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EDITORIAL

The muddy waters of the J-curve and coronary revascularization

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This editorial refers to 'Myocardial reperfusion reverses the J-curve association of cardiovascular risk and diastolic blood pressure in patients with left ventricular dysfunction and heart failure after myocardial infarction: insights from the EPHESUS trial'[†], by M. Böhm *et al.*, on page 1673.

Ever since the pioneering ventures of Freis *et al.*[1] half a century ago, we know that lowering blood pressure (BP) decreases cardiovascular events. The journey since then has also taught us that the above relationship is not identical for all cardiovascular events and that there is target organ heterogeneity in that such BP reduction decreases strokes more than heart attacks. We further know that the benefits of reduction in cardiovascular events with BP lowering is not bottomless and that this benefit is prone to plateau and even reverse, once a critically low BP level is exceeded (the so-called J-curve phenomenon). Indisputably, as BP approaches zero, mortality approximates 100%. Less clear is whether this reversal occurs within the physiological diastolic and/or systolic BP range and therefore could become critical during antihypertensive therapy. In contrast to other organs, the myocardium is perfused mostly during diastole and therefore is more vulnerable to low diastolic pressures. In fact, myocardial blood flow depends on myocardial perfusion pressure during diastole that is dependent not only on diastolic pressure but also on the degree and severity of coronary artery disease (CAD). In patients with moderate coronary artery disease, a diastolic BP of 60 mmHg or less has been shown to be associated with unacceptably low myocardial

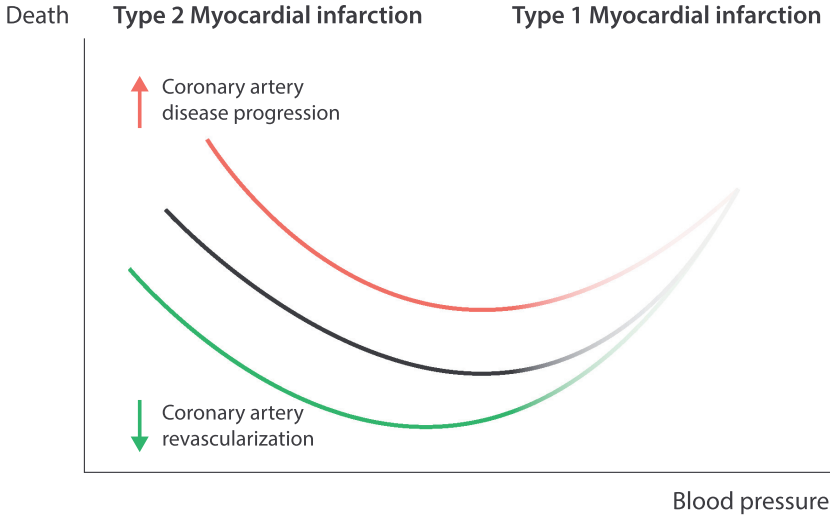

Figure 1 Schematic effect of coronary artery disease on the J-curve between BP and mortality. For any given diastolic BP there is an upward shift with CAD obstruction and a downward shift with revascularization. BP increase is a risk factor for Type 1 MI whereas BP decrease is prone to elicit Type 2 MI.

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perfusion pressure.[2] Consequently, a J-curve, if any, should be most evident in patients with limited coronary perfusion, in other words in those with obstructive CAD (*Figure 1*).

Indeed, several studies document low diastolic BP to be associated with an increased risk for major adverse cardiac events (MACE) and related mortality in older adults and in patients taking antihypertensive medications.[3–7] In an analysis of patients with known CAD enrolled in the TNT trial, a low diastolic BP was associated with increased incidence of angina, providing perhaps a clinical manifestation of ischaemia at low perfusion pressures.[8] Four decades ago, this led to the somewhat archaic thought that, 'in severe middle-aged hypertensives, attempts at 'normalization' of high blood-pressure may precipitate as many infarctions as it prevents' and that therefore 'the BP in such patients should seldom be reduced . . . to diastolic levels <104–110 mm Hg'.[9] Less archaic is the real-world realization that the discordance in the relationship between diastolic BP and target organ effect may 'leave a clinician with the uncomfortable choice of whether to prevent stroke or renal disease at the expense of coronary heart disease'.[7] In other words, there may be target organ heterogeneity with regard to the nadir of the J-curve in that the optimal BP for stroke prevention hovers at a level that increases the risk of myocardial infarction.

In the present issue of the *European Heart Journal*, in a subanalysis of the EPHESUS study, Michael Böhm *et al.*[10] again showed that patients after acute myocardial infarction (AMI) with a low diastolic BP were at an increased risk of all-cause death and altogether presented with more cardiovascular disease than patients with higher diastolic BP. These patients also were older, had more previous AMIs and heart failure, lower ejection fraction, higher Killip class, and an increased rate of revascularization. At first glance, these findings seem to be a classic example of reverse causation, i.e. the sicker the population the lower the diastolic BP. However, further analysis by Böhm *et al.* revealed that the unfavourable outcome in the low diastolic BP group was almost entirely restricted to those patients that had not been revascularized. These patients exhibited an increase of all outcomes (all-cause death and cardiovascular death or cardiovascular hospitalization), whereas no such increase was observed in those who were revascularized; their outcome was independent of diastolic BP. A sensitivity analysis in the subgroup of patients with optimal systolic BP of 120–130 mmHg showed again lower risk in those revascularized (vs. not revascularized) at low diastolic BP. A spline curve showed a J-shape, indicating an increasing risk with lower diastolic BP only in non-revascularized patients, whereas no such pattern was evident after revascularization. In contrast, for systolic BP, a J-curve was observed in patients with and without revascularization. Thus, low BP post-MI identifies patients at high risk but, in those with low diastolic BP, reperfusion therapy can mitigate this risk.

Similarly, in the INVEST cohort in which by definition all 22 000 patients had CAD and hypertension, we observed an interaction between low diastolic BP and history of revascularization.[11] Low diastolic BP was associated with a significantly lower risk for the primary outcome in revascularized patients than in those without revascularization. In contrast to the study of Böhm *et al.*,[10] the reduction in cardiovascular outcomes in patients with low diastolic pressure was confined to those with a history of coronary artery bypass graft (CAGB) but not to those with a history of percutaneous intervention (PCI). In the latter, the J-curve was comparable with those without revascularization. Further, patients enrolled in the INVEST study were presenting with stable CAD at the time point of randomization, although almost half had a history of prior MI.

All three studies, the subanalyses of EPHESUS,[10] of TNT,[8] and of INVEST[11], documented that a diastolic BP below 70 mmHg increased the risk of cardiovascular outcome. In EPHESUS and INVEST, revascularization, whether by angioplasty or CABG, seemed to shift the nadir of the J-curve to a lower BP level. Despite the agreement in the three studies, the waters remain muddy; all three studies are a retrospective exercise in data dredging, at best serving in hypothesis generating.

The waters get even muddier when we try to come up with a take-home message as is attempted in the following. The most important question is whether what we have learned in the context of acute coronary syndrome can be extrapolated to chronic stable CAD. In some patients BP is inherently low and there are some clinical situations that mandate a low systolic BP which is commonly associated with a low diastolic BP. Importantly, here we are not talking about arbitrary excessively low BP limits such such as proposed by the Lancet in the 'true grit' editorial,[12] i.e. the ill-documented proposal to lower BP across the board in 'all patients with a systolic blood pressure above the 120 mm Hg'.[13] However, in some patients with aortic syndrome, heart failure with low ejection fraction, and even with cerebrovascular disease, optimal BP, diastolic and/or systolic, may be lower than the diseased coronaries can tolerate. Myocardial perfusion pressure is prone to become critical, possibly triggering ischaemia and necrosis. Iron-clad evidence from the recent ISCHEMIA trial[14] now allows the provocative conclusion that revascularizing asymptomatic patients with stable CAD confers little if any benefits, at least throughout a 3-year period. However, when there is urgent need for low BP in patients with documented CAD, should we not consider to revascularize coronaries 'prophylactically' even if said CAD has remained asymptomatic?

Conflict of interest: none declared.

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CARDIOVASCULAR FLASHLIGHT

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Searching into the invisible: hunting for present and future ischaemia with fractional flow reserve pullback and wall shear stress

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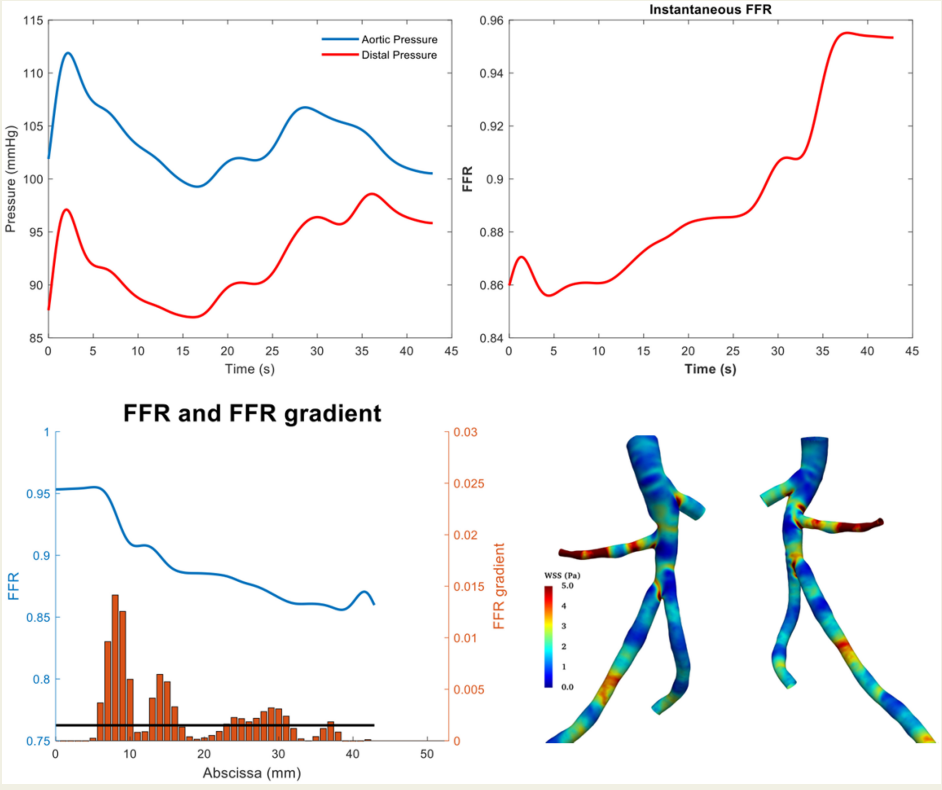
Vision is the art of seeing what is invisible to others
Jonathan Swift



We report the case of a 71 years old gentleman, with slowly worsening angina and known not significant coronary disease. At coronarography, left anterior descending (LAD) artery appeared with an intermediate patchy atherosclerotic disease: we performed an automated hyperaemic pullback fractional flow reserve (FFR) analysis, along with post-procedural evaluation of wall shear stress (WSS) base on a personalized computational haemodynamic approach, to better define the underlying functional impact and possible regions candidate to PCI.

We used the Volcano R 100 system to perform automated pullback, set at a speed of 1 mm/s; hyperaemic state was achieved with intravenous adenosine. FFR drop along the vessel demonstrated a focal proximal disease, not functionally significant (FFR 0.92), along with a diffuse non-significant disease. Therefore, stenting was not performed.

In order to better predict the potential evolution of these plaques, the coronary tree was reconstructed and WSS analysis performed, which showed an increased stress at the bifurcation between LAD and the first diagonal, in the body of the first septal branch and in the distal LAD.

In this case, FFR pullback and WSS allowed us firstly to define whether or not there was any focal disease, to clarify the ischaemic burden along the whole vessel, and finally to predict the future evolution of the disease. We are looking forward to establish what kind of relationship might be presumed by merging pullback FFR data and WSS to predict future ischaemic events.