Warm up angina

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Abstract

Walk-through angina dates back more than 200 years. It was first described in a letter to the British physician, William Heberden. The term is used to describe patients with ischemic heart disease who have reduced symptoms after an episode of angina. It is related to ''warm up'' angina or, when playing golf, ''first hole'' angina. The mechanisms responsible for warm up angina are not yet clear, although ischemic preconditioning and collateral recruitment seem to play important parts. Triggers and mediators involved in preconditioning are adenosine, bradykinin, opioid receptor agonists, ATP-sensitive potassium channels, and protein kinase C. However, only bradykinin seems to have an influence on warm up angina in humans.
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Introduction

Second wind, or warm up, angina has been recognized for more than 200 years [1]. It describes patients with ischemic heart disease and exertional angina that forces them to stop; after the first bout of angina, they are able to continue with minor, or even without any, further symptoms. On exercise testing, warm up angina can be seen to be accompanied by objective measures, as patients develop less ST-segment depression at similar workloads during a second exertion [2] (*Figure 1*). The traditional view is that angina is the result of an imbalance between the supply and demand of the myocardium for blood. The traditional explanation of warm up angina has therefore been that myocardial blood flow is enhanced on second effort by the opening of collateral channels (ie, collateral recruitment), and vasodilatation of the diseased artery or subtended vascular bed, or both. However, the observation of increased myocardial resistance to ischemia after a brief episode of ischemia, known as ischemic preconditioning, has increased the understanding of warm up or second wind angina [3]. In contrast to the traditional view, ischemic preconditioning does not depend on an increase in myocardial blood flow, but is caused by an increase in the intrinsic resistance of the heart to ischemia [4].

Ischemic preconditioning and collateral recruitment

In 1986, Murry and coworkers introduced the term ''ischemic preconditioning'' and referred to it as myocardial adaptation to ischemic stress induced by repetitive brief periods of ischemia and reperfusion [3]. Ischemic preconditioning is receptor mediated and, in animal models, several mediators are able to precondition the heart in the absence of an initial ischemic insult (see below). Not all time combinations and durations of ischemia and reperfusion will trigger the preconditioning phenomenon and afford myocardial protection. Ischemic preconditioning can be induced by a period of ischemia as short as 3 min, followed by a minimum of 1 min of reperfusion [3], but a brief 1–2 min period of ischemia followed by subsequent reperfusion has no protective effect [5]. A

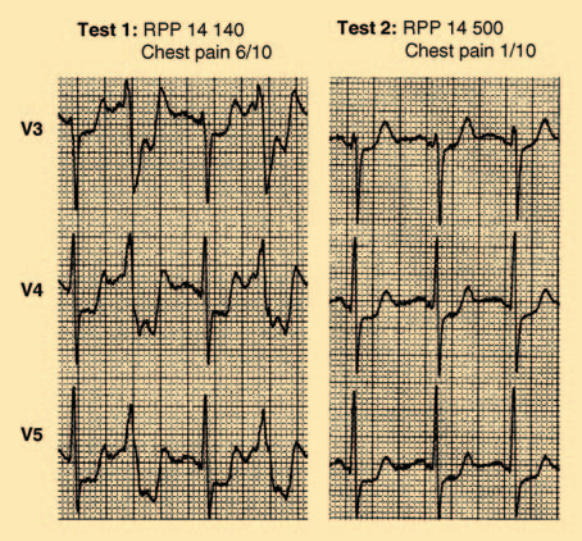

Figure 1. Surface electrocardiogram in a patient with single-vessel disease of the left anterior descending coronary artery, undergoing repetitive treadmill testing. Test 2 was separated from test 1 by a 15 min period of rest. In test 2, ST-segment depression was almost absent at the same workload, and the patient experienced less chest pain compared with test 1 (ie, second wind or warm up phenomenon). Note that the ventricular bigemini present in test 1 is absent in test 2. Calcium channel antagonists, angiotensin converting enzyme inhibitors, nicorandil, sulfonylureas, and β-blockers were discontinued at least 48 h before testing. RPP, rate–pressure product.

single episode of ischemia is needed to induce preconditioning [6], but repetitive episodes of brief ischemia are also effective [7]. It is now established that ischemic preconditioning is a biphasic phenomenon, with a first window of protection developing within minutes of an ischemic insult but lasting only 1–2 h, and a second window of protection developing between 12 and 24 h but lasting for 3–4 days [8,9]. This second window of protection has important therapeutic implications because, unlike the first window, it can protect against both myocardial stunning and infarction [10], and, unlike early ischemic preconditioning, tolerance does not occur, because repeated triggers prolong the effect [11].

As previously mentioned, the traditional view is that angina is the result of an imbalance between the supply to and demand of the myocardium for blood. Thus a component of warm up angina may result from increased resistance to ischemia in a manner analogous to ischemic preconditioning; another component may be the result of the opening of collateral channels (ie, collateral recruitment). This has been documented in humans using the coronary occlusion model during percutaneous coronary intervention at rest [12] and during exercise [13], indicating that collateral recruitment is an additional factor leading to the warm up phenomenon.

Pharmacological induction of myocardial tolerance

Ischemic preconditioning is receptor mediated, and a major objective in recent years has been the identification of the triggers and end effectors in the myocyte that are activated during ischemic preconditioning. Several triggers have been described in ischemic preconditioning in vitro and in animal models of ischemia: adenosine [14], bradykinin* [14], and opioid receptor agonists [15]. The mitochondrial ATP-sensitive potassium channel [16] and protein kinase C [17] are believed to be intracellular mediators of ischemic preconditioning. However, several human studies failed to show that adenosine receptor activation has an influence on serial angina [12,18,19]. Another investigator was unable to prevent the warm up effect with glibenclamide (an ATP-sensitive potassium channel blocker) [20].

A recent study using sequential treadmill testing investigated the influence of different drugs on warm up in humans [21] and demonstrated that the angiotensin converting enzyme (ACE) inhibitor, enalapril, did prolong the protective window of ischemic preconditioning, but had no influence on the degree of the warm up phenomenon. The angiotensin II type 1 (AT_1) receptor blocker, losartan, did not have any effect on ischemic preconditioning, suggesting that the protective effect of the ACE inhibitor is independent of the AT_1 receptor. ACE also cleaves bradykinin, and the use of ACE inhibitors therefore results in the accumulation of bradykinin. In animal models of ischemic preconditioning, ACE inhibition has been shown to reduce infarct size and decrease reperfusion arrhythmias [22,23], whereas specific bradykinin receptor blockers abolished this effect [24]. This suggests that bradykinin determines, at least in part, the protective duration of ischemic preconditioning. Nicorandil (a potassium channel opener) did not have any effect on warm up angina in the same study, indicating that opening of ATP-sensitive potassium channels may not be an essential event in triggering warm up angina in humans (*Figure 2*).

Summary

The variable relationship between exercise and angina has been recognized for more than 200 years [1]. This variability is reflected by the terms ''warm up'' or ''second wind'' angina. These describe the ability of some patients to exercise to angina, rest, and then continue exercise with reduced symptoms or none at all. After an episode of exercise-induced angina, there are significant reductions in the severity of angina, exercise limitation, and ST-segment

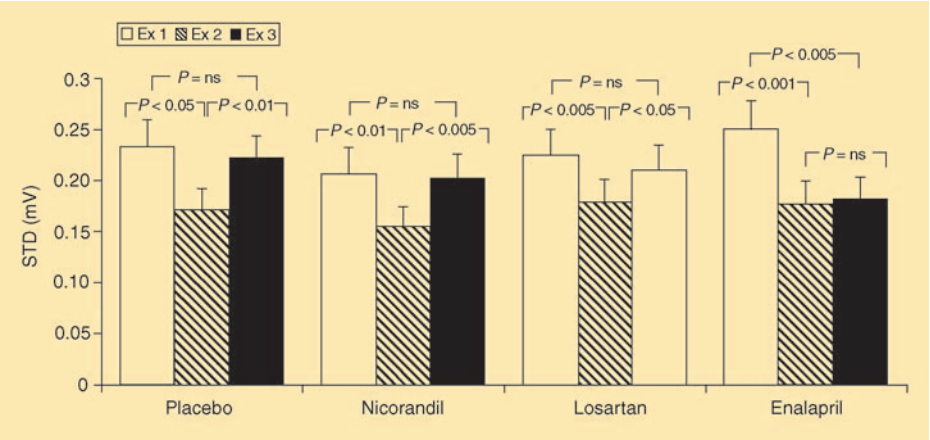

Figure 2. Mean values (±SD) of ST-segment depression (STD) at equivalent workloads during three sequential exercise treadmill tests in patients with coronary artery disease and stable angina. The second test was separated from the first by a 15 min period of rest. The third test was performed after a further 90 min of rest. Serial exercise tests were performed while patients were taking the drug indicated. The second exercise test (Ex 2) showed a consistent decrease in STD compared with the first (Ex 1), corresponding to the warm up phenomenon (second wind phenomenon). This protective effect vanished in the third test (Ex 3), except in the enalapril group, indicating a prolongation of the protective window of preconditioning with enalapril. (Adapted from Edwards et al [21], with permission.)

depression. The mechanisms that underlie warm up angina are not yet clearly understood. The adaptations of the heart that render it more resistant to ischemia during a second exertion or exercise test are believed to result from a combination of preconditioning and collateral recruitment. Possible mediators of preconditioning are adenosine, bradykinin, and opioid receptor activation. ATP-sensitive potassium channels and protein kinase C seem to be involved also. As many of these mediators are vasodilators, it is likely that they also influence collateral recruitment. Late or delayed preconditioning developing 12–24 h after the first ischemic stimulus and lasting for 3–4 days has important clinical relevance, as it can protect against myocardial stunning and infarction, and repeated triggers prolong the effect [8]. ■

* See glossary for definition of these terms.

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