

BRITISH HEART JOURNAL

Editorial

Is warm-up in angina ischaemic preconditioning?

It is more than 40 years since first effort angina was the subject of an editorial in the *British Heart Journal*.¹ Have the intervening years provided any new insights into the pathophysiology of this fascinating phenomenon?

First effort, warm-up, or first hole angina are terms used to describe the ability of some patients to exercise to angina, to rest, and then to continue exertion with few or no symptoms. These terms may be related to walk through angina or second wind in angina that describe a phenomenon where angina sufferers exercise to pain and are then able to continue exertion with few or no symptoms but, unlike warm-up angina, without an intervening period of rest. Some of these phenomena have been recognised for centuries² but they now receive less attention because of effective anti-angina treatment and changes in investigative techniques. For example treadmill exercise testing does not allow rest and imposes incremental increases in effort which make the walk through effect less likely. Only about 1 in 5 patients report symptoms of warm-up angina.³ Objective testing in recent studies showed that at least 75% of unselected patients with angina had an enhanced performance on second effort.⁴⁻⁷ In these studies exercise performance on second effort was on average 125% of that on first effort, but there was considerable individual variability. Not surprisingly those individuals who derived the greatest benefit from first effort were those with a history of warm-up angina,⁶ suggesting that objective testing is a better indicator than reports of symptoms.

The pathophysiology of warm-up angina is poorly understood. The paradox that patients recovering from an episode of angina are more resistant to further effort-induced angina superficially resembles the paradox that led to the discovery of ischaemic preconditioning. We propose that the investigation of ischaemic preconditioning may shed some light on the mechanism underlying warm-up angina.

Animal studies of ischaemic preconditioning

In 1986 Murry *et al* reported the results of an important series of experiments examining the consequences of short episodes of myocardial ischaemia in dogs.⁸ The hypothesis under investigation was that myocardium sublethally injured by a brief period of ischaemia would be more sensitive to subsequent ischaemia, so that repeated brief ischaemic insults might cumulatively cause infarction. This hypothesis proved to be incorrect. The first short ischaemic episode triggered adaptive metabolic changes within the myocardium such that subsequent

episodes of ischaemia, though they lasted as long, caused less of a decline in high energy phosphate and less lactate production. More importantly, when the last ischaemic episode was extended to 40 minutes the adaptive changes triggered by sublethal ischaemia reduced infarct size by 75%.⁸ This phenomenon was termed "ischaemic preconditioning".⁸

Ischaemic preconditioning has been further characterised in animal studies. It is now known that the protection can be triggered by as little as 3 minutes' ischaemia⁹ and that adenosine released from ischaemic ATP breakdown is the trigger.¹⁰ The adenosine released accumulates locally and acts on a subclass of adenosine receptors (the A₁ receptors) that are thought to mediate their protective effect via a G protein.¹⁰ Myocardial protection appears about 1 minute after a short episode of ischaemia¹¹ and lasts for approximately 60 minutes.¹⁰ It can be renewed by further short episodes of ischaemia.¹⁰ All the animal species examined showed ischaemic preconditioning¹² and it probably also occurs in humans.¹³

Mediation of angina

The sensation of pain during angina is likely to be the result of an accumulation of adenosine within myocardial tissue because intracoronary injections of adenosine reproduce the symptoms.¹⁴ Preliminary investigations suggest that the sensation of angina, like the preconditioning phenomenon, is mediated by adenosine binding to an adenosine receptor of the A₁ subclass.¹⁵ It is therefore possible that the ischaemia that causes angina can trigger the metabolic adaptive changes of ischaemic preconditioning and that this is the cause of the warm-up phenomenon. Closer inspection of information on warm-up provides evidence in support of this theory.

Warm-up angina traditionally was ascribed to coronary vasodilatation,^{16,17} with perhaps concomitant opening of collateral vessels to support the ischaemic myocardium. This explanation was accepted despite the fact that arterial vasodilators such as aminophylline had little effect on exercise tolerance,¹⁷ and that the presence of collaterals on angiography was not a predictor of walk through or warm-up angina.³ In addition other features of warm-up angina were difficult to explain. For example, why did the second effort reproducibly exceed the first effort provided the two were separated by a rest period of at least 2-5 minutes but not more than 30-60 minutes?¹⁷ These intervals are consistent with warm-up being a form of ischaemic preconditioning.

The suggestion that warm-up, like ischaemic preconditioning, is an adaptive phenomenon is further supported by invasive investigation. Williams *et al* examined 11 patients with stable angina caused by stenosis of the left anterior descending coronary artery (LAD).⁵ No attempt was made to elicit a history of warm-up angina before the patients were selected. Heart rate was incrementally increased by atrial pacing until angina occurred; patients were then rested for 5–10 minutes before the pacing protocol was repeated. During the second period of pacing, angina and ST segment depression were reduced. More interestingly venous blood samples taken from the distal coronary sinus close to the interventricular vein showed that lactate was still being extracted during the second protocol at a time when on average during the first pacing protocol it was being produced.⁵ This change in myocardial metabolism was mirrored by a reduction in myocardial blood flow and oxygen consumption when the second pacing period was compared with the first. This observation effectively ruled out enhanced collateral flow as the explanation for warm-up.

The results obtained above resemble those recently reported by Okazaki *et al*.⁶ They studied 13 patients with LAD stenosis by performing two sequential supine exercise tests separated by 15 minutes of rest. They also found that angina, ST segment depression, and myocardial oxygen consumption were less on second effort for an equivalent amount of work.⁹ In addition they showed that though angina occurred at the same myocardial oxygen consumption during each test this was achieved at a higher workload on second effort, suggesting that the heart had become regionally more efficient. They related these findings to an enhanced production of adenosine by the ischaemic LAD territory on second effort.⁶ Intuitively, adenosine release, like all other measures of ischaemia, should have been reduced on second effort. An identical "adenosine paradox" occurs in ischaemic preconditioning where the enhanced ischaemic production of adenosine is thought to be secondary to an increase in the activity of the adenosine-forming enzyme 5'-nucleotidase immediately after sublethal ischaemia.¹⁸

Clearly the reports by Williams *et al*⁵ and Okazaki *et al*⁶ imply that between the first and second efforts a change occurs in myocardial metabolism that reduces the requirements for substrate. One explanation is that this effect is secondary to stunning (of regional contractile function) after the first effort or rapid pacing period, which may reduce contractile protein energy requirements. This seems unlikely, however, because in both studies myocardial oxygen requirements returned to baseline after the first rapid pacing or exercise period.^{5,6} In addition it is not clear whether the metabolic demands of stunned myocardium are less or more than those of healthy tissue.¹⁹ Other possibilities such as the redistribution of myocardial blood flow (epicardial *v* endocardial) between one effort and the next seem inherently unlikely and are not easy to prove or disprove.^{6,7} The most likely explanation is that warm-up is a form of myocardial adaptation akin to ischaemic preconditioning. To demonstrate conclusively that warm-up and ischaemic preconditioning share the same triggers would require A₁ receptor blockade in the patient. However, no specific A₁ antagonist is available for use in humans.

Ischaemic preconditioning can be induced experimentally in most animals because there is little overlap in the size of infarction between intervention and control groups.¹¹ Conversely, warm-up angina is reported by only 20% of patients.³ This disparity disappears, however, with objective testing^{4,5,9} suggesting that patients are

either insensitive to their enhanced performance or unlikely spontaneously to report the effect.

Relation to walk through angina

If warm-up is related to ischaemic preconditioning, what is its relation to walk through or second wind in angina? In contrast to the "no-flow" ischaemia of most experimental ischaemic preconditioning protocols, angina is secondary to ischaemia with flow. In such a situation reperfusion or a period of rest may not be necessary to trigger preconditioning because ischaemia and reperfusion are coincident.¹⁰ Thus one can speculate that when anginal discomfort and A₁ receptor occupancy have reached a critical level, ischaemic preconditioning is triggered, the myocardium becomes more efficient, and angina diminishes or disappears. Such disappearance of pain at a critical point during exercise gives rise to the "second wind" or "toter punkt" phenomenon.²⁰ This effect is associated with the resolution of ischaemic ST segment changes²¹ and the disappearance of regional dyskinesia.²¹ Both observations are consistent with an adaptive phenomenon.

Implications

What are the possible benefits to the patient if warm-up and ischaemic preconditioning are the same phenomenon? Ischaemic preconditioning is currently being intensively investigated and if the pace of progress over the past 6 years continues the second messenger systems and final effectors will soon be characterised and exploited. These findings may make it possible to mimic warm-up pharmacologically to achieve the exercise performance usually associated with the second effort after the first. First effort angina can still enhance exercise tolerance in patients taking anti-anginal medication.⁷ The investigation of ischaemic preconditioning may therefore lead to an effective and novel additional treatment for angina. Furthermore in those patients with angina who develop a coronary artery occlusion, drugs that mimic preconditioning and warm-up should delay myocardial necrosis. This will increase the "time window" for thrombolysis and hence could reduce mortality. The mechanisms underlying preconditioning, once exploited, promise a novel treatment that may reduce symptoms as well as mortality in angina.

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MSM is the recipient of an intermediate fellowship from the British Heart Foundation. We thank the Hatter foundation for continued support.

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