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Insights into Myocardial Perfusion PET Imaging: the Coronary Flow Capacity

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Abstract

Purpose of Review The present work summarizes the clinical relevance of coronary flow capacity (CFC) with an eye on future perspectives.

Recent findings CFC concept has been recently introduced providing a comprehensive framework for coronary physiology evaluation.

Summary It has been widely demonstrated that coronary artery disease (CAD) is a complex disease with a multifactorial etiology resulting from different pathogenic mechanisms. Cardiac positron emission tomography (PET) currently represents the gold standard for CAD assessment, providing absolute myocardial perfusion data including coronary flow reserve (CFR), calculated as the ratio of hyperemic to rest absolute myocardial blood flows. CFC can be obtained from dynamic PET images by plotting the primary stress perfusion data and CFR values for each pixel on a graph of predefined exact ranges. The routine evaluation of this parameter may add diagnostic and prognostic value to clinical and conventional imaging data.

Keywords Coronary flow capacity · CFC · Coronary artery disease · CAD · Perfusion · Imaging · PET

Introduction

It has been widely demonstrated that coronary artery disease (CAD) is a complex disease with a multifactorial etiology resulting from different pathogenic mechanisms [1, 2•].

Despite great technological improvements in diagnosis and dramatic advances in therapeutic approaches, CAD is the primary single cause of mortality and global loss of disability adjusted life years [3]. Moreover, the CAD-related mortality is estimated to increase due to worsening of metabolic risk factors especially in developing countries.

The available invasive and non-invasive imaging tools have been proved being able to provide a large amount of data to identify the presence, extension, and severity of CAD with diagnostic and prognostic upshots [4 5, 6, 7, 8, 9, 10].

Cardiac positron emission tomography (PET) currently represents the gold standard for CAD assessment, providing absolute myocardial perfusion data including coronary flow reserve (CFR), calculated as the ratio of hyperemic to rest absolute myocardial blood flows (MBF). Such parameter reflects coronary vasodilator capacity. It should be taken into account that CFR depends on both coronary hemodynamics at rest and under stress conditions, and that any physiological change may accidentally affect the CFR estimation [11]. To overcome such limitations, Johnson and Gould have recently introduced the coronary flow capacity (CFC) concept, proposing a comprehensive framework for coronary physiology evaluation [12, 13•, 14].

CFC Measurement

CFC combines hyperemic MBF and CFR with thresholds for definite or possible ischemia to comprehensively assess all relevant coronary flow characteristics [15] on pixel bases. In detail, this parameter can be obtained from dynamic PET images by plotting the primary stress perfusion data and CFR values for each pixel on a graph of predefined exact ranges consistent with minimal, mild, moderate, or severely reduced CFC [12, 13•].

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On a color scale basis a map of left ventricle CFC can be interpreted as follows: red, normal, referring to healthy individuals with no risk factors (CFR > 2.9 and stress perfusion > 2.17 cc/min/g); orange, minimally reduced, defined by risk factors only without clinically manifest CAD (CFR > 2.38 to 2.9 and stress perfusion > 1.82 to 2.17 cc/min/g); yellow, mildly reduced, denoting documented stable CAD without angina or ST depression on ECG during dipyridamole stress (CFR > 1.6 to 2.38 and stress perfusion > 1.09 to 1.82 cc/min/g); green, moderately reduced, with possible ischemia (CFR > 1.27 to 1.6 and stress perfusion > 0.83 to 1.09 cc/min/g); blue, severely reduced with definite ischemia (CFR 1.0 to 1.27 and stress perfusion ≤ 0.83 cc/min/g); dark blue, defined by myocardial steal with stress perfusion falling below rest perfusion (CFR < 1.0) [13•, 14].

CFC from Diagnosis to Prognosis

The clinical meaning of this parameter takes into account that rest images may result heterogeneous and become more uniform or normalize under stress conditions due to endothelial dysfunction associated with CAD [16, 17]. Thus, resting myocardial perfusion may cause corresponding heterogeneous CFR either with or without segmental or diffuse flow limiting stenosis caused by coronary atherosclerosis. However, this heterogeneity typically does not follow specific coronary artery distributions, but it can be identified by CFP map that differentiates among endothelial mediated heterogeneity, flow limiting stenosis, and diffuse global disease [18].

Indeed, as compared with regional or global CFR or stress perfusion data, available literature demonstrates that CFC recognizes individual regional and global heterogeneities refining cardiac events risk prediction [13•, 18].

Yet, the caffeine effect on the stressor kinetic may affect the clinical meaning of CFC metrics estimation. It has been shown that even low serum caffeine levels may cause heterogeneously reduced maximal regional and global values of stress flow and CFR, with CFC distribution changing over the entire LV [19, 20].

Moreover, besides patient preparation, the pharmacological stress type may also affect the robustness of provided flow data. Kitkungvan and co-workers previously showed that standard stress PET imaging protocol using 6-min adenosine infusion with ^{82}Rb administration at 3 min is the most appropriate adenosine protocol for quantifying both CFC and CFR, with comparable results to a 4-min dipyridamole infusion with Rb-82 injection at 8 min [21]. The reported finding also highlighted how inadequate stress protocol may mislead results interpretation.

In a recent investigation, involving 3774 patients, the Authors demonstrated that CFC integrating regional CFR and regional absolute stress perfusion in cc/min/g by ^{82}Rb PET provides automated, objective, artery-specific, regional size–severity, physiologic quantification of CAD severity associated with high risk of death and myocardial infarction independently of standard risk factors and other quantitative PET parameters [13•].

More recently, in a 10-year follow-up investigation performed on a population of 5274 patients, Gould and co-workers demonstrated that severely reduced CFC predicted higher death, myocardial infarction, stroke, and revascularization than any other severity ^{82}Rb PET metric including CFR and stress MBF [22••].

In addition, the clinical benefit of revascularization guided by the evaluation of CFC has been reported by Bober and collaborators [23], who nicely proved that regions with severely reduced CFC on baseline ^{82}Rb PET showed a significant improvement in quantitative perfusion after revascularization while regions without reduced CFC demonstrated no perfusion improvement after analogue procedure.

Miura et al., using a different tracer, by mean ^{13} N-ammonia PET/CT, carried out an investigation on 137 patients without known CAD [24•]. The Authors proposed the modified CFC (mCFC) to assess microvascular dysfunction. Such parameter, integrating regional CFR and regional absolute stress perfusion, allows to define as "normal" or "minimally reduced" the flow in each left ventricle coronary territory with a color-based interpretation of the flow capacity. Interestingly, mCFC showed an incremental power for predicting cardiovascular mortality with a 25% prevalence of coronary microvascular dysfunction defined by mCFC.

The Future of the CFC Concept

The emerging role of CFC in the identification of patients with impaired coronary function opens the way to future investigations focused on challenging populations, such as women, diabetic and obese patients, not only with diagnostic implications but also aiming to achieve a deeper understanding of the pathophysiological patterns of coronary flow impairment.

As observed in the WISE study, women with reduced CFR were significantly more likely to have reduced exercise capacity and worst overall prognosis [25]. However, the relationship between functional capacity and coronary function still remains unclear and could be further explored with the CFC concept.

With regard to obese population, Upadhyaya et al. [26] nicely demonstrated, with ^{13} N-ammonia PET dynamic

imaging, a U-turn pattern of the hyperaemic MBF across the range from normal weight, overweight, obesity, and morbid obesity. In detail, the Authors showed that hyperaemic MBF gradually declined from normal weight, overweight, and obesity, while it increased again in morbid obesity with comparable data to those obtained in subjects with normal weight. The interplay between fat and coronary function is still under investigation, and a potential estimation of CFC may help to obtain a big picture of such a complex mechanism. The topic may become even more appealing if we consider the added value of hybrid imaging in evaluating not only functional data from PET modality but also CT results obtained from the integrated approach [27].

Furthermore, despite the robust knowledge accomplished [28], an unquantifiable amount of data is still missing to achieve a complete understanding of the cross talk between coronary blood flow and physiological factors involved in the metabolic asset of diabetic patients.

The diagnostic and prognostic relevance of the CFC becomes even more interesting when looking at recent introduction of novel perfusion tracers such as the ^{18}F-Flurpiridaz [29, 30, 31]. The available data have already demonstrated ^{18}F-Flurpiridaz advantageous properties for CFR and MBF quantification. In addition, when compared with myocardial perfusion imaging by single photon emission tomography (SPECT), ^{18}F-Flurpiridaz PET imaging shows better image quality and higher diagnostic value [31]. The potential implications of CFC estimation by this radiopharmaceutical may open the way to innovative applications for a deeper understanding of clinical meaning of flow heterogeneity.

Likewise, in the era of dynamic SPECT [32, 33], the opportunity to implement available quantification software with CFC estimation tool, thanks to the wide spread of cadmium-zinc-telluride technologies, may encourage innovative research on large scale and finally refine clinical practice routine in the personalized medicine direction.

It is widely accepted that the concept of CFC can be potentially applied to different imaging modalities that provide absolute quantification of myocardial perfusion including dynamic myocardial computed tomography perfusion (CTP) [34]. A CT-based approach boasts the advantage to deliver both functional and anatomical information at the same time. However, the still high radiation dose accounting for a mean effective radiation dose of 9 mSv makes these nuclear medicine techniques less appealing than the conventional ones [34, 35]. Nevertheless, it should be taken into account that dose optimization is among the main goals of hardware research, and a great reduction of administered dose is expected by the next generation imaging design.

Conclusions

The CFC parameter integrates CFR and stress MBF to improve the potential of dynamic imaging to identify coronary flow impairment. The routine evaluation of this metric may add diagnostic and prognostic value to clinical and conventional imaging data; however, its potential has not been fully investigated. The incoming PET tracers and the technological improvement of available non-invasive imaging modalities [36, 37] will be the bricks on which to build the future of CFC into clinical practice.

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Declarations

Competing Interests The authors declare no competing interests.

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• Of importance
•• Of major importance

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