The relationship between platelet aggregation and thrombotic events

The findings of this paper are curious. The authors told their patients all to take aspirin but the authors state that aspirin is a relatively weak platelet inhibitor and they note that agents such as clopidogrel selectively inhibit platelet activation by ADP and are shown to be more potent antiplatelet drugs than aspirin. The authors are tempted to speculate that the low platelet aggregation and high incidence of thrombotic events may be the consequence of platelet activation in the circulation leading to a decrease of platelet sensitivity to agonists in vitro.

The correlation findings of this paper seem to be as clear as they are surprising. It is a struggle to put together the significance of the findings and speculate on a way ahead. The authors are clearly taking the view that aspirin and low dose warfarin should be considered in the expectation of effectiveness in reducing thrombotic events in patients with peripheral vascular disease. I would have to regard this as pure speculation at this stage. I would be more than cautious about treating the patient who came to see me with some nick in the calf with exercise and anticoagulants long-term, which have their own complications and disadvantages. Certainly the authors have added to the increasing awareness that peripheral arterial disease should be seen as a mild form of generalised arterial disease and investigate from that point of view in terms of thrombotic events, mortality risks and stroke and so on. Nevertheless the claudicant should benefit from the full spectrum of best medical treatment including antismoking advice, diabetic control, hypertension control, lipid control and consideration of statins, not just thoughts about thrombotic state.

In addition to best medical treatment which every claudicant deserves, a system of supervised exercise looks as if it might be very effective in many cases. The position of angioplasty in mild peripheral arterial disease and mild to moderate intermittent claudication is to be the subject of a British national trial (the MIMIC Trial).

Correlations and ideas are one thing but they need to be put to the test. For mild to moderate intermittent claudication (MIMIC) we are prepared to test whether angioplasty is effective over and beyond best medical treatment and supervised exercise. I would like to suggest that it is just as important to prove any relevance of the findings of raised D-dimer and low platelet aggregation as associated with thrombotic events. Can anything be changed as a result of these findings in patients with intermittent claudication to improve the natural history? Important questions raised in this paper need to be tested by carefully designed clinical trials.

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Circulatory power — a new perspective on an old friend

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Ever since the observations by Harvey on the circulation of the blood, and by the Reverend Stephen Hales on the ability of the heart to maintain a column of blood from the carotid artery of his horse, it has been recognised that the mammalian heart is a truly remarkable pumping machine, and attempts have been made to quantify its function. At first observations were confined to heart rate and blood pressure, but at the turn of the last century the technology for the measurement of whole body oxygen uptake (VO₂) was developed and applied to patients with cardiac failure[1,2]. However, such tests were only an indirect measure of cardiac function, and were cumbersome and difficult to perform — the retrospective gas analysis took a considerable length of time. The development of hollow catheters for the measurement of intraluminal pressures therefore represented a notable advance[3] and the haemodynamic responses to exercise in patients with heart failure could be assessed[4–7]. The application of the Fick principle meant that cardiac output (Qt) could be measured by taking samples of blood from the pulmonary artery and a systemic artery and estimating their oxygen content. Thus:

\[ Qt = \frac{VO_2}{\text{arteriovenous O}_2 \text{ difference}}. \]
Whilst this became the reference method against which all others (such as dye dilution or thermodilution) have since been compared, it still has some disadvantages. The test is invasive, involves a moderately expensive disposable catheter, and because of the time taken to collect the exhaled air, cannot be performed at true peak exercise. Resting levels are too variable, as they depend on respiratory, preload and afterload conditions, which are subject to constant change. The goal of measuring true peak performance therefore remained elusive.

With the advent of fast gas analysers and desktop computers, measurement of respiratory gas exchange became a practical proposition for routine use. The reproducibility of such testing was defined and its value as a prognostic indicator in patients with heart failure firmly established. Furthermore, Qt can be measured non-invasively using CO2 as the indicator gas (see equation above). Recently the heart failure firmly established. Furthermore, Qt function and O2 extraction capacity. The measure which may depend in part on muscle cardiac performance than peak achieved VO2, a renewed interest in more refined indices of specific invasive methodology remain. There is therefore remained elusive.

The ‘cardiac power output’ (CPO), as defined by Tan and his colleagues, is an attractive alternative. The theoretical background to this concept is given elsewhere but in brief, cardiac power output takes into account both the flow generated by the heart and the perfusion pressure maintained, and is defined as the product of Qt and the mean arterial pressure (MAP), with a constant (K = 2.22 × 10⁻³) to convert the units to Watts (W):

\[
\text{CPO} = Q_t \times \text{MAP} \times K
\]

The resting value in normal subjects is about 1 W and is similar in patients with heart failure. The difference in the two groups is found during stress or exercise. Whereas in normal subjects the cardiac power output at peak exercise may rise to over 7 W, in patients with heart failure the mean rise was to <3 W, and those with a peak cardiac power output of <1.96 W had a significantly greater mortality over a 5-year period. This indicates that patients have a markedly reduced cardiac reserve, even when resting cardiac power output levels are normal, and that the extent of the reserve is a better prognostic indicator than PVO₂. Measurement of cardiac power output is non-invasive and holds out the promise of being more discriminating of outcome than PVO₂ alone.

There are, however, some disadvantages to this method of assessment. The facilities for the measurement of the cardiopulmonary responses to exercise are now widely available, but the equipment for the rebreathing CO₂ method of measuring Qₜ is not. Furthermore, considerable experience in the field of exercise physiology would be required to run this programme successfully, which could limit its application to a few centres only. There are also methodological problems. Qₜ was measured during a separate run at a work rate corresponding to the peak work rate in the preceding incremental test, and so represented a high work load, but not true peak cardiac power output, a target which still eludes us, mainly because of the time taken to conduct the measurements.

The non-invasive CO₂ rebreathing method derives values for CO₂ concentration in arterial and mixed venous blood, respectively, from the end-tidal PCO₂ and the plateau value of CO₂ after rebreathing. The key assumption that P̄PCO₂ ≈ P̄CO₂ may not hold in disease states and so the calculation of the arteriovenous CO₂ difference would be disturbed. More recently Sun et al. have also highlighted a problem during exercise, and cast doubt on the widely-accepted assumption that P̄PCO₂ is linearly related to CO₂ concentration in blood over a broad physiological range. During heavy exercise in both normal subjects and those with cardiac disease, lactic acidosis supervenes resulting in a buffering of H⁺ with the release of CO₂ from HCO⁻. Acidosis therefore has the effect of reducing the total CO₂ concentration at a given P̄PCO₂ and it has been calculated that the failure the take pH into consideration could potentially cause an underestimation of cardiac output by up to 50% at high levels of exercise. In addition, the measurement of diastolic blood pressure during exercise, essential for the calculation of mean arterial pressure, is notoriously difficult by conventional auscultation. Nevertheless, this method is as close as we can get at the moment to a non-invasive measure of cardiac performance.

What then of the ‘circulatory power’, an index described previously by Professor Cohen-Solal and his colleagues? This uses PVO₂ as a surrogate for Qₜ, and systolic blood pressure for mean arterial pressure. It is therefore not as ‘correct’ as cardiac power output, but the information for its calculation is available from any cardiopulmonary exercise test without the need for special equipment, and it too seems to have greater prognostic power than PVO₂ alone. The units of ‘circulatory power’ are ml O₂ × mmHg . min⁻¹, while those of true cardiac power are ml blood × mmHg . min⁻¹. As such, ‘circulatory power’ represents the volume of O₂ added to
the mixed venous blood by the lungs and transferred to the systemic arterial circulation, against a pressure gradient, by the heart. Conceptually ‘circulatory power’ is considerably more difficult to envisage than cardiac power output, as it is not really a true power at all.

What does this mean in terms of interpreting the test results and what are the possible confounding factors? Clearly the transport of O\textsubscript{2} around the circulation relies on cardiac function, but from the Fick equation (see above), O\textsubscript{2} transport is also dependent on another factor, the arteriovenous O\textsubscript{2} difference. At a given true cardiac work, variability in arteriovenous O\textsubscript{2} difference would directly cause variation in the calculated circulatory power. In normal subjects, arteriovenous O\textsubscript{2} difference rises from approximately 50 ml \textperflush\textsuperscript{-1} at rest to 150 ml \textperflush\textsuperscript{-1} at peak exercise\textsuperscript{[31–33]}. Arteriovenous O\textsubscript{2} difference rises throughout exercise and its increase is reasonably linear with respect to percent maximal VO\textsubscript{2} in normal subjects\textsuperscript{[32]} and patients with heart failure\textsuperscript{[33]}. Sub-maximal levels of exercise would be expected to affect the measurement of circulatory power more than that of cardiac power output, since arteriovenous O\textsubscript{2} difference would be lower than at maximal exercise. Arteriovenous O\textsubscript{2} difference is similar in normal subjects and in patients with heart failure at maximal exercise\textsuperscript{[33]}. There is significant inter-patient variability in the peak arteriovenous O\textsubscript{2} difference, however\textsuperscript{[33]}, and pharmacological interventions to augment cardiac output acutely may reduce the arteriovenous O\textsubscript{2} difference\textsuperscript{[34]}. Variability in haemoglobin concentration alters O\textsubscript{2} carrying capacity and hence arteriovenous O\textsubscript{2} difference. Thus anaemia or polycythaemia could potentially depress or augment the measured circulatory power. Coexisting lung disease and exercise at altitude would be expected to affect the measurement of circulatory power by reducing arteriovenous O\textsubscript{2} difference. Arteriovenous O\textsubscript{2} difference increases with increasing altitude\textsuperscript{[37]} and has been found to be an independent predictor of mortality or urgent transplantation. Decreased ventilatory efficiency during exercise, as measured by an elevated slope of the relationship between VE and VCO\textsubscript{2} correlates with poor functional capacity in heart failure\textsuperscript{[36]}. The increase in VE vs. VCO\textsubscript{2} slope may result from alveolar hypoperfusion\textsuperscript{[37]} and has been found to yield independent prognostic information\textsuperscript{[38–41]}. In one study\textsuperscript{[41]} VE vs VCO\textsubscript{2} slope was a better predictor of mortality than PVO\textsubscript{2}, although another study found the converse\textsuperscript{[40]}. Japanese investigators\textsuperscript{[42]} have recently demonstrated that slowed VO\textsubscript{2} kinetics in response to a constant work-rate predict mortality, although it has yet to be determined if the relationship is independent of PVO\textsubscript{2}.

Incorporating as it does measures of blood flow and pressure, and being simple to derive, circulatory power is certain to have widespread application. What would be interesting of course is a direct comparison of circulatory power and cardiac power output in terms of their prognostic capacity. In the meantime, ‘circulatory power’ should find its way into everyday use in the exercise laboratory, and the cardiac power output used in a more academic environment to explore further the pathophysiology of cardiac diseases.

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