Combined Sympathetic Suppression and Angiotensin-Converting Enzyme Inhibition in Congestive Heart Failure

Athanassios J. Manolis, Christoforos Olympios, Maria Sifaki, Stelios Handanis, Dennis Cockinos, Margaret Bresnahan, Irene Gavras, Haralambos Gavras

Abstract Neurohormonal activation is a pathogenic contributor and prognostic marker in congestive heart failure (CHF). While angiotensin-converting enzyme (ACE) inhibition is now first-line therapy, sympathetic inhibition has only lately been proposed to this aim. Recently, we reported improvement of preload parameters by sympathetic suppression with clonidine. In the present paper we studied the effects of a single oral dose of clonidine 0.15 mg+captopril 6.25 mg combination, compared with captopril 6.15 mg+placebo, in a single-blind parallel study on 16 patients with Class III or IV CHF (13 males, 3 females, aged 62±8 years, with an ejection fraction of 33±8%). Hemodynamic and hormonal measurements were taken at baseline after a diagnostic cardiac catheterization and again 2 hours after treatment. The results indicate that preload parameters such as RAP, PCWP and MPAP decreased significantly with the combination therapy but not with captopril alone. On the contrary, SVR decreased significantly with both treatments and SVI increased significantly with both—but the latter change was significantly greater with the captopril/clonidine combination than with captopril alone. Suppression of plasma norepinephrine occurred with the combination only (evidently attributable to clonidine), whereas plasma renin activity increased with both regimens, due apparently to captopril.

Our results indicate that the combination of clonidine with captopril induces significant improvements in both preload and afterload parameters of CHF and correction of activated neurohormones, suggesting additive hemodynamic and hormonal benefits from the two treatment modalities (Hypertension. 1997; 29[part 2]:525-530.)

Key Words • clonidine • captopril • preload reduction • afterload reduction

Neurohormonal activation is one of the biochemical characteristics of chronic CHF. Initially this is part of the adaptive processes attempting to counteract the declining left ventricular performance, however, in the long-term, stimulation of catecholamines, angiotensin and aldosterone, among others, contributes further to the anatomic alterations and hemodynamic burden that tend to aggravate CHF. Indeed, elevated levels of these hormones are now considered to be a diagnostic and prognostic sign of deteriorating cardiac function. In view of the pathophysiologic role of these hormones in CHF, it is now accepted that their inhibition is a rational approach to the treatment of CHF. Suppression of angiotensin II via ACE inhibition was the first treatment shown to improve long-term survival in CHF and has become standard therapy in this condition. A significant improvement in afterload parameters with decreased myocardial oxygen utilization is the mechanism underlying these results.

Inhibition of the SNS has been attempted via various means, including ganglionic blockers, β1-receptor and β-adrenergic receptor antagonists, and central SNS suppressants. In a recent pilot study, we found that central sympathoinhibition via clonidine produced a significant amelioration of preload parameters without much change in afterload. The acute hemodynamic effects observed within 2 hours after the first dose of clonidine were maintained after 1 week’s treatment with two daily doses of clonidine, indicating no tendency to “escape.” In the current paper, we describe the hemodynamic results of combined acute inhibition of the RAS via captopril plus central SNS suppression via clonidine in patients with CHF.

Methods

The study was designed as a single-blind, placebo-controlled trial. Patients with chronic CHF class III or IV according to the criteria set by the NYHA were randomized to receive a single oral dose of either captopril 6.25 mg+clonidine 0.15 mg or captopril 6.25 mg+placebo. Underlying causes of CHF were either coronary artery disease with ischemic cardiomyopathy or dilated cardiomyopathy of unknown origin. Patients with valvular heart disease were excluded. The first 10 consecutive patients who fulfilled these criteria and consented to participate were assigned to receive the two-drug combination and the next 7 to receive captopril+placebo.

All patients were admitted to the Cardiology Department of Tzamo Hospital with acute pulmonary edema and were treated initially with salt restriction, digoxin, diuretics and nitrates. When patients had been stable for 4 days, they were informed about the study and enrolled after signing a written informed consent form.

Throughout the study, patients were maintained on a low sodium diet (2 g daily), with all previous medications withheld the day before hemodynamic evaluation, so that baseline hemodynamics were measured at 24 hours after the last dose of medication.
Protocol

All patients were studied during diagnostic cardiac catheterization before and 2 hours after the administration of a single dose of either captopril+placebo or captopril+clonidine. Baseline pressure measurements were obtained with the patient in the supine position 2 hours after initiation of the catheterization (ie, 2 hours of resting with catheters in place) to ensure hemodynamic stability. Blood samples for PRA, catecholamines (NE and E), and AVP were drawn at baseline. Samples of 5 mL for each hormone were collected in EDTA in chilled tubes on ice. They were centrifuged immediately, and the plasma was separated and frozen immediately at −80°C until assay for PRA, 15 NE and E, 16 and AVP. 17 The two pills were then administered orally, and the same measurements were performed 2 to 3 hours later after a period of rest in the catheterization laboratory.

Hemodynamics Measurements

An 8 FR balloon-tipped flow-directed Swan-Ganz catheter (Abbott CCS) was inserted via the right femoral vein and positioned in the pulmonary artery, and connected to a standard TP-400T (Nihon-Kohden) transducer for direct (invasive) measurement of left ventricular systolic and end-diastolic pressures. The transducer had the appropriate frequency response for detection of small pressure differences. Aortic pressure was measured during the few seconds of withdrawal of the catheter in the ascending aorta. Both pressure transducers were connected to an eight-level cardiac catheterization monitor system (RMC-1100, Nihon-Kohden) and electrocardiographic and pressures waveform (graphs) were displayed and thereafter recorded at a speed of 50 or 100 mm/s on a thermal array recorder. PCWP and left ventricular end-diastolic pressure values were constantly checked to ascertain accuracy of recordings. MAP and heart rate, which turned out to be similar for the MAP and heart rate, which turned out to be similar for the MAP and heart rate, which turned out to be similar for the two groups were similar, except for heart rate, which turned out to be significantly higher in the group receiving the combination treatment.

The hemodynamic changes induced by the two treatments are shown in Figs 1 and 2. It is apparent that the clonidine/captopril combination decreased all three preload parameters (RAP, PCWP and MAPAP), whereas captopril alone had no significant effect on these values, indicating that this effect was due solely to clonidine. The changes in SVR and SVI were significant with both treatments, but were more pronounced with the captopril/clonidine combination. In fact, there was a significantly greater improvement with the combination treatment than with captopril alone in all of the above parameters, except for the decrements in SVR, that were not significantly different between the two treatments. Fig 3 depicts the hormonal data. As expected, the plasma levels of catecholamines were decreased with the clonidine combination, although only the NE change was significant, evidently due to wide variability of the baseline E levels. Captopril produced no change in plasma catecholamines, but accounted for all of the increments observed in PRA with either treatment.
AVP levels tended to increase with both treatments, but the changes were not significant.

Fig 4 shows the individual changes in RAP, PCWP, MAP and SVI. It is evident that patients with a greater degree of decompenston at baseline had more pronounced improvement with the comonent treatment. It is also notable that patients with quite low MAP at baseline had no further lowering of BP, so that no subject suffered from consequences of hypotension.

Discussion

As mentioned earlier, it is now generally accepted that activation of the renin-angiotensin system and the SNS in CHF is proportional to the degree of severity of the disease, and hence it is a marker of poor prognosis. At the same time, the hemodynamic and metabolic consequences of this activation contribute to further functional deteri-oration, thus perpetuating a vicious cycle. Blockade of one element of this cycle—the renin-angiotensin system, whether by ACE inhibition3,5,6 or by angiotensin II antagonism6,7 produces immediate and sustained amelioration, mostly by decreasing the afterload. Indeed, long-term ACE inhibition was the first and so far the only treatment of CHF shown to prolong life.3,4 In the present study, we demonstrate that a combination treatment suppressing both the renin-angio-
tensin and the sympathetic systems, produces immediate improvement in both preload and afterload parameters of CHF. In fact, comparison of the acute effects of the captopril-clonidine combination to those of captopril alone (combined with placebo) confirms that the decreases in RAP, PCWP, and MAP are again attributable to clonidine alone, whereas the decrease in SVR and the increase in SVI are due to both agents because they are more pronounced with the combination than with captopril alone. Indeed, in the case of SVI, the improvement with the combination is significantly greater than with ACE inhibition alone.

The current study was the logical extension of an earlier pilot clinical experiment, where we studied the effects of a single dose of clonidine and a week’s treatment with clonidine on various characteristics of CHF.4 Comparison of the findings from that study with those of the present paper reveals that for some parameters the results of the two drugs are additive, eg, for MAP, MPAP, SVR, PVR, and SVI. For others, the changes can be attributed solely to one of the two drugs, eg, clonidine accounts for the decrease in RAP and PCWP (as well as the acute fall in NE), whereas captopril accounts for the increase in CI. Lack of significant change in preload parameters with captopril should probably be attributed to the small single dose of the drug, since

### Hemodynamic and Hormonal Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combination Treatment (n=9)</th>
<th>Control Treatment (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 Hours</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>154±19</td>
<td>124±10</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80±11</td>
<td>68±7</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>105±14</td>
<td>84±8</td>
</tr>
<tr>
<td>RAP</td>
<td>8±3</td>
<td>6±2</td>
</tr>
<tr>
<td>MPAP</td>
<td>30±14</td>
<td>20±5</td>
</tr>
<tr>
<td>PCWP</td>
<td>21±12</td>
<td>13±5</td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>87±16</td>
<td>74±14</td>
</tr>
<tr>
<td>CI</td>
<td>225±0.7</td>
<td>267±0.2</td>
</tr>
<tr>
<td>PVR</td>
<td>180±7.8</td>
<td>101±40</td>
</tr>
<tr>
<td>SVR</td>
<td>2074±588</td>
<td>1312±260</td>
</tr>
<tr>
<td>SVI</td>
<td>27±10</td>
<td>97±6</td>
</tr>
<tr>
<td>NE</td>
<td>0.54±0.21</td>
<td>0.37±0.2</td>
</tr>
<tr>
<td>AVP</td>
<td>2.29±1.7</td>
<td>2.79±1.6</td>
</tr>
<tr>
<td>PRA</td>
<td>11.6±11.5</td>
<td>37±4.0</td>
</tr>
</tbody>
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SBP indicates systolic blood pressure, DBP, diastolic blood pressure, HR, heart rate, CI, cardiac index, and PVR, pulmonary vascular resistance. Hemodynamic and hormonal parameters at baseline and at 2 hours post-treatment with a single oral dose of clonidine/captopril combination. Control subjects received captopril/placebo.

*pSignificant difference between baselines at P< 0.05
Chronic therapy of CHF with larger maintenance doses is known to benefit both preload and afterload. Nevertheless, it should not be surprising if acute sympathetic withdrawal with venodilation were more effective in decreasing preload, than acute ACE inhibition. Importantly, the combination appears to accentuate the improvement even in those parameters that seemed to remain unaffected by one of the treatments. It should be noted that the patients in the present study were mostly normotensives, yet the small decrease in arterial pressure with the combination treatment was very well tolerated. One reason for this is probably the fact that, following ACE inhibition, there is a redistribution of regional blood flows in favor of vital organs, which retain good perfusion even with very low systemic pressures. The fact that baseline arterial pressure turned out to be significantly higher (though still in the normal range) in the group treated with the combination treatment was very well tolerated. This might account for the greater improvement in afterload parameters in this group. However, in individual subjects there was very often a discrepancy between percent fall in blood pressure and decrease in SVR. For example, a 52% fall in SVR was accompanied by a 35% decrease in MAP in a patient receiving the combination, whereas a 67% fall in SVR was accompanied by a 13% decrease in MAP with captopril alone. Overall, there was a poor correlation in magnitude of changes between these two parameters. The more pronounced slowing in heart rate observed with the combination, would, of course, contribute to improved ventricular filling time and ventricular performance, and thus clearly represents an additional benefit of central sympathetic withdrawal. In keeping with this, we have found that chronic treatment with clonidine alone (in addition to the standard digoxin and diuretics) for up to 14 months substantially improves the patients' general condition, with increased functional capacity and decreased severity of arrhythmias and frequency of rehospitalizations (Manohs et al, unpublished data). These results are therefore attributable to the sympatholytic effect of clonidine.

Of course, the definitive study, the one to show that clonidine or a clonidine/ACE inhibitor combination may prolong life in patients with CHF, has yet to be conducted. This note of caution is mandated by the fact that in the past other treatments directed against various components of the SNS (mostly blockade of peripheral adrenergic receptors) appeared to improve some of the derangements characterizing CHF.
CHF yet failed to diminish overall mortality. 8-10,20 If we were permitted to speculate as to the causes of this failure, we would propose that blockade of certain peripheral adrenergically mediated functions leaves unopposed other effects of sympathetic activation, which probably account for some of the deleterious consequences of this treatment (including the early deaths in the run-in phase of the carvedilol trial). On the contrary, central sympathetic suppression would attenuate all adrenergically mediated effects.

In summary, we conducted a study comparing the acute hemodynamic improvements induced by a single dose of clonidine+captopril versus captopril alone in normotensive patients with CHF. Despite shortcomings due to less than perfectly matched groups (especially regarding the small, but statistically significant difference in baseline arterial pressure), the results are highly encouraging even though they may not be considered as absolutely conclusive. They demonstrate that the combination of low doses of clonidine and captopril has the potential to produce immediate improvements in both preload and afterload parameters of CHF in a manner suggesting additive hemodynamic and hormonal benefits.

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