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EDITORIAL

The assessment of ANOCA: coming of age?

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Can one think of a single physiological function that does not deteriorate with age? It would have been surprising to see that the function of the coronary microcirculation behaved any differently, and this impression is supported by recent work[1].

Accordingly, the results published in this issue of EuroIntervention by Jansen et al[2] come as no surprise. However, to tackle the question of how microvascular function changes in older patients, the authors used, for the first time, continuous thermodilution-derived absolute flow and resistance measurements. Microvascular function was evaluated in a cohort of 305 patients with angina with no obstructive coronary artery disease (ANOCA). The mean age of the cohort was 59±9 years, and the vast majority of patients were female (83%). Of note, significant epicardial disease was totally excluded, both in terms of significant focal disease (any diameter stenosis >30%) and haemodynamically significant disease (fractional flow reserve [FFR] ≤0.80). In order to evaluate the impact of age on measures of microvascular function, linear regression was used with age as a continuous variable, whilst the cohort was also analysed in 3 age groups (≤52 years old, 53-64 years old, ≥65 years old).

Article, see page e690

Whilst there were no differences between groups in terms of resting absolute flow (Q_{rest}) or microvascular resistance ($R_{\mu,rest}$), the authors noted a small decrease in hyperaemic flow (Q_{max}) with increasing age and a corresponding small, but significant, increase in hyperaemic microvascular resistance ($R_{\mu,hyper}$). This translated into a significant age-associated decrease in microvascular resistance reserve (MRR) from 3.2±1.2 in patients ≤52 years old to 2.9±0.9 in those ≥65 years old. Furthermore, using an MRR cutoff of <2.7 to define coronary microvascular dysfunction (CMD), the authors found that this age-associated phenomenon occurred in patients in all 3 groups, regardless of the presence or absence of CMD.

Apart from the expected association between microvascular function and age, it is worth noting that Q_{rest} remained remarkably stable with increasing age. In fact, it was only a very modest increase in $R_{\mu,hyper}$ that resulted in the small, but significant, decrease in both Q_{max} and MRR in the elderly patients. Critically, these data demonstrate an association between age and declining microvascular function, but they do not demonstrate causation. As shown in Table 4 of the paper by Jansen et al, elderly patients had significantly more comorbidities, many of which are known to affect vascular function. As such, further work is needed in order to explore the putative pathophysiological mechanisms responsible for the link.

Yet, perhaps more valuable still, this work highlights certain methodological aspects that warrant further discussion:

1) What is the optimal modality for the assessment of microvascular function? The authors deserve praise for their approach to the microvascular assessment. Continuous thermodilution is the gold-standard intracoronary modality for assessing volumetric coronary blood flow due to its excellent accuracy, as compared with $[^{15}O]H_2O$ positron emission tomography (PET) perfusion imaging, and its superior precision over bolus thermodilution and Doppler[3,4]. Furthermore, it permits the calculation of a range of indices that can be used to assess the microvascular compartment: Q_{rest}, Q_{max}, $R_{\mu,rest}$, $R_{\mu,hyper}$, coronary flow reserve and MRR. Yet these indices can likely be condensed into just two that encapsulate microvascular function: $R_{\mu,hyper}$ and MRR.

2) $R_{\mu,hyper}$ and MRR provide complementary information on microvascular function and should be evaluated in conjunction. R_{μ} is the quintessential descriptor of microvascular

function, and continuous thermodilution stands out for its capacity to quantify it in absolute terms (Wood units). Whilst bolus thermodilution provides a dimensionless surrogate of $R_{\mu,hyper}$ – the index of microcirculatory resistance (IMR) – only continuous thermodilution permits its quantification in absolute terms. This is relevant, as there is emerging evidence that $R_{\mu,hyper}$ permits the distinction between structural and functional CMD[5]. As such, tools that accurately quantify $R_{\mu,hyper}$ will play an increasingly important role in ANOCA assessment.

Yet, R_{μ} is not sufficient as a standalone metric, as it is influenced by subtended myocardial mass; the larger the mass, the higher the flow, and thus, the lower the resistance. MRR, on the other hand, quantifies the vasodilatory reserve of the microcirculation and is independent of subtended myocardial mass[6]. In addition, whereas CFR is influenced by the presence of concomitant epicardial disease, MRR corrects for epicardial resistance (i.e., FFR), making it truly specific for the microvascular compartment. However, it is worth noting that MRR, like CFR, remains sensitive to abnormally high values of Q_{rest} that are sometimes seen during ANOCA assessments; these may not reflect the true pathology but rather patient anxiety or stress.

What remains to be ascertained is the optimal MRR and $R_{\mu,hyper}$ cutoff values for the diagnosis of CMD. Whilst Jansen et al utilised an MRR cutoff of 2.7, a value of 3.0 has recently been proposed[7]. In reality, the optimal cutoff is likely in or around this range but should ideally be defined by clinical outcomes data. This represents one of the objectives of the currently enrolling Euro-CRAFT study (ClinicalTrials.gov: NCT05805462), which will provide prognostic data on a large cohort of ANOCA patients who will undergo thorough coronary function testing, including continuous thermodilution.

To conclude, there have been considerable advances in the awareness and understanding of ANOCA in recent years. Our focus should now shift towards standardising how we assess for its underlying causes so that clinicians can make clear and consistent decisions about their patients.

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Conflict of interest statement

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