Heart
and Metabolism

Ischemic heart disease in the elderly

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Equality of care for the elderly

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Editorial

Heart and Metabolism last focused on the elderly in 2001 (issue 15), and it is timely to revisit what is becoming an ever-increasing clinical demand (and at times problem) as, certainly in the developed countries, men and women are living longer. While in this issue we adopt a very positive stance in improving health care in the elderly, sadly others lack compassion and practice age discrimination [1].

I quoted John F. Kennedy in that recent editorial, but I will not apologize for repeating his more than telling and appropriate words: "A medical revolution has extended the life of our elder citizens without providing the dignity and security those later years deserve" (July 1960). Then, in February 1962, he said, "Prolonged and costly illness in later years robs too many of our older citizens of pride, purpose and savings."

Over 50 years later these words still resonate as the ravages of conflict diverts our hard-earned tax income away from the contributors who are now the deserving. Politicians need not just to recognize the needs of the elderly, but to act on those needs, improving provision of care without financial penalty. As brave soldiers die in conflict, so do the elderly back home.

In this issue of *Heart and Metabolism*, we treat the elderly with the respect they deserve. From a better understanding of energy metabolism in the ageing heart, we envisage improved therapeutic strategies avoiding or delaying percutaneous or surgical intervention for ischemic heart disease. We illustrate this concept in the Hot Topics, Focus On, and Case Report sections.

The Main Clinical Article is a succinct and valuable practical overview of the problems and issues that occur in managing angina in the elderly. It introduces us to the importance of looking for comorbidities or co-pathologies, including aortic stenosis. This leads us to the very topical subject of transcatheter aortic valve replacement, which is reviewed by one of the major teams involved in this innovative treatment. As the population ages, cardiac CT in the elderly will become increasingly used as a means to guide clinical practice and it is therefore timely to review its strengths and limitations.

Finally and importantly, we address the issue of sexuality in older people, in an article by one of the authors of the booklets found on the website www.sexualadviceassociation.co.uk. Sex plays a valuable role in the lives of men and women, irrespective of age [2].

In this issue, we hope to establish an island of dignity and respect for old age, where equality of care is paramount and opportunity unrestricted. Old age should not be about waiting to die when there is so much that can be done to improve both quality and quantity of life. •

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Energy metabolism in the aging heart

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Abstract

Aging is a well-recognized risk factor in the development of cardiovascular disease, which is the primary cause of death and disability in the aging population. Although the mechanisms responsible for age-related cardiovascular disorders are likely multifactorial, derangements in myocardial energy substrate metabolism may play an important role in the progressive decline of cardiac function commonly observed with advancing age. Indeed, a decrease in the overall capacity for mitochondrial oxidative metabolism with reductions in both fatty acid and glucose oxidation in the aged heart has been associated with impaired cardiac performance. However, the mechanisms by which these pathophysiological changes occur have not been completely described nor is it known if changes in cardiac energy metabolism are sufficient on their own to impair cardiac performance in the aged heart. Therefore, a better understanding of the metabolic changes that occur in the heart during the normal process of aging could shed light on the pathogenesis of age-related cardiomyopathy and may ultimately lead to improved therapeutic strategies for the treatment of contractile dysfunction in the elderly.

Keywords: aging; myocardial metabolism; contractile dysfunction; mitochondria

■ Heart Metab. (2011) 52:3–7

Introduction

Age is a significant risk factor for the development of a number of cardiovascular diseases (CVDs), such as ischemic heart disease and heart failure [1, 2]. The prevalence of CVD increases dramatically with advanced age [3], and given the rapidly growing size of the aging population, this will undoubtedly increase the burden of age-related diseases on the healthcare system. Progressive alterations in cardiovascular structure and deterioration of cardiac function may be intrinsically associated with the normal process of aging even in the absence of atherosclerosis and hypertension [2, 4], which are major contributing factors to aging-related cardiac dysfunction [5, 6]. As such, these specific age-related changes in the heart may then predispose the elderly to developing age-mediated cardiomyopathy or negatively impact cardiac disease outcomes. Indeed, advanced age is associated with several cardiovascular abnormalities, including endothelial dysfunction, arterial stiffening, cardiac interstitial fibrosis, blunted β-adrenergic response and cardiomyocyte apoptosis [1, 7, 8]. These cardiac changes are considered part of the normal aging process that is then influenced by environmental factors such as diet and physical activity. Although the mechanisms responsible for age-related cardiac dysfunction are likely multifactorial, derangements in the pattern of myocardial energy metabolism is thought to play an important role in the progressive decline of cardiac function with age [9–11].
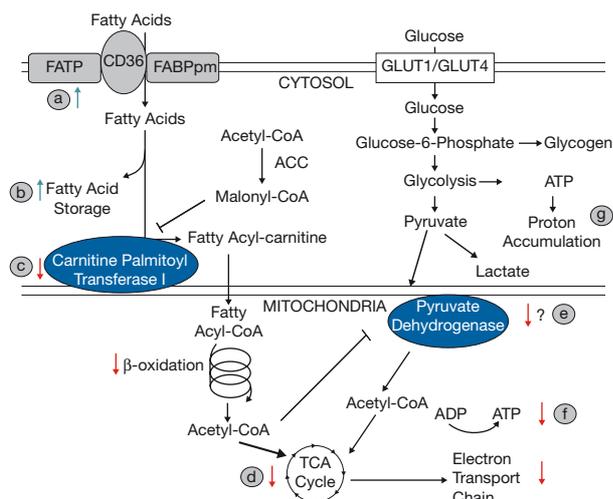
Fig. 1 *Energy metabolism in the aging heart. Increased levels of cluster of differentiation 36 (CD36) in the aged heart promotes the uptake of fatty acids across the plasma membrane (**a**) and together with reduced fatty acid oxidation rates may result in excessive accumulation of potentially toxic lipid intermediates (e.g. ceramides, diacylglycerol) and cardiac contractile dysfunction (**b**), in a phenomenon commonly known as "lipotoxic cardiomyopathy." The age-related decline in cardiac fatty acid oxidation may be the result of reduced activity of carnitine palmitoyl transferase-1 resulting in reduced uptake of fatty acids into the mitochondria for subsequent oxidation (**c**). Mitochondrial oxidative capacity has also been shown to decline in the aged heart due to decreased activity of several tricarboxylic acid (TCA) cycle enzymes and complexes of the electron transport chain (**d**). Although the alterations in glucose metabolism that occur in the aged heart have not been clearly defined, decreased levels of glucose handling proteins (e.g., glucose transporter type 4 [GLUT4], pyruvate dehydrogenase), as well as rates of glucose oxidation (**e**) may contribute to an overall deficit in adenosine-5'-triphosphate (ATP) production and produce an energetically compromised heart (**f**). Under ischemic conditions, the heart relies more heavily upon glycolysis for ATP production, however, the hydrolysis of glycolytically-derived ATP in the presence of diminished glucose oxidation results in proton and lactate accumulation that may impair cardiac function during reperfusion following ischemia (**g**). Due to potential alterations in glucose metabolism that occur in the aged heart, the degree of ischemia-reperfusion injury may be worsened in the elderly.* FATP *fatty acid transport protein,* FABPpm *plasma membrane isoform of fatty acid binding protein,* CoA *coenzyme A,* ADP *adenosine diphosphate,* ACC *acetyl CoA carboxylase*

Cardiac energy substrate metabolism

The heart possesses a high energy demand and must produce considerable amounts of adenosine-5'-triphosphate (ATP) in order to support proper contractile function and ionic homeostasis [12]. Normally, the heart displays a high degree of metabolic flexibility and can utilize multiple substrates to generate ATP including fatty acids, glucose, lactate, and ketone bodies [11, 13]. Under normal physiological conditions,

>95 % of total ATP is derived from mitochondrial oxidative phosphorylation, with the remainder coming from glycolysis [12]. The healthy adult heart has a preference for fatty acids as a fuel substrate and obtains 50–70% of its ATP from the oxidation of fatty acids, with the remainder largely accounted for by carbohydrate (glucose and lactate) oxidation [14, 15].

Glucose utilization

Glucose is taken up from the circulation by facilitative glucose transporters and can be stored in the form of glycogen or undergo glycolysis [15, 16]. Under aerobic conditions, the process of glycolysis converts glucose into pyruvate where the majority of pyruvate enters the mitochondria, is converted to acetyl coenzyme A (CoA) by pyruvate dehydrogenase (PDH) and then enters the tricarboxylic acid (TCA) cycle to eventually produce significant amounts of ATP [15]. During anaerobic conditions, mitochondrial oxidative metabolism is inhibited, and glycolysis becomes the major source of ATP [12]. How glucose utilization is altered in the aged heart and the relation that this has to age-mediated cardiac dysfunction has yet to be fully explained.

Fatty acid utilization

Long-chain fatty acids can enter the cardiac myocyte either by passive diffusion via a flip-flop mechanism of fatty acids across the lipid bilayer or by protein facilitated transport [17]. The three major fatty acid transport proteins identified to date, include fatty acid translocase (FAT)/cluster of differentiation 36 (CD36), the plasma membrane isoform of fatty acid binding protein (FABPpm), and fatty acid transport protein (FATP) 1–6 [17]. Of these, CD36 has been shown to mediate >50% of myocardial fatty acid uptake [18] and significantly impacts subsequent fatty acid oxidation in the mitochondria [19]. Another major site of regulation of fatty acid oxidation is the import of the intracellular fatty acids into the mitochondria [14]. The rate-limiting enzyme involved in this process is carnitine palmitoyl transferase (CPT)-1, and alterations in the activity of this enzyme indirectly governs mitochondrial β-oxidation and subsequent ATP production [12]. Importantly, many of these pathways involved in regulating myocardial fatty acid utilization have been shown

to be altered in the aged heart and have been suggested to contribute to cardiac dysfunction in the elderly [20, 21].

Energy metabolism in the aging heart

Alterations in cardiac energy substrate metabolism occur in several cardiac pathologies, such as myocardial ischemia, ventricular hypertrophy, and heart failure [12]. Interestingly, only a few studies have investigated the effect of advanced age on myocardial energy metabolism. Although earlier studies have reported that fatty acid oxidation is reduced in hearts from both aged rodents [22] and humans [20], detailed examination of these studies reveal that overall oxidative metabolism may be depressed as opposed to just fatty acid oxidation. Given the close relationship between metabolism and cardiac contractile function, impaired oxidative metabolism may contribute to the age-related decline in mechanical function and increases in CVD commonly observed in older patients [8, 23]. Consistent with this, we have shown using the *ex vivo* isolated working mouse heart model that both glucose and fatty acid oxidation are reduced by 2.5- and 4-fold, respectively, in hearts from aged mice as compared to young mice under both normal and high workloads [21]. This reduction in glucose and fatty acid oxidation rates translated into a 60% decrease in total acetyl CoA-derived ATP production in the aged heart [21] (Fig. 1f). However, whether this is due to a specific decrease in fatty acid oxidation or to an overall reduction in oxidative metabolism has not been fully explored. Consistent with the latter concept, Hyyti et al. [24] have recently shown that fatty acid and ketone oxidation is impaired in the aged murine heart, supporting that overall oxidative metabolism may be reduced.

In addition to reduced oxidative metabolism observed in the aged heart, accumulation of lipids within the cardiac myocyte has also been observed [21, 25]. This is relevant since increased lipid accumulation in the heart has been strongly implicated in lipotoxicity and cardiac dysfunction in the setting of obesity and diabetes [26]. As such, myocardial lipid accumulation observed in the aged heart may be deleterious to cardiac function and may result from not only reduced fatty acid oxidation but also from excessive fatty acid uptake into the heart. Indeed, upregulation of myocardial CD36 expression has been shown to occur in the aged heart [21] (Fig. 1a), thus rendering the aged heart more susceptible to lipid accumulation during increased dietary fat intake [27] (Fig. 1b). Thus, it is possible that excessive myocardial lipid accumulation in the aged heart contributes to the impairment in contractile function that is often observed in the elderly.

Although the mechanisms responsible for the potential age-related decline in fatty acid oxidation is not fully understood, reductions in activity of CPT-1 and carnitine-acylcarnitine translocase have been observed in the aged heart [22, 28, 29], which suggests impaired fatty acid entry into the mitochondria for subsequent ATP production (Fig. 1c). Consistent with this, peroxisome proliferator-activated receptor (PPAR)-α, a key transcriptional regulator of target genes controlling lipid metabolism, is markedly reduced in the aged murine myocardium [24, 30], which may also decrease fatty acid utilization.

Mitochondrial function has also been shown to decline with age [31, 32] and may be a key contributor to impaired fatty acid and glucose oxidation. Several studies have demonstrated an age-dependent reduction in mitochondrial oxidative capacity in the heart due primarily to decreased activity of complexes I, III and IV of the electron transport chain, [32–39] as well as decreased activities of TCA cycle enzymes [33] (Fig. 1d). While the exact cause of this mitochondrial dysfunction is not clear, a popular theory proposes that enhanced mitochondrial reactive oxygen species (ROS) production can lead to mitochondrial DNA damage, lipid peroxidation, and mitochondrial dysfunction, creating a vicious cycle of oxidative damage and reduced mitochondrial function [40] that may occur during aging.

Similar to fatty acid oxidation the effect of age on myocardial glucose utilization is also poorly defined, and there is a notable paucity of studies that examine glucose uptake, glycolysis, and glucose oxidation rates together in the aged heart. As mentioned above, data from our lab show that absolute glucose oxidation rates are markedly diminished in the aged heart [21] (Fig. 1e). The limited number of reports to date, suggest that myocardial glucose uptake and glycolysis are increased in the aged heart [20, 41], therefore, recapitulating the shift towards a more fetal metabolic phenotype that is commonly observed in the hypertrophied heart [9]. Indeed, a switch to increased

glucose utilization as characterized by accelerated glycolysis in the absence of a coordinated increase in glucose oxidation may contribute to the high prevalence of left ventricular hypertrophy in the aging population [2]. However, studies examining expression of glucose-handling proteins have yielded conflicting results with some reports showing increases in glucose transporter type (GLUT)-4, phosphofructokinase-1, and PDH [42, 43], while others have found age-associated declines in these enzymes and myocardial insulin resistance [44, 45]. Therefore, further study is needed to clearly elucidate the age-related alterations in myocardial glucose metabolism and their clinical implications. In particular, an acceleration of glycolysis and decrease in glucose oxidation in the aged heart may have the potential to result in uncoupling between glycolysis and glucose oxidation leading to acidosis and reduced cardiac efficiency (Fig. 1g). Of potential clinical significance, such metabolic alterations may exacerbate myocardial injury during ischemia/reperfusion [12]. Interestingly, hearts from mice with a cardiac-specific over expression of GLUT-1 are protected from age-related diastolic dysfunction and have improved recovery from ischemia/reperfusion injury [46]. Hearts from these mice have reduced fatty acid oxidation and importantly elevated glucose oxidation rates, suggesting that therapies promoting glucose oxidation, potentially by inhibiting fatty acid oxidation, may be of significant benefit to prevent ischemia/reperfusion injury in the aging population.

Conclusion

A growing body of evidence suggests that alterations in myocardial energy substrate metabolism occur with advancing age. A decline in overall mitochondrial oxidation may potentially contribute to impaired cardiac mechanical function, as well as predispose the aged heart to the development of cardiac dysfunction and susceptibility to ischemic injury. Indeed, it is clear that further studies are necessary to delineate the precise metabolic changes that occur and molecular mechanisms responsible for and, more importantly, the clinical implications of these changes. Together, this may lead to more targeted metabolic therapies for the treatment and/or prevention of the progressive decline in cardiac function that can occur with age. •

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Managing angina in the elderly: the impact of comorbidities

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Abstract

Older patients with angina represent a patient group with many clinical challenges. Coronary artery disease is particularly common in older patients and the mortality associated with cardiovascular disease is high. Furthermore, diagnosis can be difficult and comorbidities are common. Unfortunately, evidence from clinical trials based on this group of patients is limited and current treatment guidelines do not fully address the needs of elderly patients. Several recent clinical trials have highlighted some of the main considerations one should make when treating comorbidities in elderly patients with coronary artery disease. Different treatment options in the pharmacological management of angina in this age group with comorbidities are also discussed in this review.

Keywords: elderly; coronary artery disease; angina; comorbidities

■ Heart Metab. (2011) 52:8–14

<div style="writing-mode: vertical">Main Clinical Article</div>

Introduction

The prevalence of coronary artery disease (CAD) increases dramatically with age. CAD is the leading cause of death in the elderly with 84% of all CAD deaths occuring in those 65 years of age or older. In women 70–84 years old, the prevalence of angina pectoris is 19%, and it is 24.7% in those aged 85 years and older. In men aged 70 years and older, the prevalence of angina is 27.3% [1, 2]. The disease is more likely to be diffuse and severe. One should also be aware of the higher likelihood for comorbidities in elderly patients with angina. Therefore, managing angina in the elderly is an increasing challenge, and one that we cannot and must not avoid.

Comorbidities in elderly patients with angina

Elderly patients more frequently have coexisting cardiac disorders, many of which can independently cause angina or exacerbate angina due to underlying CAD [3, 4]. These, along with non-cardiac conditions that can trigger angina symptoms, should be investigated as part of the overall evaluation. Of particular relevance are renal disease, other atherothrombotic disease (e.g., peripheral arterial disease or cerebrovascular disease), diabetes mellitus and anemia. Cardiovascular (CV) risk and management of CV risk factors and comorbidities in older patients with angina are discussed in detail below. Table 1 summarizes the key features of the most frequently reported comorbidities in older CAD patients.

Hypertension [6,11]	• Isolated systolic hypertension is the commonest form of hypertension in elderly. The risk for CV events increases markedly in older patients. Even very elderly patients (>80 years) benefit from antihypertensive treatment (HYVET).
Diabetes [13]	• The prevalence of diabetes mellitus is higher in patients aged >65 years with NSTE-ACS than in those aged <65 years. Myocardial ischemia may be silent in presentation which poses further difficulties in both the diagnostic and therapeutic management of CAD.
Renal failure [30]	• Shares many risk factors with CAD. Elderly patients in whom the two conditions co-exist tend to have worse overall clinical outcomes with a higher risk for ischemic and bleeding complications.
Atrial fibrillation [21]	• Common condition in elderly patients. Of the individual components of the CHADS2 score, age ≥75 carries a worse prognosis for stroke and mortality over hypertension, diabetes, or heart failure.
Peripheral vascular disease [31]	• Elderly patients with stable angina often have atherothrombotic disease present in other arterial beds and this increases their total cardiovascular risk.
Aortic valve stenosis [20]	• Angina is the most common symptom associated with aortic stenosis in elderly patients. CAD is frequently co-exists in these patients, however, angina may also occur in the absence of CAD.
Aortic incompotence [20]	• Exertional angina may be present in patients with severe aortic regurgitation.
Mitral stenosis [20]	• In patients without CAD, myocardial ischemia may be related to right ventricular hypertrophy or embolism.
Primary pulmonary hypertension	• Chest pain is a non-specific symptom in patients with primary pulmonary hypertension. New onset of increasing severity/frequency of angina episodes can be a sign of deteriorating right ventricular function.
Anemia [27]	• Mild to moderate anemia is a highly prevalent condition and an independent predictor of long-term outcome among elderly patients with stable symptomatic CAD.
Chronic obstructive disease [32]	• This condition has common symptoms with CAD, triggered by exertion. Noninvasive assessment of CAD in COPD is difficult.
Hyperthyroidism [33]	• Thyrotoxicosis can aggravate pre-existing heart disease and can also lead to AF, congestive heart failure, or worsening of angina pectoris.

Table 1 *Comorbidities that frequently coexist in elderly patients with angina.* AF *atrial fibrillation,* CAD *coronary artery disease,* COPD *chronic obstructive pulmonary disease,* HYVET *Hypertension in the Very Elderly Trial,* NSTE-ACS *non-ST-segment elevation acute coronary syndrome.*

Clinical assessment

The assessment of angina in the elderly can be difficult because pain caused by comorbid conditions (gastro-intestinal, musculoskeletal and pulmonary pain) can mimic angina pectoris. In addition, although angina usually indicates the presence of underlying obstructive CAD, myocardial ischemia can result from a variety of conditions that lead to an imbalance between oxygen supply and demand, such as left ventricular hypertrophy, aortic valve stenosis, atrial fibrillation with rapid ventricular response and chronic obstructive pulmonary disease. Of particular importance is that reduced activity levels and blunted appreciation of ischemic symptoms become the norm with advancing age. Therefore, angina in the elderly is neither a reliable nor a sensitive marker of myocardial ischemia.

Careful physical examination can reveal coexisting conditions that mimic or deteriorate angina symptoms (e.g., ejection systolic murmur in aortic stenosis), as well as comorbidities associated with a worse prognosis (e.g., bruits in carotid and femoral arteries).

Non-invasive tests

The 12-lead echocardiogram (ECG) is abnormal in over half of older people and may identify previous silent infarction or atrial fibrillation. It also provides important information about non-CAD disorders that may provoke angina symptoms, such as left ventricular hypertrophy or arrhythmias with slow or rapid ventricular response.

Exercise stress testing remains important in the elderly. However, the interpretation of exercise test

results in the elderly differs from that in the young. False positive test results are more frequent because of the higher prevalence of confounders, such as left ventricular hypertrophy (resulting from valvular diseases and hypertension), and conduction disturbances. Despite these differences, ECG testing should remain the initial test in evaluating elderly patients with angina and co-morbidities unless the patient cannot exercise; in such a case it may be replaced by pharmacological stress imaging.

If there are indications of valvular heart disease, left ventricular dysfunction, or left ventricular hypertrophy, an echocardiogram is essential. The presence of aortic aneurysm may be indicated by a detailed medical history and careful physical examination of the abdomen, and should be further investigated with ultrasound or computed tomography (CT) scanning. Similarly, carotid bruits should be evaluated using ultrasonic testing. Routine blood tests should be performed to assess hematocrit level, renal and thyroid function, lipid status and blood glucose. Finally, pulmonary function tests for older chronic smokers with chest pain and dyspnea on exertion adds to the diagnosis and management in elderly.

Management of elderly with angina and comorbidities

Angina

The presence or absence of comorbid conditions influences the selection of therapy in elderly. Preferred initial anti-anginal drug therapy is outlined in Table 2. Metabolic agents, such as trimetazidine or ranolazine, exert anti-ischemic actions without affecting hemodynamic parameters and thus represent useful adjunct

therapeutic agents in the elderly. The antianginal efficacy of I(f) inhibition with ivabradine is consistent across all the subpopulations analyzed, independent of the severity of angina and the presence of a comorbidity [5].

Hypertension

The targets for lowering blood pressure are the same for patients of all ages: less than 140/90 mmHg, except in patients with type-2 diabetes, chronic renal disease, established atherothrombotic disease, and heart failure, in whom a level of less than 130/80 mmHg is recommended [6,7]. No specific guidelines exist for hypertension management for this particular population. The choice of the first drug often needs to be precisely tailored to individual characteristics. Many patients will need two or more drugs to control blood pressure, since in the elderly it is often particularly difficult to lower systolic pressure to below 140 mmHg. Initial trial of a beta-blocker or a calcium channel blocker is justified as these agents exert antianginal effects in addition to lowering blood pressure. Caution should be exerted in identifying impulse and conduction disturbances when administering β-blockers or rate-reducing calcium channel blockers. Additional therapy with a diuretic or other antihypertensive agent should be used to adequately control the blood pressure [8]. Nonpharmacologic approaches (e.g., decreased sodium intake, weight reduction, exercise) also should be emphasized because they are more effective in older patients than in younger patients.

Isolated systolic hypertension (i.e., systolic blood pressure 140 mmHg or higher with a diastolic blood

Concomitant disease	Long-acting nitrates	β-blockers	Long acting DHP	Non-DHP	Ivabradine
Hypertension	+	+++	++	+++	++
Diabetes	+++	++	+++	+++	+++
Aortic valve stenosis	++	+++	+	++	++
SVT	+	+++	0	+++	+++
Chronic renal disease	+++	++	+++	+++	++
Peripheral vascular disease	++	++	+++	++	++
Mild COPD	+++	+	+++	+++	+++
Severe COPD	+++	0	+++	+++	+++

Table 2 *Antianginal treatment options in older patients with comorbidities (modified from [34]).* COPD *chronic obstructive pulmonary disease,* DHP *dihydropyridine,* PVD *peripheral vascular disease,* SVT *supraventricular tachycardia.* +++ *very effective and desirable,* ++ *moderately effective and desirable; + effective but less desirable,* 0 *should be avoided.*

pressure of less than 90 mmHg) is the most common form of hypertension in the elderly. A wide pulse pressure (i.e., 50 mmHg or higher) in this population is a better marker of cardiovascular risk than mean or diastolic blood pressure, empasizing the dominant role of arterial stiffness in the pathophysiology of hypertenion in the elderly [9, 10]. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and calcium antagonists, but subanalyses of other trials also show efficacy of renin-angiotensin-aldosterone system (RAAS)-blocking agents [7]. Effects of blood pressure-lowering agents on central aortic pressure may differ despite similar effects on brachial blood pressure [11]. This finding provides a plausible explanation for increased benefit of agents, such as calcium channel blockers and RAAS-blocking agents, in the elderly. The Hypertension In the Very Elderly Trial (HYVET) was the largest-ever clinical trial to address the clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients over 80 years old [12]. HYVET showed that treating hypertension (with the aim to achieve a target blood pressure of 150/80 mmHg) with a regimen based on indapamide, with or without perindopril, is associated with reduced risks of death from stroke, death from any cause, and heart failure. The optimum diastolic blood pressure to be achieved by treatment is not clear; however, significant reduction in diastolic BP (<60 mmHg) should be avoided [7].

Diabetes

The recommended therapeutic interventions are similar across age groups and include dietary and exercise counseling, as well as pharmacologic therapies, with the goal of reducing the hemoglobin A1c level to less than 7% and achieving near-normal fasting blood glucose levels [13]. In elderly patients, lifestyle modifications leading to loss of body fat have a sizable positive impact on insulin and glucose metabolism. Exercise training improves insulin resistance and glucose control in healthy elderly persons [14]. In the ADVANCE trial, an intensive glucose control strategy involving gliclazide (modified release) and other glucose-lowering drugs as required reduced the hemoglobin A1c level to an average of 6.5%. The main benefit conferred by the ADVANCE treatment regimen was a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a

consequence of a 21% relative reduction in nephropathy [15]. It should be stressed, however, that every effort to avoid severe hypoglycemia should be made since it increases a broad range of adverse clinical ourcomes.

Preventive management in older patients with diabetes requires critical attention to correcting coexisting cardiovascular risk factors. The addition of an angiotensin-converting enzyme inhibitor to other therapies slow the progression of kidney disease and reduces the risk for cardiovascular events in patients with diabetes and established CAD. However, clinicians should be aware of a higher risk of postural symptoms (e.g., orthostatic hypotension) in these patients.

Atherothrombotic disease

Secondary and primary prevention of ischemic stroke or transient ischemic attack (TIA) in older patients is targeted at modifiable risk factors including hypertension, active and passive smoking, hyperlipidemia and lack of physical activity. Prevention strategies are also targeted at high risk, but modifiable, conditions, such as inadequately treated atrial fibrillation and carotid artery disease [16, 17]. The benefit of LDL-c reduction on prevention of stroke is less clear in the elderly and no specific guidelines for aggressive lipid lowering strategies exist. The use of antiplatelet therapy is recommended for secondary prevention of atherothrombotic events in patients with prior stroke, TIA, or myocardial infarction. Anticoagulant therapy is recommended for patients with atrial fibrillation or patients who experience stroke while already on aspirin. Because older patients receive multiple antithrombotic agents much more often than their younger counterparts, initial steps toward optimized care include attention to indications, dosing, and duration of treatment [18]. Prasugrel therapy is associated with an increased bleeding risk. Prasugrel should not be used in adults older than 75 years of age and in those who have had a recent TIA or stroke [19]. Finally, patients with severe carotid lesions or symptomatic disease are candidates for carotid artery interventions.

Aortic valve stenosis

Aortic valve stenosis is a major cause of cardiovascular morbidity and mortality in older subjects. Furthermore, angina pectoris is the most common symptom associated with aortic stenosis in elderly patients.

Coexistent CAD is frequently present in these patients. However, angina pectoris may occur in the absence of CAD as a result of myocardial oxygen demand and supply imbalance at the subendocardial level. Once symptoms develop, aortic valve replacement should be performed in patients with severe or moderate aortic stenosis [20]. Nitrates and β-blockers should be used with caution for the symptomatic relief of patients with aortic stenosis in order to prevent the occurrence of hypotension and syncope. For the same reason, caution should be also exerted in the administration of diuretics in patients with heart failure.

Atrial fibrillation

Randomized controlled trials with Vitamin K antagonists (VKA) in atrial fibrillation have shown sustained reductions in ischaemic stroke and cardiovascular events, with only a slight increase in serious bleeds, resulting in a clear positive net effect of VKA in the elderly compared with aspirin [21].

β-blockers and non-dihydropyridine calcium channel antagonists are effective for rate control that may reduce the frequency of angina episodes in older CAD patients. Several randomized controlled trials have demonstrated that a strategy aimed at restoring and maintaining sinus rhythm neither improves survival nor does it reduce the risk of stroke in patients with atrial fibrillation. The AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management) in subjects aged 65 years or older (40 % had CAD) whose atrial fibrillation was likely to be recurrent and who were at risk for stroke reported an insignificant trend toward increased mortality in the rate control group, while there was no evidence to suggest that the rhythm-control strategy protected patients from stroke [21,22].

Patients at moderate to high thrombo-embolic risk require oral anticoagulation therapy. Recently, guidelines addressing antithrombotic therapy in such patients who also undergo coronary artery stenting were reported. These guidelines take into account the hemorrhagic risk, the clinical setting and the type of stent implanted [21,18,23]. A careful clinical evaluation and assessment of thrombotic/hemorrhagic risk before the beginning of anticoagulation therapy in elderly CAD patients with atrial fibrillation is essential.

An alternative approach aiming at reducing high severe bleeding rate involves combined antiplatelet (cyclooxygenase inhibitor triflusal) and moderate-intensity anticoagulation therapy. In the NASPEAF trial, such a combination was effective in prevention of embolic events, while vascular events were significantly decreased [24].

Chronic renal failure

Chronic renal failure shares many risk factors with CAD. Control of glycemia is a priority in management of diabetic patients with impaired renal function. The target for lowering blood pressure is lower in hypertensive patients with chronic renal disease as compared to subjects with normal renal function (a level of less than 130/80 mmHg is recommended). Although no specific data to show superiority of RAAS-blocking agents for preservation of kidney function or prevention of cardiovascular end-points exist in elderly patients, it is anticipated that they indeed exert this preferential protective effect. A study in elderly patients with chronic kidney disease with a moderate decrease in GFR suggest that these drugs are tolerated and maintained in the long term as often as in patients without renal failure [4]. Dosage adjustments pose an additional treatment challenge. As many CV drugs are cleared through the kidneys, patients with renal dysfunction typically require lower doses [4]. Anticoagulant medication used in acute coronary syndromes such as enoxaparin and small molecule IIb–IIIa antagonists require a dose adjustment in the presence of renal impairment, irrespective of age [25]. Finally, age >75 years is an important predictor of contrast-induced nephropathy [26].

Anemia

Elderly patients are more likely to be anemic on initial presentation, posing a caution in the use of dual antiplatelet therapy (e.g., clopidogrel plus aspirin) and thus potentially limiting the use of percutaneous coronary intervention [27]. The challenge is to identify the best target Hb level for elderly patients with angina, taking into account any comorbid conditions (such as renal failure, gastrointestinal bleeding), concomitant medications and the patient's own expectations of therapy. In elderly patients with atherosclerosis, it is important to maintain Hb levels 10>g/dl to prevent angina pectoris or congestive heart failure [27,28]. However, it remains unknown whether and how much anemia should be corrected in elderly CAD patients in order to improve outcome.

Chronic obstructive pulmonary disease

CAD is not rare in patients with chronic obstructive pulmonary disease (COPD) because both diseases share common risk factors, especially smoking, increased age and decreased physical activity. Non-invasive diagnosis of CAD may be under- or overestimated in patients with COPD. Furthermore, due to common risk factors and similar symptoms, coronary angiography may be performed more frequently in those patients. Nevertheless, specific treatments, such as beta-blockers, should not be denied to elderly people, unless specific contraindications are present, such as a severe chronic obstructive pulmonary disease or a history of asthma [29]. Wise adjustment of dosage should also be attempted.

Conclusions

Coronary artery disease is particularly common in older patients, but diagnosis of CAD can be difficult. Comorbidities such as renal disease, other athero-thrombotic disease, diabetes mellitus and anemia are common. Unfortunately, specific clinical trial data to guide therapy in this growing population subset are limited. These patients can often be managed in the same way their younger counterparts, but additional care and considerations specific to the comorbidity is required. Given the increasing proportion of elderly patients in our aging societies and the increased CV mortality in these patients, further clinical research in this specific population is needed. •

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Cardiac computed tomography in the elderly: windows into a lifetime of exposure to cardiac risk

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Abstract

Cardiac computed tomography (CT) can non-invasively determine coronary calcium score, the extent and severity of coronary artery disease, and left ventricular function. These three elements have diagnostic and prognostic utility in the assessment of patients with suspected coronary artery disease. However cardiac CT requires high spatial and temporal resolution for an accurate assessment of these variables. The acquisition requirements of cardiac CT can be difficult to fulfil in the elderly with a higher prevalence of coronary calcification, atrial fibrillation, co-morbidities and impaired cognitive function. These potential challenges are to be weighed against the advantages of cardiac CT as a non-invasive test providing reliable anatomical data in a difficult to assess population.

Keywords: cardiac CT; coronary calcification; risk stratification; elderly

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Metabolic Imaging

Introduction

Cardiac computed tomography (CT) can determine the degree, location and extent of coronary artery disease non-invasively in patients with suspected ischemic heart disease. In the elderly, therefore cardiac CT may evaluate the cumulative impact of a lifetime of exposure to cardiac risk factors. However the utility of cardiac CT in this population has been questioned. The accumulative effects of risk factors over several decades may lead to coronary calcification with subsequent degradation of spatial resolution.

As a window on the coronary arteries, cardiac CT in the elderly may be as a white washed pane, opaque and not evaluable. Whereas for others, the "windows" may be clear, transparent and diagnostic (Fig. 1). With diagnostic scans, cardiac CT angiographic definition of high-risk coronary anatomy may be crucial for clinical decision-making. This is an important advantage in elderly patients with multiple comorbidities who are more susceptible to complications from invasive procedures.

In this review, we will consider the rationale for cardiac CT as part of a risk stratification tool in the elderly (>70 years) and examine the diagnostic and prognostic data available in these individuals.
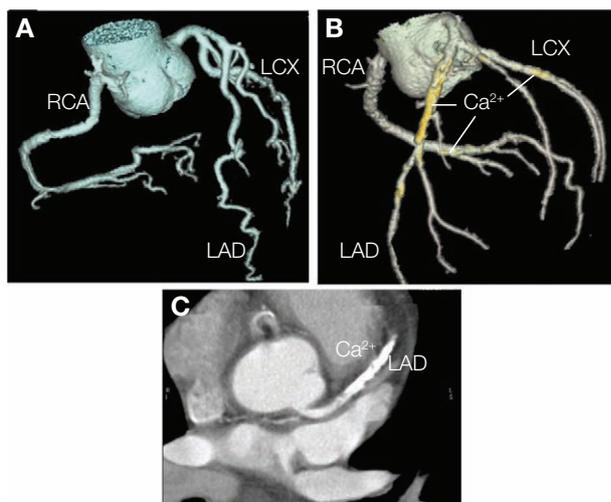
Fig. 1 *Computed tomography coronary angiography in the elderly. A+B volume rendered 3D images of coronary arteries. A) 87-year-old female with a history of exertional dyspnea. There is no coronary calcification; CT coronary angiography was normal. B) 93-year-old male with chest pain. There is extensive calcification (Ca$^2+$) of the proximal and mid left anterior descending artery (LAD) with circumferential calcium (highlighted in yellow). Calcium was also noted in the circumflex (LCX) and right (RCA) coronary arteries. C) 2D axial slice demonstrating extensive calcium in the LAD rendering this segment of the coronary circulation non evaluable.*

Evaluation of coronary artery disease in the aged

Assessment of coronary artery disease in the elderly population (>70 years old) can be problematic. A sedentary lifestyle may mask exertional symptoms. Cognitive dysfunction and impaired hearing may hinder accurate history taking. Despite these challenges, aging of the population indicates that coronary artery disease evaluation in the elderly will become an increasingly common problem.

Clinical risk stratification

Clinical risk stratification of patients with suspected coronary disease can be performed using risk factor scoring systems such as the Framingham Points Score (FPS) [1]. FPS however may be less accurate in the middle aged and elderly [2]. Other potential clinical risk stratifiers have not been well validated in an elderly population [3, 4]. The poor performance of clinical risk stratification in the elderly underscores the need for further non-invasive assessment in these individuals. Consideration could be given to exercise treadmill testing, stress testing with imaging or cardiac CT. There are however limitations in the operating

characteristics of these alternatives, particularly in the elderly.

Non-invasive functional testing

Treadmill testing may be difficult in deconditioned individuals or those with limited mobility. Functional imaging tests with pharmacological stressors such as echocardiography, magnetic resonance imaging or nuclear perfusion studies are potential alternatives to treadmill testing. Although stress echocardiography is often readily available and inexpensive, adequate imaging requires good acoustic windows and patient compliance. Similarly, nuclear perfusion studies are usually accessible. However, elderly patients may not tolerate long nuclear imaging times and have poor images due to patient motion. Magnetic resonance imaging (MRI) may be contra-indicated in the elderly as a result of joint prostheses, renal failure, poor compliance or claustrophobia.

Cardiac CT

In contrast to these functional tests, cardiac CT defines coronary calcium and coronary anatomy.

Coronary calcium and prognosis

A coronary calcium score is often performed using a low dose non-contrast CT prior to CT coronary angiography. Coronary artery calcium (CAC) scores are usually measured as an Agatston score which identifies lesions greater than 130 Hounsfield units and an area $\geq 1mm^2$ [5].

In the elderly, the additional data provided by a CAC score can provide incremental prognostic value to clinical risk predictors [2, 6]. CAC may significantly increase the ability to predict cardiac events (non fatal MI and cardiac death) and appears incremental to clinical risk prediction with FPS. CAC calculation has been associated with a 14% net reclassification improvement in risk following clinical hazard prediction (p<0.01). The largest proportion of individuals reclassified as a consequence of CAC assessment was from the moderate Framingham risk group. Fifty-one percent of this group were reclassified by CAC with 30% moving down in risk and 21% moving to a high-risk group [6].

As many elderly patients fall within the moderate risk category of FPS system due to their age (age 70–74 scores 14 points projecting to a calculated 10-year risk

of 18.4% by Framingham risk) [1], the utility of CAC to reclassify approximately 50% of these patients in high or low risk strata may help to determine medical management goals and assist in deciding whether further clinical testing is required.

The utility of coronary calcium to predict prognosis in an elderly population was noted in a large prospective observational study of 35,388 patients of whom 3,570 were ≥70 years of age [7]. Mortality rates in patients with Agatston scores <10 were less than those predicted by age alone (3.4% cumulative event rate for mean follow up of 5.8+/-3 years for males, versus age predicted death rates of 5.8% in 75–84 years olds (Office for National Statistics, UK). Whereas those with calcium scores ≥400 had mortality rates in excess of those expected as a results of their age alone. Individuals without coronary calcification ≥70 years of age had a low annualized mortality rate (2.2%) [8].

CT coronary angiography and diagnostic accuracy

Coronary calcium, although a useful risk stratification tool and prognosticator, can hinder the accurate evaluation of luminal stenoses at CT coronary angiography (CTA). Assessment of the influence CAC on CTA accuracy was investigated in 134 suspected coronary artery disease patients with a mean age of 54 +/-9 years [9]. In comparison to patients with low calcium scores, those with higher Agatston scores (<142) had more unevaluable segments. In addition, evaluable segments in those individuals with higher Agatston scores (>142) showed less correlation with invasive angiography than evaluable segments from patients with low Agatston scores.

Thus the accuracy of CTA in patients with moderate or higher Agatston scores is likely to be less than that of patients with low or zero scores [9]. It remains unclear whether the diagnostic discrepancies between CTA and invasive coronary angiography in patients with elevated calcium scores would affect the prognostic utility of CTA in the elderly.

CT coronary angiography and prognosis

In a large prognostic study of 2,172 patients with a mean age of 58 +/-11 years, normal CT coronary angiography without evidence of coronary atherosclerotic plaque was associated with an excellent prognosis of 0.1% annualized risk of cardiac events [10]. Mild non-obstructive disease was associated with a slightly higher rate of 0.5% annualized risk. This study and others have indicated that moderate (≥50%) disease in any coronary artery, severe proximal obstructive disease (≥70%) or obstructive left main stem disease (>50%) portended a poorer prognosis [10, 11]. An incremental effect of left ventricle (LV) functional data, in addition to coronary anatomy in predicting outcomes, was also demonstrated [10].

The influence of age on outcomes was noted in these papers and increasing age was an important risk factor for predicting adverse events. The results were not stratified according to age and therefore the effect of high risk anatomy on mortality rates for different age groups was not given. Consistently however proximal coronary disease and multi-vessel coronary disease has been associated with poorer outcomes and it is likely such high risk anatomy would be important in determining outcomes in the elderly.

Cardiac CT angiography and radiation

Initially images were obtained using helical, ECG-gated imaging which was associated with relatively high radiation exposures (15mSv). Newer techniques using ECG gated/triggered axial step and shoot acquisition have considerably reduced x-ray exposure (7mSv) [12]. It should be noted that the sensitivity of tissues to radiation does diminish with age and although dose reduction principles should always be pursued, the necessity to limit radiation exposure is perhaps less essential in an elderly population [13].

Perspective

The role for cardiac CT in evaluating elderly patients (≥70 years) remains ill defined. Further long-term prognostic studies are required in addition to diagnostic feasibility studies to confirm the potential of CT coronary angiography in this population.

In the absence of guidelines for the use of cardiac CT in the elderly, a strategy (Fig. 2) in symptomatic individuals could be to perform a calcium score assessment in patients with no prior history of coronary revascularization, as initial risk stratification. Following CAC imaging it may become clearer whether CT coronary angiography is likely to be non-evaluable due to the presence of circumferential coronary calcium.
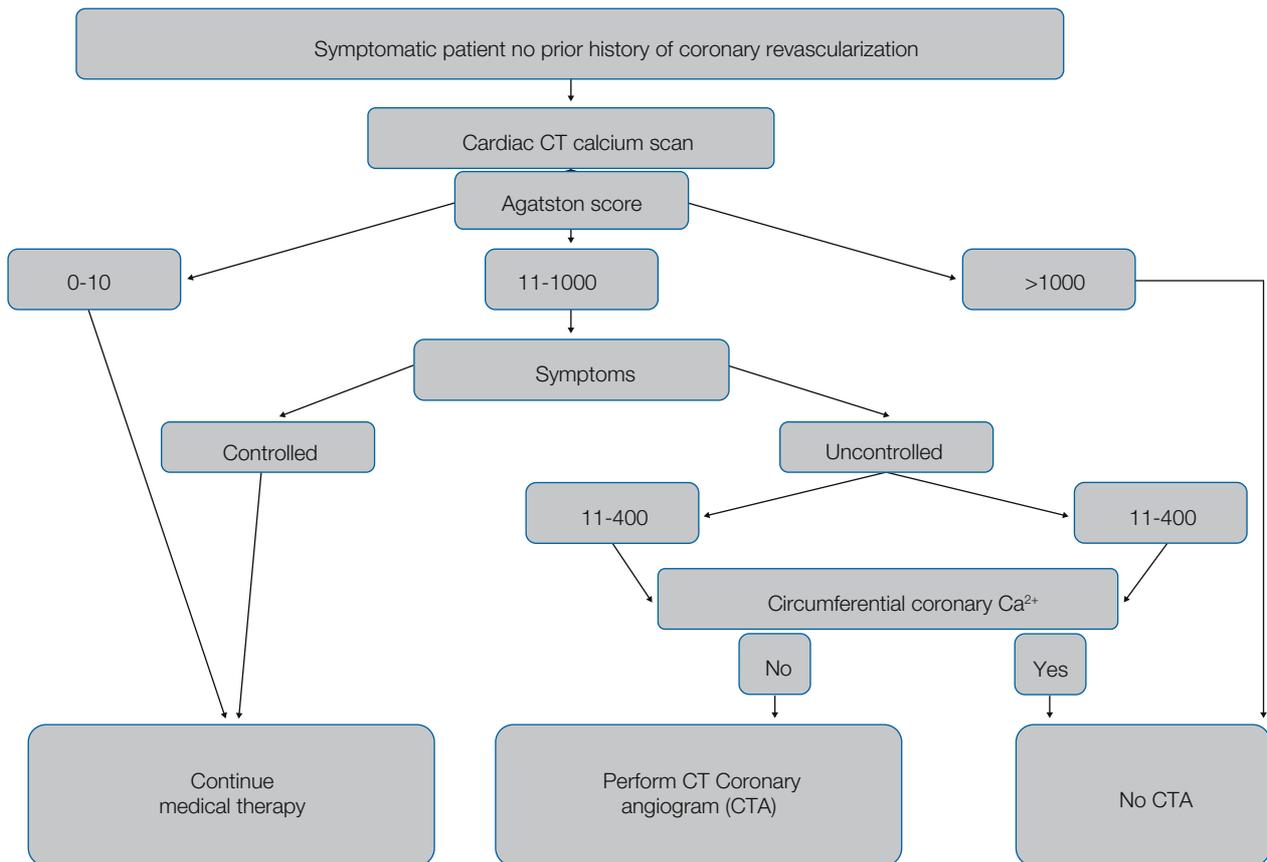
Fig. 2 Proposed strategy for investigating suspected coronary artery disease in the elderly. CT computed tomography, Ca²⁺ calcium [6,7].

In patients with uncontrolled symptoms and calcium scores 11–400, without circumferential calcium it may be useful to perform CT angiography to identify patients with high-risk coronary artery disease suitable for invasive management. In those with calcium scores 0–10 with controlled symptoms a more conservative approach with initial medical management could be pursued (Fig. 2).

Summary

Cardiac CT has been enthusiastically welcomed as a non-invasive test to investigate suspected coronary artery disease. Although used in the elderly, the increased prevalence of coronary calcification in this age group can predispose to non-diagnostic scans. Yet, in an era post COURAGE with greater acceptance of medical therapy in coronary artery disease management, further risk stratification by cardiac CT may be a useful gatekeeper for invasive testing [14]. Identification of patients with high-risk coronary anatomy for revascularization would be an important step prior to commitment to medical therapy. In light of this and especially in the elderly patient with suspected coronary artery disease, CT coronary angiography may provide a useful non-invasive window on coronary anatomy. •

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Transcatheter aortic valve implantation in the elderly: current state of play

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Abstract

Aortic stenosis is the most common acquired valvular abnormality in the Western world, with ever-increasing disease prevalence due to an aging population. Surgical aortic valve replacement remains the first-line standard of care, however, over one-third of potential patients are not candidates because of the prohibitive nature of their comorbidities and consequent peri-operative risk. In the last few years, transcatheter aortic valve implantation has emerged as a less invasive treatment strategy in high-risk patients. Recent randomized trials have shown that this is non-inferior to surgery in high-risk patients; and vastly superior to medical therapy in patients deemed unsuitable for surgical intervention. Since the "first in man" procedure was performed in 2002, there have been major advances in implantation techniques and device technology, together with a growing evidence base. It is highly likely that trans-catheter aortic valve implantation will be used in an increasing number of patients in the aortic stenosis population, but its exact role alongside surgery will need to be defined in a judicious and evidence-based manner.

Keywords: TAVI; aortic stenosis; transfemoral; transapical; stroke; surgical AVR

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New Therapeutic Approaches

Introduction

Acquired, degenerative calcific aortic stenosis (AS) is the most common valvular lesion in the Western world [1, 2], affecting almost 1 in 12 patients by 85 years of age [1]. It is expected to become increasingly relevant to healthcare economics given our aging population. Once symptoms (dyspnea, syncope, chest pain) have developed, the prognosis for untreated severe AS is dire—mortalities at 1 year and 5 years are 40% and 68% respectively [1]. The benefits of surgical aortic valve replacement (sAVR), incorporating cardiopulmonary bypass, sternotomy (or mini-sternotomy), cross-clamping of the aorta and cardioplegic arrest, are well documented. It remains a class I indication and the standard of care in symptomatic AS patients [3, 4]. However the multiple co-morbidities and age of potential recipients can often deter surgeons and over one-third of patients who could potentially benefit are not offered sAVR [2]. These patients with prohibitive peri-operative risk, as judged by the Logistic EuroScore (in the United Kingdom and Europe) or the STS Score (in the United States), are the target cohort for trans-catheter aortic valve implantation (TAVI) (Table 1 [5]). The evidence for its role in the management of AS is growing with short- and long-term registry data providing encouraging safety

Selection Criteria

- Synchronized multi-disciplinary "heart team" approach to patient selection comprising interventional and non-interventional cardiologists, cardiac surgeons, cardiac imaging specialists, cardiac anesthetists and cardiac nurses alongside the input of geriatricians.
- Confirmation of the severity of AS by standard transthoracic echocardiography (note the use of low-dose dobutamine stress echocardiography to differentiate between severe AS and "pseudo-severe AS" in those patients with a low gradient and low left ventricular ejection fraction.
- Patients must have symptoms that can be directly attributed to severe AS.
- Currently, patients with an expected mortality >20% with the Logistic EuroScore and >10% with the STS score are amenable to treatment with TAVI.
  It is important to note that these scoring systems are an imperfect science, particularly because these high-risk patients form only a small proportion of the populations from which the scoring systems have been gleaned. Ultimately sound clinical judgement within a multidisciplinary framework is key.
- An appropriately sized aortic valve annulus:
  - 19–25 mm annulus recommended for a 23 mm or 26 mm SAPIEN™ transcatheter heart valve
  - 20–27 mm annulus requires a 26 mm or 29 mm CoreValve®

N.B. A 28-mm annulus will also be treatable once the 29 mm SAPIEN XT™ THV is widely available.

Exclusion Criteria

- LVEF ≤20% contraindicates all TAVI procedures.
- Bicuspid aortic valves, due to a risk of incomplete deployment of the prosthesis (N.B. this position is likely to change in the near future).
- Apical thrombus.
- Significant asymmetric valvular calcification, which may lead to compression of the coronary arteries during valve-stent deployment.
- Not recommended for those patients who have declined sAVR merely on the basis of personal preference.
- Patients with a life expectancy of <1 year should not be recommended for TAVI.

Table 1 *A summary of inclusion and exclusion criteria for TAVI. Adapted from [5]. (N.B. Revised ESC guidelines, in collaboration with the EACTS, on the management of valvular heart disease will be published in early 2012).*

and efficacy outcomes in a real world setting [6–8], evidence of functional improvement [9], prognostic benefit [10,11] and most recently truly landmark results from both arms of a multicenter randomized controlled trial.

The evolution of TAVI

Today's exponential rise in the uptake of TAVI can be traced to the efforts of one man, Henning Rud Andersen. On May 1, 1989, he performed the "first in animal" implantation of a rudimentary aortic valve-stent prosthesis constructed from metal wire and native porcine valves obtained from a local butcher. The technique was refined in the proceeding two years with a further 40 implantations in anaesthetized pigs. Despite the potential for a paradigm shift in the management of severe AS, it was not until 1992 that the *European Heart Journal* published his findings [12]. There was also a degree of ambivalence shown by the device companies in taking up this new technology until the notion of TAVI was championed by several opinion leaders and the "first in man" percutaneous pulmonic valve implant, performed by Bonhoeffer et al, was published in 2002 [13]. Shortly thereafter the "first in man" TAVI procedure conducted by Cribier et al was published in 2002 using an antegrade trans-septal approach through a femoral vein [14]. Subsequent developments have yielded standardized techniques via retrograde trans-femoral (TF) [15] and trans-subclavian [16] approaches, the antegrade trans-apical (TA) route [6], and now a novel retrograde trans-aortic approach via a mini-sternotomy [17] (Table 2). Currently, no available randomized data compares the TF and TA routes, and therefore there is no robust evidence of which is superior.

There are currently two CE-marked prostheses in use: the Edwards SAPIEN™ transcatheter heart valve (THV) (Edwards LifeSciences, USA) and the

| Implantation Approach	Advantages	Disadvantages
Trans-femoral	Potentially allows for a fully percutaneous procedure in a conscious patient if the peripheral artery (usually femoral, rarely iliac) has an adequate caliber	Contraindicated in the presence of: • Peripheral vascular disease (PVD) • Previous aorto-femoral bypass • Tortuous vessels • Small-caliber vessels • Previous aortic surgery Associated with major, minor and critical vascular complications such as: • Vessel dissection • Vessel rupture • Vessel avulsion
Trans-apical	Potentially reduces the risk of calcium dislodgement (compared to a relatively rigid TF catheter in a diseased aorta) Can be performed in the presence of PVD Can be conducted in those patients with a history of aortic surgery A more "direct", "steady" and "straightforward" technique	Apical bleeding (very rare) Contraindicated in the presence of: • Apical thrombus • Calcified pericardium • Severe chest deformity • Poor lung function • Previous chest irradiation • Recent myocardial infarction • Inaccessible LV apex
Trans-subclavian	A more direct and steadier pathway due to the short distance from insertion site to the aortic valve An alternative to the TA route when there is PVD or a diseased aorta Does not require a thoracotomy (compare to TA)	Currently an "off label" technique Potential complications: • Postoperative bleeding • Vertebral/internal mammary ischaemia • Vessel rupture • Vessel dissection
Trans-aortic	Is a novel option when both TF and TA approaches are contraindicated or not feasible	Risk of massive postoperative bleeding Contraindicated in the presence of a "porcelain" aorta

Table 2 *A comparison of TAVI implantation approaches.*

CoreValve® ReValving system (Medtronic Inc USA). The former is a balloon-expandable tubular system, cobalt-chromium frame with bovine pericardial valve leaflets. It is currently available in 23-, 26- and 29-mm sizes and is suitable for aortic annulus sizes 18 to 27 mm in diameter (Fig. 1). The CoreValve® device consists of a porcine pericardial valve mounted within a longer, self-expanding nitinol frame. It has an hourglass shape with a central waist to accommodate the coronary ostia, and wider portions providing fixa-tion within the left-ventricular outflow tract and the ascending aorta. It is available in 26- and 29-mm sizes and requires an annulus diameter of 20–27 mm (Fig. 2). The advantage of the latter is its stability and potential retrievability, however this is countered by disadvantages such as a higher rate of conduction dis-turbance requiring permanent pacing in a third of patients [18] compared with 7% with the Edwards bio-prosthesis [7]. The CoreValve® device was at one point the sole device available in smaller 18 French

Fig. 1 Edwards SAPIEN™ transcatheter heart valve (printed with permission. ©2011 Edwards)
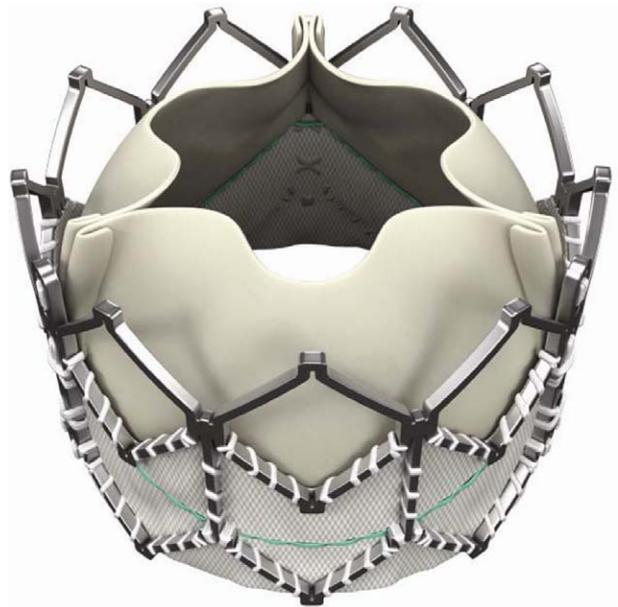
Fig. 3 Edwards SAPIEN™ XT transcatheter heart valve (printed with permission. ©2011 Edwards)

Fig. 2 CoreValve® transcatheter heart valve (printed with permission. ©2011 Medtronic)

gauge delivery systems allowing arterial access in vessels of only 6 mm in diameter. Through successive iterations culminating in the SAPIEN™ XT THV (Fig. 3), delivered via the NovaFlex platform, the Edwards device now has similar ease of access. Both devices require preparation of the valvular apparatus using balloon aortic valvuloplasty (BAV). The NovaFlex+ delivery system, which has also just received a CE Mark (May 2011), has further facilitated valve delivery and can now be delivered through an expandable 16F sheath system making access even less traumatic.

The inability to excise native calcified valve tissue and the resultant "gaps" between the circular device and the irregular annulus commonly result in paravalvular regurgitation, but this is trivial to mild in the majority of cases [19, 20] and does not significantly deteriorate at one year, with 46% actually improving [21]. The valves themselves appear durable as manifested during follow-up of up to five years [22, 23].

The PARTNER trial

Prior to the completion and reporting of results from the Placement of AoRtic TraNscathtER Valves (PARTNER) trial, there had been no robust multicenter randomized controlled trial data available comparing TAVI with conservative medical management or sAVR. The

PARTNER Trial incorporated two individually powered patient cohorts:

- PARTNER A was a non-inferiority trial comparing the safety and effectiveness of the Edwards SAPIEN™ THV with sAVR in high-risk patients with severe symptomatic AS [24].
- PARTNER B was a superiority trial comparing the safety and effectiveness of the Edwards SAPIEN™ THV against best medical management in patients with severe AS deemed too risky for surgery [10].

From the 26 centers (22 in the United States, three in Canada and one in Germany) participating in the trial a total of 3,105 high-risk AVR candidates were identified and initially screened between May 2007 and March 2009. Of these 1,057 patients were enrolled in to two parallel trials. Those patients (n=699) enrolled in PARTNER A were deemed operable, but at high risk as defined by an STS score ≥10% or assigned a predicted risk of operative mortality ≥15% at 30 days by a site surgeon and cardiologist. Those patients (n=358) enrolled in PARTNER B were deemed inoperable due to co-existing conditions that would give rise to an operative mortality of ≥50% at 30 days. Two cardiac surgeons had to agree that this was the case.

Severe AS was defined by echocardiographic criteria as a mean gradient >40 mmHg or jet velocity >4.0 m/s or an aortic valve area of <0.8 cm^2. Patients had to be symptomatic as judged by a New York Heart Association (NYHA) functional class of II or worse. Key exclusion criteria for both arms of the study included: a bicuspid or non-calcified aortic valve, an aortic annulus measurement <18 mm or >25 mm, acute myocardial infarction within the preceding month, severe LV dysfunction (EF <20%), significant coronary artery disease requiring revascularization, pre-existing severe AR or MR or a prosthetic valve already in situ, severe renal dysfunction, and a transient ischemic attack (TIA) or stroke within the last 6 months.

Of the 699 patients in Cohort A, 492 were deemed suitable for TAVI via the TF approach. The remaining 207 were deemed unsuitable for a TF procedure, and were enrolled into the TA arm of the study. Following this initial assessment, patients were then randomized in a 1:1 fashion to receive sAVR or TF TAVI or sAVR or TA TAVI. Following randomization, the aim was to treat the patient within a 2-week timeframe. Results were analyzed on an intention-to-treat (at time of randomization) and as-treated (at time of anesthesia induction)

basis depending on the endpoints studied. Of note 28 patients in the surgical arm of the study either refused treatment or withdrew from the study compared with only one patient from the TAVI arm. Patients were very evenly matched in terms of age, STS score and NYHA functional status at baseline.

The primary endpoint of all-cause mortality was numerically lower in the TAVI group at 30 days (3.4% TAVI versus 6.5% sAVR, P=0.07), but not statistically so. Out to one year both treatment arms were nearly identical (24.2% TAVI versus 26.8% sAVR, P=0.44), therefore fulfilling the predefined criteria for non-inferiority. Observed rates of mortality were lower than expected in the surgical arm at both time points suggesting that sAVR remains a safe and effective treatment modality for this group of patients (30-day mortality rates: expected—11.8%, observed—8.0% in the as-treated population). There was no statistical difference between the TA or TF arms in terms of 30-day or 1-year mortality, although numerically TA patients did suffer more fatalities. This is in keeping with patients assigned to the TA route being at slightly higher risk.

In terms of secondary safety endpoints, all strokes combined with TIAs were statistically higher in the TAVI arm at both 30 days (5.5% TAVI versus 2.4% sAVR, P=0.04) and 1 year (8.3% TAVI versus 4.3% sAVR, P=0.04). Further analysis of the neurological injury subset presented at the American Association for Thoracic Surgery Annual Meeting in May 2011 demonstrated an increased frequency of events in the first two weeks post-TAVI. Those eligible for a TF approach appeared to suffer significantly more neurological events at 30 days and 1 year compared with sAVR although proportionately TA patients suffered more events overall in the TAVI group, again confirming the higher baseline arteriosclerotic burden of TF-ineligible patients, as manifested by significantly higher rates of previous coronary artery bypass graft surgery and pre-existing cerebrovascular and peripheral vascular disease compared to the TF cohort. Major bleeding was statistically higher in the surgery arm (9.3% TAVI versus 19.5% sAVR, P<0.001), but major vascular complications were higher in patients treated by TAVI (11.0% TAVI vs. 3.2% sAVR, P<0.001). In terms of secondary efficacy endpoints, NYHA class and 6-minute-walk test were better for TAVI at 30 days but by one-year results had converged between the two treatment modalities.

It should be remembered that the PARTNER Trial was conducted at a time when TAVI was in its infancy. Clinicians, who may well have had experience of only implanting one or two valves prior to study participation, were also using large first-generation transcatheter-valve systems. We are now using fourth-generation systems. They were being compared to a surgical technique that had been honed over many years and conducted by the best cardiac surgeons at each of the participating centers. As operators gain more experience and newer, less bulky transcatheter devices with improved profiles come to the market we should expect to see rates of stroke, TIA and vascular complications fall. Further studies will determine whether new-generation, smaller-caliber delivery systems with adjunctive embolic protection devices on a background of increased operator experience will help attenuate the incidence of cerebrovascular insults caused by transcatheter manipulation. Nevertheless the trial confirms that both sAVR and TAVI are viable, safe and effective methods of managing high-risk patients with symptomatic severe AS. Dichotomous peri-procedural hazards should, however, be borne in mind when making individual case-based management decisions.

Results from PARTNER B were no less remarkable. In total 358 patients with severe AS deemed unsuitable for surgery were randomized in a 1:1 fashion to conservative management or TF TAVI. Crossover from the standard-therapy group to the TAVI group was not permitted. Patients were followed up for at least one year. The standard-care group had an unusually high frequency of BAV use (63.7% within 30 days of randomization plus an additional 20.1% thereafter) albeit with its limitations and propensity for restenosis. Despite this, the rate of death from any cause at one year was 30.7% with TAVI compared with 50.7% with medical management, indicating a staggering absolute 20% difference in mortality between the two treatment modalities. It not only confirmed that TAVI improved survival and quality of life in this particular cohort of patients but also served to reaffirm the severe natural history of untreated symptomatic AS. The rate of the composite endpoint of death from any cause or repeat hospitalization at one year was 42.5% with TAVI and 71.6% with conservative therapy (P<0.001). As with PARTNER A, the rate of major strokes was more frequent in the TAVI group and vascular complications significantly more so.

In contrast, secondary efficacy endpoints like NYHA class significantly improved in the TAVI group alongside improvements in echocardiographic parameters such as aortic valve area and mean gradient, which were maintained at one year. Although these very positive results in respect of TAVI can only be directly applied to implantation via the TF route, industry and national registry data suggest that the profound difference in outcomes in PARTNER B are not likely to be adversely affected by the slightly higher procedural mortality associated with the TA approach.

The future

With the prognostic benefits of TAVI established, further improvements in outcome are to be gained through better patient selection and honing of techniques. The question of how to optimally tackle coexisting coronary artery disease (CAD) in these patients remains a challenge. Patients receiving TAVI must undergo assessment of their coronary vasculature. For our surgical colleagues, the presence of significant CAD is a Class I indication for combined revascularisation by coronary artery bypass surgery (CABG) with sAVR [4]. CAD is highly prevalent in this group of patients [25] and has similar risk factors [26]. It has been suggested that prior revascularisation by either CABG or percutaneous coronary intervention (PCI) (used as a marker for CAD) raises the 30-day mortality risk in TAVI patients by a factor of ten [27]. The effects of PCI to treat significant coronary lesions prior to TAVI are unknown. The manufacturers' guidance for both the commercially available bioprostheses suggests treatment of significant CAD at least 30 days prior to procedure, but this is not standard practice in many centers. PCI post-TAVI has been successfully performed [28, 29].

The success of these two devices has prompted the development of newer prostheses incorporating and improving many of their features. Deliverability and retrieval of the devices to promote accurate positioning are the ultimate aims. These include the Direct Flow device (Direct Flow Medical Inc., USA), for which there is the greatest literature [30, 31], the Lotus (Boston Scientific Inc., USA), the JenaClip (JenaValve inc., Germany) and the HLT (Heart Leaflet Technologies Inc., USA). Some, such as the Ventor Embracer Valve (Ventor Technologies Inc., Israel) provide more "anatomic" positioning in the aortic root [32].

The treatment of failing sAVR bioprostheses is another area into which TAVI is expanding. Promising results with both the CoreValve® [33] and the Edwards [34] systems reflect enthusiasm among operators to reduce the enhanced risk of re-do surgery [35]. TAVI-in-TAVI procedures have successfully been performed, mostly for sub-optimal results in the initial implant [36]. This has led some to discuss the replacement of sAVR with TAVI in low-risk patients. However given the current results of sAVR, with low mortality in appropriate patients [37], and the high cost of current transcatheter devices, it would be very difficult to make TAVI cost-effective in lower-risk patients. In addition, there is a paucity of data currently available on the durability of the trans-catheter valves. There has, however, been no reported structural failure of the valves to date, with the longest implant remaining in situ for over five years. Ultimately, it is highly likely that TAVI will be used in an increasing proportion of the AS population, but this must be conducted in a prudent, carefully judged way, and in an evidence-based manner. TAVI will also no doubt stimulate our surgical colleagues to streamline and perfect the sAVR procedure, and therefore all members of the heart team will be happy: surgeons will perform more interventions, cardiologists have a new focus for their skills and, most importantly, patients will receive the most safe and effective treatment available. •

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Quality of life with trimetazidine

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Abstract

Trimetazidine, a metabolic agent with anti-ischemic properties, has strong evidence of efficacy and tolerability in the treatment of patients with ischemic cardiomyopathy, including subjects with chronic angina and heart failure. There is now a growing evidence that trimetazidine has also a positive impact on quality of life of these patients. This seems to be a consequence of the clinical benefits provided by trimetazidine on one hand, and of its optimal tolerability profile on the other. Benefits of trimetazidine administration include symptom relief, particularly reduction of episodes of angina and dyspnea with a resulting improvement in exercise tolerance. The clinical effectiveness of trimetazidine can alone explain its impact on quality of life in a disease, such as ischemic cardiomyopathy, where poor quality of life is strongly related to the limitation of daily living activities imposed by symptoms.

Keywords: ischemic cardiomyopathy; trimetazidine; quality of life

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Focus on Vastarel MR®

Introduction

Trimetazidine (TMZ) is a metabolic agent with anti-ischemic properties that acts by changing the patterns of myocardial energy substrate use during ischemia without any hemodynamic effect. TMZ has been shown to be an effective drug for the treatment of chronic angina both alone or in addition to conventional hemodynamic drugs [1]. Similarly some recent studies have demonstrated that TMZ improves symptoms and New York Heart Association (NYHA) functional class in patients with heart failure, mostly secondary to coronary artery disease (CAD) [2]. In most trials performed in patients with chronic angina and heart failure, assessment of TMZ effectiveness, as for other drugs, included objective measures of the amount of ischemia, exercise tolerance, such as duration during ergometric tests, and the threshold of symptom onset. In patients symptomatic for angina or dyspnea with reduced functional capacity, clinical improvement and the possibility of increasing daily living activities without symptoms seems to be closely linked to the improvement of quality of life (QOL) [3,4]. In fact, easy measures of disability in ischemic cardiomyopathy, such as the NYHA functional classification, are closely related to QOL scores [5,6]. Yet although these results can be translated into an improvement of QOL, in a broader sense, the latter remains an unresolved question. Currently, few data are available regarding the impact of TMZ on QOL in patients with both chronic angina and heart failure. Moreover, it should be emphasized that there is lack of data on the topic of QOL and TMZ treatment in the elderly.

Quality of life in chronic angina

Data concerning the effectiveness of TMZ as an anti-anginal drug are summarized in a meta-analysis of Ciapponi et al [1] that includes 23 studies, involving a total of 1,378 patients. According to this study, when compared both to placebo and to other anti-anginal drugs, TMZ reduces the rate of angina episodes by about 40% and nitroglycerin dosage by about 38%. Moreover TMZ, significantly improves work load—by about 13%—and extends the duration of physical exercise without anginal pain by about 10%. Very recently, a large network meta-analysis gathering the results of 218 clinical trials in over 19,000 stable angina patients completed these results. This meta-analysis assessing the anti-ischemic and anti-anginal efficacy of non-heart rate-lowering anti-anginal agents not only confirmed the significant clinical efficacy of trimetazidine compared with placebo, but it also confirmed that the benefits of trimetazidine are at least comparable if not superior (N.S.) to all of its direct therapeutic alternatives [7]. These results clearly indicate that TMZ administration in subjects with stable CAD is related to an improvement in exercise tolerance, with better performance regarding daily activities. Two studies more specifically addressed QOL using the Seattle Angina Questionnaire (SAQ), a 19-item self-administered questionnaire measuring five dimensions of coronary artery disease: physical limitations, anginal stability, anginal frequency, treatment satisfaction, and disease perception. The Trimetazidine MR in Patients with Stable Angina: Unique Metabolic Path (TRIUMPH) study [8] was an open-label, uncontrolled study that analyzed QOL in 846 patients with chronic stable angina. Patients were taking TMZ-MR for 8 weeks. At the end of the study, authors observed a significant improvement of QOL in all five dimensions of the SAQ: physical limitation scores increased from 50.7 +/- 0.7 to 61.0 +/- 0.6, angina stability improved from 57.6 +/- 0.9 to 92.5 +/- 0.7, angina frequency extended from 33.3 +/- 0.7 to 55.6 +/- 0.8, treatment satisfaction increased from 62.3 +/- 0.7 to 77.4 +/- 0.5, and disease perception improved from 36.7 +/- 0.6 to 55.5 +/- 0.7. The Trimetazidine in stable Angina twice Daily (TRIADA) study evaluated the efficacy and tolerability of 12-week treatment with modified-release TMZ in 74 patients with stable angina and positive exercise tests. The study confirmed the efficacy and safety of modified-release TMZ as a supplementary treatment in CAD. A significant reduction in the angina attack rate (p<0.05), improvement in exercise test results, reduction in the incidence of symptomatic and asymptomatic ischemia, and significant improvement in QOL (p<0.05) based on the Seattle Angina Questionnaire were also observed [9].

Another use of TMZ with possible implications for QOL is in association with sildenafil in subjects with CAD and erectile dysfunction. Rosano et al [10] demonstrated that TMZ plus sildenafil was more effective in controlling episodes of myocardial ischemia during sexual activity than nitrates alone (-45 +/- 11% versus -18 +/- 7%, p<0.04). In light of these results, authors suggested that long-term nitrate therapy could be safely switched to TMZ therapy when treatment for erectile dysfunction is required.

Quality of life in left ventricular dysfunction patients

Heart failure progressively decreases the functional capacity of patients, which impacts day-to-day activities at home, leisure-time interests and performance at work. From a patient's perspective, these limitations imposed by the disease, which adversely affect QOL, are of at least equal importance to the constellation of symptoms and signs that form the basis of the medically orientated approach to health assessment. An improvement of clinical conditions with TMZ in patients with heart failure has been observed in several studies [11–15]. This was underlined in the meta-analysis by Gao et al [2], which included 17 trials with data for 955 patients, where TMZ administration led to a significant improvement in NYHA class (p<0.01) and exercise tolerance (p<0.01) compared to placebo.

In recent years, randomized studies have focused more specifically on QOL. Vitale et al [11] evaluated QOL in a double-blind study of 62 elderly patients (mean age 78 years) with ischemic cardiomyopathy who were randomized to TMZ 20 mg three times a day or placebo. A visual analogue scale measuring the general wellbeing assessed QOL. A significantly greater number of patients allocated to trimetazidine improved their NYHA functional class compared with those allocated to placebo. QOL significantly improved in all patients treated with TMZ, while it remained unchanged in those allocated to placebo.

A study by Fragasso et al [12] enrolled 55 patients with heart failure, not only of ischemic origin, who were randomly allocated in an open-label fashion to either
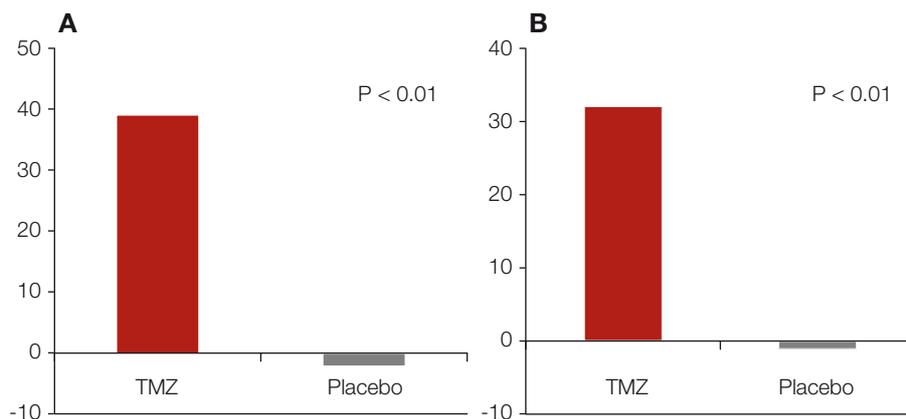
Fig. 1 *Percentage change of physical (A) and social (B) McNew QOL questionnaire with trimetazidine and placebo [16].*

conventional therapy plus TMZ (20 mg three times daily) or conventional therapy alone. At the end of the study, the TMZ group showed a substantial improvement of NYHA functional class compared to baseline, with 25% of patients in NYHA class I–II at baseline versus 89% at follow up. NYHA class worsened in the control group, with 48% of patients in NYHA class I–II at baseline versus 22% at follow up. The authors also observed an increase in exercise capacity in the TMZ group, from 7.37 ±2 metabolic equivalents (METS) to 8.7±2 METS. The authors assessed QOL with two tests: a visual analogue scale and a left ventricular (LV) dysfunction questionnaire (LVD-36) in order to measure the impact of LV dysfunction on daily life. The study demonstrated a significant decrease in LVD-36 score (from 18 to 15, p=0.038) and no significant increase of visual analogue scale, which went from 63% to 71% (p=0.07).

Improving QOL represents a challenge, especially for elderly subjects. There is lack of data in this group of patients regarding TMZ, as there is for other drugs. Our group specifically investigated the effects of TMZ on different areas of QOL in elderly patients with ischemic dilated cardiomyopathy (mean age 78±3.4 years) using a self-administered questionnaire, the MacNew Quality of Life After Myocardial Infarction. We showed a significant improvement in physical and social areas in patients randomized to TMZ, but not in those randomized to placebo [12] (Fig. 1 [16]). Benefits of TMZ on QOL could be related to several factors. First, in patients with ischemic cardiomyopathy and recurrent angina, increased well-being could be a consequence of its anti-angina effects. Moreover, the improvement

in exercise tolerance and a direct action on skeletal muscle mass could play a role [17].

Conclusions

Available data suggest that TMZ has a positive impact on QOL in patients with ischemic cardiomyopathy. This benefit is at least in part related to the improvement of symptoms and to the increase of exercise tolerance observed in such patients. However, more recent studies suggest that TMZ impacts QOL in a broader way, probably with unknown mechanisms of action. Further randomized trials, possibly focusing on QOL as a primary endpoint, are needed to better clarify TMZ's effects on QOL. •

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Metabolic approach to ischemic heart disease in the elderly

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Abstract

A 79-year-old hypertensive, diabetic woman with known ischemic heart disease, previously revascularized, was referred to our Cardiology Department because of effort-induced dyspnoea associated with bilateral calf stiffness during a walk at high altitude. A thallium scan with intravenous (i.v.) dipyridamole stress showed a fixed inferior perfusion defect and a reversible perfusion defect in the posterior and lateral wall. Medical therapy was optimized before undergoing further interventional procedures. Anti-hypertensive medications were optimized and anti-anginal therapy implemented with trimetazidine. The patient also began a cardiac rehabilitation program. After 2 weeks, dyspnoea with effort disappeared, and after 3 months her exercise capacity improved by 50%.

Keywords: elderly; ischemic heart disease; arterial peripheral disease; trimetazidine

■ Heart Metab. (2011) 52:32–34

Case report

A 79-year-old woman was referred to our Cardiology Department because of dyspnoea with effort associated with bilateral calf stiffness during a walk at high altitude (1800 m) while on holiday. The woman was a writer with a negative family history for ischemic heart disease (IHD), but one brother 18 year her younger brother with diabetes and hypertension. She had an early surgical menopause at the age of 41 years and had never received hormone replacement therapy. She was a heavy smoker (30 cigarettes/day since the age of 45) and overweight (body mass index 27 kg/m2). She had a 23-year history of arterial hypertension, treated in recent years with enalapril (5 mg/day) and manidipine (5 mg/day), and a 18-year history of type-2 diabetes treated with gliclazide (30 mg od).

At the age of 68, the patient suffered from an acute inferior myocardial infarction (MI), treated with intravenous thrombolysis, and subsequently underwent coronary artery bypass grafts (left internal mammary artery on left anterior descending artery, right mammary artery on distal right coronary and saphenous graft on I and II obtuse marginal). She was also prescribed aspirin, simvastatin and diltiazem. A low dose of beta-blockers was discontinued after 10 days because of the occurrence of fatigue and bradycardia (45 bpm).

She remained asymptomatic on conventional medical therapy, reporting general satisfactory health condition and took her medication conscientiously. Being a writer, she spent the major part of her time at home and rarely exercised.

During a trip in a mountain resort she began to feel weak and complained about vertigo and during a walk uphill she stopped because of worsening dyspnoea associated with bilateral calf claudication. Symptoms were repetitively induced by exercise at a fixed level of effort and were both partially relieved by rest.

Because she was limited in her daily activities she decided to return home and was referred to our Cardiology Department. Clinical evaluation revealed slightly elevated blood pressure values (BP 150/90 mmHg) and a non-optimal glycaemic control (fasting plasma glucose 142 mg/dl, HbAlc 7.8%). The other routine blood chemistry was normal.

An electrocardiogram showed sinus bradycardia (56 bpm), and the signs of a previous inferior MI. An echocardiogram showed left ventricular hypertrophy (septum 13 mm, posterior wall 10 mm), a dilated left ventricle (left ventricular end-diastolic diameter [LVEDD] 62 mm, left ventricular end-systolic diameter [LVESD] 48mm, left ventricular ejection fraction [LVEF] of 45%) with infero-posterior and lateral hypokinesia.

A vascular ultrasound assessment showed both the presence of a left carotid stenosis of 70% and peripheral arterial disease (ankle-brachial index 0.8 on both sides).

Due to the presence of bilateral claudicatio, we decided not to prescribe an exercise test but a thallium scan with intravenous (i.v.) dipyridamole stress. The test showed a stress-induced reversible perfusion defect of the infero-posterior and lateral wall (Fig. 1). It was, therefore, decided to prioritize the optimization of medical therapy before undergoing further interventional procedures. Her medical therapy was implemented as follows: aspirin 100 mg od; atorvastatin 20 mg od, perindopril 10 mg od, amlodipine 10 mg od, metformin 500 mg bd, and trimetazidine 35 mg bd (that she bought at the Vatican pharmacy in Rome). She was also started on a cardiac rehabilitation program. After 2 weeks she reported a significant improvement in dyspnoea on effort. At the end of the rehabilitation program her exercise capacity had improved by 270 to 540 meters and she was limited only by fatigue; she obtained a good control of blood pressure (BP 120/75 mmHg) and glucose metabolism (HbA1c 6.5%). A pre-discharge exercise test was stopped in stage 4 of the modified Bruce protocol because of fatigue at 2 minutes without symptoms or electrocardiogram (ECG) changes. The patient was
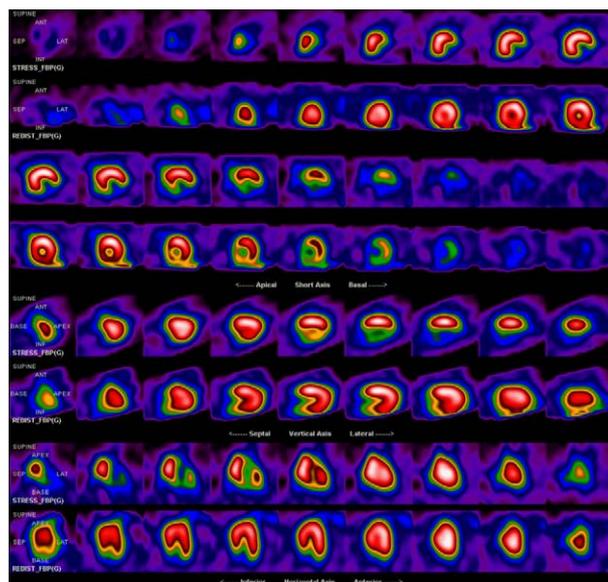
Fig. 1 *Thallium scan shows a stress-induced reversible perfusion defect of the infero-posterior and lateral wall. Ejection fraction was 45%*

seen in our outpatient clinic after 3 months and reported being well and asymptomatic. She was still smoking but she had reduced at 15 cigarettes/day. After 1 year the patient was still in good clinical condition, and she walked every day for 1 hour without dyspnea or claudication.

Discussion

This case depicts an elderly woman with type-2 diabetes and arterial hypertension affected by cardiac and peripheral atherosclerotic disease. Although she suffered a previous revascularized MI, she remained in good clinical condition for quite a long time. The absence of symptoms, however, may be related, at least in part, to her sedentary lifestyle. The low level of exercise she was used to was below her ischemic threshold for both myocardial and peripheral ischemia, and, for this reason, she remained asymptomatic despite the progression of multivessel disease. However, when she exercised, she developed both coronary and peripheral symptoms probably because the associated increase in blood pressure, due to the exposure to altitudes, lowered her ischemic threshold.

According to her clinical status and age, conservative management was adopted. Indeed, several studies have shown that the optimization of medical therapy reduces events and allows good event-free survival in the treatment of chronic patients with IHD.

The medical management included both the optimization of medical therapy and a program of cardiac and vascular rehabilitation.

It is known that diabetic elderly patients developing a multivessel and accelerated atherogenesis, involving peripheral segments of major coronary arteries and distal peripheral branches, experience changes in myocardial glucose utilization [1, 2], and may have several comorbidities that do not make them the ideal candidates for revascularization procedures (whether surgical or transcatheter) [3]. Transcatheter revascularisation should therefore be reserved for those elderly patients with refractory angina despite optimal medical therapy, and those in whom angina compromises quality of life or the activities of daily living or those with a large area of ischemic myocardium at risk. Therefore, in this elderly woman the main aim of therapy was the reduction of frequency and severity of symptoms (dyspnoea and claudicatio) and the improvement of myocardial ischemia in order to achieve an ischemic threshold greater than that reached during her daily activities, thus leading beneficial effects on quality of life.

As, in this patient, symptoms were precipitated by an instability of the clinical condition, it is clear that any optimal medical treatment cannot be unnoticed without achieving normal blood pressure and glycaemic control.

In addition to hemodynamic optimal medical therapy, a cycle of rehabilitation and trimetazidine were prescribed with the aim of increasing functional performance, to better control cardiovascular risk factors and to improve quality of life. Belardinelli et al showed that the combination of trimetazidine with exercise training is associated with a more marked improvement in functional capacity than trimetazidine or exercise training given alone [4]. More recently, our group showed that the addition of trimetazidine improves functional performance in patients with multivessel atherosclerosis and claudication undergoing regular exercise training [5], suggesting that the metabolic effect of trimetazidine may be effective not only in the heart but also in the peripheral skeletal muscle. It is, therefore, plausible that therapeutic strategies focusing on metabolic regulation of energy production may exert cardiac and systemic effects. In addition to improving cardiac symptoms, the overall cardiac effects of trimetazidine lead to an improvement of functional capacity allowing a more active lifestyle, and to an improvement in quality of life.

Conclusion

This case shows that the association of optimal medical therapy and exercise represents a valid alternative to revascularization, not only in those patients for whom surgery is contraindicated, but for most patients with IHD. The adjunct of a metabolic drug, such as trimetazidine, in a patient with multivessel atherosclerotic disease improves myocardial metabolism and may have additional positive effect on skeletal muscles that altogether translate into a beneficial effect on symptoms, functional performance, and quality of life. •

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Improving the quality of sex life in the elderly

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Abstract

In the past, men and women have been assumed to lose interest in sex as they age. This is untrue and despite the difficulties brought on by ageing, many would like to continue, if physically possible, with some form of sexual expression with their partner. Until recently, for a variety of reasons, this has not been easy or possible either for men or women. In the last few decades, the arrival of erectogenics and testosterone replacement for men, and hormone replacement therapy, including testosterone, for women, has altered the whole scenario. The message is that the quality of sex life in the elderly has a great potential for improvement as long as the physician is aware of the needs and desires of the elderly person, and this extends to staff in retirement homes.

Keywords: ageing; sex life; elderly; PDE5 inhibitors; hormone replacement therapy; retirement homes

■ Heart Metab. (2011) 52:35–37

Refresher Corner

Introduction

With the increase of life expectancy in both men and women far exceeding the biblical "three score years and ten," the hope for many people with their improved health is to continue, if possible, to have a sex life. They want good health for both partners along with retention of their sex drive and ability to express it. Keeping sex alive in later years, therefore, is very important.

However, negative myths surrounding older men and women's sex lives still persist, although they are getting fewer. The idea that men and women reaching a certain age in their lives no longer need or want sex has long been held, and seems to have arisen from religious, social and cultural attitudes. It is still assumed, even by many older people, that there is no sex after menopause, and it is the same for men of the same age group.

Young people find the idea that their grandparents still have or want sex disgusting, unbelievable or impossible. Even many middle-aged people are taken a back at the thought that their own parents still want to express their love and affection in a sexual way. However, there have been a number of studies over the last few years assessing sexuality and ageing. As recently as 1977, La Torre and Kear [1] found that sexual activity in older people was considered to be "less moral and less credible than sexual activity in the young." Since then, changes in attitudes are occurring, albeit gradually, and in a 1985 survey of American medical students, Damrosch and Fischman [2] found younger people thought a sexually active man or woman to be more content and more mentally alert compared with the sexually inactive.

Additionally, middle-aged children of older parents are becoming more relaxed and positive towards their parents' need for sexual expression, although this relaxation has not generally been accepted as the norm yet. Despite the change in attitudes in the last few decades, there is no reference to sex and sexual health in the United Kingdom's *National Service Framework for older people* in 2010 [3,4].

Several factors can hinder people who are anxious to maintain their sexual relationships, the main one being aging. The latter affects men and women, psychologically as well as physically.

Aging men and sexuality

For men, the ability to get an erection, penetrate and ejaculate is what makes a man a man—a series of events to propagate the species and their raison d'être. To make matters worse, they feel they should be able "to do what a man has to do." Not to be able to do any of these is humiliating and embarrassing and makes a man feel he has lost his masculinity. As he ages, it becomes more difficult to get and maintain an erection, penile sensation lessens, it takes longer to get to orgasm and semen quantity declines. A man may experience erectile dysfunction caused by medication, high cholesterol, high blood pressure and diabetes. Psychological causes of erectile dysfunction frequently include meeting a new partner after bereavement or divorce.

Another factor that comes with age is lower-than-expected testosterone levels [5]. This causes a series of symptoms, such as loss of sex drive, tiredness, profuse sweating, fewer or absent early morning erections with or without impotence, depression, aches and pains and severe mood changes, with marked irritability. Apart from just age, the physical causes of these symptoms are manifold and include diabetes (the metabolic syndrome), past infections such as adult mumps, mononucleosis, HIV infection, myocardial infarction, operations and alcohol excess.

Jackson [6] demonstrated that furred up penile arteries causing erectile dysfunction (ED) can be a 3–5 year warning that could be a precursor to narrowing of the larger coronary arteries within the next 3–5 years unless treated.

Aging women and sexuality

For women, menopause indicates a clear marker of aging around the age of 50, and is frequently called by women themselves, "the change" (of life). Many women have no idea what to expect in the post-menopausal era, other than what they have learned from their mother, and can be put off by their and their partner's altering sexual response. Irregular and heavy periods, hot flushes, night sweats and vaginal dryness can be very disruptive to a sexual relationship. Stress incontinence can also be a severe deterrent to having sex. This may present a point when a woman has a severe loss of confidence in herself and no longer feels she should or can be sexually attractive.

The lack of sexual desire, difficulty in becoming sexually aroused, orgasmic difficulties, as well as dyspareunia, which is the most common sexual complaint in older women, are major deterrents for a lot of women. A woman may regret the physical changes in her and her partner's body, the loss of the passion and sexual intimacy she had in the past [7]. Fortunately, for most women, this change is usually very gradual, and allows them to accept a different and often almost as enjoyable type of sexual relationship.

Improving quality

Fortunately, over the last few decades, enormous progress has been made in managing male and female problems, to their great benefit.

Men

Over centuries, a host of different weird and wonderful remedies have been suggested to help the impotent man. The great breakthrough for men and for their partners was the serendipitous finding of a drug—sildenafil, a phosphodiesterase-5 inhibitor (PDE5i)—to help overcome erectile dysfunction [8]. This drug revolutionized the sex lives of older men (and of many a younger man) when it became available in 1998 and proved to be the great breakthrough that centuries of men longed for to enable them to have a spontaneous erection. Other PDE5is—tadalafil and vardenafil—have joined sildenafil in the management of male impotence.

The second major difficulty that men find as they age is a loss of sex drive and ability, with a lot of nebulous symptoms that did not seem to connect up, such

as tiredness, alteration in mood, depression, sweating, a "middle-aged spread" with a collection of central and body fat, loss of nocturnal erections, and the inability to get a spontaneous erection despite the use of a PDE5i.

The finding that a man's testosterone level, which gently falls as he ages, could fall low enough to cause these symptoms, led to testosterone-replacement treatment in the last decade or so (following a preliminary check of prostate specific antigen [PSA] to rule out current prostatic cancer). This greatly improves quality of life and libido, makes a huge difference to welfare and to a man's partner, and is frequently accompanied by a return of PDE5i-aided erections as well.

Women

Hormone replacement therapy (HRT) in women has been a godsend for many at the time of and after the menopause, despite the various alarms over the last few years over their safety. Tablets, patches, injections and implants have all been utilized, and local vaginal estrogen creams can be a very effective treatment in a great many women for dyspareunia.

Recently, it was realized that women who have had an oophorectomy lose most of their ability to manufacture testosterone, and replacement creams or patches have provided a huge boost to a women's desire for and enjoyment of their sex lives.

Finally, it must not be forgotten that both women and men who enjoyed regular sex when they were younger will probably like to continue to do so when older, wherever they live—at home or in a retirement home. It should be emphasized that an older man or woman having a sexual relationship with another elderly person does not have to entail penetrative sex. Older couples can enjoy touching, caressing and kissing sexually and get a great deal of satisfaction and fulfillment from it. But in care homes particularly, the staff need to be aware of their charges' feelings, needs and desires and treat them sensitively [9]. Expression of this in a home is rarely possible unless the managers of the home are particularly sensitive to their residents and make it possible for couples to have privacy together, and not assume that arriving in a residential home means everyone wants to be celibate. In a survey of retirement homes, Bretschneider and McCoy [9], found that 62% of healthy men and 30% of healthy women over the age of 80 recently had sexual intercourse and that 82% and 64 % respectively had had physical intimacy. Unfortunately, there is a long way to go before this need is generally recognized [10]. •

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Medical therapy versus revascularization rounds: ischemic heart failure on focus

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Hot Topics

Ischemic heart failure (HF) has long been considered potentially reversible. In this regard, a positive test for myocardial viability would make cardiologists feel more comfortable in directing patients towards revascularization, thereby constituting a guiding practice for the past two decades [1]. Importantly, such data has been extrapolated from numerous non randomized, predominantly single-center studies [2] and meta-analyses suggesting the improved survival of revascularized patients with viable myocardium on non invasive testing [3]. However, data from randomized, multicenter studies have been lacking, and moreover, both surgical and non surgical therapies for coronary artery disease (CAD) and HF have substantially improved since then.

Recently the results of the Surgical Treatment for Ischemic Heart Failure (STICH) trial, which evaluated the role of surgery plus guideline-recommended medical therapy as compared with medical therapy alone [4], together with a sub-study that also tested the role of myocardial viability [5] in patients with ischemic HF were published. Patients with CAD amenable to coronary artery bypass grafting (CABG) and reduced ejection fraction (EF) (<35%) were eligible for the study. Those patients with a recent myocardial infarction (MI), planned aortic valve replacement or percutaneous coronary intervention (PCI), or coexisting non-cardiac disease with a projected life expectancy <3 years were instead excluded. The primary end point was death from any cause. Important secondary end points included death from cardiovascular causes and hospitalization. In all, 1,212 patients were included in the main study and 601 of them underwent a viability test before randomization. During a median of 56 months of follow-up of the main study population, the primary outcome occurred in 41% in the medical-therapy group and 36% in the CABG group (p = 0.12). Interim analysis showed that patients with viable myocardium had lower overall rates of death (37%) than those without viable myocardium (51%). However, after adjustment for baseline prognostic variables, there was no statistically significant difference in mortality between the 2 groups (p = 0.21).

These were not the expected results. In fact, the main findings of this study can be summarized as follows: patients with CAD and HF do not necessarily benefit from a revascularization procedure, and most importantly, this is true even when the presence of myocardial viability is documented.

In general, the widespread acceptance of new knowledge is directly proportional to the degree of the understanding of the concept. However, given that it was not a pre-specified objective, no pathophysiological insights responsible for such results are provided in the study. However, different hypotheses can be drawn and some of them worth mentioning.

First, provided that CAD was conceivably associated with myocardial ischemia, STICH patients represent a very complicated patient population in that they contemporaneously attain two major causes of adverse cardiovascular outcomes: ischemia and left ventricular (LV) dysfunction. Importantly, because of the particular perpetuating interactions (i.e., the greater the ischemic burden, the greater the systolic dysfunction, and vice versa), the dissection of the prevalent pathophysiological mechanism leading to the fatal outcome is often impossible. Nonetheless, as noted in the accompanying editorial [6], STICH was more of an ischemic heart disease (IHD) rather than a HF trial in that patients were younger, had more angina and fewer HF symptoms than a typical HF patient population. However, if this is the case, the data would not be surprising, being in line with other, previously published large clinical trials that compared medical versus revascularization therapy in chronic angina patients [7].

In a second hypothesis, viable but dysfunctional myocardium can be explained by the concept of hibernating myocardium. Previous studies have suggested that early revascularization of hibernating myocardium may be essential to avoid irreversible dysfunction [8]. However, no data on either the presence or the timing of the clinical ischemic event(s) of patients are provided in the STICH trial. Moreover, similar to other beliefs on this topic, such findings are based on observational, single-center data.

As for the third hyposthesis, by definition, HF patients with angiographically documented CAD have ischemic HF. From here, it is extrapolated that patients with reduced EF and no CAD have dilatative cardiomyopathy. However, the latter often also present with signs and symptoms of myocardial ischemia that are routinely referred to as a specific or "main disease" related. Conversely, "ischemic HF" patients may lack a clinical history or a test indicative of a previous, well-defined ischemic event. However, when association is documented, obstructive CAD is routinely regarded as the only causal mechanism of HF. A similar response to revascularization and medical therapy alone observed in this trial suggests that the distinction between the pathologies may not be so clear. On the other hand, it is clear that, in being too simplistic, we may have cultivated some knowledge gaps, responsible for casting a shadow over other important advances, i.e., myocardial revascularization.

In conclusion, STICH results add to those of other recently published randomized trials that enclose real threats to historical dogmas in cardiology. Not all HF patients with CAD will benefit from myocardial revascularization; this is the brand new catching up with the latter! Will we be wise enough to start acting accordingly, and win the forthcoming rounds? •

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Apoptosis

Referred to as programmed cell death, apoptosis involves a series of events resulting in cellular morphological changes and subsequent death, including cell shrinkage, blebbing, nuclear fragmentation, and chromatin condensation. One of its key features is that, unlike a necrotic cell, the cellular contents do not spill out due to phagocytic cells engulfing the apoptotic cell, which is a primary reason why apoptotic cell death does not result in inflammation.

Carbohydrates

These organic molecules contain only carbon, hydrogen, and oxygen, with the ratio of hydrogen to oxygen usually being 2:1. Important circulating carbohydrate energy sources for myocardial metabolism include glucose ($C_6H_{12}O_6$) and lactate ($C_3H_6O_3$).

Electron transport chain

This encompasses a series of five inner mitochondrial membrane protein complexes that allow electron transfer between electron donors (i.e., NADH/FADH$_2$) and electron acceptors such as O_2 (these four protein complexes themselves act as both electron acceptors and then subsequent electron donors as they pass electrons to the following complex). The transfer of electrons between these complexes causes the transfer of protons from inside the mitochondrial matrix outside into the mitochondrial inner membrane space, which drives an electrochemical proton gradient used to drive ATP synthesis in the process of oxidative phosphorylation.

Flip-flop mechanism

This term describes the movement of fatty acid molecules across the phospholipid bilayer that comprises the cell membrane. Flip-flop involves reorientation of a fatty acid molecule such that the polar carboxyl moiety originally interacting with the lipid-aqueous interface of the external leaflet and the extracellular space subsequently interacts with the lipid-aqueous interface of the internal leaflet and cytosolic space. Following this reorientation, the fatty acid molecule can dissociate from the inner leaflet of the phospholipid bilayer and completely enter the aqueous cyotosolic compartment.

Glycolysis

Glycolysis is the series of biochemical reactions occurring in the cytosolic compartment that converts a glucose molecule into two molecules of pyruvate. In the presence of oxygen (i.e., the aerobic setting), pyruvate is transported into the mitochondria, and undergoes oxidative decarboxylation yielding acetyl-CoA. In the absence of oxygen (i.e., the anaerobic setting), pyruvate is reduced to lactate by the enzyme lactate dehydrogenase, which generates NAD^+ required to maintain flux through glycolysis.

Hibernating myocardium

This state, in which segments of myocardium are viable but exhibit abnormalities in contractile function, is often observed in chronic ischemia.

Phosphorylation

Phosphorylation involves the addition of a phosphate (PO_4^{3-}) to a protein/organic molecule via the action of enzymes known as kinases. Protein phosphorylation is one of the primary cellular mechanisms by which enzyme activity can be modified post-translationally.

PPARα

Peroxisome proliferator activated receptor α is a member of the ligand-activated nuclear hormone receptor superfamily. Fatty acids function as ligands for PPARα, and fatty acid-bound PPARα forms heterodimers with the retinoid X receptor. The PPAR-retinoid X receptor heterodimer can then translocate to the nucleus where it binds to PPAR response elements present in the promoter regions of target genes, including those involved in regulating fatty acid metabolism. PPARα is predominantly expressed in tissues that exhibit a high capacity to oxidize fatty acids including the liver, skeletal muscle, and heart.

Transporters

These are integral membrane proteins involved in mediating the movement of molecules across the cell membrane. Facilitative transporters move molecules down a concentration gradient, while active transporters couple the hydrolysis of ATP to the movement of molecules against their concentration gradient. •