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Aims and Scope

Heart and Metabolism is a quarterly journal focusing on the management of myocardial ischemia. 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 discussed. Moreover, the effects of metabolic diseases such as diabetes mellitus on the heart will be highlighted. 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 pharmacotherapy in ischemic and non-ischemic heart disease.

The figures on the cover show: The transthoracic echocardiogram in the parasternal long axis view depicts moderate mitral regurgitation (Top) during atrial fibrillation, which disappears after cardioversion to sinus rhythm (Bottom).

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Is heart failure a metabolic disease?

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Although overall mortality from cardiovascular disease is declining, heart failure is increasing in prevalence and is becoming a major challenge in cardiovascular medicine. Heart failure is the endstage condition of most cardiovascular disorders including coronary artery disease, hypertension, valvular disease, congenital heart disease, and cardiomyopathy. Improved survival in these predisposing conditions, paradoxically, contributes to the overall increase in the number of patients experiencing late complications, including heart failure.

But why does the heart eventually fail?

Understanding the critical event(s) leading to heart failure is essential for the improvement of strategies to maintain circulatory function in a compensated state for as long as possible. In the 1960s, research mainly focused on the hypothesis of depleted energy for contraction and relaxation. In part because no clear relationship could be found between a reduction in myocardial ATP content and contractile dysfunction, the "energy depletion hypothesis" lost popularity in the late 1970s. Instead, observations on activation of neurohormonal systems, accumulation of cytokines, downregulation of β -receptors, as well as altered expression of cytoskeletal, contractile, and calcium-handling proteins were seminal for the development of today's therapeutic strategies.¹ Nevertheless, recent observations² in both animal models and patients have rekindled interest in myocardial energy metabolism of the failing heart and have motivated this issue of *Heart and Metabolism*.

In their introductory article, Paul Mohacsi and colleagues emphasize that despite progress in drug therapy, mortality in heart failure remains high. Some further improvement can be expected by more consequent implementation of optimal treatment with

ACE inhibitors, β -blockers, and aldosterone antagonists to all eligible patients. Even if available treatment options do not cure the disease, they can considerably delay further deterioration of the clinical condition. Progression of heart failure to NYHA classes III and IV is associated with both increased mortality and an increase in the frequency of hospital admissions, which is of concern not only in terms of quality of life but also in terms of economic cost. The authors mention that many readmissions after discharge may be prevented by improved postdischarge care of patients.

The articles by William Stanley and Frans Visser critically review recent reports on changes in myocardial glucose and fatty acid metabolism during left ventricular dysfunction. Professor Visser emphasizes the role of radionuclide imaging in extracting metabolic information from patients noninvasively. Both authors agree that the overall picture of the pathogenetic role of substrate metabolism in heart failure is incomplete. A number of studies in animal models of left ventricular overload in response to hypertension, aortic banding, aorto-caval fistula, or infarction indicate that left ventricular remodeling is associated with a decrease in fatty acid oxidation and an acceleration of glycolysis, and, in some studies, an increase in glucose oxidation.³⁻⁶ This suggests a return to a more fetal-like pattern of substrate metabolism during left ventricular remodeling, as pointed out by Professor Visser. Unfortunately, very few studies have specifically investigated the metabolic changes occurring during progression from compensated remodeling to overt heart failure. In this context, of interest are observations on the expression of regulatory genes of substrate metabolism which suggest downregulation of

protein expression of enzymes of fatty acid oxidation at the moment of cardiac decompensation.⁷ It may therefore be speculated that myocardial function might be compromised by a sudden restriction of fatty acid oxidation, leading to lack of energy and/or accumulation of potentially toxic fatty acid esters in the myocardium. However, as pointed out by Professor Visser, it remains to be determined whether these changes in gene expression are causally involved in progression to heart failure or are epiphenomena.

Dr Stanley challenges the hypothesis of restriction of fatty acid oxidation, referring to clinical observations in patients with NYHA class II–III heart failure that suggest a shift in the opposite direction in substrate use, from glucose to fatty acid oxidation.⁸ He presents arguments indicating that high, rather than low, fatty acid oxidation may trigger rapid deterioration of function in the failing heart. From studies in hearts with transient ischemia it is known that inhibition of glucose oxidation under conditions of high fatty acid oxidation lowers metabolic efficiency in terms of contractile function, most likely by accumulation of protons. In his article Dr Stanley provides initial evidence from clinical and experimental studies indicating that pharmacological inhibition of fatty acid oxidation with etomoxir or trimetazidine may improve contractile function of failing hearts, similar to observations made during postischemic reperfusion.⁹

Is heart failure a metabolic disease? The question cannot be answered at present, nor probably in the foreseeable future. Heart failure is a multifactorial process and compro-

mised energy metabolism may be just one part. However, there is increasing evidence that metabolic regulation is altered in failing hearts, potentially opening up new avenues for therapeutic interventions. ■

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Myocardial energy metabolism in heart failure: unanswered questions and therapeutic opportunities

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Introduction

Chronic heart failure is generally defined as the inability to maintain normal cardiac output, and it classically presents with left ventricular chamber dilation, impaired systolic function, and elevated diastolic filling pressure. Despite optimal medical therapy, heart failure is a progressive disease with a high rate of mortality and morbidity.¹ Multiple neuro-hormonal systems are overactivated (eg, sympathetic nervous system, renin-angiotensin system, cytokines, endothelin, atrial natriuretic peptide, etc), which contributes to the progression of left ventricular remodeling, cardiac fibrosis, and worsening of clinical symptoms.^{2,3} Current pharmacotherapies are aimed at either symptom relief (eg, diuretics for edema or dobutamine for acute cardiac decompensation), or suppression of the over-activation of the renin-angiotensin axis (ACE inhibitors and angiotensin II receptor antagonists) and the sympathetic nervous system (β -adrenergic receptor antagonists).⁴ These therapeutic approaches significantly reduce mortality in heart failure patients; however, there is still progression of left ventricular dysfunction and a high rate of mortality and morbidity. In addition, these drugs can acutely compromise hemodynamic function, and they are frequently poorly tolerated. Thus there is a clear need for agents that are free of any negative effects on cardiac function but that will stop or reverse the progression of heart failure and improve cardiac function.

Myocardial energy metabolism in heart failure

Cardiac muscle has an extremely rapid rate of metabolism. Blood flow and oxygen consumption are high and proportional to the rate of formation of ATP in the mitochondria. ATP synthesis is matched by ATP breakdown in the cytosol, which drives the contractile work of the heart and fuels the ion pumps that allow for diastolic relaxation (*Figure 1*). The content of ATP in the heart is low relative to the rate of ATP breakdown, with complete turnover of the cardiac ATP pool every 10–15 s.⁵ ATP is resynthesized via oxidative phosphorylation, a process that is driven by the combustion of carbohydrates and fat in the mitochondrial matrix, and the transfer of electrons from carbon fuels to reduced nicotinamide adenine dinucleotide (NADH) and the electron transport chain (*Figure 1*).

The electron transport chain pumps protons into the mitochondrial intermembrane space, and ATP is formed via oxidative phosphorylation by the mitochondrial ATPase (*Figure 1*). The heart is an omnivore, and forms ATP with energy released from the combustion of a mixture of lactate (10 to 25% of the total energy), glucose (10 to 25%), and fatty acids (50 to 80%).

There is growing evidence from pharmacology studies that impaired carbohydrate oxidation and high rates of fatty acid oxidation contribute to the mechanical dysfunction of the myocardium and the progression of heart failure.^{6–11} Unfortunately, our understanding of the role of changes in myocardial energy metabolism in the natural history of heart failure is poor.¹² Studies in heart failure patients and large animal models of heart failure sug-

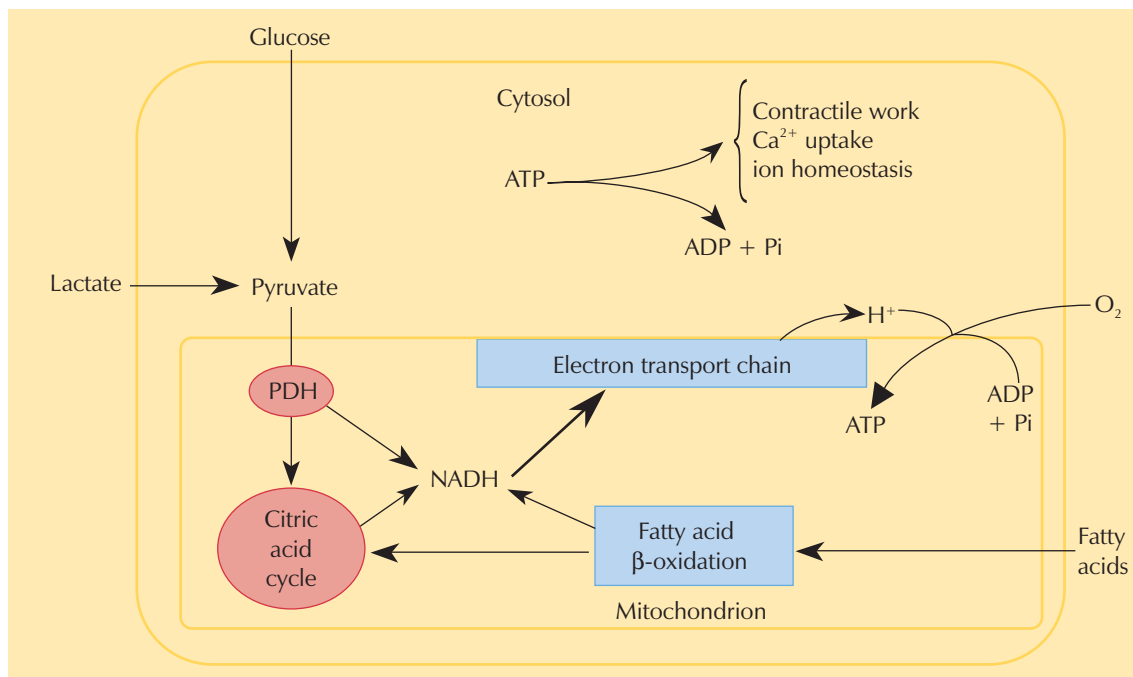


Figure 1. Pathways of myocardial energy metabolism. ATP is formed by oxidative phosphorylation on the inner mitochondrial membrane, and is broken down in the cytosol to release energy for contractile work, Ca²⁺ uptake into the sarcoplasmic reticulum, and ion pumps. The metabolism of carbon fuels transfers hydrogen atoms to reduced nicotinamide adenine dinucleotide (NADH), which fuels the electron transport chain and oxidative phosphorylation. Pi, Inorganic Phosphate; PDH, pyruvate dehydrogenase.

gest that the function of cardiac mitochondria is depressed, and there are lower ATP levels.^{13–18} Cardiac fuel selection has been measured in NYHA class II–III heart failure patients, showing a significant switch towards fatty acid metabolism, with less carbohydrate oxidation compared with age-matched healthy people.¹⁹ On the other hand, myocardium from patients²⁰ and dogs²¹ in endstage heart failure suggests a switch to glucose oxidation and away from fatty acids as the heart decompensates.

Metabolic therapies for heart failure

There are intriguing data in heart failure patients suggesting that acute treatment with agents that switch substrate oxidation away from fatty acids and towards carbohydrate oxidation improves cardiac function without eliciting any negative hemodynamic effects. Studies in humans and animals found that the

contractile performance of the heart at a given rate of oxygen consumption is greater when the heart is oxidizing glucose and lactate rather than fatty acids.^{22–24} The rate of fatty acid oxidation is mainly regulated by the concentration of free fatty acids in the plasma, the activity of carnitine palmitoyl transferase-1 (CPT-1), and the activity of a series of enzymes that catalyze the multiple steps of fatty acid β -oxidation (Figure 2).²⁵ Fatty acid oxidation strongly inhibits glucose and lactate oxidation at the level of pyruvate dehydrogenase (PDH); this inhibition is mediated by the high ratios of NADH/oxidized NAD and acetyl-CoA/free CoA induced by fatty acid oxidation, which feed back and inhibit flux through PDH (Figure 2). The rate of fatty acid oxidation can be pharmacologically decreased, and the rate of glucose and lactate oxidation increased, by inhibiting the enzymes of fatty acid oxidation or CPT-1 (Figure 2), or by activating PDH through inhibition of PDH kinase, the regulatory enzyme that phosphory-

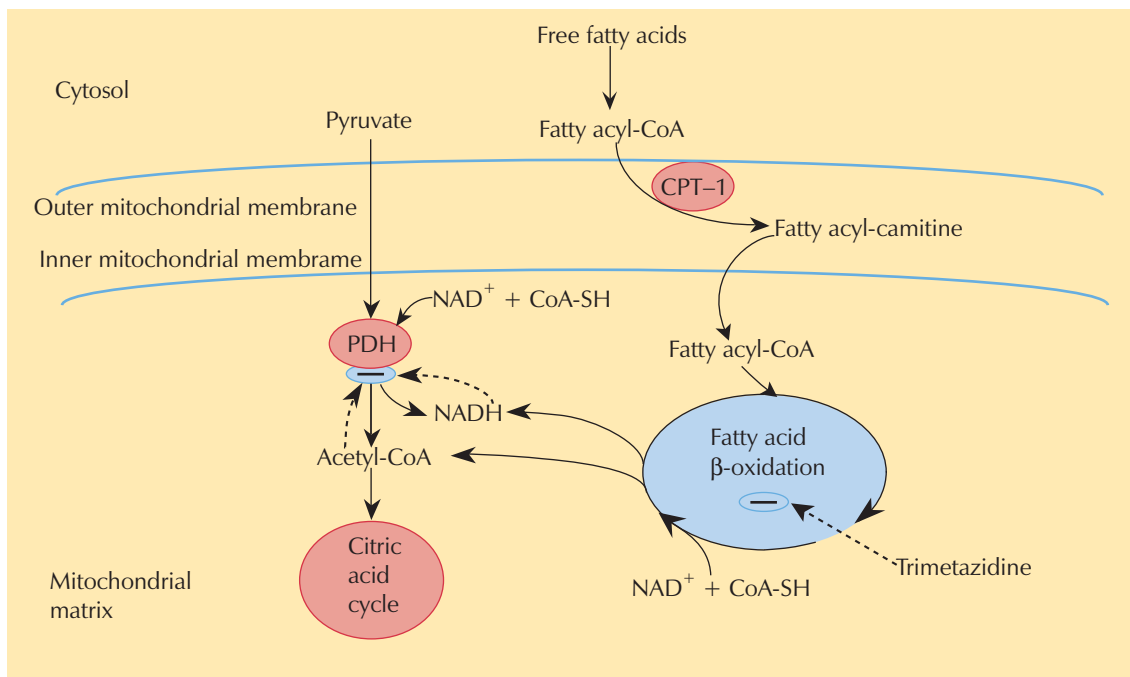


Figure 2. Regulation of mitochondrial carbohydrate and fatty acid metabolism. Fatty acids are esterified to fatty acyl-free coenzyme A (CoA) in the cytosol, which cannot pass the inner mitochondrial membrane. The enzyme carnitine palmitoyl transferase-1 (CPT-1) converts fatty acyl-CoA to fatty acyl-carnitine, which is transported into the mitochondrial matrix, reconverted back to fatty acyl-CoA, and undergoes β -oxidation to form acetyl-CoA and generate reduced nicotinamide adenine dinucleotide (NADH). Glucose and lactate are converted to pyruvate, which is oxidized by pyruvate dehydrogenases (PDH) to acetyl-CoA and NADH. The flux of pyruvate to acetyl-CoA through PDH is strongly inhibited by the NADH and acetyl-CoA formed from fatty acid β -oxidation. The antianginal drug trimetazidine inhibits the β -oxidation enzyme 3-ketoacyl thiolase, and increases the oxidation of pyruvate. CoA-SH, free Coenzyme A; NAD⁺, oxidized NADH.

lates and inhibits PDH.²⁵ When myocardial carbohydrate oxidation is acutely increased in heart failure patients by inhibiting PDH kinase with intravenous dichloroacetate there is a rapid improvement in left ventricular mechanical function.⁶ A similar effect is observed when pyruvate oxidation is increased with an intracoronary infusion of pyruvate.²⁶ We have shown that acute treatment with the partial fatty acid oxidation inhibitor ranolazine results in an increase in cardiac output and external ventricular power without an increase in myocardial oxygen consumption in dogs with microembolism-induced chronic heart failure.^{8,9} Thus there is good evidence that acutely reducing the rate of fatty acid oxidation and increasing carbohydrate oxidation improves mechanical function in the failing heart.

Is the progression of heart failure reversed or slowed by chronic treatment with drugs that switch cardiac substrate metabolism away from fat and towards carbohydrate oxidation? The answer to this question is not known. There is strong evidence that this approach works for the treatment of chronic stable angina. In double-blind placebo-controlled trials with partial inhibitors of cardiac fatty acid oxidation, such as the long-chain 3-ketoacyl-CoA-thiolase (3-KAT) inhibitor trimetazidine,^{27,28} or with perhexiline²⁹ or ranolazine,³⁰ there is a significant improvement in exercise duration and time to 1-mm ST-segment depression in patients with stable angina, despite no effect on heart rate or blood pressure. Trials specifically testing the effects of these agents in heart failure patients have not

been reported. A recent open-label study in NYHA class II–III heart failure with etomoxir (a partial inhibitor of fatty acid oxidation acting on CPT-1) showed improvement in exercise performance and left ventricular function (stroke volume and left ventricular ejection fraction at rest increased from 69 ± 4 to 92 ± 9 mL and from $21.5 \pm 2\%$ to $27.0 \pm 2.3\%$, respectively, after 3 months of treatment).^{10,31} As noted by Michael Bristow in his recent editorial in the *Lancet*,³¹ “[these results] are consistent with the hypothesis that etomoxir can favourably alter the expression of dysregulated genes that control contractile function in the failing human heart”. Preclinical results with the 3-KAT inhibitor trimetazidine suggest that direct inhibition of fatty acid oxidation improves survival in heart failure. When cardiomyopathic Syrian hamsters (a rodent model of heart failure with impaired myocardial carbohydrate oxidation)¹⁶ were given trimetazidine in the drinking water to achieve plasma levels similar to those found in clinical trials with stable angina patients, there was a significant 57% increase in survival time from 364 to 560 days.⁷ Taken together, these results suggest that inhibition of fatty acid oxidation can slow the progression of heart failure, and that therapies that chronically inhibit fatty acid oxidation and stimulate carbohydrate oxidation in the heart could result in a long-term improvement in clinical outcome.

There is some indication that the efficacy of β -adrenergic receptor antagonists in heart failure patients is associated with a switch in substrate metabolism from fat towards greater carbohydrate oxidation. Chronic treatment of heart failure patients with metoprolol³² and carvedilol³³ is associated with a significant shift in substrate metabolism away from fatty acids and towards carbohydrate oxidation and improved cardiac function. It remains to be established whether the switch in substrate use is causally related to improvement in left ventricular function.

Conclusion

In summary, the chronically failing heart has been shown to be metabolically abnormal, in both animal models and in patients. At present, there are few data on the effects of heart failure on the rates of myocardial glucose, lactate and fatty acid metabolism and oxidation; thus it is not possible to draw definitive conclusions about cardiac substrate preference in the various stages and manifestations of the disease. There is some indication that compensated NYHA class II–III heart failure patients have impaired carbohydrate oxidation, and that therapies that partially inhibit fatty acid oxidation and increase carbohydrate oxidation result in acute and chronic improvement in left ventricular function, and slow the progression of the disease. This intriguing hypothesis awaits clinical evaluation. ■

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Prevalence, increase, and costs of heart failure

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Introduction

Heart failure is recognized as a major and escalating public health problem in industrialized countries with aging populations. It is therefore of utmost importance to carry out epidemiologic and economic investigations into heart failure. Morbidity in heart failure patients, measured as quality of life or hospitalization rate, is high; if the heart failure is in an advanced stage and untreated,¹ the mortality rate in these patients is comparable to that in malignant neoplasia.² Heart failure patients may die as quickly as those suffering from pancreatic tumor and their suffering is probably no less. Nobody would question the necessity of investigating patients with a suspected malignancy using expensive CT or MRI technology. Measurement of sometimes questionable tumor markers is widely accepted, as are the costs of these treatment strategies, even in hopeless cases. Cancer patients receive treatment even at an advanced age.

Unfortunately, patients with heart failure are not managed in the same way as those with carcinoma. It is acknowledged that diagnostic evaluation and guideline-based treatment are not sufficiently widespread.³⁻⁵

Epidemiologic data on heart failure are available⁶⁻⁹ but are incomplete, for example with respect to the speed of the rising prevalence, which is certainly partly due to the increasing number of elderly. With heart failure, we may face a new medical challenge which may surpass epidemiological problems such as HIV or BSE. National and international heart failure registry data will help us to assess the magnitude of the epidemic and enable us to influence colleagues who do not adhere to heart failure guidelines, as well as health care insurance providers, administrators, and politicians.¹⁰

Prevalence

Any attempt to describe the epidemiology, growth rate and costs associated with heart failure must rely on a precise definition of what heart failure is (*Table 1*). The focus of this article is a clinical syndrome which also includes patients with asymptomatic disease labeled NYHA class I heart failure, for example asymptomatic left ventricular systolic or diastolic dysfunction.⁹ Many patients are not given a correct diagnosis, particularly those with mild to moderate heart failure in whom a diagnosis based solely on clinical findings is unreliable.¹³ In the heart failure population, cardiac function must be objectively assessed by echocardiography.^{14,15} Echocardiographic surveys of individuals within well-defined populations are needed.

Comprehensive reviews of the epidemiology and associated burden of heart failure have been published by McMurray et al⁸ and

Table 1. Definitions of heart failure.

- A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure (Wood, 1950)
- A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues (Braunwald, 1980)
- A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural, and hormonal responses (Poole-Wilson, 1985)
- Symptoms of heart failure, objective evidence of cardiac dysfunction, response to treatment directed towards heart failure (ESC Task Force, 1995)¹¹
- A complex clinical syndrome characterized by abnormalities of left ventricular function and neurohumoral regulation which are accompanied by effort intolerance, fluid retention, and reduced longevity (Packer, 1998)¹²

Cowie et al.⁷ The latter review gives a clear overview of the epidemiology of heart failure. Recently, McMurray and Stewart published a comprehensive update on the epidemiology, etiology, and prognosis of heart failure.⁹

One of the earliest articles on the epidemiology of heart failure came from the Framingham study.⁶

Analysis of 34 years of follow-up in the Framingham study provided clinically relevant insights into the prevalence, incidence, secular trends, prognosis, and modifiable risk factors of heart failure in a general population sample. Heart failure was found to be highly prevalent, affecting 1% of individuals in their fifties and rising progressively with age to afflict 10% of those in their eighties.⁶ The annual incidence also increased with age, from approximately 0.2% in individuals aged 45 to 54 years, to 4% in men aged 85 to 94 years, the incidence approximately doubling with each decade of age.

In the Framingham study, hypertension and coronary artery disease were the predominant causes of heart failure and accounted for more than 80% of all clinical events. Factors reflecting deteriorating cardiac function were associated with a substantial increase in risk for overt heart failure. These include poor vital capacity (demonstrated as pulmonary vascular engorgement resulting from malfunction of the left ventricle), sinus tachycardia, and ECG evidence of left ventricular hypertrophy. The risk of heart failure tended to increase progressively with heart rate throughout the range observed in both sexes but more prominently in men than in women. At a rate above 85 bpm, the risk of heart failure in men was almost double that of individuals with lower heart rates at all blood pressure levels. Modifiable predisposing risk factors for heart failure included hypertension, impaired glucose tolerance, elevated total:HDL cholesterol ratio, obesity, and cigarette smoking. We believe that using simple clinical evaluations and laboratory tests, it is possible to identify high-risk candidates for heart failure early in its course, thus enabling preventive management before irreversible myocardial damage occurs.⁶

During the 1980s, the annual age-adjusted incidence of congestive heart failure among individuals aged 45 years was 7.2 cases per 1000 in men and 4.7 cases per 1000 in women, whereas the age-adjusted prevalence of overt heart failure was 24 per 1000 in men and 25 per 1000 in women. Despite improved treatments for ischemic heart disease and hypertension, the age-adjusted incidence of heart failure has declined by only 11% per calendar decade in men and by 17% per calendar decade in women during a 40-year period of observation. In the pre- β -blocker era, however, congestive heart failure remained highly lethal, with a median survival of only 1.7 years in men and 3.2 years in women, and a 5-year survival of 25% in men and 38% in women.¹⁶

The abovementioned article by McMurray and Stewart,⁹ published in 2000, is the most recent on the epidemiology of heart failure. It demonstrates these data are principally available from five types of study:

- Cross-sectional and longitudinal follow-up surveys of well-defined populations: these have almost exclusively focused on individuals with clinical signs and symptoms indicative of chronic heart failure. Ongoing registries such as the IMPROVEMENT of HF,^{3,4} the Swiss Heart Failure Registry,⁵ and the future European Advanced Heart Failure Registry belong to this group. Most also include individuals from other types of study.
- Cross-sectional surveys of individuals who have been medically treated for signs and symptoms of heart failure within a well-defined region.
- Echocardiographic surveys of individuals within a well-defined population to determine the presence of left ventricular systolic dysfunction: one such survey is currently ongoing among an elderly population (age 70 to 80 years), organized by Ulf Dahlström in Sweden (personal communication).
- Nationwide studies of annual trends in heart failure-related hospitalization identified on the basis of diagnostic coding at discharge: the Euro Heart Failure Survey¹⁷ is a major attempt to describe the quality

of hospital care, both diagnostic and therapeutic, in patients with suspected or confirmed heart failure among member countries of the European Society of Cardiology (ESC). Patients will be interviewed subsequent to hospital discharge to assess their understanding of the condition, their side effects from and compliance with therapy, and their satisfaction with the management of their heart failure. The quality of management will be judged according to the recommendations contained in the ESC guidelines on the diagnosis and treatment of heart failure.^{11,19} Outcome will be further assessed by repeated interviews in 6–12 months' time. A further survey of heart failure in 2001/2002 is also planned. One article from Switzerland studied a

group of heart failure patients referred in 1998 to a university hospital.¹⁹ This study, however, was not nationwide.

- Comprehensive clinical registries collected in conjunction with clinical trials: these include a large proportion of individuals identified on the basis of having both impaired left ventricular systolic dysfunction and signs and symptoms of heart failure; the SOLVD and SPICE investigators set up this type of registry.^{20,21}

In the USA, there are some 5 to 6 million heart failure patients comprising about 600,000 new cases per year. In Switzerland, there are some 150,000 heart failure cases⁵ and equivalent to almost half the population of Zürich. The overall reported prevalence rate of heart failure in the UK, USA, and

Table II. Reported prevalence of heart failure according to McMurray and Stewart.⁹

| Study | Location | Overall prevalence rate | Prevalence rate in older age group |
|---|---|-------------------------|------------------------------------|
| Surveys of treated patients | | | |
| RCGP, 1958 ³² | UK national data | 3/1000 | — |
| Gibson et al, 1966 ³³ | Rural cohort, USA | 9–10/1000 | 65/1000 (>65 years) |
| RCGP, 1986 ³⁴ | UK national data | 11/1000 | — |
| Parameshwar et al, 1992 ²³ | London, UK | 4/1000 | 28/1000 (>65 years) |
| Rodeheffer et al, 1993 ²⁴ | Rochester, MN, USA | 3/1000 (<75 years) | — |
| Mair et al, 1994 ³⁵ | Liverpool, UK | 15/1000 | 80/1000 (>65 years) |
| RCGP, 1995 ³⁶ | UK national data | 9/1000 | 74/1000 (65–74 years) |
| Clarke et al, 1995 ²⁵ | Nottinghamshire, UK | 8–16/1000 | 40–60/1000 (>70 years) |
| Mohacsi et al, 2001 ⁵ | Switzerland | 4/1000 | — |
| Population screening | | | |
| Droller & Pemberton, 1953 ³⁷ | Sheffield, UK | — | 30–50/1000 (>62 years) |
| Garrison et al, 1966 ²⁶ | Georgia, USA | 21/1000 (45–74 years) | 35/1000 (65–74 years) |
| McKee et al, 1971 ²⁷ | Framingham, MA, USA | 3/1000 (<63 years) | 23/1000 (60–79 years) |
| Landahl et al, 1984 ²⁸ | Sweden (males only) | 3/1000 (<75 years) | 80–170/1000 (>67 years) |
| Eriksson et al, 1989 ³⁸ | Gothenburg, Sweden | — | 130/1000 (>67 years) |
| Schocken et al, 1992 ²⁹ | USA national data (NHANES) | 20/1000 | 80/1000 (>65 years) |
| Mittelmark et al, 1993 ³¹ | USA national data (Cardiovascular Health Study) | 20/1000 | 80/1000 (>65 years) |
| RCGP, 1995 | UK national data | 9/1000 (25–74 years) | 74/1000 (65–74 years) |

Table III. Reported incidence of heart failure in the literature.⁹

| Study | Location | Incidence rate | |
|--------------------------------------|------------------------------|---------------------------|--------------------------|
| | | Whole population | Older age groups |
| Eriksson et al, 1989 ³⁸ | Sweden (men born in 1913) | — | 10/1000 (61–67 years) |
| Remes, 1992 | Eastern Finland | 1–4/1000 (45–74 years) | 8/1000 (>65 years) |
| Ho et al, 1993 ¹⁶ | Framingham, MA, USA | 2/1000 | — |
| Rodeheffer et al, 1993 ²⁴ | Rochester, MN, USA | 1/1000 (<75 years) | 16/1000 (>65 years) |
| Cowie et al, 1999 ³⁹ | London, UK | 1/1000 | 12/1000 (>85 years) |

Sweden is between 3 and 20 per 1000 population and in the older age group ranges between 23 and 130 per 1000 population (Table II).^{7–9,22–31}

The reported incidence of heart failure was summarized in the literature as shown in Table III.⁹

er, to calculate a likely prognosis. Figure 1 depicts the incidence rate of congestive heart failure among Framingham heart study subjects according to gender and age. Since the aging population is growing, we will have to confront a continuing increase in the numbers of heart failure patients at least in the Western industrialized countries.

Outlook

As already indicated, we can expect a remarkable increase in the prevalence of heart failure in the foreseeable future. It is difficult, howev-

Heart failure in the elderly

Heart failure readmission rates, especially in the elderly, are high.⁴⁰ Clinical trials have shown that the case fatality related to heart failure is high but can be significantly reduced by medical therapies such as ACE inhibitors and, more recently, β -blockers. However, these studies have enrolled mainly middle-aged men and thus are unrepresentative of the general population of patients with heart failure, who tend to be elderly and distributed equally between the sexes. The prognosis of these older patients has been less well studied. MacIntyre et al⁴¹ evaluated current survival and the impact of newer therapies such as ACE inhibitors and fatality rates over a 10-year period in a large unselected population of 66,547 patients referred to hospital. The study revealed that heart failure fatality is much higher in the general population than in clinical trials, especially in the elderly. Although survival has increased significantly over the last decade, there is still room for improvement.

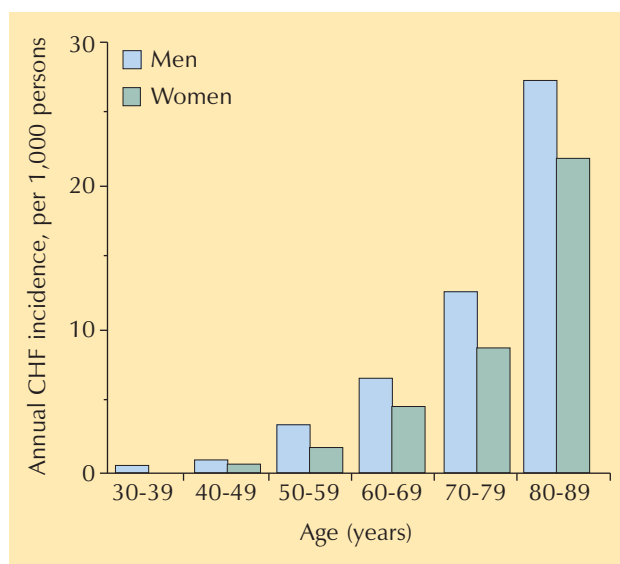


Figure 1. Incidence rate of congestive heart failure among Framingham heart study subjects according to gender and age.¹⁶

Nurse-directed, multidisciplinary intervention has been shown to improve quality of life and reduce hospital use and medical costs in elderly patients with congestive heart failure.⁴²

Impact on heart failure management

Only a small proportion of heart failure patients receive optimal treatment. There is a strong need to improve the care of patients with heart failure, encompassing the whole spectrum of patient management including diagnosis, medical treatment, and education of patients and relatives to increase their knowledge about heart failure and self-care. This could be achieved by dissemination of the specialized knowledge accumulated over many years in university-based heart failure centers. Regional heart failure centers should be established and staffed by specialist cardiologists. This strategy would enable the establishment of regional heart failure disease management programs and national cluster network systems. Since we are dealing with an epidemic, specially trained nurses must be employed in the future.⁴³ A number of countries have been using this successful comprehensive approach for many years.^{13,50,44-48}

Costs

Cardiovascular disease accounts for approximately 40% of the annual mortality in the USA, and ischemic heart disease is the main cause of death in both men and women.⁴⁹ Within the context of this enormous public health problem, there are some both encouraging and discouraging trends. On the one hand, the death rate from myocardial infarction, the main cause of death within the general category of cardiovascular disease, has been declining over the last 20 years. Yet, as patients live longer with coronary artery disease, or as it develops later in life, the related problem of heart failure from ischemic cardiomyopathy or other causes has emerged as a health problem of epidemic proportions with major socioeconomic implications.^{6,60} The high annual mortality, marked disability, and subsequent unemployability of subjects with heart failure are heavy burdens on society.

Heart failure consumes 1 to 2% of health care expenditure in a number of industrialized countries.⁸ Figure 2 depicts the heart failure admissions rate per year in Western developed countries from 1978 to 1993. Figure 3 summarizes the costs of chronic heart failure compared with total health care expenditure

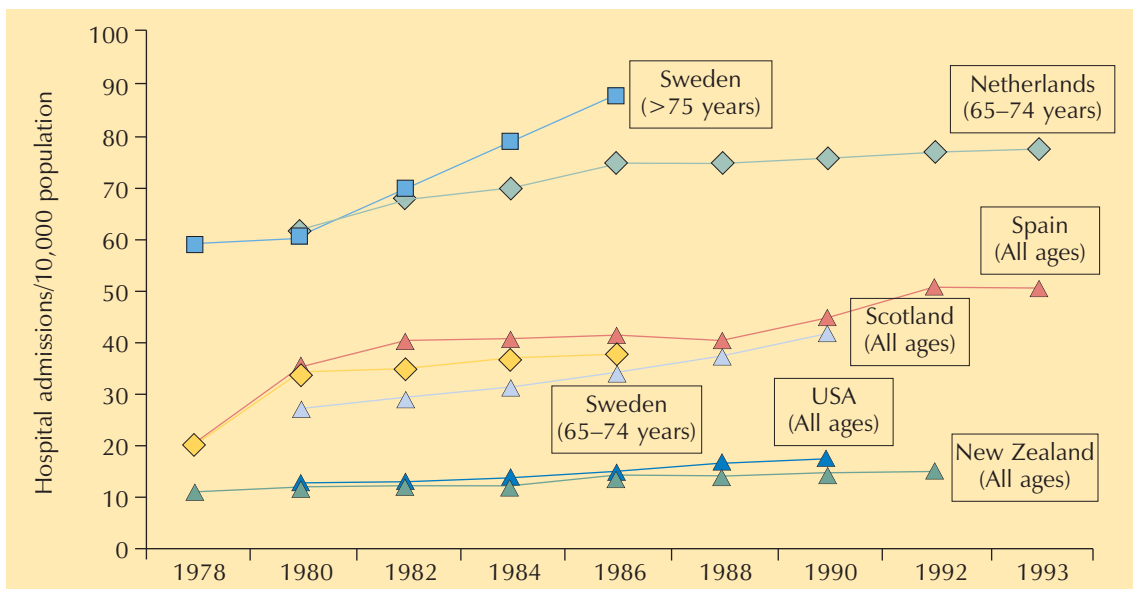


Figure 2. Heart failure admissions rate per year in Western developed countries from 1978 to 1993.⁸

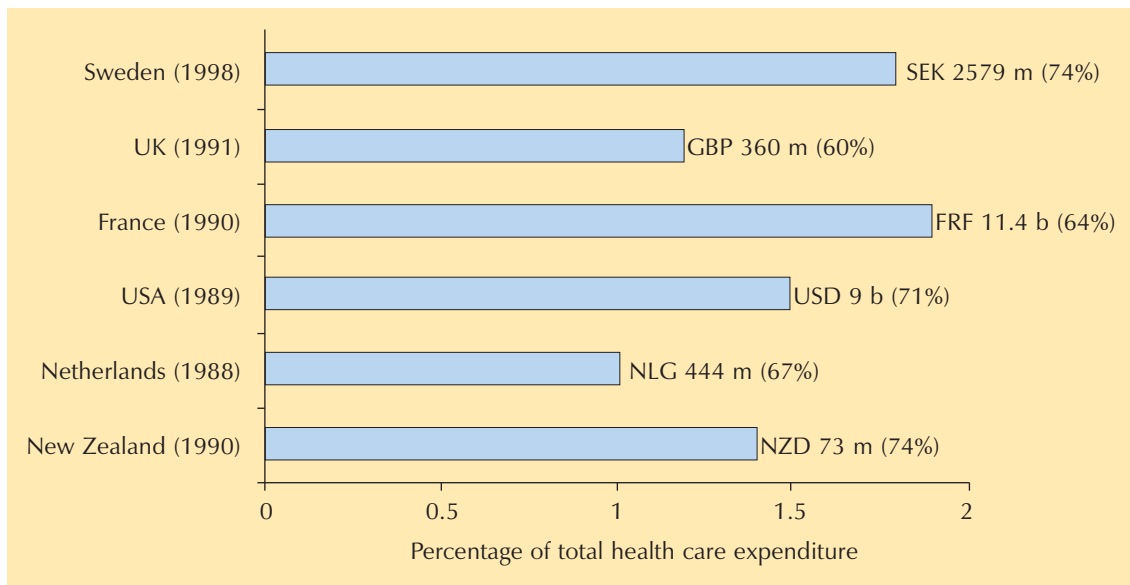


Figure 3. The component of hospital costs contributing to total expenditure quoted in the local currency and (in brackets) the percentage of chronic heart failure expenditure attributable to hospitalization.

in six different countries. Unfortunately, statistics regarding the prevalence and social costs of heart failure are only estimates because of the complexity of data collection.

In Sweden, the yearly costs associated with heart failure are estimated to be around USD 260 million;¹³ the hospital costs for heart failure account for up to 75% of total costs, whereas drugs only account for up to 8% of total costs.⁵² We know that the readmission rate for patients with heart failure is quite high (29% to 47%) within 3 months of discharge from hospital.^{40,53} Studies have shown that almost 50% of all readmissions might be preventable.^{40,53} Information and self-education among heart failure patients are inadequate and as a result compliance is low.⁵⁴

In the USA it is believed that at least USD 9 billion per year are spent caring for these patients and that about 300,000 people with heart failure die annually. These extrapolated numbers are taken from a 1993 publication.⁵⁰

Many accepted cardiovascular interventions, such as revascularization for multivessel disease (USD 50,000 per year of life gained) or the use of statins for hypercholesterolemia in middle-aged men at high risk for cardiovascular events (USD 30,000 per year of life gained), are associated with moderate

expense. By contrast, heart failure is one of the few conditions in which lives may be saved while significantly reducing costs. ACE inhibitors, β -blockers, and digoxin all appear to be cost-effective under widely differing sets of assumptions.⁵⁵ For example, calculations from the COPERNICUS study⁵⁶ revealed that if 1000 patients with heart failure similar to those in COPERNICUS were treated with carvedilol for 3 years, we would save about 200 lives (M. Packer, ESC 2000).

Being aware of the enormous impact of medical therapy of heart failure, there is no single strategy to prevent a global financial crisis in heart failure care. However, a set of recommendations has been proposed as a means to overcome major obstacles.⁵⁷⁻⁵⁹ Even with managed care and government efforts to control growth, United States' health spending per capita grew more rapidly in the 1990s than that in the average industrialized country.⁶⁰ Per capita health spending in 1997 ranged from a high of USD 3925 in the USA to a low of USD 260 in Turkey. Switzerland shares this problem as the country with the second-highest health care expenditure in the world (USD 2547 per capita). These data highlight the complexity of our modern health care system and show how economic calcula-

tions are difficult to make and can be biased. This has to be taken into account in discussions among specialist cardiologists, health care economists, and politicians. ■

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Metabolic imaging of heart failure

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Introduction

Cardiac metabolism is the basis for all cardiac processes such as contraction and maintenance of cellular structure and integrity. Therefore, abnormalities of metabolism may result in abnormalities of contractile function. In recent years, new data have become available giving insight into the metabolic abnormalities in patients with heart failure. In this overview, some of the aspects of the metabolic abnormalities in heart failure will be discussed with emphasis on energy metabolism and its noninvasive assessment using radiolabeled nutrients.

Exploring cardiac energy metabolism

Under normal conditions the heart uses a variety of substrates such as carbohydrates, lipids, and proteins. Of these nutrients, glucose, fatty acids, and acetate contribute most to the production of energy-rich phosphates, whilst other carbohydrates and proteins play a minor role. Availability (measured in plasma levels) strongly determines which substrate is oxidized. For example, during fasting there is a high blood level of fatty acids, and fatty acid oxidation provides 60 to 70% of the energy production,¹ whereas after a carbohydrate-rich meal, when glucose and insulin levels are increased, fatty acid contribution falls to approximately 30%, and 60% of the energy production is derived from glucose oxidation. During exercise the skeletal muscles produce lactate and this substrate is readily extracted by the heart, leading to a lactate energy production contribution of approximately 60%.

Under ischemic conditions with low flow and oxygen deprivation, the heart switches to anaerobic glycolysis, leading to production of lactate and a limited amount of ATP.¹

Exploring energy metabolism of the heart

Cardiac energy metabolism can be studied in patients either by invasive procedures in which the arterial system and the coronary sinus are cannulated, or by using radiolabeled nutrients. The invasive approach can only determine global extraction and uptake of nutrients. The advantage is, however, that lactate extraction and release can be measured. Radiolabeled glucose and structurally different labeled fatty acids have all successfully been employed in patient studies. The main advantage is that it is a noninvasive procedure and it can measure regional substrate uptake. No studies have yet been performed using labeled lactate.

Although glucose can be labeled with C-11, it is nowadays exclusively labeled with F-18 by replacing an OH group. After uptake, F-18 deoxyglucose (FDG) is converted to FDG-6-phosphate and is not further metabolized. Myocardial FDG uptake can be detected by both PET and SPECT.

Its main clinical application is the detection of dysfunctional but viable tissue that is able to recover in function either spontaneously (stunning after infarction) or after revascularization (hibernation or repetitive stunning). This has been discussed in detail in previous issues of *Heart and Metabolism* by Senior and Lahiri² and Bax et al.³

Free fatty acids can be labeled with C-11 (C-11 palmitate), F-18 thioheptadecanoic acid (FTHA), and I-123 (I-123 β -methyl-phenyl pentadecanoic acid, BMIPPA; heptadecanoic acid, IHDA; and ortho- and parapentadecanoic acid, oPPA and pPPA, respectively). C-11 palmitate undergoes β -oxidation and enters the Krebs cycle, releasing the radioactivity as C-11 CO₂. The rate of C-11 CO₂ release which is monitored during dynamic

PET imaging is related to the oxidation rate of fatty acids. However, several factors have limited its application. First, uptake and turnover of C-11 palmitate is dependent on substrate availability: for example, during high glucose/insulin levels, β -oxidation of palmitate is low because the heart switches to glucose oxidation. Therefore, metabolic imaging conditions need to be standardized. Second, part of the fatty acids do not undergo β -oxidation but are stored in triglycerides. Therefore, for accurate assessment of the oxidation rate, one needs to correct for the amount of stored fatty acids in triglycerides. Third, during conditions of ischemia, a variable amount of the fatty acids that are taken up by the myocardium are again released without undergoing metabolism. As this release cannot be distinguished from C-11 CO_2 release by the PET camera, accurate determination of the oxidation rate of fatty acids under ischemic conditions is difficult. Similar kinetics (and limitations) can be observed with the iodinated fatty acids IHDA and pPPA. In contrast to C-11 palmitate, the modified fatty acids FTHA, BMIPPA, and oPPA undergo only limited β -oxidation and are trapped in the myocardium, similarly to FDG.

A distinct tracer of myocardial metabolism is C-11 acetate. After uptake in the myocardium, acetate is converted to acetyl-CoA and immediately enters the Krebs cycle, releasing the radiolabel as C-11 CO_2 . Previous studies^{4,5} have demonstrated a direct relation between the rate of C-11 CO_2 release from the myocardium and oxygen consumption. In contrast to C-11 palmitate, turnover of C-11 acetate is not substrate-dependent and there is no back-diffusion under ischemic conditions. C-11 acetate imaging is therefore a unique technique to determine regional oxygen consumption of the heart (see reference 6 for an extensive overview).

These labeled fatty acids and acetate have been explored to characterize physiological and pathophysiological conditions in humans, but there are no established clinical indications in routine practice at present.

Metabolic changes in heart failure

During fetal development, the heart mainly uses glycolytic pathways for its energy metabolism. After birth the heart switches from glycolysis primarily to fatty acid oxidation. There is increasing evidence that in the failing heart, energy substrate utilization is changed: fatty acid oxidation decreases and the contribution of glycolysis increases. This pattern resembles the fetal situation.^{7–10} This changed pattern has been demonstrated both in rats and in humans. The reduction in fatty acid oxidation is not due to changes in substrate availability in the blood, since the reduced oxidation rate has also been demonstrated in isolated cardiomyocytes.¹¹ Moreover, Sack et al^{12,13} demonstrated in the failing human heart that the expression of genes that encode the cardiac enzymes for fatty acid oxidation is depressed. Thus, enzymes that are necessary for the metabolic handling of fatty acids are depressed, leading to a reduced rate of fatty acid oxidation. The main question is whether a reduction of the involved enzymes and the fatty acid oxidation rate can be a cause of (the transition to) heart failure, or whether it is only a secondary phenomenon.¹⁴ It is clear that genetic defects in fatty acid oxidation enzymes lead to childhood cardiomyopathies. However, in the adult situation the cause-effect relation is not clear and needs further study.

Metabolic imaging in heart failure

Heart failure can be caused by any cardiac disease (coronary artery disease, valvular disease, tachyarrhythmias, hypertrophic and idiopathic dilated cardiomyopathies) and also by a number of noncardiac diseases (hyperthyroidism, hypertension). Most data in the literature on metabolic imaging in heart failure are from cases of ischemic cardiomyopathy. This is not surprising given that ischemic cardiomyopathy has the highest incidence and prevalence among all cardiac diseases. However, idiopathic dilated cardiomyopathy (IDCM) is an interesting disease because coronary artery

disease is not present, and coronary under-perfusion is in principle not the primary cause of the metabolic abnormalities. Moreover, the data of Sack et al^{12,13} suggest that the abnormalities in gene expression of enzymes involved in fatty acid oxidation are present in both ischemic and nonischemic dilated cardiomyopathy.

Metabolic imaging in ischemic cardiomyopathy

From a clinical point of view it is important to distinguish irreversible necrosis from potentially reversible dysfunction (viable tissue). In necrotic/scar tissue no or little metabolic activity is present and no improvement in regional or global function after revascularization is to be expected. Necrotic tissue is characterized by a severe reduction in flow with a concomitant reduction in FDG or fatty acid uptake (flow-metabolism match). Also in these areas C-11 acetate clearance is slow.

In contrast, in dysfunctional but viable tissue, uptake of FDG is preserved relative to flow, indicating that the myocardium preferentially utilizes glucose (Figure 1). Fatty acid uptake is

decreased in viable tissue, as has been shown particularly with BMIPPA. It is more depressed than the concomitant reduced flow. Although confusing, in BMIPPA imaging the term mismatch is also used, but in this instance it indicates a more severe reduction of fatty acid uptake relative to flow, being the opposite to the flow-FDG mismatch. C-11 acetate imaging shows that in the areas of viable tissue the clearance rate of the radioactivity is reduced in comparison to that of normal myocardium. However, it is faster in comparison to the rate in infarcted tissue. These different patterns of FDG, fatty acid and C-11 acetate imaging have been extensively reviewed by Bax et al³ in *Heart and Metabolism*.

Metabolic imaging in IDCM

Although idiopathic cardiomyopathy has been studied with radiolabeled fatty acids, FDG, and C-11 acetate, the number of studies is very limited.

Geltman et al¹⁶ studied patients using C-11 palmitate and compared the cardiac fatty acid uptake with that of normal subjects and patients with myocardial infarction. These authors found that IDCM patients had, throughout the myocardium, multiple discrete regions with depressed fatty acid uptake, giving the myocardial images a “moth-eaten” appearance. This marked heterogeneity of fatty acid uptake was independent of perfusion and contractile abnormalities, and of the degree of myocardial thinning. Similar findings were observed by Höck et al,¹⁷ Ugolini et al,¹⁸ and Yazaki et al¹⁹ using various radioiodinated fatty acids.

Endocardial biopsy findings corroborate these observations: both patchy fibrosis and patchy metabolic derangements, including depression of oxidative phosphorylation and altered myocardial enzyme content, have been reported.^{20,21} Thus, abnormal myocardial fibrosis and regional depression of fatty acid oxidation may explain the observed scintigraphic abnormalities.

In contrast to the previous studies, Feinendegen et al²² did not observe heterogeneous

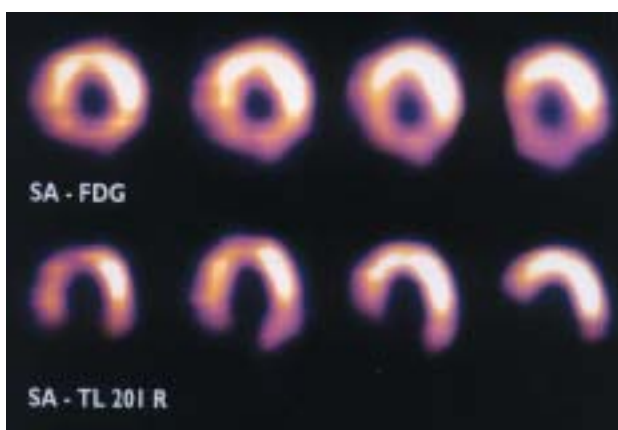


Figure 1. Short-axis views of glucose uptake (FDG) and resting perfusion (resting thallium-201) in a patient with left ventricular dysfunction. Depicted are mid-ventricular short-axis slices with the anterior wall at the top, the lateral wall on the right, the inferior wall at the bottom, and the septum on the left. A clear FDG mismatch (increased FDG relative to perfusion) is observed in the septal and inferior area. Reproduced from reference 15 with permission.

fatty acid uptake in patients with IDCM: in their study the fatty acid uptake was homogeneous, possibly related to the imaging technique. Using a combination of two fatty acids, oPPA (which is retained in myocardium) and pPPA (undergoing oxidation), they focused on the fatty acid oxidation rate. In their patients a highly variable rate of oxidation (higher, equal, and lower compared with normal subjects) was found. As the authors did not correlate their findings with hemodynamic and perfusion data, this approach needs further validation.

An interesting study has recently been reported by Yazaki et al,¹⁹ who correlated fatty acid (BMIPPA) uptake patterns with perfusion and follow-up data. First, the extent of fatty acid abnormality correlated with echocardiographic, hemodynamic, and biopsy data in the patients, suggesting that there is an association between the severity of disease and the extent of fatty acid abnormality. Second, patients with a more severe reduction of fatty acid uptake relative to perfusion, had an unfavorable follow-up in comparison to

patients with relatively preserved fatty acid metabolism (*Figure 2*).

Thus, most of the available evidence suggests that fatty acid metabolism is decreased in patients with IDCM. Preliminary results show that the degree of abnormality is correlated with the hemodynamic status and is associated with a poor prognosis.

IDCM is presumed to involve the myocardium diffusely and to have a homogeneous effect on function. However, heterogeneity in regional function has long been noted.^{23,24} Bach et al²⁵ correlated regional function with regional myocardial oxygen consumption using C-11 acetate and found that regions with relatively preserved function (although the mean ejection fraction was 21%) also had a higher oxygen consumption than regions with an average depressed function. The heterogeneity of metabolic abnormalities in this disease was also studied by van den Heuvel et al.²⁶ albeit in a different manner. These authors investigated C-11 acetate in areas with increased FDG uptake and found that C-11 acetate clearance (oxygen consumption) in this region was lower. As FDG is a tracer of glucose consumption (which can be metabolized aerobically and anaerobically), the data may indicate that a larger fraction of glucose is metabolized by anaerobic glycolysis. These observations are in line with animal experimental data showing that glucose oxidation was impaired despite acceleration of glycolysis.^{27,28} This uncoupling of increased glycolysis and unchanged or decreased glucose oxidation may lead to the production of lactate and protons. This is unfavorable since it leads to acidosis, a major cause of contractile dysfunction.¹⁴ An example of C-11 acetate images in patients with IDCM compared with normal subjects is presented in *Figure 3*.²⁹

The same group²⁶ also compared FDG uptake in these patients with that in normal subjects. Similar to uptake of fatty acids and acetate, uptake of FDG was inhomogeneous, comprising areas of normal, increased, and decreased uptake. This heterogeneity was also found by Yokoyama et al.³⁰ Interestingly, they divided IDCM patients into a group with and without events during follow-up. Although

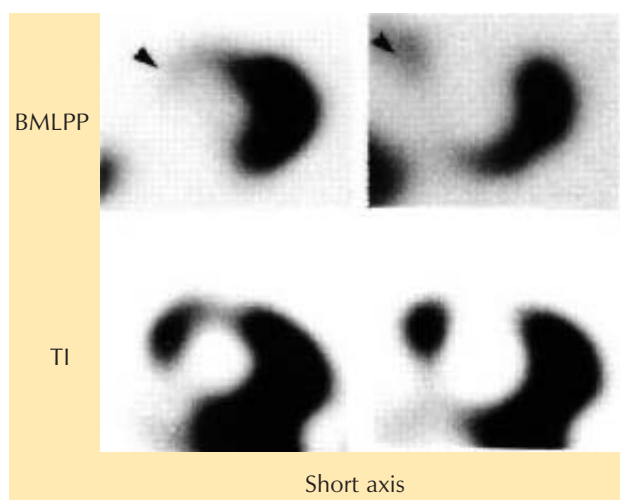


Figure 2. Short axis views of fatty acid uptake (BMIPPA) and perfusion in a patient with a cardiomyopathy. Depicted are mid-ventricular short-axis slices with the anterior wall at the top, the lateral wall on the right, the inferior wall at the bottom, and the septum on the left. Both matches (decrease of perfusion and fatty acid uptake) and mismatches (fatty acid uptake more decreased than perfusion) are observed in the septal area. Reproduced from reference 19 with permission.

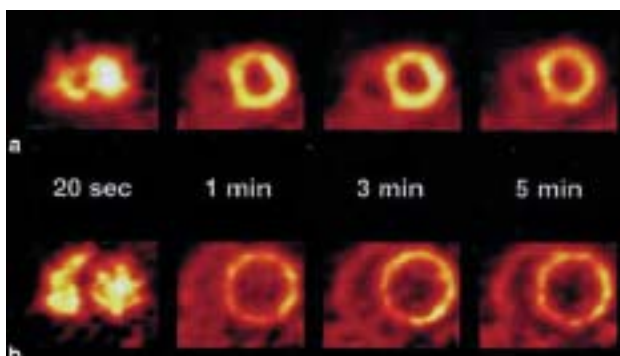


Figure 3. C-11 acetate images in a healthy individual (a) and in a patient with IDCM (b). Depicted are mid-ventricular short-axis slices with orientation similar to that shown in Figures 1 and 2. Soon after injection, activity is present in the blood pool with subsequent uptake and later washout by the myocardium. Reproduced from reference 29 with permission.

global FDG uptake was not different between the two groups and not different compared with normal subjects, the patients with events (worsening of heart failure, hospital admissions, and sudden death) had a significantly higher heterogeneity than patients with a favorable prognosis. Homogeneous FDG uptake also predicted improvement of left ventricular function on medical therapy with 85% accuracy. This accuracy was higher than that of clinical and hemodynamic parameters.

To summarize the available metabolic imaging data in IDCM, the most prominent feature is a strongly heterogeneous uptake and turnover of the different nutrients. In patients there is a reduction of fatty acid metabolism: the degree of abnormality is correlated with the hemodynamic status and is associated with an unfavorable prognosis. Similarly, regional function and regional oxygen consumption are highly variable, and there are indications that part of the increased glucose uptake is metabolized anaerobically. Finally, abnormal glucose metabolism is also an indicator of poor prognosis. It is a challenging concept that the oxidative metabolic abnormalities may contribute to the development of heart failure or to the transition from compensated to decompensated failure. If so, metabolic imaging may be powerful tool in clinical practice to discriminate between high- and low-risk patients. ■

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Latest trends in the treatment of ischemic heart failure: new perspectives using a metabolic approach

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Heart failure: a cardiovascular disease with a poor prognosis

Congestive heart failure (CHF) is a growing epidemic worldwide that results in significant morbidity and mortality, especially in aging populations.¹ Coronary artery disease, hypertension, and diabetes are the major etiologic risk factors.^{2,3} Continuing advances in the treatment of acute coronary syndromes that save many lives may result in a growing population of survivors with left ventricular dysfunction progressively leading to heart failure. Although preventive measures of cardiovascular risk factors have evolved in recent decades, including the management of hypertension, they have not reduced the incidence of CHF. Epidemiologic studies in Western Europe and the USA revealed that CHF is the leading indication for hospitalization in patients over 65 years of age.⁴⁻⁶ CHF is therefore a primary user of health care resources.

Ironically, the significant decline in mortality from coronary artery disease and hypertension, along with increasingly elderly populations, have significantly raised the prevalence and incidence of coronary heart disease.

Despite progress in the treatment of CHF with the use of ACE inhibitors,^{7,8} and more recently with the introduction of β -blockers,⁹⁻¹¹ the prognosis of this disease remains poor: in epidemiologic studies mortality has reached 40% at 1-year follow-up.¹²⁻¹⁵

Clinical examination, chest x-ray, ECG, and more recently, administration of brain natriuretic peptide, enable accurate diagnosis in most patients. Clinical practice guidelines for the management and treatment of CHF have been developed through careful evaluation of the international literature, generated from well-controlled randomized trials, large-scale epidemiologic studies, and expert opinions.

All recommendations in the European and North American guidelines emphasize the importance of both nonpharmacological (counseling, education, lifestyle modification, cardiac rehabilitation, and multidisciplinary intervention) and pharmacological treatment (ACE inhibitors, β -blockers, diuretics, digitalis). Nevertheless, experts agree that many patients do not receive the recommended optimal treatment.^{16,17} The main problem faced by physicians lies in its implementation. Indeed, the patients in unselected populations with CHF are older, include a higher percentage of women, have preserved systolic function, and have more concomitant disease than patients in clinical trials. Therefore, in applying the guidelines it is often difficult to obtain the target doses of ACE inhibitors and/or β -blockers. Adding other hemodynamic agents such as calcium channel blockers or angiotensin receptor blockers does not provide additional benefits in terms of mortality.¹⁸

Clinical research has therefore recently been oriented toward the development of new therapeutic agents to improve the status of patients with CHF.

Metabolic agents: a new therapeutic approach to myocardial ischemia

Recently introduced metabolic agents such as the new class of 3-KAT inhibitors represent a very promising and radically different approach to the treatment of coronary heart disease. Metabolic agents such as trimetazidine (Vastarel 20 mg) demonstrate interesting anti-ischemic and cardioprotective properties yet are free of any adverse hemodynamic effects. Trimetazidine, the first 3-KAT inhibitor available worldwide for clinical use in ischemic heart disease, was tested in patients

with severe cardiomyopathy and left ventricular dysfunction in three randomized trials.

The first double-blind, placebo-controlled study was reported by Brottier et al¹⁹ to examine the benefits of trimetazidine tid in addition to classic heart failure treatment in 20 patients. All patients had severe CHF (six patients in NYHA class IV, 14 in NYHA class III). At 6-month follow-up, dyspnea, left ventricular ejection fraction, and cardiac volume were significantly improved in the trimetazidine group in comparison with placebo ($P < 0.001$, $P < 0.018$, $P < 0.034$, respectively).

The initial promising results of Brottier et al were confirmed by more recent studies. Lu et al²⁰ administered oral trimetazidine tid vs placebo for 2 weeks in 15 patients with coronary artery disease and moderately reduced left ventricular ejection fraction with a positive response to dobutamine stress echocardiography. The end points of this double-blind, crossover study were improvement in the ischemic threshold, as measured by dobutamine dose and infusion time, and improvement in left ventricular function assessed by changes in wall motion score index (WMSI) at rest and at peak dobutamine. The total duration of the trial was 30 days. WMSI was significantly lower with trimetazidine tid than with placebo, both at rest and at peak dobutamine infusion ($P = 0.013$ and $P = 0.018$, respectively). Furthermore, trimetazidine significantly

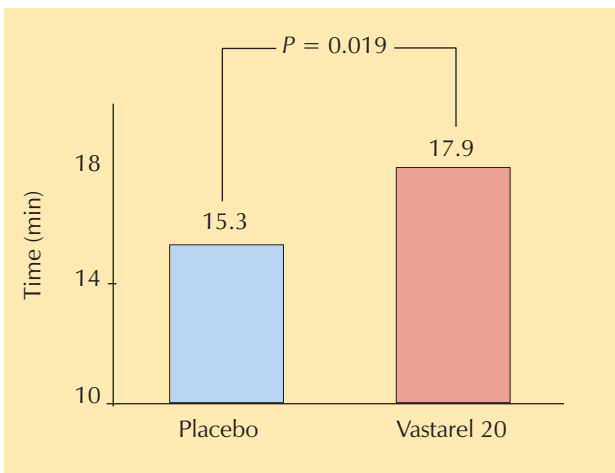


Figure 1. Vastarel 20 significantly induced a longer dobutamine infusion time.

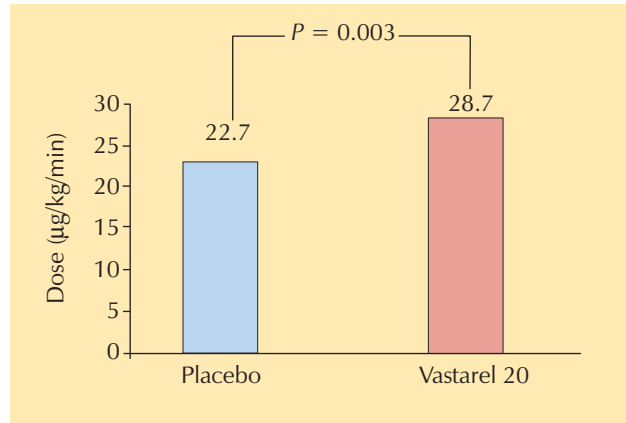


Figure 2. Vastarel 20 significantly induced a higher dobutamine infusion dose.

increased the dobutamine infusion time and provided an increase in the administered dobutamine dose ($P = 0.019$ and $P = 0.003$) (Figures 1 and 2). The results of this study indicate that trimetazidine may not only protect from dobutamine-induced ischemic dysfunction, but may also improve resting regional left ventricular function, without affecting hemodynamic parameters of myocardial oxygen consumption.

The above results are consistent with those of Belardinelli and Purcaro²¹ who, in a randomized, placebo-controlled study, examined the effects of trimetazidine tid vs placebo on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischemic cardiomyopathy. Thirty-eight patients with postnecrotic left ventricular dysfunction and multivessel coronary artery disease were randomized to either trimetazidine tid or placebo in two matched groups. At baseline and at 2-month follow-up, all patients underwent low-dose dobutamine echocardiography (5–20 µg/kg per min) and a symptom-limited exercise test. Patients treated with trimetazidine had a significant improvement in rest and peak systolic WMSI ($P < 0.001$) and in ejection fraction ($P < 0.001$), without changes in heart rate and blood pressure at follow-up. Additional benefits were observed with a significant increase in peak VO_2 in the trimetazidine group compared with placebo ($P = 0.001$).

These three randomized, double-blind,

placebo-controlled studies have demonstrated consistent results achieved with trimetazidine in chronic heart failure. Trimetazidine improves resting ventricular function in patients with coronary artery disease and various degrees of contractile impairment. It also appears to prevent or delay regional myocardial dysfunction, and ameliorate functional capacity, as assessed by peak VO_2 . Trimetazidine, which acts through inhibition of fatty acid β -oxidation, may have prognostic and therapeutic implications for the management of patients with ischemic heart failure and coronary artery disease in the future. ■

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Tachyarrhythmia-induced cardiomyopathy

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Introduction

Atrial fibrillation and heart failure are frequent cardiovascular disorders and are often connected. In the SOLVD treatment study,¹ 10% of patients with reduced left ventricular ejection fraction (<35%) and symptoms of heart failure also demonstrated atrial fibrillation. Even in patients with asymptomatic systolic left ventricular dysfunction the incidence of atrial fibrillation is as high as 4%.¹ Traditionally, the occurrence of atrial fibrillation in left ventricular dysfunction is considered to be the consequence of increased atrial loading, which in animal models favors profibrillatory changes of atrial conduction and refractoriness.² The following case report highlights the concept of tachycardia-induced heart failure, which suggests that in some patients rapid atrial fibrillation may be the cause, or at least a contributory factor, rather than the consequence of depressed left ventricular ejection fraction.

Case history

A 37-year-old housewife presented to her general practitioner complaining of dyspnea on exertion, dry cough, and palpitations persisting for 2 to 3 weeks. Her past medical history was relevant for episodes of palpitations, which had been linked to supraventricular ectopic beats. Antibiotic treatment had been started 1 week prior to her office visit but without any effect. Apart from oral contraception no other cardiovascular risk factors could be identified. An electrocardiogram showed atrial fibrillation with a fast ventricular rate of up to 190 bpm (*Figure 1*) and the patient was admitted to our hospital.

On examination she was afebrile, blood pressure was at 120/70 mm Hg, heart rate at around 160 bpm, and respiratory rate at

18/min. Heart sounds were normal, with no murmurs nor pericardial friction rub. There was bilateral basal pulmonary hypoventilation, with no pulmonary rales. Full blood count was within the normal range, and blood chemistry showed elevated D-dimers at 1680 mg/L. Echo Doppler examination of the leg veins and a pulmonary ventilation-perfusion scan ruled out pulmonary embolism. An echocardiogram showed a mildly dilated left atrium, moderate mitral regurgitation (*Figure 2A*) and severely depressed left ventricular systolic function, with an estimated ejection fraction of 20%. Thyroid function tests were normal. The patient was anticoagulated, put on an ACE inhibitor, and rate control was initially attempted with digoxin but with only a mild effect. Diuretics were given during the first days of hospitalization, which rapidly improved the symptoms of heart failure.

No specific causes for the decreased left ventricular function could be found either by history, physical examination, or ancillary tests. A cardiac angiogram showed normal coronary arteries. To reduce the heart rate, a β -blocker was started on the third hospital day but the ventricular response remained fast with an average heart rate of 110 bpm, varying between 82 bpm and 182 bpm during Holter monitoring. The decision was made to proceed with early cardioversion after exclusion of atrial thrombi by transesophageal echocardiography (TEE). This examination revealed mild spontaneous contrast in the left atrium, normal flow velocity, and no thrombus in the left atrial appendage (*Figure 3*). These findings allowed electrical cardioversion, which reverted the heart to normal sinus rhythm.

A follow-up echocardiogram performed 5 days after cardioversion showed a moderate to severe decrease of left ventricular systolic function (estimated ejection fraction 35%),

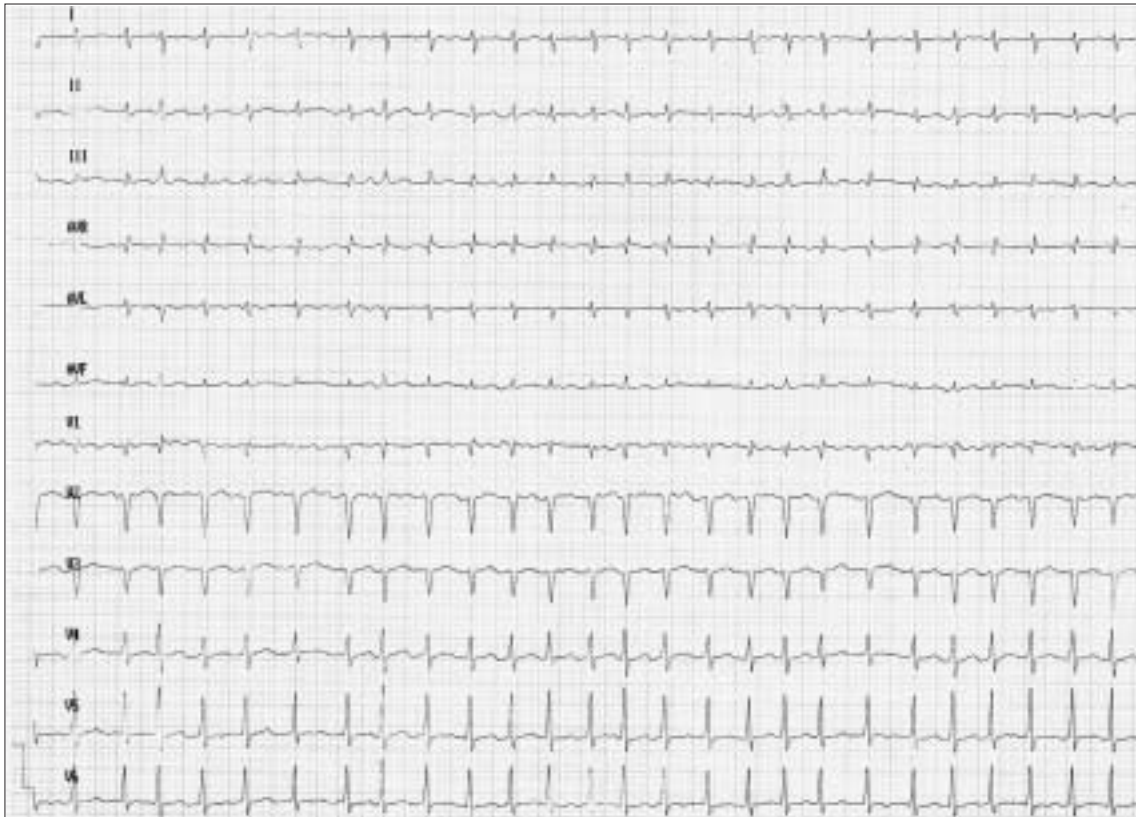


Figure 1. Twelve-lead surface electrocardiogram showing atrial fibrillation with a rapid ventricular rate of up to 190 bpm.

normal-sized cavities, and a regression of the mitral regurgitation (Figure 2B). The patient left the hospital on a β -blocker, an ACE inhibitor, digoxin, and anticoagulation.

The patient was seen again 8 months later while she was asymptomatic and remained in sinus rhythm. A new echocardiogram showed a normal-sized left ventricle and a normal left ventricular ejection fraction of 55%. In light of the fact that no other cause had been identified to explain the episode of severely decreased systolic function and the fact that the left ventricular function recovered after conversion to sinus rhythm, a diagnosis of tachyarrhythmia-induced cardiomyopathy was made.

Discussion

Tachycardia may reduce left ventricular ejec-

tion fraction by at least two mechanisms which, at the subcellular level, may be related. The first mechanism is the negative force-frequency relationship observed in heart muscle strips from severely failing explanted hearts.³ Accordingly, in contrast with normal hearts, the force of contraction, and consequently the ejection fraction at a given load, decreases with increasing heart rate. A proposed hypothesis for this “acute” deterioration of contractile force during tachycardia includes impaired calcium reuptake by the sarcoplasmic reticulum during tachycardia-related shortening of diastole.³ The second mechanism is progressive structural “remodeling” of the myocardium in response to long-lasting tachycardia, leading to persistent deterioration of myocyte function. Indeed, the hearts of pigs,⁴ dogs,⁵ and rabbits⁶ develop during rapid pacing for 2 to 4 weeks, morphological and functional alterations of the left

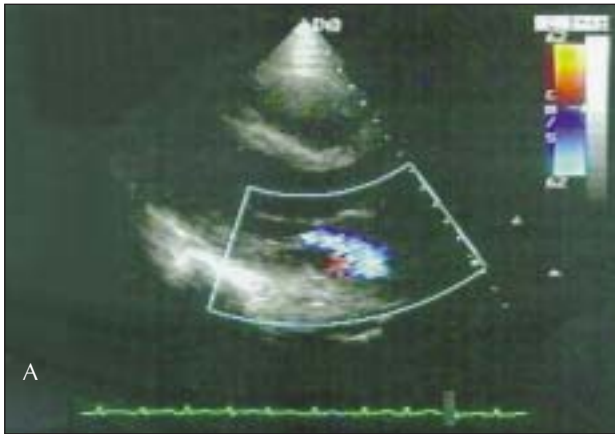


Figure 2. The transthoracic echocardiogram in the parasternal long-axis view depicts moderate mitral regurgitation (panel A) during atrial fibrillation, which disappears after cardioversion to sinus rhythm (panel B).

ventricular myocardium, which are similar to those observed in dilated cardiomyopathy. Among the observed changes in the myocyte phenotype is altered expression of cytoskeletal proteins,⁷ creatine kinase, and atrial natriuretic peptide.⁸ The reduced left ventricular function persists after cessation of rapid pacing, but may recover over a period of several weeks.

Although the concept of tachycardia-induced depression of left ventricular function has initially been documented under in vitro conditions, observations in patients indicate that the phenomenon is clinically relevant. In patients with atrial fibrillation and medically insufficient heart rate control, improvement of

left ventricular ejection fraction has been observed after direct current countershock (DC) cardioversion⁹ or ablation of the atrioventricular node and pacing.¹⁰ In our patient, ejection fraction improved only slightly immediately after cardioversion but recovered completely during the 8-month follow-up.

The case reemphasizes the importance of adequate heart rate control in patients presenting with depressed left ventricular function and atrial fibrillation. Classical treatment of decompensated heart failure by diuretics and ACE inhibitors alone may reduce heart rate to some extent by reducing sympathetic stimulation. Digoxin is often the preferred initial choice for additional heart rate control in patients with severe depression of left ventricular function. Diltiazem, which has proven at least as effective, entails the disadvantage of negative inotropy, and starting doses of β -blocker regimens of heart failure are often insufficient for this purpose, as was the case in this patient. Therefore, rapid cardioversion is often desirable.

In patients with atrial fibrillation lasting for more than 48 h, therapeutic anticoagulation for 3 to 4 weeks followed by medical or DC cardioversion is standard practice. Because of inappropriate medical heart rate control in our patient, TEE-guided cardioversion was selected. Using this approach, medical or electrical cardioversion is performed even

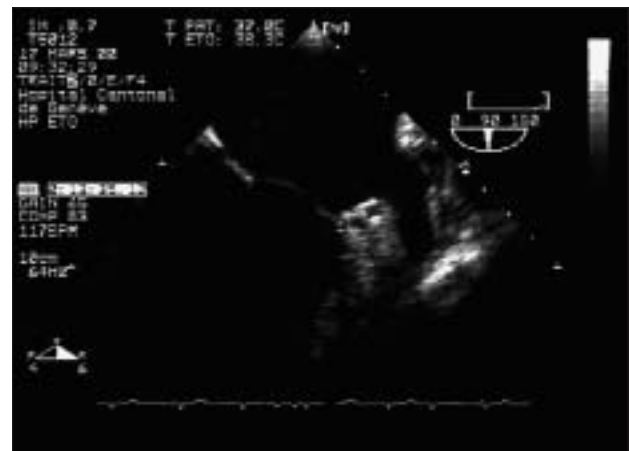


Figure 3. The left atrial appendage is examined during a TEE examination in which no thrombi could be detected.

after only a few hours of anticoagulation, provided cardiac intracavitary thrombus and intense spontaneous contrast are excluded at TEE. In the ACUTE study,¹¹ 1222 patients with atrial fibrillation and no indication for immediate cardioversion were randomized to cardioversion after either 4 weeks of anticoagulation or early exclusion of thrombus by TEE. The incidence of thromboembolic events within the 8 weeks of observation was not significantly different between groups, averaging 0.81% in the TEE group and 0.50% in the control group. Thus, TEE-guided cardioversion offers an alternative to the conventional approach and may be particularly useful in patients with severe depression of left ventricular function and insufficient medical heart rate control.

Conclusion

Although tachycardia may be considered to some extent a compensatory response of the failing heart to maintain cardiac output, inappropriate high heart rate, which is present in most cases of untreated atrial fibrillation, may be causally involved in the mechanisms underlying left ventricular dysfunction. Although a cause-effect relationship is not proven in the present case, the dramatic improvement of left ventricular function after restoration of sinus rhythm and the absence of an alternative explanation for reversible myocardial impairment suggest that tachycardia may have been a major contributory factor to heart failure. However, longer follow-up will be required to exclude subclinical myocardial disease. Furthermore, the history of this patient illustrates the interest of TEE-guided cardioversion in patients with heart failure and insufficient medical heart rate control. ■

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Featured Research

Abstracts and commentaries

Role of AMP-activated protein kinase in mechanism of metformin action

Zhou G, Myers R, Li Y, et al. *J Clin Invest.* 2001;108:1167–1174.

Metformin is a widely used drug for treatment of type 2 diabetes with no defined cellular mechanism of action. Its glucose-lowering effect results from decreased hepatic glucose production and increased glucose utilization. Metformin's beneficial effects on circulating lipids have been linked to reduced fatty liver. AMP-activated protein kinase (AMPK) is a major cellular regulator of lipid and glucose metabolism. Here we report that metformin activates AMPK in hepatocytes; as a result, acetyl-CoA carboxylase (ACC) activity is reduced, fatty acid oxidation is induced, and expression of lipogenic enzymes is suppressed. Activation of AMPK by metformin or an adenosine analog suppresses expression of SREBP-1, a key lipogenic transcription factor. In metformin-treated rats, hepatic expression of SREBP-1 (and other lipogenic) mRNAs and protein is reduced; activity of the AMPK target, ACC, is also reduced. Using a novel AMPK inhibitor, we found that AMPK activation is required for metformin's inhibitory effect on glucose production by hepatocytes. In isolated rat skeletal muscles, metformin stimulates glucose uptake coincident with AMPK activation. Activation of AMPK provides a unified explanation for the pleiotropic beneficial effects of this drug; these results also suggest that alternative means of modulating AMPK should be useful for the treatment of metabolic disorders.

Commentary

AMPK is an important regulator of energy metabolism in muscle. Activation of AMPK stimulates fatty acid oxidation and glucose

uptake in both heart and skeletal muscle. This article demonstrates that metformin, a drug used to treat type 2 diabetes mellitus, stimulates AMPK in muscle. This article also provides evidence that metformin activation of AMPK increases glucose uptake in skeletal muscle. Indirect evidence is provided to show that metformin may also activate fatty acid oxidation in muscle. Of interest is that this group uses a novel inhibitor of AMPK to overcome the effects of metformin on AMPK.

This paper provides important insights into the mechanism of action of metformin. Since AMPK is a key regulator of fatty acid oxidation and glucose uptake in the heart, it also raises the important question as to whether metformin has direct actions on cardiac energy metabolism. The identification of novel AMPK inhibitors may also have important therapeutic potential in the treatment of ischemic heart disease.

Gary Lopaschuk

Dipyridamole-induced increased glucose uptake in patients with single-vessel coronary artery disease assessed with PET

Araujo LI, McFalls EO, Lammertsma AA, Jones T, Maseri A. *J Nucl Cardiol.* 2001;8:417–420.

The aim of this study was to determine the relationship between vasodilatation-induced ischemia and post-stress glucose uptake. Coronary vasodilators may induce myocardial ischemia due to coronary steal through collateral circulation or transmural blood flow redistribution with diminished subendocardial perfusion. Myocardial ischemia can be demonstrated by increased glucose uptake as previously shown in patients with exercise-induced ischemia. We studied 11 patients with single-

vessel disease and no history of myocardial infarction. Five patients had no collateral circulation, and six had angiographic evidence of collateral vessels. We measured myocardial blood flow (MBF) and glucose uptake at baseline and after the administration of dipyridamole (0.56 mg/kg) with PET, using ^{15}O water and ^{18}F -fluorodeoxyglucose (FDG) as perfusion and glucose tracers. MBF at baseline was 0.82 ± 0.13 mL/g per min in normal areas and 0.80 ± 0.15 mL/g per min in areas supplied by stenotic arteries. MBF during dipyridamole was 2.05 ± 0.66 and 1.19 ± 0.66 mL/g per min in normal areas and areas with stenotic arteries, respectively ($P \leq 0.001$). FDG uptake at baseline was 1.36 ± 0.55 in normal areas and 1.57 ± 0.62 in areas supplied by stenotic arteries. FDG uptake after dipyridamole infusion was 1.79 ± 1.1 and 4.04 ± 0.84 in normal areas and areas with stenotic arteries, respectively ($P \leq 0.001$). MBF and FDG uptake were not different between patients with collateral circulation and those without collateral circulation. Increased myocardial glucose uptake was consistently observed after dipyridamole administration in those areas with diminished coronary vasodilatory capacity. The similar MBF and FDG findings in patients with and without collateral circulation may indicate that transmural blood flow redistribution appears to be a possible mechanism of dipyridamole-induced myocardial ischemia.

Commentary

Traditionally, the use of FDG has been limited to the assessment of myocardial viability. Patients with left ventricular dysfunction who show relatively preserved or increased FDG uptake in the dysfunctional areas (viable tissue), are likely to recover in function after revascularization.

From animal experimental studies it is known that during episodes of myocardial ischemia, uptake and turnover of glucose are increased in comparison with the nonischemic state. This observation forms the basis of the present study and of previous studies. In

1986, Camici et al¹ showed that patients with chronic coronary artery disease had an increased FDG uptake in the ischemic areas (hot spot imaging) after stress testing. In 2000, Abramson et al² compared the use of sestamibi SPECT and FDG PET after stress to detect coronary artery disease in women. The data suggested that FDG stress imaging was superior to conventional perfusion imaging due to avoidance of breast-related attenuation problems of perfusion imaging in women. Finally, in the present study, Araujo et al studied single-vessel coronary artery disease patients with FDG and perfusion PET after dipyridamole stress. The authors also found increased FDG uptake in the areas with decreased perfusion reserve and a stenosed coronary artery.

Thus, the available evidence suggests that FDG uptake is increased in post-stress ischemic tissue and this approach may be used as an alternative to detect coronary artery disease and ischemic tissue in patients. The interesting point is that this technique relies on a truly metabolic marker of ischemia rather than on using a flow tracer which indirectly points to the presence of ischemia; also that FDG can be used by both PET and SPECT systems, allowing widespread use in clinical research and practice. Nevertheless, much research needs to be done before it can be applied in cardiological practice. First, the data need to be confirmed in large clinical trials and the potential superior diagnostic and prognostic value of hot spot FDG stress imaging and its cost-effectiveness need to be established.

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Frans Visser

Left ventricular pressure-volume relations and myocardial dysfunction in pressure or volume overload

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The left ventricular (LV) end-systolic pressure-volume relation in clinical practice

The slope of the left ventricular (LV) end-systolic pressure-volume relation was first proposed as an index of LV contractility by Suga and Sagawa.¹ The slope of the LV end-systolic pressure-volume relation is called maximal LV elastance (E_{\max}) and is determined in the clinical setting by connecting, during titrated intravenous infusion of sodium nitroprusside, different LV end-systolic pressure-volume points (ie, the outer left-hand corners of the LV pressure-volume loops). LV end-systolic pressure-volume loops can be obtained clinically using invasive techniques² (ie, sequential LV contrast angiograms or sequential conductance catheter LV volume measurements and micro-manometer LV pressure recordings) or noninvasive techniques³ (ie, sequential two-dimen-

sional and targeted M-mode echocardiograms and indirect oscillometric brachial artery pressures).

Determination of the slope of an LV pressure-volume relation is cumbersome because it requires construction of at least two LV pressure-volume loops, one at rest and one after a pharmacological intervention such as an intravenous infusion of sodium nitroprusside. Numerous investigators have therefore tried to obtain similar information on LV performance from a single measurement of LV end-systolic performance. These measurements include (Figure 1): (1) LV end-systolic short-axis internal dimension and LV end-systolic volume; (2) LV end-systolic pressure/end-systolic volume ratio and LV peak-systolic pressure/end-systolic volume ratio; (3) LV end-systolic wall stress/end-systolic volume ratio and LV end-systolic wall stress/ejection fraction ratio.

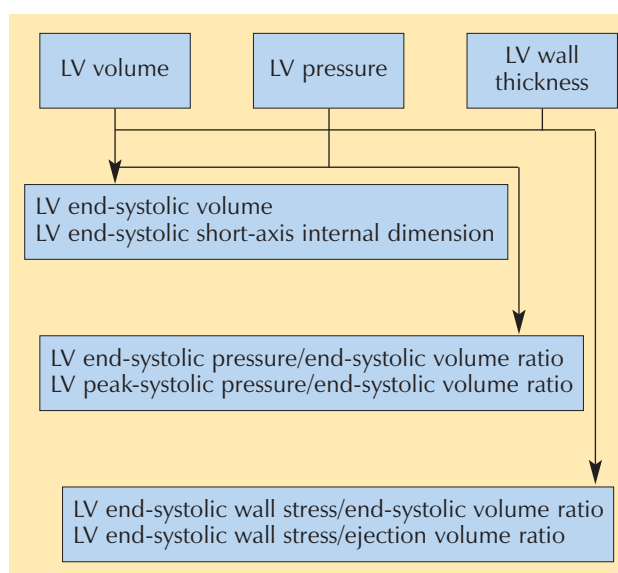


Figure 1. Overview of indices of LV end-systolic performance derived from the LV end-systolic wall stress/ejection fraction ratio.

LV end-systolic short-axis internal dimension and LV end-systolic volume

LV dimensions and volume at end-systole are independent of preload¹ and vary only with afterload. End-systolic LV dimensions and volume have therefore been proposed as an index of LV myocardial contractility in patients with LV volume overload of chronic aortic or mitral regurgitation and as a predictor of surgical outcome.^{4,5} Use of LV end-systolic dimensions or volume as an index of contractility assumes no derangement of LV afterload. This assumption is open to critique because LV afterload measured as LV end-systolic myocardial wall stress is higher in patients with chronic aortic regurgitation than in healthy subjects or patients with chronic mitral regurgitation.⁶ This higher than normal LV end-systolic wall stress in patients with chronic aortic regurgitation suggests replication of sarcom-

eres unable to increase LV wall thickness sufficiently to normalize the LV end-diastolic radius/thickness ratio⁷ and to normalize LV wall stress. This LV “afterload mismatch”⁸ should be taken into account when using LV end-systolic dimensions or volume as a guide to postoperative prognosis because correction of the afterload mismatch by valve replacement could induce a larger improvement in LV end-systolic dimensions or volume than predicted by preoperative measurements.

LV end-systolic pressure/end-systolic volume ratio and LV peak-systolic pressure/end-systolic volume ratio

To correct for afterload variability, investigators used the LV end-systolic pressure/end-systolic volume ratio or the LV peak-systolic pressure/end-systolic volume ratio as a surrogate measure of E_{\max} .⁹ In order for a ratio generated by a single point measurement to reflect the slope of a linear relation, the linear relation has to pass through the origin of the plot. This condition is not satisfied for LV pressure-volume relations in clinical practice, where the intercept of the LV end-systolic pressure-volume relation with the volume axis is variable certainly in dilated left ventricles.¹⁰ Moreover, substitution of LV end-systolic pressure by LV peak-systolic pressure is open to critique, particularly when the arterial pulse pressure is wide, as in chronic aortic regurgitation.

LV end-systolic wall stress/end-systolic volume ratio and LV end-systolic wall stress/ejection fraction ratio

To include the degree of compensatory LV hypertrophy, LV end-systolic pressure was substituted by LV end-systolic wall stress in several studies. LV end-systolic wall stress is indeed directly related to LV end-systolic pressure and LV end-systolic volume and inversely related to LV end-systolic wall thickness. The ratio between LV end-systolic stress and LV end-systolic volume was the only independent

predictor of surgical outcome in patients with LV volume overload due to chronic mitral regurgitation;¹¹ in patients with chronic aortic regurgitation the ratio between LV ejection fraction and LV end-systolic stress was a predictor of unfavorable outcome.¹²

When invasive techniques are used, other relations can be obtained simultaneously to corroborate conclusions on changes in contractility drawn from the calculation of E_{\max} . These relations include the LV dp/dt_{\max} -end-diastolic volume relation or the LV stroke volume-end-diastolic volume relation.¹³ When noninvasive techniques are used, simultaneous determination of the mean rate-corrected velocity of fiber shortening (v_{cf}) vs LV circumferential end-systolic wall stress provides another way to assess LV contractility in humans.¹⁴ This latter index corrects both for the inappropriate use of LV pressure as a measurement of LV wall force and for the unequal LV sizes and wall masses.

The LV diastolic pressure-volume relation in clinical practice

When discussing diastolic LV properties in clinical practice, a distinction needs to be made between diastolic LV distensibility, diastolic LV compliance, and diastolic LV stiffness (Figure 2).

Diastolic LV distensibility is defined by the position of the diastolic portion of the LV

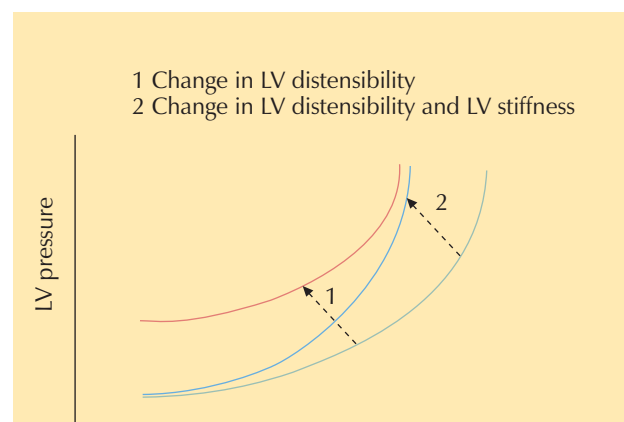


Figure 2. Distinction between LV distensibility and LV stiffness

pressure-volume relation in the LV pressure-volume plane. A reduction in diastolic LV distensibility implies an upward and leftward displacement of the diastolic portion of the LV pressure-volume relation and does not require a simultaneous increase in the slope of the diastolic portion of the LV pressure-volume relation.¹⁵ The diastolic portion of the LV pressure-volume relation can be obtained from a single beat, but such an approach includes dynamic effects related to LV relaxation and LV filling especially in the early diastolic portion of the graph.^{16–18} Using a caval balloon occlusion, several LV end-diastolic pressure-volume points can be obtained and a diastolic LV pressure-volume relation can be constructed, which is only composed of “static” LV end-diastolic pressure-volume points without “dynamic” interference related to LV relaxation or LV filling.^{19,20} End-diastolic LV distensibility is considered to be decreased if, in the presence of a normal LV end-diastolic volume index (<102 mL/m²), LV end-diastolic pressure is higher than 16 mm Hg.²¹

LV diastolic stiffness is the ratio of the change in LV diastolic pressure divided by the change in LV diastolic volume and equals the slope of the diastolic LV pressure-volume relation (dP/dV). LV diastolic compliance is the inverse of LV diastolic stiffness and therefore equals the change in LV diastolic volume divided by the change in LV diastolic pressure. As the diastolic LV pressure-volume relation changes its slope over its entire course, LV diastolic stiffness values need to be compared at a common level of LV diastolic pressure²² or the LV pressure-volume data points need to be logarithmically transformed to a linear relation, the unique slope of which equals the LV diastolic stiffness constant.²³ Recently, a relation was demonstrated between the deceleration time of the Doppler mitral flow velocity signal and the LV diastolic stiffness constant.²⁴ Myocardial diastolic stiffness has also been reported and equals the slope of the diastolic myocardial stress-myocardial strain relation and implies transformation of LV pressure to wall stress and of LV volume to myocardial strain.²³

In LV pressure overload, concentric LV

hypertrophy reduces LV diastolic distensibility and hinders LV filling at normal diastolic LV filling pressures. In order to maintain normal LV filling, left atrial filling pressures will rise and LV filling will become more dependent on left atrial contraction. Significant hemodynamic deterioration can result from the loss of atrial contraction because of the occurrence of atrial fibrillation. The reduction in LV diastolic distensibility in the hypertrophied left ventricle persists even after aortic valve replacement probably because of failure of regression of LV interstitial fibrosis.²⁵ In patients with aortic stenosis, the reduction in diastolic LV distensibility depends on both the sex and age of the patient, being most frequent in elderly men.²⁶

Summary

Indices derived from LV end-systolic pressure-volume relations have important prognostic value in LV volume overload of chronic aortic or mitral regurgitation. Their sequential determination is useful for correct timing of valve replacement or valve repair. Indices derived from diastolic LV pressure-volume relations are especially useful in concentric LV hypertrophy of aortic stenosis. They can remain abnormal for a prolonged period following valve replacement despite regression of LV hypertrophy because of persistence of LV fibrosis. ■

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Glossary

Gary Lopaschuk and William Stanley

Acetyl-coenzyme A (CoA)

Acetyl-coenzyme A (CoA) is an important intermediate of many biochemical pathways. For instance, acetyl-CoA is an important product of the mitochondrial metabolism of fatty acids and carbohydrates. Acetyl-CoA produced from these carbon substrates feeds into the mitochondrial tricarboxylic acid cycle (or Krebs cycle), which when coupled to the mitochondrial electron transport chain results in the production of energy (in the form of ATP).

Anaerobic glycolysis

Anaerobic glycolysis is the first part of the metabolic pathway for glucose. The glycolysis pathway metabolizes glucose to pyruvate, and in the process produces energy in the form of ATP. The glycolytic pathway can be considered “anaerobic” since no oxygen is required for the production of ATP (unlike aerobic mitochondrial metabolism, which requires oxygen).

Carnitine palmitoyl transferase-1 (CPT-1)

Carnitine palmitoyl transferase-1 (CPT-1) is the rate-limiting enzyme involved in the uptake of fatty acids into the mitochondria. It converts fatty acyl-coenzyme A to fatty acylcarnitine, which is then transported into the mitochondria where it is further metabolized. CPT-1 is a highly regulated enzyme that prevents excess amounts of fatty acids from being taken up into the mitochondria.

Cytokines

Cytokines refer to a group of compounds that are produced under a variety of conditions, including the immune response and inflammatory reactions. Tumor necrosis factor- α and interleukin-1 are examples of two cytokines.

Cytoskeletal proteins

Cytoskeletal proteins are important structural proteins of the cell that have an important role in maintaining cell shape and structure.

Endothelin-1

Endothelin-1 is a vasoactive peptide that is primarily produced by endothelial cells. This peptide is a very potent vasoconstrictor.

Heptadecanoic acid (IHDA)

Heptadecanoic is a 16-carbon fatty acid that can be radiolabeled and used as a tracer for fatty acid uptake into the heart. One of the radiolabels that can be attached to heptadecanoic acid is a ^{123}I group, which produces ^{123}I -heptadecanoic acid (IHDA). A gamma-camera can then be used to measure ^{123}I -heptadecanoic acid uptake into the heart. This approach is used to assess fatty acid metabolism in the heart.

I-123 β -methyl-phenyl pentadecanoic acid (BMIPPA)

I-123 β -methyl-phenyl pentadecanoic acid (BMIPPA) is a radiolabeled fatty acid analog that can be used as an imaging agent to assess fatty acid uptake into tissues. It is often used to determine whether fatty acid uptake is altered in the hearts of patients. This is established by using a gamma-camera to determine the amount of BMIPPA taken up by the heart.

Long-chain 3-ketoacyl-CoA-thiolase (3-KAT)

Long-chain 3-ketoacyl-CoA-thiolase (3-KAT) is the last enzyme in the mitochondrial pathway that is involved in the metabolism of fatty acids (fatty acid β -oxidation). Recent interest has focused on 3-KAT, since selective inhibition of this enzyme decreases fatty acid oxidation and protects the ischemic heart.

Nicotinamide adenine dinucleotide (NADH) and the electron transport chain

Nicotinamide adenine dinucleotide (NADH) is an important molecule that is both a substrate and a product of many biochemical reactions. In mitochondria, the production of NADH by the catabolism of fatty acids and carbohydrates enters the electron transport chain. The electron transport chain transfers electrons through a number of different enzyme complexes which catalyze the pumping of protons out of the mitochondrial matrix. These protons can then pass back into the mitochondria via an enzyme called ATP synthase. The downhill electrochemical gradient of this process produces energy that results in the production of ATP from ADP. ATP is a form of chemical energy used in most cellular processes requiring energy.

Orthophenylpentadecanoic acid (oPPA)

Orthophenylpentadecanoic acid (oPPA) is a fatty acid analog that can be radiolabeled (eg, with ^{123}I) and used as an imaging agent to assess fatty acid uptake into tissues. It is often used to determine whether fatty acid uptake is altered in the hearts of patients. This is established by using a gamma-camera to determine the amount of radiolabeled oPPA taken up by the heart.

Paraphenylpentadecanoic acid (pPPA)

Paraphenylpentadecanoic acid (pPPA) is a fatty acid analog that can be radiolabeled (eg,

with ^{123}I) and used as an imaging agent to assess fatty acid uptake into tissues. It is often used to determine whether fatty acid uptake is altered in the hearts of patients. This is established by using a gamma-camera to determine the amount of radiolabeled pPPA taken up by the heart.

Pyruvate dehydrogenase (PDH) kinase

Pyruvate dehydrogenase (PDH) kinase is an intramitochondrial kinase that phosphorylates and inhibits PDH. Since PDH is the rate-limiting enzyme for the mitochondrial metabolism of carbohydrates, activation of PDH kinase will result in a decrease in the mitochondrial metabolism of carbohydrates. Maintaining mitochondrial glucose metabolism is an important therapeutic strategy to protect the ischemic heart. Therefore, inhibition of PDH kinase is a potential therapeutic approach to treating ischemic heart disease.

Thioheptadecanoic acid

Thioheptadecanoic is a 16-carbon fatty acid that can be radiolabeled and used as a tracer for fatty acid uptake into the heart. One of the radiolabels that can be attached to heptadecanoic acid is an ^{18}F group resulting in 18-fluoro-thioheptadecanoic acid (FTHA). A gamma-camera can then be used to measure FTHA uptake into the heart. This approach is used to assess fatty acid metabolism in the heart.