The “Unsympathetic” Nervous System of Heart Failure

John S. Floras, MD, DPhil

Sympathetic activation in heart failure is intimately linked to disease progression and to adverse outcome.1–3 Contemporary management of heart failure relies on three antidiurenergic strategies, predicated on the hypothesis that interventions that counter sympathetic overactivity will improve both symptoms and prognosis. First, excessive central sympathetic outflow to the heart and periphery can be reduced by normalizing elevated cardiac filling pressures,4 by abolishing coexisting obstructive sleep apnea with nocturnal continuous positive airway pressure,5 or by attenuating sympathoexcitatory reflexes activated by exercising muscle through conditioning. Although rational, thus far these interventions have not been proven to improve survival.

A second approach has been to modulate the neural regulation of norepinephrine (NE) release. Examples include digitalis glycosides, which appear to sensitize acutely and therefore increase the discharge of arterial baroreceptors, and ACE inhibitors, which should diminish or block the presynaptic facilitatory effects of angiotensin II on NE release. However, the impact of ACE inhibitors on plasma NE (PNE) concentrations is relatively modest,6,7 suggesting that their mortality benefit accrues primarily through nonadrenergic mechanisms.

Third, sympathetic activation may be addressed indirectly, by blocking the actions of catecholamines on postjunctional adrenergic receptors. A series of placebo-controlled trials has demonstrated the symptomatic, hemodynamic, and mortality benefits of β-adrenoceptor antagonists,8–10 β-blockade, as exerted by metoprolol or bisoprolol, may be sufficient to achieve these effects. Whether concomitant β2-adrenoceptor antagonism, as with carvedilol or bucindolol, confers any additional benefit is the subject of an ongoing comparative mortality trial. Although carvedilol is also classified as an antioxidant, it has fewer side effects than clonidine. The hope has been that this strategy might confer greater long-term clinical benefit and patient acceptance than β-adrenoceptor blockade.

In this issue of Circulation, Swedberg et al13 report the results of their multicenter Moxonidine Safety and Efficacy (MOXSE) trial. The principal objective of this double-blind, dose-response study, involving 268 subjects, was to determine the effect of a sustained-release (SR) preparation of moxonidine on PNE concentrations in class II-IV heart failure. Patients with an ejection fraction ≤ 35% were randomly allocated placebo or one of 5 target doses of SR moxonidine (0.3, 0.6, 0.9, 1.2, or 1.5 mg BID). Background therapy included ACE inhibition or angiotensin II antagonist. β-Blocker use within the previous 30 days was an exclusion criterion. PNE was measured at baseline, at weekly visits during dose titration, and before and 4 hours after drug administration after 7 and 19 weeks of treatment. PNE was also assessed daily, for 3 days, after drug withdrawal. Ambulatory ECG recordings were obtained at baseline, 19 weeks, and at the end of the washout period. In American centers where radionuclide angiography was available, left ventricular ejection fraction (LVEF) was quantified at baseline and at 19 weeks of treatment. Tolerability and safety data were also acquired.

The key finding was a remarkable dose-related decrease in PNE at the 19th week of therapy (P<0.0005). In the group assigned the highest dose of SR moxonidine, PNE fell by >50%. In addition, there was a significant dose-related increase in LVEF (P=0.015). Demonstration of a marked reduction in this (albeit indirect) marker of sympathetic activity, coupled with increases in LVEF analogous to those obtained with long-term β-blockade would therefore appear, on first reading, to validate the concept of central sympathoinhibition in heart failure. However, there was a concerning dose-related increase in the number of patients who had serious adverse events (P=0.038). Of the 10 deaths recorded, 9 occurred in the 140 patients assigned doses of 0.9 mg BID or higher and none in placebo-treated patients.

The importance of the MOXSE study therefore extends beyond these particular observations to the context and insights these data bring to the interpretation of the subsequent Moxonidine Congestive Heart Failure (MOXCON) trial. Although not yet published, the primary end point of

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From University Health Network and Mount Sinai Hospital, Department of Medicine, and the University of Toronto, Toronto, Canada.

Correspondence to Dr John S. Floras, 1614–600 University Ave, Toronto, ON M5G 1X5 Canada. E-mail john.floras@utoronto.ca

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000013788.71817.16
this trial (led by many of the same investigators) has been widely reported at scientific forums. In MOXCON, patients with class II-IV symptoms and LVEF \(\leq 35\%\) were randomly assigned to placebo or 1.5 mg SR moxonidine BID. The primary end point was all-cause mortality. Randomization began on May 25, 1998. With only 1993 of the anticipated 4533 patients recruited, the trial was terminated prematurely on March 12, 1999, on the recommendation of the Data Monitoring Board. There was an excess of deaths (both sudden and those caused by progressive pump failure) in the active treatment group (54 versus 32; \(P=0.005\)).

What can this mortality rate excess be attributed to? The MOXSE data suggest three potential hypotheses above and beyond the play of chance.

At baseline, median values for PNE in those assigned placebo and moxonidine were 369 pg/mL (2.18 nmol/L) and 394 pg/mL, respectively (Table 2\(^1\)). For comparison, the median value (with 25% to 75% confidence intervals) for PNE in younger but healthy control subjects in the Studies of Left Ventricular Dysfunction (SOLVD) trial was 317 (242 to 450) pg/mL. Corresponding values for patients recruited to the SOLVD (asymptomatic) prevention and treatment study arms were 422 (312 to 566) and 507 (368 to 644) pg/mL, respectively.\(^1\) Thus, the first possibility is that a considerable number of the patients recruited to MOXSE were not sympathetically activated (probably as a result of appropriate medical therapy) and therefore were unlikely to benefit from central adrenergic inhibition. This concern might have been avoided had trial subjects been selected or stratified on the basis of a screening PNE.

Although the MOXSE investigators chose not to relate events in their pilot study to reductions in PNE, a second possibility is that in some patients, the higher moxonidine doses may have been inappropriately sympathoablative. Table 2\(^1\) in the MOXSE article reveals that 19 weeks of 1.5 mg SR moxonidine BID (the MOXCON study dose) lowered median values for PNE to 249 pg/mL. This corresponds to the 25th percentile of PNE values reported for healthy control subjects in the SOLVD study. The impact of this dose of moxonidine on sympathetic discharge directed at the heart, kidney, and other important vascular beds has not been reported and cannot be determined from these venous PNE concentrations, which reflect primarily the neural release of NE from forearm sympathetic nerves. However, responses to 0.1 mg clonidine IV have been documented.\(^1\) These include reductions in arterial NE concentrations, cardiac NE spillover, and LV +dP/dt of 47%, 58%, and 15%, respectively. Thus, in some moxonidine-treated patients, residual sympathetic outflow might have been insufficient to support cardiac output or peripheral resistance, leading to progressive pump failure.

In their Introduction, the authors propose an additional potential advantage of central inhibition with moxonidine over other forms of antiadrenergic therapy: “the degree of blockade can be quantified by monitoring PNE levels and thus individualizing treatment to maintain clinically appropriate levels of antiadrenergic effect.” Although intuitively attractive, this hypothesis was not tested. It is based on several key assumptions. The first is that a single PNE determination can provide a meaningful representation of the extent of sympathetic activation in a specific patient. However, as illustrated by microneurographic recordings, sympathetic nerve discharge in heart failure exhibits dynamic short-term variation. Effects on sympathetic discharge to the heart and kidney cannot be inferred reliably from changes in PNE. Thus, a single value for PNE may be as representative of the cumulative daily impact of sympathetic discharge on the heart and periphery as is a single clinic measurement of 24-hour ambulatory blood pressure. The second assumption is that patients with heart failure share quantitatively similar mechanisms of sympathetic activation and that it is therefore possible to determine a “clinically appropriate level” for each individual. Although a baroreceptor-mediated reflexive increase in sympathetic outflow (in response to decreases in stroke volume, ventricular inotropy, and blood pressure) may be common to all patients with LV systolic dysfunction, the magnitude of this response will differ from patient to patient. Additional sympathoexcitatory stimuli such as elevated atrial pressure, pulmonary congestion, coexisting sleep-related breathing disorders, and chemoreceptor or muscle metaboreceptor afferent activity will also vary considerably between patients. Without characterizing the extent of these several mechanisms of sympathetic activation, one cannot be certain that PNE in a particular patient is appropriate to their heart failure state or excessive, and if the latter, a target for judicious central sympathoinhibition. A third assumption is that any reduction in PNE must be due to sympatholysis. However, changes in cardiac output will also affect the plasma concentration of NE by altering its neuronal and extraneuronal clearance. Thus, PNE-directed heart failure management is likely to remain an elusive goal.

The dynamic nature of sympathetic discharge in heart failure is best illustrated by the section on moxonidine withdrawal, which may be the most important aspect of this study. Increases in heart rate, blood pressure, and PNE during the withdrawal phase of the MOXSE trial were greatly in excess of corresponding reductions achieved by active treatment. This may not have been anticipated, because a comparative study in hypertensive patients reported less rebound with moxonidine than with clonidine.\(^1\) In subjects assigned the highest moxonidine dose, heart rate fell by \(\approx 7\) beats/min with treatment but increased, on washout, by \(>14\) beats/min; 20% to 30% more ventricular ectopy was also noted at this time. Moxonidine did not affect systolic blood pressure, but a mean increase of 9 mm Hg occurred on its withdrawal. PNE rose significantly within a day of stopping moxonidine. By the third day, PNE increased, on average, by 709 pg/mL (+275%), reaching absolute levels associated, in previous studies, with a \(>40\%\) 6-month mortality rate.\(^1\) The rebound increases in PNE reported in Table 2\(^1\) might have been even greater had the Data Monitoring Board not recommended cautious “dose tapering to avoid the potential of rebound when moxonidine SR was acutely discontinued” “after observing the signs and symptoms of the first 55 patients during this acute withdrawal phase.” At the end of the dose maintenance phase, patients who were receiving \(>0.6\) mg BID of moxonidine were down titrated to 0.6 mg BID for 1 week before receiving placebo. Thus, when considering the
MOXCON trial of 1.5 mg SR moxonidine BID, marked noradrenergic rebound during brief periods of nonadherence must be considered a plausible mechanism of sudden death in some patients receiving active treatment.

The fundamental question raised by these observations is whether death in the MOXSE and MOXCON studies should be attributed to excessive sympatholysis (as has been invoked to explain the anomalous result of the bucindolol trial); to intense rebound surges in sympathetic drive, heart rate, and blood pressure, in occasionally noncompliant patients; or to both of these dose-related mechanisms. Until this dilemma is resolved, further investment in this once-promising class of drugs for heart failure is unlikely. Unfortunately, the MOXCON trial was initiated before these MOXSE study data were analyzed and available for consideration. A different trial design, recruiting only patients with clear evidence for excessive sympathetic drive, or testing a lower or individualized dose of SR moxonidine, might have yielded a less discouraging outcome.

Acknowledgments
The author is the recipient of a Career Investigator Award from the Heart and Stroke Foundation of Ontario.

References

KEY WORDS: Editorials, nervous system, sympathetic, norepinephrine, heart failure
The "Unsympathetic" Nervous System of Heart Failure
John S. Floras

Circulation. 2002;105:1753-1755
doi: 10.1161/01.CIR.0000013788.71817.16

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/15/1753

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/