Chronic Systolic Heart Failure, Guideline-Directed Medical Therapy, and Systemic Hypotension—Less Pressure but Maybe More Risk (Does This Clinical Scenario Need More Discussion?)

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ABSTRACT

Many clinical trials have demonstrated the survival benefit of medication regimens that modulate the neurohormonal activation that occurs with chronic heart failure (HF). These medications, however, also commonly lower systemic blood pressure (BP). Low arterial BP in patients with chronic HF has been shown to be an independent predictor of increased mortality.

Given this apparent paradox in therapeutic goals (treat aggressively but keep BP from going too low), how low should we allow systemic BP to go as a result of our medication regimens before we compromise the proven benefits of such drug therapy? Or is the association between the BP-lowering effects of standard therapy and outcomes in HF even meaningful clinically?

It is from this perspective that the merits, potential clinical implications, and the relevant published literature pertaining to this patient and practice management issue will be discussed. (*J Cardiac Fail 2009;15:101–107*)

Key Words: Heart failure, guideline-directed medical therapy, systemic hypotension, outcomes.

Despite advancements in cardiovascular drug and device therapeutics there remains a significantly high rate of mortality and morbidity in patients with systolic and diastolic heart failure (HF).[1–4] HF has become not only a medical burden for the many patients who suffer with it, but also a socioeconomic burden in most countries worldwide.[5,6] Numerous clinical trials have been or are being conducted to address this problem. Typically, trial designers identify the risk factors for adverse events and try to apply different therapeutic and preventive strategies to improve quality of life, reduce hospitalization rates, and prolong survival. In addition to device and surgical trials in chronic HF, different classes of drugs have shown significant benefit in reducing mortality and morbidity in HF.[7,8] Since activation of the renin-angiotensin-aldosterone system was shown nearly 30 years ago to adversely impact HF outcomes, drug trials have focused mainly on agents that antagonize the deleterious effects of this maladaptive neurohormonal response. These classes of medications include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-adrenergic receptor antagonists, and aldosterone antagonists.[7,8] Recently, a reprised regimen, the fixed-dose combination of hydralazine and isosorbide dinitrate, has shown a selective benefit in black patients with HF.[9] Despite the heterogeneity of this disease syndrome, all classes of these medication have shown benefit.

Based on these and other clinical trials the American College of Cardiology/American Heart Association and Heart Failure Society of America in their latest guidelines for the management of chronic HF recommend the combined use of these drugs for optimal therapy.[7,8] Current practice is directed toward attaining the recommended target doses as established by the clinical trials or the maximum tolerated doses in the absence of signs or symptoms of inadequate organ perfusion. The therapeutic goal is to establish maintenance therapy with drugs that antagonize neurohormonal activation, lower vascular impedance, improve organ/tissue blood flow, and slow cardiac structural

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Manuscript received May 9, 2008; revised manuscript received July 9, 2008; revised manuscript accepted July 14, 2008.

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No conflicts of interests and no sources of funding to disclose.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2008.07.228

remodeling. However, most evidence-based drug therapies for HF lower systemic blood pressure (BP) and most are also used for the treatment of hypertension. Certainly, it is not uncommon in clinical practice to observe systemic hypotension secondary to severe left ventricular (LV) dysfunction (low output state) in patients with chronic HF. The issue, however, to be considered is if the observed hypotension is solely secondary to the severity of the disease process or if medication-related therapy might further negatively impact BP and, therefore, outcome. It may well be that the disease state and its response to therapy drives the outcome regardless of the level of BP, but this issue needs more clarity. We do not know to what extent BP is deleteriously lowered in different HF populations (varying New York Heart Association [NYHA] functional status or etiologies of HF) or by different classes of medication (each with different mechanisms of action) or by combination treatment regimens, or even how much lowered BP contributes quantitatively to poorer outcomes. As a result, the clinical paradox arises that ''optimal'' HF medical therapy associated with low systemic BP may result in underrecognized and harmful clinical consequences. The issue is complex, but the fundamental clinical question to be addressed is how low should systemic BP be allowed to go in patients with chronic HF receiving guideline-recommended medications before we should be concerned, or is there no association between the incidental BP lowering effects of HF therapy and clinical outcomes?

Integral to this discussion is the prognostic significance of low systemic BP in HF and the potential mechanisms of action that hypotension can exert on vital organ function, particularly cardiac function, and HF-related morbidity and mortality. If persistent hypotension is related to increased risk in HF patients, what role might medical therapy-induced hypotension have in contributing to that risk? The implications of the later would potentially entail an adjustment in medication-related goals and, therefore, guidelines in the treatment of chronic HF. Although a comprehensive answer is not yet available, this issue is commonly confronted by the HF provider on a near-daily basis.

It is from this perspective that we propose to initiate a discussion on the relationship of chronic systolic HF, medication-related low systemic BP secondary to the management of HF, and their interactions on clinical outcome. In addition, we will attempt to provide a focused literature review on this issue that we hope will encourage further interest and investigation. As with any discussion, it must be framed by the available supporting data, which are sparse in relation to this topic. Although this discussion will focus on HF resulting from reduced LV systolic function, this topic also has relevance in HF with preserved left ventricular ejection fraction.

Systemic BP Regulation in Cardiovascular Disease

Normally, systemic BP is determined by stroke volume (SV) and peripheral vascular resistance. In healthy hearts, impedance to SV ejection determines the BP. In HF patients with LV dysfunction and associated neurohormonal activation, the impedance increases to a point where BP becomes most dependent on SV.[10,11] However, as SV decreases with worsening LV function, BP also decreases. Medications given to inhibit the effects of neurohormonal activation will cause lower impedance and thus also often contribute to even lower BP. The goal in HF patients is to reduce impedance without compromising organ perfusion. This afterload reduction in turn could have the effect to actually raise BP through an increase in SV as a response to drug therapy. Unfortunately, this response cannot be assured in the presence of myocardial failure and ongoing structural remodeling of the heart and circulation. In HF patients, a decrease in resistance cannot be compensated by an increase in SV to maintain BP because SV becomes fixed. As a consequence, systemic BP and organ perfusion may be compromised. Moreover, because the majority of HF patients are elderly and more susceptible (impaired autoregulation of blood flow and ''stiff'' blood vessels) to the effects of hypotension such as the orthostatic symptoms of dizziness and gait instability with falls, as well as compromised renal and myocardial perfusion.[12,13]

Blood flow is directly proportional to the difference in pressure and inversely proportional to resistance (Flow = $\Delta P/R$). In normal subjects the intrinsic mechanism of ''autoregulation'' of blood flow acts even at low systemic pressures to maintain adequate organ perfusion. In disease states such as HF and with aging, autoregulation becomes impaired and is effective only at higher systemic BP thresholds.[14,15] Thus, with lowered BP in HF, autoregulation of perfusion pressure may be lost and flow to vital organs dependent on prevailing systemic pressure and, therefore, often significantly compromised. What happens to the mechanism of autoregulation in chronic HF and what this means to organ perfusion are not well understood. At the coronary artery level, flow is proportional to the difference between the proximal and distal pressures in the coronary artery. The proximal pressure is the aortic diastolic pressure and the distal is at the level of the myocardium. With HF, the diastolic filling pressure in the heart is increased, thus increasing the distal pressure. During supine sleep, more venous return from mobilization of fluid in the lower extremities occurs, which also increases diastolic filling pressures. Meanwhile, HF medication therapy contributes to lower aortic systolic pressure. These factors lead to small changes in pressure, but significantly lower flows. This mechanism is exacerbated in the presence of the coronary artery atherosclerotic disease where stenotic lesions also further alter autoregulatory mechanisms.

A similar phenomenon occurs in the renal and cerebral circulations. End-organ perfusion pressure in HF patients is lower because of mechanical failure of the myocardium and impaired autoregulation, as well as the effects of BP lowering medications. Additionally, peripheral vascular resistance is increased especially in the elderly, who often