothelial factors in heart failure patients undergoing training of the ipsilateral arm only, which points to occurrence of local circulatory changes, as shown by our group in professional athletes subjected to asymmetrical training of the 2 arms.24 Furthermore, training may act also through a reduction in sympathetic tone,25 because an increase in sympathetic activity has also been shown to exert an adverse direct influence on endothelial function.26,27

Other results of our study deserve a brief comment. First, our findings do not score in favor of a superior therapeutic effect of a combination between an ACE inhibitor and an Ang II antagonist because they show that what can be achieved by this combination can also be achieved by the more effective blockade of the renin-angiotensin system obtained just by doubling an ordinary ACE inhibitor dose. We cannot of course exclude that this only pertains to the variable and the disease we addressed. It would be advisable, however, that studies on other therapeutic effects of the ACE inhibitor–angiotensin antagonist combination could all make use of a comparison group given an ACE inhibitor at high doses.
Second, although markedly improved, the endothelial function of heart failure patients exposed to the 3 treatment regimens remained somewhat lower than that of healthy controls. Thus, in principle, further improvement is obtainable although it remains to be seen whether there is a treatment that can lead to full endothelial normalization in patients with heart failure.

Third, because of the trend for an increased postischemic blood flow after the 2 months, treatment with either ACE inhibitor at high dose, low dose ACE inhibitor plus angiotensin antagonist, or low-dose ACE inhibitor plus physical training, an hemodynamic mechanism responsible for the improved flow-mediated dilation cannot be excluded.

Finally, in the present study, noninvasive estimate of endothelial function by short-lasting hand ischemia proved valuable both in collecting clinical and therapeutic data in a setting in which use (and re-use) of invasive techniques can hardly be planned. It should nevertheless be emphasized that this estimate is sectorial and that regional differences in the effect on endothelial function of diseases have been reported. Thus, these data have to be interpreted with a measure of caution.

References