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## Aims and Scope

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

*The figures on the cover show: Top: PET derived myocardial 1-11C-palmitate images obtained from a young female (left) and an older female (right) studied at rest after an overnight fast. Images represent data acquired from 20 to 30 minutes after injection of tracer. Images are displayed in the short axis view, S: Septum, A: Anterior, L: Lateral and I: Inferior. White indicates highest counts and blue lowest counts. Bottom: PET derived myocardial 1-11C-palmitate time-activity curves corresponding to the images shown above. The slower myocardial rate of clearance (solid lines) observed in the older female is indicative of a lower rate of fatty acid oxidation.*

<b>EDITORIAL</b>	
Age and aging <i>G. Jackson</i> .....	2
<b>BASIC ARTICLE</b>	
Alterations to cardiac metabolism with advancing age <i>G.J. van der Vusse</i> .....	3
<b>MAIN CLINICAL ARTICLE</b>	
Stable angina in the elderly <i>G. Jackson</i> .....	9
<b>METABOLIC IMAGING</b>	
Impact of aging on myocardial oxidative metabolism <i>R.J. Gropler</i> .....	14
<b>NEW THERAPEUTIC APPROACHES</b>	
Safe prescribing in the elderly <i>N. Wisniacki, M. Lye</i> .....	19
<b>FOCUS ON VASTAREL</b>	
Management of high-risk populations with coronary artery disease: rationale for improving prognosis in the elderly <i>P. Meurin</i> .....	24
<b>CASE REPORT</b>	
Unprotected left main stem stenting in elderly patients <i>A. Jain, J. Hill</i> .....	27
<b>FEATURED RESEARCH</b>	
A clinical trial of estrogen-replacement therapy after ischemic stroke .....	30
Clinical outcome of patients with previous myocardial infarction and left ventricular dysfunction assessed with myocardial <sup>99m</sup> Tc-MIBI SPECT and <sup>18</sup> F-FDG PET .....	31
<b>REFRESHER CORNER</b>	
Assessment of the elderly patient for cardiac surgery <i>C. Blauth</i> .....	32
<b>GLOSSARY</b>	
<i>G. Lopaschuk, W. Stanley</i> .....	35



# Age and aging

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Health care of the elderly assumes ever-increasing importance in developed countries as their populations age. With age come serious illnesses and increased health care utilization with important cost implications and the danger of practicing ageism. Currently, worldwide, there are 380 million people aged over 65 years of age, but by 2020 this figure will have risen to 690 million, and deaths due to noncommunicable diseases (mainly cardiovascular) will have risen to an overall figure of 49.7 million from the current 28 million. The challenge of managing cardiovascular disease in the elderly is important now, but can only increase over time.

Cardiovascular risk increases with age, whether due to age alone or combined with an increased incidence of diabetes, hypertension, or, to a lesser degree, hyperlipidemia. As a result of a greater overall risk, the potential for greater overall benefit from risk factor modification has become a reality in the elderly.

Social factors are important. Women live longer than men and therefore more often live alone and, in turn, are lonely. The elderly have more concerns about money and may rely on less healthy foods and spare themselves everyday conveniences such as proper heating. In an increasingly violent society the elderly become more vulnerable and may be afraid to go out and exercise, and, in turn, show a greater reluctance to give up smoking, which becomes their indoor recreation. Our medical advice must therefore be coupled with community action. There is a need to improve the financial circumstances of the elderly, to improve their environment (indoors and outdoors), and to promote good health with easily accessible and tailored healthy lifestyle options which are safe to pursue.

In this issue we are promoting cardiovascular health, and, importantly, putting age and health in perspective. Age may alter myocardial oxida-

tive metabolism, but as Professor Gropler concludes, we need to know the exact relevance to the elderly in the clinical context because of the potentially important therapeutic implications. The alterations in cardiac metabolism are reviewed by Professor van der Vusse, and these also have implications for general advice and prescribing. Safe prescribing in the elderly is an important issue because of the changes in physiology and pharmacology that occur with age, so the paper by Drs Wisniacki and Lye has great practical relevance. Angina in the elderly is common, and in my article I have tried to balance risk over benefit, taking into account the needs and wishes of the individual.

Christopher Blauth brings a surgeon's perspective to selecting patients for surgery. The risks rise with age, so the selection process must be individualized to that particular person's risk. The patient's family also needs to be aware of the risks as well as the benefits – fully informed consent is an essential part of our medical practice. In addition, full agreement between surgeon and cardiologist must be the key to optimizing management, so a surgeon's view is to be welcomed. Dr Meurin highlights the problem of treating high-risk patients and, in discussing the management, emphasizes the role of the metabolic agent trimetazidine as a means of avoiding haemodynamic side-effects while relieving symptoms and improving quality of life. Collectively in this issue the authors put quality of life at the forefront of our approach to treating elderly patients with cardiac disease.

We can only do so much for the elderly as health care professionals: the elderly also need committed politicians, who will support the social infrastructure, and strong family carers. The elderly do not want to be a burden nor should they be. The community, both medical and nonmedical, owes them that right.

# Alterations to cardiac metabolism with advancing age

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Because of the rapidly growing number of elderly people in Western societies, cardiac malfunction due to age-related changes in the cardiovascular system is becoming a major health problem. As thoroughly discussed in an excellent review by Lakatta,<sup>1</sup> there is no straightforward answer to the question whether aging itself is inherently associated with impaired cardiac performance, since other factors such as lifestyle and diseases may interact with the normal physiological aging process. On the one hand, the detrimental effects of, for example, sedentariness accumulate with advancing age, and on the other, diseases such as hypertension and myocardial ischemia are more often seen in the elderly.

Although pump activity of the physiologically aged heart seems not to be affected under resting conditions, cardiac performance is depressed when the heart is energetically challenged.<sup>1</sup> Moreover, profound changes at the cellular and subcellular level have been reported:  $\beta$ -adrenergic responsiveness of the cardiac system is significantly reduced,<sup>1</sup> calcium handling is altered,<sup>2</sup> and the composition of contractile proteins changed, exemplified by a shift from the  $\alpha$  to the  $\beta$  form of the myosin heavy chain.<sup>3</sup> It is of interest to note that the latter change is thought to improve the efficiency of the aging heart.<sup>1</sup>

Prompted by the pioneering studies of Abu-Erraish et al<sup>4</sup> in the late 1970s, demonstrating a decline in fatty acid oxidation with a concomitant increase in glycolytic activity in the aged rat heart, a plethora of studies has been performed to disclose the effect of aging on cardiac energy metabolism. In general, these studies point to substantial changes in the activity of the enzymes that play a key role in cardiac energy metabolism, and to alterations in the tissue content of cofactors required for

substrate oxidation, and in mitochondrial functioning. The pathophysiological significance of these changes for mechanical performance of the aging heart is, however, incompletely understood and a matter of continuous debate.

## Cardiac metabolism

Proper cardiac electromechanical performance requires unimpeded delivery of molecular oxygen and oxidizable substrates. The heart relies mainly on fatty acids and glucose for intracellular ATP production.<sup>5</sup> Under normal conditions, lactate and ketone bodies are used to a lesser extent.<sup>6</sup> Healthy coronary vessels guarantee a sufficient supply of substrates to the energy-converting myocytes. As indicated in *Figure 1*, glucose transport into the cardiomyocyte is facilitated by GLUT4. The latter protein is a glucose transporter that can be recruited from its intracellular storage site to enhance the sarcolemmal capacity to translocate glucose. Glucose is subsequently degraded to pyruvate in a stepwise fashion in the cytoplasm of the cardiac muscle cell. This process, glycolysis, yields two molecules of ATP per molecule of glucose. Under aerobic conditions, pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase, an enzyme complex associated with the mitochondrial inner membrane. Acetyl-CoA reacts with oxaloacetate, an intermediate of the citric acid cycle, yielding citrate. During one turn of the citric acid cycle, citrate is metabolized to oxaloacetate. In concerted action with the mitochondrial respiratory chain, 36 molecules of ATP are produced when one molecule of glucose is oxidized to CO<sub>2</sub> and H<sub>2</sub>O. Recent investigations have revealed that, analogous to glucose, fatty acid uptake by the cardiac mus-

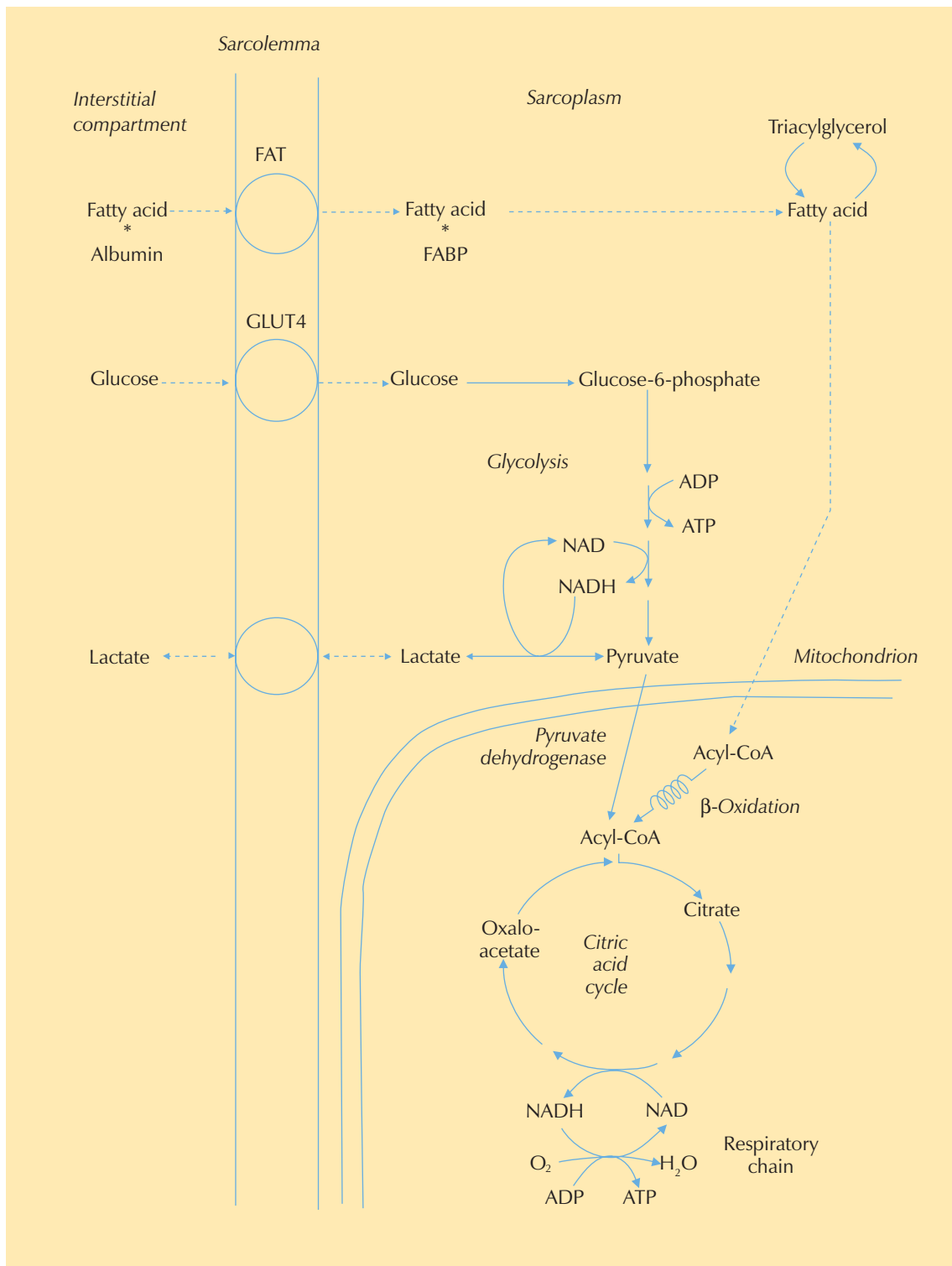


Figure 1. Schematic representation of substrate uptake and metabolism in the cardiac muscle cell. FAT, fatty acid translocase; FABP, sarcoplasmic fatty acid-binding protein; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide.

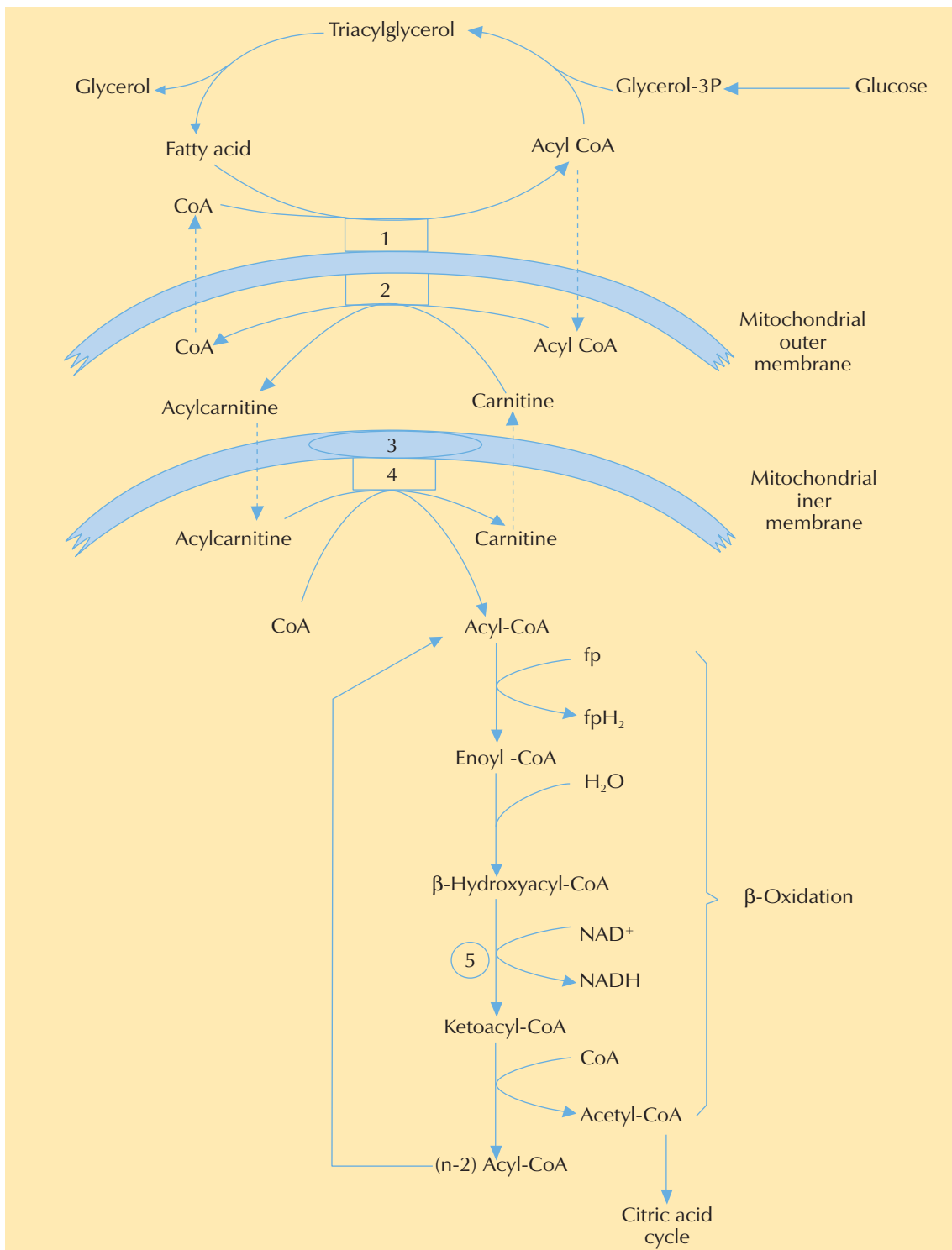


Figure 2. Detailed description of mitochondrial fatty acid uptake and degradation. Numbers 1, 2, 3, 4, and 5 refer to fatty acyl synthetase, carnitine palmitoyl transferase-1, carnitine-acylcarnitine translocase, carnitine palmitoyl transferase-2, and 3-hydroxyacyl-CoA dehydrogenase, respectively; *fp*, flavoprotein;  $NAD^+$ , oxidized nicotinamide adenine dinucleotide;  $NADH$ , reduced nicotinamide adenine dinucleotide.

cle cell is also facilitated by a sarcolemma-associated transport protein.<sup>7</sup> This protein, designated fatty acid translocase, augments the capacity of the cardiomyocyte to extract fatty acids from the extracellular compartment by increasing its sarcolemmal content through translocation from an intracellular site to the cell membrane.<sup>8</sup> Transport of fatty acids from the sarcolemma to the mitochondrial outer membrane is facilitated by cytoplasmic fatty acid-binding protein. After conversion to fatty acyl-CoA, a reaction step catalyzed by acyl-CoA synthetase, the acyl moiety is transferred across the mitochondrial inner membrane as acylcarnitine (*Figure 2*). Inside the mitochondrion, carnitine is replaced by CoA, and acyl-CoA is stepwise degraded to acetyl-CoA in a metabolic pathway termed  $\beta$ -oxidation. As described above, the acetyl moiety of acetyl-CoA is oxidized by concerted action of the citric acid cycle and the respiratory chain. Oxidation of fatty acids yields approximately 130 molecules of ATP per molecule of substrate.

### Energy conversion in the aging heart

Animal studies have clearly shown that substrate metabolism in the aging heart is different to that in the young adult heart. The capacity to oxidize fatty acids declines, while glycolytic degradation of glucose increases.<sup>4</sup> Collected data point to a multifactorial cause of the decrease in fatty acid oxidation. First, the cardiac tissue content of carnitine, indispensable for mitochondrial uptake of fatty acyl moieties, is significantly reduced in the aged myocardium.<sup>4,9</sup> The maximal activity of carnitine palmitoyl transferase-1 and carnitine-acylcarnitine translocase was also found to be decreased in mitochondria isolated from the aged heart (*Figure 2*).<sup>10–12</sup> The combined findings indicate therefore that both the enzyme and transporter, and the cofactor required for mitochondrial fatty acyl uptake, are affected in the aged myocardium. Interestingly, the tissue content of CoA, required for fatty acid activation at the mitochondrial outer membrane (*Figure 2*), is unaffected by aging.<sup>4</sup>

By contrast, the maximal activity of the enzyme catalyzing the activation step, acyl-CoA synthetase, declines significantly with advancing age.<sup>13</sup> The same holds for one of the key enzymes in the  $\beta$ -oxidation pathway, 3-hydroxyacyl-CoA dehydrogenase.<sup>13</sup>

The impact of the decline in enzyme activity and content of cofactors involved in fatty acid handling has been established in studies on intact mitochondria isolated from rat myocardium, ie, the oxidation rate of palmitoyl carnitine declines by 40%.<sup>13</sup>

It is noteworthy that in conjunction with the relative increase in cardiac glucose utilization, substantial alterations have been observed in the tissue content of transport proteins and activity of enzymes involved in carbohydrate handling in the aged heart. GLUT4 content significantly declined in the hearts of 25-month-old rats compared with animals 3.5 months of age.<sup>14</sup> These seemingly conflicting findings of increased glycolytic flux and decreased total GLUT4 content suggest that a relatively higher proportion of GLUT4 is permanently present in the sarcolemma of aged cardiomyocytes. The total activity of pyruvate dehydrogenase, controlling the mitochondrial conversion of pyruvate into acetyl-CoA, does not change in the aged heart. However, the percentage of the enzyme complex in its active form significantly decreases during aging.<sup>15</sup> The decline in proportion of pyruvate dehydrogenase in the active form might indicate that in the aged heart, pyruvate is preferentially converted to lactate rather than oxidized in the mitochondrial matrix (*Figure 1*).

Recent studies also indicate that the activity of some components of the respiratory chain, such as cytochrome *c* oxidase, is depressed in the aged heart. It is, however, unknown whether this decline affects the maximum capacity of the aged cardiac mitochondrion to utilize molecular oxygen and to regenerate ATP from ADP. Despite this uncertainty, current data point towards the mitochondrion as one of the main cellular compartments in which cardiac energy metabolism becomes affected during advancing age.

Evidence is accumulating that alterations in the phospholipid composition of the aged car-

diac mitochondria are, at least in part, responsible for the decline in mitochondrial metabolic functioning.

Cardiolipin, a phospholipid species that is specifically incorporated in mitochondrial membranes, shows a significant decline in the aging myocardium.<sup>12,16</sup> It is generally accepted that cardiolipin is an essential phospholipid moiety in the mitochondrial membrane that is required to optimize the activity of enzymes constituting the respiratory chain.

The cause of the age-related decline in mitochondrial cardiolipin content is unknown, but the relatively high proportion of polyunsaturated fatty acids in this particular phospholipid points to the damaging effect of oxygen free radicals. In this respect it is noteworthy that the production of oxygen free radicals, with their main site of production being the mitochondrion itself, is more prominent in the aged than in the young adult heart.<sup>17</sup> Alternatively, exposure to oxygen free radicals may be enhanced due to a decline in capacity to scavenge the active oxygen species in the aged heart. This notion, however, has been challenged by the observation that, as a compensatory reaction, the activities of the main oxygen radical scavenger enzymes are stimulated in the mitochondria of the aged heart.<sup>18</sup> In addition to cardiolipin, mitochondrial DNA is a ready target for oxygen free radicals.<sup>19,20</sup> Oxidative damage of cardiac mitochondrial DNA was found to be inversely related to maximum lifespan of the mammals under investigation.<sup>19</sup> Mitochondrial DNA is relatively more sensitive to oxygen free radicals than is nuclear DNA, which may explain the fact that in particular mitochondrial proteins and, hence, proteins involved in cardiac energy conversion are compromised with increasing age.

### Dietary and therapeutic strategies

Since energy metabolism has been identified as one of the processes affected in the aging heart, multiple strategies have been developed to restore cardiac substrate handling and

energy production to the juvenile level. These therapeutic strategies mostly relate to dietary interventions. Since epidemiological and laboratory evidence points to oxidative injury caused by oxygen free radicals as an important factor in the major diseases of older age, fruit and vegetables, rich in antioxidant vitamins such as vitamin E and C, have been strongly recommended.<sup>21</sup>

In vitro studies on mitochondria isolated from the aged heart have shown that restoration of the mitochondrial cardiolipin content to young adult levels promptly restores the activity of enzymes involved in the respiratory chain. At present, no strategies, however, have been developed to prevent or restore the decline in mitochondrial cardiolipin content in the intact heart in situ during advancing age by dietary supplementation of cardiolipin.

Studies on rats have provided solid evidence that chronic administration of acetylcholine via drinking water completely restores cardiac carnitine levels in aged animals to that seen in rats 5 months of age.<sup>9</sup> More recently, it was shown that acetylcarnitine treatment of rats prevented the age-related decline in activity of carnitine-acylcarnitine translocase in cardiac mitochondria. Unfortunately, information is lacking on the beneficial effect of carnitine supplementation in cardiac mechanical performance. Moreover, until now, the potentially beneficial effect of carnitine supplementation has not been explored in the aging human heart.

In addition to dietary strategies, molecular biology may provide powerful tools to restore cardiac metabolism in the aging heart. When most details of the expression of genes coding for metabolic proteins are known, one may envisage that the administration of ligands specifically interacting with nuclear factors, regulating the expression and, hence, tissue content of proteins or enzymes involved in cardiac substrate handling and conversion, will result in improved cardiac energy metabolism in the elderly. ■

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# Stable angina in the elderly

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## Introduction

In both sexes the prevalence of ischemic heart disease increases with age and is the leading cause of death in the elderly. Between 45 and 54 years of age, 2% to 5% of men and 0.5% to 1% of women have angina, but this rises to 11% to 20% of men and 10% to 14% of women aged 65 to 74 years. Over 75 years of age, the prevalence is the same for men and women at 25% to 33%.<sup>1</sup> As our population ages and more people survive myocardial infarction, managing angina in the elderly will become an increasing challenge, and one that we cannot and must not avoid.

## Natural history

As approximately 80% of all deaths due to myocardial infarction occur in those over 65 years of age, the elderly can be seen to be at higher absolute risk than younger patients and therefore may benefit more from treatment in terms of survival and symptom relief.<sup>2</sup> Stable angina has a good prognosis whatever we do. Each year only 2% to 3% will die and a similar number will suffer from nonfatal myocardial infarction.<sup>1</sup> However, some patients are more at risk of cardiac events than others and they can usually be identified by noninvasive exercise testing with or without echocardiography or nuclear imaging. Because of the low event rate we have time to stratify for risk whilst simultaneously optimizing risk factor management and medical therapy for relief of symptoms. By identifying those at increased risk (eg, left main stem disease, three-vessel disease with reduced left ventricular function), we imply the need to reduce that risk, for example by CABG. However, the elderly may not share our enthusiasm for intervention, preferring symptomatic relief rather than interven-

tion purely to improve prognosis. After a long life, quality of life assumes an ever-increasing priority, and in the presence of comorbid conditions (eg, arthritis), which may in turn limit mobility, acceptance of mild-to-moderate angina is not unusual. The elderly, however, must not be denied intervention if their quality of life is impaired, but the options are fewer and the complications more frequent due to the often diffuse CAD, reduced left ventricular function, and associated atheroma of the carotid, renal, and peripheral arteries.<sup>3</sup> We give our advice on the basis of statistics, but we need to remember always to individualize our management decision, especially in the elderly — statistics must never be allowed to hide the individual. Although we live in an era of evidence-based medicine, treatment should never be divorced from good clinical judgment: neither is valid without the other.

## Diagnosis

Anginal symptoms in the elderly may not be the textbook story of chest pain on effort. Older people often perceive the symptoms as breathlessness, so it is important to probe for what exactly makes the person feel breathless. It is often the tightness of angina which leads to a feeling of restricted breathing. More advanced CAD in the elderly can induce ischemic left ventricular dysfunction where the symptom of breathlessness on effort can be confusing, therefore CAD should always be considered, even if left ventricular function is normal on resting echocardiography.

Older people may have variable degrees of mobility which may influence their symptoms and coexisting diseases; musculoskeletal (arthritic) disorders and esophageal symptoms make history-taking a particular diagnostic challenge.<sup>4</sup> A good, basic, and simple history

Table I. Conditions other than CAD which can independently cause angina or exacerbate angina due to underlying CAD.

- Coronary spasm  
*This usually occurs as rest pain*
- Aortic stenosis  
*The patient is usually over 60 years of age*
- Aortic incompetence  
*The patient is usually over 60 years of age*
- Left ventricular hypertrophy  
*This occurs with hypertension and cardiomyopathy  
Hypertrophic cardiomyopathy can present at any age*
- Anemia
- Thyrotoxicosis
- Rapid or slow arrhythmias  
*These occur particularly in the elderly (atrial fibrillation)*
- Severe mitral stenosis  
*A very rare cause*
- Primary pulmonary hypertension  
*A very rare cause*

is essential: where is the pain, what brings it on, what does it feel like, where else is it felt, how is it relieved? I often ask older people to imagine walking up an incline and then ask them to describe what happens: using a real situation rather than an abstract concept is often of great help in extracting the history.

The elderly more frequently have coexisting cardiac disorders and these, along with the possibility of anemia or hyperthyroidism,

should be investigated as part of the overall evaluation (Table I). It is useful to have an examination checklist (Table II). Routine blood tests should be performed to assess renal function, lipid status, and blood glucose (diabetes is common in the older age group and increases cardiovascular risk).

### Noninvasive cardiac tests

If there are suggestions of valvular heart disease, left ventricular dysfunction, or left ventricular hypertrophy, an echocardiogram is essential. The 12-lead ECG is abnormal in over 50% of older people and may identify previous silent infarction or atrial fibrillation.

The fit elderly should be considered for exercise testing to stratify for risk, or where diagnostic doubts exist. Those unable to exercise can undergo pharmacologic stress echocardiography or nuclear imaging. Care is needed when embarking on risk stratification: the elderly need to understand the possibility of surgical intervention as an option which they may not wish to pursue, rendering extensive testing wasteful of time and resources. Exercise testing criteria for risk remain as valid in the elderly as in the younger population, even though maximal heart rate responses are lower (Table III).

The presence of an abdominal aortic aneurysm may be indicated by careful exami-

Table II. Examination checklist.

Sign	Location	Comment
Xanthoma	Hands, elbows, knees	Hyperlipidemia
Xanthelasma	Eyelids	Nonspecific
Arcus senilis	Eyes	Nonspecific over 40 years of age
Fourth heart sound	Apex (turn to left side)	Reduced ventricular compliance
Immediate diastolic murmur	Third or fourth left intercostal space, patient leaning forward	Aortic incompetence
Ejection systolic murmur	Apex, second right intercostal space, neck	Aortic stenosis
Late or pansystolic murmur	Apex to axilla	Mitral regurgitation
Bruits	Both carotid and femoral arteries	Peripheral arterial disease

Table III. Exercise testing end points suggesting high or low risk.

High risk
<ul style="list-style-type: none"> <li>• Significant ST depression (&gt;1 mm), usually with pain</li> <li>• Slow ST recovery to normal (≥5 min)</li> <li>• Fall in systolic blood pressure (&gt;20 mm Hg), reflecting a fall in cardiac output</li> <li>• Rise in diastolic blood pressure (&gt;15 mm Hg); a fall in output causes reflex vasoconstriction</li> <li>• Angina with or without ST changes at a low workload (&lt;6 min)</li> <li>• Dangerous arrhythmias (eg, ventricular tachycardia)</li> <li>• ST depression (&gt;3 mm) without pain</li> </ul>
Low risk
<ul style="list-style-type: none"> <li>• Able to exercise to stage 3 (over 9 min) or beyond of the Bruce treadmill protocol with no ST changes</li> <li>• Able to achieve stage 4 (12 min) or beyond despite ST changes</li> </ul>

nation of the abdomen and should be clarified by ultrasound or CT scanning. Similarly, carotid bruits should be evaluated using ultrasonic angiology.

### Medical treatment

With increasing age, there are differences in the pharmacokinetics and pharmacodynamics of cardiovascular drugs.<sup>2,5</sup> Hepatic clearance of many drugs is reduced in elderly people and there is an age-related fall in glomerular filtration rate and creatinine clearance. The elderly also have a tendency to postural hypotension secondary to age-related cardiovascular responses to posture. Drugs excreted via hepatic or renal pathways need to be used carefully, starting low and titrating to effect. Recognizing greater drug sensitivity should not lead to suboptimal therapy but a slower and

Table IV. Common adverse effects of hemodynamic antianginal drugs in the elderly.

β-Blockers	Bradycardia, lethargy, fatigue, cold peripheries
Calcium antagonists	Peripheral edema, hypotension, ankle edema, constipation
Nitrates	Headache, syncope
Nicorandil	Headache

Table V. Suggested starting doses of antianginal drugs in the elderly.

Isosorbide mononitrate	5–10 mg bid or 25 mg LA
Trimetazidine	20 mg tds
Atenolol	25 mg od or bid
Bisoprolol	1.25 or 2.5 mg od
Propranolol	20–40 mg bid
Felodipine	2.5 mg od or bid
Amlodipine	5 mg od
Diltiazem	60 mg bid
Nicorandil	5 mg bid

od, once daily; bid, twice daily; tds, three times daily; LA, long-acting.

more cautious titration.<sup>6</sup> Using conventional hemodynamic drugs (β-blockers, calcium antagonists, nitrates, nicorandil) the elderly usually obtain symptomatic benefit, but they are more vulnerable to the adverse effects (Table IV). Suggested starting doses are listed in Table V. Combining two low-dose hemodynamic agents (eg, atenolol 25 mg plus long-acting isosorbide mononitrate 25 mg) daily may maximize symptom relief and minimize adverse effects.

### Metabolic agents

Metabolic agents such as trimetazidine do not have hemodynamic actions and therefore represent useful alternative agents in the elderly, avoiding the adverse effects listed in Table IV. In the elderly substudy of Trimpol-1 (Trimetazidine in Poland), trimetazidine significantly increased exercise duration, time to onset of angina, time to 1-mm ST-segment depression, and total work during maximal exercise testing. Importantly, there was also a significant reduction in anginal episodes and glyceryl trinitrate consumption, and minimal adverse effects.<sup>7</sup> (See also page 24–26). Combining a low-dose hemodynamic agent with trimetazidine may maximize symptom relief and minimize adverse events. Patients intolerant of hemodynamic agents may benefit from trimetazidine as monotherapy. The acronym RAMPS (Table VI) offers sensible guidelines.

Table VI. The “RAMPS” approach.

Reduced body reserve	for dosing, such as the expected decrease in renal and hepatic function with age
Atypical presentation	of potentially any illness, including heart disease
Multiple pathologies	usually coexisting
Polypharmacy	making further prescribing hazardous
Social adversity	

The benefits of lipid-lowering therapy in the presence of CAD in those up to 75 years of age have recently been confirmed for pravastatin and simvastatin on the background of 80% aspirin usage.<sup>8</sup> The secondary prevention trials LIPID<sup>8</sup> (pravastatin), CARE<sup>9</sup> (pravastatin), and 4S<sup>10</sup> (simvastatin) on average reduced the risk for all cardiovascular events to the same degree in older compared with younger patients, but because of the greater prevalence of CAD in the elderly, the absolute benefit is greater: treating 1000 older patients over 6 years prevented 45 deaths, 33 myocardial infarcts, 32 unstable angina episodes, 33 coronary revascularization procedures, and 13 strokes.<sup>8</sup> In the absence of contraindications, all patients with CAD up to the age of 75 years should be commenced on statin therapy; the strongest evidence base is for pravastatin 40 mg daily. Trials in the 75+ age group are ongoing, so decision-making here must be individualized and the subject of clinical judgment.

### Interventions

If symptomatic despite medical therapy, or presenting acutely, intervention by angioplasty (± stent) or CABG benefits the elderly, so that age per se should not be a contraindication. However, we need to recognize the importance of symptom relief and not embark on an anatomic correction crusade. Symptom relief may follow from dilating the culprit stenosis with minimal risk, or allow medical therapy to gain symptomatic control. The elderly in general have more diffuse disease which is often calcified, so the careful target-

ing and stenting of lesions at angioplasty are essential. Similarly, advising on CABG assumes not only anatomic suitability but also the patients’ overall risk (are they frail, what is their renal status?) and their wishes (most do not want surgery).

Cardiac surgery in octogenarians has recently been reviewed.<sup>11</sup> Among 182 patients, 24 (13%) died in hospital and 107 (59%) had one or more major complications, with most recovering, and five (3%) suffered a stroke. Hospital mortality increased to 26.5% with combined valve and coronary surgery. Outcomes were worse if the surgery was urgent or delayed until the patient was functional class III or IV. These figures compare with an 8.2% inhospital mortality for percutaneous coronary interventions in a similar age group.<sup>12</sup> Considering overall risk, a conservative approach should be adopted and PTCA used for symptoms despite medical therapy and CABG, when PTCA is not an option.

### Lifestyle changes

Most old people believe “it’s too late to change.” Given their higher absolute risk, the elderly are likely to benefit more and the benefit will almost certainly be cost-effective. It is never too late to stop smoking, reduce weight, and take sensible exercise. Lipid-lowering therapy has proven beneficial in those up to 75 years of age, and may well reduce CAD and stroke beyond 75 years of age. Social support is important. Family and friends can help, both in the home and with the shopping, but they should not be an alternative to good medical therapy. Rather, they should be complementary. Local difficulties can be helped by a home assessment: would a stair lift help, can a mobility bus be arranged?

### Conclusions

The elderly come from an era where respect was commonplace, courtesy routine, and good manners plentiful. They now live in a

less caring world, but this should not diminish the respect they deserve. We need to acknowledge their feelings and wishes, treat them carefully and gently, and strive to maximize the quality of their remaining years. By combining advice on lifestyle with family support, using drugs selectively (and monitoring adverse effects), and choosing intervention when appropriate, we have a lot to offer: neither age nor cost should be a barrier to therapy in the elderly. ■

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# Impact of aging on myocardial oxidative metabolism

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## Introduction

There is an age-related decline in cardiac function and an increase in both the frequency and manifestation in older individuals of various cardiovascular disorders such as coronary artery disease, hypertension-induced left ventricular dysfunction, and dilated cardiomyopathy. The primary cardiac manifestation of the aging process is a decline in myocardial mechanical function during episodes of increased cardiac work.<sup>1,2</sup> The decline in mechanical function is characterized by impaired left ventricular systolic reserve capacity and diastolic filling.<sup>3</sup> Although likely multifactorial, the mechanisms responsible for the age-related decline in mechanical function are poorly understood. A decline in both  $\beta$ -adrenergic sensitivity and myocardial vasodilator function appears to be contributory.<sup>3-9</sup> Given the close coupling between myocardial oxidative metabolism and mechanical function, it would appear likely that aging may have important myocardial metabolic effects. Summarized below is what is known about the effects of aging on myocardial oxidative metabolism.

## Effects of aging on mitochondrial function

The machinery for oxidative metabolism resides within the mitochondria. Consequently, this organelle is a likely target for the effects of aging. Indeed, deletions and mutations of mitochondrial DNA (mtDNA) have been associated with aging. These age-associated mtDNA mutations appear to reflect the combined effects of intense oxidative damage and low efficiency of mtDNA repair systems.<sup>10-13</sup> Moreover, these mtDNA mutations

and deletions have been proposed as a possible cause of senescence because of their potential negative impact on mitochondrial gene expression and oxidative capacity.<sup>10</sup> However, the presence and severity of aging-related decrements in myocardial mitochondrial oxidative metabolism remains unclear. In mitochondria isolated from the hearts of aging animals, the results of some studies suggest that decreased oxidative function is present,<sup>14,15</sup> whereas the results of other studies suggest that oxidative capacity remains unchanged.<sup>16-18</sup> Furthermore, whether any of these observations is applicable to humans is unknown.

## Myocardial oxygen consumption

One of the ways to assess the impact of aging on myocardial oxidative metabolism is to determine whether the amount of oxygen consumed by the myocardium ( $MVO_2$ ) is altered by the aging process. To date, results of studies have provided conflicting results. For example, based on studies in experimental animals, it appears that  $MVO_2$  declines with age, both under resting conditions and during episodes of increased stress.<sup>19-21</sup> However, many of these differences may be explained by the fact that hearts from senescent animals achieved lower levels of cardiac work because, when corrected for the level of cardiac work, the level of  $MVO_2$  was comparable between senescent and mature animals.<sup>21</sup> However, in some studies, the amount of oxygen consumed per level of cardiac work (an index of efficiency) was slightly higher in aged animals compared with younger animals, suggesting that myocardial energy transduction may decrease with age.<sup>21</sup>

Definitive information regarding this topic in humans is lacking. Results of preliminary stud-

ies suggest that the level of  $MVO_2$  (measured by PET with  $^{11}C$ -acetate), both at rest and during catecholamine-induced stress, is comparable between younger (average age 25 years) and older (average age 65 years) healthy subjects.<sup>22</sup> However, myocardial work (calculated as the product of myocardial wall stress and strain measured by MRI) differed between the younger and older subjects. At rest, myocardial work levels were comparable between the two groups, but during catecholamine stimulation, older subjects exhibited a blunted increase in myocardial work. The blunted increase in myocardial work appears to be due to a blunted increase in myocardial strain. This resulted in myocardial efficiency (myocardial work divided by  $MVO_2$ ) being lower during catecholamine stimulation in older subjects than in younger individuals. As a result, myocardial efficiency during inotropic stimulation appears to be lower in older subjects than in younger adults. Intriguingly, these data are consistent with results obtained in experimental animals described above.<sup>21</sup> Clearly, more studies are necessary to confirm these findings and determine their significance.

However, one could speculate that the reduced efficiency in response to stress may help explain the reduced exercise capacity that is associated with aging, as well as why the hearts of older individuals are more susceptible to the manifestations of myocardial infarction.

### Myocardial substrate oxidation

Another way to evaluate the effects of aging on myocardial oxidative metabolism is to determine how aging may alter the oxidation of the various substrates used by the heart. The heart can use a variety of substrates, such as fatty acids, glucose, lactate, pyruvate, and amino acids, to support oxidative metabolism. In general, fatty acids and glucose are the most common substrates to be used by the heart, their proportional contribution to oxidative metabolism being dependent upon a variety of factors such as the plasma

substrate environment, hormonal milieu, and level of cardiac work. However, age also appears to affect this relationship. In the fetal heart, glucose utilization (the total amount of glucose used by the heart) and oxidation (the amount of glucose oxidized) predominate, most likely secondary to the relative hypoxia of the fetal state. In the normoxic state of the mature heart, fatty acids become the preferred source for oxidative metabolism. In experimental models of aging, with senescence, fatty acid oxidation declines and the proportion of glucose oxidation to overall oxidative metabolism increases even though absolute levels in glucose oxidation may still be less than those observed in mature animals.<sup>19–21,23</sup>

These observations appear to hold both under resting conditions and during episodes of increased cardiac work.

Results of a recent preliminary study suggest that a similar metabolic shift may occur in humans as they age. In this study, measurements of  $MVO_2$ , myocardial fatty acid utilization, and glucose utilization were made by PET using  $1-^{11}C$ -acetate,  $1-^{11}C$ -palmitate and  $1-^{11}C$ -glucose, respectively, in younger (average age 27 years) and older (average age 67 years) healthy adults under resting conditions.<sup>24</sup>

It was observed that myocardial fatty acid utilization and oxidation were significantly lower in the older subjects than in the younger individuals (*Figure 1A and 1B*). In contrast, myocardial glucose utilization was significantly higher in the older subjects than in the younger subjects.

This metabolic shift occurred despite similar levels in hemodynamics and plasma insulin and substrate levels between the two groups. Although, this study did not measure the oxidation of glucose, the similar shift in utilization of fatty acids and glucose seen in experimental models of aging suggests that senescence alters the oxidation of these substrates in a similar way. Currently, no data are available on the impact of aging on the oxidation of glucose and fatty acids in humans during stress.

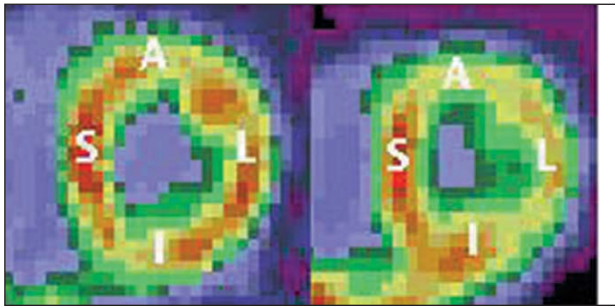


Figure 1A.-PET derived myocardial 1-11C-palmitate images obtained from a young female (left) and older female (right) studied at rest after an overnight fast. Images represent data acquired from 20 to 30 minutes after injection of tracer. Images are displayed in the short axis view, S:Septum, A: Anterior,L: Lateral and I: Inferior. White indicates highest counts and blue lowest counts.

### Potential mechanisms for the age-related shift in substrate oxidation

Potential mechanisms for the shift in substrate utilization and oxidation include changes in mitochondrial lipid content, lipid composition, and protein interactions as well as oxygen free radical injury with subsequent lipid peroxidation of mitochondrial membranes leading to significant membrane dysfunction.<sup>11,12,25-28</sup> Furthermore, oxygen free radical injury to key enzyme systems for fatty acid oxidation may play a role. Another potential mechanism includes changes in nitric oxide levels with age. Recently it has become apparent that nitric oxide, produced from endothelial nitric oxide synthase, plays an important role in the regulation of myocardial substrate metabolism. In various experimental models designed to alter the activity of this enzyme system, it has been shown that cardiac nitric oxide production inhibits myocardial glucose utilization. As a consequence, myocardial fatty utilization is increased.<sup>29,30</sup> It is unknown whether nitric oxide levels alter the oxidation of these substrates or indeed whether these observations are applicable to aging in humans. However, given that nitric oxide production decreases with age, it is tempting to speculate that the cardiac metabolic alterations observed with aging are at least partial-

ly due to changes in nitric oxide production.

The peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) is another intriguing potential site for age-related changes in substrate oxidation. PPAR $\alpha$  is a member of the nuclear receptor superfamily of transcription factors and is involved in the metabolic control of fatty acid oxidation enzyme gene expression.<sup>31,32</sup> In experimental animal models lacking PPAR $\alpha$ , myocardial fatty acid oxidation is markedly reduced. Moreover, it appears that levels of PPAR $\alpha$  (at least in splenic tissue) decrease with age.<sup>33</sup> Consequently, an age-related decline in PPAR $\alpha$  levels in the myocardium would also provide a partial explanation for the decrease in fatty acid oxidation in senescence.

### Clinical implications

The clinical consequences of age-related alterations in myocardial oxidative metabolism are manifold. With advancing age, there is an increased incidence of impaired glucose tolerance and diabetes mellitus

Consequently, a potential detrimental effect associated with this age-related shift in myocardial substrate metabolism includes impaired mechanical function due to the inability to increase glucose metabolism in

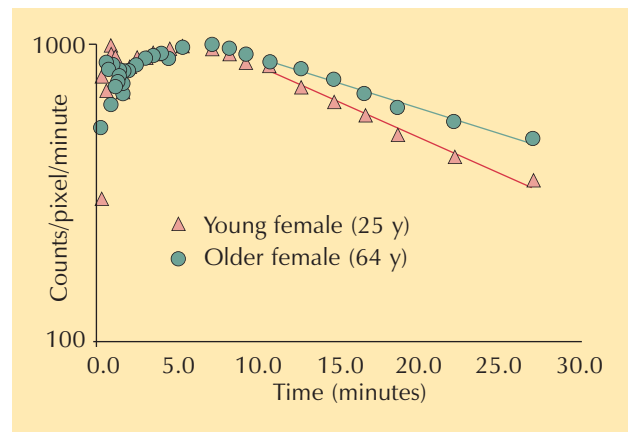


Figure 1B.- PET derived myocardial 1-11C-palmitate time-activity curves corresponding to the images shown above. The slower myocardial rate of clearance (solid lines) observed in the older female is indicative of a lower rate of fatty acid oxidation.

response to an increase in myocardial work. Recent studies in experimental models of left ventricular hypertrophy and initial studies in humans with hypertension-induced left ventricular hypertrophy have shown that myocardial energy substrate utilization is altered in association with hypertrophy as fatty acid utilization and oxidation decrease while glycolysis increases.<sup>34,35</sup> This switch in substrate metabolism is consistent with observations of the re-expression of fetal isoforms of a variety of contractile and calcium regulatory proteins in hypertrophied myocardium, suggesting that the development of left ventricular hypertrophy recapitulates the fetal heart phenotype.<sup>36</sup> Of note, these metabolic alterations in pressure-overload-induced hypertrophied myocardium may become more pronounced when left ventricular systolic dysfunction occurs, suggesting that this metabolic shift in substrate use is partly responsible, or at least presages, the transition from hypertrophy alone to hypertrophy with left ventricular dysfunction.<sup>37,38</sup>

These metabolic alterations would be additive to those due to aging. Consequently, the age-related changes in myocardial oxidative metabolism would provide at least a partial explanation as to why the incidence and manifestations of left ventricular hypertrophy and dilated cardiomyopathy are more pronounced in older subjects.

## Conclusion

There is an ever-growing body of evidence that aging alters myocardial oxidative metabolism, both with respect to  $MVO_2$  and to the oxidation of specific substrates. However, most of this information has been obtained in experimental models of aging. More studies are necessary to determine whether these observations are applicable to aging humans. Moreover, further studies are necessary to delineate the mechanisms responsible for these metabolic alterations as well as the physiologic and pathologic implications of these changes. Once gathered, such information may prove useful in guiding the develop-

ment of novel therapies designed to treat various cardiac diseases as well as potentially ameliorate the effects of aging on the heart. ■

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# New therapeutic approaches: safe prescribing in the elderly

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## Introduction

Elderly patients comprise 18% of the population but receive almost 25% of all prescribed medications.<sup>1</sup> However, the bases for some of these prescriptions are not well established and many may be unnecessary.<sup>2,3</sup> The prevalence of inappropriate drug prescription in older patients may be as high as 14% to 24% in community-dwelling older people<sup>4,5</sup> and 12% to 40% in nursing home residents.<sup>5,6</sup> It has been suggested that improving prescribing practices for elderly patients may substantially reduce morbidity and health care expenses.<sup>6</sup>

Our aim in this review is to discuss some important features and difficulties found in the process of prescription for elderly patients. We will include aspects of pharmacological and nonpharmacological treatment, and, as an example, will focus on congestive heart failure due to its high incidence and prevalence among the elderly.

## Drugs and aging

It is difficult to generalize the pharmacokinetic and pharmacological characteristics of drugs taken by elderly patients. Several factors, such as multiple diseases, environmental influences, genetic variation, and the physiological changes of aging, may influence drug effect and metabolism in this group of patients.<sup>7</sup>

## Pharmacokinetics

The pharmacokinetic characteristics of drugs are associated with age-related changes in the elderly. Drug absorption appears to be unchanged with increasing age.<sup>7</sup> The volume

of distribution of water-soluble drugs (eg, digoxin) is smaller in the elderly, with a consequent higher plasma concentration than in the younger patient given the same dose.<sup>8</sup> Conversely, an age-related increase in body fat at the expense of muscle, leads to a greater volume of distribution of lipid-soluble drugs (eg, amiodarone).<sup>9</sup> Both pathways of drug excretion, liver metabolism and renal excretion, may be changed in elderly patients. Hepatic mass decreases with age and the clearance of drugs with low intrinsic clearance would therefore be expected to be reduced. Increasing age is associated with a reduction in presystemic metabolism (first pass) of drugs with a high rate of hepatic extraction (eg, propranolol, tricyclic antidepressants, and antiarrhythmic agents).<sup>7</sup> Age-related decline in glomerular filtration rate and tubular excretion modifies the half-life and plasma concentration of drugs with predominantly renal excretion.<sup>10</sup> Simple prerenal impairment associated with dehydration secondary to influenza or a chest infection may lead to life-threatening intoxication by an otherwise safely administered drug.<sup>11</sup>

## Pharmacodynamics

Drug effects on the body also show modifications by the aging process.  $\beta$ -Adrenergic agonists and antagonists have been shown to be less effective in this population due to receptor downregulation.<sup>12,13</sup> The clinical relevance of this requires further investigation.

Adverse drug reactions in elderly patients have been extensively studied. However, the available information is incomplete because older people have been systematically excluded from the clinical trials that have given us

the most reliable information.<sup>14</sup> The frequency of adverse drug reactions is higher in older patients because of the increased number of prescribed medications and the higher incidence of comorbidity. After controlling for the number of medications prescribed, the effect of age disappears, as shown in some studies.<sup>15</sup> Adverse drug reactions have been recognized as an important reason for hospital admission of elderly patients, contributing to between 3% and 12% of all geriatric admissions.<sup>3,16,17</sup>

### Evidence-based prescribing

Randomized, placebo-controlled trials provide the strongest evidence available to take into account before selecting treatment. Several powerful randomized clinical trials have established the role of pharmacological treatments for patients with congestive heart failure. These include the use of ACE inhibitors,<sup>18,19</sup>  $\beta$ -blockade,<sup>10,20,21</sup> and spironolactone,<sup>22</sup> which impact positively on mortality and morbidity, and digoxin,<sup>23</sup> which reduces hospitalization and improves symptoms in chronic heart failure.

Although there is important evidence to support the use of these drugs, the majority of the trials have excluded patients older than 70 years, and the number of very old patients (over the age of 85 years) is practically minimal (*Table I*).<sup>14</sup> Only the ELITE trials (Evaluation of Losartan in the Elderly), originally designed to demonstrate equivalence

between drugs, were focused on a population of elderly heart failure patients. Surprisingly, only some of the landmark clinical trials actually had an upper age limit for inclusion: VHeFT-II<sup>27</sup> (Vasodilator Therapy with Hydralazine Isosorbide Dinitrate Trial II), 75 years; CIBIS-I<sup>28</sup> (Cardiac Insufficiency Bisoprolol Study I), 75 years; US Carvedilol Heart Failure Study,<sup>10</sup> 85 years. The number of females recruited in some trials was as low as 20% (*Table I*), and the exclusion of women at least in part reflects the exclusion of older patients, as older females with heart failure are more prevalent.<sup>24</sup> Ongoing trials such as PEP-CHF<sup>29</sup> or PREAMI<sup>30</sup>, specifically designed to include elderly patients over 70 years with heart failure or over 65 with post myocardial infarction will help to identify the role of ACE inhibitors in those patients.

Can we extrapolate the results from the randomized clinical trials in relatively young individuals to the treatment of older people? Clinical guidelines suggest that the therapeutic approach in elderly patients with systolic dysfunction should be similar to that in younger patients.<sup>31</sup> As discussed previously, precautions need to be taken and doses adapted due to altered pharmacokinetic and pharmacodynamic properties in the light of older age and comorbidities. The prescription of short-acting, powerful loop diuretics to elderly patients with relative immobility due to Parkinson's disease should be circumspect at the very least. Older patients with congestive heart failure are more likely to have preserved systolic function. Such patients have not been included in the major treatment trials.<sup>32</sup> Patients with comorbidities are usually excluded from clinical trials and there is a lack of information about potential drug and disease interactions. In clinical trials, patients receive special care, including better monitoring for adverse reactions, plasma biochemistry, and, in some cases, a careful monitoring of plasma drug levels, whereas in clinical practice this is impossible.

We know that the evidence available fails to cover a large majority of patients with heart failure who are older than those in the trials, and we therefore have to rely on clinical acu-

*Table I. Participation by age and gender in randomized clinical trials (adapted from reference 24).*

Study	Mean age (years)	Age >70 years (%)	Female (%)
ELITE I <sup>25</sup>	73	70	33
ELITE II <sup>26</sup>	71	70	30
CONSENSUS <sup>18</sup>	71	50	30
MERIT-HF <sup>21</sup>	64	32	23
DIG <sup>23</sup>	63	27	22
SOLVD <sup>19</sup>	61	15	20

men and general principles when treating these older patients.

### Concordance with treatment

Nonconcordance with treatment may be one of the most important problems in the management of elderly patients.<sup>33</sup> In clinical practice, almost half of the patients for whom appropriate therapy has been prescribed fail to receive full benefit through inadequate concordance with treatment.<sup>33,34</sup> Concordance is reduced when the regimen is complex, of long duration, dependent on an alteration to the patient's lifestyle, inconvenient, or expensive.

For example, treatment for chronic congestive heart failure is complex, includes a minimum of two different medications (in most cases four or five), requires following multiple dosing schedules, and is for life. Nonconcordance with drug treatment and diet has been reported to be the leading cause of decompensation in chronic heart failure, accounting for almost 50% of hospital readmissions.<sup>35</sup>

The limitations of the different methods available to monitor drug concordance and the restricted information from randomized clinical trials do not reflect the real magnitude of the problem. In the DIG (Digitalis Investigators' Group) trial,<sup>23</sup> 70% of patients in the digoxin arm were still taking digoxin at the end of the follow-up period, demonstrating the high adherence to treatment in the clinical trial situation. An epidemiological study evaluated the compliance of digoxin in elderly patients in clinical practice and showed that only 10% of the patients filled enough prescriptions to acquire the amount of drug prescribed.<sup>36</sup> Clinical trials reflect idealized circumstances, whereas most patients are treated in the real world of poor concordance and limited monitoring.

Changes could be introduced to the treatment strategy to improve all patients' drug concordance. These include a less complex regimen by reducing the number of different medications required, avoiding nonessential medicine and unnecessary doses; and break-

ing the treatment regimen into less complex stages that can be implemented sequentially, minimizing both inconvenience and forgetfulness by matching the regimen schedule to the patient's regular daily activities.<sup>33</sup> Other helpful approaches are the use of tablets with drug combinations, longer acting drugs, and regimens that require less frequent doses. Relatives and carers can be recruited to aid concordance and are especially beneficial for a cognitively impaired patient.

### Nonpharmacological interventions

Nonpharmacological management, including diet and lifestyle modification, are therapeutic strategies that have shown benefit in several conditions such as hypertension,<sup>37</sup> coronary heart disease, and congestive heart failure.<sup>31</sup> To improve the therapeutic effect of the pharmacological and nonpharmacological treatments in elderly patients, multidisciplinary interventions have been established to augment patients' information and improve concordance.<sup>38,39</sup> Support programs that may well include teaching sessions or pharmacists' home visits to reinforce the information on pharmacological treatment, have increased medication compliance by up to 85% and reduced the hospital readmission rate in approximately 50%.<sup>40,41</sup>

The overall effect of the multidisciplinary approach in elderly patients with congestive heart failure includes a decrease in readmissions, improvement of quality of life, and, most importantly, reduction of cost of care.<sup>38</sup> The effect of the relatively inexpensive interventions seems to continue for a long period, and not only immediately after the moment of the intervention.<sup>41</sup>

### Conclusions

Drug therapy should be adjusted according to individual age effects on pharmacokinetics and pharmacodynamics in older people. Unnecessary medications should be avoided to reduce adverse reactions and nonconcor-

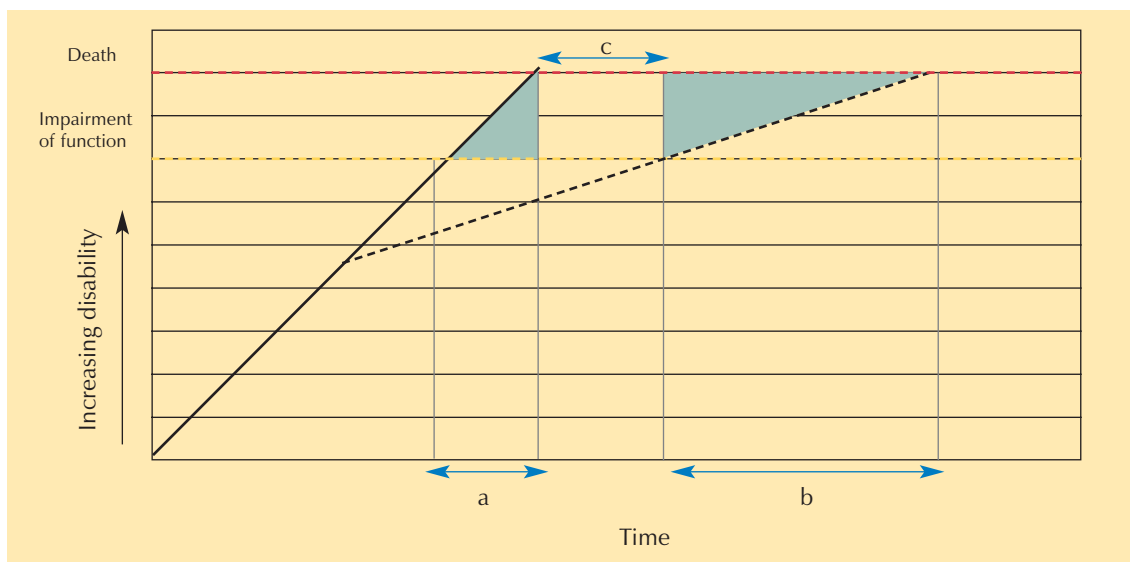


Figure 1. Life-prolonging intervention and effect on handicap. Without intervention (solid line) time spent handicapped (a) is short. Intervention (broken line) prolongs life (c + b) but if period of handicap is much longer than the non-handicapped gain (c) the value of the intervention must be questioned.

dance associated with multiple drug therapies. Simplicity should be the watchword. Non-pharmacological management including lifestyle and diet modifications, and multidisciplinary support programs should be more widely used. Further studies that include more elderly patients are urgently needed to establish the best management protocols based on cost-benefit results.

### Future perspective

Our ability to prolong life with pharmacological interventions is an obvious benefit of research. However, years gained must not be at the expense of quality of life (Figure 1). If the years gained are to be characterized by increasing disability and handicap, are they really worthwhile? Our objective, especially in older patients, must be to “compress morbidity,” thus relieving disability rather than simply adding worthless years to life. ■

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# Management of high-risk populations with coronary artery disease: rationale for improving prognosis in the elderly

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## Introduction

The prevalence of ischemic heart disease increases continuously with aging and is becoming a major problem in the elderly and the leading cause of death in this age group.<sup>1</sup> The management of acute coronary syndromes, especially acute myocardial infarction, in elderly patients is challenging and represents a major growing health problem. Those at highest risk of acute myocardial infarction are clearly the elderly, who account for more than half of all deaths among hospitalized patients. Elderly patients are prone to have multivessel disease, prior myocardial infarction, diminished ejection fraction, increased risk of cardiac rupture, and more comorbidities.<sup>2-6</sup>

Although an elevated risk of morbidity is observed in the elderly undergoing PTCA combined with stenting, this therapeutic approach should be utilized more aggressively in these patients, since there is a significant benefit of reduction in mortality and disabling stroke in this population, in comparison with fibrinolytic and/or medical treatment alone.<sup>6</sup>

Primary angioplasty and/or stenting can be used in the elderly and is associated with a lesser risk of hemorrhagic stroke or major bleeding. Nonthrombolytic therapies such as revascularization procedures are preferred in the appropriate settings and should be strongly considered when there is marked concern about hemorrhagic stroke or major bleeding, particularly in patients with absolute or relative contraindications to thrombolytic therapy.

Stable angina pectoris occurs frequently in the elderly, affecting some 25% of patients over the age of 75. Elderly patients with stable angina are at significantly higher absolute risk of cardiovascular events and death. In this population, the higher risk of complications

associated with revascularization procedures favors the need for a pharmacological approach to the treatment of stable angina.

## Aims of treatment in elderly populations with angina pectoris

Treatment of stable angina aims to significantly decrease the severity and frequency of episodes of angina and to increase the functional capacity, with few or no adverse effects, in order to improve quality of life, which is of paramount importance in this population.<sup>3</sup>

The general approach to adequate management of elderly patients includes education, lifestyle modification, and conservative management of coronary artery disease by medical therapy in most cases.

## Choice of drug therapy in the elderly

Antianginal therapy can improve symptoms by increasing blood flow in ischemic areas of the myocardium, by reducing myocardial oxygen demand, or by protecting the metabolism of myocardial cells. The high proportion of elderly patients with multiple coexisting medical conditions also requiring treatment and the frequent alterations in hepatic and renal function should be taken into consideration when selecting drug therapy.

In general, the elderly are more sensitive to drugs and more prone to serious adverse events. Because of prescriptions for concomitant disease, they are more likely to experience deleterious drug interactions.<sup>3,4,7,8</sup>

Elderly patients treated with hemodynamic agents (nitrates,  $\beta$ -blockers, calcium channel blockers) are often exposed to adverse effects. Nitrates are potent vasodilators, acting by

venous and, to a lesser extent, arterial dilatation. In elderly patients, baroreceptor function decreases with aging and nitrates may lead to an increase in postural adverse effects which may be poorly tolerated.  $\beta$ -Blockers expose to bradycardia, conduction disturbances, and hypotension at lower doses than in younger patients. As regards calcium channel blockers, patients treated by phenylalkylamines (eg, verapamil) or benzothiazepines (eg, diltiazem) are also exposed to bradycardia and atrioventricular block. With dihydropyridines, decreased hepatic first-pass metabolism in the elderly can lead to raised plasma concentrations of the drug. As with all hemodynamic drugs in the elderly, symptomatic hypotension is a concern due to a higher risk of falls and consequent fractures, and a high risk of thromboembolic complications.<sup>3</sup> Therefore, elderly patients treated with hemodynamic drugs should be closely monitored. The general prescribing rules for these drugs are: start at a lower dose than for younger patients; carefully look for any adverse effects; and be prepared to change to another drug if the effects prove troublesome.

The development of a new class of metabolic agents promises a favorable prospect for the management of patients with coronary artery disease, especially the elderly.

### **Trimetazidine: a specific metabolic mechanism of action**

Changes in cardiac metabolism are an inevitable step in the ischemic cascade that leads to the development of coronary artery disease. A better understanding of the pathophysiology of myocardial ischemia has paved the way for the development of a new therapeutic approach in the form of metabolic antianginal agents, first among which is trimetazidine (Vastarel 20). Trimetazidine has been proven to exert antianginal properties due to its specific metabolic mechanism of action. It reduces the metabolic damage that occurs during ischemia and provides cytoprotection through improvement in the metabolic status of myocytes. The efficacy and tolerability

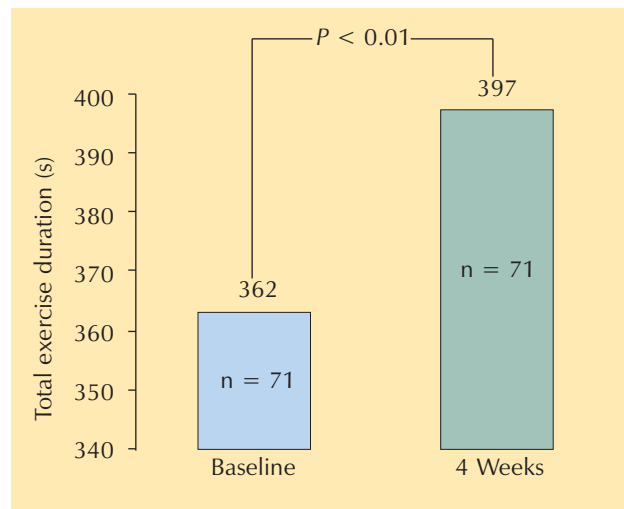


Figure 1. Significant increase in exercise duration in elderly coronary patients taking trimetazidine 20 mg tid.

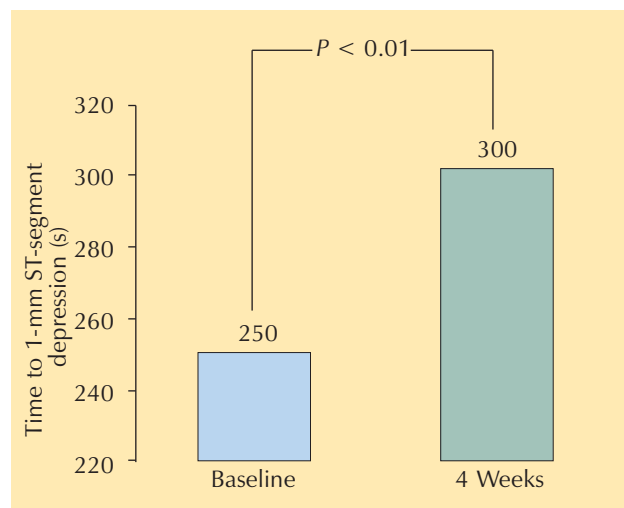


Figure 2. Significant increase in time to 1-mm ST-segment depression in elderly coronary patients taking trimetazidine 20 mg tid.

ty of trimetazidine have been proven in numerous clinical trials in both monotherapy and combination therapy in patients with chronic stable angina. Trimetazidine was the first metabolic agent to be quoted by the European Society of Cardiology guidelines on the management of stable angina pectoris. The specific metabolic mechanism of action of trimetazidine, which does not alter hemodynamic parameters, offers a strong rationale for

treating elderly patients with coronary artery disease. The potential benefits of trimetazidine in elderly coronary patients have been recently confirmed in terms of efficacy, tolerability, and improvement in quality of life.

The TRIMPOL-1 (Trimetazidine in Poland) substudy<sup>9</sup> assessed the efficacy and safety of trimetazidine in elderly patients (>65 years) with coronary artery disease. In this open-label, daily-practice-based study, 71 patients receiving a hemodynamic drug (nitrate,  $\beta$ -blocker, or calcium channel blocker) were given trimetazidine 20 mg tid. Trimetazidine significantly improved all exercise parameters (time to onset of angina, total exercise duration, time to 1-mm ST-segment depression) (Figures 1 and 2). Tolerance was excellent and no patient treated with trimetazidine withdrew due to adverse events.

The efficacy and acceptability of trimetazidine have been confirmed by Kölbl and Bada (unpublished data) in 120 elderly coronary patients (65–86 years) resistant to hemodynamic monotherapy. At 12 weeks' follow-up, trimetazidine 20 mg tid significantly improved all exercise parameters (1-mm ST-segment depression, exercise duration). Patient-assessed quality of life was rated good or excellent in 89% of cases. Only two minor adverse events (gastric pain and dyspepsia) were reported.

## Summary

**Coronary artery disease in the elderly represents a growing health care problem. Since revascularization procedures carry a high risk of morbidity, a conservative therapeutic**

**approach is recommended in this population. Use of conventional hemodynamic agents can be inappropriate due to drug interactions, concomitant diseases, and severe adverse events. Trimetazidine, the first of a new class of metabolic agents known as 3-KAT inhibitors, has proven to be effective and well tolerated in elderly coronary patients. This is due to its original and specific mechanism of action which confers a direct myocardial cytoprotective effect, free of any hemodynamic effects and drug interaction. This promising approach improves the symptoms and quality of life of this at-risk population. ■**

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# Unprotected left main stem stenting in elderly patients

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## Introduction

We present a case which outlines the management decisions regarding coronary revascularization in elderly patients with chronic symptomatic coronary artery disease. We discuss the implications of ischemia-guided revascularization and aggressive percutaneous strategies in patients with concomitant non-cardiac risk factors.

## Case

An 84-year-old Caucasian woman presented with a 9-month history of CCS class 3 angina. Apart from her age, her only cardiac risk factor was hyperlipidemia, which was well controlled on hMG-CoA reductase therapy. Medication at the time of presentation included bisoprolol, amlodipine, isosorbide dinitrate, and atorvastatin. Despite this treatment her symptoms were severely limiting her normal daily activities.

Pertinent medical history included severe cervical and thoracic osteoarthritis associated with moderate kyphoscoliosis, and continued warfarin therapy for recurrent deep venous thrombosis. She was also treated for hypothyroidism. Initial examination confirmed kyphoscoliosis with severely reduced movements of the cervical spine with limited flexion and extension. Cardiovascular examination was unremarkable; respiratory examination, however, revealed poor chest expansion with markedly reduced FEV<sub>1</sub> and FVC related to kyphoscoliosis. ECG was normal. Transthoracic echocardiography showed well-preserved left ventricular function with no regional wall motion abnormality. Mild mitral and tricuspid regurgitation was noted. Thallium myocardial perfusion imaging with adenosine stress showed reduced tracer uptake in the

anterior wall after stress, consistent with reversible ischemia. Coronary angiography revealed a left main stem equivalent stenosis with tight proximal stenoses of the left anterior descending and left circumflex coronary arteries. The distal portions of these vessels were both normal. Minor disease only was seen in the nondominant right coronary artery. The left ventriculogram was normal.

Referral for surgical revascularization was made, but surgery was refused on the grounds of high peri- and postoperative risk assessment related to impaired respiratory function, difficult intubation and high probability of prolonged postoperative intensive care. Despite additional medical therapy, the patient remained severely limited.

Following extensive counseling the patient then underwent unprotected elective angioplasty with placement of two stents. Prior to the procedure the anticoagulation regime was switched to heparin. Abciximab infusion was commenced at the start of the procedure following elective placement of an intra-aortic balloon pump. Two wires were passed into the distal LAD and Cx vessels and the LAD lesion was directly stented with a 3.5 x 15 mm slotted tube stent, whilst the Cx lesion was predilated prior to placement of a 3.5 x 20 mm stent. Following the procedure the patient was commenced on clopidogrel. The patient made an uneventful recovery and was discharged after 5 days. After 6 months, coronary angiography revealed no in-stent restenosis, and a subsequent myocardial perfusion scan showed complete resolution of the anterior wall defect.

## Discussion

### *Invasive vs medical therapy in elderly patients with coronary artery disease*

Randomized trials for treatment of coronary artery disease have traditionally concentrated on a younger target population, excluding patients over 75 years of age. Findings from these trials may not be directly relevant to very elderly patients in whom the risk of complications from invasive treatment is significantly higher. In addition, as in this case, non-cardiac risk factors, such as impaired respiratory function and high anesthetic risk, have led to the exclusion of such patients from clinical trials.

The patient population over 75 years of age is the fastest-growing age group and therefore requires well-defined management strategies based on evidence from randomized trials. The TIME investigators<sup>1</sup> recently reported the results of a prospective, randomized, multicenter study in patients over 75 years of age. Comparison was made between an invasive strategy of cardiac catheterization followed by percutaneous or surgical intervention, and a noninvasive strategy of optimized medical therapy. The primary end point assessed quality of life indices, which included the incidence of major adverse cardiac events. In both groups a reduction in angina score and an increase in quality of life were reported, but these changes were significantly better in the invasively treated group. Nearly half of the patients treated noninvasively experienced major adverse cardiac events, whereas in the invasive group this was reduced to 1 in 5 ( $P < 0.0001$ ). This would strongly support an invasive strategy in patients over 75 years of age, who despite many comorbid risk factors, often derive the greatest symptomatic benefit from aggressive revascularization. The method of revascularization should be dictated by the preoperative risk assessment and the feasibility of a percutaneous approach, and age should no longer be a bar to aggressive revascularization.<sup>2,3</sup>

### *Unprotected left main stem angioplasty*

The feasibility and safety of unprotected left main stem stenting have continued to improve in recent years. Improvements in stent technology, better adjuvant therapies such as glycoprotein lib/IIIa receptor blockade, and improved treatments for restenosis have all made a percutaneous revascularization strategy a more attractive option than cardiac surgery with its higher complication rate, especially in more elderly patients. With good case selection and the elective use of supportive devices such as intra-aortic balloon pumping, the long-term outcome even in elderly patients is increasingly favorable.

Tan et al<sup>4</sup> recently reported results from 279 consecutive patients who underwent unprotected left main stem angioplasty between 1993 and 1998. Forty-six percent of these patients were inoperable or were of high surgical risk, as in the case described here; 13.7% of patients died in hospital. Cardiac mortality after 1 year was 20.2%: low ejection fraction, impaired renal function, severe mitral valve disease, myocardial infarction or shock, and lesion calcification were all independent predictors of mortality. In a low-risk subset of patients <65 years old with well-preserved left ventricular function and no adverse risk factors, there were no periprocedural deaths and 1-year mortality was 3.4%. A percutaneous strategy may be appropriate for highly symptomatic inoperable patients, the decision based on objective evidence of ischemic comorbidity and procedural risk rather than on biological age.

Choussat et al<sup>5</sup> reported the immediate and mid-term results of unprotected left main stem stenting in 92 patients out of 6006 patients undergoing coronary angioplasty. The average age of the patients was 74.3 years. The reported angiographic success rate was 100%, with no patients requiring emergency bypass surgery. Four patients died during their hospital stay and a further six deaths occurred over the next 6 months of follow-up. One-year actuarial survival was 89%, with 85% reported at 3 years. There are many more reports of the success of a percutaneous

approach to revascularization in an increasingly elderly population.<sup>6,7</sup>

## Conclusions

This case outlines treatment strategies in elderly patients with chronic symptomatic coronary artery disease and accumulating evidence in support of an invasive vs an optimized medical approach. In addition, the feasibility of unprotected left main stem stenting is now well reported and there is a growing body of evidence to support an aggressive percutaneous strategy in selected patients. ■

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# Featured Research

## Abstracts and commentaries

### A clinical trial of estrogen-replacement therapy after ischemic stroke

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RJ. *N Engl J Med.* 2001;345:1243–1249.

Observational studies have suggested that estrogen replacement therapy (ERT) may reduce a woman's risk of stroke and death. We conducted a randomized, double-blind, placebo-controlled trial of estrogen therapy (1 mg of 17 $\beta$ -estradiol/day) in 664 postmenopausal women (mean age, 71 years) who had recently had an ischemic stroke or transient ischemic attack. Women were recruited from 21 hospitals in the United States and were followed for the occurrence of stroke or death. During a mean follow-up period of 2.8 years, there were 99 strokes or deaths among the women in the estradiol group, and 93 among those in the placebo group (relative risk in the estradiol group 1.1, 95% CI 0.8–1.4). Estrogen therapy did not reduce the risk of death alone (relative risk 1.2, 95% CI 0.8–1.8) or the risk of nonfatal stroke (relative risk 1.0, 95% CI 0.7–1.4). The women who were randomly assigned to receive estrogen therapy had a higher risk of fatal stroke (relative risk 2.9, 95% CI 0.9–9.0), and their nonfatal strokes were associated with slightly worse neurologic and functional deficits. Estrogen does not reduce mortality or the recurrence of stroke in postmenopausal women with cerebrovascular disease. This therapy should not be prescribed for the secondary prevention of cerebrovascular disease.

attack with 1 mg 17 $\beta$ -estradiol/day or placebo. Observational studies had suggested that ERT may reduce the risk of stroke, myocardial infarction, or death. Here is our first problem with regard to comparing results: observational data are essentially primary prevention, whereas the WEST data are secondary prevention. This problem arose with the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) studies, both of which reported no benefit of ERT in slowing the progression of the clinical or arteriographic manifestations of coronary artery disease in women with established disease. Comparing secondary prevention trial data with observational primary prevention data is akin to comparing apples with pears. The WEST study did not show any benefit for estradiol with regard to reducing mortality or the recurrence of stroke in postmenopausal women with established cerebrovascular disease. Current practice for ERT is confined to its use for menopausal symptoms and osteoporosis prevention, not for the secondary prevention of cardio- or cerebrovascular disease. We need, however, to keep an open mind — not all ERTs are the same and trials cannot be considered generic for ERT. Furthermore, prospective primary prevention trials are underway and we need to await the results before closing the door to ERT as a means of cardiovascular disease prevention.

Graham Jackson

### Commentary

The Women's Estrogen for Stroke Trial (WEST) treated for 3 years women with a recent history of ischemic stroke or transient ischemic

## Clinical outcome of patients with previous myocardial infarction and left ventricular dysfunction assessed with myocardial $^{99m}\text{Tc}$ -MIBI SPECT and $^{18}\text{F}$ -FDG PET

Zhang X, Liu X-J, Wu Q, et al. *J Nucl Med.* 2001;42:1166–1173.

Myocardial viability was assessed by  $^{99m}\text{Tc}$ -methoxyisobutylisonitrile (MIBI) SPECT and  $^{18}\text{F}$ -FDG PET to evaluate the prognosis and treatment strategy of patients with myocardial infarction (MI) and left ventricular (LV) dysfunction. One hundred twenty-three consecutive patients with previous MI and LV dysfunction (LV ejection fraction [LVEF]  $35 \pm 6\%$  [mean  $\pm$  SD]) who underwent  $^{99m}\text{Tc}$ -MIBI SPECT and FDG PET were followed for  $26 \pm 10$  months. Distributions of the two radiotracers in myocardial segments were classified into two patterns: myocardial perfusion-metabolism mismatch (MM) and match. LVEF and LV end-diastolic diameter (EDD) were measured by echocardiography at baseline, and at 3 months (Pos1) and 6 months (Pos2) after revascularization. Cardiac death, acute MI, unstable angina, and late revascularization ( $>3$  months) experienced by the patients during follow-up were defined as cardiac events. Sixty-seven patients underwent revascularization and 56 patients were treated medically. Of the 72 patients with two MM segments, 42 underwent revascularization (group A1) and 30 were treated medically (group A2). Of the 51 patients with less than two MM segments, 25 underwent revascularization (group B1) and 26 were treated medically (group B2). The four groups had similar baseline characteristics and resting LVEF. After revascularization, EF increased in group A1 from  $36 \pm 5\%$  to  $44 \pm 8\%$  ( $P < 0.0001$ ) in Pos1 and to  $51 \pm 9\%$  ( $P < 0.0001$ ) in Pos2. EDD decreased from  $62 \pm 8$  mm to  $56 \pm 5$  mm ( $P < 0.001$ ) in Pos1 and to  $55 \pm 5$  mm ( $P < 0.001$ ) in Pos2. However, EF and EDD were unchanged in group B1 ( $P > 0.05$ ). During follow-up, 22 patients (17.9%) suffered cardiac events, including 11 cardiac deaths, four acute MI, six late coronary artery bypass grafts, and one

unstable angina pectoris. The cardiac event rate in group A2 (50%) was significantly higher than that of groups A1 (2.4%;  $P < 0.0001$ ), B1 (12%;  $P = 0.003$ ), and B2 (11.5%;  $P = 0.002$ ). Assessment of myocardial viability using hybrid  $^{99m}\text{Tc}$ -MIBI SPECT and FDG PET can predict the clinical outcome and is helpful in decision-making in the treatment strategy of patients with MI and LV dysfunction. Revascularization can improve the LV function and clinical outcome of patients with more than two viable myocardial segments.

### Commentary

This study highlights the previously known observation that patients with LV dysfunction and viable tissue are at risk for future complications. The concept of viable tissue — dysfunctional myocardium with preserved metabolic activity that can improve in function after revascularization — has been extensively discussed in issue 10 of *Heart and Metabolism*. The present study is important because: (1) patients were studied after MI, in contrast with most viability-prognosis studies; and (2) the patients were consecutively included, suggesting less inclusion bias. Interestingly, the event rate of this study is very similar to the mean event rate from previous studies in patients with chronic LV dysfunction. Also in this study the authors found that revascularization improved the LVEF and reduced event rates only in patients with viable tissue. Thus, residual viable tissue both after an acute coronary syndrome and in the chronic state is associated with an increased adverse event rate. However, the missing evidence is a study in which patients with viable tissue are randomized to optimal conservative treatment vs revascularization. Such studies are ongoing and the results will determine whether standard viability assessment, possibly followed by revascularization, is mandatory in every patient with LV dysfunction.

Frans Visser

# Assessment of the elderly patient for cardiac surgery

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## Introduction

We expect the seventh age of man to be a period of decline, but none of the afflictions of old age should go unchallenged. As the techniques and safety of cardiac surgery continue to improve, there has been a parallel increase in the mean age of our patients. With this has come an increased appreciation of the benefits that can be achieved by successfully relieving the cardiovascular symptoms of angina, breathlessness, and fatigue even in older age groups, and the possibility of prolonged survival. These benefits, however, come at the cost of greater operative risk.

Since age alone is probably the single most powerful risk factor for early mortality after cardiac surgery in all preoperative risk stratification models, and since most models are least accurate in predicting outcome at the highest levels of risk, surgeons need other means of assessing risk in the elderly. Primarily this becomes an exercise in utilizing the full breadth of basic clinical skills and it relies heavily on experience and clinical judgment, some of which will be largely intuitive.

The risks need to be balanced against a realistic appraisal of the potential benefits for the individual patient. In the elderly, a careful and unhurried consultation is required and the presence of a partner or family member is essential. My own practice is to consider four general questions, ordered according to the strength of the evidence base available to guide the surgeon in answering them.

## How strongly is surgery indicated?

This is the first question to address. In this context, syncopal or very symptomatic severe aortic stenosis and severely symptomatic coronary disease with left main stem stenosis constitute compelling indications, whereas mitral regurgitation or diffuse coronary disease may offer more scope for successful medical management. The joint American Heart Association and American College of Cardiology guidelines for coronary artery bypass grafting<sup>1</sup> and valve surgery<sup>2</sup> are valuable for their ranking of indications, and in high-risk groups it is sensible to restrict surgical intervention for class I indications.

Cardiac surgery may be indicated to relieve symptoms or to improve survival, or both, and an evidence base exists for both indications. Unfortunately this evidence base is deficient for patients over the age of 70, which is uncomfortably close to the mean age of the patient population undergoing surgery in the UK.<sup>3</sup> This means that prognostic indications for surgery in the elderly are based on extrapolation of data from a younger population and must be treated with caution. Data are not available because rigorous studies have not been performed, but there is no reason to believe that improved survival cannot be achieved in carefully selected patients. However, clinical prudence favors emphasis on symptomatic indications for surgery in the elderly, and the limitations of achieving prolonged survival must be discussed candidly.

Left ventricular function must be considered at an early stage in the decision to operate. Poor left ventricular function, if irreversible in the short term, can negate any symptomatic benefit of surgery and is also a powerful risk

factor for perioperative mortality. This is of less concern in severe aortic stenosis; but in ischemic heart disease, accurate differentiation between stunned or hibernating myocardium and infarction is essential and is best accomplished by stress echocardiography.

### **Are there any patient-related factors which might impede the successful technical accomplishment of the proposed operation or significantly increase its complexity?**

Such factors may be pathological, iatrogenic or related to unusual anatomy. Pathological aspects which require careful consideration include calcification and pericarditis. Calcification of the ascending aorta renders cannulation for cardiopulmonary bypass and aortic occlusion by clamping particularly hazardous. Other arteries are available for cannulation, most commonly the femoral artery; but this too is not free of risk and may be impossible in severe arteriopathy, as well as risking retrograde dissection, which is almost invariably fatal. An alternative is infraclavicular cannulation of the subclavian artery as it becomes the axillary artery.<sup>4</sup> The more important limitation imposed by a severely calcific or atheromatous aorta is the inability to achieve occlusion by simple clamping. Pedicled internal mammary arterial grafts and proximal anastomosis of free grafts to them can avoid the need for manipulation of the ascending aorta for coronary bypass grafting, and off-pump surgery offers another strategy which can be employed in this situation. Access to the aortic valve is more problematic with a diseased aorta and may necessitate profound hypothermia and a period of total circulatory arrest, neither of which is desirable in the elderly. The fragility of calcified tissues can make aortic closure difficult and insecure, as well as predisposing to systemic atheroembolism, which is a major cause of stroke, and enteric ischemia.<sup>5</sup>

Important iatrogenic factors to consider include previous cardiac surgery, deficiency of conduits for coronary bypass following surgery

for varicose veins, or mediastinal irradiation.

Obesity in the elderly can also cause major intraoperative difficulties. In obese patients, extensive fatty infiltration of mediastinal tissues and cardiac structures can impede access and increase tissue fragility. Such tissues tear and bruise easily and can be troublesome to suture, resulting in problems with postoperative hemostasis which can be severe and even fatal.

### **Does the patient present with comorbidity known to increase operative risk?**

Neurological, pulmonary, vascular, and renal pathology are known determinants of operative risk. A history of previous stroke and increased age are the most important predictors of perioperative stroke which also carries a high mortality. A history of transient ischemic attack and known cerebrovascular disease are also significant risk factors. The presence of asthma requiring medication, known chronic obstructive pulmonary disease, or current smoking increases the probability of bronchopneumonia and ventilator dependency. Renal impairment invariably worsens temporarily after cardiac surgery, and artificial renal support may be required. All these factors are liable to prolong intensive care stay, increase the likelihood of sepsis, and produce a catabolic state which is particularly poorly tolerated in the elderly. In the very elderly, any of these factors is a strong contraindication to cardiac surgery.

### **What is the patient's biological age?**

Clinicians of all specialties are aware of potential discrepancies between chronological age and biological age. This discrepancy becomes more marked with advancing chronological age, and can be very striking. Energetic 80 year olds who play sports regularly and continue to care for dependants are now as common in my practice as sedentary 60 year olds who require carers. This relates largely to

mobility and motivation, and the clinician needs to unravel from the patient's history and the contributions of family members or carers how much of the patient's current incapacity is due directly to the cardiac condition, and therefore potentially reversible, and how much relates to longstanding lifestyle choices and attitudes which are beyond the remit of the cardiac surgeon.

Despite all the technical and pharmacological improvements of recent years, cardiac surgery remains a major physical and psychological stress for the patient. Successful recovery can take up to 3 months and requires a considerable degree of effort in self-motivation and mobilization. At the same time, it is a frequent clinical observation that elderly patients often seem to embrace postoperative rehabilitation with an exemplary enthusiasm and vigor. Identifying such patients preoperatively is important.

## Conclusion

Elderly patients must not be denied the opportunity of seeking relief from symptoms or life-threatening cardiac pathology through cardiac surgery. Thorough investigation and referral for assessment by an experienced surgeon are recommended. A clear and decisive surgical opinion should be expected, and the patient should leave the consultation confident that the right decision has been made. ■

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# Glossary

Gary Lopaschuk and William Stanley

### **3-hydroxyacyl-CoA dehydrogenase**

3-hydroxyacyl-CoA dehydrogenase is the third enzyme in the intramitochondrial pathway that is involved in the metabolism of fatty acids (fatty acid  $\beta$ -oxidation). Recent interest has focused on inhibition of fatty acid oxidation as a way to protect the ischemic heart.

### **Carnitine palmitoyl transferase-1 (CPT-1) and carnitine-acylcarnitine translocase**

Carnitine palmitoyltransferase-1 (CPT-1) and carnitine-acylcarnitine translocase are two important enzymes involved in the mitochondrial uptake of fatty acids. CPT-1 is the rate-limiting enzyme involved in the uptake of fatty acids into the mitochondria. It converts fatty acyl-CoA to fatty acylcarnitine, which is then transported into the mitochondria where it is further metabolized. CPT-1 is a highly regulated enzyme that prevents excess amounts of fatty acids from being taken up into the mitochondria. Carnitine-acylcarnitine translocase is the enzyme responsible for translocating acylcarnitine across the mitochondrial membrane in exchange for carnitine.

### **Cytochrome c oxidase**

Cytochrome c oxidase is a mitochondrial enzyme that has an important role in the electron transport function of mitochondrial respiration. The oxidation of cytochrome c by cytochrome c oxidase is one of the steps that results in electron transport via this pathway. The electron transport chain transfers electrons through a number of different enzyme complexes which catalyze the pumping of protons out of the mitochondrial matrix. These protons can then pass back into the mitochondria via an enzyme called ATP synthase. The downhill electrochemical gradient of this process produces energy that results in the production of ATP from ADP. ATP is a form of chemical energy used in most cellular processes requiring energy.

### **Endothelial nitric oxide synthase**

Nitric oxide synthase is the enzyme responsible for synthesizing nitric oxide. Nitric oxide has received considerable research attention, since it is not only a vasodilator but is also important in numerous other processes, including apoptosis. Nitric oxide synthase present in endothelial cells is an important source of nitric oxide.

### **Fatty acid binding protein (FABP)**

Fatty acid binding protein is an abundant cytoplasmic protein (especially cardiac cells) that binds fatty acids and facilitates their transport to intracellular compartments. One of its functions is to transport fatty acids from the cell membrane to the mitochondria.

### **Fatty acid translocase (FAT)**

Fatty acid translocase (FAT) is a protein found in the plasma membrane of many cells and is thought to be involved in the transport of fatty acids across the membrane and into the cell. It has been suggested that FAT is responsible for a significant portion of fatty acid uptake into the cardiac cell.

### **GLUT4**

GLUT4 is a protein that transports glucose across cell membranes. In insulin-responsive tissues (such as the heart), insulin will cause GLUT4 to be translocated from inside the cell to the plasma membrane, thereby stimulating glucose uptake.

### **Myosin heavy chain**

Myosin heavy chain is a key component of the contractile apparatus of muscle cells and comprises the thick filament of muscle fibers. Sliding of myosin by actin (another major structure of contractile proteins) is an important step in muscle contraction.

**Oxygen radical scavenger enzymes**

Oxygen-derived free radicals are highly reactive compounds that can react with and damage cellular components (lipid membranes, protein, and DNA/RNA). In order to protect the cell from these oxygen-derived free radicals, cells have a number of different oxygen radical scavenger enzymes that are used to neutralize these free radicals.

**Peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ )**

Peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) is a nuclear receptor involved in transcriptional regulation of proteins. PPAR $\alpha$  has many functions, including regulating enzymes involved in the control of fatty acid oxidation in the heart.

**Pyruvate dehydrogenase (PDH)**

Pyruvate dehydrogenase (PDH) is an intramitochondrial complex that converts pyruvate (which primarily originates from glucose or lactate) into acetyl-CoA. PDH is the rate-limiting enzyme for the mitochondrial metabolism of carbohydrates. Maintaining mitochondrial glucose metabolism is an important therapeutic strategy to protect the ischemic heart. Therefore, activating PDH is a potential therapeutic approach to treating ischemic heart disease.

**Strain measured by MRI**

Magnetic resonance imaging is a sophisticated technique that produces high-quality images of the body. Newer MRI techniques allow for high resolution of the heart structure and chamber dimensions. Strain measured by MRI is an approach to investigate heart function and wall tension.