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JACC REVIEW TOPIC OF THE WEEK

Assessing Microvascular Dysfunction in Angina With Unobstructed Coronary Arteries

JACC Review Topic of the Week

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ABSTRACT

Coronary microvascular dysfunction is a highly prevalent condition of both structural and functional coronary disorders in patients with angina and nonobstructive coronary artery disease (ANOCA). Current diagnostic modalities to assess microvascular function are related to prognosis, but these modalities have several technical shortcomings and lack the opportunity to determine true coronary blood flow and microvascular resistance. Intracoronary continuous thermodilution assessment of absolute coronary flow (Q) and microvascular resistance (R) was recently shown to be safe and feasible in ANOCA. Further exploration and implementation could lead to a better understanding and treatment of patients with ANOCA. This review discuss the coronary pathophysiology of microvascular dysfunction, provides an overview of noninvasive and invasive diagnostics, and focuses on the novel continuous thermodilution method. Finally, how these measurements of absolute Q and R could be integrated and how this would affect future clinical care are discussed. (J Am Coll Cardiol 2021;78:1471–1479) © 2021 by the American College of Cardiology Foundation.

Angina affects >100 million people worldwide and is the most common symptom of myocardial ischemia (1). Angina is generally ascribed to obstructive coronary artery disease (CAD), but ~40% of patients undergoing invasive coronary angiography for angina do not have CAD (2,3). Coronary vasomotor dysfunction is often considered an important problem in these patients with so-called angina and no obstructive coronary artery disease (ANOCA), but the exact prevalence remains uncertain because of the absence of robust metrics (4). The main pathophysiological mechanisms (endotypes) are epicardial and/or microvascular vasospasm and coronary microvascular dysfunction (CMD) consisting of impaired vasodilator reserve caused by disordered autoregulation or an increased minimal microvascular resistance (MVR) (2). Patients with coronary vasomotor dysfunction have increased cardiovascular risk, high morbidity, and impaired quality of life, and they are a source of considerable health resource utilization (3,5,6). Evidence is accumulating that identification of the specific vasomotor dysfunction endotype has major implications for patient-tailored treatment and may affect quality of life and prognosis (3). However, this goal is hampered by limitations of the

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ABBREVIATIONS AND ACRONYMS

ANOCA = angina and no obstructive coronary artery disease

APV = average peak velocity

CAD = coronary artery disease

CCTA = coronary computed tomographic angiography

CFR = coronary flow reserve

CFT = coronary function test

CMD = coronary microvascular dysfunction

ICC = intraclass correlation coefficient

IMR = index of microvascular resistance

LAD = left anterior descending

MRR = microvascular resistance reserve

MVR = microvascular resistance

PCI = percutaneous coronary intervention

PET = positron emission tomography

Q = absolute coronary flow

R = absolute coronary resistance

T = distal temperature

Tmn = mean transit time

current diagnostic armamentarium leading to ambiguity in diagnostic strategies in ANOCA. With regard to CMD, the diagnostic process can be improved using metrics that are capable of assessing true coronary flow and MVR. A novel invasive method has recently become available that is easy, reproducible, and safe: continuous thermodilution assessment of the microcirculation (7,8). Implementation of this technique might improve our understanding of the prevalence of CMD in ANOCA and the associated treatment and outcomes. In this review we discuss the contemporary diagnosis of CMD, pathophysiology, and current noninvasive and invasive diagnostics, and we will detail the advantages and limitations of the continuous thermodilution method.

PATHOPHYSIOLOGY OF CMD

Two specific endotype groups of ANOCA have been described: functional arteriolar dysregulation and structural microcirculatory remodeling. Functional arteriolar dysregulation, including epicardial and microvascular spasm, are beyond the scope of this review. Structural microcirculatory remodeling or CMD can be categorized in vasodilatory abnormalities of the microvascular compartment and increased minimal MVR.

Structural remodeling of the coronary microvasculature is typically caused by inward remodeling of coronary arterioles, with an increase in wall-to-lumen ratio, loss of myocardial capillary density (capillary rarefaction), or both. It is associated with an increased minimal MVR, leading to a decreased microcirculatory conductance and impaired oxygen delivery capacity (9). Remodeling may occur as a result of cardiovascular risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states), obstructive atherosclerosis, left ventricular hypertrophy, or primary and secondary cardiomyopathies (10). These pathologic changes result in a decreased microvascular vasodilatory capacity, limiting blood and oxygen reserve to the myocardium triggered by stress or exercise.

DIAGNOSIS OF MICROVASCULAR DYSFUNCTION

Currently no technique allows a direct anatomical visualization of the coronary microcirculation in vivo in humans, thus its assessment relies on the measurement of coronary blood flow parameters that reflect its functional status (**Central Illustration**). The COVADIS (Coronary Vasomotion Disorders International Study Group) have published international standardized diagnostic criteria for CMD (11). According to these criteria, coronary flow reserve (CFR), reflecting microvascular dilatory reserve capacity and the index of microvascular resistance (IMR), representing minimal MVR in hyperemic conditions, should be used to assess CMD. A major advantage of IMR compared with CFR is that IMR does not depend on resting physiology. Both can be assessed with invasive intracoronary physiology measurements, and the CFR can also be determined by some noninvasive modalities (12). In the absence of flow-limiting stenosis, these measurements have been validated for assessment of microvascular function and are associated with prognosis (12-14).

HIGHLIGHTS

- Microvascular coronary blood flow and resistance can be safely and accurately measured by continuous thermodilution.
- Abnormal flow and resistance values can be useful for diagnosis of microvascular dysfunction in patients with ANOCA.
- Continuous thermodilution data have the potential to guide therapy in patients with CMD.

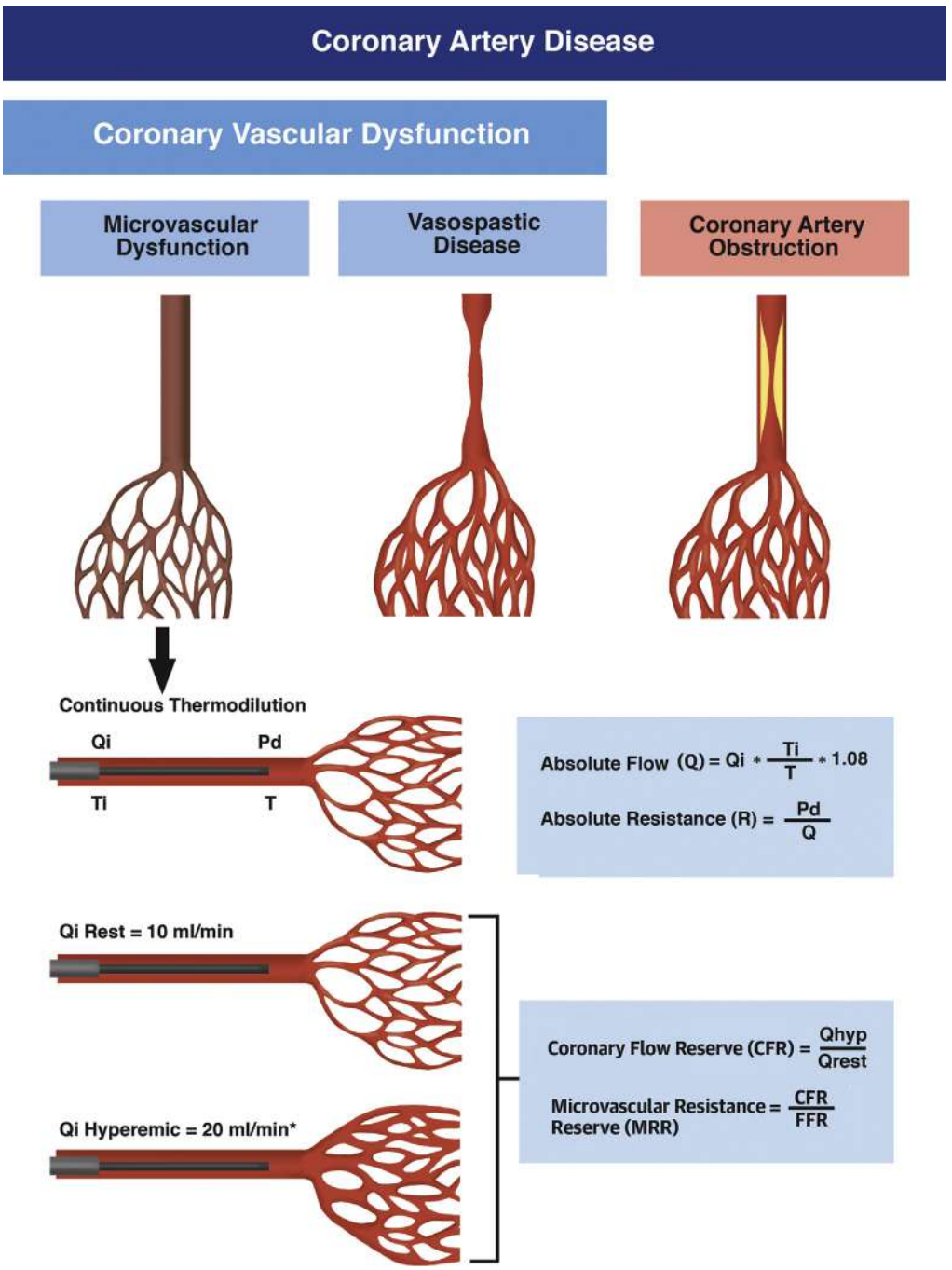
NONINVASIVE TESTING

Several noninvasive methods can be used to assess CMD. These rely on the measurement of surrogates of blood flow and CFR.

Positron emission tomography (PET), a radionuclide imaging technique, is able to assess absolute levels of tracer concentration. Using dynamic acquisition time-activity curves can be generated of tracer flux for arterial blood and myocardium. Automated software then computes resting and hyperemic myocardial blood flow in absolute terms and in order to calculate CFR. This technique is considered the gold standard for the noninvasive assessment of these indices (15). However, PET is not widely used because of limitations including high expense, the necessity of on-site availability of a cyclotron, and the requisite application of x-ray (16).

Cardiac magnetic resonance can be used to determine myocardial perfusion. The contrast medium (gadolinium), diffusing from the microvasculature into the interstitial space, results in an increase in T_1 signal intensity that is proportional to the perfusion

CENTRAL ILLUSTRATION **The Assessment of Coronary Microvascular Dysfunction Parameters by Continuous Thermodilution in Angina and No Obstructive Coronary Artery Disease**



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The **top** gives an overview of the main classification of coronary artery disease and the place of coronary vascular dysfunction. The **bottom** is a simplified overview of the continuous thermodilution method and the calculation of the different measurements is given. *Depending on the size of the left anterior descending coronary artery, 15-25 mL/min can be used to induce hyperemia. FFR = fractional flow reserve; hyp = hyperemic; MRR = microvascular resistance reserve; Pd = distal coronary pressure; Q = absolute flow; Qi = infusion flow; R = absolute resistance; rest = resting; T = mixing temperature; Ti = infusion temperature.

and blood volume (17). When evaluating perfusion signal intensity upslopes in stress versus rest, the myocardial perfusion reserve index can be assessed, which is considered a surrogate for CFR (18). This method is more readily available than PET, is less expensive, and no radiation is necessary. However, further validation studies are needed to determine its accuracy.

Transthoracic Doppler echocardiography allows the assessment of coronary blood flow velocity at baseline and hyperemia by means of pulsed-wave Doppler echocardiography. The technique is limited by the need for highly trained personnel and the inability to assess other coronary vessels than the left anterior descending (LAD) coronary artery (19,20).

While coronary computed tomographic angiography (CCTA) is an anatomical noninvasive imaging method to rule out obstructive CAD, it currently does not provide information on CMD (21,22). With the advent of CCTA perfusion, assessment of both CCTA-fractional flow reserve and CCTA-CFR might prove an attractive first step to exclude obstructive CAD and assess CMD (23).

To summarize, PET, transthoracic Doppler echocardiography, and cardiac magnetic resonance may be considered for the detection of CMD, but they only provide surrogates of flow (22). In addition, perfusion assessment lacks the sensitivity to diagnose the relative contributions of epicardial and microvascular disease to myocardial blood flow reduction. Therefore, it is not always possible to distinguish ischemia because of obstructive CAD or CMD. The aforementioned limitation also means it is currently not possible to assess MVR. These caveats emphasize the need for invasive evaluation of coronary arteries and microvasculature to derive definitive conclusions on the causes of ANOCA.

INVASIVE DIAGNOSTICS

Coronary vasomotor dysfunction can be assessed invasively with a coronary function test (CFT). CFT is a comprehensive standardized invasive evaluation, which allows assessment of epicardial/microvascular spasm using acetylcholine provocation testing, and CMD using endothelium-independent vasodilators such as adenosine to assess CFR and IMR. We note that acetylcholine provocation cannot be replaced by CMD assessment, as these both focus on different ANOCA endotypes.

The assessment of CMD can be performed using Doppler flow velocity or coronary bolus-thermodilution methods (24). Using an intracoronary guidewire tipped with a Doppler crystal, phasic flow velocity patterns can be measured and the average peak velocity (APV) can be determined (25). Doppler CFR is defined as the ratio between APV at hyperemia and APV during resting conditions. The bolus-thermodilution method makes it possible to measure coronary flow by calculating the average mean transit time (Tmn) of a bolus of saline. For this, a saline bolus is hand-injected in triplicate into the coronary artery through the guiding catheter, both at rest and during hyperemia, and CFR is defined as the ratio of hyperemic Tmn to resting Tmn (26). With regard to the technical disadvantages of both methods, the Doppler method proves to be challenging in obtaining high-quality Doppler flow signals, resulting in relatively high percentages (up to 30%) of insufficient quality data (27). Moreover, off-line interobserver variability is around 9% and is significantly higher than that of the thermodilution method (24). The bolus-thermodilution method seems to be technically more feasible, but because of manual rapid injection of saline it has large intraobserver variability and it overestimates CFR at higher values (24). In addition, it is susceptible to subjectivity because operators are able to replace Tmn values if they are not satisfied with the result. Yet, when bolus-thermodilution and Doppler velocity CFR were compared with PET as the reference test by experienced operators, Doppler velocity CFR was documented to have a significantly higher agreement with PET than coronary thermodilution CFR was. Thus, both methods have technical disadvantages, which may importantly affect clinical diagnosis. From a patient perspective, the methods require hyperemia for which intravenous or intracoronary adenosine is administered. Adenosine, particularly when administered intravenously by continuous infusion, is associated with multiple side effects including but not limited to flushing, chest pain, dyspnea, and atrioventricular blocks. Furthermore, it should generally be avoided in patients with severe chronic obstructive pulmonary disease and is contraindicated in patients with asthma. Finally, as mentioned earlier, both methods rely on assessment of a surrogate of coronary flow.

To overcome the difficulties of Doppler-based measurements, the intraobserver variability of bolus-thermodilution, a quantitative and operator-independent method should be preferred. Recently, a novel method has been validated using a continuous thermodilution method that allows direct and operator-independent quantification of absolute coronary blood flow (Q) and resistance (R) (7,28,29). A comparison of bolus and continuous thermodilution

techniques has recently been extensively reviewed by Candreva et al (30).

CONTINUOUS THERMODILUTION

METHODOLOGY. The method of continuous thermodilution has been described and validated by the groups in the Catharina Hospital in Eindhoven and the Cardiovascular Center in Aalst. First, direct assessment of coronary flow and resistance was proven feasible in 2006, when Aarnoudse et al (8) evaluated the continuous thermodilution in dogs and showed that it correlated well with true coronary flow. Absolute blood flow measurements (Q_{cor}) are based on thermodilution and continuous infusion of saline at room temperature through a dedicated monorail catheter (RayFlow, Hexacath), advanced over a pressure/temperature sensor-tipped guidewire. Assuming that the heat exchanges with the arterial wall are minimal, the colder saline is homogenously mixed in the volume of blood to be measured and can therefore be considered a constant portion of this volume (30). Therefore, during steady-state hyperemia, coronary flow Q_{cor} can be calculated as a derivative of intracoronary temperature differences:

$$Q_{cor} = 1.08 \cdot \frac{T_b - T_i}{T_b - T} \cdot Q_i$$

where Q_i represents the volumetric infusion rate of the saline (in mL/min), T_b the temperature of the blood before the start of saline infusion, T_i the temperature of the infusate at the tip of the infusion catheter, and T the temperature at the sensor in the distal coronary artery during steady-state infusion (ie, the temperature of the blood after complete mixing with the infused saline). The correction factor 1.08 is necessary to compensate for the difference in specific heat between saline and blood (31). When T_b is set to 0 and T_i and T are expressed as the deviation of the respective temperatures from T_b, the equation can be rewritten as:

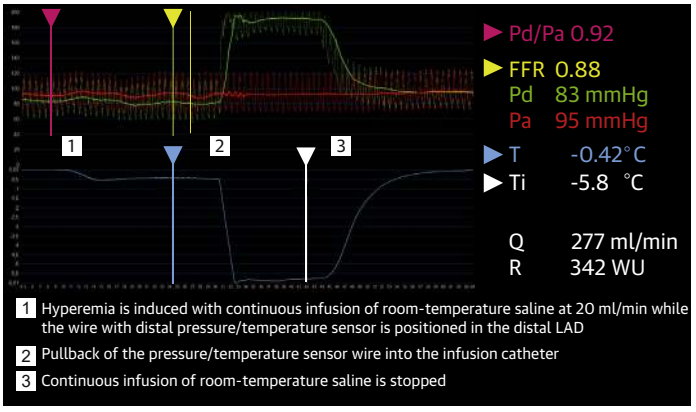
$$Q_{cor} = 1.08 \cdot \frac{T_i}{T} \cdot Q_i$$

Using absolute flow measurements, absolute resistances can be calculated. Because distal coronary pressure (P_d) is also measured by the temperature/pressure wire, the MVR (R) can be calculated by applying Ohm's law.

$$R = \frac{P_d}{Q_{cor}}$$

R is expressed in WU or mm Hg × L/min (8).

FIGURE 1 Example of the Continuous Thermodilution Measurements



This is an example measurement of the absolute coronary flow and resistance with the continuous thermodilution method to induce hyperemia. Aortic pressure (Pa) **(red tracing),** distal coronary pressure (Pd) **(green tracing),** and coronary temperature (T) can be recorded simultaneously. From this, the fractional flow reserve (FFR), absolute flow (Q), and absolute resistance (R) can be calculated. Note that the pressure gradient increases during hyperemia and that the measured Pd increases when the wire is pulled back into infusion catheter because of the infusion. LAD = left anterior descending coronary artery; Ti = infusion temperature.

TECHNIQUE. The continuous thermodilution method can easily be added to a routine catheterization or a CFT. The guiding catheters and the pressure/temperature wire should be advanced as usual, with the tip of the guidewire in the distal part of the coronary artery. Next, the dedicated monorail infusion catheter is advanced over the pressure wire with its tip in the proximal part of the coronary artery. Subsequently, room-temperature saline infusion is started at a rate of 15-25 mL/min. Steady-state maximum hyperemia is induced by the saline infusion itself within 10-20 seconds (32). After steady-state, the distal temperature (T) can be recorded by the guidewire. When the temperature sensor is pulled back to the opening of the infusion catheter, the infusion temperature can be determined. Dedicated software use these variables to automatically calculate absolute Q and R (**Figure 1**).

AGREEMENT WITH GOLD STANDARD. Central to this new technique is the validation study by Everaars et al (28), who demonstrated that hyperemic flow measured by continuous thermodilution correlates well with the gold standard PET. In a prospective study of 25 patients with CTA-confirmed single-vessel disease, all patients underwent PET followed by invasive assessment within 7 days. Invasive measurements were performed with and without the use of adenosine. Invasive and noninvasive

measurements of adenosine-induced hyperemic flow and MVR showed strong correlation ($r = 0.91$; $P < 0.001$ for flow and $r = 0.85$; $P < 0.001$ for MVR) and good agreement (intraclass correlation coefficient [ICC]: 0.90; $P < 0.001$ for flow and ICC: 0.79; $P < 0.001$ for MVR). Absolute flow and MVR also positively correlated with measurements with and without adenosine ($r = 0.97$; $P < 0.001$ for flow and $r = 0.98$; $P < 0.001$ for MVR) and showed good agreement (ICC: 0.96; $P < 0.001$ for flow and ICC: 0.98; $P < 0.001$ for MVR), which confirms that continuous thermodilution can be performed without using a pharmacological vasodilator (28). This substantially simplifies the technique and improves its feasibility.

RESTING CORONARY BLOOD FLOW MEASUREMENTS. Because flow and resistance—in contrast to pressure—are directly proportional to myocardial mass, the clinical significance of maximal flow or minimal MVR remains elusive from an interpatient comparison perspective, as long as the hyperemic values are not corrected for myocardial mass or a relative measure of microvascular function can be assessed.

Recently, resting flow measurements were proposed and validated against simultaneous intracoronary pressure and Doppler-derived flow measurements (33). Continuous thermodilution using saline infusion rates between 8 and 10 mL/min were documented as allowable measurements of resting coronary flow, because these low infusion rates did not lead to alterations of APV or vessel pressure gradients excluding the presence of saline-induced partial vasodilatation at these low infusion rates. Consequently, mean values of CFR from thermodilution and Doppler were similar (2.78 ± 0.91 vs 2.76 ± 1.06; $P = 0.935$) and their individual values correlated closely ($r = 0.89$; $P < 0.001$). The availability of both resting and hyperemic measurements allows the calculation of the relative functional measurements CFR and microvascular resistance reserve (MRR), which is the ratio of baseline and hyperemic resistance, from continuous thermodilution and the ability to make interpatient comparisons (**Central Illustration**). Conceptually, the MRR assesses the dynamic dimension of the microcirculation under both rest and hyperemia. Theoretically, in the absence of any epicardial CAD (fractional flow reserve or resting physiological index of 1), CFR and MRR should be identical. The presence of atherosclerosis will lead to compensatory microvascular vasodilation affecting CFR. Because the MRR incorporates basal and hyperemic pressures, it is corrected for the epicardial conductance and unaffected by atherosclerosis. Therefore, the MRR might be superior in the specific assessment of the microcirculation.

SAFETY AND REPRODUCIBILITY. Two studies have evaluated safety and reproducibility of continuous thermodilution measurements (7,34).

With regards to safety, Xaplanteris et al (7) observed no significant periprocedural adverse events in 203 absolute Q and R measurements in 135 patients undergoing clinically indicated coronary angiography. A small percentage (8.1%) of patients experienced transient bradycardia and concomitant atrioventricular block that were reversed immediately on interruption of the infusion. Keulards et al (34) observed 1 catheter-induced coronary dissection requiring percutaneous coronary intervention (PCI) in 467 absolute Q and R measurements from 100 consecutive patients undergoing clinically indicated invasive fractional flow reserve measurements. They observed only 2.6% cases of bradycardia and atrioventricular block and 2 patients experiencing transient chest discomfort during infusion, without electrocardiographic abnormalities.

Xaplanteris et al (7) also assessed reproducibility in their cohort. Duplicate measurements were performed in 80 patients, which had a strong correlation both for Q ($\rho = 0.841$; $P < 0.001$; ICC: 0.89; $P < 0.001$) and R ($\rho = 0.780$; $P < 0.001$; ICC: 0.89; $P < 0.001$).

An additional considerable advantage of this methodology is its operator-independency: the vast majority of patients does not experience anything during the saline infusion and although a steady-state tracing is mostly obtained within 30-60 seconds, tracings can be continued for minutes while the operator just stands back and does not even touch the patient.

In conclusion, the invasive continuous thermodilution based method to assess absolute coronary blood flow and MVR shows good correlation to the current gold standard, proves to be safe and feasible, and has high reproducibility, making it highly attractive for clinical practice.

CLINICAL IMPLEMENTATION

NORMAL VALUES. A necessary prerequisite for clinical application is to define a range of normal values (Supplemental Table 1). Fournier et al (35) were the first to assess absolute flow and resistance ranges of all 3 major coronary arteries. Both indices were measured in all 3 vessels in 25 individuals with a normal coronary circulation (normal coronary arteries, normal left ventricular function, no valvular disease).

They found a mean value of hyperemic Q of 293 ± 102 mL/min and a mean of microvascular R around 336 ± 134 WU in the LAD in the healthy population. Of interest, after adjustment for vessel-specific myocardial mass, which was available in 15 individuals, hyperemic Q was similar in the 3 vascular territories (5.9 ± 1.9 mL/min/g, 4.9 ± 1.7 mL/min/g, and 5.3 ± 2.1 mL/min/g; $P = 0.44$, in the LAD, left circumflex, and right coronary arteries, respectively) (35). Fournier et al (35) also evaluated absolute flow and resistance in 44 atherosclerotic, but nonobstructive, LAD arteries, in which a mean Q of 228 ± 71 mL/min and mean R of 379 ± 147 WU were measured.

For intraindividual follow-up, no range of normal values is mandatory because every patient/artery serves as its own control. Care should be taken that both the tip of the Rayflow catheter as well as the sensor of the pressure wire are at exactly the same location within the coronary artery during follow-up.

RELATION WITH SYMPTOMS, CFR, AND IMR. Konst et al (36) reported on the use of continuous thermodilution-derived measurements in ANOCA. The aim of the study was to explore the relation between Q and R and the existing indices CFR and IMR, and the relation with self-reported angina. In 84 patients undergoing clinically indicated CFT, we found that the absolute R value was higher in patients with CMD, defined as abnormal CFR or IMR, than in the control group (495 WU vs 374 WU). Absolute Q was not different between these groups (191 mL/min vs 208 mL/min). Furthermore, we observed that low Q (defined as <198 mL/min) and high R (defined as >416 WU) were associated with the severity of angina. Therefore, continuous thermodilution-derived measurements correlated with microvascular dysfunction and anginal complaints.

These results were corroborated by another study in which absolute R was associated with CMD, defined as an IMR ≥25. In 120 patients with suspected CMD, 42% demonstrated an IMR ≥25. The median IMR was 23 [interquartile range: 14, 34] and median R was 464 WU [interquartile range: 354-636 WU]. In receiver-operating characteristic analyses 500 WU was identified as the optimal R cutoff to identify patients with an IMR ≥25, with an area under the receiver-operating characteristic curve of 0.83. This is similar to the 495 WU described by Konst et al (36) in patients with microvascular dysfunction. Interestingly, the upper limit of the 95% CI for "normal" R in the LAD territory, as established in the study of Fournier et al (35), was 475 WU, which is very close to the threshold of 500 WU found by Rivero et al (37). Still, reference values for the absolute Q and R have to be validated in larger trials.

In contrast to CFR and IMR, no reports are currently available on the correlation with clinical outcomes. However, we have described the relation between continuous thermodilution and self-reported anginal complaints. Absolute Q and R could be a potential guidance in patient-tailored therapy, by measuring the effects of periprocedural administered therapy on absolute Q and R (38).

Of interest, we found that the absolute Q and R were not associated with endothelium-dependent coronary spasm during acetylcholine testing. Therefore, a coronary function test should include both measurements of endothelium-dependent and -independent function.

Additional data with larger samples should be able to demonstrate the role of absolute Q and R measurements in diagnostic work-up for ANOCA.

FUTURE PERSPECTIVES

Based on the safe, reproducible continuous thermodilution method, we have reviewed 4 measurements, the absolute Q and R, and the relative CFR and MRR. Because flow and resistance are dependent on the location in the coronary tree where they are measured, there is a considerable variability in normal values. This can partly be subscribed to differences in myocardial mass perfused by the concerning artery; however, the variability persists even after normalization for CT-derived myocardial mass, indicating an intrinsic interpatient variation (39). This makes these measurements particularly useful for intraindividual patient follow-up for the assessment of microvascular dysfunction and associated complaints. An example of intraindividual follow-up is a pilot study in which continuous thermodilution measurements were performed immediately after successful PCI of a chronic total occlusion and at 1-week follow-up. Absolute coronary blood flow in the recanalized artery increased during follow-up in the days after the PCI. In addition, absolute resistance decreased (40). Furthermore, we are currently performing a randomized-controlled trial in which the effect of calcium-channel antagonists on vasomotor dysfunction endotypes at repeated invasive CFT are compared with placebo. In this trial, we additionally measure the effect of calcium channel antagonists (CCAs) on Q an R measured by thermodilution. Next to the effect of CCAs, we can also evaluate reproducibility over a longer time period in the placebo group (EDIT-CMD [Efficacy of Diltiazem to Improve Coronary Microvascular Dysfunction: A Randomized

Clinical Trial]; NCT04777045). To further improve the incorporation of these absolute values, normalization by myocardial mass is a potential future research subject. Myocardial mass might potentially be estimated by intracoronary physiology or angiographic estimation (41).

Recently the continuous thermodilution-derived CFR and MRR have become available (33). CFR is the classical ratio of maximum blood flow and resting blood flow (and as such is confounded by epicardial disease), whereas MRR is the ratio of true resting MVR (which is not confounded by epicardial disease) and hyperemic MVR and might be the most specific index of microvascular disease. While these measurements have not been validated in larger populations, they bear the promise for interindividual comparisons and more widespread use (42). An important potential advantage is that CFR and MRR theoretically rely on baseline and hyperemic measurements in the same epicardial territory and therefore are independent of myocardial mass. The MRR, being specific for the microcirculation and operator independent, has the potential to replace CFR and other ratios and plays a central role in the assessment of the microcirculation (43).

Implementation of continuous thermodilution in more catheterization laboratories might improve our understanding of the true prevalence of CMD within ANOCA and provide a better understanding of the underlying physiology of the different endotypes. The next steps for continuous thermodilution will be the association of the individual parameters Q, R, CFR, and MRR with clinical outcomes and the demonstration of improvements in anginal complaints and clinical outcomes by individual patient-tailored (pharmacologic) care of microvascular dysfunction.

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KEY WORDS absolute coronary blood flow, acetylcholine, adenosine, ANOCA, coronary function test, coronary physiology, continuous thermodilution

APPENDIX For a supplemental table, please see the online version of this paper.