

Should we be screening for myocardial hibernation in heart failure?

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Heart failure is an emerging epidemic afflicting all established market economies.¹ In the United States, there are an estimated 400,000 new cases of heart failure each year. At the same time, the prevalence of heart failure is only approximately 2%. This reflects the high mortality rate associated with heart failure; around 50% of those diagnosed with heart failure will be dead by 5 years. The economic costs of heart failure are also substantial. Although the direct cost of heart failure in most European countries is only 1% to 2% of all health care expenditure, the indirect costs are likely to be much greater.

Two key reasons underlie the emergence of this trend. First, the population in the established market economies is aging. Second, the majority of cases of heart failure (approximately 60%) are attributable to ischemic heart disease.² As the immediate mortality rate from acute myocardial infarction falls, the survivors become ever more likely to have heart failure develop.

Before the 1960s, the accepted wisdom was that loss of myocardial contractility after myocardial infarction was irreversible. In the 1960s, when coronary artery bypass grafting (CABG) developed into an accepted treatment, clinical observations by surgeons showed that this was not so.³ In some (but not all) individuals, the function of even akinetic myocardium could be restored by revascularization. However, at the time, there was no apparent way of distinguishing those who benefited from revascularization from those who did not.

In 1974 Horn et al⁴ showed that in patients with chronic coronary artery disease and asynergy, inotropic stimulation with epinephrine could induce transient improvements in contractile function in akinetic myocardium. This was the first means of identifying functionally dormant but still viable myocardium. By 1978, Diamond

et al⁵ were able to coin the term *myocardial hibernation*, a term that was later popularized by Rahimtoola⁶ in the 1980s.

However, even now, nearly 3 decades later, there are still many unresolved questions surrounding the mechanisms of hibernation, as well as important clinical questions that need to be answered. In particular, can imaging tests be used to identify hibernating myocardium and optimize treatment for ischemic heart failure?

THE CHRISTMAS TRIAL: MEDICAL THERAPY FOR HEART FAILURE

The recently published CHRISTMAS trial (Carvedilol Hibernation Reversible Ischaemia Trial) is unique in examining the interaction between hibernating myocardium and β -blocker treatment.⁷ As such, we will describe this trial in some detail.

CHRISTMAS was a multinational trial involving 38 centers from 6 countries.⁷ Three hundred eighty-seven patients with stable chronic heart failure were enrolled. Only patients with proven coronary artery disease were eligible. Left ventricular (LV) systolic dysfunction was defined by an echocardiographic wall motion index of 1.3 or less in a 9-segment model.

In each patient, hibernation was identified by a mismatch between echocardiographic regional wall motion and nitrate-enhanced technetium 99m sestamibi perfusion (a method previously shown to be superior to non-nitrate-enhanced Tc-99m sestamibi imaging in predicting functional recovery after revascularization). Such a method is attractive because, compared with positron emission tomography and stress echocardiography, it is more widely available to the general medical community.

Ninety percent of participants were white men. The mean age was 62 years. All patients were in New York Heart Association class I to III; the majority (60%) were in class II. Sixty percent did not report having any angina at any time, though all were believed to have ischemic heart failure.

All patients were then randomized to either β -blocker therapy (carvedilol) or placebo. Carvedilol was the chosen β -blocker, having previously been shown by the US Carvedilol Program to reduce the total

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mortality rate from 7.8% to 3.2% and the sudden death mortality rate from 3.8% to 1.7%.

The primary endpoint of the CHRISTMAS trial was an improvement in LV ejection fraction, measured by radionuclide ventriculography, in hibernators versus hibernators and in those taking carvedilol versus those who were not.

The first key finding from the CHRISTMAS trial was the very high prevalence of hibernation in the general population, irrespective of the presence or absence of angina. The core laboratory identified 59% as hibernators. The estimated proportion of total myocardial mass affected by hibernation was approximately 30%, and in nearly one fifth, the proportion was greater than 44%. Similar findings have been reported from other studies.⁸ This conclusion is consistent with, and implicit in, previous studies showing that revascularization can lead to remarkable improvements in LV ejection fraction.

The second key finding from the CHRISTMAS trial was the relationship between hibernation and improvement in LV ejection fraction with carvedilol treatment. No significant change in LV ejection fraction was found between hibernators and nonhibernators in the mean increase in LV ejection fraction in response to carvedilol (3.6% vs 3.2%, respectively; $P = .644$). However, there was a striking and highly statistically significant linear trend between quantity of hibernating or ischemic myocardium and improvement in LV ejection fraction. In the absence of hibernation, no increase in LV ejection fraction was found, whereas in those with 5 or more segments affected, an absolute increase in LV ejection fraction of 7% was observed. This may explain why improvements in symptoms and LV ejection fraction are unpredictable when patients with ischemic heart failure start taking β -blockers. In comparison, improvement is much more uniform when β -blockers are used to treat nonischemic dilated cardiomyopathy. According to this view, the quantity of hibernating myocardium governs the response to treatment (measured by improvement in LV ejection fraction). Conversely, it may also be hypothesized that response to β -blockade implies significant salvageable underlying myocardial substrate. This finding is intriguing, as it implies that those who respond best to β -blocker therapy may also be the patients who respond best to revascularization.

CHRISTMAS did not demonstrate an improved mortality rate in the carvedilol-treated group, although this was not surprising because the trial was not adequately powered to do so.

Although CHRISTMAS has important implications for our understanding of ischemic heart failure, its results are unlikely to directly change current clinical practice. It suggests that the quantity of hibernating myocardium is

important in mediating the improvement in ejection fraction after β -blocker treatment. However, even patients with no hibernating myocardium should be commenced on β -blocker therapy, because β -blockers are likely to have effects beyond improvement in LV function, such as suppression of lethal ventricular tachyarrhythmias.

REVASCULARIZATION FOR HEART FAILURE

In contrast to CHRISTMAS, which examined the interaction between myocardial hibernation and medical therapy, there are many trials examining the interaction between myocardial hibernation and revascularization. The most comprehensive review is the meta-analysis by Allman et al,⁹ which summarizes 24 trials performed between 1966 and August 1999. Among them, these trials encompassed all of the clinically available techniques for identifying hibernation.

Three thousand eighty-eight patients were included in the meta-analysis. The mean ejection fraction was $32\% \pm 8\%$. In patients with viability, revascularization was associated with a striking 80% reduction in the annual mortality rate (from 16% to 3.2%) compared with medical treatment alone. The benefit observed was directly related to the severity of LV dysfunction, but in the absence of viability, no benefit of revascularization was found at any level of ejection fraction.

The meta-analysis did not include the quantitative relationship between extent of myocardial viability/hibernation and improved outcome after revascularization. However, individual studies have attempted to address this issue. Most studies suggest that between one third to one half of total myocardial mass needs to be affected before a survival benefit from revascularization is seen.¹⁰

In interpreting these data, it is important to note that since the meta-analysis was conducted, medical therapy has advanced. For example, in addition to angiotensin-converting enzyme inhibitors, spironolactone and β -blockers have been shown to be effective for heart failure. In the RALES trial (Randomized Aldactone Evaluation Study), published in 1999, there was a 30% reduction in mortality rate.¹¹ In 1996 the US Carvedilol Program results first clearly showed the benefit of β -blocker therapy, a finding that was subsequently confirmed by the CIBIS-II (Cardiac Insufficiency Bisoprolol Study II)¹² and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure) trials.¹³ These were published in 1999 and 2000, respectively, and both demonstrated a reduction of 30% to 35% in the mortality rate.

As neither spironolactone nor β -blockers were widely used for the treatment of heart failure before 1999, this still leaves open the question of whether

revascularization is superior to current best medical therapy. Individually, the drug treatments produce a less dramatic reduction in mortality rate than revascularization, but together, the difference may be significantly diminished. Furthermore, CABG in the presence of severe heart failure is still a risky business; in-hospital mortality rate figures as high as 8% have been reported even in the mid 1990s.¹⁴ These figures may well underestimate the true mortality rate, as selection bias is highly likely.

A further intriguing observation comes from a study by Brown et al.¹⁵ This study showed (unsurprisingly) that the extent of scintigraphic perfusion defect predicted the annual cardiac event rate after myocardial infarction. However, unusually, reversible perfusion defects were also associated with higher annual cardiac event rates than fixed defects of similar size. Several explanations are possible. Patients with fixed defects may simply have a higher early mortality rate and are "selected out" accordingly. The more interesting alternative explanation is that reversibly ischemic and possibly hibernating myocardium may be an unstable substrate promoting sudden cardiac death or infarction, another reason supporting screening for myocardial viability.

THE UK HEART TRIAL AND THE US STICH TRIAL

These unresolved issues have provided the impetus for a new trial that is currently recruiting in the United Kingdom. In the UK HEART trial (Heart failure Revascularisation Trial),¹⁶ 800 patients with ischemic heart failure will be randomized to either best medical therapy or best medical therapy plus revascularization (which may be accomplished by surgical or percutaneous methods). Before treatment, the extent of myocardial viability will first be ascertained (by any recognized technique).

In fact, a recent observational study of 10,627 patients with suspected coronary artery disease (but not necessarily heart failure) has suggested that the overall survival rate of patients treated medically was greater than that of those who underwent revascularization.¹⁷ However, if the percentage of myocardium that was ischemic was taken into account, this was no longer the case. Provided the proportion of myocardium that was ischemic exceeded 12.5% (as determined by myocardial perfusion imaging), revascularization was superior to medical therapy. It may be that UK HEART will report findings of a similar nature, the crucial question being what extent of myocardial viability is necessary before revascularization becomes superior to best medical therapy.

The results of UK HEART may well have implications for other areas for cardiology. For example, the Multicenter Automatic Defibrillator Implantation Tri-

al-II trial (MADIT-II) showed that implantable cardioversion-defibrillators are effective in preventing arrhythmic death in patients with impaired LV function (LV ejection fraction <35%).¹⁸ However, cardioversion-defibrillator therapy is enormously expensive. Would the money be better spent in a search for myocardial viability and revascularization?

Thus far, UK HEART has been slow to recruit. This may be due in part to reluctance on the part of clinicians to randomize patients with more severe grades of heart failure but much myocardial viability. This is a serious flaw that may compromise the integrity of the study by introducing selection bias. There is frequently a perceived lack of " equipoise " between medical therapy and revascularization when imaging tests show the presence of myocardial viability; whether this is justified depends on interpretation of the data presented earlier.

A similar trial is recruiting in the United States and elsewhere. The STICH (Surgical Treatment for Ischemic Heart Failure) trial plans to enroll 2,800 patients with coronary artery disease and LV ejection fraction of 35% or less. Patients will be placed in 3 subgroups, or strata, based on presenting information. Stratum A (n = 1,600) includes patients without severe regional dysfunction who will be randomized to CABG versus medical therapy. Stratum B (n = 600) includes patients with severe regional dysfunction who are candidates for surgical ventricular restoration (SVR); this group will be randomized to medical therapy versus CABG versus CABG plus SVR. Stratum C (n = 600) includes patients who are candidates for SVR because of severe regional dysfunction but who also have angina, in whom medical therapy is not an option; these patients will be randomized to CABG versus CABG plus SVR. Viability testing with single photon emission computed tomography is mandatory in all patients in strata A and B (n = 2,200), and so viability information will be available for all patients in the arms in which surgery is compared with medical therapy. The preferred viability protocol for STICH is rest-redistribution thallium imaging or nitrate-enhanced sestamibi imaging. Viability information may also be available for some patients in stratum C but is not mandatory. Unlike the UK HEART trial, revascularization by means of percutaneous coronary intervention (PCI) is not an option.

CONCLUSION

To summarize, myocardium can exist in a functionally dormant but still viable state. The CHRISTMAS trial showed that the quantity of viable myocardium is likely to govern response to medical therapy (β -blockers). Many other trials have suggested that myocardial viability is likely to be an important determinant of response to

surgical revascularization. Furthermore, an important meta-analysis by Allman et al⁹ suggests that revascularization is preferable to medical therapy when there is significant myocardial viability. However, the majority of these studies predate the landmark trials of β -blocker and spironolactone therapy, leaving some uncertainty about the superiority of revascularization over best medical therapy. The emergence of techniques able to not only reliably identify but also quantify myocardial viability is likely to become increasingly important, as this appears to be the most promising means of allowing revascularization to be targeted to those most likely to benefit, without risking those with little to gain. The UK HEART and US STICH trials, when complete, will be invaluable in this respect.

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