Exercise training with ischaemia: is warming up the key?

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This editorial refers to ‘Can prolonged exercise-induced myocardial ischaemia be innocuous?’ by M. Noël et al., on page 1559

Exercise testing remains a key tool in the management of patients with ischaemic heart disease (IHD) both in a diagnostic and rehabilitation setting. A familiar scenario involves performing an exercise test to identify inducible ischaemia either to determine whether IHD is a likely diagnosis or as a prelude to a structured exercise programme in individuals with a recent acute coronary syndrome or with chronic symptoms in whom IHD has already been diagnosed. Consequently, the prospect of prescribing exercise to patients is a problem faced regularly by clinicians. However, there is still an appropriate level of concern in recommending an activity which increases myocardial work and may provoke an imbalance between myocardial oxygen supply and demand. This is despite the risk of exercise testing being remarkably low, particularly in those that have continuous ECG monitoring.1 One of the methods by which adverse events may be reduced is by identifying those individuals at greatest risk and therefore pre-training risk assessment constitutes a substantial part of current guidelines.2 Long-standing experimental evidence supports the advantages of exercise training from the perspective of both cardiac metabolic benefits and psychological well being.3,4 However, disquiet often persists with regard to the safety of such an undertaking in a clinical setting. This disquiet has been nurtured in part by previous data,5 suggesting that ventricular arrhythmias may be provoked by exercise in these patients and partly by the lack of a clear assessment of safety in previous studies assessing the impact of training individuals with known coronary stenoses.3,4,6 Furthermore, although current guidelines contain comprehensive instructions for exercising patients with coronary artery disease, they are notable for the relative paucity of detail for those with inducible ischaemia.2 Specifically, the guidance states that exercise should be performed at a moderate intensity, 40–60% of VO₂max, yet at all times ensuring that the pre-identified ‘ischaemic threshold’ is not crossed by monitoring the heart rate so that it remains 10 b.p.m. less than the rate at which 1 mm ST-depression or angina occurred. Although these instructions may ensure patient safety, they may also be prohibitively conservative and thereby restrict any benefit. There is some evidence confirming that exercising at higher intensities produces improvements in VO₂max and lipid profile in individuals without IHD.7 Is it possible to extend these potential benefits to patients who would otherwise be excluded from higher intensity training by current guidelines?

The paper by Noël et al.8 investigates the safety of endurance exercise in patients with angina. Twenty-two patients with documented evidence of coronary disease and unequivocal ST-depression during exercise testing were randomly allocated to one of two types of exercise protocol each for up to 60 min, performed three times a week over a 6-week period. In the traditional group, exercise was performed within guideline-set limits so that heart rate stayed at 10 b.p.m. below the ischaemic threshold. In the ischaemia group, the level of ST-depression was carefully controlled between 1 and 3 mm by exercise intensity. The findings appear to demonstrate that ischaemia-inducing endurance training for IHD patients can be performed without significant arrhythmias (as measured during exercise by intensive ambulatory monitoring), myocardial injury (as measured by repeated high-sensitivity troponin T assays), or left ventricular dysfunction (as measured by echocardiography after, compared with before, the 6-week training period). In contrast to the previous work5 in which arrhythmias appeared to occur as a consequence of exercise with ischaemia, the patients were required to undergo a 5–10 min period of warming up before commencing their endurance exercise regime. It is possible therefore that the relative safety experienced by the study group was a manifestation of the protective effect of ischaemic preconditioning, effectively demonstrating that ‘warming up’ for exercise appears to be the key to successfully exercising patients with ischaemia. Therefore, this study is potentially more than simply an exposition of safety: a framework is described upon which the physiological effects of training...
above the ischaemic threshold can be investigated. More tantalizing perhaps is the prospect of further investigating the phenomenon of warm-up angina.

Warm-up angina is a phenomenon describing the attenuation of angina when it is preceded by a recent, angina-provoking exertion. In this respect, there is a casual resemblance to the effect of ischaemic preconditioning, originally demonstrated by Murry et al.9 They described a profound reduction (40%) in myocardial infarct size in dogs if they were pre-treated with repeated brief episodes of non-lethal ischaemia. The parallels between these phenomena have been the subject of much interest.10 Despite the clinical application of preconditioning being almost impossible, requiring foreknowledge of the ‘lethal’ ischaemic event, translational work from animal models may find a practical relevance in warm-up experiments. Hence, the study of warm-up angina may be a tool for understanding and potentially exploiting some of the adaptive mechanisms that protect the heart during ischaemia, such that a pharmacological agent could be used to improve angina by reproducing the warm-up effect without the patient needing to perform the symptom-limiting, ischaemia-provoking exercise. However, several differences between these phenomena have also been demonstrated, suggesting that their mechanisms are distinct and require further evaluation.11

Previously published work by the author’s group established that non-strenuous exercise alone appears to be sufficient to reduce subsequent angina on exertion.12 However, when ischaemia is measured more rigorously by monitoring the rate pressure product as a correlate of myocardial oxygen consumption13 at specific levels of ST-depression, it was found not to be reduced unless the initial exertion was of a greater intensity. This was achieved by symptom-limited exercise. Hence, a separation emerged between the patient’s perception of ischaemia and an objective measurement of it. More importantly, myocardial protection against ischaemia did not emerge unless the preceding exercise was sufficiently extreme.

Although the study by Noël et al. provides reassurance that repeated and prolonged exercise above a patient’s ischaemic threshold appears safe, there are caveats that the authors themselves point out. The number of patients in the intensive exercise group was too small (n = 11) to assess safety and even, arguably, pathophysiological changes such as LV dysfunction due to repetitive stunning.14 In addition, the study seems to have been performed primarily to determine whether a more intensive ischaemia-inducing training regime would be superior to a traditional guideline-driven approach. Despite the patients in the more intensive ischaemia group maintaining prolonged periods of ST-depression, there was no measurable improvement in aerobic capacity or rate pressure product. Although in part this may be the result of imperfect matching of baseline exercise performance between groups, it does not provide an immediate impetus to set up the personal monitoring by exercise specialists that such an ‘ischaemia-targeted’ regime requires. In essence, although regular exercise above the ischaemic threshold should have the theoretical added benefit of triggering long-lived preconditioning-like effects15 and collateral growth,16 these were not observed.

In summary, the authors are to be congratulated in performing a careful study that achieved the ambitious objective of allocating patients to two exercise training regimes: one that caused prolonged and the other that caused little or no, ST-depression. Unfortunately, despite heroic efforts, the predicted benefits of prolonged ischaemia were not apparent. Thankfully, neither were the risks. However, neither risk nor benefit can be adequately assessed without a larger equally well-controlled follow-on study. Any volunteers?

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References