adenosine A<sub>1</sub>-receptor antagonists worsen ischaemia-induced myocardial damage. Protection of ischaemic myocardium was also provided by K<sub>ATP</sub>-channel openers (cromakalim, pinacidil) and the reverse was true with K<sub>ATP</sub>-channel blockers (glibenclamide). Kirsch et al.<sup>[5]</sup> demonstrated that the adenosine A<sub>1</sub>-receptors are coupled to the K<sub>ATP</sub>-channels via G-proteins. The protective effect of an adenosine A<sub>1</sub>-receptor agonist (R-PIA) was completely abolished if a K<sub>ATP</sub>-channel blocker (glibenclamide) was given as well. The pharmacological characteristics of adenosine A<sub>1</sub>-receptors include an inhibition of adenylate cyclase, coupling to pertussis toxin-sensitive G-protein, activation of K<sub>ATP</sub>-channels, enhanced glucose transport, and activation of Na<sup>+</sup>/Ca<sup>2+</sup> exchange.<sup>[8]</sup> Since adenosine and adenosine A<sub>1</sub>-receptor agonists have been shown to elicit a preconditioning response, the time has come to explore their value in the management of ischaemia in human hearts. In fact, Claeyjs et al. did the opposite by showing that aminophylline, a non-selective adenosine receptor antagonist, abolished the preconditioning effect. With these experiments they provide better insight into the mechanisms involved in preconditioning in man. At the same time they demonstrate that PTCA allows these mechanisms to be studied in vivo in a relatively harmless manner. However, as the authors admit, it should be realized that aminophylline is not an adenosine A<sub>1</sub>-receptor specific antagonist because it also inhibits cyclic nucleotide phosphodiesterase activity and activates a-adrenoceptors in nervous tissue.

Newly developed specific adenosine A<sub>1</sub>-receptor agonists merit testing to determine their efficacy to induce preconditioning and the mechanism of their action should be elucidated. In carefully designed prospective and controlled studies in man, interventions and unambiguous endpoints should be chosen in such a manner that it may be proven that myocardial preconditioning has the potential to improve the outcome of patients with ischaemic heart disease.

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Stress induced T wave normalization: a new marker of myocardial ischaemia

See page 526 for the article to which this Editorial refers

Detection of persistent myocardial ischaemia after myocardial infarction has been an important target for the last 20 years. Several studies have shown that the presence of myocardial ischaemia, often silent, after myocardial infarction was predictive of future cardiac events, ischaemia being detected by means of exercise testing<sup>[11]</sup>. Holter monitoring, myocardial perfusion scintigraphy or stress echocardiography. It must be made clear, however, that the events which were predicted were mostly 'soft' events (need for revascularization or unstable angina) and not 'hard' events (such as cardiac death or recurrent myocardial infarction). Furthermore, some conflicting results have been published more recently, suggesting that
persistent myocardial ischaemia was no longer a major prognostic factor, in comparison, for example, to left ventricular function.

The presence of persistent myocardial ischaemia at a distance from the myocardial infarction site is generally related to multivessel disease and may constitute an indication for myocardial revascularization. Detection of persistent myocardial ischaemia in the peri-infarction zone is an indicator of the presence of jeopardised viable myocardium which may be potentially preserved by revascularization procedures[2]. An important number of studies have been published on this topic, in which the detection of persistent myocardial ischaemia was performed using radionuclide myocardial scintigraphy or echocardiography, myocardial ischaemia being produced by exercise or stress testing. The criteria, or markers, of myocardial ischaemia are, in these cases, reversible perfusion defects (radionuclide imaging) or new, or worsening left ventricular wall motion abnormalities (echocardiography). Their interest, both for confirmation of myocardial ischaemia and localization of area at risk, has been largely confirmed.

However, historically ST and T wave abnormalities were the first markers used to detect myocardial ischaemia induced by exercise testing. ST depression, being both sensitive and specific, was rapidly recognised as a useful marker of myocardial ischaemia. For many years it was suggested that T wave changes in general, and T wave normalization in particular, could be used to detect myocardial ischaemia. However, the result of the studies evaluating the diagnostic value of T wave changes have, until now, been globally disappointing. During exercise testing, normalization of inverted T waves at rest is not uncommon, but it has long been debated as to whether T wave normalization was a specific criterion of myocardial ischaemia. Arguments have been found both for[3] and against[4] this hypothesis. During 24-h ECG monitoring, T wave changes and T wave normalization have been tested as criteria for myocardial ischaemia[5]. In general, T wave changes were considered as non-specific, susceptible to induction by body position, respiratory movements, etc., and were finally of no diagnostic value.

T wave normalization may have different causes. It may be observed in cases of myocardial ischaemia related to coronary artery disease, occurring frequently, but not always, with simultaneous ST depression. T wave normalization may be seen in athletes as a result of the direct effect of sympathetic stimulation on normal myocardium. It may be observed in other diseases such as mitral valve prolapse, left ventricular hypertrophy or metabolic abnormalities.

In this issue, Elhendy et al.[6] address the use of T wave normalization as a marker of myocardial ischaemia during dobutamine stress testing in patients with non-Q wave myocardial infarction. Thirty-six patients were included in this study. All had negative T waves at rest, and T wave normalization occurred in 16 patients during dobutamine stress testing. Myocardial ischaemia was confirmed by SPECT imaging (presence of reversible defects; perfusion scores based on 6 myocardial segments) and echocardiography (occurrence of new or worsening wall motion abnormalities; wall motion scores based on 16 myocardial segments). The prevalence of ischaemia was higher in group 1 (T wave normalization) than group 2 (T waves remaining negative), as well as by scintigraphy (85% vs 38%, P=0.004) and echocardiography (70% vs 32%, P=0.02). The sensitivity and specificity of T wave normalization for the detection of ischaemia were 74% and 77% by SPECT, 74% and 65% by echocardiography, respectively.

However, there are some limitations to this study. The population of patients is highly selected and small. Only 24 patients out of 36 underwent coronary angiography to define coronary anatomy. There is also some concern about the rather peculiar left ventricular segmentation in six segments detected by SPECT; only the septal segment was divided into two (anterior and posterior). The mixing of 201 thallium and Sestamibi investigations to detect myocardial ischaemia may also be criticised. Even if both investigations performed similarly, it would have been better, from a scientific point of view, to have a more homogeneous investigation procedure. The substitution of a post-resting thallium study for a redistribution study followed by reinjection (not universally accepted) may lead to an underestimation of the amount of available myocardium. It has been demonstrated[7] that in some patients the redistribution images show improvement compared to the stress images, where a subsequent reinjection does not. Finally, it would have been interesting if patients had performed an exercise test to compare the effects of dobutamine stress testing and exercise on T wave changes.

Despite these limitations, this study supports the use of T wave normalization as an additional marker for identification of myocardial ischaemia in a patient population with a high prevalence of coronary artery disease, particularly in cases with poor quality cardiac stress images. To our knowledge, no other paper has been published on this topic, using the same population of patients and the same dobutamine stress protocol. However, other authors have suggested that ST elevation or T wave normalization may be helpful to support the diagnosis of myocardial viability using low does dobutamine in Q wave myocardial infarction patients.
Although a further method for the detection of myocardial ischaemia, and possibly also for the assessment of myocardial viability, is potentially interesting, we suggest that further investigations should be performed to confirm the interesting results of Elhendy et al. before using T wave normalization as a routine marker of myocardial ischaemia.

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Doppler diastolic transmitial ventricular filling patterns — towards a better understanding

See page 612 for the article to which this Editorial refers

The 20th century has witnessed remarkable strides in our understanding of the cardiac contraction–relaxation sequence. Although initial studies focused primarily on systolic ventricular function, during the last two decades a great deal of information has been gathered regarding ventricular diastole.

Pathophysiology of ventricular diastole

There is general agreement that there are very distinct and different phases to ventricular diastole. Diastole commences at the end of ventricular ejection or at the time of the second heart sound. According to Brutsaert, true diastole commences at the end of the contraction–relaxation cycle and refers only to the period of diastasis and to the changes occurring during and after atrial systole[1].

Active ventricular relaxation, an ATP-dependent energy-dependent process, with calcium reuptake by the sarcoplasmic reticulum, is accompanied by a rapid decrease in ventricular wall tension and intracavitary pressure. Clinical events coinciding with the period of active ventricular relaxation include the isovolumic relaxation period and the period of rapid ventricular filling following mitral valve opening. At a given point in time, ventricular inflow overtakes the relaxation capability of the ventricle and the fall in ventricular pressure ceases (O point on LV pressure curve, nadir of 'y' descent on atrial tracing). An important contribution to the end of rapid filling is the constraint to filling offered by the pericardium and right heart structures, and the elastic limits of the non-myocardial component, the 'parallel elastic' element of the heart. A small rise in ventricular pressure represents the continued momentum of blood flow into the ventricle until a new steady state is reached, the plateau phase of diastole (diastasis). The end of the rapid filling period may be audible or palpable at the bedside as a third heart sound or diastolic filling halt.

Atrial contraction imposes an external test on the stiffness or compliance of the ventriculo-pericardial system. During atrial systole, a given volume of blood is injected into the ventricle and the response of the ventricle in terms of its pressure-volume relationship characterizes the 'chamber compliance' and in terms of its stress–strain relationship the 'muscle compliance' of the system. The ventricular end-diastolic pressure, a chance point on the ventricular pressure curve, depends on the entire series of events and factors discussed above.