

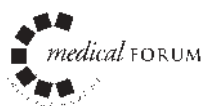
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Aims and Scope

Heart and Metabolism is a quarterly
 journal focusing on the management
 of myocardial ischaemia. Its aim is
 to inform cardiologists and other
 specialists about the newest findings
 of the role of metabolism in cardiac
 disease and to create awareness of
 its potential clinical implications.
 The management of patients with
 angina, as well as those with heart
 failure and hypertrophic or dilated
 cardiomyopathy, will also be dis-
 cussed. Moreover, the effects of
 metabolic diseases such as diabetes
 mellitus on the heart will be high-
 lighted. Each issue will include an
 editorial, followed by articles on a
 key topic. Experts in the field will
 explain the metabolic consequences
 of cardiac disease and the multiple
 potential targets for pharmacothe-
 rapy in ischaemic and non-ischaemic
 heart disease.

*The cover photographs show short axis slices of
 the left ventricle using PET scan. (Left) Normal to
 mildly reduced ¹³N-ammonia uptake in the ante-
 rior wall and absent perfusion in the posterior
 wall. (Right) Increased FDG uptake in the anterior
 wall suggestive of hibernating myocardium, and
 absent uptake in the posterior wall suggestive of
 necrosis. See article on page 12.*

Systolic heart failure



Dr Graham Jackson

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When buying or selling a property, the agent always emphasizes 'location, location, location'. Cardiologists approaching heart failure would do well to begin with 'prevention, prevention, prevention'. The prognosis for the patient with heart failure is poor, but it worsens alarmingly with deteriorating left ventricular systolic function, so that the mortality rate may be as high as 60% at 1 year for New York Heart Association (NYHA) class III/IV heart failure (Table 1).¹ Prevention is therefore paramount — preventing left ventricular dysfunction occurring and preventing it worsening once it has developed.

We are all aware that modern treatments have improved survival and reduced morbidity, but we are probably seduced into a false sense of security by benefits being presented as relative rather than absolute differences. For example, a relative reduction in events of 30% sounds more convincing than an absolute change of say 5–7%. As we treat our heart failure patients we need to keep a sense of perspective: the presentation of current benefits may disguise continuing problems of increasing morbidity and mortality over time. Whilst we need to be critical of the evidence, we also need to embrace the positive aspects so that we can offer currently established optimal care

while continuing to seek further improvements. Both the neurohormonal compensatory but counterproductive overactivation of the renin-angiotensin system and the sympathetic nervous system have formed the basis for intervention to improve the long-term outcome for systolic heart failure patients.²

The angiotensin-converting enzyme (ACE) inhibitors attack one part of the neurohormonal basis of systolic heart failure and their use has led to significant improvements in both morbidity and mortality. The Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS) was the breakthrough study.³ Enalapril was compared with placebo in addition to conventional digoxin and diuretics in patients with severe heart failure (NYHA IV). In doses of up to 40 mg daily, enalapril reduced mortality from 52% in the placebo group to 36%, and the symptoms and signs of heart failure also improved. Presented as a 27% reduction in mortality, we could be forgiven for overlooking the high residual 36% death rate in spite of ACE inhibition. It is also important to note the high doses of enalapril used in this study because of the dose-related benefits demonstrated in the ATLAS study using lisinopril.⁴

Recently, in similarly severe cases, spironolactone was compared with placebo and

Table 1. Classification of heart failure (NYHA).

	Definition	Disability	Prognosis
Class I	No limitation of physical exercise	No symptoms on ordinary activity	Poor
Class II	Slight limitation of physical activity	Symptoms on ordinary activity	Bad
Class III	Marked limitation of physical activity	Symptoms on less than ordinary activity	Awful
Class IV	Inability to carry out any physical activity without discomfort	Symptoms at rest	Terminal

added to conventional therapy including ACE inhibitors.⁵ The spironolactone group reported a reduction in all-cause mortality from 46 to 35% with a significant reduction in morbidity. The interesting similar residual mortality to that in the enalapril group in the CONSENSUS Trial was attributed to a beneficial effect of spironolactone whereas the possibility of suboptimal doses of ACE inhibitors influencing the result was not considered (mean daily doses of captopril 63.4 mg, enalapril 13.5 mg, lisinopril 15.5 mg). This begs the question as to whether angiotensin II antagonists, by having a more complete and selective endpoint inhibition of the angiotensin II receptor, will offer or improve on the combined benefit of spironolactone and ACE inhibition; with a

residual mortality of 35% we clearly need to make further progress.

Preventing the progression of left ventricular dysfunction by early intervention at the time of acute myocardial infarction in patients with clinical heart failure using ramipril in comparison with placebo reduced 15-month mortality from 23 to 17% (relative risk reduction 27%).⁷ In the Survival and Ventricular Enlargement (SAVE) Study,⁸ postinfarction patients who were asymptomatic but with an ejection fraction of less than 40% were treated with high-dose captopril (up to 50 mg t.i.d.) or placebo. Captopril reduced the all-cause mortality at 42 months from 24.6 to 20.4% (relative risk reduction of 19%). These two studies have led to the recommendation that ACE inhibitors be adopted

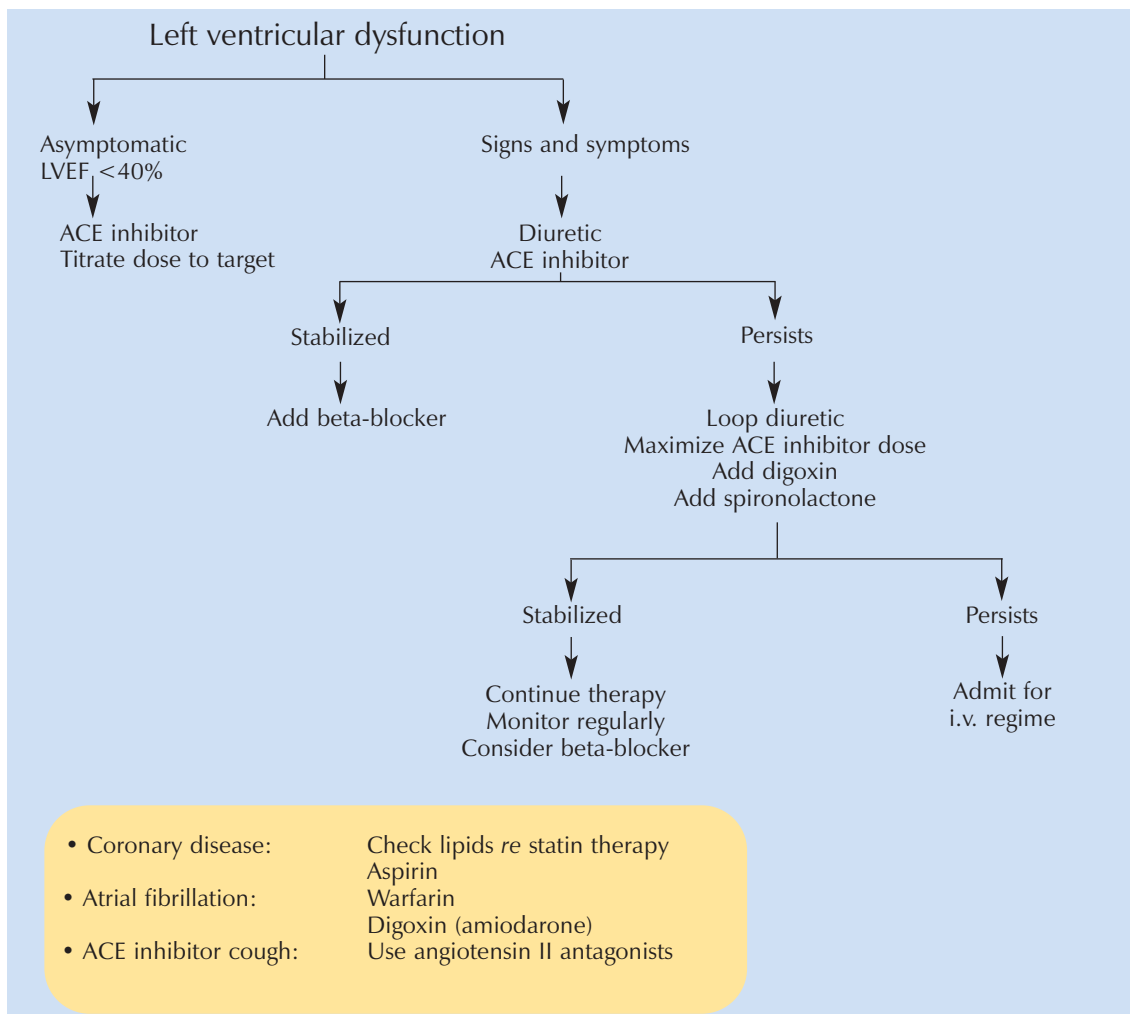


Figure 1. A checklist for management of left ventricular dysfunction. LVEF, left ventricular ejection fraction.

as standard therapy when there is evidence of left ventricular dysfunction (symptomatic or not) following myocardial infarction. By using ACE inhibitors early, prior to the development of class III/IV failure, we have one means of reducing the grim morbidity and mortality of severe heart failure.

Beta-blockade may be another means.⁹ Once more in common with ACE inhibition, beta-blockers attack one aspect of the neuro-hormonal pathophysiology of heart failure. Patients who were clinically stable (and in general not NYHA IV) with left ventricular systolic dysfunction and established on standard therapy were randomized to carvedilol, bisoprolol, metoprolol or placebo in separate studies. The MERIT-HF Trial¹⁰ of metoprolol is the largest study and included NYHA II-IV patients, although one has to be cautious when interpreting 'stable class IV' patients. The trial was stopped early because of a reduction in overall annual mortality from 11.0 to 7.2% (relative risk reduction 34%) in the metoprolol group — figures similar to those in a meta-analysis of beta-blocker studies which demonstrated a 9.7–7.5% mortality reduction (relative risk reduction 31%).¹¹ By 18 months, cumulative mortality was approximately 16% on placebo and 11% on metoprolol. The curves, as in all heart failure studies, showed a relentless progression in the incidence of sudden death, worsening heart failure, cardiovascular and overall mortality, though the pharmacological benefit was sustained.

The curves should, however, remind us that life itself is a kind of dose-response curve with an inevitable endpoint. The 10-year follow-up of the CONSENSUS Trial¹² of 253 patients identified only five long-term survivors, all of whom had been in the enalapril group. Thus the long-term prognosis remained poor although ACE inhibition prolonged survival by 50% to 781 days from 521 days.

New avenues are needed. More vigorous control of diabetes and hypertension should not be forgotten and some evidence exists for the preventative role of lipid-lowering therapy. The metabolic aspects of heart failure and their modification have not been explored to the same degree as the neurohormonal aspects. There is no room for complacency or

comfort from reassuring relative risk benefits. We can optimize our use of diuretics, ACE inhibitors, digoxin and beta-blockers and hope that further studies of newer agents will reduce the burden of heart failure. In the meantime we can construct a management checklist to allow us to optimize the evidence-base we have to date (*Figure 1*). ■

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Beta-blockers in congestive heart failure

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It has been known for almost 20 years that beta-blockers improve survival as secondary prevention after acute myocardial infarction and in hypertension.¹⁻⁴ *Post hoc* analyses have shown that patients with either large infarcts and compromised left ventricular function or with clinical signs of congestive heart failure during the acute stage of disease are those who benefit most from secondary prevention with beta-blockers.^{5,6}

Our first uncontrolled studies with beta-blockers in dilated cardiomyopathy suggested a very positive effect on both symptoms and left ventricular systolic and diastolic function.⁷⁻⁹ Despite these observations it has been very difficult to carry out trials of sufficient size to conclusively prove the value of beta-blockers in congestive heart failure. One important reason is the difficulty in acceptance of the concept that congestive heart failure should be treated with drugs which suppress contractility when the prevailing treatment has focused on inotropic drugs. Another reason is the fact that in most patients there is a transient depression of cardiac function during initiation of beta-blocker treatment¹⁰ as well as an increase in heart failure symptoms. However, since a conclusive evaluation of inotropic and potent vasodilators showed that their beneficial effect is only temporary and that the long-term effects are harmful with regard to both morbidity and mortality, it has been easier to stimulate renewed interest in beta-blockers in heart failure.¹¹

Moreover, longitudinal studies of neuroendocrine activation in heart failure have shown the strong predictive value of catecholamines for mortality and that serum catecholamine concentration is only marginally affected by treatment with angiotensin-converting enzyme (ACE) inhibitors.

Table 1. Possible mechanisms of action of beta-blockers in congestive heart failure.

- Decrease in myocardial energy consumption¹²
- Redistribution of coronary flow to subendocardium
- Inhibition of renin and endothelin₁ synthesis and release
- Antioxidative and antiproliferative effect¹³
- Antiapoptotic effect
- Competitive inhibition of autoantibodies against beta₁-receptors

Possible mechanisms of action of beta-blockers

At present we are far from knowing why beta-blockers are so effective in congestive heart failure. It is believed that complex mechanisms are involved which include direct haemodynamic effects on heart rate and blood pressure mediated through blockade of beta-adrenergic cardiac receptors, but also through blockade of the central nervous system receptors thereby decreasing sympathetic outflow to the heart, kidney, immune system and peripheral muscles, as well as interaction between catecholamines and other neurohormones such as renin, endothelin and atrial natriuretic peptide. *Table 1* shows the possible mechanisms of action of beta-blockers and *Table 2* describes the findings after long-term beta-blockade.

Table 2. Proven long-term effects of beta-blockers in congestive heart failure.

- Increased myocardial efficiency
- Reversed ventricular remodelling
- Increased contractility
- Decreased filling pressures
- Improved diastolic function
- Beta-receptor upregulation

Clinical effects of beta-blockers

The earliest uncontrolled beta-blocker studies in dilated cardiomyopathy, which often showed dramatic improvement in patients from New York Heart Association (NYHA) class IV to class I, were strongly criticized. One argument countered that the selected population had acute-phase tachycardia and that, given that there was no placebo group, it could not be shown that these patients would not have improved spontaneously. Later studies of cardiac function after withdrawal of beta-blockade showed, however, a consistent pattern of deterioration followed by improvement when treatment was reinstated.^{10,15} The Metoprolol in Dilated Cardiomyopathy (MDC) trial confirmed that there was an improvement in the placebo group but that it was significantly less than that seen in the beta-blocker group.¹⁶ A consistent pattern in most trials was that treatment for at least 3 months was required in order to achieve significant improvement in left ventricular systolic function which could last for at least 12 months, particularly in patients with very poor systolic function.¹⁶

Tolerability of beta-blockers

When beta-blockers are titrated slowly over 6–12 weeks, starting with doses <10% of the target dose, an excellent tolerability is achieved expressed as a low withdrawal rate during the titration period, which does not differ from that of placebo. The early placebo-controlled studies had an open run-in period of 2–14 days with active drug, excluding those who did not tolerate beta-blockers and consequently had very low withdrawal rates during titration.^{16,17} Later studies with no run-in period such as the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II),¹⁸ or with a placebo run-in such as the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),¹⁹ had a withdrawal rate of around 15%, which did not differ from that of placebo.

If one looks specifically at the risk of developing heart failure there was a strong trend

towards less heart failure in the beta-blocker group. Bradycardia, hypotension and dizziness occurred more often in the beta-blocker group but in absolute values affected only about 1% of cases. Those complications should be considered less serious than the increased incidence of worsening heart failure seen in the placebo group.

The rate of complications was highest in NYHA class IV patients in whom hospitalization for heart failure was somewhat higher than in the placebo group during titration of beta-blockers. The total number of hospitalizations in this group over the whole study period was, however, similar to that of the placebo group and there was a trend in both the CIBIS-II and MERIT-HF trials to lower mortality in the beta-blocker groups. The proportion of patients in NYHA class IV is generally low in most trials. Except for the CIBIS-II trial which had 17% of NYHA class IV patients, the proportion is usually 5%. This implies that a large proportion of NYHA class IV patients are excluded from these trials because they are judged unable to tolerate beta-blockers, probably due to the fact that it has not been possible to stabilize them with conventional heart failure treatment with diuretics, ACE inhibitors and digoxin. Patients excluded from beta-blocker treatment often have low blood pressure and more advanced signs of organ failure. Based on evidence from controlled trials we therefore cannot give a general recommendation to treat patients in NYHA class IV with beta-blockers. These patients should be referred for evaluation to specialists with experience in treating patients with beta-blockers. In the right hands, some patients make a remarkable recovery.

Dose-effect relationship

A linear relation between the final dose and improvement in ejection fraction and mortality was found in a prospective study of carvedilol in heart failure. It has to be emphasized, however, that a less favourable response may be seen in patients who cannot tolerate a high beta-blocker dose. It can therefore not be concluded that the beta-blocker dose is

the only factor which decides the response. In later trials there have been attempts to reach the highest possible tolerated dose which gives a high degree of beta-blockade. For example, in the CIBIS-II trial the target dose was twice that of the CIBIS-I trial and in the MERIT-HF trial the target dose was one-third higher than that of the MDC trial.

Importance of baseline heart rate and decrease in heart rate

Since the early studies with beta-blockers included patients with tachycardia the prevailing opinion was that (1) patients with tachycardia had a better response than patients with a normal or a low heart rate and that (2) the degree of improvement was related to the degree of reduction of heart rate. Analyses of the CIBIS-I trial with bisoprolol showed, however, no consistent pattern on which to base this assumption.²¹ In the MERIT-HF Trial¹⁹ there was no difference in survival between those in the lowest tertile for heart rate and those in the highest two tertiles for heart rate. This finding suggests that mechanisms other than reduction in heart rate play an important role for improved survival.

Role of heart failure aetiology

For a long time it was believed that improvement could only be achieved in patients with dilated cardiomyopathy. A contributing factor to this belief was that more dramatic improvement could be achieved in dilated cardiomyopathy because treatment with beta-blockers was started at the same time as ACE inhibitors and it was thought that it might have been a myocarditis which healed during the treatment period. The first patients with ischaemic cardiomyopathy who had been treated with beta-blockers already had irreversible damage caused by an infarction and therefore did not have the same potential for improvement compared with the patients with dilated cardiomyopathy.²² Later studies confirmed that patients in the beta-blocker group with less pronounced damage often improved signifi-

cantly while patients in the placebo group remained unchanged.²³ Later studies also showed that there is no difference in survival between ischaemic and non-ischaemic heart failure,^{8,19} which is in agreement with the *post hoc* analyses of secondary prophylaxis after myocardial infarction in subgroups with heart failure or impaired left ventricular function.^{2,3,6}

Combined treatment of heart failure

There was no combined treatment with ACE inhibitors in the early beta-blocker studies, which shows that patients can be improved by beta-blockers alone. A direct comparison between captopril and metoprolol in dilated cardiomyopathy showed that metoprolol caused a more marked improvement in left ventricular function.²⁴ In the MDC trial, on the other hand, ejection fraction was increased when the beta-blocker was combined with ACE inhibitors compared with metoprolol alone. It cannot be assessed from this study whether this was due to the fact that ACE inhibitors were given only to patients with more serious failure or whether treatment with ACE inhibitors was just a matter of chance. A prospective, randomized study is needed to answer this question.

The same argument applies for combined treatment with digoxin. Even if digoxin was shown to reduce morbidity and mortality from heart failure in the DIG study, one cannot draw the conclusion that combined treatment is to be preferred. *Ad hoc* analyses from studies with carvedilol imply reduced morbidity and mortality when treatment was combined with digoxin compared with carvedilol alone.²⁵ Again, however, this interpretation may be criticized since there is no guarantee that the risk profile was identical in the two treatment groups. A prospective, randomized study is therefore required.

Should treatment be combined with spironolactone in NYHA groups III and IV? This question may possibly be answered after a thorough analysis of the Randomized Aldactone Evaluation Study.²⁶ Even if this seems to be the case, since the mechanisms will differ

from that of ACE inhibitors and beta-blockers, one has to perform a prospective, randomized study to answer the question correctly and to obtain a measure of the possible gain in mortality reduction by the combined treatment.

Treatment of NYHA class IV patients with beta-blockade

In all the reported studies there have been few patients in NYHA class IV (<5%), which means that many NYHA class IV patients are judged to be unable to tolerate beta-blockade since they have not been stabilized by conventional treatment with diuretics, ACE inhibitors and digoxin. Such patients have often proven to have very low blood pressure and signs of organ failure.

A nominal reduction in deaths was seen in the treatment groups in both the CIBIS-II and the MERIT-HF trials, but this reduction is not significant even when the data from both studies are pooled. Thus, based on these studies one cannot issue a general treatment recommendation since considerable experience will be needed to master any complication that might be caused by the treatment. An ongoing trial with captopril given to these patients might be able to answer this question. At present it is not possible to issue a general recommendation that NYHA class patients should be treated with beta-blockers. These patients should be taken care of by specialists with experience in beta-blockade.

A possible alternative use of beta-blocker treatment in this group of seriously ill patients was proposed by the Bristow group.²⁷ These investigators stabilized patients who were unable to tolerate beta-blockade using the phosphodiesterase inhibitor enoximone. They claimed to have successfully enabled patients to tolerate metoprolol after slow down-titration of enoximone treatment.²⁷ This alternative treatment must, however, be tested in a randomized study.

Difference in effect between beta-blockers

A great number of beta-blockers have been shown to improve myocardial function (*Table 3*): beta₁-selective blockers with various degrees of selectivity, unselective beta-blockers, beta-blockers with a certain degree of intrinsic activity and beta-blockers with vasodilatory activity. Beta-blockers with marked intrinsic activity have been shown to worsen survival despite improvement in heart function.²⁸ There are only a few studies in which different beta-blockers were directly compared and no significant differences in effect on ejection fraction were seen. The problem with these direct studies is that one cannot be sure whether equipotent doses were given. There is a dose-dependent effect on heart function, morbidity and survival. Some of the new beta-blockers, the so-called third generation beta-blockers, have been shown in experimental studies to differ in antioxidative capacity from the first and second generation beta-blockers. It is therefore argued that the third generation beta-blockers are better at counteracting ischaemic cell death and apoptosis in humans. More recent direct comparisons of the antioxidative effect in humans cannot, however, confirm that such differences exist.¹³ It has also been stated that blockade of both beta₁- and beta₂-receptors at the same time would give better protection against sudden cardiac death than beta₁receptor blockade alone. The two large studies, CIBIS-II and MERIT-HF, using selective beta-blockers, demonstrated a marked effect on sudden cardiac death; a prospective, randomized study of carvedilol,

Table 3. Beta-blockers proven to improve ejection fraction in chronic heart failure.

- Practolol
- Alprenolol
- Propranolol
- Nebivolol
- Atenolol
- Metoprolol
- Bisoprolol
- Carvedilol
- Celiprolol
- Bucindolol

Table 4. Comparison between the two survival studies, CIBIS-II¹⁸ and MERIT-HF.¹⁹

	CIBIS-II	MERIT-HF
Number of patients treated with beta-blockade	1327	2001
Males/females	77/23	81/19
Age (years)	61	64
NYHA classes included	III–IV	II–IV
Class IV patients (%)	17	3.4
Placebo mortality (%)	17.3	11.0
Ejection fraction	27.5	28
Ischaemic/non ischaemic (%)	50/50	65/35
Reduction (%)		
Total mortality	34	34
Cardiovascular mortality	29	38
Sudden cardiac death	44	41
Heart failure	26 (P=0.17)	49
Total hospitalization	20	19
Hospitalization due to heart failure	36	31
Withdrawal: % difference compared with placebo	0	-1.1 (NS)

using death as a predefined endpoint, needs to be performed. A third study using a third generation unselective dilated beta-blocker, bucindolol, has been stopped prematurely without reaching a conclusion regarding its effect on survival.

In an ongoing survival study which directly compares carvedilol and metoprolol, it is hoped that the differences in effect will be elucidated. Unfortunately, in this study a lower dose of short-acting metoprolol has been used as a target dose compared with that used in earlier studies. The calculated

median target dose may be as low as 50% of the total dose of 159 mg of slow-release metoprolol used in the MERIT-HF study. One can therefore question whether the two beta-blockers have been given in equipotent doses.

Supplementary therapy in those at high risk of arrhythmias

Even if beta-blockers markedly diminish the risk of sudden cardiac death they do not

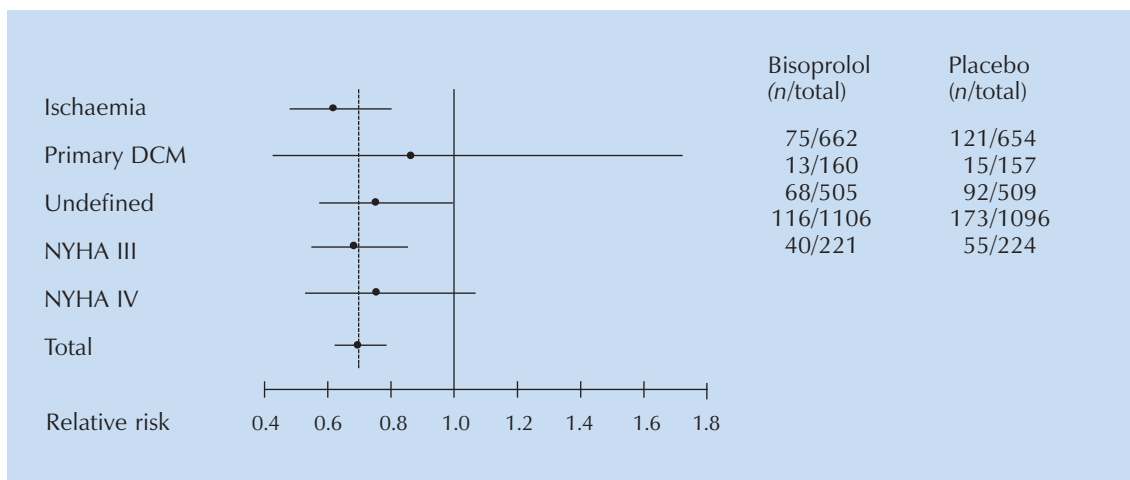


Figure 1. Subgroup mortality in the CIBIS-II trial.¹⁸ DCM, dilated cardiomyopathy. EF, ejection fraction; MI, myocardial infarction; HR, heart rate; BP, blood pressure.

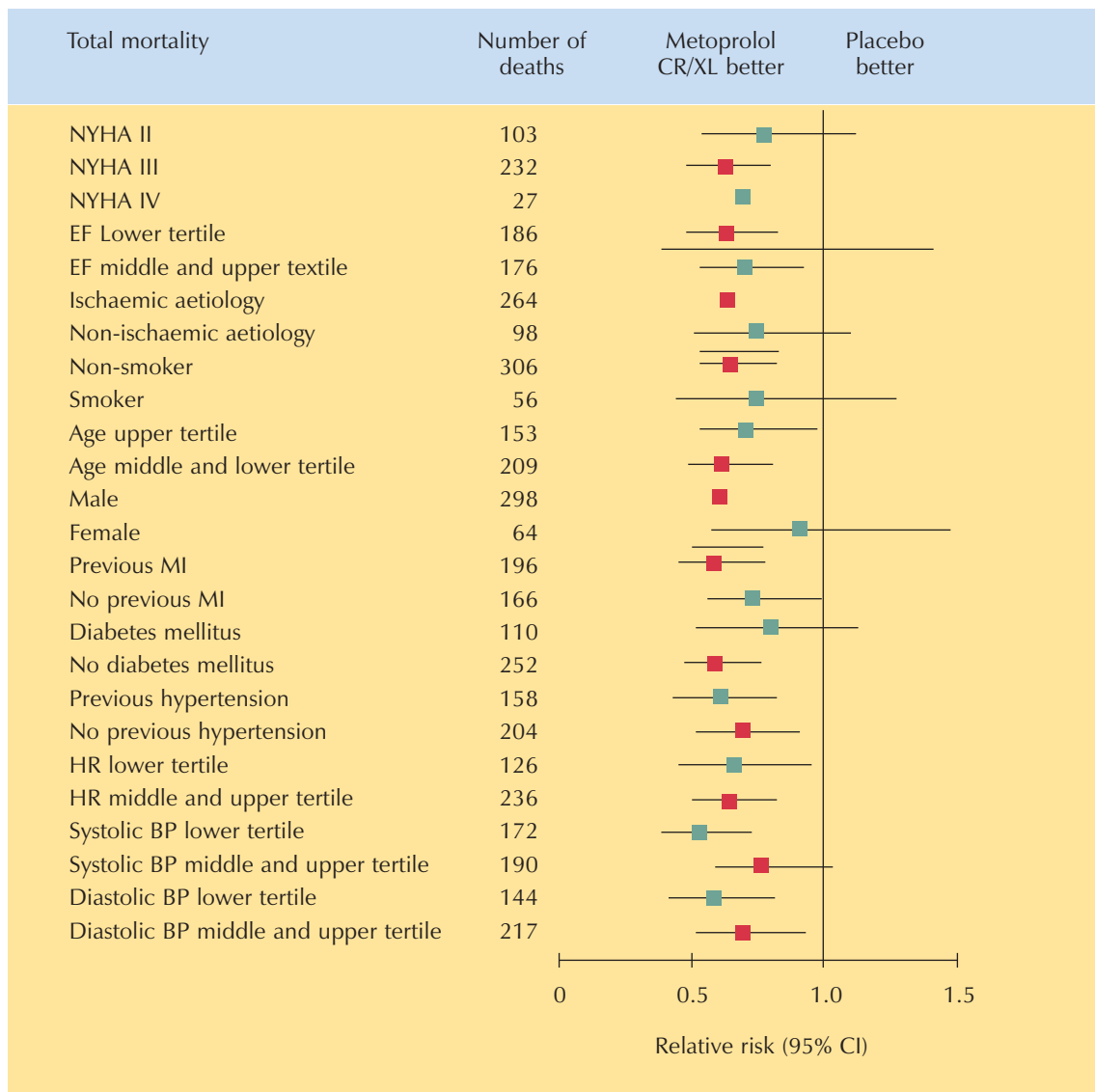


Figure 2. Subgroup mortality in the MERIT-HF trial.¹⁹

entirely eliminate it. Amiodarone has been suggested as an alternative. Placebo-controlled studies on amiodarone have not, however, shown clear-cut positive effects on total mortality even if death from arrhythmia is reduced. A meta-analysis demonstrated 10% reduced mortality,²⁹ the most marked effect being in patients simultaneously treated with beta-blockade. ICD-30, which causes a more marked decrease in mortality in high-risk patients compared with beta-blockers and treatment with amiodarone, should therefore

be used as a supplementary treatment in selected populations.

Effects on survival

There are presently two large placebo-controlled studies using the predefined primary endpoints of 'death' and 'combined death and hospitalization' (Table 4, Figures 1–4). These two studies correlate surprisingly well with regard to effect and tolerability despite the

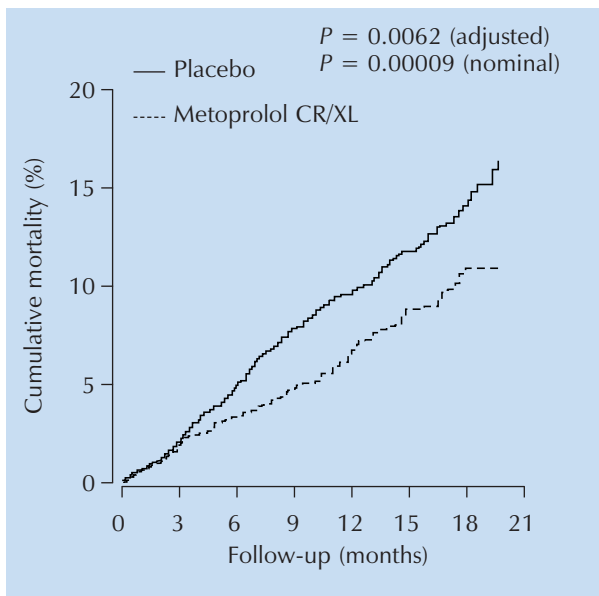


Figure 3. Kaplan-Meier survival curve in the CIBIS-II trial.¹⁸

fact that the CIBIS-II trial, which included only NYHA class III and IV patients, demonstrated approximately 50% higher placebo mortality than the MERIT-HF trial.

Comparable effects were seen in the different NYHA functional classes, in ischaemic and non-ischaemic heart failure and between different age groups in both the CIBIS-II and the MERIT-HF trials. The MERIT-HF trial demonstrated an effect on mortality that was independent of baseline blood pressure, heart rate and ejection fraction. The most impressive findings in both trials were the great number of sudden cardiac deaths in NYHA functional classes II and III and the marked effect on sudden death. This emphasizes the fact that ACE inhibitors alone do not provide sufficient protection against sudden cardiac death and it confirms the great effect on sudden death which has been previously demonstrated in post-infarction trials using beta-blockers. It should be stressed that none of these heart failure studies should be considered as post-infarction studies since, for example, only 14% of the infarct patients in the MERIT-HF trial were included within 6 months of an acute myocardial infarction.

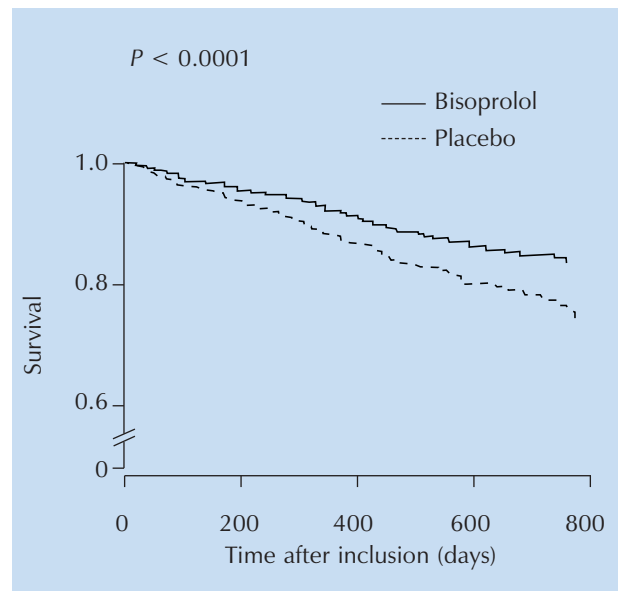


Figure 4. Kaplan-Meier survival curve in the MERIT-HF trial.¹⁹

Conclusion

More than 6600 patients with heart failure treated with beta-blockers or placebo have clearly demonstrated that beta-blockade as a supplement to ACE inhibitors or angiotensin I receptor blockade should be standard treatment of heart failure in patients with depressed systolic left ventricular function <0.40. This combination of treatment can achieve a 34% reduction in total mortality. Tolerance is excellent since there is no difference in withdrawal rate from placebo and the number of readmissions for heart failure is significantly reduced. ■

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Metabolic imaging: predicting recovery of function in heart failure

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During the past 20–30 years, coronary heart disease mortality rates have declined steadily in Western countries.^{1,2} Despite this trend, which has been attributed to a combination of primary preventive measures and improved disease management,^{2,3} heart failure remains an important and increasing public health problem.^{4–7} Admissions to hospital because of heart failure seem to be increasing, due partly to ageing populations and to greater survival of patients with coronary heart disease. Substantial health care expenditure is required for heart failure management, of which hospital-related costs account for the largest proportion.^{7,8}

Coronary artery disease (CAD) is the commonest cause of heart failure in the Western world accounting for up to 60% of cases.⁹ It was demonstrated more than 20 years ago that resting wall motion abnormality in patients with CAD can improve after administration of an inotropic agent, nitroglycerine or after coronary artery bypass.^{10–12} The term ‘hibernation’ was first used by Diamond et al.¹³ in 1978 to describe chronic wall motion abnormalities in patients with CAD but no previous myocardial infarction and their reversibility after revascularization, and this term was subsequently popularized by Rahimtoola.¹⁴

Thus for the first time it was realized that patients with heart failure secondary to CAD may have dysfunctional myocardium that may become functional following revascularization.

Pathophysiology of reversible dysfunctional myocardium

Histological studies on bioptic material obtained at the time of surgery have produced evidence of profound structural changes in chronically dysfunctional but viable myocardium.^{15,16} These changes comprise: progressive

loss of contractile proteins (sarcomeres) without loss of cell volume, distinct from atrophic degeneration; increase in glycogen; loss of sarcoplasmic reticulum; and loss of T-tubules. These changes are suggestive of dedifferentiation because they resemble fetal cardiomyocytes. Myocardial tissue characterized by such changes is not likely to regain function immediately after revascularization but might require time to regain sufficient contractile material. However, the finding that some patients regain function rapidly whereas others have a delayed recovery suggests that the histological pattern cannot be the same in all patients with CAD and chronic left ventricular dysfunction.

Positron emission tomography (PET) with positron-emitting radiopharmaceuticals has made possible the study in vivo of myocardial perfusion and metabolism in man. In this technique, ¹³N-ammonia serves as an indicator of relative regional myocardial blood flow. Relative myocardial glucose utilization is assessed with ¹⁸F-2 fluoro-2-deoxyglucose (FDG) a labelled glucose analogue that under-

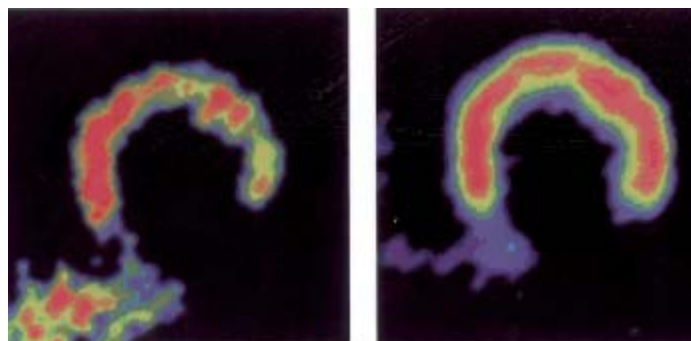


Figure 1. Short axis slices of the left ventricle using PET scan. (Left) Normal to mildly reduced ¹³N-ammonia uptake in the anterior wall and absent perfusion in the posterior wall. (Right) Increased FDG uptake in the anterior wall suggestive of hibernating myocardium, and absent uptake in the posterior wall suggestive of necrosis.

Table 1. Sensitivity and specificity of FDG PET for detection of improved regional contractile function after revascularization. (References to all listed studies can be found in Bax et al.²⁴)

Study	No. of patients	Males (%)	Mean age (years)	Mean LVEF (SD) (%)	Pts with MVD (%)	Pts with prev MI (%)	Segs with recovery (%)	Technique assessing RWM after revasc	Sens (%) (no. of segs)	Spec (%) (no. of segs)
Marwick et al.	16	88	NA	NA	44	100	41	Echo	71 (25/35)	76 (38/50)
Gerber et al.	39	87	60	33 (+10)	85	59	62	Echo	75 (18/24)	67 (10/15)
Tamaki et al.	22	91	57	NA	NA	77	50	RNV	78 (18/23)	78 (18/23)
Gropler et al.	34	76	60	NA	76	62	40	Echo/RNV	83 (38/46)	50 (35/70)
Maes et al.	23	NA	NA	41 (+13)	NA	NA	52	RNV	83 (10/12)	91 (10/11)
Tamaki et al.	43	95	58	41 (NA)	NA	100	39	CV/RNV	88 (45/51)	82 (65/79)
Knuuti et al.	48	96	54	53 (+11)	85	100	30	Echo	92 (23/25)	85 (50/59)
Baer et al.	42	90	59	40 (+13)	74	100	62	Echo	92 (24/26)	88 (14/16)
Lucignani et al.	14	86	61	38 (+5)	93	NA	74	RNV	93 (37/40)	86 (12/14)
Carrel et al.	23	91	56	34 (+14)	NA	100	74	Echo	94 (16/17)	50 (3/6)
Tillish et al.	17	94	NA	NA	NA	94	55	CV/RNV	95 (35/37)	80 (24/30)
Tamaki et al.	11	NA	NA	NA	NA	NA	71	RNV	100(40/40)	38 (6/16)
Average	28	90	58	40	78	88	51			
Weighted mean									88 (329/376)	73 (285/390)

LVEF, left ventricular ejection fraction; MVD, multivessel disease; MI, myocardial infarction; RWM = regional wall motion; NA, not available; Echo, echocardiography; RNV, radionuclide ventriculography; CV, contrast ventriculography. Pts, patients; prev, previous; revasc, revascularization; segs, segments; sens, sensivity; spec, specificity.

goes facilitated transport into the cell and phosphorylation by hexokinase. Metabolically chronically dysfunctional myocardium is characterized by increased glucose utilization as shown by increased FDG uptake assessed by PET. These data have been confirmed by two other groups.^{19,20} In normal subjects studied after overnight fasting, myocardial FDG uptake is extremely low due to prevailing lipid utilization. In contrast, myocardial blood flow as assessed by ¹³N-ammonia using PET is either normal²² or reduced in the dysfunctional myocardium. Thus, three scenarios may

exist in a patient with heart failure and left ventricular dysfunction due to CAD (Figure 1):

- reduced ¹³N-ammonia uptake and reduced glucose uptake suggestive of necrotic myocardium;
- reduced ¹³N-ammonia but increased FDG uptake (perfusion metabolism mismatch) suggestive of hibernating myocardium;
- normal ¹³N-ammonia uptake with increased FDG uptake suggestive of repetitive stunning.

Currently PET with FDG is considered one of the most accurate techniques for identifying viable myocardium.

Diagnostic accuracy of predicting regional improvement after revascularization

Many studies have shown that FDG PET is accurate in predicting functional recovery in patients undergoing revascularization.²⁴ The results of these studies are summarized in Table 1. The sensitivity ranged from 71 to 100% with a weighted mean of 88%. The specificity ranged from 38 to 91% with a weighted mean of 73%.

Diagnostic accuracy of predicting global improvement after revascularization

Revascularization in patients with preserved FDG uptake was shown to result in improved left ventricular ejection fraction (LVEF).^{25–29} In one study, LVEF improved from 30 ± 11% to 45 ± 14% (mean ± SD) in patients with two or more viable dysfunctional segments on FDG PET whereas LVEF did not improve in patients with one or fewer viable dysfunctional segments. Comparable findings have been recently reported.^{25,26}

Recently, single photon emission computed tomography (SPECT) has been used with FDG to evaluate viable myocardium in conjunction with thallium-201 SPECT to assess perfusion. This method has been found to be successful in predicting recovery of regional and global

function in patients with left ventricular dysfunction due to CAD.^{31,32} Since SPECT is widely available, this technique may contribute to the more routine use of FDG for determination of viability.

Contractile reserve and metabolic activity in dysfunctional myocardium

Low doses of dobutamine have been shown to reliably detect contractile reserve in patients with left ventricular dysfunction due to CAD.^{33–36} In a recently published study by our group, in patients with heart failure and contractile reserve (identified by low-dose dobutamine echocardiography) who underwent revascularization, mortality was significantly reduced compared with those with contractile reserve who were on medical therapy.³⁷ Several studies have compared contractile reserve using this technique and metabolic activities using FDG PET.^{38–40}

Table 2 compares the relevant sensitivity and specificity for recovery of regional function between different imaging techniques.²⁴ While the sensitivity of FDG PET is higher, the specificity of dobutamine echocardiography is higher for predicting recovery of function following revascularization. This is not surprising. Metabolic activity of viable cells may be present in a severely differentiated myocardial region which might not recover function at all following revascularization and these regions

Table 2. Sensitivity and specificity of different imaging techniques (based on weighted mean values from available studies).²⁴

	No. of Patients	Sensitivity	95% CI	Specificity (%)	95% CI	99% CI
Technetium 99m MIBI	207	83	78–87	69	63–74	61–76
LDDE	448	84	82–86	81	79–84	79–84
Thallium 201 reinjection	209	86	83–89	47	43–51	42–52
¹⁸ F]FDG PET	332	88	84–91	73	69–77	69–77
Thallium 201 redistribution	145	90	86–94	54	49–60	48–61

CI, confidence interval; [¹⁸F]FDG, Fluorine 18 Fluorodeoxyglucose; LDDE, low-dose dobutamine echocardiography.

are unlikely to show contractile reserve because of lack of contractile protein.

However, what is not known is the time interval of recovery of function of these regions and the effect of these viable cells on remodelling and hence prognosis. In an elegant study by Melon et al.,⁴¹ the relation between contractile reserve and patterns of perfusion and glucose utilization on PET in chronic ischaemic left ventricular dysfunction was investigated. Six patterns of perfusion and metabolism were identified. These were compared to the presence or absence of contractile reserve (Figure 2). In this study, myocardial regions with a traditional mismatch pattern of viability showed contractile reserve in 50% of segments. In segments with moderate reduction of FDG, the contractile response to dobutamine was linked to the level of rest perfusion. Most segments with preserved perfusion and increased FDG uptake have impaired rest function but contractile reserve was still present. Thus there is a heterogeneous existence of contractile reserve, metabolism and perfusion characteristics in patients with chronic ischaemic cardiomyopathy.

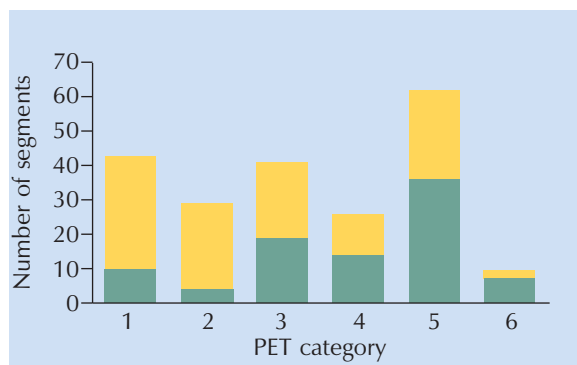


Figure 2. Distribution of segments with (yellow portions) and without (green portions) contractile reserve according to the six categories of perfusion and [¹⁸F]FDG uptake. Category 1: reduced perfusion and moderate FDG reduction; category 2: proportional reduction of perfusion and FDG; category 3: perfusion metabolism mismatch; category 4: preserved perfusion but moderate reduction of FDG; category 5: preserved perfusion and FDG uptake; category 6: normal perfusion and increased FDG uptake.⁴¹

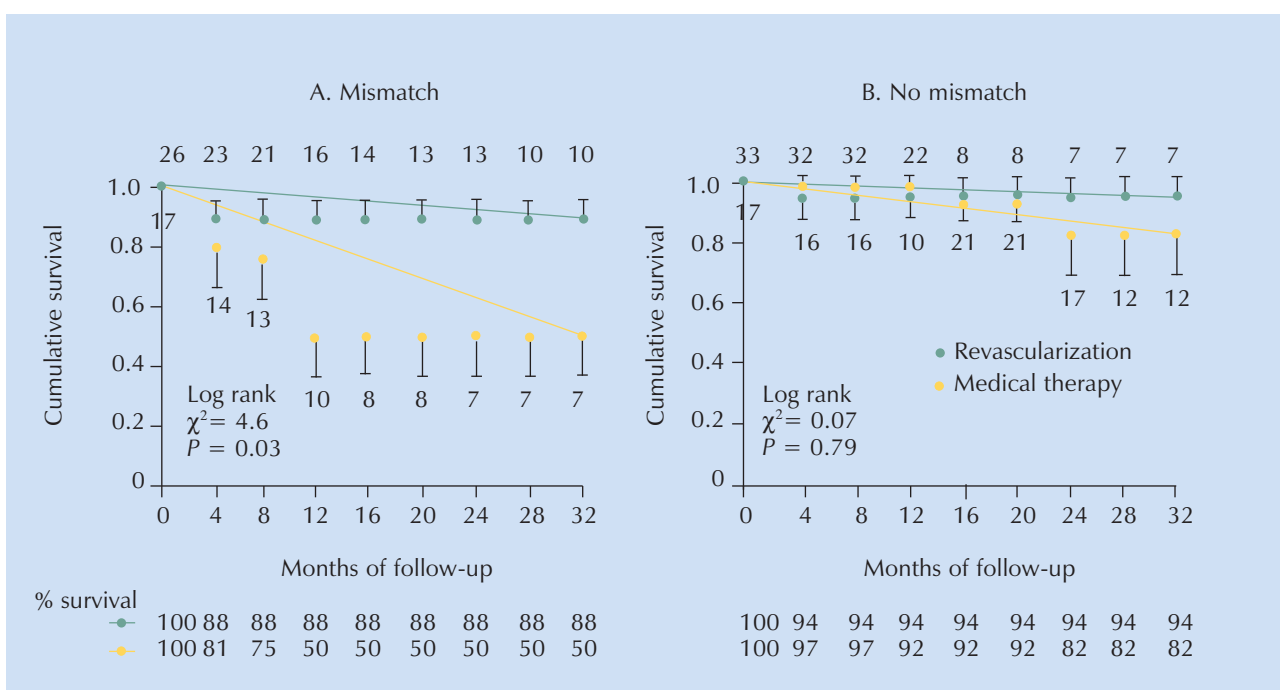


Figure 3. Cumulative survival of patients by presence or absence of PET mismatch and mode of treatment (i.e. medical therapy or revascularization).⁴²

Survival and presence of metabolically active myocardium

Di Carli et al.⁴² showed that the mere presence of dysfunctional myocardium which was metabolically active as determined by PET had an improved survival following revascularization in comparison with medical therapy. *Figure 3* shows the Kaplan-Meier survival curves in the study.

In another study by Di Carli et al.,⁴³ the authors found that PET mismatch of more than 18% was associated with a sensitivity and specificity of 76% and 78%, respectively, for predicting change in functional status after revascularization. Patients with a mismatch greater than 18% achieved a significantly higher functional status compared with those with a minimal or no PET mismatch.

Conclusion

In patients with heart failure and left ventricular dysfunction due to CAD it is important to assess the presence and extent of viable myocardium. Mortality is high in this group of patients on medical therapy. Mortality is also high in these patients who undergo revascularization. However, the presence and extent of viable myocardium considerably improves survival following revascularization. Although there are no randomized studies supporting this concept, there are numerous non-randomized studies favouring this strategy. It is important, however, to conduct a randomized study in patients with heart failure and CAD to establish the benefit of revascularization in patients with metabolically active but dysfunctional myocardium. ■

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Energy starvation and the metabolic approach to ventricular dysfunction

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Heart failure afflicts 1–2% of the overall population, increasing to at least 7% in the over-75s, and has an annual mortality rate of up to 20%.¹ Heart failure is also an increasingly common cause of hospital admissions, almost doubling over the past 15 years.² The aging of the population, the increasing prevalence of diabetes mellitus and the improving survival of patients after myocardial infarction are several of the major epidemiological trends behind the increasing prevalence of heart failure.³

Conventional therapy for heart failure unloads the heart but does not directly improve the cardiac function itself. The positive inotropes, which increase myocardial energy expenditure, have proven to be disappointing or even dangerous in heart failure.⁴ In fact, a decrease in the availability of adenosine triphosphate (ATP), or 'energy starvation' as it has been called,⁵ is likely to be a major factor in the development and progression of heart failure.

Energy starvation in heart failure

The work of Starling during and after World War I led to the idea that the overloaded heart has increased energy demands. Over the past few decades, it has become clear that cardiomyocytes in the overloaded heart are characterized by reduced ATP availability. Multiple factors are responsible for this decrease in ATP availability in heart failure, including regional ischemia, reduced oxygen delivery (decreased capillary supply, reduced coronary flow reserve), impaired oxygen diffusion (increased cardiomyocyte size, fibrosis) and altered oxidative phosphorylation due to mitochondrial abnormalities.⁵ Furthermore, it has recently been demonstrated that abnormalities in glucose metabolism play an important role in the energy starvation of heart failure.

The combination of an increased energy demand on the ventricle, as described by Starling, and the reduced ATP availability leads to decreases in both ATP concentrations and the ATP:adenosine diphosphate ratio. As a result, there is a reduction in energy-consuming reactions involved in contractility and ion exchange and an attenuation of certain allosteric effects which are attributable to high ATP concentrations. These allosteric effects of ATP, likened to those of a lubricant, allow ATP, without undergoing hydrolysis, to accelerate a number of ion pumps and ion exchangers as well as passive ion fluxes through membrane channels and movements of the thick and thin filaments of the sarcomere.⁵ As a result, when ATP levels fall in the heart, both contractility and relaxation are inhibited.

Insulin resistance and metabolic disturbances in heart failure

Contributing to the energy starvation in heart failure are abnormalities in glucose metabolism, including changes in enzyme activity⁶ and abnormalities in insulin sensitivity. The main effect of insulin on insulin-sensitive tissues, such as the heart and skeletal muscle, is to increase glucose uptake and utilization while reducing free fatty acid metabolism. While glycolysis normally accounts for only about 5–10% of total ATP production in cardiomyocytes,⁷ it is thought to have a particularly important role in supplying ATP to nearby energy-consuming reactions involving the contractile proteins and energy pumps.⁸ This is because, unlike glucose and fatty acid oxidation, glycolysis takes place in the cytoplasm and not in the mitochondria. This role for glucose in providing local energy for contractile function may be particularly important under pathologic conditions of energy starvation found in heart failure.

Cellular insulin resistance can thus reduce the availability of glucose and the ability of cardiomyocytes to metabolize glucose. Heart failure, whether ischemic or idiopathic, is a state of insulin resistance.⁹ It has been shown that patients with coronary artery disease who have no signs of heart failure have significant insulin resistance compared with healthy controls and have basal and stimulated (after a glucose load) elevations in insulin and C-peptide levels.¹⁰ A similar degree of insulin resistance, along with similar elevations in insulin and C-peptide levels, has been observed in patients with idiopathic dilated cardiomyopathy.¹⁰ In patients with congestive heart failure due to ischemic cardiomyopathy, insulin resistance is even further increased, as though the two conditions, coronary artery disease and congestive heart failure, exerted an additive effect on inhibiting glucose metabolism.¹⁰ Thus, both coronary artery disease and heart failure are states of insulin resistance, and patients with ischemic cardiomyopathy are particularly affected.

Positron emission tomography (PET) studies on insulin resistance

The above findings, based on laboratory blood tests, have been supported by data from positron emission tomography (PET) scanning, which has been used to evaluate myocardial insulin resistance using a labeled deoxyglucose tracer fluorine-18 fluorodeoxyglucose (¹⁸FDG). Paternostro et al. showed that non-diabetic patients with previous myocardial infarction, left ventricular dysfunction and heart failure are insulin-resistant.¹¹ They also showed that myocardial uptake of glucose in myocardium remote from the site of infarction was approximately 50% of that found in control subjects, despite comparable blood flow. To standardize conditions, the authors used the hyperinsulinemic-euglycemic clamp technique whereby supraphysiologic levels of insulin can be given to optimize glucose uptake. In this way, glucose uptake can be considered to be limited only by the sensitivity of tissue to insulin. The authors proposed that the reduced glucose uptake by cardiomyocytes in the non-infarcted

(remote) myocardium is a feature of adaptive hypertrophy and remodeling. In a separate study, also standardized using ¹⁸FDG PET and the euglycemic clamp, they showed that myocardial glucose uptake in the normally contracting segments in patients with coronary artery disease and associated chronic left ventricular dysfunction was 35% lower than in the myocardium of normal subjects.¹² Thus, in patients with ischemia-induced left ventricular dysfunction, myocardium in both ischemic and non-ischemic regions is insulin-resistant.

From a molecular viewpoint, reduced insulin sensitivity may be due to a reduction in GLUT-4 transporter protein.⁹

While therapy with vasodilators and diuretics is certainly effective in improving symptoms, new approaches which more directly respond to the problems posed by energy starvation and insulin resistance are needed to improve the management of patients with heart failure — of both ischemic and non-ischemic origin — and with ischemia-induced ventricular dysfunction.

Metabolic strategies to treat heart failure

Among the possible strategies to overcome energy starvation in heart failure, two recent papers by the group of Hasenfuss in Germany have assessed the effects of pyruvate on contractility.^{13,14} Pyruvate is the product of glycolysis which goes on to be converted to acetyl coenzyme A, which can then go on to be oxidized in the Krebs cycle to produce nicotinamide adenine dinucleotide (NADH). NADH provides H⁺ ions necessary for the electron transport chain used in oxidative phosphorylation to generate ATP.

By adding pyruvate 20 mM to rabbit and failing human myocardium, the authors found significant increases in contractility. Despite this, with pyruvate, there was a non-significant trend toward improved utilization of oxygen, as shown by an improved economy of myocardial contraction relative to oxygen consumption.⁵

This experiment shows that a metabolic therapy, unlike other types of positive inotrop-

ic therapy, can improve contractility without a corresponding increase in energy and oxygen expenditure which, over time, is likely to be harmful.⁵

Strategies to switch energy substrate

Another approach to metabolic therapy is with agents which decrease fatty acid oxidation and increase glucose metabolism. Such agents can be of double value: they can reduce the toxic byproducts of fatty acid metabolism known to be harmful in terms of contractility and ion exchange,³ while increasing glucose metabolism which is more efficient than fatty acid metabolism in terms of ATP production per mole of oxygen utilized. Furthermore, such an approach can stimulate glycolysis, which is suppressed by fatty acid metabolism. As seen above, this can be very important for local energy-demanding reactions, including contractility and ion exchange. Additionally, agents which stimulate glucose oxidation reduce the lactate accumulation and the acidosis that are produced by glycolysis when it is uncoupled from the second step of glucose metabolism, known as glucose oxidation, in which acetyl coenzyme A from pyruvate is metabolized in the Krebs cycle.¹⁵

Trimetazidine is a metabolic agent which works by inhibiting a key step in fatty acid beta-oxidation. This inhibition secondarily stimulates glucose oxidation.¹⁶ In this way, trimetazidine causes a switch in energy substrate utilization from fatty acids toward glucose.

Several studies have now shown that trimetazidine, due to this metabolic mechanism of action, can have a significantly favorable effect on contractility in different clinical situations.^{17,18}

Evidence for the benefit of trimetazidine in stress-induced ischemic left ventricular dysfunction

Supporting the importance of metabolic abnormalities in contractile dysfunction and

the great potential offered by therapies that modulate cardiac metabolism, several clinical studies have shown that trimetazidine, through a metabolic switch from fatty acids to glucose metabolism, can produce marked clinical benefits.

Lu et al., using dobutamine stress echocardiography (DSE), evaluated trimetazidine in a double-blind, randomized, crossover trial in 15 patients with documented coronary artery disease and stress-induced wall motion abnormalities.¹⁷ DSE was carried out at the end of two 15-day treatment periods, during which patients received trimetazidine (20 mg t.i.d.) or placebo. Although wall motion function was generally well preserved in these patients, patients had significant improvement in the wall motion score index (WMSI) both at rest and at peak dobutamine stress when they were receiving trimetazidine. Since dobutamine infusion dose and time were also increased by trimetazidine, the reduction in the WMSI actually occurred at a greater cardiac workload. Confirming the findings of previous studies, trimetazidine had no effect on heart rate or blood pressure.^{19,20}

Metabolic approach with trimetazidine in ischemic cardiomyopathy

The results of the study discussed above address a particular population with predominantly stress-induced ventricular dysfunction. A separate study evaluated the effect of trimetazidine in a population with chronic dysfunctional but viable myocardium.¹⁸ This was a randomized, double-blind, placebo-controlled trial in 22 patients (mean age 53 ± 7 years) with a history of myocardial infarction, reduced left ventricular ejection fraction (mean $33 \pm 7\%$) and New York Heart Association class II–III heart failure. All patients were taking conventional therapy for heart failure and angina, including diuretics, angiotensin-converting enzyme inhibitors and nitrates. Patients were randomized to trimetazidine 20 mg t.i.d. or placebo in addition to their conventional therapy.

To evaluate the effect of trimetazidine on regional contractility, dobutamine stress

echocardiography was performed at baseline and after 2 months of study treatment.

The trimetazidine-treated patients had significant reductions in WMSI both at rest (2.05 ± 0.5 to 1.61 ± 0.4 ; $P < 0.05$) and at peak infusion (1.66 ± 0.3 to 1.32 ± 0.4 ; $P < 0.05$) (Figure 1). There was no change in WMSI in the placebo group and there was no difference in any of the hemodynamic variables between the two groups.

The results of these two studies, while not addressing the efficacy of the metabolic approach in heart failure of non-ischemic origin, do show that the metabolic approach, already proven effective (in the case of trimetazidine) in improving ergometric parameters in ischemic patients, can also improve cardiac contractile function in the setting of both chronic and stress-induced ischemia.

The benefit of trimetazidine in these patients is due to its effects on fatty acid and glucose metabolism. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including both glycolysis and glucose oxidation.²¹ Since glycolysis is coupled to glucose oxidation, lactate and proton accumulation, which could otherwise lead to intracellular acidosis and calcium overload, is prevented. Furthermore, it is known that administration of trimetazidine increases the incorporation of long-chain fatty acids into the cardiomyocyte membrane,²² thus significantly

reducing the availability of cytosolic free fatty acids and acylcarnitine, which can have deleterious effects on calcium handling.²³

Conclusion

Heart failure and ischemic left ventricular dysfunction are increasingly common syndromes. It is becoming clear that metabolic abnormalities such as energy starvation and insulin resistance play an important role in the pathophysiology of contractile dysfunction and heart failure, particularly in the setting of ischemic cardiomyopathy. Treatment for heart failure has classically included positive inotropic agents (likened to 'whipping a tired horse') and vasodilators (likened to 'unloading the wagon'). As pointed out by Katz, the short-term gain from whipping the horse is likely to be at the expense of an adverse long-term outcome, and drugs that improve symptoms in heart failure at the expense of an increase in cardiac energy expenditure can be expected to worsen prognosis.⁵ Trimetazidine improves cardiac metabolism through a switch which reduces fatty acid metabolism and increases glucose metabolism. Studies with this agent demonstrate that it is possible to improve cardiac function without altering blood pressure or heart rate. As recently observed, the heart is more than a pump, it is also an organ that needs energy from metabolism.²⁴ By directly improving cardiac metabolism, trimetazidine, which is currently widely used for the treatment of angina pectoris, improves ventricular function without hemodynamic side effects or drug interactions, opening up a new strategy in the treatment of ischemic heart failure and ventricular dysfunction. ■

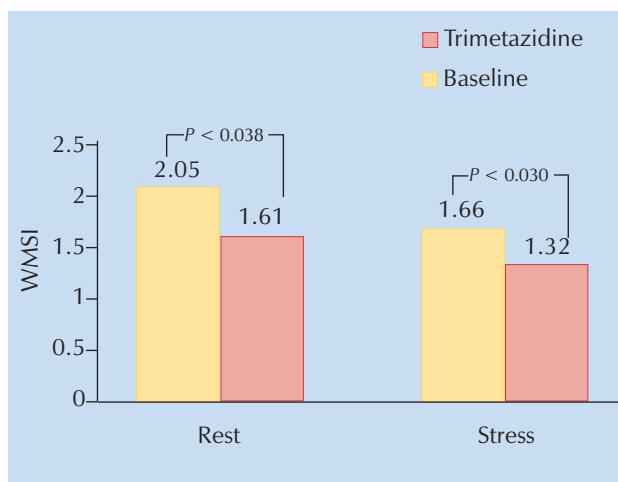


Figure 1. Effect of trimetazidine on WMSI at rest and at stress in patients with hibernating myocardium.¹⁸

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Case report

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I saw a 74-year-old male patient for the first time at the outpatient clinic 6 weeks after discharge from hospital where he had stayed for 12 days for the treatment of heart failure. Since 1996 his GP had been treating him with aspirin and long-acting nitrates for mild angina, retrospectively estimated as New York Heart Association (NYHA) class II angina. In early 1999 he was admitted to hospital due to acute dyspnoea after a short period of increasing breathlessness during exercise. Prior to admission he had also been experiencing some increase in anginal symptoms on exercise.

On admission, the patient was tachypnoeic (blood pressure 180/90, pulse 92 regular, central venous pressure not elevated), his temperature was normal and there were no audible carotid bruits. Heart sounds were normal and at the apex a soft holosystolic murmur was audible, radiating to the axilla, compatible with mitral regurgitation. Rales were audible over the lungs up to the axilla. His liver was not enlarged and he had no signs of peripheral oedema.

The ECG on admission showed a sinus rhythm of 100/min, normal PQ times and a QRS duration of 0.09 s, q-waves in leads V4–V6 with positive T waves, compatible with a previous silent lateral infarction. There were mild repolarization abnormalities in the inferior leads. Chest x-ray revealed an enlarged heart and signs of interstitial oedema.

The echocardiogram, made several days after admission, showed a dilated, poorly contracting left ventricle with regional wall motion abnormalities and end-diastolic and end-systolic dimensions of 70 and 56 mm, respectively. There was moderate mitral and mild-to-moderate tricuspid regurgitation. Radionuclide angiography (RNA) was performed and the calculated ejection fraction (EF) was 23%.

The patient's laboratory examination revealed no increase in cardiac enzymes, no

anaemia, slightly increased creatine (114 mmol/l) and slightly elevated liver enzymes, which returned to normal during hospitalization.

He was treated with diuretics and angiotensin-converting enzyme inhibitors; the long-acting nitrates were continued and because of his poor left ventricular function, aspirin was replaced by warfarin. He recovered very quickly, and no rales were subsequently heard, no signs of congestion were seen on chest x-ray and his ECG remained essentially unchanged.

Six weeks after discharge the patient continued to complain of dyspnoea on exercise, but his exercise tolerance was increased in comparison with the weeks before submission. No signs of overt heart failure were present on physical examination. Because of the absence of heart failure, the patient was treated with the beta-blocker carvedilol, starting with a low dose of 3.125 mg twice daily and gradually increasing to 25 mg twice daily over a period of 4 months. Within the first week of beta-blocker treatment, RNA was repeated and showed an EF of 28%.

Additional diagnostic procedures were performed because of a suspected ischaemic aetiology of the heart failure. A dipyridamole and rest perfusion single photon emission computed tomographic (SPECT) scintigram was obtained. The vertical long-axis views

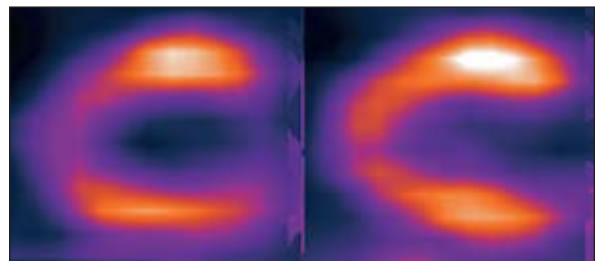


Figure 1. Vertical long-axis view of the dipyridamole and rest MIBI SPECT study. A partially reversible defect at the distal anterior segment and apex can be seen.

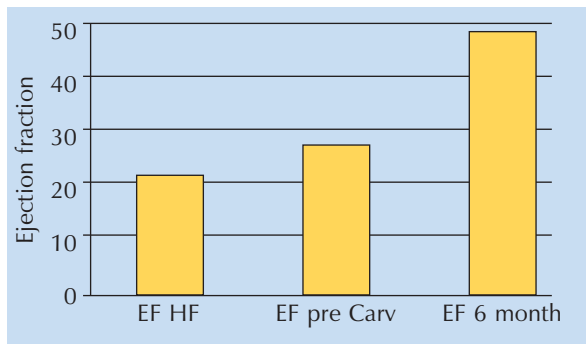


Figure 2. Improved EF following treatment with beta-blockers.

(Figure 1) showed a perfusion defect at the apex and distal anterior, which was partly reversible. The rest perfusion image showed moderately decreased activity in the area of the infarction, suggesting the presence of viable tissue. The other areas showed no perfusion defects. The left ventricle was dilated.

Coronary angiography was performed 3 months after discharge from hospital. The ventriculogram showed moderately contracting left ventricle and slightly elevated end-diastolic pressures; the angiogram showed three-vessel disease with significant stenoses in the RCA, LAD and LCx.

Over time the patient reported less dyspnoea and his exercise tolerance increased substantially. His estimated functional class, 6 months after discharge, was NYHA II. He was also almost without anginal complaints. RNA repeated 7 months after discharge showed an EF of 49% (Figure 2). At present his symptoms remain unaltered.

Discussion

This patient with a history of (probably ischaemic) heart failure showed a remarkable improvement of left ventricular function after treatment with beta-blockers. Moreover, despite the fact that he had three-vessel disease, his perfusion scintigram showed only mild signs of ischaemia in the area of his previous silent infarction.

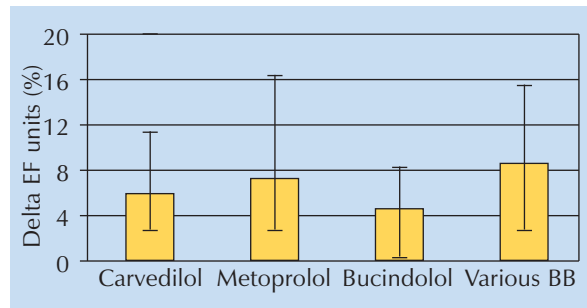


Figure 3. Mean increase and range in EF units of several beta-blockers.

Beta-blockers in heart failure

The beneficial effects of beta-blockers have been discussed elsewhere in this issue. We have performed a pooled analysis of the effects of beta-blockers on left ventricular function (Figure 3).¹ Although the effects of beta-blockers are generally mild in patients with severe left ventricular dysfunction, with a mean increase in EF between 0 and 15%, a clinically significant improvement in individual patients may occur. In this patient the improvement in left ventricular function was at least 21 EF units.

Angiographic data versus perfusion data

In the recommendations of the American College of Cardiology/American Heart Association,² a class I indication for revascularization is the presence of three-vessel disease, independent of the severity of symptoms and the degree of left ventricular dysfunction.

However, it has long been recognized that there is a poor correlation between the angiographic and nuclear perfusion data. Patients with significant coronary artery disease on angiography may have normal perfusion in the area of the stenosed coronary arteries, indicating that the functional significance of the anatomic lesion is limited. Also nuclear stress-perfusion data have shown that the prognosis in patients with mild ischaemia on stress perfusion imaging is excellent. In a recent study of a large group of patients undergoing stress-rest perfusion imaging,

Hachamovitch et al.³ showed that survival of these patients is almost similar to that of patients without perfusion defects. Earlier studies have also shown that when adding angiographic data to perfusion imaging data, no significant increase in prognostic value can be expected.⁴

Viable tissue and improvement of left ventricular function after revascularization

One of the most important determinants of prognosis in patients with coronary artery disease is the degree of left ventricular dysfunction. Dr Roxy Senior, in this issue, clearly shows that dysfunctional but viable tissue improves its function after revascularization. Although patients in the viable tissue-revascularization studies may have used beta-blockers, the degree of improvement of left ventricular function in heart failure patients who favourably react to treatment with beta-blockers is unknown. The impact of revascularization in these patients is therefore unknown.

Summary

There are conflicting arguments surrounding the need for revascularization in this patient. On one hand, the argument in favour of revascularization is the presence of three-vessel disease and the history of heart failure, but on the other is the absence of extensive ischaemia and the improvement of left ventricular function and symptoms.

I decided to treat this patient conservatively. So far, 11 months after admission, the patient is stable and has no signs or symptoms of heart failure and almost no anginal complaints. ■

If you have arguments for or against revascularization in this patient, please email me at fc.visser@azvu.nl with your opinion. Opinions will be published in a future issue of Heart and Metabolism.

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