VIEWPOINT

Acute Heart Failure Syndromes and Coronary Perfusion

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Acute heart failure syndromes (AHFS), with a high post-discharge mortality and rehospitalization rate, represent a significant public health burden. The treatment of patients hospitalized with AHFS often includes the use of vasoactive medications such as inotropes and vasodilators. Although such agents are frequently used, their safety and efficacy remain controversial. A significant number of patients with heart failure have underlying coronary artery disease and may be at greater risk from hemodynamic alterations that can diminish coronary perfusion. In AHFS, the relationship among vasoactive medications, coronary perfusion, and potential myocardial injury needs further investigation. Newer techniques now available to evaluate coronary perfusion should provide guidance for the evaluation of existing and future vasoactive therapies for AHFS. (J Am Coll Cardiol 2008;52: 13–6) © 2008 by the American College of Cardiology Foundation

Acute heart failure syndromes (AHFS) can be defined as a rapid or gradual change in heart failure signs and symptoms that necessitates urgent therapy (1). In spite of the apparent initial improvement with in-hospital therapies, the post-discharge event rates (mortality and rehospitalization) can be as high as 30% to 50% (2). The available data suggest that vasoactive agents given for less than 24 to 48 h may increase post-discharge mortality, particularly in patients with coronary artery disease (CAD) who develop drug-related hypotension (3,4). This may be due in part to a decrease in coronary perfusion leading to myocardial injury. The assessment of coronary perfusion, however, has to date not been included in the evaluation of vasoactive drug therapies for AHFS.

Background

Pathophysiology of AHFS and myocardial injury. The pathophysiology of AHFS is complex. Coronary artery disease is the most significant disease state in patients with AHFS (5), and these patients have a worse prognosis than patients with nonischemic etiologies (6). The CHRISTMAS (Carvedilol Hibernation Reversible Ischaemia Trial) reported that 60% of patients with heart failure and CAD had hibernating myocardium (7). Hibernating

myocardium is at risk for injury when confronted with the hemodynamic alterations seen in patients with AHFS. These changes include increased left ventricular filling pressures, hypotension, and increased contractility in response to vasoactive medications (8). These changes, together with further neurohormonal activation, result in worsening endothelial dysfunction and may create a "perfect storm" of myocardial injury (1).

Schulz et al. (9) demonstrated in an experimental model that increasing myocardial contractility in hibernating myocardium by a brief infusion of low-dose dobutamine can lead to myocardial necrosis. Additionally, in the PRESERVD-HF (Pilot Randomized Study of Nesiritide Versus Dobutamine in Heart Failure) trial, the majority of patients presenting with AHFS and a history of CAD (in whom acute coronary syndrome was not suspected clinically) had a troponin release suggesting myocardial injury (10).

The OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study randomized patients admitted with AHFS and reduced left ventricular ejection fraction to placebo or milrinone. The 48-h infusion of milrinone was associated with a 35% increase in post-discharge mortality in patients with CAD who developed infusion-related hypotension (3). It can be postulated that a decrease in blood pressure and coronary perfusion secondary to milrinone contributed to increased mortality as a result of myocardial injury.

In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effective-

ness) trial, short-term therapy with inotropes, but not vasodilators, was associated with an increased post-discharge mortality rate (11). The results of ES-CAPE are particularly pertinent, as this trial enrolled high-risk patients, who are often considered to benefit the most from vasoactive therapies.

Vasoactive medications and coronary perfusion in AHFS. Maintenance of coronary perfusion may play an important role in preventing myocardial injury in AHFS (8). Coronary perfusion is dependent on both epicardial coronary artery blood flow and microvascular flow. Under normal physiological conditions, coronary perfusion pressure and coronary vasoactive tone act in concert to optimize coronary blood flow and achieve a supply-demand balance (autoregulation) (12). In AHFS and CAD, autoregulation may become exhausted, with coronary blood flow becoming totally dependent on systemic pressure.

Vasoactive medications that are known to affect cardiac function, such as nitroprusside, nesiritide, dobutamine, dopamine, and milrinone, may cause a supply-demand mismatch by increasing contractility and/or heart rate while simultaneously decreasing blood pressure. The resultant decrease in coronary perfusion may lead to myocardial injury. This may explain why the short-term use of these medications in AHFS, particularly in patients with CAD, can temporarily improve hemodynamics and symptoms while increasing post-discharge mortality (13).

Because these therapies have the potential to cause harm, it is imperative to use them in a manner that leads to improved hemodynamics without causing myocardial injury (14). An improved understanding of the degree to which current and future heart failure therapies affect coronary perfusion may help differentiate protective strategies from detrimental ones. Until now, however, accurate and reproducible techniques for assessing coronary perfusion (taking into account both epicardial flow and microcirculation) have been lacking.

Assessment of Coronary Perfusion

Invasive assessment of coronary perfusion. Coronary flow reserve (CFR) is one traditional method that has been used to assess coronary perfusion. It is calculated as the ratio of maximal blood velocity (during hyperemia) to resting blood velocity for a given coronary artery.

In chronic heart failure, resting coronary blood flow (measured using velocity-encoded cine magnetic resonance imaging) appears to be reduced in primary but not ischemic cardiomyopathy. Coronary flow reserve, however, is compromised irrespective of etiology (15,16). The technique of CFR is somewhat limited in that when abnormal, it is unclear whether the culprit lies in the epicardial arteries, arterioles, or capillaries (as CFR decreases with increased resistance at any level of the coronary circulation). Furthermore, CFR can be altered by changes in baseline or stress-induced flow, which are influenced by loading conditions, hemodynamics, and contractility (17). To overcome this limitation, Gould et al. (18) proposed the concept of relative CFR (rCFR), defined as the ratio of maximal flow in a coronary artery with stenosis to maximal flow in a coronary artery without stenosis (requires the interrogation of an additional coronary vessel). This technique is of limited value in patients with multivessel CAD, as there is no "normal" vessel available for comparison. Moreover, rCFR relies on the assumption that microcirculatory resistance is uniformly distributed, which is not the case in patients with a prior history of myocardial infarction, regional left ventricular dysfunction, myocardial fibrosis, or asymmetric hypertrophy (17).

To better quantify coronary perfusion at the epicardial level, Pijls et al. (19) introduced the concept of fractional flow reserve (FFR), defined as the ratio of the mean distal coronary artery pressure to the aortic pressure during maximal vasodilatation. The normal value of the index is 1.0, with the threshold for ischemia being <0.75, which correlates with ischemia detected by noninvasive stress testing. The main limitation of this technique is that it is unable to assess perfusion of the microcirculation.

With new advances in sensor guidewire technology, combined pressure (pressure sensor at tip of wire) and flow (measured by Doppler velocity or thermodilution) values can now be calculated (20,21). Thermodilution measurements can be used to calculate CFR (20). However, the same limitations that apply to traditional measurements of CFR exist with this technique as well.

Meuwissen et al. (21) improved on this technique by developing a hyperemic stenosis resistance (HSR) index, calculated as (mean aortic pressure − mean distal coronary pressure)/average peak velocity at hyperemia (Doppler velocity). This allows for the separate assessment of microvascular resistance, independent of stenoses at the epicardial level. In a fashion similar to FFR, HSR has a normal reference value (HSR = 0) and is largely independent of hemodynamic changes.

More recently, Fearon et al. (22) described the index of microcirculatory resistance (IMR) calculated by dividing distal coronary pressure by the inverse of the hyperemic mean transit time (thermodilution). The main advantage of the IMR is that it is again independent of resistance in the epicardial artery and (unlike CFR) is less affected by variations in hemodynamic parameters such as blood pressure and heart rate. Ng et al. (23) have validated the use of IMR in the cardiac catheterization laboratory. The main

difference between the HSR and IMR techniques lies in the type of wire used (Doppler wire vs. thermodilution), a decision that likely will be based on the comfort and experience of the operator.

Compared to CFR, both FFR (at the epicardial level) and HSR/IMR (microcirculation) were highly reproducible and largely independent of hemodynamic perturbations. The simultaneous measurement of FFR together with HSR or IMR is now capable of providing a simple and accurate means of assessing coronary perfusion across the entire circulatory tree.

Noninvasive assessment of coronary perfusion. Myocardial perfusion imaging with single-photon emission computed tomography (SPECT) remains the most widely used technique for the clinical evaluation of myocardial perfusion, but clinical SPECT images are scaled to the most intense area of uptake in the ventricular myocardium (24). This enables semiquantitative assessment of relative regional myocardial blood flow but does not allow quantification of absolute regional blood flow or myocardial perfusion reserve.

Coronary flow velocity can also be measured by transthoracic Doppler echocardiography at rest and during pharmacologic vasodilation to calculate CFR (25). Although this technique is usually limited to the left anterior descending coronary artery, its low cost and portability are clear advantages.

Positron emission tomography has become the preferred technique for more sensitive and accurate perfusion analysis. Quantitative measurements of myocardial flow per unit weight (i.e., ml/min/g) can be derived from perfusion imaging studies. Myocardial perfusion reserve can then be calculated from measurements obtained at rest and during hyperemic stress (26). Widespread clinical application has been slowed by limited access to positron emission tomography facilities and cyclotron-produced radiopharmaceuticals.

Absolute myocardial blood flow can also be measured by first-pass cardiac magnetic resonance perfusion imaging (27). Cardiac magnetic resonance perfusion imaging has a higher spatial resolution than nuclear perfusion techniques, allowing visualization of subendocardial perfusion abnormalities (28). This unique characteristic may be particularly advantageous for investigating AHFS because the subendocardium is the first region to be affected by perturbations in myocardial blood flow.

Another advantage of magnetic resonance imaging is that it allows for viability analysis. Patients with AHFS often harbor viable but noncontractile myocardium secondary to chronic ischemia (hibernating myocardium). As observed by Schultz et al. (9) in their animal model, infusion of dobutamine is associated with necrosis of hibernating myocardium. Cardiac viability imaging with magnetic resonance imaging provides an accurate, high-resolution method for detecting myocardial necrosis. This may be particularly valuable in evaluating inotropes

or vasodilators and monitoring for their potential detrimental effects in AHFS (29).

Future Perspectives for Coronary Perfusion Assessment

The accurate assessment of coronary perfusion remains a difficult task, mainly because of the complexities involved in the quantification of perfusion at the microvascular level. The methods described earlier by Meuwissen et al. (21) and Fearon et al. (22) represent novel techniques for the assessment of coronary microcirculation. These techniques can now be readily and easily applied in the catheterization laboratory and, when combined with additional measures such as FFR, provide accurate and reproducible information concerning the functional status of the entire coronary circulation. Future research is needed to explore the role of distal pressure and coronary flow velocity and to couple the assessment of microvascular resistance with clinical outcomes. Larger human clinical trials are needed to establish the accuracy and reproducibility of invasive IMR and HSR measurements, as well as noninvasive methodologies to assess perfusion and myocardial viability. As these methods and technologies evolve, future trials will provide clinical relevance to the assessment of coronary perfusion in patients admitted to the hospital with AHFS. Furthermore, preclinical studies must be encouraged to explore the effects of currently used drugs as well as novel drugs on coronary perfusion and on dysfunctional but viable myocardium.

Conclusions

Evaluation of coronary perfusion promises to become an important component in determining clinical outcomes in patients with AHFS. Certain vasoactive agents used routinely in heart failure therapy, although successful in improving the hemodynamic profiles of patients, have been linked to higher rates of mortality. The exact mechanisms behind these findings still need to be elucidated but may be related to myocardial injury worsened by the impact of vasoactive medications and underlying disease states such as CAD. New methods of assessing and monitoring coronary perfusion may help to clarify the pathophysiology underlying these processes, as well as to identify patients who may be at greater risk from these therapies. Given the recent advances and improved techniques (both invasive and noninvasive) for the evaluation of coronary perfusion, this information should now begin to be used as part of the assessment of existing heart failure medications, as well as for the development of novel therapies in the future.

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