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Chronic ischemic heart disease

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The average annual mortality for patients with chronic ischemic heart disease and stable angina is 2–3% – that is, twice that of age-matched controls. Certain patients, however, are at much higher risk. This high-risk subgroup includes patients with easily inducible ischemia, and patients who have suffered previous myocardial infarction.

After many years in which cardiologists mostly focused on acute ischemic syndromes, today more attention is being paid to chronic ischemic heart disease. Chronic ischemic heart disease is increasingly recognized as a very dynamic condition. In addition to overt acute myocardial infarction, which can precipitate at any time in patients with “stable” angina pectoris, clinical and subclinical ischemic events may accumulate and, in the long term, generate diverse states of chronic cardiac dysfunction. Repetitive episodes of ischemia, whether stress induced or spontaneous, symptomatic or silent, may progressively impair myocardial contractile performance through myocardial stunning or hibernation, and eventually lead to left ventricular remodeling and heart failure.

Evidence is accumulating that genetic variability and altered gene and protein expression contribute significantly to clinical outcomes in ischemic heart disease. Data from “omics” studies show potential to help in the development of novel, more individualized, therapeutic approaches in coronary artery disease.

New imaging techniques may help in diagnosing heart failure, its causes, course, and prognosis. Positron emission tomography, by enabling the assessment of myocardial perfusion and metabolism, and magnetic resonance imaging, allowing the evaluation of myocardial necrosis and microvascular damage, can predict contractile recovery after revascularization procedures.

Papers in this issue of Heart and Metabolism contribute to a better appreciation of the complexity of chronic ischemic syndromes and a better understanding of the prognostic impact of current therapies, stimulating the search for innovative approaches to the evaluation and treatment of this common disorder.
Genomics, transcriptomics, and proteomics of the ischemic heart

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Abstract
Recurring ischemia and hypertension present the major risk factors for coronary artery disease with its main acute (myocardial infarction) and chronic (chronic heart failure) manifestations. Both pathologies have a strong genetic basis. To unravel the complexity of these conditions, biomedical research is evolving from reductionism focusing on specific candidate genes toward a more integrative view (‘systems biology’). Based on newly available high-throughput technologies, evidence is accumulating that genetic variability and altered gene and protein expression contribute significantly to pathophysiologic outcomes. Data from ‘omics’ studies will help to develop novel, more individualized therapeutic approaches in coronary artery disease.

Keywords: Genome, hypertension, ischemia, proteome, transcriptome

Introduction
The term “omics” is a general one describing the science of integrating the biological information about genes and proteins and finding their inter-relationships, with the ultimate aims of understanding and manipulating the regulatory mechanisms (Figure 1). “Genomics” refers to the study of the overall structure and expression of the entire genetic inheritance, including molecular genetics (DNA level or genotype), transcriptomics (mRNA level), and proteomics (protein level). Recently, the term “omics” has been further expanded to include metabolomics (study of all small-molecular-weight organic and inorganic compounds produced by the cell) [1] and kinomics (a subgroup of the proteome, encompassing all protein kinases as they exert crucial roles in eukaryotic cell biology) [2,3].

Acute and chronic ischemia
An ischemic heart is not just an “ischemic heart”. Thus the following brief characterization of the most common ischemic states is given, to enable a better summary of the literature on the “omics” in ischemic...
heart disease. Myocardial infarction is the most acute manifestation of coronary heart disease (CAD). More than 60% of myocardial infarctions occur in patients older than 65 years, and age is the strongest predictor of 30-day mortality after acute myocardial infarction. Clinical and subclinical myocardial acute ischemic events may accumulate and – in the long term – generate diverse states of chronic cardiac ischemia. Protracted reduction of blood flow or repetitive episodes of ischemia may lead to the states called “preconditioning”, “stunning”, and “hibernation” [4–7]. Stunning is characterized by contractile dysfunction while blood flow and metabolism remain normal; hibernation presents a more severe state in which blood flow and energy production are reduced in combination with almost no contractility. Persistent stunning can lead to hibernation [8]. In reality these two states are gradually interchanging, and cannot be clearly distinguished. Very little or no cell death occurs during stunning and hibernation and, consequently, these states are reversible [6]. In contrast to stunning and hibernation, ischemic and pharmacological preconditioning have been reported to have a beneficial effect on long-term outcome in patients with chronic ischemic heart disease [9,10]. Clinically and subclinically acute ischemic events may accumulate over a period of time, generating a state of chronic cardiac ischemia. Unlike acute ischemic episodes, whatever the nature of a chronic ischemic state, transcriptional profiling poses difficulties for analysis and interpretation. In particular, chronic human heart disease may present widely varying transcriptome and proteome patterns, influenced by the patient’s age, sex, and inheritance, the time point in the course of the disease, and the underlying disease etiologies such as atherosclerosis, hypertension, or diabetes.

In addition, valid controls for comparison are difficult to obtain in human studies. For these reasons, the available information relates mostly to animal models.

**Genetics of ischemic heart disease**

A genome-wide search using high-throughput sequencing technologies is required to map single nucleotide polymorphisms (SNPs) and the different structural variants of DNA such as microsatellites, minisatellites, insertions or deletions, reversions, multiple gene copy numbers, and expanded nucleotide repeats (Figure 2) [11,12]. The most comprehensive catalog of known structural variations is the Database of Genomic Variants (http://projects.tcag.ca/variation/) with around 4000 entries at ~2200 loci, covering a staggering 405 Mb (14%) of the human genome sequence. The sizes of the entries in the Database range from 1 kb to 3.89 Mb, with a median of 103 kb. Alternatively, as of March 2008, the International HapMap Consortium (http://www.hapmap.org) has developed a map covering the entire human genome, representing ~3.9 million SNPs or one SNP per ~700 bp [13,14]. The HapMap project is designed to provide the means to link genetic variants to the risk for specific diseases and to correlate SNP profiles with drug response patterns. Because of structural variants and SNPs, the identity of the genomic sequence between two individuals is reduced to a mere 85%.

In CAD and its associated risk factors, several genes predispose to the final phenotype, each contributing only a modest amount. Thus only after all genetic modifiers and their functions have been identified will it be possible to develop more appropriate therapies. Furthermore, multigene disorders require genome-wide association studies involving genotyping hundreds of thousands of DNA markers in a large number of individuals, and with replication in independent populations. The first confirmed locus associated with CAD is located on chromosome 9p21.3 [15–18]. In essential hypertension – the most common risk factor for cardiovascular morbidity and
mortality – genome-wide linkage analyses provide some consistency of linkage results in few chromosomal regions on chromosomes 1, 2, 3, 17 and 18 [19,20].

Transcriptome after myocardial infarction

The changes in the transcriptional profile found after acute global ischemia followed by reperfusion or in vivo after regional ischemia strongly depend on the duration or the severity, or both, of the ischemic insult [21–24]. A microarray analysis of the rat heart during infarction and remodeling revealed a strong increase in the expression of atrial natriuretic peptide and smaller but significant changes in genes involved in protein synthesis, cytoskeletal and extracellular matrix proteins, and genes related to energy metabolism [24]. The infarct zone (50% of the left ventricle) associated with a permanently ligated left anterior descending coronary artery was found to be characterized within the first 24 h by transforming growth factor β-1 and an overriding depression in transcription, signal transduction, inflammation, and extracellular pathways. Within the same first 24 h of infarction, in the unlesioned remote zone, expression of genes was reciprocally activated, including interleukins 6 and 18 among others, and tumor necrosis factor-α [21]. At day 28 after the ligation procedure, genes for signal transduction, inflammation, transcription factors, metabolism, and detoxification – all classes previously depressed in the day-1 infarct zone – dominated the day 28 infarct zone. Genes for extracellular matrix components were also high, whereas indices of cell growth and replacement remained low. Gene expression in the remote zone on day 28 followed the day-1 pattern, with a reduction in the number of affected genes. Thus survival in the face of a massive infarct induces a compensatory strategy in the remote zone, followed by a delayed activation of the same pattern in the infarct zone. The transcriptional program activated in the surviving myocardium after a long period of ischemia thus supports the concept that postinfarct remodeling proceeds globally as a result of the sustained pathologic activation of initially compensatory molecular responses [21,25].

Transcriptome in chronic ischemia and human heart failure

Ischemic heart disease is the most common underlying cause eventually leading to left ventricular hypertrophy and heart failure. Non ischemic hypertrophic (HCM) and dilated (DCM) cardiomyopathies (25–35%) may derive from hypertension (~17%), valve pathologies (~13%), and hereditary gene defects in the contractile and cytoskeletal proteins (≥20%). The concept that genes encoding proteins with similar functions or involved in the same pathway are responsible for a particular disease has led to the hypothesis of a “final common pathway” operating in DCM [26]. The hypothesis may be further supported by the fact that consistent changes in genes related to energy metabolism (already detected early in acute ischemia, as reported in the previous section) occur across HCM, DCM, and ischemic (ICM) cardiomyopathies, despite the conditions having quite different etiologies [27]. Moreover, in contrast to previously reported data [28], it has been found that ICM and non ischemic cardiomyopathy exhibit substantial heterogeneity at the transcriptomic level and do not display a characteristic etiology-specific signature [29]. If the concept of the “final common pathway” postulated for DCM with different etiologies is extrapolated to endstage heart failure, one would expect that a common signature of the transcriptome may develop in the terminally failing heart, independent of the initial disease. Because this important question could not be solved by a series of studies examining sets of genes in the human cardiac transcriptome associated with heart failure [30], a novel approach was adopted in which it was hypothesized that a discrete set of cardiac transcription factors may regulate gene activity in the pathogenesis of heart failure. Insight into transcription factor function was obtained by comparing data on microarray gene expression in cardiac tissue collected at a single time point from patients with advanced heart failure (DCM or ICM) against murine genome sequence data. The results indicated that, besides the known transcription factor families, nuclear factors of activated T-cells (NFAT), myocyte enhancer factor-2 (MEF2), Nkx, and GATA, several additional transcription factors are active in human heart failure, notably the Forkhead Box (FOX) family (FOXC1, C2, P1, P4, and O1A). However, NFAT activity is more closely associated with heart failure in DCM (suggesting a more prominent role for abnormal Ca²⁺ signaling and calcineurin-mediated transcription), and the transcription factor family CCAAT-enhancer-binding proteins (C/EBP) (which are modulated by inflammation and mitogen-activated protein kinases) with heart failure in ICM. These findings would indicate that different subsets of genes are altered in different types of human heart failure, possibly reflecting the different disease etiologies [30].

Studies of patients with a left ventricular assist device (LVAD) ([31] and references therein) have shown that the failing human heart retains plasticity. LVAD support induces a regression of pathological hypertrophy, improvements in contractile performance and contractile reserve, regression of pathological electrophysiological markers, and reduction
in myocardial cytokines and apoptosis. However, it is sobering to note that, from more than 3000 genes showing significant changes in failing hearts, only 16 reverted to normal levels (four displaying overcorrection) and 27 showed only partial reversion after LVAD treatment. Almost 200 genes exhibited persistence or even exacerbation of the dysregulation associated with heart failure [31]. This indicates transcriptional “hysteresis”, in as much as many transcriptional changes in severe heart failure do not follow the functional recovery achieved by the LVAD treatment. More generally, it seems that the molecular adaptations leading to myocardial recovery may not simply be the inverse of those associated with the development of heart failure.

In a recent clinical study of our own, in which we attempted to move in the direction of functional genomics, towards which the future is aiming [32], we demonstrated correlations between the transcriptional changes after cardiac surgery (with and without cardioprotective treatment: sevoflurane compared with propofol) and cardiac function and changes in biomarkers (Figure 3).

![Figure 3. Postoperative blood levels of N-terminal pro brain natriuretic peptide (NT-proBNP) and correlations between anesthetic-induced transcriptional phenotypes with postoperative cardiac function recovery of patients subjected to coronary artery bypass graft (CABG) surgery. (A) Plasma levels of NT-proBNP are significantly higher in the PROP (squares) than the SEVO (circles) group from 24 up to 72 h after operation (time effect \( P < 0.001 \); treatment effect \( P < 0.002 \)). (B) Differential regulation of the FA oxidation pathway. (C) Correlation between FA oxidation and DNA damage pathway. (D) Correlation between FA oxidation and NT-proBNP. (E) Correlation between DNA damage pathway and cardiac index (CI). (F) Correlation between diastolic wall motion velocity, as determined by tissue Doppler flow transesophageal echocardiography, and G-CSF (granulocyte-colony stimulating factor). Collectively, these data imply that higher FA oxidation, as observed with propofol, put the heart at higher risk of postoperative contractile dysfunction. Reduced DNA-damage signalling may reflect the protection resulting from metabolic fuel shift. G-CSF survival pathway may have a direct role in cardiac fuel selection by regulating STAT3-mediated insulin sensitivity in the heart. Members of this pathway are JAK2/3, STAT3, vascular endothelial growth factor, and protein kinase B, which promote cell survival and angiogenesis. SEVO = sevoflurane; PROP = propofol. (Modified from Lucchinetti et al [32], with permission.)](chart.png)
Proteomic analysis in heart disease

Efforts are continuing to characterize the protein-related changes associated with cardiac dysfunction after ischemia-reperfusion injury. Changes in the abundance of proteins and, in particular, posttranslational modifications, increase with increasing severity and duration of experimentally applied ischemia-reperfusion injury [33–35]. Some of these changes are also present in chronic ischemic hearts. In a dog model of pacing-induced heart failure, Heinke et al [36] found a decreased abundance of the enzymes of mitochondrial oxidative phosphorylation, an increased expression of glycolytic enzymes, and varying changes in structural and cytoskeletal proteins. Proteomic profiles of human DCM and patients with ischemic heart disease [37,38] have revealed that a large proportion of the protein changes are associated with mitochondria and energy metabolism, including pyruvate dehydrogenase and isocitrate dehydrogenase subunits, creatine kinase M, and fatty acid binding protein. For this reason, the field of investigation has now moved on to cellular fractionation combined with proteomic analyses, to achieve better tracking of subcellular protein translocation and posttranslational modifications. Some recent studies focused on phosphorylation of mitochondrial proteins in relation to their function. Schwertz and coworkers [39] subjected rabbit hearts to 60 min of ligation of the left anterior descending coronary artery followed by 3 h of reperfusion and found a 4-fold increase in phosphorylation of voltage-dependent anion channel 1 compared with that in control hearts. Our group reported a novel phosphorylation site in adenine nucleotide translocase 1 (at residue Tyr194) [40] that might be involved in coordination of mitochondrial energy metabolism and cardioprotection. In a genetically modified yeast model, this phosphorylation site was critically linked to cellular respiration. Tyr194 phosphorylation was equal in mitochondria from control and protected – that is, pre- and postconditioned – hearts, whereas ischemia-reperfusion damage alone significantly reduced Tyr194 phosphorylation [40].

Outlook

Future developments in the “omics” field will further modify the definition of complex cardiovascular disease states. To date, the initial promise that “omics” may support the identification of disease biomarkers and potential targets for drugs, and thus improve therapy, has been partly fulfilled. Importantly, identified biomarkers need to be carefully validated in large populations of patients, particularly when they are to be used to predict long-term prognosis [41,42].

See glossary for definition of these terms.

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Abstract

Left ventricular remodeling is a strong predictor of cardiovascular events after acute myocardial infarction. Although transient, in only a few months this process will lead to heart failure. Recent improvements in therapeutic strategies have not led to the abolition of left ventricular remodeling, which remains a relatively frequent event after an initial acute myocardial infarction. Investigation of several approaches to the prevention and reversal of cardiac remodeling is needed, to reduce the number of patients progressing from myocardial infarction to endstage heart failure. The clinical setting of left ventricular remodeling after acute myocardial infarction lends itself to the use of global approaches in the search for circulating biomarkers of this progression, to help to identify patients who are at high risk of heart failure after myocardial infarction.

Keywords: Heart failure, left ventricle, myocardial infarction, plasma markers, remodeling
to analyze left ventricular remodeling in patients with acute AMI, using serial echocardiography at baseline, 3 months and 1 year after AMI [7]. The investigators chose to use echocardiographic indices of left ventricular remodeling because other studies have shown that these are strong predictors of heart failure and death [8]. Their findings demonstrated that left ventricular remodeling remains a frequent event after anterior wall AMI (31% of patients), despite recent improvements in the management of myocardial infarction [7].

**Current status of cardiovascular biomarkers**

Circulating biomarkers that have been used successfully in cardiology and classified as diagnostic biomarkers of heart failure include troponin I and troponin T (myocardial infarction), and brain natriuretic peptide. However, the concentrations of biomarkers vary widely, and concentrations in individuals with and without disease overlap substantially [9].

Left ventricular remodeling after AMI is a clinical situation that lends itself to the search for circulating biomarkers that control the progression from myocardial infarction to endstage heart failure [2] using a global approach without knowledge of pre-existing conditions. The study performed by Savoye et al [7] enabled patients to be carefully phenotyped and classified into groups exhibiting no (10.9%), or low (+7.5%) or high (+39.7%) degrees of left ventricular remodeling, for a comparative analysis. Despite having the same baseline end-diastolic volume during their stay in hospital after AMI and undergoing the same therapeutic strategies, the patients could be classified according to the percentage of left ventricular remodeling that they exhibited (Figure 1). A greater than 20% increase in end-diastolic volume has previously been taken to indicate severe remodeling [10]; thus it would be very helpful to discover biomarkers that made it possible to identify patients at risk of a high degree of remodeling earlier than 1 year after AMI.

**Global approaches**

Emerging technologies are making possible the systematic, unbiased characterization of variations in genes, RNA, proteins, and metabolites that are associated with disease conditions (Figure 2). From among the growing flow of new data and approaches, the selection that follows has been chosen to give a better illustration of the potential of such a global approach in the search for new biomarkers to explain the mechanisms of cardiovascular disease. Several approaches will be considered in relation to genetics, transcriptomics, and proteomics, with additional reference to the models used in comparing them: well phenotyped patients, and appropriate experimental models. The samples to be analyzed – mainly plasma, serum, or both, in the case of cardiovascular diseases – will also be mentioned. Independent of the global analysis chosen, the research strategy utilized will have been the same (Figure 3): comparison of “control” and “case” samples using the best technique for genetic, transcriptomic, proteomic, or metabolomic analysis. A further requirement in our choice was that the discovery of a potential biomarker was...
validated using another population and other techniques. After clinic validation and comparison with traditional markers used in the clinic setting, the discovered biomarker could then be used as a clinic biomarker.

**Genetics**

Genetic studies will identify variants that could be biomarkers themselves or will point to circulating biomarkers for further exploration. However, interindividual variability exists, with some patients experiencing significant left ventricular dilatation despite the absence of evident risk factors. Conversely, other patients, classified as high risk on initial evaluation, do not exhibit left ventricular remodeling.

Several studies with conflicting results have focused on the possible effects of gene polymorphisms in left ventricular remodeling after myocardial infarction. Three studies in which the impact of the angiotensin I-converting enzyme I/D polymorphism on left ventricular remodeling was analyzed yielded divergent findings: two were positive [11,12] with presence of D (deletion) allele associated with ventricle dysfunction and one was negative [13]. Another study analyzed the –1607 1G/2G polymorphism in the promoter of matrix metalloproteinase-1 and found an association with left ventricular remodeling for patients with 2GG alleles compared with homozygotes for the G allele [14].

A recent prospective study was designed to assess the impact of gene polymorphisms on left ventricular remodeling after a first anterior myocardial infarction. On the basis of the pathophysiology of left ventricular remodeling after myocardial infarction, three systems were chosen: the renin–angiotensin–aldosterone, adrenergic, and matrix metalloproteinase systems. The investigators found that left ventricular remodeling after myocardial infarction was not associated with common polymorphisms of these three systems [15].

Genome-wide association studies could be the next step in the identification of genes operative in susceptibility to disease [16]. This technological approach will require large groups of investigators to obtain a substantial cohort of patients. In the case of left ventricular remodeling studies, the largest cohort obtained to date was that of Savoye et al [7], with 266 patients enrolled. One third of that population would form the “control” population and one-third the “case” population, providing fewer than 90 patients per group. However, in order to perform a reliable genome-wide association study, at least 3000 case and 3000 control patients are required.

**Transcriptomics**

Gene expression profiling may provide a finer molecular classification of patients with cardiovascular diseases and indicate new markers useful for prognostic and therapeutic strategies [17]. Another obstacle to the discovery of biomarkers of heart disease is that the biomarkers identified might reflect pathological mechanisms that are associated, not with events that trigger disease, but instead with the downstream consequences of the resultant pathology. A comparative study performed by Gao et al [18], who used the canine tachypacing model, transgenic...

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**Figure 3. Schematic representation of the strategies behind research into biomarkers using comparative analysis of “case” and “control” samples. The techniques used for genetic, transcriptomic, proteomic, and metabolomic analyses are chosen according to the nature and number of the samples to be analyzed.**
Proteomics and metabolomics

Proteomics and metabolomics offer complementary insights to the full complexity of the disease phenotype, because transcript analysis does not always reflect the corresponding protein/metabolite profiling. Furthermore, proteins and metabolites can change rapidly in response to a changed environment.

The proteome represents, at a given time, the complement of proteins itself or the posttranslational modifications of those proteins, or both. Proteomic biomarkers differ from traditional biochemical markers, in that several interacting protein species are evaluated simultaneously to reflect the response of a cell or an organism to disease [21].

Recently, using samples from the prospective cohort of Savoye et al [7], we performed a systematic comparative proteomic analysis to select circulating biomarkers that may be associated with left ventricular remodeling. We used surface-enhanced laser desorption ionization—time-of-flight mass spectrometry to compare blood from patients with no left ventricular remodeling against that from those with a high degree of remodeling, and found four peaks differentially expressed between the two groups. Mass spectrometry led to the identification of more abundant protein/peptide variants and posttranslational modifications (300 000 species) is represented in the human plasma proteome [25]. However, many of the biologically interesting molecules relevant to human disease are proteins that are low in abundance; for example, cardiac biomarkers such as troponin are found in the nanomolar range, insulin in the picomolar range, and tumor necrosis factor-α in the femtomolar range. This has been addressed in a recent technique of “equalization” of serum/plasma that was established in order to study minor proteins of the plasma and serum by dilution of high-abundance proteins and concentration of low-abundance proteins [26].

Future directions

The application of proteomics or metabolomics to common cardiovascular diseases has potential obstacles. For acute events, such as myocardial infarction, the unpredictability of when the event occurs often precludes blood sampling. In some cases, experimental animal models can help for the first screening as myocardial infarction is programmed. A recent paper has demonstrated the usefulness of a rat experimental model of heart failure for the study of protein profiling in the early and late phases of left ventricular remodeling [27].

With the aim of discovering biomarkers of left ventricular remodeling after AMI, it will be important to be able to follow the change in abundance of plasma biomarkers that accompanies the development of left ventricular remodeling.

The interindividual variability of the human proteome and metabolome may prove to be a problem, but this should be overcome by using for comparison...
coHORTS OF ABOUT 30 PATIENTS PER GROUP, CAREFULLY
PHENOTYPED WITH A VIEW TO DISCOVERING BIOMARKERS
THAT CAN SUBSEQUENTLY BE VALIDATED IN LARGE, MORE
HETEROGENEOUS POPULATIONS.

THE IDENTIFICATION OF BIOMARKERS OF CARDIOVASCULAR
DISEASES WILL DEPEND ON THE COMPLEMENTARY POWERS OF
GENETICS, TRANSCRIPTOME PROFILING, PROTEOMICS, AND
METABOLICOMICS. THE NEWLY DISCOVERED BIOMARKERS,
WHEN COMBINED WITH EXISTING CLINICAL RISK FACTORS,
WILL IMPROVE THE PREDICTION OF RISK IN AN INDIVIDUAL
AND CONTRIBUTE TO THE DEVELOPMENT OF INDIVIDUALIZED MEDICATION.

*SEE GLOSSARY FOR DEFINITION OF THESE TERMS.*

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Magnetic resonance imaging and positron emission tomography as predictors of heart failure

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Conflicts of interest: None.

Abstract
Heart failure is a clinical syndrome of ischemic and non-ischemic etiology. Imaging plays a major part in diagnosing its cause, course, and prognosis. In the ischemic heart, positron emission tomography (PET), by, for example, assessing myocardial perfusion and glucose metabolism, and magnetic resonance imaging (MRI), by evaluating myocardial function, myocardial necrosis, and/or inotropic contractile reserve, can predict contractile recovery, and therefore potential improvement of heart failure, after revascularization. In non-ischemic cardiomyopathies such as dilative or hypertrophic cardiomyopathy, PET serves as an important tool for the assessment of metabolic changes, whereas MRI serves as the gold standard for measuring cardiac volumes and mass. In addition, late gadolinium enhancement MRI, which assesses regional fibrotic alteration of the myocardium, serves as a potential marker of disease progression and patient prognosis.


Keywords: Cardiomyopathy, heart failure, magnetic resonance imaging, positron emission tomography, viability*

Introduction
Heart failure is a clinical syndrome in which patients have symptoms (eg, shortness of breath at rest or on exercise) and signs (eg, tachycardia, tachypnea, pulmonary râles, or peripheral edema) typical of heart failure, together with objective evidence of a structural or functional abnormality of the heart at rest (eg, cardiomegaly, cardiac murmurs, abnormal echocardiogram, increased natriuretic peptide concentration) [1]. The prevalence of heart failure, whether symptomatic or asymptomatic, is approximately 4% in the population as a whole; however, as the condition is age related, its prevalence is between 10 and 20% in people aged 70–80 years. The prognosis in general is poor, as approximately 50% of patients die within 4 years. The etiology of heart failure is manifold. Coronary artery disease is the most common etiology in the western world, being the initiating cause in approximately 70% of patients. Valve disease and cardiomyopathies each account for 10%. Other causes include hypertension, drugs, toxins, endocrine disorders, and infiltrative disorders. In addition to clinical evaluation, cardiac imaging has a major role in diagnosing heart failure and characterizing its cause, course, and prognosis.

Positron emission tomography
Positron emission tomography (PET) can incorporate positron-emitting radionuclides into biochemical
Molecules and can, therefore, not only image their distribution, but also quantify their uptake. In this way myocardial perfusion, glucose utilization, fatty acid uptake, oxygen consumption, and pre- and postsynaptic neuronal activity can be assessed.

**Magnetic resonance imaging**

The strength of magnetic resonance imaging (MRI) lies in its intrinsic tissue contrast. It has emerged as the gold standard for measurement of cardiac volumes, mass, and ejection fraction. Tissue characterization is possible with different imaging weighting (T1/T2) and with the application of gadolinium-containing extracellular T1-shortening contrast agents. Myocardial edema, often present in acute inflammation of whatever cause, results in a high signal in T2-weighted imaging [2]. Extracellular, gadolinium-containing contrast agents distribute in the vascular and interstitial spaces, but are excluded from the cellular space. If the interstitial space is enlarged as in myocardial fibrosis (whether for ischemic or non-ischemic reasons), or if the ability of the myocyte to exclude the contrast agent is impaired as in acute myocardial infarction, the concentration of the contrast agent is increased in that region, resulting in a high signal in special T1-weighted imaging late after the application of the contrast agent. This is called “late gadolinium enhancement” (LGE) [3]. Because of the high spatial resolution, the transmural extent or the distribution, or both, of LGE, and therefore a pathological structural process, can be quantified.

**Ischemic heart failure**

Besides reducing exercise capacity, coronary artery disease is the major cause of heart failure, as a result of (a) myocardial infarction resulting in necrosis (non viability), or (b) reduced perfusion at rest or impaired perfusion reserve resulting in stunning/hibernation, both leading to reduced contractile capacity (viability). Distinguishing between these two states is of crucial importance: after revascularization, areas of transmural necrosis will not show any improvement in contractile performance, whereas areas of stunning/hibernation or non transmural infarct may exhibit improved contractile performance leading to an improvement in left ventricular ejection fraction and, thus, a beneficial alteration in the prognosis for the patient.

PET can be used to evaluate myocardial viability. The most widely used technique is the combination of myocardial perfusion using ammonia (NH₃) or water (H₂O) and glucose metabolism using [¹⁸F]fluoro-2-deoxy-D-glucose. Dysfunctional areas with normal or reduced perfusion and maintained glucose metabolism are suggestive of hibernating myocardium.
myocardium or non transmural infarct and have a high chance of contractile recovery after revascularization compared with regions having both reduced perfusion and glucose metabolism. Although the spatial resolution of PET is not sufficient to measure the transmural extent of viable and non viable myocardium, assessment of relative tracer uptake does provide some information. Approximately 50% tracer uptake may serve as the threshold for functional recovery [4]. Several studies have demonstrated sensitivity and specificity of 86–93% and 58–73%, respectively [5]. An exact threshold for the amount of viable dysfunctional myocardium for the prediction of improvement in global myocardial function has not been clearly defined, but it appears to be around 25–30% of viability [6]. Besides contractile recovery, PET can predict outcome [7] and perioperative complications [8].

After the application of extracellular contrast agents, MRI can identify myocardial necrosis that correlates with data derived from PET [9] (Figure 1). However, because of its greater spatial resolution, MRI not only enables the exact assessment of the transmural extent of the infarction, but, additionally, is more sensitive in identifying even small subendocardial infarcts [9] and peri-infarct zones [10], which is of prognostic relevance [11]. In the acute and chronic settings, the transmural extent of necrosis is a parameter of functional recovery after revascularization [12,13], as areas with no or any subendocardial infarcts have a high, and areas with a near-transmural infarct a very low, chance of recovery. Thus the transmural extent of LGE is a marker of the progression or reversibility of ischemic heart failure. By adding edema imaging (T2-weighted) in the case of an acute event, the difference between edema and LGE represents the salvaged myocardium [14] and is therefore a marker of the course of myocardial function and prognosis [15] (Figure 2). In addition to the detection and identification of the transmurality of infarction, by adding parameters such as wall thickness and inotropic reserve in response to low-dose dobutamine, MRI offers an excellent tool for predicting functional recovery [16], especially in areas with non transmural infarction of intermediate transmurality. Furthermore, after an acute myocardial infarction, infarct size measured by MRI has been found to be a strong predictor of left ventricular remodeling [17]. As for PET, there is no valid information from MRI studies concerning the amount of viable tissue needed for improved heart failure and prognosis. It remains unknown whether the revascularization of small epicardial viable rims without contractile improvement is of any prognostic value – for example in terms of less left ventricular remodeling or electrical stability – but this question is the subject of current research. Although the use of MRI in cardiology is a fairly young discipline for which there are relatively few

![Figure 2](image-url)
clinical data, because – in particular – of the greater availability and the high quality of information on function and tissue characterization that it affords, it is very attractive for the assessment of clinical viability and has been classified, alongside nuclear and echocardiographic methods, as a Class I indication [18].

Table I lists the MRI and PET features of different types of myocardial tissues and their prediction of contractile improvement.

Non ischemic cardiomyopathies

Non ischemic cardiomyopathies have unique functional, morphological, and tissue characteristics. It has recently been acknowledged that, in addition to the functional information it provides, MRI can further characterize non ischemic cardiomyopathies by the presence, extent, and pattern of edema/LGE imaging, and detect cardiac involvement of systemic diseases such as sarcoidosis or amyloidosis [19]. LGE is an unspecific marker of increased regional fibrosis. In idiopathic cardiomyopathy, it is present in approximately 30–40% of patients and is a marker of worse prognosis in terms of progressive disease, reduced likelihood of response to medical treatment, and susceptibility to arrhythmogenic events. In hypertrophic cardiomyopathy, functional MRI is more sensitive than echocardiography in detecting areas of hypertrophy [20]. In addition, left ventricular mass [21] and the presence of LGE [22] may be more sensitive markers than, for example, septum thickness for progressive disease and risk for sudden cardiac death. Similarly, MRI can be useful for the diagnosis and prognosis of patients with myocarditis, as the presence of edema and globally and regionally increased uptake of contrast agents suggest myocardial inflammation, whereas certain patterns of LGE may even indicate irreversible myocardial damage and progression to heart failure [23]. One problem that needs to be addressed is that LGE is an unspecific sign of fibrosis of whatever cause. However, the pattern and distribution of LGE and their combination with other functional and morphological features offer clues as to a specific cardiomyopathy. Figure 3 shows the patterns of LGE in different cardiomyopathies [19]. Although experience remains too limited to allow the drawing of definite clinical conclusions (for example, the need for implantation of an intracardiac defibrillator because of increased risk of sudden cardiac death), MRI offers a tool with which to look deeper into the myocardial changes that occur in non ischemic cardiomyopathies, and is likely to have an impact on clinical management in the near future.

Heart failure is associated with several changes in myocardial perfusion, oxygen metabolism, and Metabolic imaging

Christoph Klein

Table I. Patterns of perfusion and metabolism assessed by positron emission tomography (PET), and of late gadolinium enhancement (LGE) and inotropic reserve assessed by magnetic resonance imaging (MRI) in ischemic, myocardial dysfunction and prediction of functional recovery after revascularization.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>PET</th>
<th>MRI</th>
<th>PET + FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stunned</td>
<td>Normal</td>
<td>No</td>
<td>Non transmural LGE possible</td>
</tr>
<tr>
<td>Hibernation</td>
<td>Mildly reduced</td>
<td>LGE possible</td>
<td>0–25% transmurality</td>
</tr>
<tr>
<td>Non transmural infarction</td>
<td>Partly reduced</td>
<td>Partly reduced</td>
<td>26–50% transmurality</td>
</tr>
<tr>
<td>Transmural infarction</td>
<td>Severely reduced</td>
<td>Severely reduced</td>
<td>&gt;75% transmurality</td>
</tr>
<tr>
<td>FDG, [18F]fluoro-2-deoxy-D-glucose.</td>
<td></td>
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pre- and postsynaptic innervation. In addition to its application in basic research into primary and secondary alterations to innervation and metabolism in heart failure, PET may be able to provide valuable prognostic information in patients with hypertrophic and dilative cardiomyopathies, according to their responsiveness to vasodilators or the presence of scar tissue [24,25].

**Conclusion**

Whereas PET provides biological information, the strength of MRI lies mainly in assessment of function, morphology, and structural alteration of the myocardium. The combination of both methods may provide the most complete information about the cause and course of heart failure, and may shed more light on the processes underlying functional and morphological abnormalities.

*See glossary for definition of these terms.*

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**Metabolic imaging**

Christoph Klein

Heart Metab. 2009; 42:15–20
Targeting oxidative stress in heart failure

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Abstract

Increased oxidative stress is recognized to be important in the pathogenesis of cardiovascular disease, including heart failure. Reactive oxygen species (ROS) can be derived from diverse sources, including mitochondria, NADPH oxidase, and xanthine oxidase. Many agents established in the treatment of heart failure (including angiotensin-converting enzyme inhibitors, statins, β-blockers, hydralazine) may act indirectly by reducing the generation of ROS. In contrast, direct ROS scavengers (e.g., vitamin E) have been less successful in treatment. Newer ROS scavengers are being evaluated, and novel concepts for limiting the damage of ROS, such as the use of poly(ADP-ribose) polymerase 1 inhibitors, remain to be explored in clinical studies.

Heart Metab. 2009;42:21–24.

Keywords: Heart failure, oxidative stress, therapeutics

Introduction

Heart failure is a leading cause of mortality, and recent advances in therapeutic agents have substantially improved the prognosis for patients, especially with the introduction of angiotensin-converting enzyme (ACE) inhibitors, β-adrenoceptor blockers, and aldosterone antagonists. Recent evidence suggests that oxidative stress is increased in patients with heart failure [1,2], and the heart itself may be the source of these free radicals [3], but no successful large scale trials specifically targeting free radicals in heart failure have been published.

Reactive oxygen species (ROS) can damage cardiac tissue through oxidation of lipids, proteins, and DNA, producing diverse effects such as reduced cardiac contractility, malfunction of ion transporters, and calcium cycling. Their toxic effects are limited by free radical scavengers such as superoxide dismutase (SOD) which catalyzes the formation of H₂O₂ from superoxide (O₂•–), glutathione peroxidase, catalase which catalyzes the breakdown of H₂O₂ to water, and other non enzymatic antioxidants such as vitamins E, C and β-carotene, ubiquinone (coenzyme Q10), lipoic acid, and urate. There is no deficiency of these enzymatic defenses in heart failure [4], although manganese SOD protein may be reduced [5]; hence damage may ensue from excessive production of ROS. In addition, ROS can also act as an intracellular signaling mechanism, affecting transcription factors such as NFκB and activator protein-1.

Sources of ROS and their effects in the heart

Cellular sources of ROS include neutrophils/monoocytes, cardiomyocytes, and endothelial cells, through enzymes such as the NAD(P)H oxidases (phox proteins), xanthine oxidase, cytochrome P-450, nitric oxide synthase, and mitochondria (Figure 1). Production of ROS in the heart can be induced by a number of cytokines and growth factors, such as angiotensin II, platelet-derived growth factor, and tumor necrosis factor α through activation of
NAD(P)H oxidases. Uncoupled mitochondria could also be a major source of ROS in heart failure [6]. The neutrophil enzyme, myeloperoxidase, is increased in heart failure, suggesting these cells to be another source of ROS [7,8].

Activation of the G protein coupled receptors such as the angiotensin II receptor leads to enhanced production of ROS through the NAD(P)H oxidases (NOX2). Intracellular ROS can activate the redox-sensitive kinase, apoptosis-regulating signal kinase 1 (ASK-1), which leads to activation of other kinases such as mitogen-activated protein kinases (MAPKs), p38MAPKs and Jun kinases, all of which are signaling intermediates in the pathways to cellular hypertrophy and apoptosis [9]. Dominant negative mutant ASK-1 attenuated the agonist-mediated activation of NFκB and inhibited cardiac hypertrophy in response to ROS-generating G protein receptor agonists such as angiotensin and adrenoceptor agonists [10].

ROS can also increase cardiac remodeling through the activation of matrix metalloproteinases (MMPs), which have been implicated in the pathogenesis of heart failure [11–13]. DNA can also be damaged by ROS, and the breaks lead to activation of the DNA base-repair nuclear enzyme, poly(ADP ribose) polymerase 1 (PARP-1), which in turn leads to cell death from depletion of intracellular NAD(+) and ATP [14].

Existing treatments targeting oxidative stress in heart failure

Drugs that are established for treatment in heart failure may act indirectly to ameliorate the excessive oxidative stress in heart failure. For example, ACE inhibitors and angiotensin receptor blockers may reduce the G protein linked signaling response to NOX2, hence reducing the ROS burden in target tissues. This may also apply to β-adrenoceptor blockers, as β1-adrenoceptor-mediated actions on heart cells may also be mediated through the generation of ROS, activation of Jun kinases, and stimulation of apoptosis [15]. In addition, drugs such as carvedilol [16] and nebivolol [17] may have additional antioxidant properties independent of their β-adrenoceptor blocking effect.

Statins have pleiotropic effects independent of their cholesterol-lowering activity. Mevalonate produced from hydroxymethyl glutaryl coenzyme A reductase is a precursor for the synthesis of ubiquinone and isoprenoids, and isoprenylation of the γ-subunit of G proteins is a prerequisite for their activity. Statin treatment leads to reduced isoprenylation of G protein γ-subunits [18], in addition to the small GTPases, Rho and rac [19]. This may lead to both reduced production of ROS through agonist stimulation and a direct effect on the NOX2s, which require rac as a cofactor. In a recent clinical trial in patients with heart...
failure (Controlled Rosuvastatin Multinational Trial in Heart Failure [CORONA]), rosuvastatin reduced admissions to hospital significantly, although there was no effect on mortality [20]. Whether depletion of ubiquinone (see below) could have influenced the outcome of the CORONA trial is unknown.

Hydralazine used in combination with nitrates has been demonstrated to reduce mortality in heart failure [21]. Hydralazine, an arterial vasodilator, also has additional inhibitory effects on the generation of superoxide and peroxynitrite [22], which may provide a basis for its salutary effect.

In view of the potential importance of xanthine oxidase as a source of ROS, inhibitors of this enzyme may be expected to have an effect in heart failure. In addition, angiotensin II and NAD(P)H oxidases may have a role in upregulating xanthine oxidase activity. The findings of certain small trials tended to suggest that allopurinol may attenuate remodeling after myocardial infarction [23]. However, larger trials with oxypurinol [24], the active metabolite of allopurinol, have not confirmed a clinical benefit on mortality or admissions to hospital because of heart failure. The subgroup of patients in that trial with higher uric acid concentrations may have benefited to some extent, but definitive studies are needed to test this specifically. Uric acid itself is an endogenous free radical scavenger, and could act concurrently as a biomarker surrogate of xanthine oxidase activity, which may explain the disparate results with inhibition of that enzyme.

**Free radical scavengers in heart failure**

Ubiquinone (coenzyme Q10) is a natural antioxidant, and is essential for mitochondrial electron chain transport activity. There may be evidence of ubiquinone depletion in heart failure, and this may be a theoretical drawback to the use of statins – as, for example, in the CORONA study [20] – which may have limited the positive effects of statins. Many of the trials utilizing ubiquinone have been small and underpowered. A meta-analysis of 11 randomized clinical trials with ubiquinone suggested a small but significant improvement in ejection fraction (3.7%) in those individuals who received ubiquinone – especially those patients who were not receiving ACE inhibitors [25]. A multinational trial of ubiquinone as adjunctive therapy in heart failure (“Q-symbio”) is in progress, and results are eagerly awaited [26].

Large clinical trials of the antioxidant vitamins (A, E) or their precursors have been disappointing, with no evidence of benefit on cardiac mortality or morbidity [27,28]. In general, the vitamin E isomer that is used in trials is predominantly α-tocopherol, and different bioactivity of the various vitamin E isomers (eg, γ-tocopherol and the tocotrienols) has not been studied extensively.

Other drugs with antioxidant properties, such as probucol, may improve ventricular function in heart failure [29], but larger human studies may be necessary to establish their true place in the therapeutic armamentarium.

**Future perspectives**

In addition to further studies on the aforementioned agents, there may be further possible avenues for heart failure research. For example, 3-methyl-1-phenyl-2-pyrazolin-5-one (Edaravone), a novel free radical scavenger, has been used in the treatment of diseases in which oxidative stress is implicated (eg, cerebral infarction) [30]. Its antioxidant properties remain to be tested in heart failure. As previously mentioned, ROS may cause DNA strand breaks and activation of the repair enzyme, PARP-1, leading to intracellular depletion of NAD(+) and ATP, resulting in cell death [14]. Novel compounds targeting PARP-1 may be of use in abrogating this ROS-induced damage, and several have been described in the literature:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
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<tr>
<td>BGP-15</td>
<td>O-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid-amidoxime</td>
</tr>
<tr>
<td>GPI 6150</td>
<td>1,11b-dihydro-[7H]benzopyranon [4,1,2-de]isoquinolin-3-one</td>
</tr>
<tr>
<td>PJ-34</td>
<td>11C(2-(dimethylamino)-N-(5,6-dihydro-6-oxo-phenanthridin-2-y)acetamide</td>
</tr>
<tr>
<td>INO-1001</td>
<td></td>
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</tbody>
</table>

Their use in heart failure remains to be investigated.

**Conclusion**

Heart failure is associated with increased oxidative stress, and many of our therapies proven to be of clinical benefit may have mechanisms of action related to reducing this stress in vivo. However, some exciting new therapies remain to be tested in this challenging clinical condition.

*See glossary for definition of these terms.*

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New therapeutic approaches
Leong L. Ng


Beneficial long-term effects of Vastarel MR in patients with stable coronary artery disease developing left ventricular dysfunction

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Abstract

During the past two decades, the management of chronic coronary artery diseases has improved considerably, as a result of both pharmacotherapy and revascularization procedures. However, the course of chronic coronary artery disease, with an increase in the number of patients surviving after acute coronary syndrome, has led to an increase in the number of patients with ischemic left ventricular dysfunction. Despite treatment with conventional drugs, a high proportion of patients remain symptomatic. Both experimental and clinical studies in patients with heart failure have demonstrated that agents that inhibit fatty acid oxidation, with a consequent stimulation of glucose oxidation, may increase contractile function and have cytoprotective effect on cardiomyocytes in the failing heart. Trimetazidine (Vastarel MR) is the first cytoprotective agent to exert an anti-ischemic effect. Its lack of effects on hemodynamic parameters gives this drug a potential advantage. This article aims to review the current data on effects of Vastarel MR in patients with chronic coronary artery disease and left ventricular dysfunction.


Keywords: Cardiac metabolism, coronary artery disease, heart failure, ischemic cardiomyopathy, left ventricular dysfunction, trimetazidine

Introduction

Myocardial ischemia most commonly develops as an imbalance between coronary artery blood flow and increased demands for myocardial power and oxygen consumption. As a result of myocardial ischemia, there is a reduction in aerobic formation of ATP, and consequently anaerobic glycolysis, lactate formation, and a decrease in cell pH may develop [1]. The increase in myocardial oxygen demand is compensated by an increased blood flow and coronary oxygen supply in normal individuals. In most patients with chronic CAD, angina is caused by increased myocardial oxygen demands of exercise or emotional stress that cannot be met by an increase in coronary blood flow.

Three classes of drugs traditionally have been used for treatment of chronic coronary artery disease...
Trimetazidine (Vastarel MR) in the treatment of stable angina

On the basis of the pathogenetic mechanism described above, the treatment of stable angina has been directed primarily towards increasing myocardial blood flow and decreasing oxygen demand in the myocardium. In myocardial ischemia, fatty acid oxidation and glucose oxidation are decreased, whereas glycolysis becomes a more prominent source of ATP [4]. High levels of fatty acid oxidation are associated with a decrease in glucose oxidation; thus the inhibition of fatty acid oxidation may have a beneficial metabolic action because, in the ischemic heart, fatty acids are a less efficient source of myocardial energy than glucose with respect to oxygen consumption [5–7]. Many experimental and clinical data have shown that shifting the energy substrate preference from fatty acid metabolism to glucose oxidation may be a metabolically economic way of producing ATP with decreased consumption of oxygen [8,9]. Trimetazidine (Vastarel MR) is the first agent to be developed that selectively and partially inhibits long-chain 3-ketoacyl coenzyme A thiolase (3-KAT), an enzyme involved in fatty acid β-oxidation.

There are several mechanisms of action by which trimetazidine promotes the preservation of the membrane structure and cellular composition of cardiomyocytes: limitation of intracellular acidosis, prevention of the excessive production of free radicals and calcium overload, and correction of disturbances in transmembrane ion exchange [10,11]. A meta-analysis of 12 double-blind, randomized, controlled clinical trials of trimetazidine in the treatment of stable angina [12] showed that trimetazidine caused significant reductions in the number of angina attacks and improved the time to 1 mm ST-segment depression and the total work at peak exercise. Meta-analysis confirmed that trimetazidine is effective as an antianginal agent when used alone or in combination with traditional hemodynamic agents, without compromising hemodynamics and without side effects. In a multinational, randomized, double-blind, placebo-controlled study [13], the modified-release formulation of trimetazidine, Vastarel MR, has been shown to improve both symptoms and myocardial ischemia significantly. Patients with stable angina received atenolol 50 mg per day and Vastarel MR 35 mg or placebo. The primary endpoint, time to 1 mm ST-segment depression, was increased significantly in the group receiving the modified-release formulation of trimetazidine, compared with the group receiving placebo. Another open clinical trial included 906 patients with stable angina experiencing at least three angina attacks per week for more than 6 months despite traditional angina treatment with long-acting nitrates, β-blockers, or calcium antagonists. After 2 months of treatment with Vastarel MR 35 mg twice a day, there was a significant ($P < 0.0001$) decrease (67%) in the number of angina attacks per week and a significant ($P < 0.0001$) decrease (71%) in the number of short-acting nitrates taken per week in the group treated with the modified-release formulation of trimetazidine [14]. The findings of these studies suggest that the modified-release formulation of trimetazidine may be more effective than the immediate-release formulation with respect to relief of angina. In an Indian multicenter prospective study of 279 patients with stable angina, the immediate-release formulation of trimetazidine was substituted with the modified-release formulation, leading to a reduction in the mean frequency of angina by four attacks per week and the consumption of glyceryl trinitrate by 3.6 tablets per week [15].

Trimetazidine (Vastarel MR) in the treatment of left ventricular dysfunction

Treatment of angina in patients with heart failure represents a multicomponent pharmacologic approach. In patients with left ventricular dysfunction, treatment of angina with combinations of classic hemodynamic antianginal drugs may often have adverse effects on hemodynamics and ventricular function. Thus there is a need also to treat angina with hemodynamically “neutral” drugs without compromising hemodynamic parameters. The antiischemic effects of trimetazidine, by decreasing fatty acid oxidation and preserving ATP production at the cellular level and thereby reducing intracellular acidosis, influence these overlapping pathogenetic processes in ischemic heart failure. Several data show that myocardial contractile dysfunction in patients with heart failure is conditioned by the alteration of substrate metabolism [7,16]. Prevention of intracellular acidosis and calcium overload can be important “cardioprotective” effects in both ischemia and heart failure [17]. The beneficial effect of trimetazidine on energy metabolism may contribute to an improvement in myocardial systolic function in patients with left ventricular dysfunction caused by CAD.

Brottier et al [18] first showed that treatment with trimetazidine for 6 months increased radionuclide ejection fraction by 9.3% in patients with ischemic cardiomyopathy. The effects of trimetazidine in…
patients with left ventricular dysfunction and diabetes were assessed in randomized studies by Fraga et al [19] and Rosano et al [20]. In both studies, 6 months of treatment with trimetazidine resulted in a significant increase in left ventricular ejection fraction (LVEF) and a decrease in end-diastolic volumes. Vitale and colleagues [21] showed similar effects of trimetazidine on ventricular function and volumes in elderly patients: LVEF increased by 5.3 ± 1.3% (P < 0.05) after 6 months in the trimetazidine group and remained unchanged in the placebo group (1.8% before treatment; 1.9% after treatment; a difference of 0.1% which was NS).

In a recent study of 82 stable patients with ischemic cardiomyopathy [22], my colleagues and I found that a subgroup of patients treated with a daily dose of 70 mg trimetazidine in conjunction with standard therapy over a 3 month period exhibited an increase in LVEF by 3.5 ± 6.72% in the trimetazidine group (compared with 0.8 ± 8.06% in controls; P = 0.05; Figure 1) and an improvement in tolerance to physical activity of 30.0 ± 0.7 m in the trimetazidine group (compared with 2.0 ± 18.85 m in controls, P < 0.001; Figure 2). The increase in LVEF in the trimetazidine group was accompanied by a decrease in left ventricular volumes: left ventricular end-systolic volume decreased by 23 ± 28.4 ml (from 143 ± 22 ml to 120 ± 18 ml) in the trimetazidine group and by 9.0 ± 31.9 ml (from 148 ± 24 ml to 139 ± 21 ml) in the control group (P < 0.05). These findings showed that, in patients with moderate ischemic left ventricular dysfunction, modified-release trimetazidine is able to relieve the symptoms of heart failure and improve left ventricular function. The drug was well tolerated and did not cause any hemodynamic adverse effects. Our study was the first to test the effect of modified-release trimetazidine in a daily dose of 70 mg in patients with ischemic cardiomyopathy.

Figure 1. Changes in left ventricular ejection fraction (LVEF) in patients with stable ischemic cardiomyopathy treated with a daily dose of 70 mg trimetazidine (TMZ; Vastarel MR) in conjunction with standard therapy for 3 months (red column), compared with that in controls (blue column). The difference between groups was significant (P = 0.05).

Figure 2. Changes in tolerance to physical activity in patients with stable ischemic cardiomyopathy treated with a daily dose of 70 mg trimetazidine (TMZ; Vastarel MR) in conjunction with standard therapy for 3 months (red column), compared with that in controls (blue column). The difference between groups was significant (P < 0.001).

El-Kady and associates studied 200 patients aged 55 ± 12 years with ischemic left ventricular dysfunction resulting from multivessel CAD, who were allocated randomly to either a study group receiving trimetazidine or a placebo group for 2 years. After the 2 years, there was an increase in left ventricular function of 23% in the trimetazidine group, compared with one of only 0.5% in the placebo group; left ventricular volumes, assessed by single photon emission computed tomography, showed decreases [23]. A significant survival benefit was observed in the trimetazidine group, with a mortality rate of 8% compared with one of 38% in the placebo group. In the recent post-hoc analysis of the Villa Pini D’Abruzzo Trimetazidine Trial involving 61 patients with ischemic cardiomyopathy in a 48-month follow-up period, trimetazidine significantly reduced all-cause mortality (by 56%; hazard ratio 0.258, 95% confidence interval 0.097 to 0.687; log-rank test, P = 0.0047) and number of admissions to hospital because of heart failure (47% decrease; log-rank test, P = 0.002). In trimetazidine-treated patients, a significant increase in LVEF and improvement in 6 min walk test was observed [24].

The findings of these last two studies showing significant effects of long-term treatment with trimetazidine on mortality in patients with CAD and left ventricular dysfunction emphasize the importance of confirming the effects of trimetazidine in a multicenter, randomized, placebo-controlled trial, to demonstrate its impact on mortality.

Conclusions

Analysis of clinical trials suggests that metabolic intervention in the management of patients with CAD and
left ventricular dysfunction represents a promising therapeutic approach. Its anti-ischemic properties and absence of hemodynamic effects make the modified-release formulation of trimetazidine, Vastarel MR, a good treatment option in patients with left ventricular dysfunction. This modified-release formulation has no any adverse effects in patients with ischemic cardiomyopathy and may afford better patient compliance with treatment, because of its reduced frequency of administration compared with the conventional formulation. Improvements in left ventricular contractility and functional class demonstrated in clinical trials with Vastarel MR are further indications that addition of this agent to conventional treatment may have beneficial effects for patients with ischemic left ventricular dysfunction. Recent studies demonstrating beneficial effects on mortality derived from long-term administration of trimetazidine in patients with ischemic left ventricular dysfunction suggest the necessity for a large multicenter trial to prove this influence.

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Case report

Changing ischemic symptoms despite stable coronary anatomy

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Conflicts of interest: None.

Abstract

A 67-year-old man with known ischemic heart disease was referred to our Cardiology Department because of dyspnea on effort and exertional angina. An exercise stress test showed significant progression of ischemic signs on the electrocardiogram, also involving the area of a totally occluded coronary artery. Repeated angiography confirmed the absence of angiographic changes to support the clinical progression of the ischemic syndrome.

Keywords: Angina, chronic ischemic heart disease, chronic total coronary occlusion, dyspnea, exercise stress testing

Introduction

Chronic total coronary occlusions are observed in 35–50% of patients with significant coronary disease undergoing diagnostic angiography [1,2]. It is expected that the extent of the corresponding ischemic region remains essentially unchanged unless a significant progression of atherosclerotic lesions in other vessels occurs, but, as often documented, there is no close relationship between the severity of epicardial coronary stenosis and that of the ischemic syndrome. We report here the case of a patient with chronic total occlusion of the right coronary artery, who presented with a worsening of his ischemic syndrome despite no appreciable changes in coronary angiographic features.

Case report

A 67-year-old man was admitted to our Cardiology Department in October 2008. His cardiac history had begun in 2002, when he was admitted after an acute myocardial infarction. Subsequently, he presented occasional episodes of chest pain and, in January 2007, he underwent an exercise stress test, as part of a preoperative evaluation for abdominal surgery. At peak exercise ST-segment depression was present in anterior leads from V4 to V6 and in the inferior leads, in the absence of any symptom (125 W, 6.5 metabolic equivalent of task units [METS], maximal heart rate 131 beats/min; maximal blood pressure 210/100 mmHg) (Figure 1).

In April 2007, a stress scintigraphy confirmed inducible ischemia in the proximal inferolateral segments. Coronary angiography revealed a total occlusion of the right coronary artery (Figure 2), a 50% proximal stenosis and a 70% mid-distal stenosis of the first obtuse marginal branch and an intercoronary collateral circulation between the left circumflex coronary artery and the distal right coronary artery (Figure 3; Rentrop 1).

Given the absence of anginal symptoms, no percutaneous coronary intervention was performed in that setting. Five months later, the patient started to complain of dyspnea on effort and occasional exertional angina; in the meantime he had been scheduled to undergo surgical repair of an inguinal hernia. A second exercise stress test was therefore performed which documented ST-segment depression in leads DII, DIII, aVF, and V5–V6 (100 W, 5.3 METS,
maximal heart rate 110 beats/min; maximal blood pressure 165/90 mm Hg (Figure 4).

The patient was admitted to our division. His cardiovascular risk profile included hypertension, diabetes mellitus, and dyslipidemia; other routine blood chemistry was normal. An echocardiogram revealed normal left ventricular contractile function and volume. Coronary angiography was repeated and confirmed total occlusion of the right coronary artery and the 50% proximal and 70% mid-distal stenosis of the first obtuse marginal branch (Figure 5). With the aim of improving the collateral circulation to the distal right coronary artery, angioplasty (Figure 6) and stenting (Cypher 3.0/8) (Figure 7) were performed on the marginal branch.

The patient was discharged receiving aspirin, clopidogrel, verapamil, furosemide, and candesartan.

Ten days after the procedure, he performed an exercise stress test that showed ST-segment depression in leads DI, DII, and DIII, in the absence of symptoms (125 W, 6.1 METS, maximal heart rate 108 beats/min; maximal blood pressure 200/80 mm Hg) (Figure 8).

Comment

In patients with chronic angina, changes in ischemic threshold are commonly attributed to progression of coronary atherosclerotic lesions. Here, however, we have reported a case of changing severity of ischemia, in the absence of significant progression of coronary atherosclerosis in other vessels.

At the time of the first exercise stress test, the patient was almost asymptomatic for angina or dyspnea; the
Case report
Changing ischemic symptoms despite stable coronary anatomy

onset of his symptoms was associated with an extension of ischemic signs in a control exercise stress testing. Indeed, a similar pattern on the electrocardiogram was present at lower working load, lower METS, and lower double-product values. We hypothesized that a revascularization procedure might improve the collateral circulation and myocardial perfusion, and therefore we performed percutaneous transluminal coronary angioplasty and stenting on the only treatable lesion. Nevertheless, the exercise stress test undertaken after this “successful” percutaneous coronary intervention showed a similar electrocardiographic pattern at equivalent METS and double-product values, confirming the absence of any obvious link between coronary anatomy and progression of the ischemia over time.

This case report emphasizes that we frequently adopt the position of passive bystander in the management of chronic ischemic heart disease. For this reason, we perhaps need to see beyond the plaque and have the confidence to leave plaques alone; alternative mechanisms, including microvascular dysfunction and coagulation abnormalities, may be important determinants of chronic ischemic heart disease. The awareness of several underlying mechanisms could help us to avoid ineffective, expensive, and possibly harmful revascularization procedures and to optimize treatment by other means.

REFERENCES
Hibernation or repetitive stunning – does it matter?

The basic perspective

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Abstract

The long-lasting controversy on whether the contractile dysfunction observed in patients with coronary artery disease reflects hibernation – that is, a regulatory adaptation to persistent ischemia – or stunning – that is, an accumulation of reversible damage due to repeated periods of ischemia/reperfusion – is resolved. The perfect adaptation to persistent ischemia as seen experimentally can not be maintained for more than several hours (arguing against pure hibernation), but dysfunctional myocardium does not only display signs of damage but also an up-regulation of cardioprotective genes (arguing against pure stunning). Thus, as is often the case, both sides were wrong and right.

Keywords: Contractile dysfunction, coronary artery occlusion, hibernation, stunning

The question in the title refers to a historic controversy. Stunning was originally characterized in studies in dogs with coronary artery occlusions of too short a duration to cause irreversible damage but which were nevertheless followed by prolonged, yet spontaneously and fully reversible, contractile dysfunction during reperfusion [1]; the term “stunning” for such prolonged yet reversible postischemic contractile dysfunction was proposed later [2]. The concept of “hibernating myocardium” was first introduced by Rahimtoola in 1985, when he reviewed the results of the first coronary revascularization trials and identified patients with coronary artery disease and chronic left ventricular dysfunction that recovered on revascularization [3]. He proposed the idea that the reduction in contractile function served to match the reduced supply, restore an energetic equilibrium, and preserve viability. Rahimtoola’s more clinically based idea of hibernating myocardium quickly received support from a number of experimental studies that demonstrated matching of reduced regional myocardial blood flow to reduced regional contractile function [4,5], recovery of energy and substrate metabolism [6,7], persistence of inotropic reserve at the expense of such metabolic recovery, and preservation of viability over several hours of continuing ischemia [8] – that is, evidence for downregulation of contractile function in short-term myocardial hibernation.

Although it became increasingly clear that chronic contractile ventricular dysfunction in patients with coronary artery disease did not necessarily reflect irreversible damage and scar, but was in fact amenable to revascularization, a heated debate developed...
as to whether the observed contractile dysfunction reflected hibernation – that is, it was regulatory in nature and an adaptation to continuing ischemia – or stunning – that is, it was an accumulated consequence of repeated bouts of ischemia-reperfusion that left the myocardium in a continuous, yet spontaneously fully reversible contractile deficit even while fully reperfused. The controversy focused on the question whether the clinically observed hibernating myocardium had reduced or normal baseline flow at rest [9,10]. Much of this debate appears to be obsolete today, but it is worthwhile remembering that the essential question was: does chronic contractile dysfunction distal to a coronary stenosis reflect adaptation or damage?

Today, the historic controversy is largely resolved, and – as is often the case – both sides were both wrong and right. The perfect adaptation as observed in short-term hibernating myocardium could not be maintained over more than several hours [11]. Stunning as such is almost entirely a laboratory phenomenon, and of little clinical significance other than in its cumulative manifestation as hibernating myocardium [12]. The contractile dysfunction in stunned myocardium can be attenuated by a variety of interventions, including selective heart rate reduction [13]. Resting blood flow is reduced in hibernating myocardium [14]; however, this is not the result of continuing ischemia, but rather the consequence of repetitive episodes of ischemia-reperfusion in which blood flow is reduced in adaptation to contractile dysfunction [14–16]. Most importantly, in our view, the observed chronically dysfunctional myocardium has features both of damage and replacement fibrosis, and of the upregulation of a cardioprotective gene program [17,18], which puts it into the context of ischemic pre- and postconditioning [14].

To answer the initial question. No, it does not matter whether chronic contractile dysfunction distal to a coronary stenosis is viewed as hibernation or repetitive stunning. Yes, it does matter that we realize that such chronic contractile dysfunction is associated with both destructive and protective features, and is amenable to revascularization.

REFERENCES

Acute myocardial ischemia impairs contractile function [1], but, if the ischemic event is not lethal and reperfusion occurs, contractility is restored [2]. However, despite reperfusion, contractile dysfunction may persist for several hours and this phenomenon is termed “myocardial stunning” [3–5]. Thus in myocardial stunning there is a mismatch of perfusion and contraction. Repeated episodes of ischemia may lead to repetitive stunning with a cumulative reduction in contractility, and this may be one mechanism of chronic postischemic left ventricular dysfunction [6].

The phenomenon of “myocardial hibernation” was proposed to explain the finding that revascularization in patients with coronary artery disease (CAD) and chronic postischemic left ventricular dysfunction could lead to an improvement in left ventricular function [7–9]. Initially, it was proposed that, during a prolonged state of sublethal ischemia, contractility and metabolism could be depressed in parallel with the reduced blood supply [9]. Thus hibernating myocardium is adaptive, with necrosis prevented by a reversible downregulation of function and energetics, but with retained perfusion–contraction matching in affected segments [10]. Hibernating myocardium may not, therefore, be ischemic at rest, as a result of the matched reduction in energy requirement [11,12].

The stress of oxygen and substrate deprivation activates endogenous mechanisms of cell survival [13]. These adaptations may differ between repetitive stunning and hibernating myocardium [14]. Hibernating myocardium has greater concentrations of cAMP, whereas the cardioprotective heat-shock protein, Hsp-72, is increased in myocardial stunning [14]. In hibernating myocardium, depletion of contractile elements, cytoskeletal disorganization, and alterations in adrenoreceptor density have been reported, together with activation of the inflammatory cascade, induction of cytokines and chemokines, recruitment of leucocytes, interstitial remodeling, and fibrosis [15]. These findings are progressive and reflect the severity of the cumulative ischemic insult.

In normal myocardium, myocardial blood flow increases in parallel with an increased contractile demand during stress. Both repetitive stunning and hibernation represent an inability to enhance
Myocardial blood flow across the range of demand: a reduction in coronary flow reserve [6,16]. Restoration of coronary flow reserve allows post-stunning recovery and upregulation of metabolism and contractility in hibernation. Any segment of chronic postischemic left ventricular dysfunction may contain an admixture of scar tissue resulting from lethal ischemia, hibernating myocardium, stunned and repetitively stunned myocardium, and normally contractile myocytes [17]. All but the irreversibly scarred myocardium is viable, and the proportion of viable but dysfunctional myocardium subtended by stenosed epicardial coronary arteries amenable to revascularization becomes an index of how much contractility could be restored by correction of coronary flow reserve [18,19].

This concept of viable reversibly dysfunctional myocardium is important. CAD is the most common cause of congestive heart failure [20,21], and many patients will retain a significant quantum of viable reversibly dysfunctional myocardium in which function could be improved [22]. As myocardial function is an exquisite index of prognosis, interventions that improve function are also likely to improve prognosis [23,24]. Typically, patients with CAD and chronic postischemic left ventricular dysfunction have multivessel disease and increased left ventricular volumes [20]. Dysfunction in one region leads to increased demands in others and promotes adverse remodeling [25]. Successful revascularization can improve function in viable reversibly dysfunctional myocardium segments, improving overall left ventricular function and reducing adverse remodeling in affected and remote segments.

Viable reversibly dysfunctional myocardium has several features that can be used to facilitate its identification. Except in its most severe forms, it remains responsive to β-adrenergic stimulation [26]. Thus dobutamine stress echocardiography can detect increased wall motion in segments of viable reversibly dysfunctional myocardium, whereas wall motion in predominantly scarred segments remains unchanged [27]. With high-dose dobutamine stress echocardiography, initially improved contractility can diminish, reflecting inducible ischemia. This “biphasic” response is highly predictive of recovery [26].

Echocardiography can also detect wall thinning, most probably as a result of transmural infarction and scarring. Scarring results in obstruction of the coronary microcirculation. The reduced perfusion can be detected by myocardial contrast echocardiography, which uses small (<7 μm; smaller than the red corpuscle) gaseous microbubbles to determine tissue capillary blood flow [28,29]. Myocardial contrast echocardiography also improves chamber opacification and identification of left ventricular wall borders, facilitating assessment of function and wall thickness. Intramyocardial contrast enhancement detects [30] viable reversibly dysfunctional myocardium, whereas lack of enhancement indicates non viability. The utility of myocardial contrast echocardiography in detection of viable reversibly dysfunctional myocardium is increased when combined with dobutamine stress echocardiography [31,32].

Viable reversibly dysfunctional myocardium retains the functional integrity of the myocyte sarcolemma to exchange potassium and other ions [33]. This can be examined by single photon emission computed tomography, which uses the labeled potassium analog, thallium-201, or technetium-99m. Initial administration of tracer provides an index of myocardial blood flow, whereas delayed tracer uptake reflects sarcolemmal integrity and viability; absence of delayed uptake indicates non viability [33,34].

Unlike scar, viable reversibly dysfunctional myocardium also retains the ability to metabolize significant amounts of glucose [35,36]. This can be probed using positron emission tomography (PET) and the glucose analog, [18F]fluoro-deoxyglucose (FDG) [37]. FDG-PET is often combined with a perfusion tracer study. Regions demonstrating a parallel reduction of flow and FDG uptake may be considered irreversibly injured, whereas maintenance of FDG uptake, even in the presence of a perfusion abnormality, may indicate viability with ischemia [35]. During FDG-PET, the use of insulin as a hyperinsulinemic euglycemic clamp reduces free fatty acids and promotes entry of glucose or FDG, enhancing image quality [38–40]. On occasion, some segments display DG-PET viability, but not contractile reserve. In this circumstance, contractile recovery may be delayed and occur to a lesser extent, suggesting a more advanced downregulation of the myocyte [17].

Cardiac magnetic resonance imaging can be used in conjunction with dopamine stress echocardiography to assess both contractile reserve and assesses wall thickness [41,42]. Importantly, it can be used with gadolinium-chelated contrast agents, which gradually accumulate in areas of scar. This allows assessment of the transmurality of infarction [43,44]. The absence of late gadolinium accumulation, even in thinned (<5 mm) hypokinetic ventricular wall, is associated with postrevascularization recovery.

Although we do not have controlled prospective randomized studies indicating that the revascularization of viable reversibly dysfunctional myocardium improves prognosis, there are studies that suggest benefit [20]. Several investigators have found that revascularization of viable reversibly dysfunctional myocardium increases left ventricular ejection fraction by at least 5% and that the increase is related to the number of viable reversibly dysfunctional myocardium segments [37,45,46]. To achieve an increase of at least 5% in left ventricular ejection fraction,
approximately 25% of the left ventricle needs to be viable in dopamine stress echocardiography [22]. Meta-analyses have suggested a prognostic advantage of revascularization in the presence of viable reversibly dysfunctional myocardium, and a prognostic disadvantage if that tissue is not revascularized [47]. Symptoms of heart failure and objective measures of exercise tolerance may improve [48]. Importantly, delayed revascularization of viable reversibly dysfunctional myocardium allows further deterioration, and frustrates the benefits accrued by prompt treatment [49,50].

Chronic postischemic left ventricular dysfunction in CAD is common, and contributes to the epidemic of heart failure. Although hibernation and repetitive stunning may both be contributory mechanisms, currently, the distinction is less relevant than an overall assessment of viability and the subsequent decision-making process of whether revascularization, often applied in combination with other heart failure therapies, is applicable in the individual patient.

REFERENCES


Featured research

Abstracts and commentaries

Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery

Over the past decade, the incidence of diabetes mellitus has increased markedly in developed countries. Knowledge of a patient’s diabetic status before they undergo surgery has led to advances in perioperative clinical management, including active and continuous blood glucose control, with improved clinical outcome. Nevertheless, derangement of glucose metabolism after surgery is not specific to patients with diabetes mellitus. It has been reported that up to 90% of those without diabetes mellitus had problems with their blood glucose homeostasis as a result of various surgical stresses. In such patients, the disturbances in blood glucose homeostasis have been attributed to insulin resistance, or a failure of pancreatic β-cell function caused by the systemic inflammatory response syndrome after cardiopulmonary bypass and its effects on systemic temperature, or both. More recently, investigators have been focusing on undiagnosed diabetes mellitus, patients without diabetes mellitus, and their likelihood of suffering postoperative derangement of glucose metabolism leading to postoperative complications. The aim of this study was to investigate the effect of different degrees of inadequate blood glucose control on clinical outcomes in a large consecutive series of patients undergoing cardiac surgery.

Commentary

The authors analyzed the findings from 8727 adults operated on between April 1996 and March 2004. The greatest blood glucose concentration recorded over the first 60 h after operation was used to classify patients as having good (≤200 mg/dL), moderate (200–250 mg/dL), or poor (>250 mg/dL) blood glucose control. Among the 8727 patients studied, 7547 (85%) had good, 905 (10%) had moderate, and 365 (4%) had poor control of their blood glucose. Patients with inadequate control of blood glucose were more likely to present with advanced New York Heart Association class, congestive heart failure, hypertension, renal dysfunction, and ejection fraction less than 50% (P ≤ 0.001).

It was found that 52% of patients with poor, 31% with moderate, and 8% with good blood glucose control had diabetes mellitus. Inadequate blood glucose control, but not diabetes mellitus (P = 0.79), was associated with in-hospital mortality (good, 1.8%; moderate, 4.2%; poor, 9.6%). The adjusted odds ratio (OR) for poor compared with good blood glucose control was 3.90 (95% confidence interval [CI] 2.47 to 6.15); that for moderate compared with good blood glucose control was 1.68 (95% CI 1.25 to 2.25). Inadequate blood glucose control also was associated with postoperative myocardial infarction (eg, OR for poor compared with good blood glucose control 2.73 [95% CI 1.74 to 4.26]) and with pulmonary and renal complications in patients without known diabetes mellitus (eg, OR for poor compared with good blood glucose control 2.27 [95% CI 1.65 to 3.12] and 2.82 [95% CI 1.54 to 5.14], respectively).

This study showed that more than 50% of patients developing moderate to poor blood glucose control after cardiac surgery were not previously identified as diabetic. The stress of cardiac surgery might uncover a borderline diabetic status causing marked transient or permanent imbalance in body sugar control and leading to hyperglycemia. These findings suggest that inadequate control of blood glucose, regardless of diabetic status, is an independent predictor of in-hospital mortality and postoperative myocardial infarction in patients undergoing cardiac surgery. The projected future number of adults with diabetes mellitus is an underestimate of the number likely to be affected by deranged glucose metabolism and its related complications. These data suggest that strict protocols to maintain blood glucose control should be used for all patients. However, the efficacy of these protocols and the pathophysiologic mechanisms of this condition need further research.

Danielle Feuvray

CD36 expression contributes to age-induced cardiomyopathy in mice

Cardiac remodeling and impaired cardiac performance in the elderly significantly increase the risk
of developing heart disease. Although vascular abnormalities associated with aging contribute to the age-related decline in cardiac function, myocardium-specific events may also be involved. We found that intramyocardial accumulation of lipid, in addition to a reduction in both fatty acid and glucose oxidation and a subsequent deterioration in cardiac ATP supply, also occurs in aged mice. Consistent with an energetically compromised heart, hearts from aged mice displayed depressed myocardial performance and cardiac hypertrophy. Associated with this was a dramatic increase in the fatty acid transport protein, CD36, in aged hearts compared with young hearts, which suggests that CD36 is a mediator of these multiple metabolic, functional, and structural alterations in the aged heart. In accordance with this, hearts from aged CD36-deficient mice had lower concentrations of intramyocardial lipids, demonstrated improved production of mitochondria-derived ATP, had significantly enhanced function compared with aged wild-type mice, and had a blunted hypertrophic response. These findings provide evidence that CD36 mediates an age-induced cardiomyopathy in mice and suggest that inhibition of CD36 may be an approach for the treatment of detrimental age-related effects on cardiac performance.

Commentary

Aging is a well recognized risk factor for the development of heart disease. It is associated with a number of changes within the heart muscle, including alterations in cardiac energy metabolism. In addition, a decrease in cardiac mitochondrial function occurs with age, and this has been suggested to result in a decrease in cardiac energy reserve that may compromise cardiac function. A decrease in mitochondrial function is associated with a decrease in both fatty acid oxidation and carbohydrate oxidation, the two major sources of the ATP necessary to maintain contractile function. It has also been suggested that an impaired ability of the heart to oxidize fatty acids can lead to an accumulation of lipids within the cardiac myocyte, termed “cardiac lipotoxicity”. As a result, age-related lipotoxicity could potentially result in the development of lipotoxic cardiomyopathy in the aging heart.

This study by Koonen et al addressed the relationship between fatty acid metabolism and cardiac function in aging mice. To modify fatty acid metabolism in the heart, the authors utilized mice that lacked cardiac CD36, a major protein involved in the uptake of fatty acids into the heart. The authors showed that, as expected, old wild-type mice have a decrease in both cardiac fatty acid and glucose oxidation, which would be expected if mitochondrial function is compromised. Accompanying this was an increase in intracellular accumulation of lipid and a decrease in cardiac function compared with those in young mice.

Of interest is that deletion of CD36 resulted in a decreased accumulation of lipid, an improvement in glucose oxidation, and an improvement in cardiac function. The absence of CD36 did not modify the low rates of fatty acid oxidation seen in the old mice. These interesting findings support the concepts that lipid accumulation may compromise cardiac function in the aging heart, and that inhibiting myocardial fatty acid uptake can prevent this abnormal accumulation of lipid and improve heart function. The second important observation from this study is that low rates of fatty acid oxidation in the old heart are not contributing either to lipid accumulation or to impaired contractile function. In contrast, the data suggest that decreasing fatty acid uptake in the heart can markedly increase glucose oxidation in the old heart, which is associated with a marked improvement in cardiac function.

These observations have important implications as to whether stimulating or inhibiting fatty acid oxidation has therapeutic potential in treating the elderly patient with heart disease. The data are consistent with inhibition of fatty acid metabolism and stimulation of glucose oxidation as an approach to improve heart function in the elderly. It suggests that agents such as trimetazidine that stimulate glucose oxidation secondary to the inhibition of fatty acid oxidation may be particularly effective in the elderly patient. Further studies are warranted to examine this possibility.

Gary D. Lopaschuk
Glossary

Gary D. Lopaschuk

Biomarker
A biomarker is a substance whose detection indicates a particular disease state, and more specifically, changes in that substance’s expression or state will often correlate with the risk or progression of a particular disease. For example, the appearance of troponin in the blood is a biomarker indicative of a myocardial infarction. Biomarkers can be used to assess disease risk, presence of disease in an individual, or to modify treatment for disease in an individual.

Genomics
Genomics is the study of an organism’s genome (full DNA sequence). Genomics includes an intensive effort to determine the complete DNA sequence of organisms and fine-scale genetic mapping efforts. Also included in this field are studies of intragenomic-phenomena such as epistasis, heterosis, pleiotropy, and other interactions between alleles and loci within the genome.

Hibernation
Hibernation refers to a segment of myocardium that exhibits some type of abnormality in contractile function (i.e., hypokinetic myocardial wall segment), often in the scenario of chronic ischemia. Hibernating myocardium is relevant in the clinical setting because although the segment of myocardium in hibernation has contractile dysfunction, it remains viable and if revascularized in time, can be saved with a restoration of its contractile function.

Metabolomics
Metabolomics is the systematic study of the unique chemical fingerprint that a cellular process will leave behind. Metabolomics encompasses the cellular process’ small-molecule metabolite profile, and provides an instantaneous snapshot of a cell’s physiology.

Proteomics
Proteomics is the large-scale study of proteins, focusing primarily on a particular protein’s structure and function (often in regards to growth, health, disease, and/or resistance to disease).

Remodeling
Remodeling of the heart refers to the alterations in the size, shape, and function of the heart after injury (primarily of ischemic nature). However, remodeling can also arise from increases in pressure or volume overload on the heart. During remodeling, a number of histopathological and structural changes occur to the left ventricular myocardium, resulting in a progressive impairment in left ventricular performance. Eventually, the effects of the ventricular remodeling may be too severe that systolic performance is greatly diminished, resulting in heart failure.

Scavenger
A scavenger is in general, an antioxidant molecule capable of slowing or preventing the oxidation of other molecules. In the setting of cardiovascular disease, reactive oxygen species transfer electrons to oxidizing agents, often producing free radicals that may initiate a chain reaction of oxidative reactions that damage myocardial cells. The scavenger molecule may act as an oxidizing agent itself and terminate the chain reaction being initiated by the free radical(s).

Viability
In terms of cardiovascular disease, and more specifically, ischemic heart disease, viability refers to the status of myocardial cells/tissue that are rendered ischemic and what their capacity for survival is. Viable myocardium is the myocardium that is still alive during ischemia, and thus can be saved with timely revascularization.