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Review

A new approach to treatment of acute heart failure

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ABSTRACT

Conventional therapies for acute decongestion have yielded uniformly poor results in patients with acute heart failure (AHF). The failure of current strategies may be due to advanced disease in hospitalized patients, incomplete therapy, inherent limitations to existing therapy, or some combination of all three factors. Loop diuretics are the mainstay of current therapy and are in theory not ideal since while producing immediate intravascular volume reduction and relief of symptoms they activate neurohormonal forces that are deleterious to both the heart and the kidney. Ultrafiltration is an alternative to loop diuretics but has not proved advantageous in the setting of renal dysfunction, and if not carefully applied may also aggravate neurohormonal imbalance. In theory decongestive therapy for AHF should remove large volumes of fluid quickly and safely and improve symptoms, particularly dyspnea, without aggravating renal dysfunction or causing neurohormonal activation. Several studies have now suggested that the use of aquaretics such as antagonists to the V2 receptor for arginine vasopressin may be useful as adjunctive therapy in AHF, particularly when renal dysfunction and/or hyponatremia are present. These agents leverage osmotic forces to produce tissue decongestion while causing a water diuresis. They do not adversely affect renal function or neurohormonal balance. Building on the current base of knowledge about outcomes in AHF together with the only study of vasopressin antagonists as short-term monotherapy in chronic heart failure, it would be reasonable to design a trial in AHF in which the use of loop diuretics was minimized in favor of these agents.

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Despite substantial improvement in outcomes for patients with chronic heart failure (HF), at least in those with reduced ejection fraction, there has been essentially no progress in the treatment of acute heart failure (AHF) for several decades. Most admissions for AHF occur in patients with chronic HF, and in the USA these are now evenly divided between those with normal and reduced ejection fraction. The vast majority of these admissions are due to clinical congestion, not hypotension or shock, regardless of whether the patient has normal or reduced ejection fraction. It follows that current treatment for congestion, while successful in the acute relief of symptoms, is not having a favorable effect on near-term readmissions or mortality [1]. Annualized mortality rates in patients with chronic HF due to reduced ejection fraction on contemporary therapy are in the range of 6–7%, while after an admission for AHF, recent data continue to demonstrate short-term mortality rates of 11–15% [2]. Outcomes are similar in those with normal and reduced ejection fraction. It is possible that patients admitted with AHF are simply sicker than those not admitted for AHF and that worse outcomes are inevitable, although baseline characteristics of those admitted are similar to those not admitted, other than the findings of acute congestion. It is, perhaps, more likely that an admission for AHF implies deterioration in some aspect of ventricular loading conditions or ventricular function which, if not treated with sufficient skill, leads to worse outcomes in the short and near term. It is also possible that our treatment for AHF could actually be contributing to worse outcomes. Randomized controlled trials have, in fact, shown harm with the use of agents such as milrinone [3].

A hallmark of both chronic and acute HF is neurohormonal activation [4,5]. Originally, neurohormonal activation was felt to

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be an epiphenomenon secondary to the presence of HF and not directly related to the pathophysiology of progressive HF. The success of neurohormonally directed therapy has emphatically shown that this assumption was not true, at least in patients with reduced ejection fraction, as incremental improvements in survival have been demonstrated with sequential interference with elements of the renin–angiotensin–aldosterone axis, the sympathetic nervous system, and most recently, the addition of neprilysin inhibition to angiotensin II antagonism, which presumably acts by boosting the levels of counterregulatory vasodilatory and growth-inhibiting peptides [6]. In AHF, however, despite being on background therapy with these agents, patients frequently present with hypertension, tachycardia, vasoconstriction, and intense sodium avidity. As either a cause or a consequence (or both) of AHF, there is, therefore, evidence of aggravated neurohormonal imbalance. Directing therapy at this exacerbated neurohormonal imbalance would represent a new approach to treating AHF. If, as with chronic HF, neurohormonal imbalance is directly involved in the pathophysiology of AHF, either diminishing or at least not aggravating this heightened imbalance might hold the key to improving outcomes.

Current treatment for AHF relies on loop diuretics and the adjunctive use of vasodilators. Loop diuretics aggravate neurohormonal imbalance acutely and may do so chronically as well [7,8]. These agents cause acute vasoconstriction and deterioration in systemic hemodynamics and also have adverse acute and chronic effects on renal function. As such, they are hardly ideal agents for treating a syndrome in which there is acute vasoconstriction and sodium avidity along with neurohormonal imbalance and, commonly, renal impairment. Yet they continue to be used, since alternatives have been lacking [9].

Ultrafiltration (UF) is an alternative decongestive modality associated with less neurohormonal activation than loop diuretics [10]. One randomized controlled trial in patients with chronic HF comparing loop diuretics and UF showed more sustained hemodynamic benefit in patients treated with UF despite comparable acute effects [10]. Another study in AHF showed similar results [11], while a third showed both greater early weight loss and fewer admissions for recurrent acute HF [12]. Neither this trial nor a subsequent study of UF in the cardiorenal syndrome showed benefit on renal function, however [13]. Of interest was a recent observation from CARRESS that neurohormonal activation in the UF arm of that study was actually greater than in the control arm [5], although contrary to protocol intent, a large fraction of the patients in the UF arm also received loop diuretics after randomization. In both the DOSE and CARRESS trials, neurohormonal activation correlated well with decreases in renal function [5].

Several studies have tested whether adjunctive vasodilator use improves outcomes in AHF. These studies, employing B-type natriuretic peptide [14] and endothelin antagonists [15], were negative. A retrospective evaluation of the use of carperitide, or atrial natriuretic peptide, showed that it worsened outcomes [16]. No data are available with nitrates in AHF. We, therefore, have no signal from any recent study other than those with UF that suggests any improvement in outcomes compared with a loop-diuretic-based regimen with or without adjunctive therapy.

While outcomes overall remain poor in AHF, not all patients fare as badly as others. Potentially modifiable markers of worse outcome include renal failure, hyponatremia, and the severity of congestion [17]. It is certainly plausible that greater neurohormonal activation could underlie each of these adverse prognostic factors. As already noted, recent data from DOSE and CARRESS link neurohormonal activation during treatment with adverse renal function [5], although neither study was powered sufficiently to test for an adverse effect of changes in renal function on survival. The relationship between worsening renal function and outcomes, however, may be more complex than originally thought [18,19].

Hyponatremia is strongly associated with poor outcome and is driven by increased secretion of arginine vasopressin, one component of the original "neurohumoral axis" [20]. There are no prospective trials of treatment of hyponatremia in AHF, but a retrospective analysis of EVEREST showed a strong benefit in patients treated with the V2 receptor antagonist tolvaptan who had serum sodium under 130 mq/l [21].

Finally, congestion itself is likely driven by the vasoconstriction and sodium retention caused by neurohormonal activation, but there are no studies that have looked prospectively or retrospectively at the relationships among decongestive efficacy, neurohormonal responses to therapy, and outcomes.

No treatment for AHF has, therefore, been convincingly proven to be better than 'standard of care,' which has been based on loop diuretics in all recent trials. Various vasodilators have failed to improve outcome, while, as noted, inodilators and inotropes have worsened outcome. UF has promise but has not yet been shown to improve outcomes in a prospective study with outcomes as the primary endpoint, and as noted, may not necessarily be favorable to renal function, at least in those with impaired renal function at baseline. Given the failure of recent treatments to improve outcomes, the use of agents which directly or indirectly reduce neurohormonal activation might make sense. At a minimum, avoiding further neurohormonal activation should be an obvious goal. New trials in AHF could certainly test these approaches. Clonidine directly reduces sympathetic activity and could be studied as adjunctive therapy. Digoxin has been shown to reduce renal sympathetic activity in canine studies and has never been studied as adjunctive therapy in AHF. Neither agent, however, would likely have a direct effect on volume expansion, and while congestion may be due to disturbances in afterload leading to decreased LV function and increased LV filling pressure, most patients with AHF have at least some, and in most cases substantial, increases in total body volume. A decongestive agent that did not aggravate neurohormonal imbalance or adversely affect renal function would, in theory, be very attractive in HF and most particularly in high-risk AHF where neurohormonal imbalance is extreme.

Tolvaptan is such an agent. As an antagonist to the V2 receptor for arginine vasopressin, tolvaptan causes a free water diuresis and raises serum osmolality. This is the basis for its beneficial effect on hyponatremia. An increase in serum osmolality would be expected to have a beneficial effect on decongesting water-logged tissues in HF (Fig. 1). Indeed, the use of tolvaptan uniformly has produced superior effects on dyspnea compared to the use of loop diuretics alone [16,21]. Tolvaptan does not adversely affect renal function nor does it cause neurohormonal activation [22]. Acute hemodynamic effects are minimal [23]. In theory, therefore, tolvaptan should lead to a sustained decongestive benefit without some of the adverse effects of furosemide.

Clinical trials using tolvaptan as adjunctive therapy to furosemide have shown incremental weight loss and better relief of dyspnea with no prejudice to renal function [21]. Outcomes, however, were not improved in the EVEREST trial [24], either in the short or long term despite the early benefits. This is the only trial with sufficient power to address the question of outcomes. This may represent just another failure of short-term responses to predict long-term outcomes. However, all of the current AHF trials with tolvaptan have also used large doses of furosemide or similar agents. If, in fact, loop diuretics themselves might be contributing to renal dysfunction, neurohormonal activation, and poor outcome, then we have not fully tested the potential impact of using as the primary decongestive therapy an agent that is not associated with either renal dysfunction or neurohormonal activation. A trial