Editorial

The Failing Heart and the Hemodynamic Response to Vasodilator Therapy

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Clinicians grapple daily with the problem of multiple different endpoints in the evaluation of heart failure therapy: New York Heart Association class, exercise capacity, neurohormonal activity, B-type peptide levels, and survival all offer parameters to assess our interventions.¹ Compounding the difficulty of assessing these multiple measures, the responses of different parameters to various interventions are not consistent. Hydralazine and isosorbide dinitrate, for example, improve both exercise tolerance and ejection fraction more effectively than angiotensin-converting enzyme inhibitors (ACEIs). However, ACEIs significantly enhance short- and intermediate-term survival.² Similarly, drugs with positive inotropic properties quickly improve symptoms but have uniformly shown adverse effects on survival.³

When managing patients with decompensated heart failure in the hospital setting, the lack of data from prospective randomized clinical trials and the lack of consensus regarding evidence-based guidelines have further compounded these endpoint problems.

In the available clinical trials evaluating management of acutely decompensated heart failure, hemodynamic parameters are the favored endpoints. With Stevenson's studies using nitroprusside^{4,5} and a series of recent trials using nesiritide,^{6–8} culminating in the recent publication of the VMAC (Vasodilation in the Management of Acute Congestive heart failure) trial data,⁹ cardiologists now have abundant data reflecting the hemodynamic responses of patients with heart failure to three widely used parenteral vasodilator drugs: nitroprusside, nitroglycerin, and nesiritide. Although the drugs have profound clinical and pharmacologic differences, the uniformity of the hemodynamic responses justifies the use of the term "the vasodilator response" to describe the findings when these drugs are used in decompensated heart failure.

In short, the hemodynamic data confirm that right and left atrial pressures decline promptly with a moderate increase in measured forward cardiac output and little or no change in stroke volume (Fig. 1). Weiland *et al.*¹⁰ and others⁴ have convincingly demonstrated that redistribution of mitral regurgitant flow in response to systemic vasodilation is the primary mechanism for this response. Other beneficial effects may include improvement in subendocardial blood flow as left ventricular diastolic pressure falls, as well as a direct improvement in myocardial mechanics due to reduced wall tension. The critical variables in determining the clinical response to vasodilator therapy with left ventricular systolic dysfunction and mitral regurgitation are the systemic vascular resistance, the severity of mitral regurgitation, and the degree of left ventricular dysfunction. Unfortunately, the interplay of these dynamic factors is difficult to quantitate.

Recognizing the phenomenon of the vasodilator response, clinicians who care for patients with failing hearts can begin to impose some order on what has previously been a chaotic, inconsistent set of therapeutic options. Clearly, vasodilators offer a generally effective and more benign form of parenteral support for decompensated heart failure than inotropes. As Poole-Wilson³ pointed out in his editorial comments accompanying the publication of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of chronic heart failure (OPTIME)¹¹ and VMAC⁹ trials, the weight of current evidence supports the hypothesis that drugs acting to increase intracellular cyclic adenosine monophosphate in the myocardium are associated with adverse long-term outcomes, most prominently, increased mortality. Diuretics alone in this setting stimulate rather than suppress the neurohormonal response to heart failure¹² and do not constitute adequate therapy. Vasodilator therapy, then, is likely to become "first line" therapy to stabilize promptly decompensated patients with heart failure who require hospitalization. The choice of effective agents will depend on the anticipated duration of therapy, the setting of in-patient care, and the need for invasive monitoring. The VMAC data⁹ convincingly show nitroglycerin tachyphylaxis beginning within 1 to 2 h after initiating therapy, after an initial favorable response. Nesiritide offers simplicity of administration, a predictable hemodynamic response without the need for invasive monitoring, a favorable neurohumoral response at the recommended dose, and no tachyphylaxis.⁹ Nitroprusside offers the advantage of exquisitely sensitive dose titration for critically ill patients,

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	Pre		Post
SVR	Elevated	————→	Normal
PCW	Elevated	————→	Lower
CO (measured)	Low	————→	Increased
Stroke volume	Low	————→	No change
MR volume	High	————→	Decreased

FIG. 1 Heart failure due to systolic dysfunction. The hemodynamics of “the vasodilator response.” SVR = systemic vascular resistance, PCW = pulmonary capillary wedge, CO = cardiac output, MR = mitral regurgitation.

but requires invasive monitoring and skilled nursing in an intensive care setting.

The choice to employ positive inotropic agents, given the data available today, will involve a conscious decision to trade long-term outcome for short-term benefit. This may, indeed, be an appropriate choice in some individuals with chronic refractory heart failure. However, given the demonstrated effectiveness of vasodilator therapy, most of our patients with recurrent episodes of cardiac decompensation will benefit from “the vasodilator response” to one of these highly effective drugs.

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