Writing on the topic of pectoris dolor:

With respect to the treatment of this complaint, I have little or nothing to advance: nor indeed is it to be expected we should have made much progress in the cure of a disease, which has hitherto hardly had a place, or a name in medical books… Opium taken at bed-time will prevent the attacks at night. I know one who set himself a task of sawing wood for half an hour every day, and was nearly cured.

—William Heberden

The salient observation defining the clinical syndrome of warm-up angina, namely that anginal symptoms may be reduced with repeated episodes of work, was initially made >200 years ago by the London physician William Heberden. Consistent with his original description, contemporary demonstrations of warm-up angina either involves greater time to ischemic signs or symptoms (ie, ST-segment depression or chest pain) or a reduction in ischemic manifestations at equivalent workload in patients with coronary artery disease undergoing repeated bouts of exercise. Multiple theories have been proposed to explain this physiological phenomenon, ranging from changes in myocardial signaling to increased collateral recruitment and ischemic preconditioning.2–4 Greater appreciation of physiological adaptations occurring with exercise vis-à-vis ventricular vascular coupling combined with novel methodologic approaches has provided a fresh mechanistic insights and advanced our understanding of this clinical entity.3–7

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At its most basic level, warm-up angina implies a favorable modulation of the myocardial supply–demand equation whereby the oxygen supply is enhanced or demand is reduced after an initial bout of exercise. To address this complex question, Lockie et al7 studied 16 patients (15 male) with exercise vis-a'-vis ventricular vascular coupling combined with novel methodologic approaches has provided a fresh mechanistic insights and advanced our understanding of this clinical entity.3–7

Exercise Physiology in the Catheterization Laboratory
Still Alive and Well!

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mand and supply were measured invasively by using a dual-sensor pressure/flow wire in the culprit coronary vessel and a separate wire in the ascending aorta. Subjects underwent exercise by using a supine cycle ergometer, rested, and then exercised again. Time between exercise periods was ~8 minutes. Hemodynamic indices were compared at equivalent time points between the exertion periods. Consistent with a warm-up effect, time to ischemia (1 mm ST-segment depression) was significantly greater during the second versus the first exercise period (313±35 versus 260±31 seconds, P=0.003). In addition to documenting its presence, however, the authors also demonstrate synergistic physiological changes with exercise that, in concert, account for the observed warm-up effect. The difficulty to perform this type of protocol has been underlined by a significant percentage of study noncompleters (11/27) because of a variety of clinically meaningful reasons.

With respect to oxygen demand, the authors found that the tension time index, a metric that quantifies ventricular loading and is strongly related to myocardial oxygen consumption,8 was significantly lower at each time point during the second exercise period. Reductions in the area under the systolic portion of the aortic pulse waveform are partially attributable to the concordant shortening of left ventricular ejection time in the second exercise portion. In addition, the augmentation index, representing the incremental contribution of reflected waves on left ventricular afterload was significantly reduced at each measured time point between exercise periods. This could potentially be a key parameter to follow.

Studying healthy volunteers, Munir et al6 previously demonstrated that favorable changes in augmentation index resulting from exercise are most likely due to greater vasodilation of muscular arterial beds rather than changes in arterial stiffness or stroke volume. These conclusions were based on the finding that at 60 minutes following bicycle ergometry, the augmentation index remained significantly lower in comparison with baseline values, whereas heart rate and pulse wave velocity (an index of arterial stiffness) had returned to preexercise levels. In addition, changes in the arterial waveform after exercise were similar to those occurring after nitroglycerin infusion, suggesting a shared pathophysiologic mechanism. Lockie et al have now expanded these earlier findings to patients with coronary artery disease who have stable angina and using in vivo techniques, they have further shown that the reductions in augmentation index with exercise are a relevant physiological adaption that underlies warm-up angina. Together, these studies highlight the important role of enhanced ventricular-vascular coupling as an exercise-induced mechanism accounting for the atten-
uation of myocardial oxygen demand observed with serial exercise.

Oxygen delivery to any organ is a function of the amount of blood delivered to and oxygen extraction by that respective organ. In the human heart, oxygen extraction is constantly near maximal capacity, thereby implying that any improvement in oxygen delivery depends on increasing coronary blood flow. As elsewhere in the arterial vasculature, coronary flow is driven by the gradient between the aortic ($P_a$) and distal coronary ($P_d$) pressures ($\Delta P$). Because resistance beyond a culprit coronary stenosis is thought to be near minimal at the time of angina and exercise is accompanied by changes in left ventricular afterload, one might anticipate that enhancing coronary blood flow would not be a physiological correlate of warm-up angina. In their study, however, Lockie et al found that mean coronary blood flow velocity (27 versus 22 cm/s, $P=0.03$) and mean pressure gradient across the coronary stenosis, $\Delta P$ (18 versus 11 mm Hg, $P=0.02$), were significantly greater during the second in comparison with first exercise period. These changes were accompanied by concordant reductions in microvascular resistance without any change in the coronary stenosis resistance. As Davies et al previously mentioned, however, the coronary flow/velocity profile is an effect and not the cause of changes in hemodynamic parameters. To address this gap and provide mechanistic insight, Lockie et al applied the novel technique of wave intensity analysis to study the observed changes in coronary flow between exercise periods. Within this paradigm, phasic blood flow is explained by a series of wave fronts that underlie observed changes in pressure or flow. Waves may be characterized by origin and direction (forward-traveling versus backward-traveling), character (pushing or suction), and effect on coronary blood flow velocity (acceleration or deceleration); these are shown in graphically in the Figure. Quantifying these wave fronts informs on the relative importance of aortic and microcirculatory contributions to coronary blood flow. Davies et al In their study, Lockie et al found a marked and consistent increase in the energy of the backward-traveling expansion wave at all measured time points between exercise periods. These findings suggest that myocardial relaxation and microcirculatory decompression are enhanced after initial exercise and are important contributors to increasing coronary blood flow during subsequent exercise in warm-up angina.

It is important to note that recruitment of coronary collaterals increases after exercise and may also diminish angina after repeated exercise. As the authors point out, however, such measurements were not practical in their study and therefore, the relative contribution of collateral recruitment in enhancing coronary flow was not assessed. In addition, most subjects in studies examining the warm-up angina have been male. This is an important limitation because sex-related

\textbf{Figure.} Sequence of energy waves in the human coronary artery during the cardiac cycle. Arrows represent the direction of wave motion rather than the direction of blood flow. Reprinted with permission from Davies et al.®
differences in the central arterial pressure waveform may differentially effect changes in hemodynamic parameters with exercise.\textsuperscript{15} Finally, although this elegant study by Lockie et al substantially advances the conceptual physiological framework for the warm-up angina phenomenon, underlying molecular signaling pathways accounting for this clinical entity require further study. Nonetheless, Lockie et al are to be congratulated for taking advantage of radial access angioplasty/stent set-up and technological advances, as well, to conduct a painstaking exercise physiology study in the current era of mostly device-based research in the cardiac catheterization laboratory. Because percutaneous coronary intervention aims to reduce ischemic symptoms, we would be reasonably expecting a continuation study on the effects of percutaneous coronary intervention on the hemodynamic parameters that characterize the target lesion and vessel.

Disclosures

None.

References


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