Vasodilator Therapy in Cardiac Failure
What Was New Is Old

The paper by Mullens et al. (1) and editorial comment by Yancy (2) draw attention to use of vasodilators in treatment of acute and chronic refractory cardiac failure. The importance of left ventricular (LV) afterload is stressed, but this is described only in terms of peripheral resistance as the ratio of mean arterial pressure and cardiac output, with the latter requiring and justifying right heart catheterization. There is a problem with this approach over and above the risks of Swan-Ganz catheter use; peripheral resistance is only part of LV afterload, which is best expressed as aortic input impedance (3,4). In addition to peripheral resistance, impedance also considers aortic stiffness and wave reflection, and the effects of vasodilator drugs on these (3–5). In the recent articles, brachial systolic pressure is taken as an index of LV afterload, but this is considerably higher than aortic and LV systolic pressure, especially in patients with cardiac failure and during use of vasodilators (4–6). Vascular impedance in cardiac failure during use of vasodilator drugs is not mentioned in either article, but has been described in major journals over the past 3 decades, and forms the basis for modern treatment of this condition (3,4). Central aortic pressure also can be estimated accurately through noninvasive methods (4,6), as can indices of arterial stiffness and wave reflection (4,5).

Persons wishing to apply the principles described by Mullens et al. (1) and Yancy (2) are advised to consider these issues. They can measure LV afterload better, and avoid invasive catheterization completely. They can also obtain a more accurate measure of mean arterial pressure from integration of the arterial pressure waveform using applanation tonometry, rather than estimating this from the inaccurate formula of diastolic + one-third pulse pressure (4).

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Please note: Dr. O’Rourke is a founding director of ArCor Medical Pty Limited, manufacturer of systems for analyzing the arterial pulse.

REFERENCES

Reply

We thank Drs. O’Rourke and Nichols for their enthusiastic interest and insightful comments regarding our report on the potential benefits of sodium nitroprusside (SNP) in the setting of advanced decompensated heart failure (ADHF) (1). We are in complete agreement regarding the many factors that influence left ventricular (LV) afterload, including the concept that aortic impedance can be a more integrated measure of LV afterload. We would like to emphasize that throughout the article there had not been any assertion or assumptions that measuring systemic vascular resistance in ADHF better reflects LV afterload compared with aortic input impedance. It is also not the intention of our retrospective case series to compare the effectiveness or safety of administration of SNP guided by a reduction in vascular resistance or aortic input impedance. In fact, titration of SNP doses was based on achieving a measured target mean arterial blood pressure of 65 to 70 mm Hg and not on achieving a normal derived systemic vascular resistance. Nevertheless, even with this relatively crude method in the absence of specialized equipment, the substantial improvement in cardiac output secondary to sodium nitroprusside therapy was associated with more favorable (rather than adverse) long-term outcomes. Although invasive measurements were used in our protocol, it is not the intention of these data to always imply the need for invasive monitoring, but solely to understand the hemodynamic contributors and subsequent changes induced by sodium nitroprusside during the treatment of ADHF. As with interpreting the clinical utility of any biomarker, there is an important distinction between identifying individual patients who may have the appropriate hemodynamic profiles to benefit from a specific intervention versus using specific indexes of LV afterload as targets of therapeutic interventions. We agree that much promise exists regarding the use of noninvasive hemodynamic monitoring. Nevertheless, in much the same way that pharmaco-therapeutics require rigorous placebo-controlled testing in the specific population with the specific treatment goals to be certain of benefit, diagnostic tools intended to guide therapy may require the same validation, especially regarding use in the acutely ill heart failure population.
The letter by Drs. O’Rourke and Nichols appropriately addresses alternative modalities for assessing aortic impedance (a component of left ventricular afterload), and importantly expands on our earlier discussion regarding the measurement of peripheral resistance and incorporating the use of those measurements in the treatment of advanced decompensated heart failure. The paper by Mullens et al. (1) and accompanying editorial comment (2) do not exclude other monitoring modalities, but rather address what is practically available and importantly highlight the potential benefit of vasodilator therapy and emphasize the need to consider decompensated heart failure as a disease entity driven not only by congestion but also by altered ventricular loading conditions. There is reasonable hesitancy to the full embrace of the use of nitroprusside if indeed that use requires invasive hemodynamic monitoring. Not only does invasive hemodynamic monitoring seem to be necessary, but also skill in caring for such catheters in an intensive care unit setting and skill in interpreting the data are required. Titrating the vasodilator dose to hemodynamics is yet another unique skill set required to use nitroprusside successfully in this clinical scenario.

A noninvasive strategy that addresses one of several components of left ventricular afterload, be it aortic impedance, brachial/radial arterial resistance, or transthoracic bioimpedance, would be preferable. The dilemma is that use of those noninvasive strategies in an intensive care unit setting for patients with advanced decompensated heart failure cannot be assumed to be accurate and reproducible without undergoing prospective testing. The test should be proven to be reliable, reproducible, and accurate when compared with a known conventional hemodynamic parameter. Utility of certain modalities in the realm of hypertension is not sufficient to verify utility in the setting of heart failure, especially when aortic flow characteristics and tissue factors related to impedance may be strikingly different. As well, if the noninvasive strategy introduces a new metric, the ability to titrate therapy according to that metric should be proven.

It is agreed that any evidence-based beneficial measurement of peripheral resistance that obviates the need for right heart catheterization would be preferable as greater use of vasodilator therapy seems warranted in the setting of advanced decompensated heart failure.

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**Caloric Restriction Models Reverse Metabolic Syndrome**

The major metabolic effects of substantial weight loss in obese patients with type 2 diabetes mellitus (1) provide a novel insight into the mechanisms postulated to underlie the metabolic syndrome. The diagnosis of metabolic syndrome requires the presence of 3 of 5 characteristics: increased abdominal waist, hyperglycemia, high blood triglycerides, high blood pressure, and low high-density lipoprotein (HDL) cholesterol. To tie these apparently disparate manifestations together, an interesting hypothesis is that the crucial initial event is the increased concentrations of circulating free fatty acids (FFAs) and cytokines derived from the excess visceral abdominal fat (2). Although there are well-established links whereby increased circulating FFAs decrease the uptake of glucose by heart (3) and skeletal muscle (4), it has been much more difficult to link chronically increased circulating FFAs to increased blood triglycerides and decreased HDL cholesterol in humans.

The data of Hammer et al. (1) lead to the novel concept of the “reverse metabolic syndrome,” which can link excess circulating FFAs to the other metabolic changes in humans. Substantial weight loss in obese patients with type 2 diabetes led to decreased waist measurement (Fig. 1 of Hammer et al. [1]), decreased circulating concentrations of glucose and triglycerides (and, hence, by inference, increased HDL cholesterol), and decreased concentrations of the adverse cytokine, leptin. Another example of reversed metabolic syndrome is the acute inhibition of lipolysis by acipimox, which abruptly reduced circulating FFAs in obese patients with type 2 diabetes, with rapid falls in plasma glucose and insulin, and decreases in muscle content of long-chain fatty acid (as derivatives) (5). Furthermore, Hammer et al. (1) showed that as plasma FFAs decrease, so do myocardial triglycerides. Conversely, chronically increased circulating FFAs, when taken up by the heart, form excess myocardial triglycerides (6), the basis of the diastolic dysfunction that can extend to lipotoxic cardiomyopathy, described in humans by Taegtmeyer’s group (6,7). These novel concepts add a potentially new dimension to the adverse effects of excessively high blood FFAs in metabolic syndrome.

Overall, the study by Hammer et al. (1) shows that unloading the human body of adipose tissue induces a “reverse metabolic syndrome.” This study provides additional data to support the concept that excess circulating FFA, as associated with abdominal visceral obesity, is fundamental in the genesis of an increasingly common human disease, namely, metabolic syndrome.