Chronic ACE Inhibition Enhances the Endothelial Control of Arterial Mechanics and Flow-Dependent Vasodilatation in Heart Failure

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Abstract—Reduced conduit arteries flow-dependent dilatation and altered compliance have been described during heart failure. However, the role of shear stress, the relation between endothelial dysfunction and mechanics, and the effect of chronic ACE inhibition on this relationship have not been investigated. The present study was designed to evaluate in heart failure patients the relationship between flow-dependent dilatation and radial artery mechanics at known shear stress levels and to assess the effect of chronic ACE inhibition. Sixteen stable congestive heart failure patients, who had never been treated with ACE inhibitors, participated in the study. Arterial pressure, cardiac output (bioimpedance), radial artery diameter (echo tracking) and flow (Doppler), total blood viscosity, and mean artery wall shear stress were assessed before and during a gradual increase in the forearm blood flow in response to gradual distal hand skin heating. Cross-sectional radial artery compliance and distensibility indexes were calculated at 34°C, 40°C, and 44°C. The endothelium-independent vasodilatation was evaluated by use of glyceryl trinitrate. All parameters were assessed before and 24 hours after the last administration of perindopril (4 mg once daily) or placebo in a 2-month double-blind randomized study. Before treatment, there was no difference between the 2 groups for all parameters. After chronic ACE inhibition, systolic arterial pressure decreased at baseline from 126±11 to 118±10 mm Hg (P<0.05). During heating, the increase in diameter in response to shear stress was higher after ACE inhibition than after placebo (time/treatment interaction, P<0.05). Moreover, in contrast to placebo, at the same shear stress, there was a significant increase in compliance (3.23±0.79×10⁻⁷ to 6.82±2.47×10⁻⁷ m²/kPa, P<0.05) and distensibility (5.71±1.35×10⁻³ to 8.87±1.88×10⁻³ m²/kPa, P<0.05) during heating after ACE inhibition. The effect of glyceryl trinitrate did not change. The present study demonstrates that chronic administration of the ACE inhibitor perindopril increases the magnitude of the flow-dependent dilatation and restores the flow-dependent increase in compliance and distensibility of the radial artery evaluated at stable shear stress. In addition, the decrease in baseline systolic arterial pressure after ACE inhibitor suggests an associated increase in the distensibility of the proximal elastic conduit arteries. (Hypertension. 2001;38: 1446-1450.)

Key Words: arteries ■ endothelium ■ flow-mediated ■ elasticity ■ angiotensin-converting enzyme inhibitors

Endothelium mediates flow-dependent vasodilatation and contributes to the regulation of arterial mechanics by releasing vasoactive factors that modify arterial tone and trophicity.1–5 In heart failure, reduced conduit artery flow-dependent dilatation and altered arterial compliance have been described.4,6–11 Moreover, reduced increase in distensibility during exercise also contributes to an increase in left ventricular afterload and an inadequate cardiovascular coupling.12 However, the role of change in shear stress associated with endothelial dysfunction, the relationship between endothelial dysfunction and mechanics, and the effect of chronic ACE inhibition on this relationship have not been investigated.12–14 The present study was thus designed to evaluate in heart failure patients, at known levels of shear stress calculated at different peripheral blood flow levels induced by hand skin heating, the relationship between flow-dependent dilatation and muscular conduit arteries mechanics and to assess the effect of chronic ACE inhibition on this relationship.

Methods

Subjects
The study was performed in 16 patients (61±3 years, 15 men) with clinically stable congestive heart failure (14 in New York Heart Association functional class III and 2 in class II) and a mean echocardiographic left ventricular ejection fraction (LVEF) of

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33±2% (5 ischemic/11 nonischemic dilated cardiopathy), who had never been treated with ACE inhibitor and had a known decrease in forearm postischemic hyperemia. All patients were clinically stable for >4 weeks and received digitalis and diuretics; 3 patients took nitravasodilators, which were withdrawn 24 hours before examination. Smokers or patients with arterial hypertension, hypercholesterolemia, or significant valvular dysfunction were excluded from the study. The protocol was approved by the regional ethical committee, and written informed consent was obtained from all participants.

**Hemodynamical Measurements**
Measurements were performed while subjects were supine in a quiet, air-conditioned room maintained at a constant temperature (22°C to 24°C). Arterial pressure and heart rate were measured by means of a brachial cuff oscillometric device (Dinamap 8103, Critikon) and cardiac output by bioimpedance (Bomed NCCOM3, Novacor). Total peripheral resistance was calculated as the mean blood pressure–cardiac output ratio. Radial artery internal diameter and blood flow velocity were continuously measured using a high-precision echotripping device coupled to a Doppler system (NIUS 02, Asulab) as previously described.2,3 Radial artery flow was calculated from the measurement of velocity and diameter. Total blood viscosity was measured using a cone-plate viscometer (Ex100 CTB, Brookfield) at a shear rate of 241 sec⁻¹ at 37°C. This choice was in agreement with previous experiments in peripheral conduit arteries.15 Moreover, it has been demonstrated that viscosity becomes relatively constant for values of shear rate >100 sec⁻¹.15,16 The distal hand skin temperature was modified by use of a water-filled thermocontrolled device (Polystat 1, Bioblock Scientific).

**Study Protocol**
The dominant hand was introduced in the device, and the water temperature was fixed at 34°C (neutrality) for at least 20 minutes. At the end of this period, heart rate, arterial pressure, radial artery flow, and diameter were recorded for 5 minutes. The water temperature was then increased by 10-minute steps from 34°C to 38°C, to 40°C, to 42°C, and to 44°C. Systemic and radial artery measurements were repeated during the last 3 minutes of each step. From the individual values of radial artery internal diameter (d), blood flow (Q), and total blood viscosity (μ), the mean arterial wall shear stress was calculated at each level of flow assuming a Poiseuille velocity distribution as \( \tau = \frac{4\mu Q}{(\pi d^2)} \), and the diameter-wall shear stress curve was constructed.17 The reproducibility of the skin heating method was assessed in 8 healthy volunteers, by repeating the operating scheme after a 60-day interval. The coefficient of repeatability of diameter and flow measurement were, respectively, 121 μm and 3.6 mL/min at 34°C and 116 μm and 6.0 mL/min at 44°C. In addition, there was no significant difference between the mean results obtained during the first and second day for the minimal and maximal values and for the increase in flow and diameter. The endothelium-independent vasodilatation was evaluated by use of glyceryl trinitrate (TNG) spray (0.4 mg). Cross-sectional radial artery compliance and distensibility indexes were calculated at 34°C, 40°C, and 44°C as, respectively, compliance = \[ 3.14 \cdot \frac{d}{2} \cdot \frac{d}{\Delta P} \] and D = \[ 2(\Delta d)/(d^2 \cdot \Delta P) \], where d is the arterial diameter at end diastole; \( \Delta d \), the increase in diameter during the cardiac cycle; and \( \Delta P \), the pulse pressure.18

**Results**

**Systemic and Radial Artery Hemodynamics**
Before treatment, there was no significant difference between the 2 groups for patient characteristics and for all measured parameters (Table). After chronic ACE inhibition, systolic arterial pressure decreased (\( P<0.05 \)). Diastolic arterial pressure, heart rate, and cardiac output did not change. In addition, there was no significant change in radial artery flow, radial artery diameter, total blood viscosity, and radial artery wall shear stress obtained at baseline before distal skin heating.

During heating, the radial artery flow increased similarly from 11.8±2.3×10⁻³ to 46.7±6.9×10⁻³ L/min (\( P<0.05 \)) after placebo and from 19.3±5.1×10⁻³ to 45.7±11.2×10⁻³ L/min (\( P<0.05 \)) after chronic ACE inhibition without significant effect on systemic blood pressure and heart rate.

**Radial Artery Endothelium-Dependent and -Independent Dilatation**
Figure 1 illustrates the radial artery diameter/shear stress relationship obtained during distal skin heating after 2 months of treatment by placebo or after chronic ACE inhibition. Diameter increased when shear stress increased in the 2 groups (\( P<0.05 \)). After chronic ACE inhibition, arterial diameter is slightly but not significantly higher than that after placebo (\( P=NS \)). Moreover, the increase in diameter with
Figure 1. Left, Radial artery diameter/shear stress relationship obtained in heart failure patients during distal heating performed after administration of placebo (■) or ACE inhibitor (●). Right, Radial artery diameter (RAD) and flow (RAF) obtained at peak after TNG administration in heart failure patients after administration of placebo (open bars) or ACE inhibitor (solid bars). The increase in diameter with shear stress was significantly higher after chronic ACE inhibition than after placebo (time treatment/interaction, \( P<0.05 \)). There was no significant change in the endothelium-independent vasodilating effect of TNG.

Shear stress was higher after chronic ACE inhibition than after placebo, thus demonstrating an increase in the magnitude of radial artery flow-dependent vasodilatation (time treatment/interaction, \( P<0.05 \)).

In contrast, the vasodilating effect of TNG on radial artery diameter and flow was not modified by the treatment (Figure 1).

Radial Artery Mechanics

After 2 months of treatment, there was no difference between groups in the radial artery compliance and distensibility indexes measured at baseline before heating (Figure 2). However, there was a significant increase in compliance and distensibility indexes during heating after ACE inhibition compared with those of placebo at the same increase in wall shear stress (all, \( P<0.05 \)) (Figure 2).

Discussion

The present study demonstrates that (1) in heart failure the increase in radial artery wall shear stress is not associated with an increase in arterial compliance and distensibility, thus suggesting the presence of an altered endothelium-mediated control of arterial mechanics; (2) the chronic administration of the ACE inhibitor perindopril increases the magnitude of the flow-dependent dilatation and restores the flow-dependent increase in compliance and distensibility of the radial artery evaluated at stable shear stress; and (3) the decrease in systolic arterial pressure, observed at baseline after treatment by ACE inhibition, with no change in diastolic pressure and cardiac index suggests an associated increase in the distensibility of the proximal elastic conduit arteries.

Conduit artery flow-dependent dilatation is currently investigated in clinical experiments by use of postischemic hyperemia.\(^2,4,6\) The reproducible method of distal skin heating we used in the present study was developed to allow a gradual increase in flow, the calculation of the mean wall shear stress at each level of flow, and thus the comparison of the flow-dependent dilatation between treatments at known levels of stimulus, by use of the diameter/shear stress relationship.\(^19\) This is of particular importance in heart failure because reported decrease in reactive hyperemia in control conditions and flow modification after treatment could modify the flow-dependent stimulus and thus interfere with the evaluation of the direct effect of drug on conduit artery flow-dependent dilatation.\(^6,12–14\) Furthermore, this method enables the evaluation of muscular conduit artery mechanics at increasing levels of stable shear stress and thus the control of arterial mechanics by endothelium. This is probably of importance in heart failure because vasodilatory effects induced by drugs that do not influence distensibility and endothelium function are probably less beneficial in terms of adaptation to exercise and cardiovascular coupling.\(^20,21\)

In these experimental conditions, we demonstrate that chronic ACE inhibition is associated with an increase in the magnitude of the radial artery flow-dependent dilatation. This effect is probably moderate, but the evaluation of the time/treatment interaction indicates a significant phenomenon that seems to be more marked at high levels of shear stress. Thus, whatever the value of arterial diameter, the increase in diameter with shear stress is more marked after ACE inhibition than after placebo. These results are in accordance with those obtained after acute administration of ACE inhibitors in heart failure patients at the level of the conduit arteries by use of postischemic hyperemia, and they support a persistent effect of the treatment over time despite the absence of significant increase in arterial diameter.\(^22,23\) In addition, they support the results obtained after acute and chronic ACE inhibition at the level of the forearm resistance arteries in response to acetylcholine.\(^24,25\) This result, observed in absence of alteration in non–endothelium-mediated dilatation in response to exogenous NO, could be explained by the increase in endothelial NO production in response to bradykinin, as observed after acute ACE inhibition in human,\(^23\) or by the increase in NO synthase expression in response to the chronic decrease in angiotensin II production.\(^26\) In the absence of marked constrictive effect of angiotensin II in brachial artery in human, other factors—such as the decrease in NO neutralization by free radicals, as expected from the decrease NADPH oxidase activity; the increase in extracellular superoxide dismutase activity after angiotensin II suppression\(^11,26–29\); or an increase in endothelin-derived hyperpolarizing factor bioavailability—could contribute to this effect in this experimental condition of increase in flow.\(^30\)

Figure 2. Radial artery compliance, distensibility, and wall shear stress measured at 34°C, 40°C, and 44°C during distal skin heating performed after administration of placebo (open bars) or ACE inhibitor (solid bars) during 2 months. Values are mean±SEM. Compliance and distensibility increase with shear stress after chronic ACE inhibition but not after placebo.

\(^p<0.05\) vs 34°C; \(^\dagger p<0.05\) vs placebo.
Concerning the mechanical properties of the radial artery, we observed during the heating procedure that the physiological flow-dependent increase in arterial compliance and distensibility was suppressed in our patients. The radial artery dilatation after placebo is lower than that observed after chronic ACE inhibition and is associated with a slight decrease in distensibility, which probably explains the absence of increase in compliance despite the increase in diameter. After chronic ACE inhibition, the increase in diameter is higher for the same increase in shear stress, as suggested by the upward shift of the diameter/shear stress relationship toward the higher values of diameter at high level of shear stress, and is associated with an increase in arterial distensibility. This suggests a decrease in the isometric vascular tone which contributes to the increase in compliance. This simultaneous improvement in endothelium-mediated flow-dependent dilation and in mechanical properties of radial artery after treatment supports the relation between endothelial dysfunction and vascular mechanics in heart failure and demonstrates the beneficial effects of chronic ACE inhibition at these 2 levels. Furthermore, the distal skin heating method we developed enables us to evaluate these parameters at known and identical shear stress levels during flow and diameter changes and thus enables us to avoid the passive effects of difference in flow-stimulus on these parameters. The beneficial effect of chronic ACE inhibition on radial artery compliance in heart failure was previously reported at baseline, but there was no investigation concerning the effects of treatment on the flow-dependent regulation of mechanics. Because previous results have shown that vascular endothelium contributes to the regulation of conduit arteries mechanics by releasing endothelial factors that modify arterial tone, our results could be explained by alterations in NO, which could be restored by chronic ACE inhibition. Thus, NO, as previously shown in experimental models, could decrease the elevated isometric vascular tone associated with chronic sympathetic activation and altered mechanics observed in heart failure. Furthermore, the relative short duration of drug administration does not support a potential role of arterial wall structural changes, which could also contribute to modification in arterial mechanics.

Finally, the associated decrease in systolic arterial pressure, observed at baseline after treatment by ACE inhibitors, with no change in diastolic pressure, cardiac output, and heart rate, suggests an associated increase in the distensibility of the systemic proximal elastic conduit arteries. This effect observed in absence of any change in total peripheral resistance could be explained by an associated decrease in isometric vascular smooth muscle tone of proximal elastic conduit arteries.

In conclusion, the present study demonstrates for the first time that chronic administration of ACE inhibitor perindopril increases the magnitude of the flow-dependent dilatation and restores the flow-dependent increase in compliance and distensibility of the radial artery evaluated at stable shear stress. This phenomenon and the associated decrease in systolic arterial pressure, which suggests an increase in distensibility of proximal conduit arteries, could both contribute to the decrease in end systolic left ventricular pressure and afterload and to a more appropriate cardiovascular coupling during treatment by ACE inhibitors in heart failure.

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