Effects of Cilazapril on Endothelial Function and Pulmonary Hypertension in Patients with Congestive Heart Failure

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SUMMARY

Flow-mediated vasodilation (FMV), brachial artery flow (BAF), and brachial artery diameter were evaluated in 30 patients with congestive heart failure before and after cilazapril treatment.

While mean pulmonary artery pressure and pulmonary capillary wedge pressure decreased significantly, flow-mediated vasodilation and left ventricular ejection fraction increased significantly following cilazapril administration ($P<0.001$). Brachial artery diameter and brachial artery flow did not change following the treatment period ($P>0.05$).

In conclusion, short term cilazapril administration improved endothelial function and pulmonary pressure in patients with congestive heart failure. (Jpn Heart J 2002; 43: 667-674)

Key words: Endothelial function, Cilazapril, Pulmonary hypertension, Congestive heart failure

ANGIOTENSIN-CONVERTING enzyme (ACE) inhibitors have been shown to be highly effective against a variety of vascular disorders.1) Endothelial dysfunction represents one of the earliest events in the process of atherosclerosis. The endothelial cell is important in maintaining vascular integrity through a variety of mechanisms. Endothelium-dependent vasodilatation is mediated through the release of vasodilators such as nitric oxide (NO).2) The endothelium releases NO in response to physiologic stimulus, such as shear stress induced by blood flow, which causes smooth muscle cell relaxation via an increased concentration of cGMP.3) Impaired NO activity is associated with atherosclerosis and subsequent development of vascular disease.4) A functional ACE system present in vascular endothelium contributes to the regulation of vascular tone.5) Studies have suggested that bradykinin is the mediator responsible for the beneficial effects of ACE inhibition on endothelial function and development of atherosclerosis.6-7)
Angiotensin II has a direct vasoactive role in the release of endothelin-1, which is a potent vasoconstrictor.\(^8\)\(^{-11}\) Endothelin is also a component of the local tissue compensatory mechanisms activated in heart failure.\(^12\) The activity of vascular NADH/NADPH oxidases, which is increased by angiotensin II, is required for the inactivation of vascular nitric oxide. Recent investigations have attempted to define whether endothelium-dependent vasodilatation is impaired in the peripheral vasculature of patients with chronic congestive heart failure.\(^12\) Evidence for activation of the sympathetic and renin-angiotensin-aldosterone systems in circulatory failure supports the hypothesis that short-term compensatory responses contribute to long-term progression of the heart failure.\(^12\) The effects of cilazapril in congestive heart failure have been described. The haemodynamic effects of a single dose of 2.5 or 5 mg cilazapril were studied in 33 patients with stable chronic congestive heart failure. Cilazapril was shown to significantly decrease mean arterial pressure, systemic vascular resistance, pulmonary capillary wedge pressure, pulmonary artery pressure, and right atrial pressure, while the cardiac index and stroke volume index increased at rest and during submaximal exercise.\(^13\)

The aim of this study was to determine the acute effect of angiotensin-converting enzyme inhibition on brachial flow mediated vasodilatation (FMD) and pulmonary artery pressure in patients with congestive heart failure and coronary artery disease (CAD).

**SUBJECTS AND METHODS**

The study population was comprised of 30 consecutive patients (16 males and 14 females, mean age, 65±18) diagnosed with coronary artery disease (documented CAD with coronary angiography) and congestive heart failure (documented left ventricular systolic and diastolic dysfunction, New York Heart Association III-IV functional capacity) recruited from the University Hospital of Celal Bayar. Written, informed consent was obtained from all patients.

**Determination of endothelial function:** Long-acting vasoactive medications were withheld within 24 hours of endothelial function testing. Smokers refrained from smoking on the morning of the test. Patients were studied after fasting over night for 12 hours. Endothelium-dependent and endothelium-independent dilation of the brachial artery were assessed noninvasively using a high resolution ultrasound system (Hewlett-Packard View Point) with a 7.5 mHz linear array vascular transducer.\(^14\),\(^15\) The brachial artery was imaged longitudinally, 2 to 15 cm above the antecubital crease, ensuring optimal visualization of the anterior and posterior wall-lumen interfaces. The position was maintained throughout the test, and a similar position was used in the subsequent studies. Baseline images and
pulsed Doppler flow velocity measurements were taken (Figure). A pneumatic tourniquet was then placed proximally on the forearm and inflated to 250 mmHg of pressure for 5 minutes and rapidly deflated resulting in reactive hyperemia. Doppler measurements were obtained immediately after deflation, and repeat brachial artery images were continuously recorded for 120 seconds to assess the response to reactive hyperemia. After 10 minutes of resting, brachial artery scans were obtained before and after administration of sublingual 5 mg nitroglycerin to assess endothelium-independent vasodilation. All images were recorded on super VHS videotapes for subsequent quantitative analysis. The end-diastolic frames (coincident with the peak of the R wave) were digitized with a media 100 qx video card from three consecutive cardiac cycles. Average end-diastolic brachial artery diameters were measured using image software by one observer who had no knowledge of the treatment schedule. Unless the intima-lumen border was clearly defined, the media-lumen border for the anterior and posterior walls was manually traced over a 10 to 20 mm straight arterial segment, and the average diameter over this segment was determined. Measurements of three sequential frames were averaged for each phase. Endothelium-dependent FMD was calculated as the percent change in brachial artery diameter after reactive hyperemia as compared with the baseline value (reactive hyperemia - baseline/baseline × 100.

Figure. Baseline images and pulsed Doppler velocity measurements.
Brachial artery flow was calculated as the product of the Doppler velocity time integral, heart rate, and brachial artery cross-sectional area (XD²/4), where D is the average arterial diameter at that phase. Reactive hyperemia was calculated as the percent change in arterial flow after tourniquet deflation, as compared with the baseline value. The intraobserver and interobserver variability of echocardiographic determinations was calculated as 2%.

**Invasive assessment of hemodynamic parameters:** All patients underwent right heart catheterization via the right subclavian approach with a Swan Ganz catheter. Pulmonary arterial pressure, left ventricular end diastolic pressure, pulmonary capillary wedge pressure, and right ventricular and right atrial pressures were obtained. Hemodynamic parameters were measured before and after three days of treatment.

**Treatment and follow up:** Following assessment of baseline endothelial function and hemodynamic parameters at baseline, the patients were started on Cilazapril (5 mg/day). The treatment was continued for three days. All other medications were held constant throughout the study. None of the patients quit smoking during the study. Patients underwent reassessment of endothelial function and hemodynamic measurements at the end of three days.

**Statistics:** All data are presented as mean ± standard deviation. The baseline characteristics of the two groups were compared using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for variable categories. The effect of treatment on endothelium-dependent FMD was assessed by two-way repeated measures (ANOVA). Two-sided P values of <0.05 were considered statistically significant.

**RESULTS**

The baseline hemodynamic parameters of the 30 study patients are shown in Table I. Pulmonary capillary wedge pressure, left ventricular ejection fraction, and mean pulmonary artery pressure were significantly decreased after treatment. Heart rate and mean arterial pressure did not change after treatment (P>0.05).

Brachial artery diameter and brachial artery flow did not change significantly during the treatment (P>0.05, Table II). An example of flow mediated dila-

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**Table I.** Baseline Parameters before Treatment and after Three Week Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Treatment (n=30)</th>
<th>After Treatment (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery diameter (mm)</td>
<td>3.55±0.62</td>
<td>3.92±0.74</td>
<td>0.693</td>
</tr>
<tr>
<td>Brachial artery flow (mL/min)</td>
<td>130±102</td>
<td>142±111</td>
<td>0.664</td>
</tr>
<tr>
<td>Flow-mediated vasodilation</td>
<td>5.1±1.6</td>
<td>9.0±2.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>
tion before and after treatment is shown in the Figure. FMD changed significantly after treatment \((P<0.002)\). FMD has been shown to be inversely related to baseline brachial artery diameter in previous studies.\(^{16}\) The baseline brachial artery diameter did not change after treatment, despite the use of vasodilators which had no significant effect on brachial diameter after 12 weeks of therapy (Table II).

Upper arm occlusion resulted in an increase in forearm blood flow, which was the same at baseline and only slightly increased after treatment.

Treatment with cilazapril resulted in a significant increase in FMD from baseline \((0.5\pm7 \text{ pretreatment}; 0.9\pm4, \text{ posttreatment}; P<0.003)\). These results suggest that there was a significant improvement in endothelium-dependent vasodilation after 3 months of treatment with cilazapril. Pulmonary arterial mean pressure was reduced significantly \((44\pm10 \text{ mmHg to } 25\pm9 \text{ mmHg}; P<0.001)\) and the functional class improved from NYHA III to II and from IV to III, respectively, following treatment with cilazapril.

**DISCUSSION**

Angiotensin-converting enzyme inhibition in hypertensive patients has been previously shown to have a beneficial effect on the arterial wall morphology of vessel resistance.\(^{16}\) Angiotensin converting enzyme inhibition is thought to improve vascular function through several mechanisms. It decreases the concentrations of angiotensin II and hence endothelin, increases the concentrations of bradykinin, which is a vasodilator and stimulator of NO, endothelial derived hyperpolarizing factor, and prostacyclin, and decreases superoxide anion concentration.\(^{17}\) The evaluation of flow mediated dilation induced by hyperemia follow-
The release of a forearm occluding cuff is an established method for assessing endothelial function which was first described in 1992, providing important insights into the risk factors of atherosclerosis. The method of inducing increased blood flow following ischemia produced by forearm occlusion has shown excellent reproducibility and has been found to be valid in the assessment of endothelium-dependent FMD.

The effect of cilazapril on endothelial function in patients with congestive heart failure has not been investigated previously using noninvasive FMD techniques.

Angiotensin II causes pulmonary vasoconstriction in humans and animals, and angiotensin-converting enzyme (ACE) inhibitors have prevented the development of pulmonary hypertension in animal models. Angiotensin II may contribute to lung vascular remodeling in pulmonary hypertensive disease, since cilazapril, an inhibitor of ACE, reduces pulmonary vascular medial thickening in chronically hypoxic rats with established pulmonary hypertension.

We assessed cardiopulmonary hemodynamics using invasive methods in patients with secondary pulmonary hypertension. Mean pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure were found to be significantly decreased in patients with pulmonary hypertension associated with congestive heart failure. On the other hand, mean arterial pressure did not change after cilazapril therapy. Several studies in animal models have shown the beneficial effects of chronic treatment with angiotensin-converting enzyme inhibitors in association with propranolol and nifedipine in the prevention of pulmonary hypertension. Unfortunately, there are no large or short term clinical trials with ACE inhibitors in patients with pulmonary hypertension. Consequently, it may be stated that pharmacological interventions directed at the various elements of the renin-angiotensin system should be useful strategies in the treatment of pulmonary hypertension.

An augmentation of endothelium-dependent vasodilation has been demonstrated for several ACE inhibitors in animal studies. Animal studies have suggested that the beneficial vascular effect of ACE inhibition is mediated through bradykinin and nitric oxide (NO). The enhanced lipophilicity of cilazapril may allow better cellular penetration with beneficial effects on enzymatic processes such as eNOS activity.

Many trials including the Cooperative North Scandinavian Enalapril Survival Study, (CONCENSUS), the Studies of Left Ventricular Dysfunction (SOLVD), and the Survival and Ventricular Enlargement (SAVE) trial have demonstrated the ability of ACE inhibitors to improve hemodynamic parameters and reduce mortality within a wide range of heart failure. The current study demonstrated that 3 months of cilazapril therapy improves impaired endothelium-
dependent vasodilatation in the brachial circulation of patients with atherosclerotic diseases and heart failure. During the past two decades, it has been well established that vascular endothelium plays a pivotal role in maintaining vascular tone. In the BANFF Study (Brachial Artery Normalization of Forearm Function) enalapril, an ACE inhibitor with low tissue affinity, was found to be less effective than quinapril which is an ACE inhibitor with high tissue affinity. Losartan and amlodipin have been found to be ineffective. However, in the TREND study (Trial on Reversing Endothelial Dysfunction) treatment with quinapril was compared only to placebo and quinapril was found to be effective.\(^\text{20}\) However, in the TREND study (Trial on Reversing Endothelial Dysfunction) treatment with quinapril was compared only to placebo and quinapril was found to be effective.\(^\text{20}\)

The effects of ACE inhibition on systemic circulation dynamics has been well known for quite a period of time. There may be differences between vasoactive drugs in their ability to improve vascular endothelial function, although further dose ranging and time course studies are required with different drugs. Endothelial dysfunction in the pulmonary circulation may be regulated better with ACE inhibition. Pulmonary artery pressures may be markers for endothelial dysfunction in the pulmonary circulation. In conclusion, the endothelia have been established as a target organ for the treatment of cardiovascular diseases and have been shown to be modified by vasoactive drugs.

**REFERENCES**