Quality and consistency in microvascular research

Editor—We read the recent article by Maier and colleagues,1 in which they assess the microcirculatory effects of phenylephrine during cardiopulmonary bypass. The authors are to be commended for focusing their research on the microcirculation, as that is where actual delivery of oxygen and nutrients to tissue takes place. Their study adds to the body of evidence that systemic haemodynamic measurements do not necessarily reflect microvascular perfusion.

However, having extensive experience with the technique used by the authors to visualize the microcirculation, that is, sidestream dark-field (SDF) imaging, we feel the following comments may be of great importance. Many different scoring systems and video acquisition procedures have been developed in microcirculation research. This has the potential for hampered comparison between different studies using the same measuring technique. We are also aware of the round table conference held in 2006. Using the Delphi methodology, a vast number of recommendations were made in order to improve quality and consistency in microvascular research.5

Unfortunately, the authors did not fully adhere to these recommendations. Although there are multiple differences from the consensus statement, two may be critical and are discussed below. First, it was recommended to measure at least three, but preferably five sites, per patient per time-point, because of the intrinsic variability of the microcirculation. This also allows for better reporting of an index of heterogeneity. This is not stated and they only measured two sequences per time-point. It is therefore possible that the measurements they have made do not truly represent the state of the microcirculation. This also allows for better reporting of an index of functional capillary density, which was omitted. The problem with this is that MFI is a semi-quantitative way to describe microvascular flow but does not take into account the number of vessels per area. This is important because with SDF imaging, different imaging sites are used at different time-points which may hence have different capillary densities.

Secondly, it was recommended to report both MFI, as the authors did, and an index of functional capillary density, which was omitted. The problem with this is that MFI is a semi-quantitative way to describe microvascular flow but does not take into account the number of vessels per area. This is important because with SDF imaging, different imaging sites are used at different time-points which may hence have different capillary densities. Obviously from a perspective of oxygen and nutrient delivery to tissue, a large capillary density with some sluggish and some continuous flow would be preferable over very low capillary density albeit with only continuous flow. Because an index of perfused vessel density was not reported, the given MFI values may not truly represent the state of the microcirculation. Of course, trade-offs have to be made in microvascular research between detail of analysis and the time it takes to perform the analysis. However, it was recently suggested that using a fast-track analysis approach, it is quite reasonable to report on both indices of microvascular perfusion.6

In summary, failure to adhere to the recommendations mentioned above may have led to a biased representation of the microcirculation. This is not to say that the results are false by definition. However, we feel that they should be approached with caution.

Their conclusion would be greatly strengthened by reporting on more microvascular sites per time-point and by extending the analysis to include an index of functional capillary density. Although the former is not feasible, it is relatively easy to perform the latter using the existing videos of the microcirculation. Therefore, we would strongly recommend the authors to do so.

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Editor—We agree with Drs Elbers and Atasever that a uniform investigation process would facilitate the comparison between different studies using the same measuring technique. We are also aware of the round table conference report2 by excellent investigators in this field published in September 2007, at a time-point, where our present study already had begun.

In our present study,1 we demonstrated that alteration of the systemic vascular conductivity (systemic blood flow/arterial perfusion pressure) has direct effects on the microcirculation. In detail, arterial pressure increase induced with phenylephrine at constant cardiopulmonary bypass blood flow leads to a microvascular blood flow shunting in the sublingual mucosal microcirculation.

We arrived at this conclusion mainly by interpretation of the quantitatively assessed microcirculatory measurement techniques (laser Doppler flowmetry and tissue
Diastolic dysfunction and off-pump coronary artery bypass

Editor—I would like to thank Shim and colleagues for their interesting paper exploring the relationship between diastolic dysfunction and haemodynamic derangement during off-pump coronary bypass (OPCAB) surgery. However, there are some important differences between the groups that I feel should have been discussed. The $E'/e'$ group tended to be older (66 vs 62) with a greater incidence of hypertension (13 of 25 vs 19 of 25 patients). Perhaps unsurprisingly, therefore, they were also more likely to be on antihypertensive medications. Although, in isolation, none of these differences reached statistical significance, they may have made the groups to behave clinically different. The $E'/e'$ group received a significantly greater amount of norepinephrine ($P=0.029$). This may, in part, have been influenced by preoperative antihypertensive medication and not diastolic dysfunction. In addition, norepinephrine itself can cause a decrease in cardiac output. The paper rightly highlights the importance of diastolic dysfunction in OPCAB, but a discussion of these potential confounders should have been included.

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Editor—We thank Dr Edsell for his constructive comments on our manuscript. As he pointed out, increasing age and hypertension are well-known risk factors of diastolic dysfunction. The cause of diastolic dysfunction with age is largely unknown, but it is most likely that the age-related changes in the ventricle’s passive elastic properties cause decrease in the rate of ventricular relaxation. Similar mechanism can also be applied in patients with hypertension. Therefore, it is not surprising that older patients with hypertension would have greater incidence of diastolic dysfunction manifested as elevated $E'/e'$, since $e'$ reflects the rate of myocardial relaxation. Thus, possibilities exist that these two variables could be confounders. However, no statistical significance was reached with regard to these variables between the groups, and the ventricular wall thicknesses during diastole between the groups were also similar [posterior wall 9.6 (1.4) mm, $P=0.430$, vs 10 (1.6) mm, $P=0.040$, interventricular septum 9.8 (1.4) mm, $P=0.407$, vs 10.2 (2.0) mm, $P=0.047$, in the $E'/e'$ <8 and >15 group, respectively]. Furthermore, none of the studies addressing the risk factors for haemodynamic deterioration and conversion to cardiopulmonary bypass during OPCAB surgery has identified age or hypertension as risk factors, and we feel that the results of our study clearly validate the prognostic importance of $E'/e'$ in terms of intraoperative haemodynamic changes during OPCAB surgery. As to the use of greater amount of norepinephrine in the $E'/e'$ >15 group and the possible association with antihypertensive medications and decreased cardiac index, our answers are as follows. The numbers of patients taking antihypertensive medications were all similar, especially with regard to the angiotensin-converting enzyme inhibitor which is associated with increased hypotensive episodes during anaesthesia than the beta-blockers or calcium channel blockers. Moreover, greater amount of norepinephrine in the $E'/e'$ >15 group was used during grafting of left circumflex artery [64 (56) vs 29 (29) µg, $P=0.016$] and right coronary artery [58 (36) vs 20 (27) µg, $P=0.019$] and after sternum closure [28 (46) vs 8 (20) µg, $P=0.049$]. Before that the amount used was similar between the groups and thus the association with antihypertensive medication should be negligible. Also, norepinephrine was used to...