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Usefulness of coronary flow reserve measured by transthoracic coronary Doppler ultrasound in the elderly

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1 Introduction

The left anterior descending (LAD) coronary artery is the main vessel of human coronary circulation, and life-threatening consequences are seen when flow in this area is impaired.[1] Noninvasive measurement of coronary flow reserve (CFR), defined as the ratio of maximal to baseline coronary blood flow, has been repeatedly shown to be a feasible technique by ultrasound transthoracic Doppler (TTD) both in the LAD and, with some limitations, in the posterior descending (PD) coronary artery.[2–7] CFR by TTD offers two important pieces of information: information about patency and flow through the large epicardial coronary artery proximal to the site of CFR assessment and information about the functional integrity of coronary microcirculation distal to the site of CFR assessment.[4] CFR by TTD is a valuable research tool for investigating the pathophysiology of coronary circulation. However, CFR by TTD is also an important clinical decision-making instrument, enabling functional assessment of epicardial coronary stenosis, particularly in cases of anatomically borderline stenosis, i.e., 50%–70% of cases.[8] CFR by TTD enables insight downstream into coronary microvascular function that might be impaired due to primary coronary microvascular disease, as a consequence of myocardial diseases with extramural compression and microvascular remodeling and rarefaction (in left ventricular hypertrophy, dilated or hypertrophic cardiomyopathy, or aortic stenosis), or as a consequence of microvascular obstruction due to micro-embolization by plaque and thrombus debris during percutaneous coronary interventions.[9]

Epicardial coronary artery patency and flow may be particularly jeopardized in the elderly as a result of advanced atherosclerosis (a disease of aging). Coronary microcirculatory function might also be impaired in the elderly even in the absence of obstructive epicardial atherosclerosis due to accumulated risk factors (e.g., hypertension, diabetes, obesity) and co-morbidities (e.g., chronic kidney, aortic stenosis).[10,11] As a technique that is noninvasive, inexpensive, easily repeatable, and that does not require radiation, TTD CFR may be very useful in the fragile population of the elderly, offering a better understanding of coronary vascular aging as well as clinically important information regarding the diagnosis and prognosis of coronary artery disease.

2 How to measure CFR by transthoracic Doppler?

CFR can be measured noninvasively by TTD and positron emission tomography and invasively using intra-coronary Doppler flow wire. TTD provides reliable measurements of CFR in the distal or middle LAD using pulsed wave Doppler under the guidance of color Doppler flow mapping, usually obtained by a modified apical approach. Coronary flow is biphasic (systolic and diastolic), with a predominant diastolic component. The systolic and diastolic coronary flow velocity spectrum is obtained at baseline and during the peak of hyperemia. From diastolic coronary flow in the basal condition and during induced vasodilatation, the following parameters can be measured: peak diastolic ve-

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locity (cm/s), mean diastolic velocity (cm/s), velocity-time integral (VTI, m), and diastolic deceleration time (DDT, ms). CFR is the ratio of hyperemic to basal peak diastolic flow velocities.

Coronary flow velocity can also be measured by TTD in PD that originated 85% from the right coronary artery (RCA), thus enabling the measurement of CFR of the RCA/PD. The feasibility of TTD CFR may be improved by contrast enhancement combined with second-harmonic imaging technique, and may even reach 100% for LAD and 65%–80% for RCA/PD.

The measurement of CFR assumes that maximal vasodilatation is achieved, usually by the endothelium-independent intravenously applied vasodilators adenosine and dipyridamole. Both of these stressors are better than exercise and dobutamine, because the latter two are submaximal to recruit CFR and more technically demanding. Adenosine has a shorter duration of action (up to 30 s) and a shorter time to maximal effect (30–55 s) compared to dipyridamole, which requires 6–16 min to maximal effect and has a duration of action of approximately 30 min. Dipyridamole offers the possibility of assessing both CFR and wall motion abnormalities during the same examination. The main advantages of adenosine are its more potent action, short time to maximal effect, short action and short duration of potential adverse effects (hyperventilation, flushing, sometimes hypotension and headache) that enables repetition of the test during the same session, if needed.[12] Adenosine may induce AV conduction delay and hyperventilation, whereas dipyridamole may induce prolonged ischemia, hypotension, flushing, headache and hyperventilation.

Dipyridamole and adenosine may not produce the same increase in coronary flow, which is an element necessitating close consideration when deciding which stressor is most suitable for Doppler studies.[12,13] When comparing dipyridamole and adenosine, the Italian National Council research group from Pisa showed that adenosine produced the highest flow velocity at hyperemia and that CFR was significantly higher with adenosine in patients with CAD, and it concluded that "the most prominent vasodilator response is observed during the adenosine infusion," and therefore, "adenosine is preferable to dipyridamole". Indeed, the effect of dipyridamole on coronary vessels is indirect, as it inhibits the reuptake and catabolism of endogenous adenosine. Therefore, the local, microvascular concentration of adenosine is less certain with dipyridamole than with adenosine infusion. It is noteworthy that dipyridamole produces a more than twofold increase in heart rate compared to adenosine, which may lead to measurement bias.[13] Very often, heart rate at peak dipyridamole approaches 100 beats/min, which makes the recording of peak hyperemic velocities difficult and prone to wall motion artifacts.[13]

3 Clinical spectrum of CFR application by TTD

Important clinical information was obtained by applying LAD and PD coronary flow reserve by TTD, revealing significant epicardial coronary stenosis, stent restenosis, graft function, functional assessment of the collateral-dependent circulation in chronic total coronary occlusion and improved identification of significant LAD stenosis compared to multi-detector computed tomography.[5–7,14–17] Results regarding the prognostic value of CFR measured in LAD or PD were obtained more recently, although in the case of dipyridamole used as an active agent in a relatively large series.[8,12,18–24]

CFR with different stressor agents was also used for diagnostic or prognostic purposes regarding actual myocardial ischemia and assessment of coronary microcirculation in a plethora of conditions, including severe psoriasis, systemic hypertension, left bundle branch block, Tako-Tsubo cardiomyopathy, Chagas disease, hypertrophic cardiomyopathy, type 2 diabetes, in the estimation of infarct size after primary percutaneous coronary intervention, and in patients submitted to intra-aortic counter pulsation.[9–11,25–32] CFR was also tested as an additive predictor to traditional scores in septic shock or prognostic factor of long-term cardiovascular outcome in patients with chronic kidney disease.[33,34] Finally, CFR was used to investigate the effects of the anti-ischemic agent ranolazine in patients with myocardial ischemia but without obstructive coronary artery disease and of the anti-cholesterol agent rosuvastatin in patients with severe hypertension.[35,36]

Indeed, coronary artery imaging with TTD echocardiography can be a simple and useful technique for diagnosing significant coronary artery stenosis.[22] The visualization of mosaic, turbulent flow in the proximal LAD (but also in PD) may suggest the presence of significant stenosis at the corresponding site, even during routine echocardiography. CFR has a high diagnostic accuracy and feasibility in detecting the presence of functionally significant coronary stenosis. On the other hand, CFR measured flow response to downstream microvascular bed vasodilatation during the infusion of either endothelium-dependent or endothelium-independent dilators.[37] From the classical concept, microvascular dysfunction may be announced when CFR is reduced in the absence of significant epicardial obstructive coronary artery disease, as documented, for example, by the presence of normal intravascular ultrasound signals.[37,38]

The profile of epicardial coronary flow assessed by TTD (diastolic deceleration time, presence and duration of early and late systolic retrograde flow) as well as CFR by TTD may provide insight into coronary perfusion physiology, whereas measurements of absolute coronary blood flow (mL/min per gram of tissue) and index of microcirculatory resistance are possible invasively using thermodilution during a continuous infusion of saline.[37]

When LAD CFR was used as a continuous covariate to predict 1-year composite events (including both cardiac and revascularization) in patients with suspected CAD, different predictive models were used, either accounting (Cox's model) or not (logistic regression and neural network) for time-to-event and either considering (forced models) or not (stepwise logistic regression and neural network models) a combination among 21 potential predictors.[12] Multivariable LAD CFR-based prediction of events was independent of accounting or not for revascularization events, and receiver operating characteristic (ROC) areas under the curve were extremely high (> 0.90). These results were obtained for the first time with adenosine as a stressor, in a very large series of consecutive patients investigated at a single clinical site, with few patients (5.6%) lost to follow-up.[12] On the other hand, Rigo, *et al*.,[8] using dipyridamole, evaluated 86 patients with angiographically assessed single-vessel CAD, who were followed up for a median of 14 months after coronary angiography, and reported that a dichotomous LAD CFR (< 2) was the only independent prognostic predictor of outcome (hazard ratio, by Cox's analysis, 24.2; 95% CI: 3.2–179.7, $P < 0.002$). Later, this group extended the observation to 329 and 1145 patients (in multicenter cooperative investigations), and the multivariate predictive role of dipyridamole-obtained LAD CFR was confirmed with Cox's hazard ratios for LAD CFR (lower than 1.92) equal to 16.52 (95% CI: 5.76–47.40, $P < 0.0001$) and for continuous LAD CFR (2.2 ± 0.5) equal to 2.4 (95% CI: 1.1–5.4, $P = 0.03$).[18,19] This investigation was recently further enlarged.[23,24]

It is important to note that LAD CFR overshadowed the contribution of regional wall motion abnormality (RWMA) in studies in which these were assessed, also highlighting the relative interest in investigating LAD CFR in the elderly or geriatric patients, among whom RWMAs are quite frequently seen.[12,39,40]

4 TTD CFR and aging

The impact of aging and atherosclerotic risk factors on TTD CFR in subjects with normal coronary angiography was evaluated in a multicenter study by Galderisi, *et al*.[41] A total of 335 subjects (mean age: 61 years) with at least one risk factor but normal coronary angiography underwent high-dose dipyridamole stress-echo with TTD evaluation of LAD CFR. CFR was progressively reduced with aging, predominately due to a gradual increase in resting velocity, while the reduction of hyperemic velocities remained unaffected. When age quartiles and risk factors were entered into a regression model, the following were the independent determinants of CFR in the whole population: third and fourth age quartile ($P < 0.0005$ and $P < 0.0001$, respectively), left ventricular mass index ($P < 0.0001$), diastolic blood pressure ($P < 0.001$), total cholesterol ($P < 0.002$), fasting blood glucose ($P < 0.01$), and male gender ($P < 0.05$). These results indicated that aging impairs CFR in patients with angiographically normal coronary arteries due to a gradual increase in resting coronary flow velocity and that CFR is also affected by atherosclerotic risk factors and left ventricular hypertrophy.

5 TTD CFR in the elderly

It was only recently recognized that LAD CFR evaluated by TTD might be of particular interest in the geriatric population and that senior patients might benefit most from this noninvasive technique, both for diagnostic and prognostic purposes.

Cortigiani, *et al*.,[42] investigated the capability of LAD CFR to predict outcome in an unselected cohort of patients older than 80 years of age having stress echo negative by wall motion criteria. There were 369 patients aged > 80 years who had undergone dipyridamole stress echocardiography with LAD CFR assessment of known ($n = 144$) or suspected ($n = 225$) coronary artery disease. Mean CFR was 2.07 ± 0.53. During a median follow-up period of 21 months, there were 62 major adverse cardiac events (MACEs; 45 deaths and 17 non-fatal myocardial infarctions). In individual patient analysis, 152 (41%) subjects had a CFR of < 1.93 (the cut-off determined by receiver operating characteristic curve analysis). Annual mortality was 9.8% in patients with CFR < 1.93 and 3.7% in those with CFR > 1.93 ($P = 0.001$). Of 15 clinical and echocardiographic parameters analyzed, CFR ≤ 1.93 [hazard ratio (HR) = 2.17, 95% CI: 1.14–4.10] and resting wall motion abnormality (RWMA; HR = 2.60; 95% CI: 1.35–5.00) were multivariable indicators of mortality and MACEs. The authors concluded that a reduced LAD CFR among known or suspected CAD patients over 80 years of age is a strong and independent indicator of both mortality and MACE, adding prognostic information over clinical evaluation and RWMA, whereas a preserved CFR predicts a favorable outcome, particularly in subjects with no RWMA.[42]

There are areas in which CFR determination may indeed be useful in the elderly. One such area is coronary microcirculatory function after primary percutaneous coronary intervention (pPCI) in patients with acute myocardial infarction.[9] In 59 patients, TTD analysis of infarct-related artery blood flow was done on the second day following pPCI for acute anterior myocardial infarction, including measurements of CFR, baseline diastolic deceleration time (DDT), and DDT during adenosine infusion (DDT-adeno). Killip class, myocardial blush grade, resolution of ST segment elevation, peak creatine kinase-myocardial band and conventional echocardiographic parameters were determined. Single-photon emission computed tomography myocardial perfusion imaging was done six weeks later to define final infarct size (percentage of myocardium with fixed perfusion abnormality). In a multivariate analysis, CFR and DDT-adeno remained independent predictors of infarct size after adjustment for other covariates and offered incremental prognostic value in models based on conventional clinical, angiographic, electrocardiographic and enzymatic variables. In predicting large infarction (> 20%), the best cut-off for CFR was < 1.73 (sensitivity 65%, specificity 96%) and the best cut-off for DDT-adeno was ≤ 720 ms (sensitivity 81%, specificity 96%). CFR and DDT-adeno are therefore independent and powerful early predictors of final infarct size. As large infarction may be more frequent among the elderly, CFR by adenosine offers incremental prognostic information over conventional parameters of myocardial and microvascular damage and tissue reperfusion for better risk stratification of patients.[9]

Another group of patients for whom reduced CFR may provide important information is critically ill patients, who are frequently represented among elderly and geriatric populations. A study was recently conducted regarding whether CFR is associated with tissue ischemia and acidosis, impaired myocardial deformation, and adverse outcome in 70 mechanically ventilated patients with septic shock.[33] Again, LAD CFR was assessed by adenosine infusion. Lactate, pyruvate, and glycerol in tissue were measured by microdialysis catheter inserted into the subcutaneous adipose tissue as markers of tissue ischemia and acidosis. LAD CFR was 1.8 ± 0.42 in non-survivors (n = 34), versus 2.08 ± 0.44 in survivors (P = 0.007). A LAD CFR < 1.90 predicted mortality with sensitivity of 70% and specificity of 69% (ROC = 77%, P = 0.003). Notably, LAD CFR had an additive value to APACHE (chi-square change: 4.358, P = 0.03) and SOFA (chi-square change: 3.692, P = 0.04) for the prediction of mortality. Tissue ischemia and acidosis are common pathophysiological links between decreased LAD CFR and impaired LV myocardial deformation in septic shock, and with CFR, an important additive predictor of ICU mortality is provided that should be considered in addition to traditional risk scores in septic shock.

6 Future directives

Interestingly, Gould highlighted that although coronary flow is a major focus of the cardiology profession that justifies procedures based on improving it, few cardiologists quantify myocardial perfusion or measure CFR or have ever measured it, or even understand how to use the information if obtained.[43] This situation may be similar to other areas of cardiology in which few professionals are involved in or understand the particulars of risk prediction, pure inotropism, endothelial dysfunction, or deep multivariate statistics to assess outcome comparatively, or to assess gender-related differences in clinical presentation of symptoms and outcome.[44–51]

Nevertheless, it is increasingly evident that coronary flow is not always related to the angiographic severity of stenosis and that revascularization may improve mortality over medical treatment in patients with intermediate (50%–70%) coronary stenosis only if flow is reduced.[52–54] It is likely that the concept of anatomically "critical" stenosis should always be accompanied by the concept of "critical" flow reduction for managing coronary artery disease patients.[43,54] Thus, since a cut-off value for both LAD and PD CFR may dissociate those individuals who are prone to presenting follow-up events, as illustrated here, it may be of interest to examine whether this may be a prevailing patho-physiological element as opposed to the anatomical standard of critical coronary stenosis, which may be easily obtained noninvasively by adenosine and TTD.[12] Comparative performance investigations of adenosine versus dipyridamole are still badly needed.[12,13]

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