MicroRNAs to take the place of collateral flow index measurements and Rentrop scoring?—Reply to Papageorgiou *et al*.

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We thank Papageorgiou *et al*. for their thoughtful comments on our recent publication regarding circulating microRNAs (miRNAs) associated with coronary collateral artery capacity (1). The benefits of a vast collateral network have been widely accepted to prevent mortality in patients with chronic stable coronary artery disease (CAD) (2,3). Identifying patients with a limited collateral network can in turn distinguish patients at risk to substantial debilitation from adverse cardiac events. Nonetheless, current methods to identify patients with insufficient collateralization are limited to invasive intracoronary collateral flow index (CFI) measurements or angiographic grading (4). Clinical parameters associated with collateral development have been identified (5). However, there remained a lack of biomarkers to discriminate between patients with sufficient or insufficient collateralization.

Genetic heterogeneity in CAD patients has been identified at the messenger RNA level of circulating monocytes and macrophage phenotypes (6,7). This led us to hypothesize that differential miRNA expression in patients with insufficient *vs*. sufficient collateralization must also be present. We identified 4 miRNAs that were significantly upregulated in the plasma of patients with low collateral capacity. We further determined that these miRNAs (miR423-5p, miR10b, miR30d, miR126) could serve as circulating biomarkers to significantly distinguish between chronic total occlusion (CTO) patients with high or low collateral capacity. These miRNAs can discriminate between these patient groups with a positive likelihood ratio between 3.0 and 6.1 depending on the respective miRNA. This revelation can be of immense clinical significance, whereby patients with low collateralization can be potentially identified with a simple blood sample rather than invasive intracoronary catheterization. However, our study warrants further studies with larger patient cohorts, along with examining the utility of these miRNAs as biomarkers for collateralization in CAD patients.

Papageorgiou *et al*. point out that the utility of these miRNAs is also dependent on a generally accepted definition of low collateral capacity, whereby some studies use Rentrop scoring and others use different thresholds of pressure-derived CFI (CFI_p) to establish the level of collateralization. Rentrop scoring provides only a semi-quantitative measure and is limited to collateral vessels above 100 μm diameter. In relation to CFI_p measurements, it is important to recognize the difference between CAD and CTO patients, whereby CTO patients provide no variability in coronary lesion severity as compared to CAD patients. As a result, the distribution of CFI_p measurements in CTO patient populations differs from that in CAD patients. The mean CFI_p in a cohort of 295 patients was deemed to be 0.39 (5), while in CAD patients the frequency distribution of CFI_p is dependent on the severity of CAD (2).

As both Papageorgiou *et al*. and we have mentioned, a number of co-existing parameters may affect the diagnostic ability of miRNAs in the general population. Medication usage, gender, age as well as diabetes mellitus have been shown to affect both collateral vessel development as well as miRNA expression levels (8-11). In our study, gender and age significantly impacted the predictive power of the respective miRNAs as suitable biomarkers. However, miR126 demonstrated significant predictive power to

discriminate between patients with high and low collateral capacity even without consideration of age and gender. MiRNA126 has been largely linked to angiogenesis, as well as atherosclerosis, whereby the mature miRNA-126-5p plays a role in endothelial turnover (12). Examining larger patient cohorts will likely elucidate the exact threshold of the respective miRNA expression levels that can distinguish between these patient groups, and provide additional insight in the effects of other co-existing parameters on this threshold.

In conclusion, circulating miRNAs offer a new method for patient stratification. Nonetheless, there still remains a large step before miRNA examination can become a part of routine clinical application. As the possibility to distinguish the coronary collateral artery capacity of patients without the need for invasive catheterization is of great clinical significance, our results warrant further investigation in larger CTO patient cohorts, along with examining the predictive power of these miRNAs in CAD patients.

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Footnote

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