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A man is as young as his endothelium

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I have read the interesting Features Article by Raya All-Maskari & Yasmin entitled 'A man is as old as his arteries: a scientific journey of ageing and aortic function', published in issue 98 of *Physiology News*. The article is enjoyable and easy to read. However, it is necessary to point out that the effects **on coronary flow** of arterial stiffening described are true only in chronic unhealthy conditions, when pulse pressure increases for some non-physiological condition, such as marked atherosclerosis, for example. A casual reader may take the misconception that increased pulse pressure (increased systolic and reduced diastolic pressure) necessarily implies a reduction of coronary blood flow. Unfortunately this false idea is sometimes reported in the textbooks of physiology: when the arterial diastolic pressure decreases myocardium is less perfused, because it is mainly perfused in diastole. This is not correct. In a healthy individual an acute increase in pulse pressure (increased systolic and reduced diastolic pressure at the same mean pressure) may induce an increase in coronary flow in the left coronary artery (Pagliaro *et al.* 1999; Paolocci *et al.* 2001). Actually, during intense dynamic exercise, in a healthy subject pulse pressure may double and mean pressure does not change appreciably (Lind & McNicol, 1967). In these conditions coronary flow may increase greatly.

No one doubts that exercise is a primary stimulus for the increased demand of myocardial oxygen, which may increase by about 5 times during intense effort. This increased oxygen demand is met mainly by increasing coronary blood flow (approximately 5 times). In fact, the extraction of oxygen (which is already ~ 70% at rest) can increase only slightly. As a result, in an healthy young subject the coronary blood flow increases **because of vasodilatation** and is closely coupled to the myocardial oxygen consumption. This tight coupling has been proposed to depend on tissue oxygen tension, signals released from cardiomyocytes, neuro-humoral influences, and the endothelial factors. Although the interactions of these regulatory factors to determine exercise-induced coronary hyperaemia is not completely understood, there are plethora of articles pointing out the importance of endothelium in coronary regulation during acute exercise and in training (Westerhof *et al.* 2006, Duncker & Bache, 2008).

When pulsatility increases in unhealthy individuals for a long time the raised systolic pressure and the reduced diastolic pressure may compromise coronary perfusion, because of an unmatched increase in cardiac oxygen demand, especially in the presence of cardiac hypertrophy. In these conditions it is likely that the increase in pulsatility is a cause and/or an effect of endothelial dysfunction. However, in a young individual with a healthy endothelium, when there is an acute increase in pulsatility, it is likely that coronary flow increases because the vasodilator endothelial factors concur to determine coronary flow. In fact, during exercise the pulsatility may increase considerably and in these conditions the increased oxygen demand is matched by increased coronary flow with the fundamental help of endothelial factors.

Duncker DJ, Bache RJ (2008). Regulation of coronary blood flow during exercise. *Physiol Rev* **88**, 1009-1086.

Lind AR, McNicol GW (1967). Muscular factors which determine the cardiovascular responses to sustained and rhythmic exercise. *Can Med Assoc J* **96**, 706-715.

Pagliaro P, Senzaki H, Paolocci N, Isoda T, Sunagawa G, Recchia FA, Kass DA (1999). Specificity of synergistic coronary flow enhancement by adenosine and pulsatile perfusion in the dog. *J Physiol* **520**, 271-280.

Paolocci N, Pagliaro P, Isoda T, Saavedra FW, Kass DA (2001). Role of calcium-sensitive K(+) channels and nitric oxide in *in vivo* coronary vasodilation from enhanced perfusion pulsatility. *Circulation* **103**, 119-124.

Westerhof N, Boer C, Lamberts RR, Sipkema P (2006). Cross-talk between cardiac muscle and coronary vasculature. *Physiol Rev* **86**, 1263-1308.

In response to Pasquale Pagliaro's letter 'A man is as young as his endothelium'

Raya Al-Maskari & Yasmin
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We are delighted that our Feature Article has sparked interest and prompted some constructive feedback from Prof. Pagliaro. Given the complex nature of age associated stiffening of the arteries we aimed to highlight its pathological consequences with particular emphasis on the remodelling of the extracellular matrix and not the distending pressure or vascular smooth muscle tone. As such, we maintain that Prof. Pagliaro's argument complements the discussion in our article. Pulse pressure (PP) has long been recognized as a surrogate marker for central artery stiffness as Bramwell and Hill noted '...other things being equal, [pulse pressure] will vary directly as the rigidity of the arterial walls' (Bramwell and Hill, 1922). In support of Prof. Pagliaro's views on exercise and endothelium, we showed that PP increases with habitual exercise in younger (<30 years) but not in older (>50 years) adults compared with their age-matched sedentary counterparts. The decline in endothelial function with aging also associates with increased stiffness in healthy people and in isolated systolic hypertensives. Enhanced endothelial function with regular exercise underlies this improved vascular profile in habitually active individuals (McDonnell *et al.* 2013, McEniery *et al.* 2006, Wallace *et al.* 2007).

As a corrigendum to our article in *PN*98, Figure numbers 4 and 5 should be reversed.

Bramwell JC & Hill AV (1922). Velocity of transmission of the pulse-wave: and elasticity of arteries. *The Lancet* **199**, 891-892.

McDonnell, BJ, Maki-Petaja KM, Munnery M, Yasmin, Wilkinson IB, Cockcroft JR & McEniery CM (2013). Habitual exercise and blood pressure: age dependency and underlying mechanisms. *Am J Hypertens* **26**, 334-41.

McEniery CM, Wallace S, Mackenzie IS, McDonnell B, Yasmin, Newby DE, Cockcroft JR & Wilkinson IB (2006). Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension* **48**, 602-8.

Wallace SM, Yasmin, McEniery CM, Mäki-Petäjä KM, Booth AD, Cockcroft JR & Wilkinson IB (2007). Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. *Hypertension* **50**, 228-33.

'Zero Gravity' – a weighty problem?

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The fascinating article by Harridge *et al.* 'Space Flight and ageing' in *PN*98 (pp26-29) deployed the subtitle (or standfirst) 'Zero gravity mimics some of the effects of ageing', but in the text itself referred to microgravity: these terms refer (in subtly different ways) to the status of those a few hundred km 'up' in orbit around our planet. But we struggle to find a term other than 'free fall' that covers the physics without risking a serious muddle of comprehension for the unwary: every utterance of 'zero gravity' will have Newton and Einstein spinning in their graves.

OK, so we all know that gravity is everywhere; that its magnitude falls with the inverse square of the distance between massive objects, etc. So how come that, a mere stone's throw above the Earth in