Regional Sympathetic Effects of Low-Dose Clonidine in Heart Failure

Anuradha Aggarwal, Murray D. Esler, Margaret J. Morris, Gavin Lambert, David M. Kaye

Abstract—This study examined the effects of low doses of intravenous clonidine on regional and global sympathetic nervous system activity in heart failure. In heart failure, adrenoceptor-blocking treatments have a limited sphere of activity. Centrally acting sympatholytic therapies should be further investigated, with a specific emphasis on targeting cardiac and renal sympathetic overactivity. In 10 patients with moderate-severe congestive heart failure, we examined the effect of intravenous clonidine on systemic, cardiac, and renal sympathetic activity and on brain monoamine turnover using the norepinephrine spillover method. In addition, we assessed the effect of clonidine on cardiac release of the sympathetic cotransmitter neuropeptide Y. A dose of 1 μg/kg of clonidine resulted in a fall in cardiac (326±73 to 160±40 pmol/min, \( P<0.001 \)), renal (2.5±0.6 to 1.5±0.3 nmol/min, \( P=0.01 \)), and global norepinephrine spillover (4.0±0.6 to 3.1±0.5 nmol/min, \( P<0.01 \)), with a significantly disproportionate reduction in cardiac versus total-body sympathetic activity (\( P<0.05 \)). No significant changes in cardiac neuropeptide Y release or in central monoamine turnover were demonstrated. Clonidine, at modest doses, significantly attenuates cardiac and renal sympathetic tone in heart failure. In addition to the beneficial effects of antiadrenergic therapy in the heart, the renal sympatholytic effect may counter the salt and water retention that is a hallmark of the condition. (Hypertension. 2003;41:553-557.)

Key Words: heart failure ■ clonidine ■ renal ■ norepinephrine

Congestive heart failure (CHF) is characterized by heightened sympathetic activity, particularly directed to the heart and kidneys.1 Neurohormonal activation is initially beneficial, helping to maintain systemic blood pressure and perfusion to vital organs, but is maladaptive in the long-term, contributing to worsening of CHF and sudden cardiac death.2 β-Adrenergic antagonists have become a cornerstone of modern heart failure management, resulting in major gains in prognosis.3 However, β-adrenoceptor antagonism cannot attenuate the effects of vasoactive cotransmitters such as neuropeptide Y (NPY) that are coreleased with norepinephrine (NE).4 In addition, although it is probable that β-blockade reduces neurally induced renin release,5 the high renal sympathetic tone observed in CHF, which may contribute to sodium retention and circulatory overload, may not be altered by β-blockade6 (although this remains controversial). These limitations, when coupled with the observation that there is increased central monoamine turnover in CHF,7,8 suggest that therapy to attenuate central sympathetic drive directly should be investigated.

Clonidine is a potent sympatholytic drug with central and peripheral effects.9 In CHF, it appears to act predominantly via stimulation of sympathoinhibitory α₂-adrenergic and/or imidazoline receptors in the central nervous system,10 and chronic administration has been demonstrated to attenuate the systemic sympathetic activation in CHF.11–13 Azevedo et al14 have shown that acute administration of intravenous clonidine to CHF patients resulted in a significant reduction in cardiac and systemic NE spillover, a measure of cardiac sympathetic activity. Nevertheless, the only controlled clinical trial to date using a strategy of attenuating sympathetic drive in CHF, the Moxonidine in Congestive Heart Failure (MOXCON) trial, was terminated early because of excess mortality in the treatment arm. This outcome was surprising in light of evidence that moxonidine has a powerful sympatholytic effect in heart failure.15 A possible explanation for this apparent contradiction may be that the doses of moxonidine used were excessive, leading to hemodynamic decompensation.

In the present study, our aims were to test the hypothesis that clonidine attenuates regional sympathetic tone in both the heart and kidney, sites of marked sympathoexcitation in CHF. Further, given that the extent of cardiac adrenergic drive is related to prognosis,2 we also tested the dose-dependence of the sympatholytic effect of clonidine in the heart. The effect of clonidine on sympathetic nerve cotransmitter release was evaluated by measuring transcardiac NPY levels, and finally, we studied the effect of clonidine on central monoamine turnover.

Methods

Ten patients with CHF (mean age, 57 years; range 49, to 67 years; all male) participated in this study. Study subjects had New York
Heart Association class II to III symptoms with a left ventricular ejection fraction of $<$40% (mean±SD, 25.4±8.0%). Medications consisted of an ACE inhibitor (n=9), carvedilol (n=9), antiarrhythmic therapy (amiodarone, n=2; sotalol, n=1), Aldactone (n=6), digoxin (n=3), and furosemide (n=9). The study was performed with written informed consent and the approval of the Alfred Hospital Ethics Review Committee.

Under local anesthesia, the radial artery was cannulated, and a venous introducer sheath was placed in the right antecubital fossa (n=7) or, when not possible, in the right internal jugular vein (n=3).

After a priming bolus of 12 μCi of [1-ring-2,5,6-3H]-NE (New England Nuclear; specific activity, 40 to 50 Ci/mmol) and 120 mg of p-aminohippurate (PAH, Clinalfa) via a peripheral vein, infusions of intravenous clonidine at 0.1, 0.25, and 1 μg/kg. Each dose was given as an infusion over 15 minutes. There was then a 20-minute delay before the next dose. Blood sampling and flow measurements were taken at the end of this 20-minute period. This protocol was derived from the observation that the hemodynamic effects of a single intravenous bolus of clonidine peak at 15 to 20 minutes and return to baseline by 45 minutes. There was then a 20-minute delay before the next dose.

Cardiac output, coronary sinus blood flow, and coronary sinus plasma flow from clearance of PAH.1 Clonidine (Boehringer-Ingelheim) was given via a peripheral vein at the following doses: 0.1, 0.25, and 1 μg/kg clonidine produced a 23% reduction in global sympathetic activity. Across the heart, although there was a trend toward a decrease with the first 2 doses, only a dose of 1 μg/kg clonidine produced a significant reduction in cardiac NE spillover (from 326±73 to 160±40 pmol/min, P<0.001). This represented a 50% reduction in cardiac sympathetic activity. At this final dose of clonidine, a significant decrease in coronary sinus blood flow of 27% (P<0.001) was also observed.

Cardiac NPY Release
Data are available from 9 patients for NPY dynamics across the heart and are also presented in the Table. At rest, a net
cardiac extraction of NPY was demonstrated. Clonidine did not result in any significant change in cardiac NPY release.

Renal NE Release
Data are available from 9 patients and are presented in Figure 1. Baseline renal plasma flow was 739±111 mL/min, and renal NE spillover was 2.5±0.6 nmol/min. After the final dose of clonidine, this reduced to 494±59 mL/min ($P=0.01$) and 1.5±0.3 nmol/min ($P=0.01$), a reduction of 26% and 32%, respectively.

Regional Versus Total Sympathetic Outflow Sensitivities to Clonidine
When comparing the regional sympathetic responses to clonidine, the heart was significantly more sensitive than the global sympathetic outflow (Figure 2). There was a 32±9%, 50±10%, and 23±4% reduction in renal, cardiac, and total-body sympathetic outflow achieved with 1 μg/kg of clonidine. Furthermore, cardiac NE spillover, when expressed as a proportion of total systemic NE spillover, demonstrated a trend toward increasingly selective cardiac sympathoinhibition with increasing clonidine dose: 8±1%, 8±1%, 6±1%, and 5±1% ($P<0.05$, between baseline and final dose results).

Effects of Clonidine on Brain NE Turnover
The right internal jugular vein (RIJV) was cannulated in 7 patients. Baseline RIJV blood flow was 405±41 mL/min, and this reduced to 320±44 mL/min after the highest dose of clonidine ($P<0.05$). Clonidine did not result in any significant reduction in the release of NE and its lipophilic metabolites (dihydroxyphenylglycol and 3-methoxy-4-hydroxyphenylglycol) from the brain into the RIJV (1048±557 to 981±267 pmol/min).

Discussion
Activation of the sympathetic nervous system is an important pathophysiological feature in CHF, with attendant links to mortality and progression of CHF, and arrhythmogenesis being clearly established. Although β-adrenoceptor antagonists have become an integral component of modern CHF management, their activity is limited by virtue of their receptor-specific action and lack of effect on potentially deleterious sympathetic cotransmitters. A logical progression in the therapy of CHF has been to investigate centrally mediated sympatholytic approaches, using pharmacological central suppression of sympathetic outflow. The sympathetic excitation observed in CHF is not uniform but regional, with the major focus on the heart and the kidneys. A further refinement of the sympatholytic approach may then be to selectively target these organs. Some supportive evidence to this contention already exists in alcoholic cirrhosis, another disease model of sympathetic overactivation. In this condition, Esler et al21 have previously demonstrated that sympathetic outflow to the hepatomesenteric circulation was more sensitive to pharmacological suppression with clonidine than was the systemic sympathetic outflow.

Although the cardiac effects of sympathoinhibitory treatments in CHF have been previously studied,12-14 little work has been performed with regards to renal sympathetic tone. In a rat model of CHF, increased activity of the efferent renal sympathetic nerves have been shown to exert a potent antidiuretic and antinatriuretic influence.8 By extrapolation, in human CHF, the exaggerated renal sympathetic activity may possibly play a major role in salt and water retention, which is characteristic of the disease. Attenuation of this sympathetic drive could offer symptomatic and prognostic benefit. Carvedilol, which blocks α- and β-adrenoreceptors, appears to have neutral effects on surrogate markers of renal sympathetic tone such as renal blood flow and glomerular filtration rate.23 Although the effects of carvedilol on cardiac and systemic sympathetic activity have been studied,24 possible effects on renal sympathetic tone remain to be investigated. In hepatic cirrhosis, Esler et al21 have demonstrated increased sympathetic neural outflow to the kidneys in humans, with a reduction in renal sympathetic tone and an increase in glomerular filtration rate with intravenous clonidine. However, to our knowledge, the effects of clonidine on renal sympathetic tone in human CHF have not been previously investigated. In the present study, we demonstrated a substantial reduction in renal NE spillover with clonidine. Although clonidine did produce a significant reduction in renal blood flow (26%), we believe that the decrease in NE spillover resulted from a true reduction in sympathetic discharge, rather than from a reduction in flow. We have previously shown that there is no direct effect of lowering blood flow on renal NE spillover determination with blood flow reductions of <30%.17 The mechanism(s) for the reduction in regional blood flow (cardiac, renal, and internal jugular) that we and others14 have demonstrated remains unclear. Across the renal bed, we did not observe a change in

![Figure 1](http://hyper.ahajournals.org/)

Figure 1. Renal NE spillover, at baseline and after 1 μg/kg clonidine. *$P=0.01$.

![Figure 2](http://hyper.ahajournals.org/)

Figure 2. From baseline, percentage of reduction in NE spillover after 1 μg/kg clonidine.
renal vascular resistance, and it is possible that the significant reduction in systemic blood pressure resulted directly in a reduction in driving pressure. It is also possible that this mechanism led to changes in coronary blood flow. A limitation of this current study is that we did not measure possible functional effects of sympathoinhibition on such parameters as glomerular filtration rate or urinary sodium excretion.

In the present study, we have confirmed the finding of Azevedo et al that clonidine suppresses cardiac sympathetic drive in CHF. We have extended this observation by showing that the heart is disproportionately more sensitive to the sympatholytic effects of this drug than is global sympathetic activity. It is known that cardiac sympathetic activation is a more powerful prognostic indicator than generalized sympathetic tone, as indicated by plasma NE. Therefore, an implication from this finding is that low doses of sympatholytic drugs may possibly produce prognostic benefit, by selectively suppressing cardiac sympathetic drive, in the absence of significant systemic side-effects associated with pronounced sympathetic withdrawal such as hypotension.

One of the potential advantages of central sympatholytic therapy is that release of vasoactive sympathetic co-transmitters, such as NPY, could also be suppressed. Previous investigators have shown that transcardiac and arterial plasma NPY levels are increased in CHF. These findings were in an era before the routine use of β-adrenergic blockers. Interestingly, in the current study, we were not able to demonstrate net cardiac release of NPY at rest or any change after clonidine. A possible explanation for this is evidence that this current group of patients was in a state of more optimal control of their CHF. In our earlier report, the mean cardiac and total NE spillover values were 394 ± 46 pmol/min and 5.5 ± 0.4 nmol/min, respectively (compared with 326 ± 73 pmol/min and 4.0 ± 0.6 nmol/min in the present study). Further, the mean pulmonary capillary wedge pressure in the previous group was 21.5 ± 1.3 mm Hg, whereas in the current group this was 14.8 ± 2.4 mm Hg, again reflecting the better control of CHF in this group. Kaye et al reported cardiac NPY release at baseline to be 1759 ± 786 pg/min in their group of CHF patients; in our current group, we observed a net cardiac extraction of NPY at rest. It is possible that relatively minor reductions in cardiac sympathetic nerve activity have resulted in major decreases in cardiac NPY release, given that NPY sympathetic co-transmission only occurs at high rates of sympathetic nerve firing.

A final aspect of the current study was to investigate the effects of clonidine on central monoamine turnover, a measure of brain noradrenergic activity. We have previously established an association between the degree of activation of central noradrenergic neurons and the level of sympathetic nervous tone in the heart in CHF. The cell bodies of the noradrenergic groups, designated A1–7, are confined to medullary and pontine parts of the brainstem but exhibit complex ascending and descending projections in addition to local destinations in the brainstem, with the majority of brain NE located in the pontine locus caeruleus (A6). Clonidine is a centrally acting suppressant of sympathetic nervous activity that is known to inhibit the firing rate of locus caeruleus neurons and to decrease the concentration of MHPG in rat brain. Maas et al have demonstrated a reduction in MHPG jugular overflow from the brain of stump-tailed monkeys after clonidine administration, and this finding has been subsequently reproduced in healthy human subjects.

In the present study, we were unable to demonstrate a significant decrease in the right internal jugular venous spillover of NE and its lipophilic metabolites with clonidine. This may have been because in this report, the values for central monoamine turnover at baseline were substantially lower than in our earlier reports. A possible explanation for this is, again, that the mean pulmonary capillary wedge pressure in the present study is lower. A trend has been previously observed for mean pulmonary artery pressure and central monoamine turnover to be related in human heart failure, and from animal studies, it is known that pulmonary afferents do project to the locus coeruleus. There are 2 additional explanations for the observed resistance of central NE turnover to clonidine in CHF. First, we did not use radionuclide cerebral venous scanning to lateralize the venous drainage of the brain. As would be inferred from studies of central sympathetic organization in rats and from studies in human hypertension, central monoamine turnover is significantly higher in the jugular vein that receives drainage from the subcortical areas of the brain. In the majority of humans, this area drains to the left internal jugular vein. In the present study, we elected to sample the right vein, as it is technically easier to cannulate. Therefore, in this small group of 7 patients, we may have failed to see a clonidine effect because of insufficient sampling of subcortical venous drainage. A second possible explanation is that the central noradrenergic centers in CHF are resistant to the relatively modest doses of clonidine used in the current study. When previously given to healthy humans, a dose of 150 to 225 μg of clonidine was used to effect a substantial reduction in central monoamine turnover.

Conclusions
The novel findings of this study are that in heart failure, cardiac sympathetic activity is more sensitive to central sympatholytic therapy with clonidine than is systemic sympathetic tone, and that renal sympathetic tone is also significantly reduced. Further studies need to be performed to assess effects of sympatholytic agents on glomerular filtration rate and renal salt excretion in heart failure.

Perspectives
Although medical therapy of heart failure with neurohormonal antagonists such as ACE inhibitors, β-adrenoceptor blockers, and spironolactone have led to major gains in prognosis, mortality in CHF remains high. A possible additional therapeutic approach may be to investigate sympathoinhibitory agents. Although the only large-scale study to date to investigate this approach, MOXCON, was terminated early because of excess mortality in the treatment arm, perhaps because of the aggressive forced titration protocol. We believe the findings of this study lend ongoing support for the further clinical evaluation of the utility of central sympathoinhibition in CHF patients.
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References


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