Contents

What's new in angina pectoris?

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The characteristics of the clinical syndrome chronic stable angina pectoris is very well known. Epidemiological data show that a very large number of persons are afflicted [1], especially in western societies. Risk factors for developing coronary artery disease [2] and, once angina pectoris is present, for development of cardiac events, have been well documented [3]. For the diagnosis of coronary artery disease quite a few diagnostic tests are available, both invasive and noninvasive. The noninvasive tests are in general based on demonstration of ECG, wall motion, and perfusion abnormalities and all have their merits in terms of diagnostic accuracy and cost effectiveness [4]. Although angiography as gold standard for the diagnosis of coronary artery disease can be debated, it is still the method of choice when considering bypass surgery (CABG) or a percutaneous intervention (PCI) in a patient.

In general, treatment principles are simple: apart from preventive therapy and lifestyle modification, chronic stable angina patients are treated with pharmacological agents that reduce the supply-demand imbalance and thereby reduce symptoms and improve quality of life. If patients have symptoms despite pharmacological therapy, revascularization may be performed. Finally, prognosis is well known. Not surprisingly, many excellent reviews and guidelines are available in the literature [5, 6].

So, if there is nothing new, why devote an issue of *Heart and Metabolism* to this subject? First of all, let's think about the term chronic stable angina. My opinion is that chronic stable angina is not a stable disease: data show that annual mortality is 1.6% to 3.2% [3]. Apart from these mortality figures, a multiple of this number of patients is admitted to hospital because of complications like infarction, unstable angina, urgent revascularization, progression to heart failure, etc. Therefore, this is not a stable disease affecting a substantial portion of patients. Second, it has major socioeconomic effects: because the general population gets older, it is to be expected that the total number of coronary artery disease patients will increase rapidly. Medication will be life-long, and the number of patients undergoing re-PCIs or CABG ''redos'' will increase. In this respect, a previous issue of *Heart and Metabolism* was devoted to ''focus on the elderly''[7]. It is worthwhile reading it again (also available at www.heartandmetabolism.org). Another worrying aspect is refractory angina, defined as severe disabling angina in spite of optimal medical therapy, where revascularization is not feasible. In Issue 16 of *Heart and Metabolism* (Refractory angina) M.R. Chester states in his summary: all the available evidence indicates that the size of the chronic refractory angina population will grow inexorably to present a major clinical problem within a decade [8]. In summary, these are reasons enough to discuss some clinical problems associated with angina pectoris.

The nature of ischemic pain perception is not well known by clinicians, and Filippo Crea explains very clearly in the Basic Article the various components of pain perception. An important issue on the management of stable angina pectoris is discussed by Mario Marzilli in the Main Clinical Article. In view of the fact that we have accurate techniques available to detect the impact of the ischemia on the heart and also that stable angina is associated with significant mortality and morbidity, it no longer suffices to treat all angina patients in a similar manner. An important

issue is risk stratification: to stratify patients into those with a high and a low risk for future coronary events. Needless to say high-risk patients need more aggressive management than low-risk patients.

One of the fascinating new developments is the noninvasive imaging of the coronary arteries. Nico Mollet and coworkers will show in the Imaging section the potential of CT imaging for this purpose. In the Refresher Corner a similar topic is discussed by Gerald Werner: the collateral circulation. I had the feeling that collateral circulation was something everybody talked about, but nobody knew what it really was. Using new techniques, collateral circulation can now be quantified, which opens the way to further understanding and possibly to new therapeutic interventions.

In New Therapeutic Approaches Pieter van Zwieten discusses the fine-tuning of current pharmacotherapy for the treatment of angina and shows the potential advantages of drugs other than β-blockers, calcium-antagonists, and nitrates. In Focus on Vastarel, G Rosano elaborates on the safety of antianginal drugs in combination with phosphodiesterase type 5 (PDE5) inhibitors, indicating that switching from nitrates to trimetazidine is safe in patients with coronary artery disease requiring treatment with PDE5-inhibitors. Finally, not everything is coronary artery disease related. We present in the Case Report a patient with ECG changes and LV dysfunction due to cerebral bleeding.

In short, this issue presents many new aspects on chronic stable angina pectoris. Enjoy reading. ■

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Molecular mechanisms of cardiac ischemic pain

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Abstract

At the turn of the last century, Colbeck proposed that ischemic cardiac pain might be related to distention of the ventricular wall (the 'mechanical hypothesis'). Three decades later, Lewis hypothesized that ischemic pain might be elicited by the intramyocardial release of pain-producing substances induced by ischemia ('chemical hypothesis'). Studies carried out in the past 10 years have given strong support to the chemical hypothesis, as they have consistently shown that adenosine is a mediator of ischemic cardiac pain. Adenosine-induced ischemic cardiac pain is mainly mediated by stimulation of A_1 receptors located in cardiac nerve endings and is potentiated by substance P. Conversely, the magnitude and rate of left ventricular dilatation during ischemia do not predict the severity of angina. It is worth noting, however, that stretching of epicardial coronary arteries may cause angina in the absence of myocardial ischemia.
■ *Heart Metab.* 2004;24:5–7.

Keywords: Angina pectoris, adenosine, myocardial ischemia, substance P, theophylline

Causes of angina

At the turn of the last century, Colbeck [1] proposed that ischemic cardiac pain might be related to distention of the ventricular wall (the 'mechanical hypothesis'). Three decades later, Lewis [2] hypothesized that ischemic pain might be elicited by the intramyocardial release of algogenic substances induced by ischemia ('chemical hypothesis'). However, only in the past 10 years have several clinical investigations contributed to clarification of the causes of angina.

Mechanical hypothesis

The negligible importance of mechanical distortion and distention of ventricular fibers in the genesis of angina is supported by the observation that ventricular dilatation, such as occurs during acute ventricular failure, myocardial biopsy, or valvuloplasty, does not tend to cause any painful sensation [3].

Mechanical factors, however, may play a part in the activation of sensory receptors localized at the periarterial level. This mechanism of cardiac pain may explain the localized chest pain frequently experienced by patients after successful stent implantation in the absence of myocardial ischemia [4–6].

Chemical hypothesis: the central role of adenosine

In the mid 1980s, Sylven et al observed that, during the infusion of adenosine, patients without evidence of coronary artery disease often complained of a short-lasting chest pain with features similar to those of anginal pain. As adenosine is rapidly formed during myocardial ischemia and released into the vascular bed [7], they hypothesized that adenosine could be a mediator of cardiac ischemic pain, and they tested this hypothesis by assessing the effects of intravenous boluses of increasing doses of adenosine in healthy volunteers [8]. Crea et al [9] showed subsequently that, in patients with chronic stable angina, intracoronary infusion of adenosine consistently caused pain with features identical to those experienced during daily-life episodes of transient

myocardial ischemia, but in the absence of detectable signs of myocardial ischemia. Infusion of a similar dose of adenosine into the right atrium failed to elicit pain, thus proving that the pain elicited by the intracoronary infusion of adenosine originated from the heart.

Adenosine-induced cardiac pain is not secondary to myocardial ischemia, as it typically occurs in the absence of ischemic-like electrocardiographic changes and can be elicited by infusing adenosine into angiographically normal coronary branches and into vascular beds, such as those supplied by the brachial or the femoral arteries, where steal-induced ischemia cannot occur [9–12]. Of note, the pain caused by adenosine does not appear to be related to the mechanical distention of periarteriolar nerve endings, as the infusion of nifedipine or papaverine, which produce a comparable degree of vasodilatation, do not cause pain [13]. Furthermore, adenosine causes pain at doses larger than those provoking maximal vasodilatation [9]. In patients with exercise-induced angina, the severity of the anginal pain is significantly reduced by pretreatment with theophylline, a potent nonselective antagonist of adenosine P_1 receptors, in the presence of a similar degree of myocardial ischemia, thus suggesting that endogenous adenosine is, at least partially, responsible for the anginal pain [9]. Furthermore, theophylline reduces forearm ischemic pain [14], an effect that can not be mediated by improvement of an adenosine-induced steal phenomenon [15].

Taken together, these observations support the hypothesis that adenosine is an adequate stimulus for cardiac sensory receptors and that endogenous adenosine is a mediator, the first hitherto identified in man, of cardiac and muscular ischemic pain. Adenosine-induced pain does not appear to be influenced by β-blockade, atropine, naloxone, nitroglycerin, nifedipine, clonidine, cyclo-oxygenase inhibitors, and steroids, whereas it is increased by systemic pretreatment with nicotine, probably because of a central modulation of pain perception [16–19]. Recently, Gaspardone et al [20] have shown that, in man, the intra-arterial and intracoronary infusion of substance P, a polypeptide present in perivascular nerves and involved in the generation of neurogenic inflammation and in the mechanism of hyperalgesia, does not cause muscular or cardiac pain, yet it enhances adenosine-induced pain.

Receptors mediating the algogenic effects of adenosine

The cardiac effects of adenosine are caused by the stimulation of at least two subtypes (A_1 and A_2) of surface membrane P_1 receptors [21–23]. The stimulation of A_1 receptors, present in cardiomyocytes and perivascular sympathetic nerves [23,24], causes electrophysiological effects [25] and inhibits the neuronal release of catecholamines [23]. The stimulation of A_2 receptors, present in endothelial and vascular smooth muscle cells, causes coronary vasodilatation [26–29].

The identification of the receptor subtype involved in the genesis of adenosine-induced pain has been investigated with the use of bamiphylline [30]. In crude synaptic membranes prepared from rat brain, bamiphylline displaced radioligands from A_1 adenosine receptors, with a potency similar to that of 8-phenyl-theophylline; in contrast, it showed a negligible potency on A_2 adenosine receptors. This results in a high degree of A_1 receptor selectivity [31]. In humans, Pappagallo et al [32] found that bamiphylline reduced the pain induced by intradermal injection of adenosine, but not the A_2-receptor-mediated adenosine-induced cutaneous hyperemia, thus suggesting that A_1 receptors are involved in cutaneous nociception. In agreement with this, Gaspardone et al [33] subsequently found that the intravenous infusion of bamiphylline reduced adenosine-induced muscular and cardiac pain, but did not affect adenosine-induced coronary vasodilatation. Similarly, it has been confirmed that N-0861 (*N*6-endonorboran-2-yl-9-methyladenine), a selective A_1 adenosine antagonist, at a dose that blocks A_1-mediated electrophysiologic but not A_2-mediated vasodilatory effects of adenosine, reduces the pain caused by intravenous administration of adenosine [34]. Finally, in patients with exercise-induced angina, bamiphylline reduced the severity of anginal pain normalized for the maximal ST-segment depression, thus suggesting that, in man, the algogenic effects of endogenous adenosine also are mainly mediated by A_1-receptors [35].■

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Risk stratification in chronic stable angina

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Abstract

To improve the cost-benefit ratio, intensity of diagnostic and treatment strategies should be related to individual patient's risk level. History, physical examination, and resting ECG allow an estimation of the probability of coronary heart disease in most patients. Left ventricular function, stress testing, and imaging studies allow adequate risk stratification and assessment of treatment. Myocardial perfusion scanning identifies silent ischemia and extension of the area at risk before and after coronary revascularization. For imaging of the coronary lumen, angiography remains the technique of choice. Recurrence of pain after revascularization is an indication to repeat angiography.
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Keywords: Risk stratification, stable angina, stress testing, imaging studies, coronary angiography, guidelines

Introduction

Since the Framingham Heart Study, algorithms have been developed to stratify patients in low, intermediate, and high risk categories in order to relate the intensity of diagnostic and treatment strategies to risk category [1–2].

Changes in population risk profile and identification of novel risk factors, in addition to documentation of new preventive measures, all necessitate a continuous update of diagnostic and therapeutic procedures. Consequently, testing algorithms and guidelines are continuously being refined on the basis of new research [3–4].

Diagnosis of angina pectoris

A detailed history, focused physical examination, and risk factor assessment provide the clinician with an estimate of the probability of coronary heart disease [5].

If the diagnosis remains uncertain, exercise testing should be performed. Interpretation of the exercise test includes symptomatic response, exercise capacity, hemodynamic response, and ECG response. In patients who are unable to exercise or present with abnormalities in the resting ECG, an echocardiographic or nuclear stress imaging study is recommended [6–7].

For imaging the coronary artery lumen, coronary angiography remains the most accurate technique.

Risk stratification

The prognosis of patients with chronic stable angina and a normal resting ECG and low clinical risk for severe coronary artery disease is excellent.

Clinical parameters that are independent predictors of three-vessel disease or left main coronary artery disease include age and sex, typical angina, diabetes, and previous myocardial infarction. A 5-point cardiac risk score has been developed that is based on these parameters, and patients found to be at a high likelihood of severe disease may be directly referred for angiography.

Other clinical parameters relevant to prognosis include history of hypertension, hypercholesterolemia, smoking, and peripheral arterial disease.

Patients with chronic stable angina with resting ECG abnormalities, or cardiomegaly or pulmonary

venous congestion on chest X-ray are at greater risk.

Left ventricular function

Left ventricular global systolic function and volumes are important prognostic factors in patients with cardiac disease, including those with chronic stable angina. Left ventricular ejection fraction is an important measure of left ventricular systolic function, and can be obtained with echocardiography or radionuclide imaging.

In patients with chronic stable angina and with previous myocardial infarction, assessment of systolic and diastolic left ventricular function becomes relevant to the choice of appropriate treatment and in making recommendations about lifestyle, work activity, etc [5].

In patients with signs or symptoms of heart failure, cardiac imaging is necessary to identify the mechanism of the cardiac disease and determine the most appropriate therapy.

Stress testing for risk stratification and prognosis

Maximum exercise capacity remains one of the strongest and most consistent prognostic markers and may be measured as maximal exercise duration, maximum metabolic equivalent of task units achieved, maximum workload achieved, maximum heart rate, and double product [6].

Exercise-induced ST-segment depression or elevation summarize the prognostic information related to ischemia. Other variables, including angina, number of leads with ST-segment shift, pattern of ST-segment shift, and time to recovery of ST-segment deviation, are less powerful prognostic indicators [6].

A patient's performance and ECG changes may be combined to calculate risk and predict mortality. Annual cardiac mortality is predicted by the Duke Treadmill Score: [exercise time in minutes (5 times the ST-segment deviation in millimeters)] minus (4 times the angina index), where the angina index is: 0 for no angina, 1 for angina, and 2 if angina is the reason for stopping the test). Patients with a predicted mortality rate $\leqslant 1\%$ can be managed medically; those with a risk $\geqslant 3\%$ should be referred for cardiac catheterization. Patients with intermediate risk should undergo either cardiac catheterization or an imaging study.

The standard treadmill ECG remains the best choice for coronary risk stratification in men with normal resting ECG and capable of exercise. A normal stress echocardiogram in patients with known or suspected coronary heart disease confers a favorable prognosis. In patients with an intermediate risk, myocardial perfusion imaging appears to be of value for further risk stratification [6].

Imaging studies for risk stratification

The exercise test remains the most appropriate test for risk stratification and assessment of treatment in patients with chronic stable angina. It provides useful information on patient symptoms, cardiovascular function, and hemodynamic response during daily activity.

In patients who cannot exercise adequately, various types of pharmacological stress combined with imaging techniques are available.

Myocardial perfusion imaging

Stress myocardial perfusion single-photon emission computed tomography (SPECT), or myocardial perfusion scan, provide clinically useful information in patients with a high pre-test likelihood of coronary artery disease [7–9].

A normal stress thallium test is associated with a rate of cardiac death and myocardial infarction of 0.5% to 0.9% per year, which is close to that of the general population, even in patients with known coronary artery disease. In patients with a normal thallium stress test, the likelihood of significant coronary artery disease is so low that coronary angiography is not indicated unless the patients has a high Duke Treadmill Score.

Rates of cardiac death and myocardial infarction increase significantly with worsening scan abnormalities, particularly in the setting of severely abnormal scans. Other scintigraphic findings predictive of adverse events include cavity dilatation, ejection fraction and end-systolic and end-diastolic volumes, and post-stress myocardial stunning. Patients with severe perfusion defects and low ejection fraction are at greatest risk for subsequent events [10–11].

Stress echocardiography

Stress echocardiography is routinely used for the diagnosis of coronary heart disease in patients with angina, and is a sensitive and specific alternative to stress thallium for detecting inducible myocardial ischemia and for risk stratification [12]. The annual cardiac event rate increases as a function of the extent and severity of abnormal contractile response during stress, expressed as wall motion score index (WMSI) [13]. A normal contractile response (peak WMSI = 1.0) is associated with a favorable prognosis (0.9% per year), whereas mild-to-moderate dysfunc-

tion (peak WMSI = 1.1–1.7) and severe dysfunction (peak WMSI greater than 1.7) are associated with increasing rates of cardiac events (3.1% per year and 5.2% per year, respectively). The prognostic value of ejection fraction is additive to WMSI (*Figure 1*), ejection fractions less than 45% being associated with a high cardiac event rate, even in patients with mild contractile dysfunction during stress. A peak WMSI greater than 1.7 associated with ejection fractions less than 45% identifies patients at greatest risk of adverse events. The prognostic value of WMSI and ejection fraction are also confirmed by data on cumulative survival at 40 months (*Figures 2, 3*).

In low-risk patients, risk factor modification may be an adequate approach to therapy. High-risk patients should be referred for cardiac catheterization and potential coronary revascularization. In patients at intermediate risk, aggressive risk factor modification may be cost-effective and referral to catheterization may be reserved for those with refractory symptoms [14].

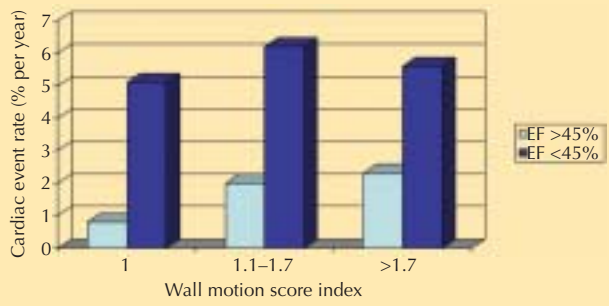

Figure 1. Wall motion score index and ejection fraction (EF) are independent predictors of cardiac events in patients with known or suspected ischemic heart disease. (Adapted from Yao et al [13], with permission.)

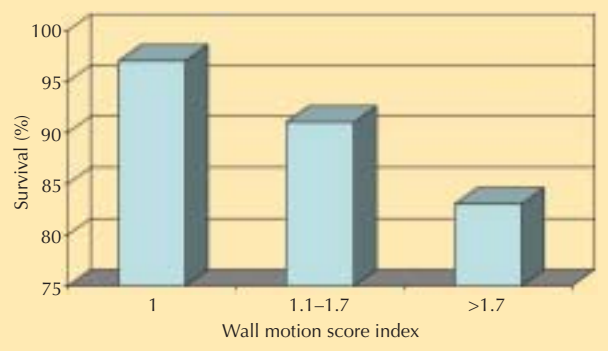

Figure 2. Cumulative survival at 40 months as a function of wall motion score index. (Adapted from Yao et al [13], with permission.)

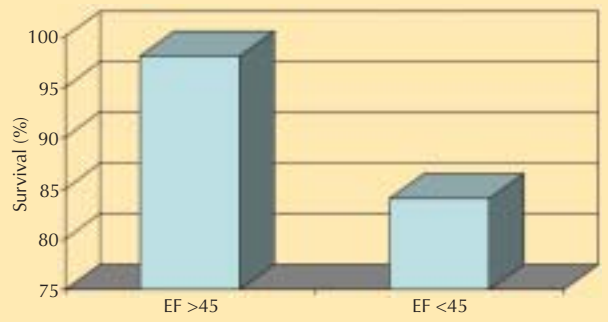

Fig.3 Cumulative survival at 40 months as a function of ejection fraction (EF). (Adapted from Yao et al [13], with permission.)

Invasive testing for risk stratification

Patients identified as being at increased risk on the basis of clinical evaluation and noninvasive testing are generally referred for coronary angiography.

Coronary angiography is not a reliable indicator of the functional significance of a coronary stenosis and does not allow prediction of which coronary lesion will eventually cause an acute coronary event. Conversely, the extent and severity of coronary disease and left ventricular dysfunction are powerful predictors of long-term patient outcome. Several prognostic indexes based on coronary angiography have been proposed, the most popular being classification as 1-, 2-, or 3-vessel, or left main coronary artery disease.

Catheterization laboratory derived measures of the severity of coronary stenosis show a good relationship with myocardial perfusion imaging in the population with single-vessel disease [15–17], but the comparability of the two approaches is low in multivessel disease, for which nuclear or echocardiographic techniques retain higher prognostic power [18–19].

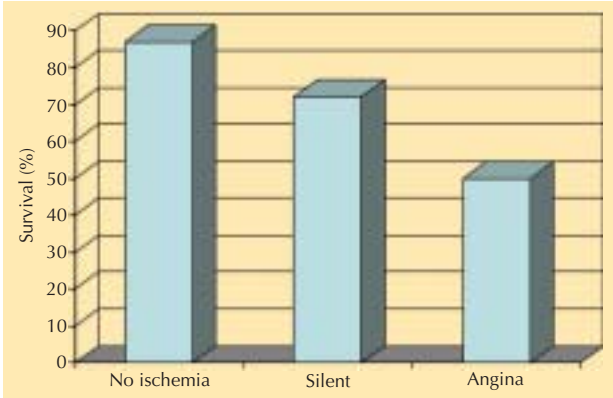

Figure 4. Event-free survival after percutaneous coronary intervention as a function of symptoms. (Adapted from Krone et al [21], with permission.)

Risk stratification after coronary revascularization

In asymptomatic patients, routine stress testing for risk stratification is not useful and may be harmful [20–21]. However, coronary atherosclerosis is a progressive disease, and recurrent cardiac events are to be expected even after a successful procedure.

Recurrence of chest pain within 6 months after coronary revascularization constitutes an indication to repeat coronary angiography (*Figure 4*). When angina recurs after the time interval of possible restenosis, the exercise stress test regains its diagnostic and prognostic role.

Myocardial perfusion scanning can enable diagnosis of silent ischemia and differentiation between restenosis and progression of disease in remote areas [22]. Patients with a large ischemic region or symptomatic ischemia, or both, have the greatest rate of subsequent events, whereas a smaller ischemic area, as frequently found in silent ischemia, is associated with a lower event rate (*Figure 4*). ■

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Imaging the coronary vasculature using multislice computed tomography

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Abstract

Current multislice computed tomography technology allows noninvasive evaluation of coronary lumen and plaques in selected patients in sinus rhythm able to breath-hold for 20 seconds. Sensitivity and specificity of about 90% have been reported for detection of significant obstructive stenoses, and results for detection of coronary plaques, and their classification as soft, fibrous, or calcified, are promising. With introduction of new-generation, faster-rotating MSCT scanners equipped with more detector rows, this technique should mature into a noninvasive diagnostic tool for evaluating coronary artery disease in wider patient populations.

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Keywords: Multislice computed tomography, noninvasive coronary imaging, atherosclerosis, coronary plaques

Introduction

Multislice computed tomography (MSCT) is developing rapidly. First generation four-row MSCT scanners were introduced in the late 1990s and have brought promising results, but image quality of the small and rapidly moving coronary arteries was inadequate in a significant number of imaged vessels [1–4]. Current 16-row MSCT scanners have increased temporal and spatial resolution, allowing more reliable evaluation of both coronary lumen and plaques, and left ventricular function can also be easily evaluated from the same scan. Here we summarize the technique and diagnostic performance of this imaging method.

Technique of MSCT coronary angiography

Current state-of-the-art MSCT scanners are equipped with 16 detector rows. The entire heart can be scanned within a single breath-hold of about 20 seconds, which is a manageable for practically all patients. Little iodinated contrast material (100 mL, injected at 4 mL/s) is needed to perform the scan. The ECG is recorded during the scan and used, retrospectively, to reconstruct images during the mid-to-end diastolic cardiac phase when least motion of the heart is present. This retrospective gating technique 'freezes' the contraction of the heart and allows flexibility in the position of reconstruction windows to diminish artefacts related to rapid coronary motion and premature beats. Current MSCT scanners have a temporal resolution that allows reconstruction of nearly motion-free images in patients with a regular, slow heart rate (below 70 beats/min); in the absence of contraindications, patients presenting with faster heart rates receive oral or intravenous β-blockers to reduce the heart rate, thereby improving image quality.

The high radiation exposure during MSCT coronary angiography, reported as between 6.7 and 13.0 mSv [5–8], is a matter of concern. Development of radiation sparing techniques such as prospective x-ray tube modulation (reducing the radiation exposure by nearly 50% in patients with low heart rates [5,8]) is highly desirable.

Diagnostic performance of MSCT coronary angiography

Results with first-generation four-row MSCT scanners in detecting significant coronary stenoses (*Table I*) are promising in comparison with conventional angiography [1–4]. However, these were obtained after exclusion of approximately 30% of imaged vessels from analysis, because of insufficient image quality. Current-generation 16-row MSCT scanners have increased temporal and spatial resolution that give greater diagnostic performance in evaluating coronary stenoses (*Figures 1, 2*). In all currently available studies, oral β-blockers were administered to patients with heart rates above 60 or 65 beats/min, and sensitivity and specificity around 90% were reported [9–11]. The number of vessels with low image quality ranged between 7% and 12%, but two studies yielded a high diagnostic accuracy despite including these vessels (*Table I*) [9,11]. These results indicate that MSCT coronary angiography can be a viable alternative for conventional angiography in selected patients in sinus rhythm, with low heart rates, able to breath-hold for 20 seconds. Patients with irregular or faster ($\geqslant$70 beats/min) heart rates (which cause motion artefacts on the MSCT scan) and those with extensive coronary calcifications (which cause artefactual blooming masking the coronary lumen) are less suitable candidates. Some investigators perform a low-dose, nonenhanced calcium scoring scan before the contrast-enhanced computed tomography (CT) angiography scan, to exclude patients with an unfavorably high coronary calcium load [12].

Functional parameters derived from MSCT coronary angiography

Important functional parameters regarding left ventricular performance can be extracted from the angiography scan. Studies comparing results of MSCT coronary angiography with those of biplane conventional angiography, magnetic resonance imaging, or two-dimensional echocardiography found good correlation between the ejection fraction and volumes from both techniques [13–15]. However, MSCT is a less reliable technique for evaluating regional wall motion abnormalities, because of limited temporal resolution [15]. Furthermore, β-blockers, often used before the MSCT angiography scan, can negatively affect left ventricular performance.

MSCT coronary plaque imaging

MSCT coronary angiography allows evaluation of both the coronary lumen and coronary plaques (*Figure 2*). Even plaques without encroachment of the coronary lumen from compensatory outward

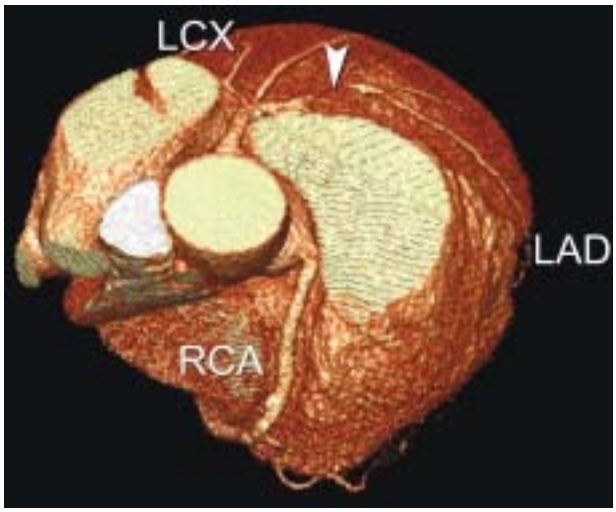

Figure 1. Volume-rendered computed tomography image: 3-dimensional overview of the coronary arteries. Arrowhead: presence of a significant obstructive coronary lesion located in the left anterior descending coronary artery (LAD). LCX, left circumflex coronary artery; RCA, right coronary artery.

Table 1. Studies comparing 4-row and 16-row multislice computed tomography (MSCT) coronary angiography scanners.

Study	n	Excluded (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
4-row scanner						
Nieman et al [1]	31	27	81	97	81	97
Achenbach et al [2]	64	32	85	76	56	94
Knez et al [3]	44	6	78	98	84	96
Vogl et al [4]	38	19	75	99	92	98
16-row scanner						
Nieman et al [9]	58	0[a]	95	86	80	97
Ropers et al [10]	77	12	92	93	79	97
Mollet et al [11]	128	0[a]	92	95	79	98

n, number of patients; PPV, positive predictive value; NPV, negative predictive value. [a]Nieman et al and Mollet et al reported that 7% of the coronary vessels had low image quality, but included these vessels in the analysis for the diagnostic performance of MSCT coronary angiography.

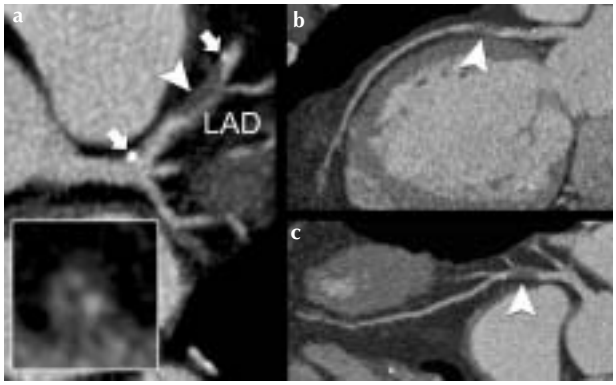

Figure 2. (a) Maximum intensity projected and (b, c) curved multiplanar reconstructed computed tomography images, confirming the presence of the coronary lesion in the left anterior descending coronary artery (LAD) (arrowhead), and providing information regarding both the coronary lumen and the underlying plaque. Clearly visualized: noncalcified plaque (gray) at the level of the coronary lesion has two small calcified plaques (arrows) proximal and distal to it. Inset: Cross-sectional image at the level of the noncalcified plaque, providing more detailed information of the coronary lumen and adjacent noncalcified plaque tissue.

remodeling of the coronary vessel ('positive remodeling') can be detected, and the different plaques can be classified as noncalcified, calcified, and mixed [16–22].

Two published studies compared the diagnostic performances of 16-row MSCT coronary angiography and of intravascular ultrasound, for detection of plaques. They reported sensitivities of 82% and 86% for detection of any plaque, and specificities of 88% and 92% [16,18]. However, lower sensitivity was found for detection of noncalcified plaques, one study reporting a sensitivity of only 53% [16].

Schroeder et al [20] were the first to compare intravascular ultrasound and MSCT; they reported that noncalcified coronary plaques can be further classified as soft or fibrous, on the basis of CT density measurements. These findings were confirmed in ex-vivo and in-vivo studies comparing results of CT density measurements with those of histopathology or intravascular ultrasound [18,21,22], and may have important implications for the identification of high-risk coronary plaques. For instance, Leber et al [23] found significantly more noncalcified plaques in patients with an acute coronary syndrome than in stable patients. However, there is overlap between the range of CT density measurements in soft and fibrous plaques, probably related to the mixture of both tissue components within a single plaque.

Current MSCT technology allows assessment of the extent, severity, and localization of coronary plaques, and classification of plaque tissue components as non-calcified, mixed, and calcified. This might permit more advanced risk stratification by noninvasive assessment of the coronary plaque burden. We evaluated the coronary plaque burden in 40 patients with stable angina pectoris (current research), and found plaques in nearly 60% of all coronary segments $\geqslant$2 mm and more than six plaques per patient. Plaque composition was: calcified in 62%, noncalcified in 27%, and mixed in 11%; plaques were predominantly located in proximal and mid parts of the main coronary vessels.

It is noteworthy that the spatial resolution of 16-row MSCT scanners allows detection only of advanced coronary plaques; earlier phases of atherosclerosis remain undetected [18]. Therefore, evaluation of the coronary plaques using MSCT coronary angiography will still underestimate the coronary plaque burden when compared with histopathological findings. ■

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New developments in the drug treatment of stable angina pectoris

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Abstract

Stable angina pectoris is treated pharmacologically and by means of revascularization techniques (percutaneous coronary intervention, coronary artery bypass grafting). Classical antianginal drugs, such as nitrates, β-blockers, and calcium antagonists, owe their beneficial actions predominantly to hemodynamic effects, which are aimed at correcting the imbalance between myocardial oxygen supply and consumption. In addition, patients with angina usually receive acetylsalicylic acid and statins. This review deals with new developments in drug treatment, such as: β-blockers with a vasodilator component; newer calcium antagonists; nicorandil (a combined K^+ channel opener and nitrate); bradycardic agents; metabolic drugs, such as trimetazidine, that optimize oxygen utilization and favor glucose oxidation at the expense of impaired fatty acid oxidation. Trimetazidine is free of relevant hemodynamic actions.

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Keywords: Antianginal agents, nicorandil, bradycardic agents (ivabradine), metabolic therapy, trimetazidine

Introduction

Chronic stable angina pectoris has a relatively benign prognosis, with an average annual mortality of 2% to 3% [1,2]. Stable angina pectoris is traditionally treated by drugs, which improve symptoms and quality of life, but drug treatment has not been shown to reduce mortality or the incidence of myocardial infarction [1,2]. Revascularization techniques, such as percutaneous coronary intervention or coronary artery bypass surgery (CABG), have been introduced and were found to enrich the therapeutic management of angina pectoris. Although these procedures offer a more causative approach for the correction of the myocardial ischemia, they are associated with a greater risk than treatment with classical antianginal drugs [1].

Taken together, both drug treatment and revascularization procedures should be considered as a balanced approach in the management of angina pectoris, depending upon the detailed characteristics of the individual patient.

This review deals with the newer approaches in the drug treatment of angina pectoris. Unstable angina pectoris requires a different and more aggressive management, involving both medical and interventional treatment, and is not discussed here.

New approaches concerning classical antianginal agents

Nitrates

Nitroglycerin and isosorbide continue to be the classical nitrates used in the acute management of angina pectoris. In spite of vast investment in research, genuine innovation in this field has not been achieved. Several new galenic preparations of

these classical drugs have been introduced, such as sprays, ointments, etc. Some of these new preparations may offer some pharmacokinetic advantages, although such advantages are probably not substantial and not supported by appropriate clinical studies. They have been reviewed by Parker and Parker [3].

It goes without saying that the mode of action of the nitrates, discovered about a decade ago, must be considered to be a highly relevant innovation: in vivo, the nitrates release nitric oxide, which brings about the vasodilator action. The enhanced release of nitric oxide from the drugs is endothelium-independent and therefore persists in conditions of endothelial dysfunction/damage, as in coronary artery disease. Attempts have been made to develop new molecules that also release nitric oxide. Molsidomine is an example of such agents, and the anti-anginal activity of this nitric oxide donor has been demonstrated, although the position of this drug in the management of angina pectoris is not fully established [4].

β-Blockers

Since their introduction in the 1960s, several new β-blockers have been introduced, with the aim of improving their efficacy and tolerability. However, genuine innovation has not really been achieved. Current recommendations are that a selective β-blocker with a sufficiently long duration of action should be used, allowing once-daily administration.

Several β-blockers would fulfill these criteria. In clinical practice, metoprolol, atenolol, or bisoprolol are frequently used for the long-term treatment of angina pectoris [2].

Because a reduction in heart rate is one of the most relevant mechanisms explaining the beneficial effect of β-blockers, those that possess intrinsic sympathomimetic activity (oxprenolol, pindolol) should not be used in the treatment of angina pectoris, as they do not, or barely, reduce heart rate.

A new tendency in the development of β-blockers deserves mention here. On theoretical grounds, it would be desirable to combine β-adrenoceptor blockade with peripheral arterial vasodilatation, to reduce both heart rate and cardiac afterload. Indeed, a few β-blockers with vasodilator activity have been introduced, such as carvedilol, celiprolol, labetalol, and nebivolol. However, the vasodilator component of these agents is much weaker than their β-adrenoceptor antagonistic activity. For this reason, the relevance of the vasodilatation caused by these β-blockers remains uncertain, and does not justify their being preferred agents in the treatment of angina pectoris.

Calcium antagonists

As regards the long-term treatment of angina pectoris, little innovation has occurred in the field of calcium antagonists. For most of the classical calcium antagonists of the various subtypes (verapamil, diltiazem, nifedipine, and related compounds), retarded slow-release preparations have been developed, in order to improve the usually poor pharmacokinetic profile of these agents. Accordingly, the action of these drugs develops more slowly, which has the additional benefit that the problem of reflex tachycardia with dihydropyridine-type calcium antagonists is avoided. In addition, retarded preparations allow once-daily administration [5]. Nifedipine-gastrointestinal therapeutic system (nifedipine-GITS) is an elegant example of a retarded preparation that has the kinetic advantages mentioned above. Genuinely new calcium antagonists aiming at the long-term treatment of angina pectoris have not been introduced in recent years.

Nicorandil

Nicorandil, a nicotinamide ester, displays a dual mechanism of action. The drug opens up ATP-sensitive K^+ channels, thereby causing dilatation of peripheral and coronary resistant arterioles [6]. In addition, it contains an NO_2-moiety, which dilates systemic veins and epicardial coronary arteries (*Figure 1*). Accordingly, nicorandil decreases cardiac preload and afterload, and it increases coronary blood flow. Its antianginal activity and safety profile somehow resemble a combination of those of oral nitrates, β-blockers, and calcium antagonists. The ability of nicorandil to relieve symptoms of ischemia is well documented, although its position in regimens for the treatment for angina pectoris remains to be established.

It has recently been claimed, in the Impact Of Nicorandil in Angina (IONA) Study, that nicorandil,

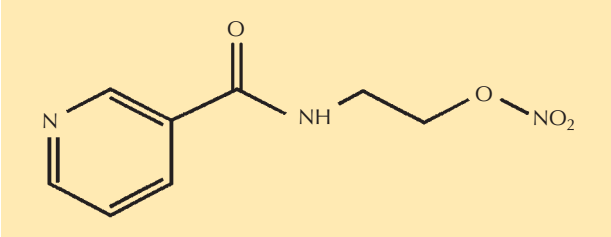

Figure 1. Chemical structure of the anti-ischemic/anti-anginal agent, nicorandil. Nicorandil opens ATP-sensitive K^+ channels, but is also a nitrate, as indicated by the NO_2-moiety in its molecule.

in addition to providing symptom relief, possesses cardioprotective activities [7]. Accordingly, patients with angina pectoris received standard antianginal treatment, and either nicorandil (20 mg twice daily) or placebo was added in a random design. Nicorandil appeared to decrease the composite end-point of death from coronary heart disease, nonfatal myocardial infarction, and unstable angina by 21%. Total mortality remained unchanged. The findings of the IONA Study strongly suggest that the cardioprotective and clinical benefits were elicited by the activation of mitochondrial K^+-ATP channels.

It has been suggested by the IONA Study investigators that nicorandil acts as a pharmacological mimetic of the phenomenon of ischemic preconditioning, which also involves the opening of mitochondrial K^+-ATP channels [8]. Consequently, both clinical observations and more fundamental mechanistic factors indicate that nicorandil deserves further evaluation of its cardioprotective activity in patients with stable angina pectoris.

Bradycardic agents

Increased heart rate is well known as an important cardiac risk factor and, more specifically, as a determinant challenge for angina pectoris attacks in patients with myocardial ischemia. Conversely, a reduction in heart rate, and in particular, reduction of an increased heart rate, appears to be a useful therapeutic approach. The antianginal actions of β-blockers and of verapamil-type calcium antagonists are well documented, and largely explained by a reduction in heart rate. Efforts to develop specific bradycardic drugs that act through mechanisms other than β-adrenoceptor blockade or L-type calcium antagonism have been in progress for at least two decades. Attempts were made to achieve bradycardic activity by manipulating particular Ca^{2+} or K^+ channels, or both. However, most of the compounds discovered, such as alinidine, falipamil, and zatebradine, were rejected, for a variety of reasons [9].

Ivabradine is a new heart rate-decreasing agent that selectively inhibits the primary pacemaker I_f current (or funny current) in the sinus node. The I_f current is a mixed Na^+/K^+ inward current that is activated by hyperpolarization, thus reducing heart rate at rest and during exercise, in experimental animals and in healthy volunteers [10,11]. Its bradycardic action does not involve β-adrenoceptors or L-type calcium channel blockade. The anti-ischemic activity of this agent was recently demonstrated in patients with stable angina pectoris, who received either ivabradine or placebo in addition to their standard anginal medication [12]. The reduction in heart rate caused by ivabradine appeared to be accompanied by improved exercise tolerance. Withdrawal of ivabradine after treatment for several months caused significant deterioration when the group were compared with patients who continued to receive the drug. The findings of that study indicate that ivabradine could be a valuable alternative to current treatments for angina pectoris [12].

Metabolic therapy

As discussed in the preceding paragraphs, the classical interventions in the management of ischemic heart disease/angina pectoris are aimed at improving the imbalance between myocardial oxygen supply and demand, via hemodynamic procedures. A new approach to treating ischemia/angina pectoris involves improving the efficiency of oxygen utilization by the cardiac tissues.

Several biochemically based approaches to bring about improved oxygen utilization can be envisaged, such as inhibition of tumor necrosis factor (TNF) β activity or its release by appropriate antagonists [13], inhibition of Na^+/H^+ exchange by cariporide (HOE 642) and other inhibitors [14,15], and inhibition of fatty acid oxidation and stimulation of glucose oxidation, by trimetazidine and related drugs.

Suppression of the formation or the effects of TNF β has not yet been studied to any significant extent in conditions of ischemic heart disease [13]. The first clinical trial (Guard During Ischemia Against Necrosis) of cariporide in myocardial ischemia provoked by percutaneous coronary intervention or high-risk coronary surgery did not show any protective effect in terms of death or myocardial infarction [14,15].

Trimetazidine

The third of the possible metabolic mechanisms is the only one that, to date, has led to a clinically useful approach to the drug treatment of angina pectoris. Trimetazidine, indeed, appears to be a metabolic agent for the treatment of stable angina pectoris that is largely free of hemodynamic activities. It has repeatedly been discussed and reviewed in *Heart and Metabolism* (see for example [16]). Here, we will refer only to some of its major pharmacologic and clinical characteristics.

Mode of action

Trimetazidine inhibits mitochondrial long-chain 3-keto acyl coenzyme A thiolase, thus favoring glucose oxidation at the expense of fatty acid oxidation,

which is impaired (*Figure 2*). Trimetazidine can thus be classified as an example of a new class of anti-anginal drugs, the 3-keto acyl coenzyme A thiolase inhibitors.

The decrease in fatty acid oxidation and the stimulation of glucose oxidation provoked by trimetazidine improve the coupling between glycolysis and carbohydrate oxidation. Accordingly, ATP production is achieved with consumption of less oxygen. Moreover, trimetazidine stimulates membrane phospholipid turnover during ischemia, thus redirecting fatty acids toward phospholipids. The pharmacology of trimetazidine has been reviewed by Stanley and Marzilli [17].

Clinical effects

The beneficial effects of trimetazidine in the treatment of stable angina pectoris and possible other sequelae of ischemic heart disease have been described in great detail and reviewed several times. We mention here only the most relevant properties of the drug.

Trimetazidine significantly improved symptom-limited exercise in patients with stable angina pectoris when used either as monotherapy or when combined with β-blockers or calcium antagonists. Clinical benefits were also observed in patients with recurrent angina.

Trimetazidine also proved beneficial in patients with angina pectoris with diabetes or congestive heart failure. It is usually well tolerated; in fact better so than nifedipine or propranolol when used as monotherapy in clinical trials with stable angina pectoris. Mild gastrointestinal disorders such as heartburn were the most frequently reported adverse reactions, but their overall incidence was low.

We have mentioned already that trimetazidine is free of hemodynamic activities. It can be combined with classical, 'hemodynamic' anti-anginal drugs such as nitrates, β-blockers or calcium antagonists. Furthermore, trimetazidine can be considered a useful alternative to classic hemodynamic agents, even in patients who are resistant to treatment with the aforementioned classical drugs. The clinical characteristics of trimetazidine have been reviewed elsewhere [17–19].

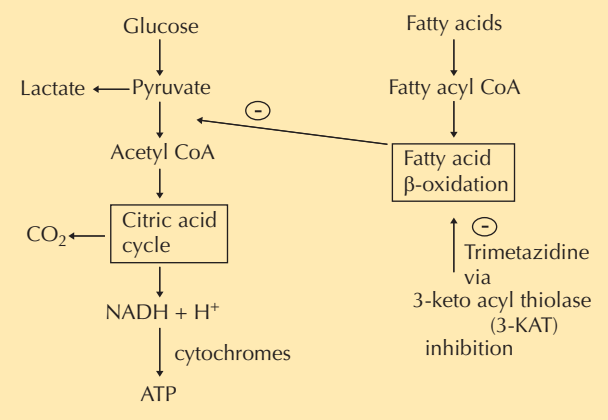

Figure 2. Glucose and fatty acid metabolism in the heart. After the formation of acetyl coenzyme A (CoA), both processes follow a common pathway, whereas glucose is able to continue with glycolysis. Oxidation of fatty acids impairs pyruvate oxidation. Trimetazidine suppresses fatty acid oxidation via inhibition of the enzyme 3-keto acyl thiolase, and enhances the process of glucose oxidation.

Other metabolic agents

It is very likely that other metabolic drugs for the treatment of ischemic heart disease are in the process of being developed, although very few data have been published to date. Ranolazine showed minimal clinical benefit in patients with coronary artery disease [20].

Conclusion

Major innovations in the pharmacological treatment of stable angina pectoris concern the following categories of drugs: newer calcium antagonists (in particular slow-release preparations); nicorandil, a K^+ channel opener and nitrate; bradycardiac agents (in particular ivabradine); metabolic drugs, which owe their beneficial effects to improved oxygen utilization. Trimetazidine is the best-known example of the metabolic drugs. It enhances glucose oxidation at the expense of fatty acid oxidation, thus leading to improved preservation of ATP. Trimetazidine is free of hemodynamic actions. Further development of this category of metabolic drugs seems well worthwhile. ■

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Vastarel MR: effective and safe for coronary patients treated with a phosphodiesterase type 5 inhibitor

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Abstract

In middle-aged and elderly men, vasculogenic erectile dysfunction (ED) is frequently related to the presence of overt atherosclerosis, the effect of cardiovascular drugs, the presence of cardiovascular risk factors, or a combination of all these mechanisms. The association between coronary artery disease and erectile dysfunction is supported by the findings of several studies that have correlated the presence of coronary artery disease (CAD) risk factors and degree of coronary atherosclerosis with difficulties in achieving and maintaining erections.

The introduction of orally active phosphodiesterase type 5 (PDE5) inhibitors has changed the therapeutic approach to patients with erectile dysfunction. However, there is significant concern about systemic hemodynamic effects of PDE5 inhibitors when they are associated with nitric oxide donors such as nitrates, because both drugs potentiate vasodilatation through a similar pathway and may increase the risk of potentially life-threatening hypotension. Several studies have shown that PDE5 inhibitors may be safely used in patients with stable coronary artery disease, in whom the limitation for their use relates to their ability to perform the level of exercise required by sexual activity without experiencing myocardial ischemia.

To find an alternative treatment for patients with coronary artery disease receiving nitrates and requiring treatment for erectile dysfunction, we have recently conducted studies in which patients with proven myocardial ischemia were allocated randomly to groups to receive either chronic treatment with nitrates or chronic treatment with trimetazidine (Vastarel) plus sildenafil before sexual activity, while undergoing ambulatory ECG monitoring or before exercise testing. In these studies we have shown that, in patients with chronic stable coronary artery disease and documented exercise-induced myocardial ischemia, trimetazidine decreases daily life ischemic episodes to the same extent as nitrates, and that the combination of trimetazidine plus a single dose of sildenafil 100 mg is superior to nitrate treatment in controlling ischemic episodes occurring during sexual activity and during exercise testing. The results of these studies indicate that the switch from nitrate to trimetazidine can be safely performed in patients with coronary artery disease requiring treatment with PDE5 inhibitors.
■ *Heart Metab.* 2004;24:23–26.

Keywords: Trimetazidine, sildenafil, coronary artery disease, erectile dysfunction, PDE5 inhibitors

In middle aged and elderly men, erectile dysfunction (ED) is frequently related to a vascular problem that may be the consequence of overt atherosclerosis, the effect of cardiovascular drugs, the presence of cardiovascular risk factors that reduce endothelial function, or a combination of all these mechanisms [1–2]. The association between coronary artery disease (CAD) and ED is supported by several studies that have correlated the presence of coronary artery disease risk factors and degree of coronary atherosclerosis with difficulties in achieving and maintaining erections [1].

As vasculogenic ED is primarily related to impaired endothelial function, and as endothelial dysfunction is an early stage in the development and progression of atherosclerosis, it is clear that reduction of erectile function may manifest well before the onset of clinically manifest atherosclerosis. Indeed, it has been proposed recently that ED may precede the onset of the clinical manifestation of CAD and may therefore be, in asymptomatic patients, a marker for the presence of CAD [3–5]. Pritzker [4] have reported that, among a group of 50 men with vasculogenic ED but asymptomatic for angina, 28 had a positive exercise test response and the 20 who agreed to undergo coronary angiography were found to have significant coronary atherosclerosis. Similar findings have been reported by Montorsi et al [3], who have shown that ED may precede the clinical manifestation of angina by nearly 3 years.

The introduction of orally active phosphodiesterase type 5 (PDE5) inhibitors has changed the therapeutic approach to patients with ED. As a result, more men – including those with cardiac disease – are now seeking treatment for ED. However, there is significant concern about systemic hemodynamic effects of PDE5 inhibitors when they are associated with nitric oxide donors such as nitrates, because both drugs potentiate vasodilatation through a similar pathway and may increase the risk of potentially life-threatening hypotension [6]. The use of PDE5 inhibitors is strictly contraindicated in patients receiving any form of nitrate, as stated by the joint guidelines issued by the American College of Cardiology and the American Heart Association [6]. Several studies have shown that PDE5 inhibitors may be safely used in patients with stable CAD [7–10]. In these patients the limitation for the use of PDE5 inhibitors relates to their ability to perform the level of exercise required by sexual activity without experiencing myocardial ischemia [7,11]. It has been shown that metabolic consumption during sexual activity (when performed with the usual partner) is around 3 metabolic equivalent of task units (METs), and that patients who do not have inducible ischemia at this level of effort may safely engage in such activity [11].

The therapeutic approach for patients with CAD and ED should be directed towards drugs that may improve myocardial ischemia without a negative effect on erectile function. Patrizi et al [12] have shown that, in patients with CAD receiving atenolol, the administration of sildenafil did not impair exercise tolerance. β-Blockers and calcium channel blockers, drugs commonly used for the treatment of angina, may further impair and worsen erectile function in those patients with a moderately impaired function. Therefore there is a need for a therapeutic option that reduces myocardial ischemia and does not impair erectile function in patients with CAD.

Trimetazidine (Vastarel), a metabolic anti-ischemic agent widely used and recognized in the treatment of angina pectoris and effort-induced myocardial ischemia, directly modifies the use of energy substrates in the heart, thereby improving myocardial ischemia and angina without significant changes in heart rate, blood pressure, or rate–pressure product at rest or during exercise [13–18]. Because of its mode of action and absence of negative effects upon erectile function, trimetazidine seems to be the drug of choice for the treatment of patients with CAD and ED who require treatment with PDE5 inhibitors.

In order to find an alternative treatment for patients with CAD receiving nitrates and requiring treatment for ED, we have recently conducted a study [19] in which patients with proven myocardial ischemia were allocated randomly to groups to receive either chronic treatment with nitrates or chronic treatment with trimetazidine plus sildenafil before sexual activity, and who underwent ambulatory ECG monitoring during daily life and during sexual activity. In this study we have shown that, in patients with chronic stable CAD and documented exercise-induced myocardial ischemia, trimetazidine decreased daily life ischemic episodes to the same extent as nitrates, and that the combination of trimetazidine plus a single dose of sildenafil 100 mg was superior to

*Figure 1. Effects of a combination of trimetazidine and sildenafil (TMZ+S) or nitrates on ischemic episodes during sexual activity. *P < 0.04 compared with the combination treatment.*

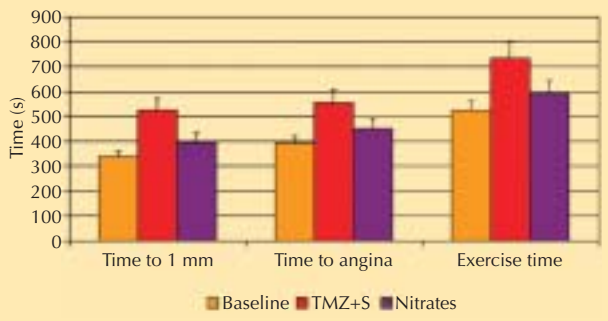

Figure 2. Effects of a combination of trimetazidine plus sildenafil (TMZ+S) or nitrates on exercise test parameters. Time to ischemia. P< 0.01 for all comparisons of TMZ+S with baseline; P < 0.05 for all comparisons of TMZ+S compared with nitrates plus placebo (P). (Adapted from Rosano et al [20], with permission.)

nitrate treatment in controlling ischemic episodes occurring during sexual activity (*Figure 1*). The results of this study indicate that the switch from nitrate to trimetazidine can be safely performed in patients with CAD requiring treatment with PDE5 inhibitors. Of importance, the association of sildenafil plus trimetazidine was significantly more effective than nitrates alone in controlling episodes of myocardial ischemia recorded during sexual activity.

In another, cross-over, study [20] we have compared the effect of trimetazidine plus sildenafil with that of chronic treatment with nitrates on exercise-induced myocardial ischemia in patients with CAD. Again, the combination of trimetazidine plus sildenafil was more effective than chronic nitrate treatment in improving exercise test parameters such as time to exercise, time to angina, and time to maximum exercise (*Figure 2*), further supporting the superiority of combination therapy over chronic nitrate therapy.

The findings of these studies are most likely related to the potentiation of the anti-ischemic effect of the two drugs. In patients with CAD, sildenafil did not impair the cardiovascular response to exercise and was effective in improving exercise time, time to angina, and myocardial ischemia, suggesting that sildenafil given to patients with CAD does not impair the ability to exercise at a level considered equivalent to sexual intercourse, and may have anti-ischemic properties.

Trimetazidine thus could be considered as an ideal anti-ischemic treatment for patients with cardiovascular disease and ED requiring a treatment with PDE5 inhibitors. Furthermore, in those patients receiving nitrate treatment, which is an absolute contraindication to the use of PDE5 inhibitors, nitrates can be effectively and safely replaced by trimetazidine. These outstanding results should encourage prescribing physicians to consider this association in patients with CAD requiring treatment for ED. ■

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Neurogenic induced myocardial dysfunction

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Abstract

Reversible myocardial dysfunction and pulmonary edema may occur after central nervous system events such as subarachnoid hemorrhage, Guillain–Barré syndrome, subdural hematoma, and head injury. The epidemiology and pathophysiology remain uncertain, but may involve a neurogenic-mediated catecholamine storm through local nerve endings. We describe a patient without medical history who suffered thalamic hemorrhage, secondary myocardial dysfunction, and pulmonary edema. ■ *Heart Metab.* 2004;24:27–30.

Keywords: Subarachnoid hemorrhage, neurogenic stunned myocardium, neurogenic pulmonary edema, echocardiography

Introduction

ECG changes following central nervous system (CNS) events have been reported extensively [1–12]. Segmental wall motion abnormalities (SWMA), increases in cardiac-specific enzymes, and subendocardial infarctions or band necrosis may also occur in these patients [4,8,10,13–18]. These clinical signs might be interpreted as representing myocardial ischemia. Also, reversible SWMA and hemodynamic and ECG changes have been reported in patients with subarachnoid hemorrhage, Guillain–Barré syndrome [19], and subdural hematoma [20]. This may imply a neurogenic stunned myocardium, but insufficient evidence makes this diagnosis uncertain. Without appropriate tests, ischemic ECG changes and SWMA are difficult to differentiate from coronary insufficiency. Pulmonary edema has also been described in relation to subarachnoid hemorrhage [21], head injury, and status epilepticus. We describe a patient with myocardial dysfunction and pulmonary edema after a thalamic bleed.

Case report

A 59-year-old man, without medical history, presented to our First Heart Aid unit. He had collapsed suddenly while eating. On arrival, he responded when spoken to by moving his eyes and making unrecognizable noises.

On physical examination, communication was just possible by eye movement. He was sweating. Blood pressure was 200/110 mm Hg, heart rate 60 beat/min, central venous pressure not increased. There were no heart and lung abnormalities or edema on the extremities, but right-sided hemiparesis and a right nystagmus were present. Glasgow Coma Score was: E4M6V1, isocoric pupils, normal light reflex.

The ECG at admission (*Figure 1*) showed a 60 beats/min sinus rhythm, left axis deviation, negative T-waves in leads I, II, AvL, V5-V6, and ST-segment elevations in leads AvR, V1-V5. QRS complex voltages suggested left ventricular hypertrophy. ECGs weeks later showed minimal changes. An echocardiogram on day 1 showed a dilated left atrium, no significant valve regurgitation, good left ventricular

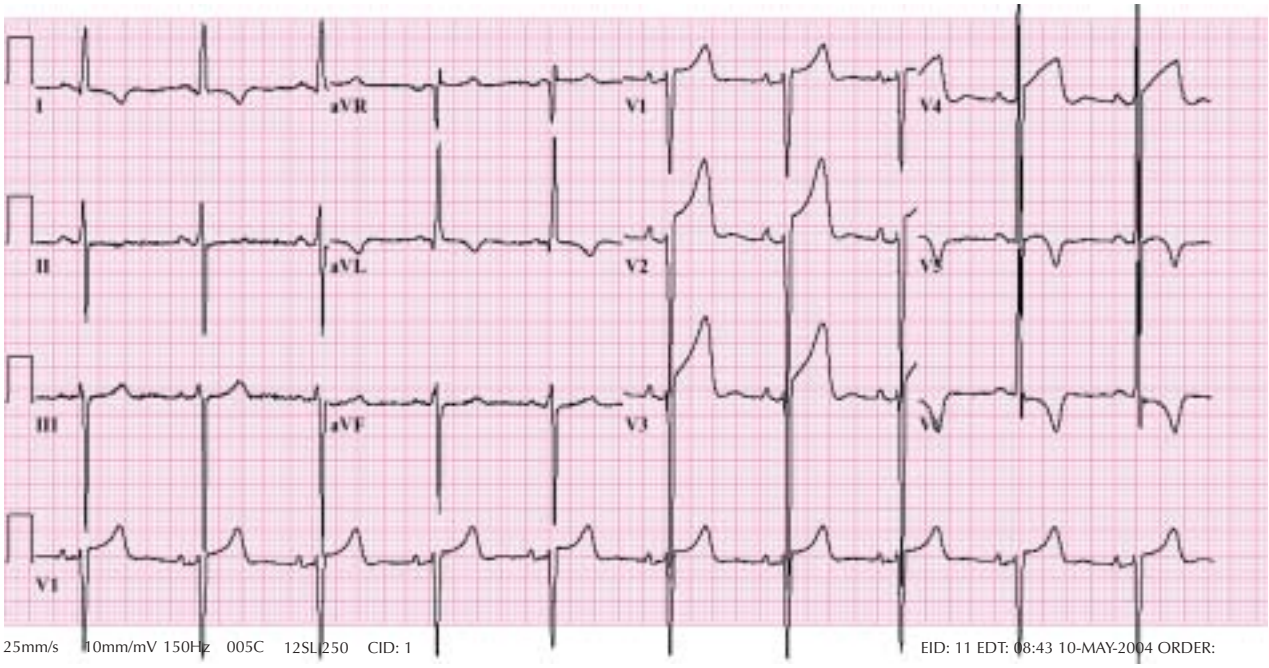

Figure 1. The patient's ECG at his admission to hospital.

function without SWMA, and no signs of left ventricular hypertrophy. Computed tomography (*Figure 2*) revealed a thalamic bleed with breakthrough to the ventricles, and blood in the posterior horns, 3rd and 4th ventricles, and aqueductus. Chest X-ray (*Figure 3*) on admission showed an enlarged heart with enlarged pulmonary veins and minimal signs of pulmonary edema. The blood results showed normal cardiac-specific enzymes during admission.

The neurosurgeon inserted a ventricular cerebrospinal fluid drain because of signs of hydrocephalus and the patient was admitted to the neurosurgical ward.

Interestingly, an echocardiogram 7 days later showed a diastolic dysfunction without SWMA but, 3 weeks later, basal, posterolateral, inferobasal-distal, laterobasal-distal, and anterobasal-distal SWMAs were seen. The pulmonary edema disappeared after 2 weeks.

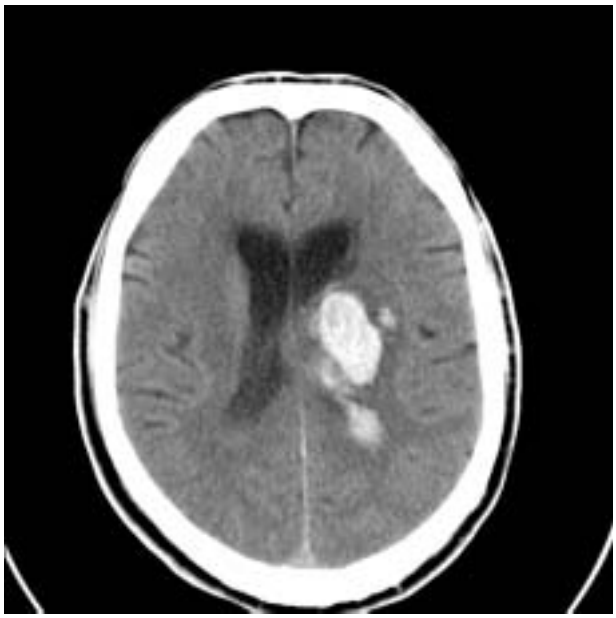

Figure 2. Computed tomography scan, showing a thalamic bleed with breakthrough to the ventricles, and blood in the posterior horns, 3rd and 4th ventricles, and aqueductus.

Discussion

ECG changes occur with a frequency of 50% to 90% in association with subarachnoid hemorrhage [1,2,4,6–8,10,11]. Serial ECG monitoring reveals abnormalities in 100% of cases [2,9]. Common ECG changes in subarachnoid hemorrhage are sinus bradycardia (50%), ST-segment changes (50%), T-wave abnormalities (48%), prominent U-wave (44%), Q–T_c interval abnormalities (39%), signs of left ventricular hypertrophy (36%), sinus tachycardia (20%) [2,9,10]. Arrhythmias associated with increased isoenzyme concentration occur in 91% of patients [5]. Brouwers et al. [2] found that poor outcome in patients with subarachnoid hemorrhage was associated with fast rhythm disturbances and/or cardiac ischemia. Thus ECG changes indicate myocardial damage after subarachnoid hemorrhage, and may reflect severity of bleed and poor outcome.

ECG changes do not reflect purely electrical phenomenon: affected patients frequently show

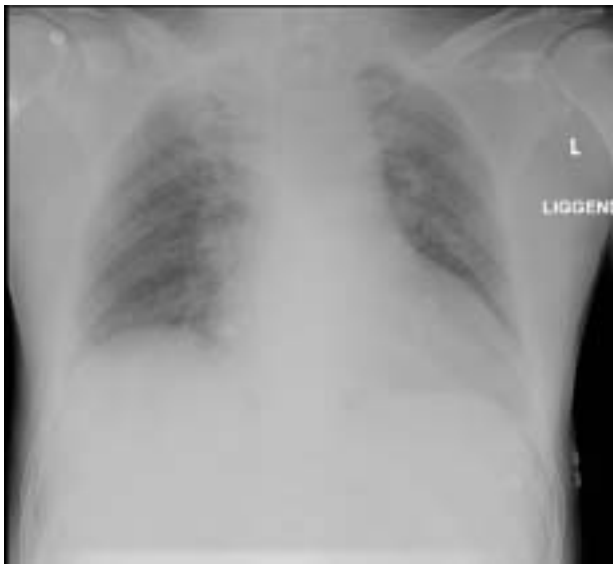

Figure 3. Chest X-ray on admission.

evidence of structural cardiac damage [10,13]. Mayer et al. [10] found that the presence of T-waves or Q–T_c segment prolongation on any ECG was associated with 100% sensitivity and 81% specificity for left ventricular dysfunction. Increased creatine kinase myocardial band (2%) was associated with 100% sensitivity and 94% specificity. Increased plasma myocardial enzymes and characteristic pathological lesions (contraction band necrosis or myofibrillar degeneration), and subendocardial infarctions are common in patients with subarachnoid hemorrhage [10], but pathological studies [10] and coronary angiography [15,17,22] have failed to demonstrate coronary disease, as confirmed in dogs: SWMA after subarachnoid hemorrhage occurred in the absence of myocardial hypoperfusion [12]. In catecholamine infusion in animals, and in patients with pheochromocytoma, identical cardiac lesions and focal and subendocardial myofibrillar degeneration were found. These lesions can be induced in adrenalectomized animals, so a neurogenic mechanism is plausible [13].

Increased release of catecholamines from local nerve endings in the heart may mediate these cardiac abnormalities. Transient severe coronary vasoconstriction leads to ischemia followed by postischemic ventricular failure and subendocardial myocardial damage. Also, a direct cardiotoxic effect of catecholamines may cause the development of subendocardial damage [13,15,18]. We describe ECG changes, SWMA, and signs of pulmonary edema in a patient with a thalamic bleed. The pulmonary edema might not be caused by left–sided heart failure. The blast injury theory [23] states that pulmonary edema after CNS events could be caused by a transient catecholamine burst in the pulmonary veins, the blast. The increased pulmonary vessel pressure caused by the increased sympathetic activity is of short duration, but of such extent that it leads to pulmonary capillary wall damage and acute pulmonary edema with pinky foamy sputum. After this initial stage the pulmonary arterial pressure normalizes, but pulmonary edema will not be restored for several days. ■

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Assessment of collateral circulation

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Abstract

Collateral circulation can maintain myocardial function and viability in chronic total coronary occlusion. Assessment of collateral circulation in man has developed from the 'classic' widespread angiographic semiquantitative grading of collateral filling of the segment downstream of an obstructed artery. Now microsensors for Doppler flow velocity and pressure allow quantitative description of collateral function and assessment of the components of the collateral circulation, enabling study of the impact of coronary interventions on collateral function, assessment of therapeutic interventions to promote collateral function, and study of specific pathophysiologic conditions such as coronary steal. ■ *Heart Metab.* 2004;24:31–34.

Keywords: Collateral circulation, assessment, coronary angiography, intracoronary Doppler, intracoronary pressure

Historical background

Among the first to describe connections between the major coronary arteries was the Dutch anatomist Richard Lower, in the 17th century. Ever since, there has been continuing dispute over whether these connections exist as preformed interarterial connections or develop only as the consequence of an occluded coronary artery. These so-called collaterals are often capable of fully supplementing blood flow to the myocardium distal to a coronary occlusion, preserving myocardial function (*Figure 1*), but collaterals are also observed in patients after myocardial infarction, and the question arises whether these collaterals had been insufficient to prevent the myocardial infarction or started to develop only after the acute coronary occlusion.

Angiographic assessment of collaterals

Assessment of collaterals in man became possible with the development of coronary angiography [1,2]. This is the most widely used method, being available during routine diagnostic angiography, but it is only semiquantitative, based on the description of collateral filling by Rentrop and Cohen [3] (*Table I*). Even in early angiographic studies, detailed analysis was made of the collateral anatomy, but no relationship was found between specific patterns of collaterals and well preserved or impaired myocardial function [1]. This limitation is probably technique related, and semiquantitative assessment of the collateral diameters may help to refine the classic Rentrop grading [4] (*Table I*). This approach is also of potential value to assess collateral development over the course of time [5].

Experimental assessment of collaterals

The collateral circulation has been extensively studied in experimental animal models, but species differences in the coronary anatomy limit extrapolation of these findings to man [6,7]. Better understanding of collateral circulation in man would provide insight to specific features of human coronary pathophysiology; however, recent therapeutic attempts to induce collateral development in man now also make more refined methods a necessity, to enable assessment of this angiogenesis [8]. A quantitative assessment of new therapeutic strategies would be superior to angiographic methods [9].

One important finding from animal experiments is that collateral perfusion is best achieved through large epicardial channels, developed in a process called arteriogenesis that is triggered by pressure gradients along arterioles and resulting shear stress, and not

through capillary structures developed in response to ischemia in a process called angiogenesis [10].

Invasive assessment of collaterals in man

Noninvasive methods allow accurate assessment of coronary perfusion if the coronary anatomy is known [11], but their interpretation is impaired in multivessel disease [12,13].

Physiologically viewed, collateral function is characterized by the ability of the collaterals to maintain adequate perfusion pressure and perfusion volume to the myocardium distal to an occluded or severely obstructed artery. Assessment of pressure and flow in the collateralized vascular region would provide the best physiologic measure of collateral function; they are the basic parameters describing the fluid dynamics of blood flow from which the properties (vascular resistances) can be derived.

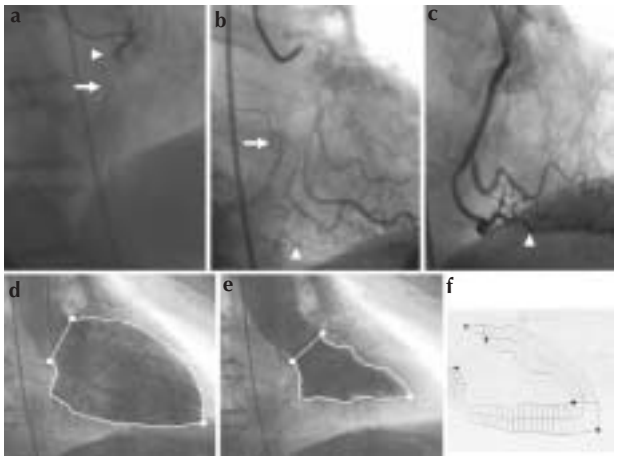

Figure 1. (a) 71-year-old male patient with a proximal occlusion of the right coronary artery (arrowhead); the distal end of the occlusion is opacified via bridging collaterals (arrow). (b) Collaterals from the left coronary artery completely fill the distal right coronary artery up to the occlusion site (arrow); arrowhead indicates the posterior descending branch of the right coronary artery. (c) Reopened right coronary artery after coronary angioplasty; arrowhead, posterior descending branch. (d, e) Normal left ventricular contraction during diastole and systole, respectively; there are no wall motion abnormalities, as indicated by quantitative wall motion analysis (f).

Direct assessment of collaterals became available with the development of percutaneous transluminal coronary angioplasty (PTCA). The pressure measured through balloon catheters during a balloon occlusion is a measure of collateral supply, and patients with greater distal occlusion pressures less often had angina during balloon occlusion [14]. The small fluid-filled central lumen of these catheters provided only damped pressure recordings, but the approach was similar to that used when microsensors became available to record pressure at the tip of 0.36 mm (0.014 inch) wires and to record coronary flow velocity [15]. The first studies of collateral circulation with these new tools were carried out during PTCA of high-grade coronary lesions, and quantitative indices of collateral function were introduced [16–19] (*Table II*). The collaterals in these patients either were already visible during diagnostic angiography or become visible during balloon occlusion, as recruitable collaterals.

Another means of assessing collateral physiology in man was to study collaterals in chronic total coronary occlusions before reopening the artery [20,21] (*Figure 2*). It became possible to study specific features of collateral physiology such as the incidence of coronary steal in patients with such occlusions. About 30% of patients with a chronic total coronary occlusion show a decrease in collateral flow during maximum hyperemia, as blood flow is redirected from the collateral bed to the arterial bed of the collateral donor artery [22–24].

Determinants of collateral function

About every fifth person appears to have some well-developed, preformed interarterial connections that

Table I. Semiquantitative angiographic assessment of the collateral circulation. [a]According to Rentrop and Cohen [3]; [b]Modified from [2,4], with permission.

Grading	Description
	Angiographic grading of collateral filling[a]
Grade 0	No distal filling of the occluded artery
Grade 1	Filling of side branches of the occluded artery, but not the main segment
Grade 2	Partial epicardial filling of the occluded artery
Grade 3	Complete epicardial filling of the occluded artery
	Grading of collateral connection diameters[b]
CC0	No continuous connection between donor and recipient artery
CC1	Continuous, thread-like connection
CC2	Continuous, small (side branch-like) size of the collateral connection throughout its course

Table II. Calculation of physiologic components of collateral circulation.

Component	Calculation
Collateral pressure index (no unit)	$(P_D - P_{RA}) / (P_{Ao} - P_{RA})$
Fractional collateral flow reserve (no unit)	$(P_D - P_{RA}) / (P_{Ao} - P_{RA})$ during maximum hyperemia
Collateral flow index (no unit)	APV_D / APV
Collateral resistance index (mmHg/cm per s)	$(P_{Ao} - P_D) / APV_D$
Peripheral resistance index (mmHg/cm per s)	$(P_D - P_{RA}) / APV_D$

APV (cm/s), coronary flow velocity in the reopened artery at point X; APV_D (cm/s), coronary flow velocity distal to the occlusion taken at point X; P_{Ao} (mmHg), aortic pressure; P_D (mmHg), pressure distal to the occlusion; P_{RA} (mmHg), right atrial pressure. In an open coronary artery, P_D can be measured only during balloon occlusion.

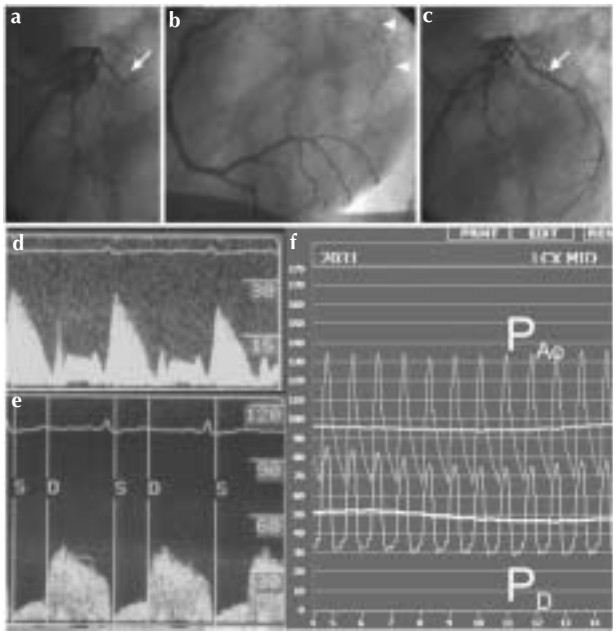

Figure 2. Assessment of collateral function by Doppler flow velocity and pressure recordings in a 63-year-old male patient with a proximal occlusion of the left circumflex artery (a, arrow), filled via collaterals from the right coronary artery (b, arrowheads). (c) The reopened artery. (d) Flow velocity signal distal to the occlusion. (e) Flow velocity signal in the reopened artery. The collateral signal shows predominantly systolic flow; normal flow in the artery is predominantly diastolic. (f) Recordings of aortic (P_{Ao}) and distal pressure (P_D).

can serve immediately as collaterals during a coronary occlusion [25] and which remain as a functional reserve if a coronary lesion is treated successfully [26]. In contrast, the majority of collaterals disappear immediately after angioplasty and may not be able to prevent an acute myocardial infarction [20].

Collateral development is determined by the severity of stenosis of the artery to which they connect, and they are best developed in totally occluded arteries [27]. If a stenosis deteriorates gradually, collaterals have time to develop, but in cases of acute myocardial infarction without prior collateral formation, they start to appear within a few days [28], and reach full functional competence within 3 months [21].

Differences in the angiographic grading of collaterals between diabetic and nondiabetic patients have led to continuing debate as to whether diabetes would affect collateral development [29]. However, a number of studies contradict this observation [30,31]. When invasive methods were applied, no adverse influence of diabetes on collateral development was observed [32,33]; however, the development of collaterals may be delayed compared with that in nondiabetic patients [33]. ■

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Featured research

Abstracts and commentaries

NECA and bradykinin at reperfusion reduce infarction in rabbit hearts by signaling through PI3K, ERK, and NO

Yang X-M, Krieg T, Cui L, Downey JM, Cohen MV. *J Mol Cell Cardiol.* 2004;36:411–421.

This study compared the signal transduction pathways responsible for the anti-infarct effect of the A_1/A_2 adenosine receptor agonist 5′-*N*-ethyl carboxamido adenosine (NECA) and bradykinin. Receptor agonists were administered to isolated rabbit hearts, starting 25 min after the onset of a 30-min period of ischemia and continuing into the 2-h reperfusion period. The results show that both NECA and bradykinin significantly decrease infarct size when administered at reperfusion. They do so through a mechanism that involves activation of phosphatidylinositol 3-kinase (PI3K), nitric oxide, and extracellular regulated kinase (ERK).

Commentary

Although mimetics of ischemic and pharmacological preconditioning are very effective at limiting infarction during an ischemic insult, the requirement for pretreatment has greatly limited their clinical usefulness, because patients with acute myocardial infarction mainly present after the onset of coronary occlusion. What is needed is a cardioprotective intervention that can be applied after ischemia has begun. Adenosine, the first preconditioning mimetic identified, was initially examined in this setting, with very mixed results. In contrast to the inconsistent data with adenosine, AMP579, an adenosine agonist with nearly equivalent affinities for A_1 and A_{2A} receptors, has without exception salvaged ischemic myocardium when administered at the time of reperfusion. The authors observed that NECA, a closely related compound, salvaged ischemic myocardium when infused for 70 min, beginning 5 min before reperfusion in isolated rabbit hearts. The salutary effect of NECA depended on A_2 receptors in addition to PI3K, nitric oxide synthase (NOS), and ERKs 1/2. Bradykinin was equally as effective as NECA, and inhibitor studies indicated that its protection was also dependent on PI3K, NOS, and ERKs 1/2. These findings challenge the concept that preconditioning mimetic agents must be administered before reperfusion in order to protect. Bradykinin protected at reperfusion by utilizing the same pathway, PI3K and NOS, that it uses to trigger preconditioning. The authors therefore speculate that other preconditioning mimetics such as opioids, angiotensin, norepinephrine, and endothelin [1] may also be protective in this setting, and the effects of these agents will be the subject of future studies. As noted, protection by both bradykinin and NECA at reperfusion was dependent on PI3K and NOS. However, ERK, which is used in multiple signaling units, has not been associated with either PI3K or NOS, so that at present it is not clear why ERK activation causes cardioprotection. Nevertheless, both NECA and bradykinin administered at reperfusion protect through a common signaling pathway. Moreover, as bradykinin at reperfusion protects through part of the same pathway that it uses to precondition the heart, it is likely that other preconditioning mimetics may protect when administered at reperfusion.

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Danielle Feuvray

Metabolic manipulation in ischemic heart disease: a novel approach to treatment

Lee L, Horowitz J, Frenneaux M. *Eur Heart J* 2004;25:634–641.

Antianginal drugs that exert their anti-ischemic effects primarily by altering myocardial metabolism have recently attracted attention. They have the potential to relieve symptoms in patients with refractory angina who are already on 'optimal' medical therapy and have disease that is not amenable to revascularization, making these drugs an attractive addition to therapy, particularly for the elderly population. In some cases, they may even be used as first-line treatment. These drugs increase glucose metabolism at the expense of free fatty acid metabolism, enhancing oxygen efficiency during myocardial ischemia. They have been demonstrated to reduce ischemia in several clinical trials, but their use remains limited. This review aims to draw attention to these 'metabolic' antianginal drugs while surveying the evidence supporting their use and mode of action. Four metabolic antianginal drugs are reviewed: perhexiline, trimetazidine, ranolazine, and etomoxir. We also discuss the metabolic actions of glucose–insulin–potassium and β-blockers and describe myocardial metabolism during normal and ischemic conditions. The potential of these metabolic agents may extend beyond the treatment of ischemia secondary to coronary artery disease. They offer significant promise for the treatment of symptoms caused by inoperable aortic stenosis, hypertrophic cardiomyopathy, and chronic heart failure.

Commentary

This is an important and useful review of the metabolic approach to ischemic heart disease. Treatments assessed include β-blockers, glucose–insulin–potassium, perhexiline (which I have not previously considered a metabolic agent), trimetazidine, ranolazine, and etomoxir. Trimetazidine has to date the largest body of information confirming its efficacy and safety. A query concerning its metabolic mode of action was allayed recently and its cause attributed to inappropriate methodology. Ranolazine in high dosage as monotherapy or in combination with either a calcium antagonist or β-blocker has proven anti-ischemic effects. There are slight anxieties about a minor prolongation of the Q–T interval, but no cases of torsades de pointes have been recorded. The potential for these drugs is considerable and long term morbidity and mortality studies are necessary. In addition, it should not be forgotten that trimetazidine can replace oral nitrates in restoring quality of life to men with erectile dysfunction.

Graham Jackon

Anti-ischemic effects and long term survival during ranolazine monotherapy in patients with chronic severe angina

Chaitman BR, Skettino SL, Parker JO, et al, for the MARISA Investigators. *J Am Coll Cardiol*. 2004; 43:1375–1382.

The primary objective of the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial was to determine the dose–response relationship of ranolazine, a new potentially antianginal compound, on symptom-limited exercise duration. Fatty acids increase precipitously in response to stress, including acute myocardial ischemia. Ranolazine is believed to partially inhibit fatty acid oxidation, shift metabolism toward carbohydrate oxidation, and increase the efficiency of oxygen use. Patients (n = 191) with angina-limited exercise discontinued antianginal medications and were randomized to groups in a double-blind four-period crossover study of sustained release ranolazine 500, 1000, or 1500 mg, or placebo, each administered twice daily for 1 week. Exercise testing was performed at the end of each treatment during both trough and peak ranolazine plasma concentrations. Exercise duration at trough increased with ranolazine 500, 1000, and 1500 mg twice daily, by 94, 103, and 116 s, respectively, all greater ($P < 0.005$) than the 70 s increase with placebo. Dose related increases in exercise duration at peak, in times to 1 mm ST-segment depression at trough and peak, and to angina at trough and peak were also demonstrated (all $P < 0.005$). Ranolazine had negligible effects on heart rate and blood pressure. One-year survival rate combining data from the MARISA trial and its open-label follow-on study was 96.3 1.7%. In patients with chronic angina, ranolazine monotherapy was well tolerated and increased exercise performance throughout its dosing interval at all doses studied, without clinically meaningful hemodynamic effects. One-year survival was not less than expected in this high-risk patient population. This metabolic approach to treating myocardial ischemia may offer a new therapeutic option for patients with chronic angina.

Commentary

Inhibiting fatty acid oxidation has recently been demonstrated to have therapeutic benefit in the treatment of angina pectoris and other forms of ischemic heart disease. The inhibition of fatty acid

oxidation results in a stimulation of glucose oxidation, resulting in a more oxygen-efficient production of energy in the heart. One approach to inhibiting fatty acid oxidation is with the antianginal drug, trimetazidine, which inhibits a key enzyme of fatty acid β-oxidation, long chain 3-keto acyl coenzyme A thiolase. Trimetazidine, which is available for clinical use as an antianginal agent in more than 80 countries, is the first clinically used agent recognized to act by optimizing energy metabolism in the heart. In this article by Bernard Chaitman and colleagues, the anti-ischemic effect of ranolazine used as monotherapy for angina treatment is described. Ranolazine, which we have shown to inhibit fatty acid oxidation in the heart [1], is the second clinically effective antianginal agent known to act by optimizing energy metabolism. Like trimetazidine, ranolazine exerts antianginal effects when used in combination with hemodynamic agents such as β-blockers, calcium antagonists or nitrates. Although ranolazine has not yet been approved for clinical use, along with trimetazidine it highlights the potential of modulating energy metabolism as an approach to treating ischemic heart disease.

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Gary D. Lopaschuk

Glossary

Gary D. Lopaschuk

ATP-sensitive K^+- channels
ATP-sensitive potassium (KATP) channels are potassium channels that are present in either the plasma membrane of the cell, or the mitochondrial membrane of the cell. These channels are inhibited by ATP, and the KATP in the plasma membrane serve to couple the metabolic status of the cell to its membrane potential. KATP regulates a number of cell actions, including muscle contractility (skeletal, cardiac and vascular smooth muscle). The opening of sarcolemmal and mitochondrial ATP-sensitive K(+) (KATP) channels in the heart is believed to mediate ischemic preconditioning, a phenomenon whereby brief periods of ischemia/reperfusion protect the heart against myocardial infarction.

Bamiphylline
Bamiphylline is a specific A1 adenosine receptor antagonist. By inhibiting A1 receptors it antagonizes the actions of adenosine on these receptors. This includes any cardioprotective effects of adenosine in the ischemic heart.

cGMP
cGMP stands for cyclic guanosine monophosphate. It is a very important intracellular signalling molecule in cells. In smooth muscle, an increase in cGMP results in vasodilation. The vasodilator effects of nitric oxide (NO) are mediated by cGMP.

Guanylate cyclase
Guanylate cyclase is an enzyme that catalyzes the formation of cGMP from guanosine triphosphate. Guanylate cyclase is a target of nitric oxide (NO), and is primarily responsible for NO mediated vasodilation.

I_f current
I_f is the abbreviation for a current that actively hyperpolarizes cells. The ''f'' stands for ''funny'' because this unusual current hyperpolarizes cells. I_f current is primarily present in the autonomic tissue of the heart (i.e sinoatrial and AV node). It contributes to the phase 4 depolarization of the cell.

Membrane phospholipid turnover
Cellular membranes consist of a number of phospholipids that are arranged in a bilayer. There are a number of different phospholipids in these membranes. These phospholipids are not static and are constantly turning over. Some phospholipids, such as phosphatidyl inositol, can turnover quite rapidly, resulting in the production of products that are important in cellular signalling processes (i.e. inositol triphosphate and diacylglycerol).

Mitochondrial K^+-ATP channels
Mitochondrial ATP-sensitive potassium (KATP) channels are potassium channels that are present in the mitochondrial membrane of cells. These channels are inhibited by ATP. The opening of the mitochondrial ATP-sensitive K(+) (KATP) channels in the heart is believed to have cardioprotective effects in the setting of ischemia and ischemia and reperfusion. Despite a major research effort, the molecular characterization of the mitochondrial K^+-ATP channel remains unknown.

Na^+/H^+ exchanger
The Na^+/H^+ exchanger is a membrane ion transporter that exchanges Na^+ for H^+. In the heart, it is one of a number of pathways to extrude protons (H^+) from the heart. However,

this is coupled with a net inward flux of Na+. During and following ischemia, Na^+/H^+ exchanger activity increases, due to the ischemic-induced increase in intracellular acidosis. The increased Na^+/H^+ exchanger activity can lead to Na^+ overload in the ischemic heart, which can decrease cardiac efficiency (energy is needed to extrude this Na^+) and contribute to cell injury.

Phosphodiesterase type 5 (PDE5)
Phosphodiesterases are enzymes that cleave cyclic nucleotides such as cAMP and cGMP. PDE 5 is a phosphodiesterase isoform that cleaves cGMP. Inhibition of PDE5 results in smooth muscle relaxation, and is the target for sildenafil (Viagra). This explains the coronary vasodilatory effect of sildenafil, as well as the effects on penial erection.

Tumor necrosis factor (TNF-α)
Tumor necrosis factor (TNF-α) is a cytokine that acts via receptors to mediate a number of biological effects, including the inflammatory response. The role of cytokines in the pathogenesis of systolic heart failure (HF) has been well established. TNF-α can also activate the intrinsic mitochondrial death pathway that is responsible for the cardiac myocyte apoptosis.

Subtypes (A_1 and A_2) of surface membrane P1 receptors
Purinergic receptors (designated ''P'' receptors) use purine nucleotides as ligands. The P1 class of purinergic receptors use adenosine as a ligand. These P1 receptors can further be classified as A1, A2, and A3 receptors. The vasodilatory effects of adenosine are primarily mediated by binding to A2 receptors. The direct chronotropic effects of adenosine on the heart, and many of its cardioprotective actions are mediated by adenosine binding to A1 receptors. Ischemic preconditioning involves a series of intracellular events that are initiated with the activation of the A1 receptor, and end at the sensitive K+ ATP channels of the mitochondria. New evidence points to a role for adenosine in promoting neovascularization through a mechanism that requires interaction between the adenosine receptor subtype 2A (A(2A)R).