



Mechanisms underlying coronary autoregulation continue to await clarification

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Coronary autoregulation is defined as the mechanism that keeps coronary perfusion constant despite a change in perfusion pressure. Although the phenomenon is well known since its early description in the mid of the last century, the underlying mechanisms have not been completely resolved. In particular, the aspects of myogenic versus metabolic control of coronary autoregulation have both been supported by different datasets. In the current issue Kiel et al. [5] set out to add new experimental data to this issue aiming to better characterize coronary autoregulation. In a technically challenging *in vivo* study on anesthetized pigs they studied the metabolic hypothesis of coronary autoregulation through alterations in overall vasomotor tone and stimulation of myocardial oxygen consumption. Coronary perfusion pressure was systematically varied between 140 and 40 mmHg under otherwise control conditions, in the presence of euvolemic hemodilution (50% percent hematocrit decline), and also under conditions of combined hemodilution plus dobutamine infusion. As readout of myocardial oxygenation they used measurements of coronary venous PO_2 and as readout of coronary vessel tone they employed measurements of zero-flow pressure. They found that coronary venous PO_2 was neither associated with changes in coronary blood flow nor autoregulatory gain. However, coronary zero-flow pressure was related to vascular resistance and autoregulatory gain. Kiel et al. [5] have thus concluded that the data support the view that coronary autoregulation is predominantly controlled by vasomotor tone but independent of myocardial oxygenation.

While I personally very much favor the view that coronary vasomotor tone is the prevailing factor contributing to autoregulatory behavior of the coronary circulation, I feel that one should advise some caution in the interpretation of the current quite detailed dataset. A major assumption of Kiel and associates is that coronary venous PO_2 accurately reflects myocardial oxygenation. This approach has frequently been used before, and under many conditions measured coronary venous PO_2 met with expected changes in myocardial PO_2 . However, as I will try to argue, the current comprehensive dataset sheds some shadow on this assumption which may prove not to be universally valid.

Kiel et al. used euvolemic hemodilution to increase coronary blood flow in the absence of major changes in coronary venous PO_2 , an approach used before [6, 7]. As Kiel and associates [5] show in Table 1, this intervention nearly doubled coronary flow while coronary venous PO_2 remained, as the authors remark, quite unchanged for each level of coronary perfusion pressure investigated. However, if one takes a closer look at the dataset, one will notice that below a coronary perfusion pressure of 130 mmHg coronary venous PO_2 was higher during hemodilution than under control conditions, resulting in a very consistent difference of 2–3 mmHg. At the same time, myocardial oxygen consumption was lower during hemodilution than under control conditions, again a very consistent difference of approximately 10%. It is unclear whether the authors tested if these differences were statistically significant. Actually, the study may have been underpowered to critically assess these effects as this was not addressed as the major experimental goal. However, the association of a higher coronary PO_2 with a lower oxygen consumption rate may argue against the view that coronary venous PO_2 is a reliable estimate of myocardial PO_2 or the slope of the capillary–mitochondrial PO_2 gradient. Thus, the current dataset does not really rule out that there might have been an oxygen sensing mechanism between the capillary and the cardiomyocyte mitochondrion that was involved in the regulation of coronary vessel tone under this specific

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condition. How could the combination of elevated coronary venous PO_2 and lowered myocardial consumption rate be explained? One likely explanation is related to the hematocrit dependent spacing of erythrocytes [8]. Because hematocrit was lowered from 33 to 17%, the erythrocyte free blood volume increased from 67 to 83%. (The condition in the microcirculation may have been even more disadvantageous for oxygen transport to tissue, if microvessel hematocrit is considered, which is lower than systemic hematocrit.) The rather low physical solubility of oxygen may have enhanced the intracapillary resistance for oxygen diffusion and thereby changed the capillary–mitochondrial PO_2 gradient. The authors were careful to state in their discussion that their interpretation rests on the assumption that coronary venous PO_2 is a valid measure of myocardial PO_2 . This, however, may not be the case.

The model of hemodilution has been used before [6, 7]. Interestingly, in these studies neither an increase of coronary venous PO_2 nor a decrease of myocardial oxygen consumption during hemodilution has been reported. However, these studies fall short with respect to the systematic assessment of graded coronary perfusion pressure reduction over the full range of coronary autoregulation which was only addressed in the current publication [5].

The authors continued in their experiments to assess the implications of coronary vessel tone for the autoregulation response. They used, as mentioned above, coronary zero-flow pressure as an index of vascular tone. They observed solid statistical relationships of zero-flow pressure with coronary resistance and autoregulatory gain (their Fig. 4). However, as hemodilution was invoked, changes of blood viscosity may have affected measured resistance according to the model of Hagen and Poiseuille. In fact, coronary blood flow doubled as hematocrit was decreased by 50%, which suggests a major impact of viscosity on flow. Therefore, differences of coronary resistance between control conditions and hemodilution cannot be attributed exclusively to a changing vessel tone. Interestingly, when looking at data shown in Fig. 4 of Kiel et al. [5] one may obtain the impression that the relationship of coronary zero-flow pressure with coronary resistance vanishes, if the analysis is applied to each experimental group separately. At least this suggests that viscosity might have had a considerable impact on presumed estimates of coronary resistance and vascular tone. Does zero-flow pressure give us a reliable estimate of vascular tone under this condition? Also this assumption does not appear fully settled for conditions of severe hemodilution. The effect of perfusate rheology on diastolic pressure–flow relationships has been addressed by Drossner and Aversano [3]. Although their study differs in many aspects from the current Kiel et al. study [5], it suggests that in the range of 48–20%, hematocrit did not change the zero-flow pressure intercept. However, if those authors replaced

blood by a crystalloid medium (zero hematocrit) they found a clear decrease of zero-flow pressure. Kiel et al. [5] lowered hematocrit to 17% which, although closer to 20%, is between the two conditions assessed by Drossner and Aversano [3]. Thus, we are left with some ambiguity also in this regard.

Kiel et al. have provided us with a detailed dataset aimed to clarify the importance of metabolic as opposed to myogenic regulation of coronary autoregulation. The study fully rests on assumptions quite generally applied in coronary physiology. However, we have to face the fact that indexes used because of lack of direct measures (e.g. local oxygenation, local vascular tone) may be misleading or may at least require very complex further analyses. Moreover, we need to acknowledge with respect to coronary autoregulation that there may exist substantial differences in the regulatory principles between myocardial regions [4]. The coronary flow reserve is exhausted in subendocardial regions at higher perfusion pressures as compared to subepicardial regions resulting in transmural gradients of ischemia [2]. Even under resting physiological conditions regional myocardial blood flow is heterogeneous as is coronary flow reserve [1].

In conclusion, the phenomenon of coronary autoregulation—well documented for many decades—is a lifesaving mechanism in many individuals which develop stable coronary atherosclerosis. By this mechanism post-stenotic vascular resistance is adjusted to alleviate the effect of stenosis resistance on total vascular resistance keeping resting perfusion constant. However, for now despite the comprehensive dataset contributed by Kiel and associates [5] coronary physiologists are still left with some insecurity about the precise mechanisms that control coronary vessel tone in response to changes in blood pressure.

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