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# Radial, Carotid and Aortic Distensibility in Congestive Heart Failure: Effects of High-Dose Angiotensin-Converting Enzyme Inhibitor or Low-Dose Association With Angiotensin Type 1 Receptor Blockade

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**OBJECTIVES** The aim of this study was to determine whether in patients with congestive heart failure (CHF) a distensibility (Dist) reduction: 1) similarly occurs in different arteries; 2) is related to CHF severity; and 3) is reversible with treatment.

**BACKGROUND** Several studies suggest that CHF is accompanied by a reduced arterial Dist.

**METHODS** We measured diameter in radial artery, carotid artery (CA) and abdominal aorta (AO) by echotracking. Distensibility was obtained by relating it to blood pressure. Data were collected in 30 patients with CHF (New York Heart Association functional class I to III) under standard treatment with diuretic, digitalis and angiotensin-converting enzyme (ACE) inhibitor in whom CHF severity was assessed by maximum oxygen consumption ($Vo_2max$) percentage and in 30 age- and gender-matched controls. Patients with CHF were then randomized to maintain standard treatment (n = 10), double the ACE inhibitor dose (n = 10) or add an angiotensin II antagonist (n = 10) and restudied after two months.

**RESULTS** Distensibility was markedly reduced in the CHF group in all three vessels ($p < 0.01$), CA and AO Dist being related to CHF severity ($p < 0.05$). After two months, Dist did not change in the group maintained under standard treatment, but it increased significantly ($p < 0.05$) and similarly when the ACE inhibitor dose was doubled or an angiotensin II antagonist was added.

**CONCLUSIONS** Congestive heart failure is characterized by a reduction of Dist of large-elastic and middle-sized muscular arteries. The reduction of large-elastic artery Dist is related to the CHF severity. These alterations can be reversed by drugs, effectively interfering with the renin-angiotensin system either at the ACE or at the angiotensin receptor level. (J Am Coll Cardiol 2002;39:1275–82) © 2002 by the American College of Cardiology Foundation

Several cardiovascular diseases are characterized by a reduced distensibility (Dist) of large arteries (1–11). This has undesirable consequences because a reduction of arterial Dist leads to: 1) an increase in arterial impedance and, thus, in cardiac afterload; 2) a reduction in diastolic pressure and, thus, in perfusion of organs such as the heart; and 3) an acceleration of atherosclerosis due to an increase in systolic and pulse pressure and to a greater traumatic effect on the vessel walls (1–11). It has been suggested that congestive heart failure (CHF) is associated with a reduction of arterial Dist (12–16). However, information on this phenomenon is largely incomplete. For example, no data have been obtained on whether a reduction of arterial Dist occurs similarly or differently in large-elastic and smaller muscle-type arteries. Furthermore, whether the reduction of arterial Dist relates to the heart failure severity is unknown. Finally, it is also not known whether the arterial stiffening that characterizes heart failure is reversible with different drug approaches that interfere with the renin-angiotensin system. In the present study we have addressed these issues by measuring middle-sized and large-elastic artery Dist in controls and in patients with CHF of different severity before and after two months of a standard therapy (angiotensin-converting enzyme [ACE] inhibitor, diuretic and digitalis) and therapy based on doubling the dose of the ACE inhibitor or associating an angiotensin type 1 receptor antagonist to the low-dose ACE inhibitor.

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## METHODS

**Subjects.** We investigated 60 subjects. Thirty subjects (CHF: 27 men; age: 60.4 ± 1.4 years) were selected on a consecutive basis if they had: 1) age <75 years; 2) chronic heart failure belonging to New York Heart Association functional class I (n = 10), II (n = 13) or III (n = 7) with either an ischemic (n = 20) or nonischemic (n = 10) origin; 3) no major valvular abnormalities; 4) a left ventricular ejection fraction ≤40% (as described in the following text); 5) a standard medical treatment (diuretic, digitalis and enalapril at a dose <20 mg daily) stable for at least three

**Abbreviations and Acronyms**

| | |
|---|---|
| ACE | = angiotensin-converting enzyme |
| ANOVA | = analysis of variance |
| AO | = abdominal aorta |
| BP | = blood pressure |
| CA | = carotid artery |
| CHF | = congestive heart failure |
| Dd | = diastolic diameter |
| Dist | = distensibility |
| Ds | = systolic diameter |
| E/A | = ratio between early and atrial transmitral peak flow |
| RA | = radial artery |
| $V_{O_2}$ | = volume of oxygen consumption |
| $V_{O_2}max$ | = maximum oxygen consumption |
| WT | = wall thickness |

months; 6) no hemodynamically significant atherosclerotic carotid, femoral or aortic lesions (echocolor-Doppler examination), no chronic arrhythmias, no major disease besides heart failure and no chronic treatment with drugs other than those mentioned in the preceding text; and 7) an adequate ultrasonographic window for visualization of the abdominal aorta (AO) (as described in the following text). The remaining 30 subjects (controls: 28 men; age: 56.9 ± 1.5 years) were age-matched normotensive healthy individuals. Two patients with CHF and three control subjects 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.

**Radial artery (RA) Dist and wall thickness (WT).** Radial artery diameter and WT were measured by an A-mode ultrasonic device (NIUS 02, Omega, Bienne, Switzerland) (17). Briefly, a highly focalized transducer operating at a frequency of 10 MHz was stereotaxically positioned over the RA using a gel as a medium. With the subject supine and the arm immobile at the heart level, the transducer was oriented perpendicularly to the longitudinal axis of the vessel based on the acoustic Doppler signal. After switching to A-mode, the echocardiography beams corresponding to the posterior lumen-intima and media-adventitia interfaces were visualized on a computer screen, and RA WT was measured as the distance between the inner and outer wall echoes (18). The back-scattered echoes from the inner posterior and anterior wall of the artery were also visualized and electronically digitized (analogic/digital fast transducer) to allow internal diameter variations to be derived at 50 Hz with a spatial dynamic resolution of 0.0025 mm (17,18).

A photopletysmographic system (Finapres 2003, Ohmeda, Englewood, Colorado) allowed blood pressure (BP) to be concomitantly recorded at 50 Hz from a finger ipsilateral to the RA examined, with an accuracy similar to intra-arterial BP recording (19). The concomitant acquisition of continuous diameter and BP signals allowed the calculation of diameter across the diastolic-systolic BP range. The diameter/BP curve was analyzed according to its fitting with the arctangent model of Langewouters and then cross-sectional Dist derived (cross-sectional compliance ÷ vessel area) (20).

**Carotid artery (CA) Dist, WT and AO Dist.** With the subject supine and the neck in partial extension, the diameter motion of the right common CA was measured 2 cm below the CA bifurcation by a B-M mode echo-tracking device based on Doppler shift (Wall Track System, PIE Medical, Maastricht, the Netherlands) and on a transducer operating at a frequency of 7.5 MHz (21). The transducer was manually oriented perpendicularly to the longitudinal axis of the vessel under B-mode and Doppler guidance. After switching to A-mode, the back-scattered echoes from the anterior and posterior CA walls were visualized and the corresponding radiofrequency signal tracked to allow the digitalized signal of the internal diameter variations to be derived at 50 Hz. The spatial resolution was 300 $\mu$m (21). Blood pressure was measured from the brachial artery at the same time of the ultrasound evaluation via a semiautomatic device (Dinamap 1846 SX/SXP, Critikon, Chatenay Malabry Cedex, France), and CA Dist was derived according to the following formula (21):

$$\text{Dist} = 2 \times (\text{Ds} - \text{Dd}) / (\text{Dd}) / (\text{PP})$$

where Ds is the systolic diameter, Dd is the diastolic diameter and PP is the corresponding pulse pressure (systolic BP − diastolic BP, average of three measurements).

The same procedure with a 3.5 MHz transducer was employed to measure the diameter motion of the subdiaphragmatic portion of the aorta, 2 to 3 cm above the origin of the celiac plexus and to calculate AO Dist (21,22). For technical reasons, however, no measurement of AO WT could be reliably made. Carotid artery intima-media WT was measured at a posterior wall site located 3 cm below bifurcation through an ultrasonographic device (Hewlett Packard Sonos 5500, Palo Alto, California). Measurements were obtained by first scanning the artery in B-mode, then freezing the digitized image in M-mode and finally tracking the inner ipoechogenic and the middle anechogenic layers (23).

All RA, CA and AO measurements were made by a single operator. The within-operator variability of RA, CA and AO diameter measurements at diastole (i.e., the coefficient of variation of the mean values of two measurements performed at two different times) was on average 2.3%, 2.8% and 3.9%, respectively. The within-operator variability for RA and CA WT were 2.0% and 3.0%, respectively.

**Additional evaluations.** One week before the study, each subject underwent a standard echocardiocolor-Doppler to obtain clinical information on left ventricular end-diastolic diameter, left ventricular WT (septal plus posterior wall), early and atrial transmitral flow and left ventricular ejection fraction (Simpson formula). In addition, each patient with CHF underwent two cardiopulmonary stress tests (at a one week interval) with a cycloergometer ramp protocol (10

W/min) using a breath-by-breath volume of oxygen consumption ($V_{O_2}$) and $C_{O_2}$ sampling for continuous gas analysis, averaging expiratory data over 15-s periods and calculating the maximum oxygen consumption ($V_{O_2}$max) (%) during the test (24). The maximal exercise time was also calculated. The $V_{O_2}$max and maximal exercise time were obtained also after two months of therapy.

In each subject, BP was measured also by a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. Heart rate was derived continuously from the finger pressure signal as the reciprocal of the pulse interval between consecutive beats. A venous blood sample was obtained after a 30-min supine position and used (after storage at −80°) to measure plasma-renin activity (radioimmunoassay).

**Protocol and data analysis.** Each subject was asked to come to the outpatient clinic of the San Gerardo Hospital in the morning after a 12-h abstinence from alcohol, caffeine consumption and cigarette smoking. The study (which began 3 h after a light meal) had the following protocol: 1) BP was measured three times by mercury sphygmomanometer with the subject in the sitting position; 2) the subject was placed supine in a quiet room at a constant temperature (21°C) and fitted with the finger BP and the RA echo-tracking devices; 3) after a 15-min resting interval, finger BP, heart rate and RA diameter were continuously measured for 15 min; 4) RA echo-tracking device was disconnected, the semiautomatic BP measuring device was placed on the brachial artery, and the probe for CA evaluation was positioned on the neck; 5) five 6-s acquisitions of CA diameter throughout the cardiac cycle were obtained during a 10-min period together with semiautomatic BP measurements; 6) the probe for evaluation of the AO was positioned; 7) five 6-s acquisitions of the AO diameter throughout the cardiac cycle were obtained during a 10-min period together with semiautomatic BP measurements.

The above-mentioned measurements were obtained in the same fashion after two months during which the patients with CHF had been randomly assigned to: 1) continuation of the previous standard therapy (10 patients); 2) modification of the previous therapy by increasing the dose of enalapril up to 40 mg daily (10 patients); and 3) modification of the previous therapy by adding losartan 50 mg daily (10 patients). Treatment was continued for two months. Compliance to treatment was checked by pill counting. Vascular measurements were made by operators unaware of therapy assignation.

In each subject and for each study session, the sphygmomanometric and Dinamap BP values were averaged. In the baseline condition, RA diameter and Dist/BP curves were obtained by averaging data from five periods of 30 s each, taken at 2-min intervals. The area under the RA Dist/BP curve was corrected for pulse pressure and used as a single integrated Dist value, which was called "operative" RA Dist index. Comparisons between different groups and conditions were also made by using the portion of the curve having the same BP range, that is, the isobaric RA Dist index (25). Carotid artery and AO diameter and Dist were obtained by averaging data from the five 6-s acquisition periods. Radial artery WT was measured over a 30-s period, based on the ultrasound image.

**Table 1.** Hemodynamic Characteristics of Patients with CHF and Controls

| | Control (n = 30) | | Heart Failure (n = 30) |
|---|---|---|---|
| SBP (mm Hg) | 136.0 ± 3.6 | * | 120.5 ± 3.8 |
| DBP (mm Hg) | 80.9 ± 5.6 | | 75.8 ± 1.9 |
| PP (mm Hg) | 55.0 ± 3.2 | | 45.2 ± 2.5 |
| SBP Din (mm Hg) | 128.5 ± 3.6 | | 118.6 ± 3.2 |
| DBP Din (mm Hg) | 75.0 ± 1.7 | | 69.5 ± 1.6 |
| PP Din (mm Hg) | 53.5 ± 2.0 | | 49.1 ± 1.5 |
| HR (beats/min) | 66.8 ± 2.4 | | 69.6 ± 2.8 |
| LVEDD (mm) | 50.8 ± 1.3 | † | 66.8 ± 1.2 |
| LVWT (mm) | 18.2 ± 0.3 | * | 20.8 ± 0.5 |
| LVEF (%) | 67.4 ± 2.8 | † | 31.2 ± 0.8 |
| E/A | 1.1 ± 0.1 | * | 1.4 ± 0.2 |
| PRA (pg/ml) | 1.0 ± 0.6 | * | 7.2 ± 1.5 |
| $V_{O_2}$ max (%) | — | | 66.6 ± 3.0 |
| Max Ex Time (min) | — | | 8.7 ± 0.6 |
| RA diameter (mm) | 2.5 ± 0.07 | | 2.7 ± 0.09 |
| CA diameter (mm) | 7.3 ± 0.14 | † | 8.1 ± 0.5 |
| AO diameter (mm) | 16.2 ± 0.3 | † | 18.1 ± 0.5 |
| RA Dist Isob (1/mm Hg $10^{-3}$) | 0.7 ± 0.06 | * | 0.4 ± 0.05 |

*$p < 0.05$; †$p < 0.01$. Data are shown as means ± SE.

AO = abdominal aorta; CA = carotid artery; CHF = congestive heart failure; DBP = diastolic blood pressure; Din = Dinamap; Dist. = distensibility; E/A = ratio between early and atrial transmitral peak flow; Ex = exercise; HR = heart rate; Isob = isobaric; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVWT = left ventricular wall thickness; PP = pulse pressure; PRA = plasma renin activity; RA = radial artery; SBP = systolic blood pressure.

Results from individual subjects were averaged and shown as means ± SE, separately for the control group, the CHF group as a whole and the CHF groups under different treatments. The statistical significance of the differences in mean values was assessed by two-way analysis of variance (ANOVA) and ANOVA for repeated measurements (period and group, interactions, Stat View software, Abacus Concepts Inc.). The two-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. Data were also analyzed by univariate regression taking Dist or WT as the dependent variables and echocardiographic, laboratory or ergospirometric variables as the independent ones. Significant correlations were then tested by multivariate analysis. A p value $<0.05$ was taken as the minimum level of statistical significance.

## RESULTS

Table 1 shows that, compared with controls, patients with CHF had a lower systolic BP and left ventricular ejection fraction but a greater left ventricular end-diastolic diameter, left ventricular WT, ratio between early and atrial transmitral peak flow (E/A),CA and AO diameter. Heart rate was

similar in the two groups, whereas the CHF group showed a much greater plasma renin activity than controls.

As shown in Figure 1 and Table 1, in all three vessels the operative and isobaric RA Dist values were markedly smaller in the former than in the latter group, the difference being more marked for CA and AO and always statistically significant. In the RA, the reduced Dist of CHF was visible through the systolic-diastolic pressure range (Fig. 2). The reduced Dist of CHF was accompanied by a significantly greater WT both in the thinner RA and in the thicker CA. Radial artery and CA WT showed an inverse relationship with the respective Dist values ($-0.38$ and $-0.32$, $p < 0.01$). Radial artery Dist was not related to CA and AO Dist, which were, on the other hand, positively related to each other ($r = 0.51$, $p < 0.01$). There was also a positive relationship between CA and AO Dist and $Vo_2max$ ($r = 0.45$ and 0.41, $p < 0.01$) or E/A values ($r = 0.51$ and 0.62, $p < 0.01$) but not with left ventricular ejection fraction.

Table 2 shows the data obtained in the three groups that underwent different treatments for two months. Compared with the initial values, in no group did BP, heart rate, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular WT or E/A show any significant change. In each group $Vo_2max$ percentage was also not significantly different from baseline. Maximal exercise time significantly increased both after the two months of the greater dose ACE inhibitor administration and after the two months of administration of the ACE inhibitor plus angiotensin II antagonist. Plasma-renin activity was unchanged in the group with unchanged treatment and not significantly increased in the group given an ACE inhibitor at a greater dose or the lower dose of ACE inhibitor plus the angiotensin II receptor antagonist. No treatment modified diameter and WT. In contrast, while in the group kept on previous treatment, Dist also did not show any modification in the groups given either the ACE inhibitor at the greater dose or the low-dose ACE inhibitor plus the angiotensin II receptor antagonist; Dist showed an increase that was significant also when tested by ANOVA two-way analysis for repeated measurements (main, period effect 0.01, interaction NS) in all three arteries (Fig. 3). In the RA this was the case, also when isobaric Dist was considered.

## DISCUSSION

**Arterial stiffening in CHF.** In our patients with CHF, arterial Dist was markedly less than in age-matched controls both at the level of the RA and at the level of the CA and the AO. Furthermore, the reduction of CA and AO Dist was directly related to an objective measure of the severity of heart failure such as the $Vo_2max$ estimated by cardiopulmonary stress test. Finally, the reduction of RA and CA Dist of CHF was accompanied by, and correlated with, an increase in WT. This provides an answer to several questions that were addressed by our study. Namely, in heart failure either muscle-type middle-size arteries and larger elastic-type arteries are characterized by a clear-cut stiffening, which implies that in this condition arterial mechanical properties are impaired throughout the arterial tree. Secondly, in the large elastic arteries (which account for the larger portion of overall arterial Dist), this impairment is related to the severity of heart failure, which implies that the arterial stiffening of heart failure is not an all or none but rather a gradual phenomenon. And thirdly, because of the concomitant increase in arterial WT, the stiffening can be ascribed to an alteration of the composition of the vessel wall, that is, it can be accounted for, at least in part, by a structural factor (26).

**Effects of treatment on arterial stiffness.** In a previous study we have shown that adding an ACE inhibitor to a treatment regimen based on diuretics and digitalis increased RA Dist (27). In the present study patients were already under treatment with diuretics, digitalis and an ACE inhibitor. The novel finding, however, is that when treatment was modified by either doubling the ACE inhibitor dose or by adding to the treatment regimen an angiotensin II antagonist, RA Dist was further improved, the change being significant also when tested by ANOVA for repeated measures (main effects and interactions). Furthermore, an improvement was seen also in the Dist of larger more elastic vessels such as AO and CA. Thus, a more effective blockade of the renin-angiotensin system has favorable consequences on impaired arterial mechanical properties of CHF. This is the case regardless of whether the more effective blockade is obtained by enhancing the ACE inhibitory effect on formation of angiotensin II or by preventing the action of this substance at the receptor level.

**Methodologic aspects of Dist measurement.** Several other findings deserve to be mentioned. One, in our study AO and CA Dist were measured by the changes in vessel diameter induced by pulse pressure changes, which were quantified in the brachial artery. Although being a commonly used approach, this represents a limitation because, ideally, vessel diameter and BP changes should be measured at the same vascular site (2,4,6,7,11,15). However, this cannot be obtained for the AO unless invasive (and hardly feasible) BP measurements are employed. It is also difficult to be obtained for the CA because: 1) patients with CHF cannot easily sustain the relatively prolonged vessel compression and breath-holding procedures that are necessary for direct assessment of CA pulse pressure through tonometry; and 2) this assessment is not devoid of inconveniences, among which is limited reproducibility (28). More importantly, although the pulse pressure modification along the arterial tree has not been thoroughly investigated in patients with CHF, it is unlikely this condition could be characterized by a greater difference between values measured peripherally and more centrally and, thus, by a greater than normal attenuation in CA and AO pulse pressure that could have been responsible for a reduced excursion of vessel diameter. First, differences between central and peripheral pulse pressure are more evident during vasodilation, that is,

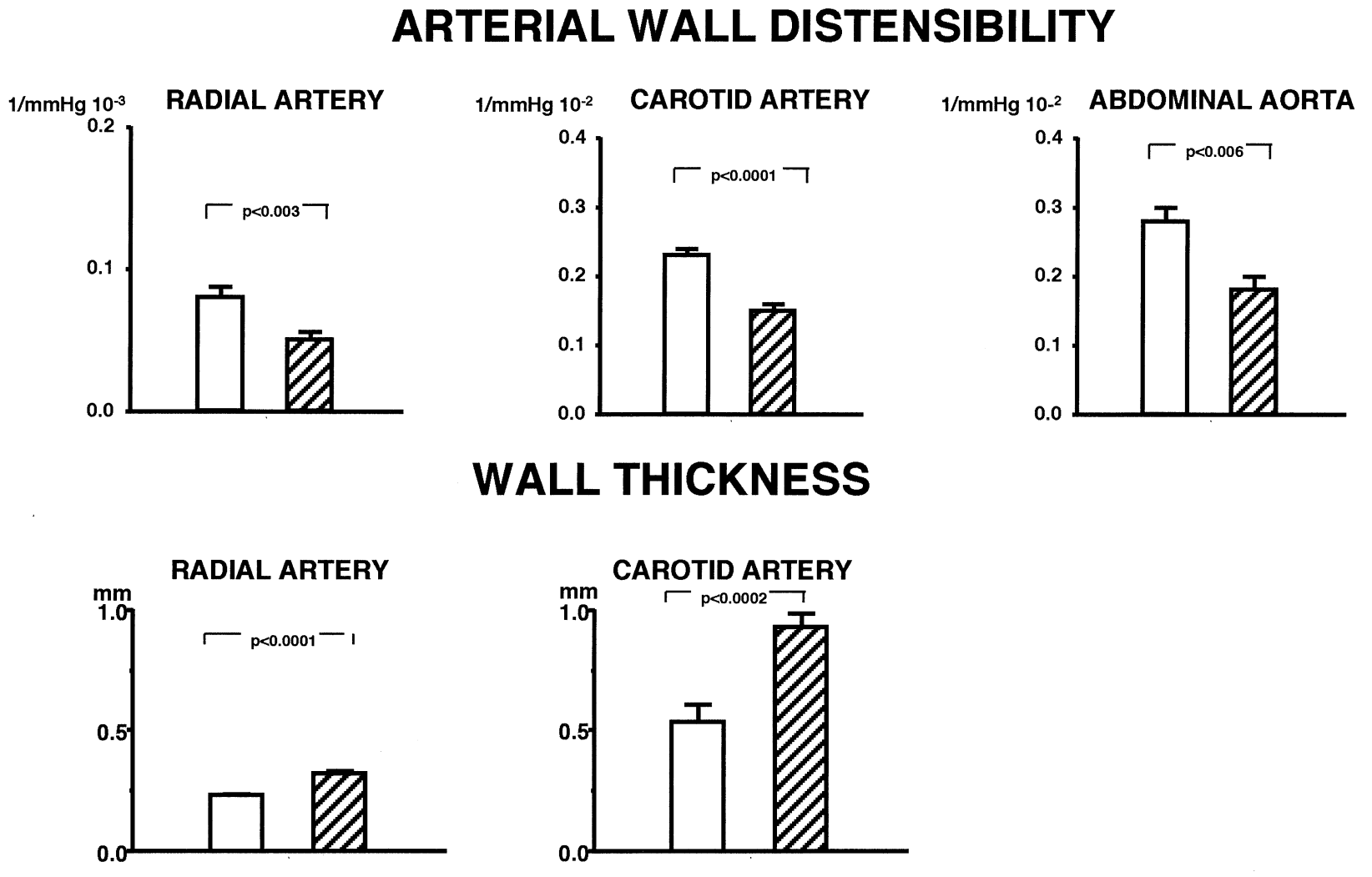


**Figure 1.** Radial artery (RA) and carotid artery (CA) wall thickness and RA, CA and abdominal aorta distensibility in control subjects (n = 30) and in patients with congestive heart failure (n = 30). Data are shown as mean ± SE. **Open bar** = controls (n = 30); **hatched bar** = heart failure (n = 30).

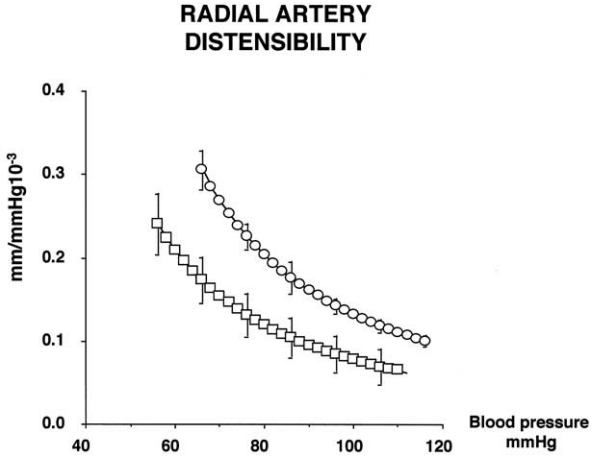


**Figure 2.** Radial artery (RA) distensibility-pressure curves in the control and congestive heart failure groups of Figure 1. **Open circle** = controls, n = 30; **open square** = heart failure, n = 30.

conditions opposite of that typical of CHF, which is characterized by an increase in vascular resistance (29). Second, in our patients with CHF, a reduced Dist was documented also in the RA whose diameter changes were quantified for nearby measured changes in BP. We can, therefore, substantially conclude that there is a generalized arterial stiffening in CHF, which can be improved by the treatments we employed.

**Arterial stiffness in CHF: possible mechanisms.** In patients with CHF, CA and AO Dist correlated in a relatively close fashion both to each other and to the E/A value while showing no relation with RA Dist. This suggests that after cardiac pump failure there might be a nonuniform progression of arterial stiffening in smaller and larger arteries. It also suggests, however, that the stiffening progresses in a rather uniform fashion throughout the large elastic portion of the arterial tree and that this progression reflects a similar progression of the stiffening in the heart (30).

Our results, however, do not clarify the nature of the structural alteration that leads to the arterial stiffening of patients with CHF. We can speculate that in the vessel wall of these patients the less extensible tissue (e.g., collagen) grows more than the more extensible one (elastin and smooth muscle), presumably because of the influence of the variety of growth factors (e.g., increase in norepinephrine, increase in endothelins and reduction in nitric oxide secretion, etc.) whose circulating and tissue concentration is increased when the cardiac pump fails (31–33). We can also speculate, however, that the arterial stiffening of CHF is just vascular "waterlogging," that is, an increase within the vessel wall of "incompressible" water due to sodium retention (34,35). We cannot, however, exclude that functional factors are additionally involved because "growth" substances that can alter tissue composition of the vessel wall can in many instances also powerfully contract the smooth muscle cells that can be found both in muscle-type arteries and (although to a lesser extent) in elastic-type ones, with an increase in vessel elastic modulus with respect to the condition in which smooth muscle is relaxed. Indeed, the exclusive participation of structural factors to the reduction of Dist seen in CHF is made unlikely both by the observations made in a previous study and data obtained in the present study. In a previous study on CHF we have shown RA Dist to be increased after four to eight weeks of administration of an ACE inhibitor (27). This may be too short a time for major structural changes to take place. In the present study we have seen the increase in CA and RA Dist after two months of treatment to be associated with no change in arterial WT. This makes it possible that a pulse pressure independent functional factor such as reduction of

**Table 2.** Effects of Treatment Modifications in Patients with CHF

| | T Unchanged (n = 10) | | T Modified (ACEI Doubled) (n = 10) | | T Modified (ACEI Unchanged + ATA) (n = 10) | |
|---|---|---|---|---|---|---|
| | B | T | B | T | B | T |
| SBP (mm Hg) | 117.3 ± 4.3 | 114.0 ± 7.9 | 128.8 ± 6.9 | 122.4 ± 3.5 | 123.9 ± 3.6 | 118.3 ± 4.6 |
| DBP (mm Hg) | 75.8 ± 2.7 | 72.7 ± 3.9 | 74.9 ± 2.8 | 72.3 ± 3.9 | 77.8 ± 3.4 | 74.3 ± 2.9 |
| HR (beats/min) | 70.3 ± 2.7 | 72.5 ± 3.2 | 67.5 ± 5.2 | 64.3 ± 4.1 | 69.3 ± 4.2 | 71.3 ± 4.8 |
| LVEDD (mm) | 67.4 ± 2.3 | 66.1 ± 1.8 | 65.9 ± 3.7 | 63.4 ± 4.7 | 68.4 ± 2.7 | 66.3 ± 3.1 |
| LVWT (mm) | 20.5 ± 0.8 | 21.0 ± 1.1 | 20.7 ± 0.9 | 21.4 ± 0.9 | 20.3 ± 0.9 | 21.1 ± 0.9 |
| LVEF (%) | 31.2 ± 0.4 | 31.9 ± 2.3 | 31.7 ± 0.9 | 34.2 ± 2.1 | 30.8 ± 1.9 | 34.8 ± 1.9 |
| E/A | 1.8 ± 0.5 | 1.6 ± 0.5 | 1.3 ± 0.6 | 1.4 ± 0.4 | 1.5 ± 0.4 | 1.1 ± 0.2 |
| PRA (pg/ml) | 6.5 ± 2.2 | 6.7 ± 1.8 | 7.2 ± 2.2 | 12.1 ± 6.8 | 5.1 ± 1.8 | 21.7 ± 8.0 |
| Max $V_{O_2}$max (%) | 65.8 ± 6.5 | 69.8 ± 6.4 | 67.9 ± 5.6 | 71.2 ± 5.2 | 63.9 ± 4.8 | 71.2 ± 3.8 |
| Max Ex Time (min) | 8.5 ± 1.2 | 8.6 ± 1.1 | 8.5 ± 0.8 | * 9.4 ± 0.6 | 9.2 ± 1.3 | * 10.4 ± 0.8 |
| AO diameter (mm) | 17.0 ± 0.9 | 17.3 ± 1.6 | 18.0 ± 1.0 | 16.3 ± 1.2 | 19.2 ± 1.0 | * 15.7 ± 1.0 |
| CA diameter (mm) | 7.7 ± 0.4 | 7.9 ± 1.0 | 8.5 ± 0.4 | 8.4 ± 0.5 | 8.1 ± 0.4 | 8.0 ± 0.4 |
| RA diameter (mm) | 2.47 ± 0.08 | 2.52 ± 0.09 | 2.56 ± 0.18 | 2.52 ± 0.16 | 2.62 ± 0.14 | 2.73 ± 0.15 |
| RA WT (mm) | 0.30 ± 0.02 | 0.29 ± 0.02 | 0.30 ± 0.02 | 0.32 ± 0.02 | 0.35 ± 0.02 | 0.33 ± 0.02 |
| CA WT (mm) | 0.78 ± 0.05 | 0.82 ± 0.06 | 0.99 ± 0.11 | 1.02 ± 0.13 | 0.99 ± 0.12 | 0.96 ± 0.11 |
| RA Dist Isob (1/mm Hg $10^{-3}$) | 0.39 ± 0.06 | 0.41 ± 0.07 | 0.38 ± 0.04 | * 0.69 ± 0.09 | 0.45 ± 0.07 | * 0.78 ± 0.08 |

*$p < 0.05$. Data are shown as means ± SE.
ACEI = ACE-inhibitor; ATA = angiotensin antagonist; B = baseline; T = treatment; WT = wall thickness; all other abbreviations as in Table 1.

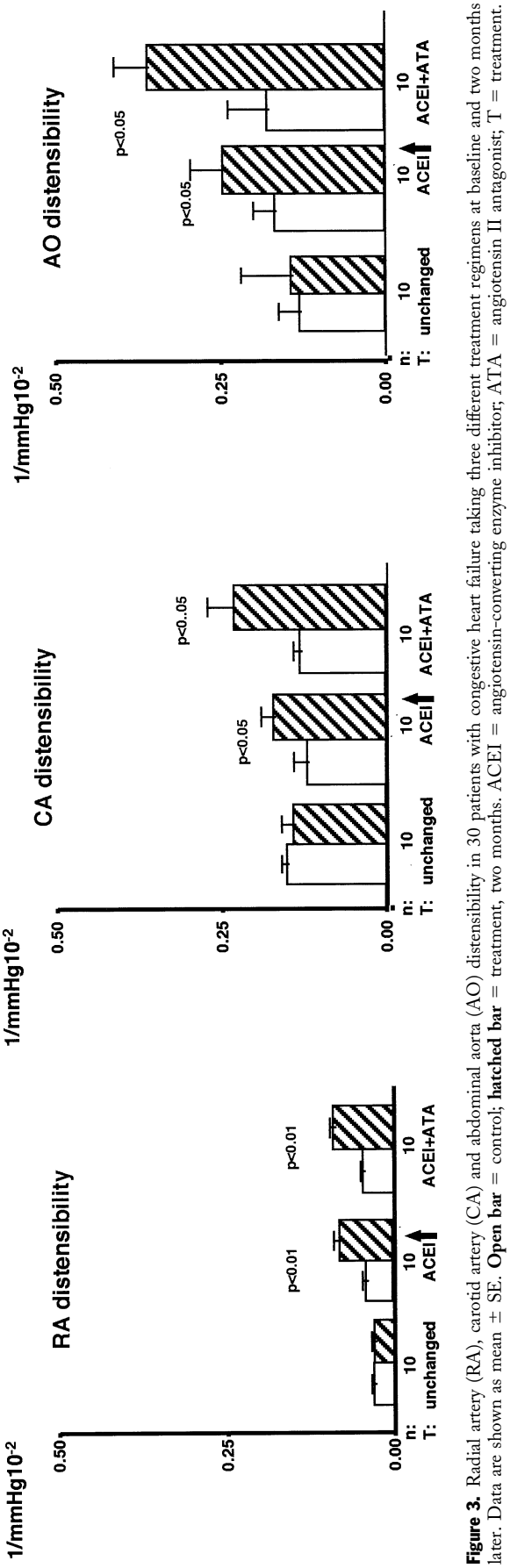


**Figure 3.** Radial artery (RA), carotid artery (CA) and abdominal aorta (AO) distensibility in 30 patients with congestive heart failure taking three different treatment regimens at baseline and two months later. Data are shown as mean ± SE. **Open bar** = control; **hatched bar** = treatment, two months. ACEI = angiotensin-converting enzyme inhibitor; ATA = angiotensin II antagonist; T = treatment.

smooth muscle contraction within the arterial wall by blockade of the renin-angiotensin system is also involved.

**Clinical implications.** Our results have clinical implications. First, the progressive reduction of Dist as CHF becomes more severe implies a progressive increase in arterial impedance and cardiac afterload when the ability of the heart to face the need of a greater performance is compromised. Second, the arterial stiffening of patients with CHF also means a greater traumatic effect of intravascular pressure on the vessel wall, with a greater chance of damaging its endothelial and intimal-medial structure (1,2). Third, the reduced Dist of the CA and the AO in patients with CHF means a reduced ability of baroreceptors to sense BP changes and, consequently, reflexively restrain sympathetic tone, renin release and vasopressin release (36). The arterial stiffening may, therefore, represent an important mechanism involved in the neurohumoral activation of heart failure. All these consequences can be favorably counteracted by treatments that block the renin-angiotensin system and more so if the blockade is made highly effective by high ACE inhibitor doses or by opposing the system at different sites.

Fourth, the similar increase in Dist seen in patients taking the ACE inhibitor/angiotensin II antagonist combination and the ACE inhibitor alone at a greater dose speaks against a specific advantage of blocking the renin-angiotensin system at two different sites as compared with making the blockade more effective at the ACE site only. With the caution required by the limited number of patients studied, this negative finding emphasizes that for a specific advantage of an ACE inhibitor/angiotensin II antagonist combination the protocol of the study should include comparison with subjects in which an ACE inhibitor is given at a greater dose. This has rarely been done in studies claiming the superiority of combining an ACE inhibitor with an angiotensin II antagonist over ACE inhibition alone.

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