

JACC STATE-OF-THE-ART REVIEW

Coronary Physiology Beyond Coronary Flow Reserve in Microvascular Angina

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K. Lance Gould, MD, Nils P. Johnson, MD, MS



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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) diagnose the primary pathophysiologic cause of angina without angiographic stenosis; 2) explain it to the patient; and 3) recommend optimal personalized treatment.

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ABSTRACT

Angina with no angiographic stenosis, commonly called "microvascular angina," encompasses a wide continuum of coronary pathophysiology in conflicting published reports. Comprehensive quantitative myocardial perfusion offers new insights beyond overly simplistic coronary flow reserve. Integrating regional absolute stress flow, relative stress flow, coronary flow reserve, and qualitative subendocardial perfusion gradient on tomograms of relative images, provides correct diagnosis, quantitative physiological classification, and potential treatment. Angina without angiographic stenosis is associated with abnormal quantitative perfusion with rare, but instructive, exceptions. However, microvascular dysfunction without angina is common, particularly associated with risk factors. Reduced subendocardial/epicardial relative activity is common with diffuse coronary artery disease without focal stenosis with or without angina depending on the severity of reduced subendocardial perfusion. Precision quantitative myocardial perfusion in 5,900 cases objectively classifies angina with no angiographic stenosis into 4 categories: subendocardial ischemia due to diffuse coronary artery disease (most common), overlooked stenosis, diffuse microvascular dysfunction due to risk factors or specific microvasculopathies, and nonischemic cardiac pain mechanisms (rare), or some mix of these prototypes, of which 95% associate with risk factors, or subclinical or clinically manifest coronary atherosclerosis needing vigorous risk factor treatment. (J Am Coll Cardiol 2018;72:2642–62)

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"Microvascular angina" encompasses a vast number of published reports: 333 documents use the term, with 1,812 references on syndrome X, 2,104 on small vessel disease, 2,502 on coronary flow reserve, 402 on coronary flow velocity reserve, and 522 on myocardial perfusion or flow reserve (1). Our review of these published reports on quantitative perfusion imaging in microvascular disease reveals widespread conflicting reports with opposite conclusions, definitions, prevalence, mechanisms, treatment, outcomes, cardiovascular risk, and measures of myocardial perfusion. Despite large numbers of publications, no definitive quantitative perfusion metric, marker, classification, or therapeutic option has emerged or withstood scrutiny (2). Coronary microvasculopathies are well described by biopsy or post-mortem histology reflecting anatomic disease processes (3). However,

histological classification has not found a distinctive clinical role that is dominated by coronary function or physiology in the absence of angiographic stenosis.

Our review suggests that these conflicting published reports are explained by analytical synthesis of highly variable perfusion data thereby potentially redefining physiological mechanisms of microvascular angina as the basis for a systematic, quantitative, physiological classification relevant to treatment. We then illustrate this synthesis of physiological mechanisms for angina without angiographic stenosis by typical case examples. Finally, we test our synthesis by analyzing 5,900 serial diagnostic positron emission tomography (PET) cases in our detailed database with systematic follow-up in 95% of cases for up to 9 years.

On the basis of our integrative review and analysis of microvascular angina, we scientifically submit that

an institutional licensing/consulting agreement with Boston Scientific for the smart minimum FFR algorithm; and has received institutional research support from St. Jude Medical (CONTRAST, NCT02184117) and Volcano/Philips Corporation (DEFINE-FLOW, NCT02328820) for studies using intracoronary pressure/flow sensors.

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**ABBREVIATIONS
AND ACRONYMS**

- CAD** = coronary artery disease
CFC = coronary flow capacity
CFR = coronary flow reserve
CT = computed tomography
D1 = first diagonal branch
ECG = electrocardiogram
FDA = U.S. Food and Drug Administration
FFR = fractional flow reserve
LAD = left anterior descending coronary artery
LV = left ventricle/ventricular
MACE = major adverse cardiovascular events
MI = myocardial infarction
MRI = magnetic resonance imaging
PET = positron emission tomography
RCA = right coronary artery
SPECT = single-photon emission computed tomography

precision physiological imaging of myocardial perfusion beyond coronary flow reserve (CFR) restructures understanding of this condition by providing objective, evidence-based new concepts, classification, mechanisms, and potential management of angina without angiographic stenosis.

“NORMAL” ANGIOGRAM AND CORONARY PHYSIOLOGY OF MICROVASCULAR ANGINA

Up to 20% or more of patients with angina reportedly have no angiographic stenosis (4), and symptoms are attributed to abnormal CFR. However, as detailed subsequently, most patients with angina and “normal” angiograms have subclinical, diffuse, epicardial coronary atherosclerosis by intravascular imaging (4). Conversely, angina is commonly absent despite endothelial or microvascular dysfunction associated with nonobstructive coronary atherosclerosis or risk factors. In other patients, angina may occur despite high regional and transmural coronary blood flow during vasodilator stress, mediated in some cases by unobserved subendocardial ischemia and in other cases by aberrant pain mechanisms as discussed subsequently. Therefore, the causal link between symptoms and reduced CFR is unsubstantiated and tenuous.

The multifaceted mechanisms for controlling coronary blood flow are complex, with physiology in the subendocardium differing profoundly from the subepicardium (5). As a result, transmural perfusion gradients and subendocardial ischemia are well established although not identified on routine clinical imaging. Common pathophysiological mechanisms include heterogeneous endothelial dysfunction associated with risk factors or subclinical atherosclerosis (6), increased intercapillary oxygen perfusion distances due to hypertrophy, microvasculopathy or microemboli (7), falling coronary perfusion pressure across a stenosis or diffuse epicardial narrowing with even mildly increased flow (5,8), and differential hyperemic responses of subendocardium versus subepicardium (9). Microvascular histopathology includes thickened walls of small coronary arterioles by medial hypertrophy, intimal proliferation associated with risk factors, small vessel pruning or “drop out” due to hypertrophy, cardiomyopathy, microvasculopathy, microemboli, inflammatory disease, or idiopathic cause (3,5).

As a brief summary, with details and references to follow, our review of invasive imaging and physiological measurements indicates the following: 1) in the absence of angiographic stenosis, angina may occur with either very high or low CFR; 2) patients with risk factors and “normal” angiography usually have diffuse atherosclerosis by intravascular imaging associated with adverse outcomes; 3) risk factors or subclinical coronary atherosclerosis associate with heterogeneous endothelial dysfunction and impaired microvascular function; 4) angina without angiographic stenosis commonly arises with risk factors, diffuse epicardial atherosclerosis, and subendocardial ischemia not routinely or specifically examined with current clinical single-photon emission computed tomography (SPECT), computed tomography (CT), PET, or magnetic resonance imaging (MRI) perfusion imaging; and 5) microvascular dysfunction with reduced CFR is common with and without angina.

For example, in a recent report (4), 139 subjects with angina and normal angiography or no stenosis $\geq 50\%$ diameter narrowing had excellent CFR of 4.1 by flow velocity wire. Yet 44% had endothelial dysfunction defined as 20% or more decreased angiographic lumen diameter after intracoronary acetylcholine. All subjects had diffuse nonobstructive atherosclerosis by intravascular imaging (4). In patients with risk factors without angiographic severe stenosis, intracoronary acetylcholine (normally a vasodilator) caused abnormal heterogeneous coronary vasoconstriction in different coronary arteries of the same patient or in different segments of the same artery (6). In a study of women with risk factors (10), CFR by flow velocity wire at an empiric threshold of ≤ 2.32 added prognostic value (hazard ratio: 1.2) to risk factors, but a substantial proportion had no angina despite microvascular dysfunction or had angina with higher CFR values.

In 207 patients with exertional angina, positive exercise stress testing, and “normal” coronary angiography, 17.9% had adverse events during a median of 16 years follow-up, driven primarily by repeat angiography, with 3.75% cardiovascular deaths over 16 years, or approximately 0.2% per year (11). Although CFR was not measured, a majority had 1 or more classic cardiovascular risk factors known to associate with comparable event rates over this long period. In women and men with chest pain without angiographic stenosis, abnormal coronary vasoconstriction after intracoronary acetylcholine predicted a modest, but significantly higher, risk of clinically manifest coronary artery disease (CAD) over

long-term follow-up compared with those with normal vasodilatory responses (12,13).

Patients undergoing cardiac PET imaging for chest pain or dyspnea ascribed to microvascular dysfunction based on global CFR <2.0 compared with CFR >2 experienced a higher rate of adverse outcomes (14). However, as shown in the following text, global CFR fails to distinguish flow-limiting stenosis from diffuse or microvascular disease. By contrast, for other patients with angina and regional abnormalities by hybrid PET-CT, only 1% had reduced stress perfusion with no evidence of coronary atherosclerosis (15), whereas the remaining 99% had evidence of CAD. Moreover, other patients with angina and non-obstructive CAD had a high CFR of 4.0 by thermodilation with sex differences (16), potentially attributable in part to differences in myocardial mass.

In patients with angina, positive exercise stress testing, risk factors, no known CAD, no segmental perfusion defects, and “normal” angiography, CFR was reduced <2.0 by MRI with subendocardial hypoperfusion (17). Even without risk factors, in patients with syndrome X based on angina, positive exercise testing, and “normal” angiography, MRI during adenosine stress showed increased subepicardial perfusion and decreased subendocardial perfusion associated with severe angina (18). Alternatively, some patients with angina and “normal” coronary angiograms had low CFR associated with high resting perfusion but adequate stress perfusion (19).

Regional or global CFR by PET provides different views of microvascular syndromes with prevalence ranging from <1% by regional PET measurement in subjects without stenosis (15) to >50% by global PET measurements not accounting for focal stenosis (14) exemplifying conflicting published reports, with a corresponding wide range of associated risk factors, diagnostic classifications, and differing outcomes.

Subendocardial ischemia during vasodilator stress results from a fall in distal coronary pressure during sufficiently increased coronary blood flow through diffusely narrowed coronary arteries to produce a transmural subepicardial to subendocardial perfusion gradient (5,8). Reduced subendocardial perfusion, therefore, indicates adequate microvascular function to produce the increased coronary blood flow, thence a low distal coronary perfusion pressure and corresponding subendocardial ischemia (5,8). With risk factors without angiographic stenosis, coronary intravascular ultrasound commonly shows diffuse coronary atherosclerosis, reportedly in all patients in one report on microvascular angina (4). This diffuse CAD may cause a pressure gradient, low coronary perfusion pressure, and subendocardial ischemia

during vasodilator stress without regional perfusion defects due to balanced diffuse atherosclerosis. However, published reports on microvascular disease largely ignore this established physiology of subendocardial ischemia with few relevant reports as detailed subsequently.

ANALYTICAL SYNTHESIS OF PUBLISHED REPORTS ON MYOCARDIAL PERFUSION IN MICROVASCULAR ANGINA

Our analysis of the published reports identifies several systematic issues about myocardial perfusion measurements to explain the aforementioned conflicts with a potential objective solution.

1. *Global CFR* as widely reported in the published reports fails to account for regional perfusion defects or resting perfusion or CFR heterogeneity, thereby also failing to separate primarily segmental, or diffuse CAD, or their combination from microvascular disease or some mix essential for diagnosing, classifying, risk stratifying, and treating microvascular disease and CAD.
2. *Heterogeneous* resting perfusion commonly causes heterogeneous CFR due to endothelial dysfunction or other microvasculopathies. High global or regional rest flow frequently causes global or regional low CFR that may be misinterpreted as due to stenosis or diffuse low CFR of microvascular disease, hence, falsely positive CFR. Alternatively, low global or regional rest flow frequently causes adequate global or regional CFR that obscures the diagnosis of regional or diffusely reduced stress flow due to microvascular disease, hence falsely negative CFR.
3. *Subendocardial ischemia* is common with even mild diffuse CAD in the absence of angiographic stenosis due to an increased coronary pressure gradient and fall in coronary perfusion pressure during vasodilator stress. The fall in coronary pressure during vasodilator stress may cause subendocardial ischemia that is not imaged currently and hence erroneously interpreted as microvascular angina when actually due to epicardial narrowing with good microvascular function causing reduced coronary perfusion pressure.
4. *Flush occlusion* of even small secondary coronary artery branches not seen on visually apparent “normal” angiogram without stenosis is common, leading to erroneous diagnosis of microvascular angina.
5. *Caffeine* blunts vasodilator stress hyperemia thereby mimicking microvascular dysfunction.

6. *Nonischemic pain mechanisms* explain severe angina during vasodilator stress with exceptionally high stress perfusion and CFR greater than healthy, risk-free, young volunteers and without regional perfusion defects, subendocardial/subepicardial perfusion gradient, or angiographic abnormalities.

We now address each of these issues regarding quantitative myocardial perfusion by reviewing their physiology with case examples followed by statistical analysis of their applicability in a cohort of 5,900 routine serial clinical PETs in our database.

GLOBAL VERSUS REGIONAL CFR. Diagnostic criteria for microvascular angina require reduced CFR below 2.0 to 2.5 (10,14,15). Originally, CFR for assessing stenosis severity was developed by the first author 44 years ago (20), leading to over 5,000 peer-reviewed references on the topic (1), suggesting that coronary physiology trumps coronary anatomy (5,21). Although gratifying to its originator, the widely accepted, powerful simplicity of CFR limits its assessing common, regionally heterogeneous, complex interactions among focal coronary stenosis, diffuse epicardial atherosclerosis, and microvascular dysfunction. Accordingly, defining the full range of mixed clinical coronary pathophysiology requires 3 concepts beyond CFR: 1) regional size-severity quantification versus global perfusion; 2) integration of regional resting and hyperemic heterogeneous quantification into coronary flow capacity (CFC) in addition to their ratio as CFR; and 3) subendocardial perfusion on relative tomographic images.

Nonuniformity or heterogeneity of resting perfusion and CFR within a patient or between different patients reflects true biological variability consistently seen on serial PETs associated with endothelial dysfunction, variable pressure-rate product, sex, medications, and a myriad of other factors affecting regional and global coronary blood flow (5).

Rather than ignoring regional variation, we must understand its mechanisms and implications as “signal” rather than “noise” for understanding clinically relevant coronary physiology. Some published reports overlook this essential point by claiming, for example, a 50% prevalence of microvascular disease based on global CFR (14,22) while failing to separate regional perfusion abnormalities due to flow-limiting stenosis from homogeneous global reductions in CFR due to microvascular disease without regional stress abnormalities. Similarly, claims that global stress perfusion or CFC adds no statistically significant prognostic value to global CFR (22) are misleading

and wrong with erroneous risk stratification as shown subsequently in our large clinical cohort.

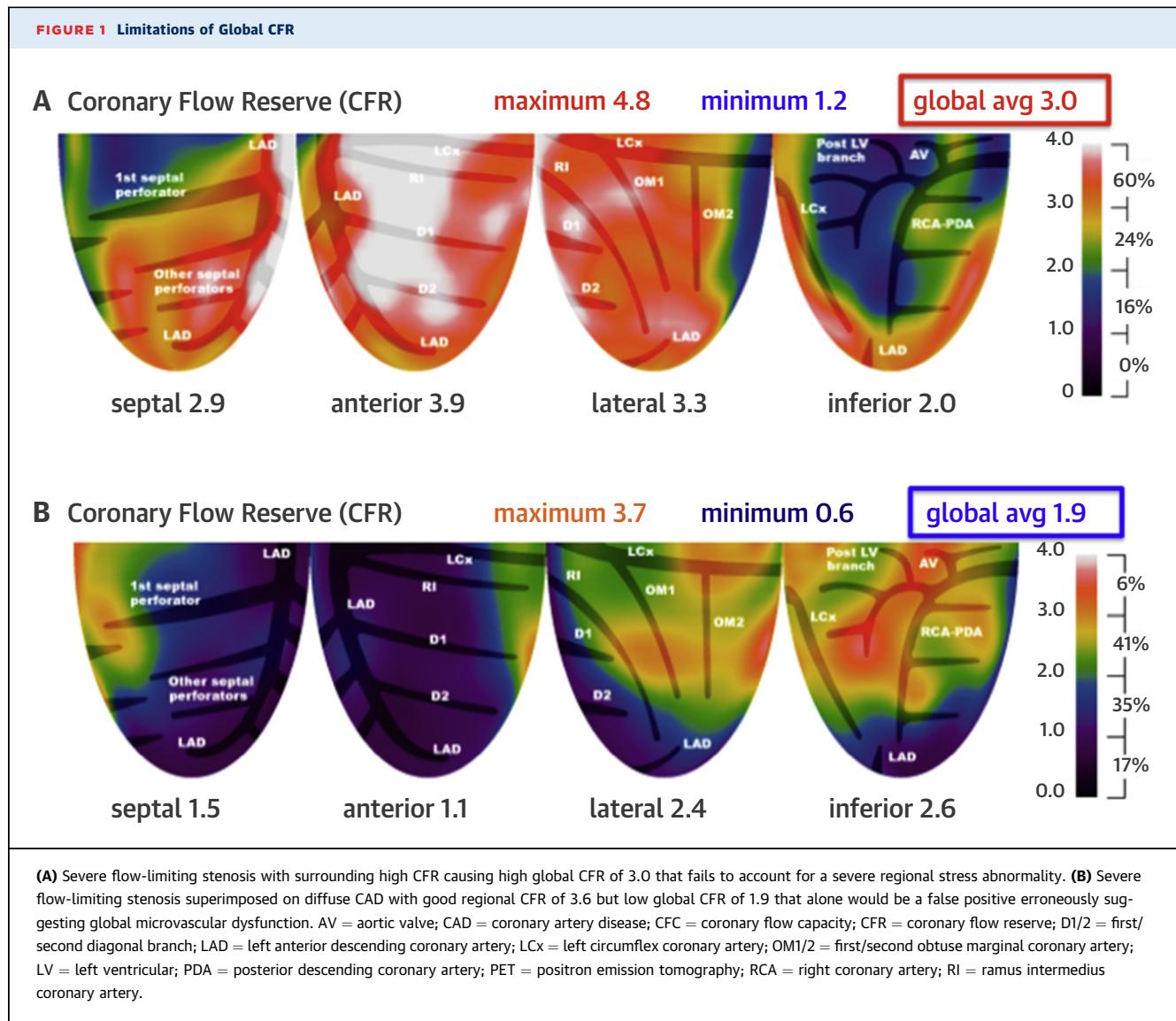
As clinical examples emphasizing this point, **Figure 1A** shows an inferior, severe, stress defect with regional CFR of 1.2 in right coronary artery (RCA) distribution without scar on resting perfusion images (not shown). However, the global CFR of 3.0 is good, thereby failing to account for significant focal disease by averaging excellent CFR in the surrounding left ventricle (LV) with the severely reduced CFR in the RCA distribution. Analyzing only global CFR as reported (14,22) overlooks such common findings and contravenes optimal risk stratification.

The example in **Figure 1B** has a global CFR reduction to 1.9 suggesting diffuse microvascular dysfunction. However, that conclusion is also wrong because the low global CFR reflects a large, severe, anterior, and apical stress defect with myocardial steal (CFR = 0.6) due to left anterior descending coronary artery (LAD) occlusion wrapping around the apex, averaged with surrounding myocardium having excellent CFR up to 3.7. The low global CFR is therefore falsely positive for diffuse microvascular dysfunction instead of severe segmental disease observed with regional quantification.

CFC: SIMULTANEOUS ASSESSMENT OF REST AND STRESS FLOW

CFC integrates the simultaneous regional size severity of resting flow, hyperemic flow, and their ratio, CFR, as in **Figure 2**. The concept of CFC has been validated in the published reports (23–26) and after rigorous review by the Food and Drug Administration (FDA) over the 5 years from 2012 to 2017 as the basis for FDA validation and approval based on data shown subsequently (510(k) number 171303, September 22, 2017). Although originally developed using noninvasive imaging (23–26), CFC has also been validated by invasive pressure and Doppler flow velocity measurements (27), attesting to its universal physiological insights distinct from methodology.

As previously reported (23–26) (FDA 510(k) number 171303), CFC groups an infinite range of combined stress perfusion in ml/min/g and CFR values for each of 1,344 LV pixels into the following objectively determined ranges of combined values for each regional pixel: excellent (CFR >2.9 and stress perfusion >2.17 ml/min/g, colored red in our work), typical (CFR >2.38 to 2.9 and stress perfusion >1.82 to 2.17, colored orange), mildly reduced but not ischemic (CFR >1.6 to 2.38 and stress perfusion >1.09 to 1.82, colored yellow), moderately reduced (CFR >1.27 to 1.6



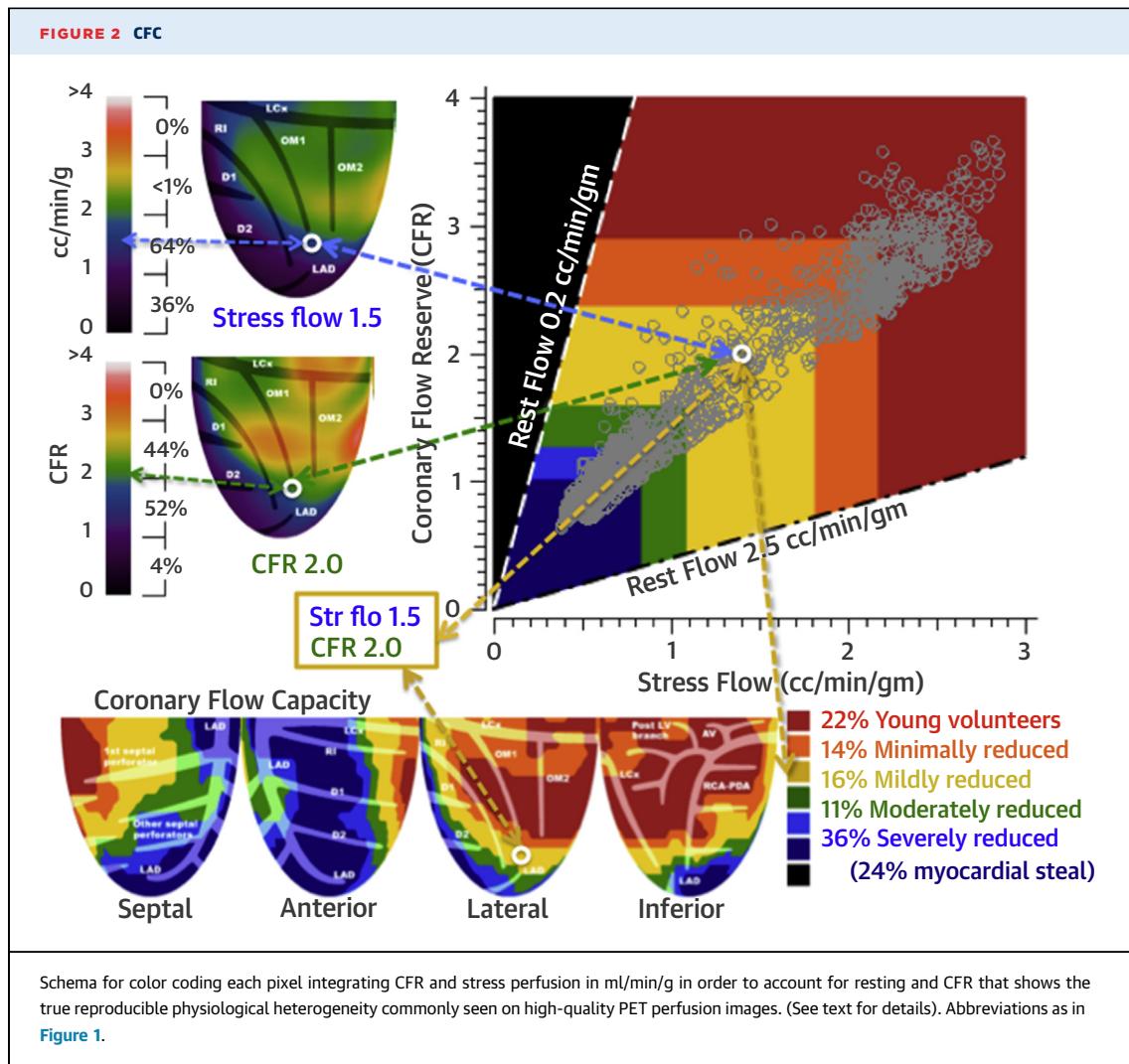
and stress perfusion >0.83 to 1.09 , colored green), severely reduced (CFR 1.0 to 1.27 and stress perfusion ≤ 0.83 , colored blue), and myocardial steal (CFR <1.0 , colored purple).

Each color-coded pixel is spatially mapped back onto its LV location with percent of LV calculated for each range of combined both CFR and stress perfusion pixel values listed in the CFC color histogram bar. The regional, color-coded 1,344 pixels provide integrated, size/severity quantification for a specific epicardial territory down to tertiary branches.

In Figure 2, the 4 panel views show the regional range of stress flow, and CFR in coronary artery distributions with severely reduced CFC coded blue in RCA distribution and myocardial steal (CFR <1.0)

associated with collateralized complete or subtotal occlusion, confirmed by angiography. In anterior and lateral regions in the distributions of diagonal and marginal branches, coronary flow capacity is adequate (orange), indicating microvascular function sufficient to cause hyperemia revealing the myocardial steal. In mid-LAD distribution CFC is mildly reduced (yellow) due to mild stenosis or diffuse CAD.

The presence of regionally adequate vasodilatory response (orange) indicates that the mildly reduced flow capacity in the distal LAD arises from mild diffuse or focal epicardial narrowing, not a failure of hyperemia from diffuse microvascular dysfunction. Heterogeneity of CFC characterizes focal stenosis mixed with diffuse epicardial CAD and underlying



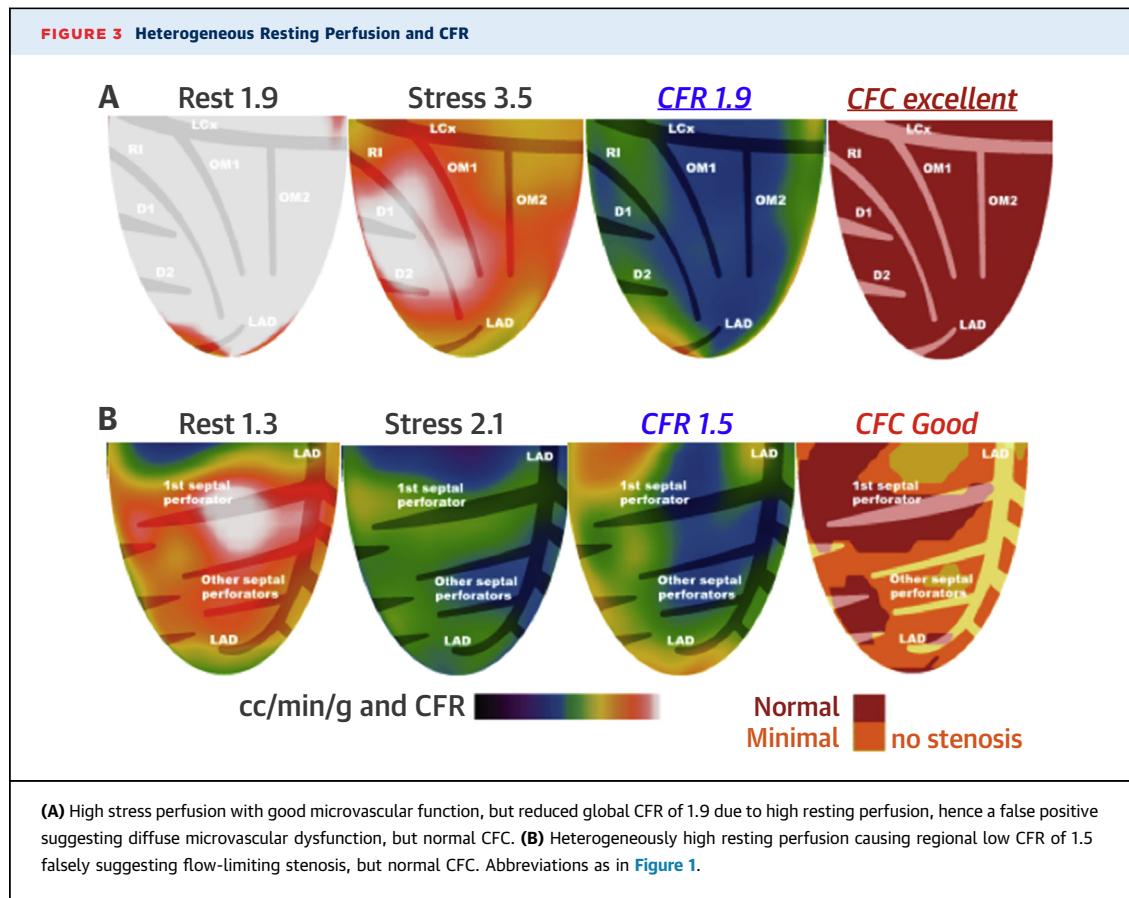
adequate microvascular function inherently necessary to cause regional stress defects and myocardial steal.

Thus, CFC provides essential distinctions among microvascular, diffuse, and focal CAD by accounting for perfusion heterogeneity that mimics these pathophysiologies. It also serves to explain angina and subendocardial ischemia far beyond CFR alone as also illustrated in Figure 3. For case A, global CFR for this example was 1.9, which might be incorrectly interpreted as microvascular disease. However, stress perfusion is uniformly excellent (3.5 ml/min/g) with regional quadrant CFR being reduced by the high rest perfusion (1.9 ml/min/g) commonly seen with hypertension or anxiety that is accounted for by CFC being excellent (red). For case B, regional quadrant CFR is severely reduced to 1.5 in the LAD distribution due to heterogeneously high rest

perfusion (1.3 ml/min/g) with uniform adequate stress perfusion (2.1 ml/min/g). The CFC is minimally reduced in the LAD distribution beyond the first septal perforator (orange) but well above low-flow ischemic levels.

SUBENDOCARDIAL ISCHEMIA: THE UNDERAPPRECIATED ELEPHANT IN THE ROOM

Angina associated with ST-segment depression is reported as subendocardial ischemia. The term is so common as to overlook the void of quantifying its size or severity by imaging except for rare reports by MRI (17,18) or PET (28). Figure 4 shows the first experimental post-mortem images of abnormal subendocardial-to-subepicardial perfusion ratio or transmural perfusion gradient due to epicardial



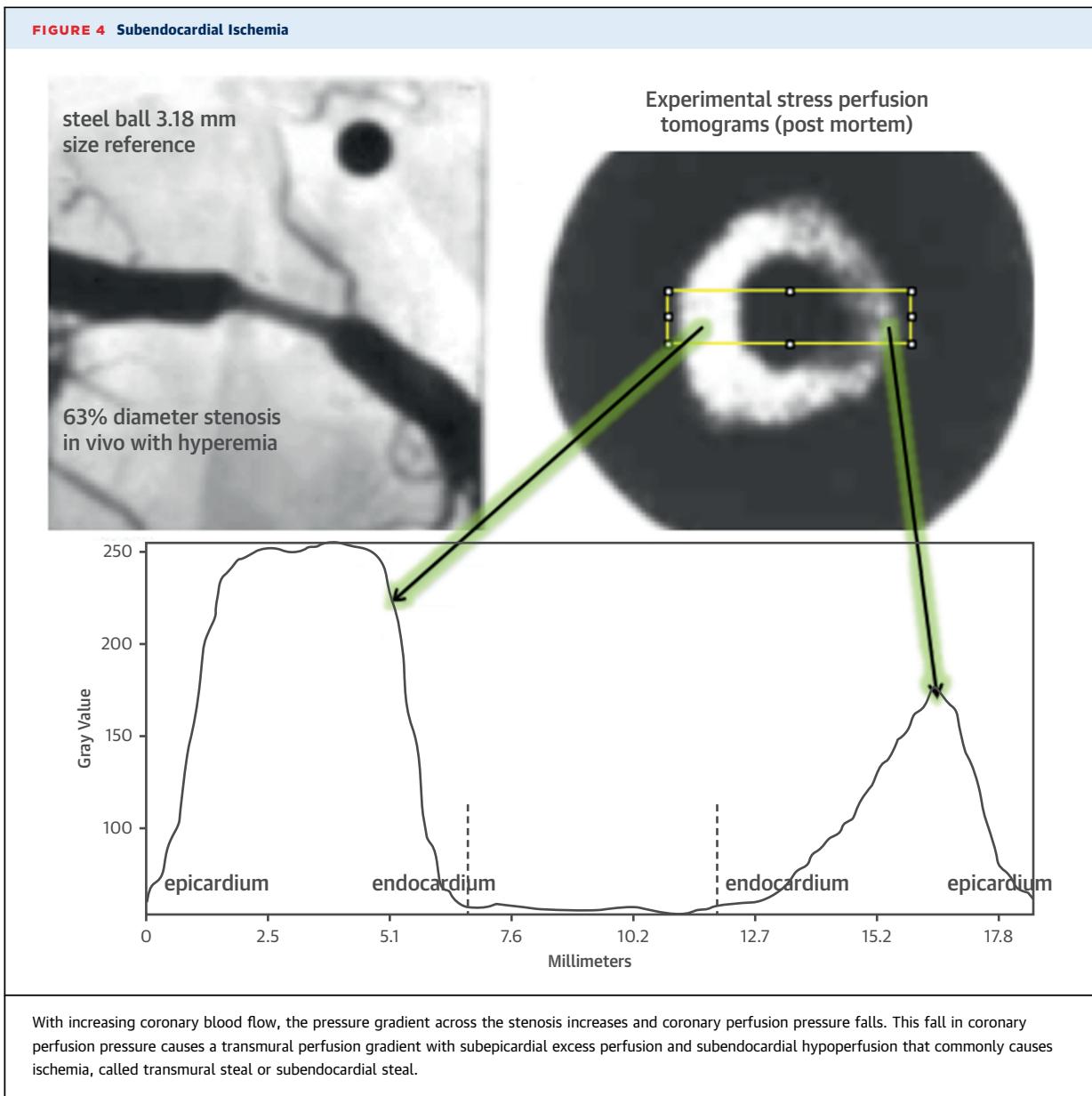
stenosis during pharmacological stress (29). Experimentally, the fall in subendocardial perfusion parallels the fall in coronary perfusion pressure down to 31 to 37 mm Hg (5,24,29-34), the ischemic subendocardial/subepicardial threshold that impairs ventricular function (31) or causes angina (32). These experimental data correspond to patients with a coronary occlusion pressure threshold of approximately 35 mm Hg associated with angina and ST-segment depression indicating subendocardial ischemia (32,33) and with increased risk of adverse events versus higher coronary pressures (34).

This relation of low perfusion pressure to low subendocardial perfusion has an important, often overlooked clinical corollary. Fractional flow reserve (FFR) was originally validated by comparison to PET expressed as relative absolute stress perfusion because FFR reflects relative, not absolute, stress perfusion. Relative stress images of absolute stress perfusion are the original true perfusion FFR based on quantitative PET. Invasive pressure-derived FFR is therefore the derivative approximation of the relative regional distribution of stress perfusion expressed as a fraction of maximum stress perfusion in ml/min/g.

Pressure-based FFR is therefore physiologically related to subendocardial perfusion and, potentially, subendocardial ischemia at values <0.6 (5,24,29-34). However, relative regional stress perfusion by PET quantifies the percentage of affected ventricle that is not identified or quantified by pressure-based FFR.

Typical PET resolution of 1 cm full width at half maximum precludes quantitative subendocardial perfusion. However, physics/physiological insight turns the limited resolution backwards into a powerful tomographic image that is very sensitive to low subendocardial perfusion. The backward reasoning is that as subendocardial perfusion falls, the remaining thin subepicardium has a greater partial volume loss than the full thickness LV wall perfusion without subendocardial ischemia. Therefore, relative absolute stress perfusion imaging becomes exquisitely sensitive for qualitatively visualizing low subendocardial perfusion as illustrated in Figures 5 to 8.

Two clinical examples relate these concepts to the differential diagnosis of angina due to epicardial artery or microvascular disease. The patient in Figure 5 had a prior proximal LAD stent with no residual or

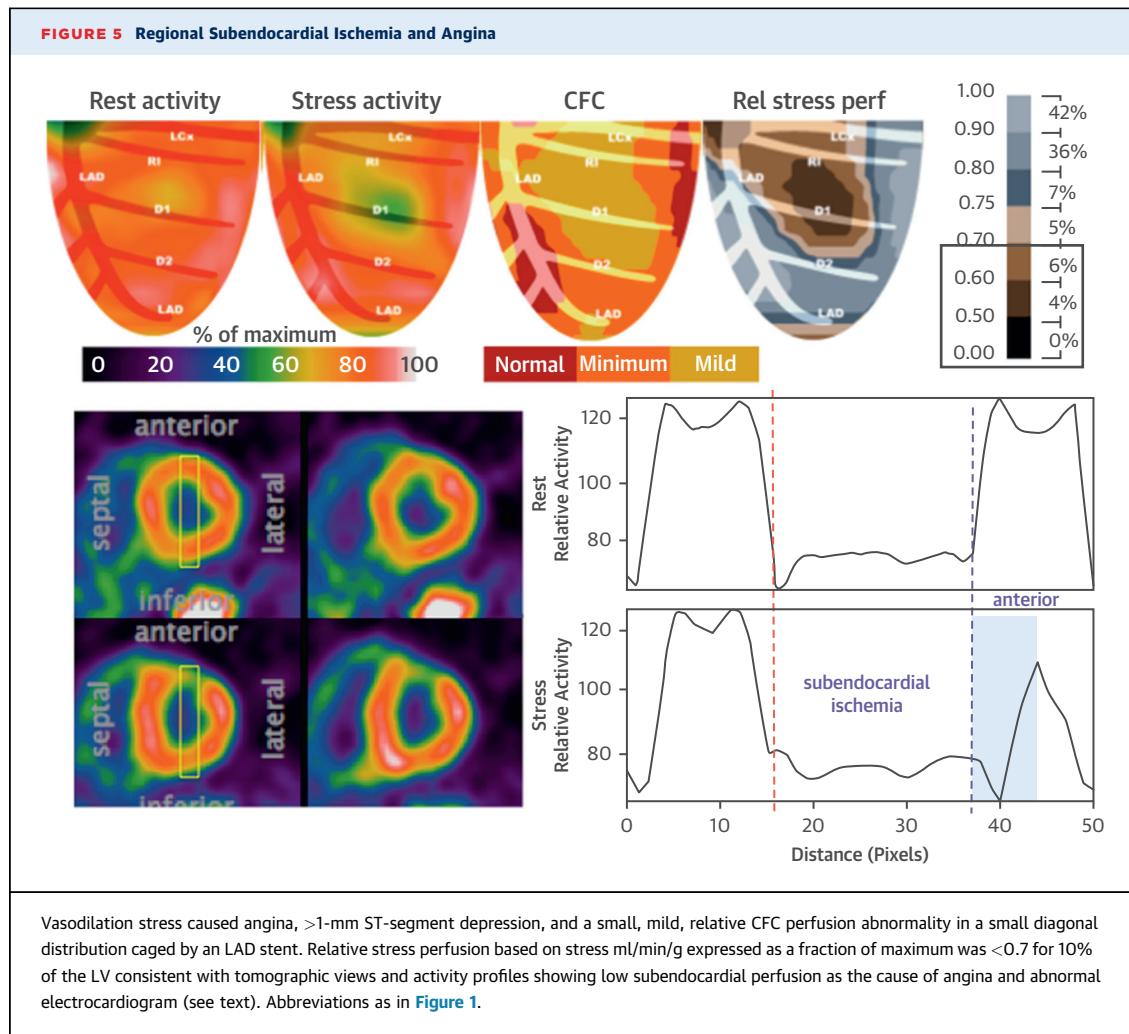


other angiographic stenosis. However, his exertional angina persisted after the angiographically successful stent, leading to repeat PET imaging in **Figure 5**. It shows a mild, small, basal anterior stress defect on relative stress images with mildly reduced CFC (yellow) in the distribution of a small first diagonal branch (D1) caged by the LAD stent. The surrounding myocardium had excellent stress flow, CFR, and CFC, indicating good microvascular function (red and orange) around reduced CFC (yellow) in the small D1 distribution.

However, dipyridamole stress caused moderately severe angina and >1-mm ST-segment depression. Relative stress perfusion based on stress ml/min/g as

a fraction of maximum was <0.7 for 10% of ventricle in the caged diagonal distribution. Short-axis tomogram of relative images show a small, basal anterior region of reduced transmural perfusion due to reduced subendocardial perfusion delineated by the blue-shaded zone of the tomographic stress activity profile plot. Relative stress perfusion and CFC yellow regions quantified the size and severity of this small region of subendocardial ischemia, resolving after aminophylline reversal of dipyridamole.

This case illustrates that even small regions of subendocardial ischemia causing angina are common, as shown statistically subsequently but overlooked by conventional imaging. Therefore,

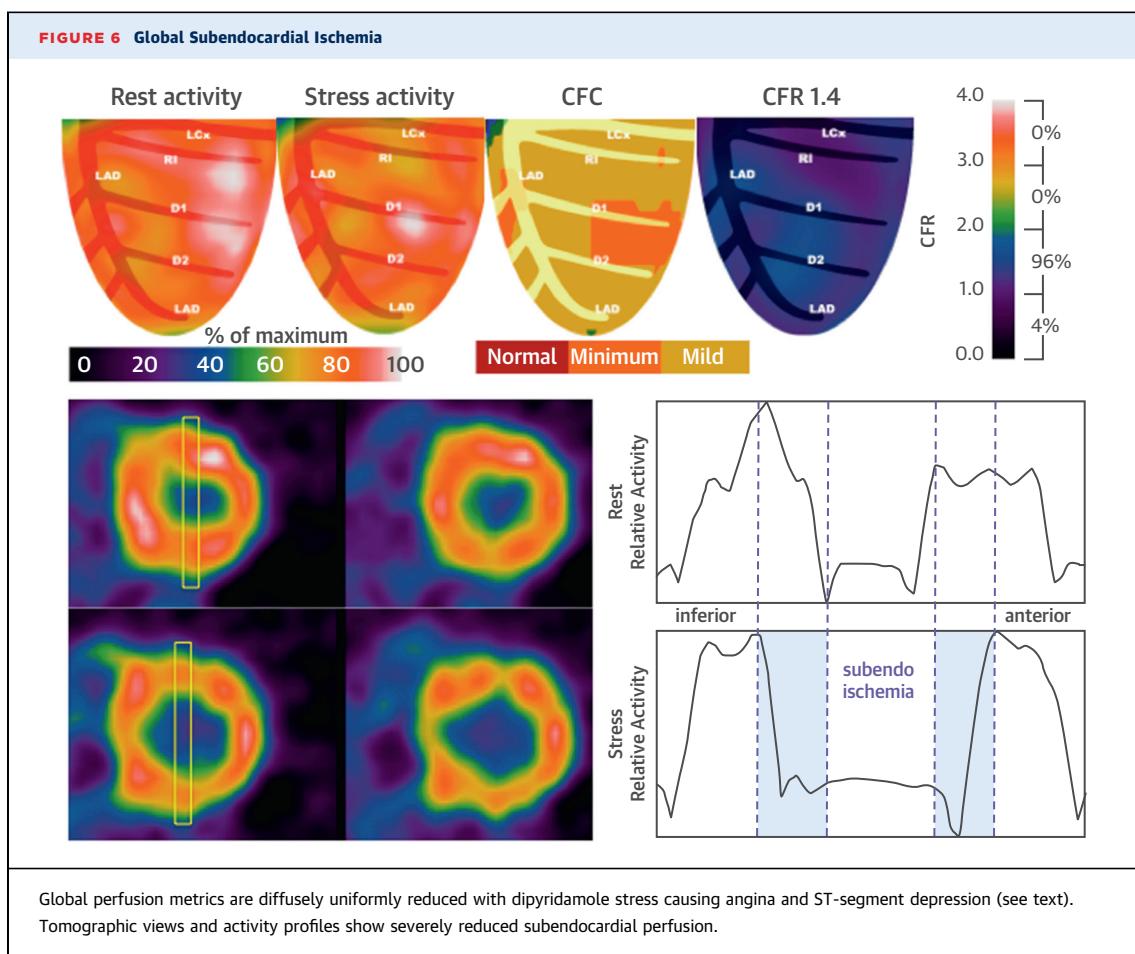


comprehensive quantitative perfusion is essential for assessing angina without angiographic abnormalities that is commonly called microvascular angina in the absence of comprehensive integrated physiological imaging.

As a more severe example of subendocardial ischemia, the patient in Figure 6 is a 75-year-old woman with multiple coronary stents, dense coronary calcium, poorly controlled risk factors, and hypertension, renal insufficiency, normal SPECT stress perfusion images with preserved ejection fraction, and progressing dyspnea. Relative rest and stress PET images showed no regional stress defect. CFR of 1.4, stress perfusion of 1.7 ml/min/g, and CFC were diffusely reduced (yellow) but above the average transmural ischemic threshold of 1.2 and 0.8 ml/min/g respectively (no blue). During dipyridamole stress, she experienced angina and dyspnea with over 2 mm ST-segment depression and stable blood

pressure. Ejection fraction was 69% at rest and 65% during stress, which is within measurement error, and transient ischemic dilation was 1.24.

Relative tomographic sections showed globally reduced subendocardial perfusion, delineated as the blue-shaded regions in the stress tomographic profile plots. For such diffuse “balanced” coronary atherosclerosis, global subendocardial ischemia during vasodilator stress may cause symptoms without regional defects. Such findings might be attributed to microvascular disease commonly associated with coronary atherosclerosis. In this case, however, microvascular function was sufficient to increase subepicardial stress flow, suggesting only mildly impaired transmural perfusion on CFR and CFC display. However, reduced subendocardial perfusion on tomographic images caused angina and electrocardiogram (ECG) changes, but without clinically significant contractile dysfunction.



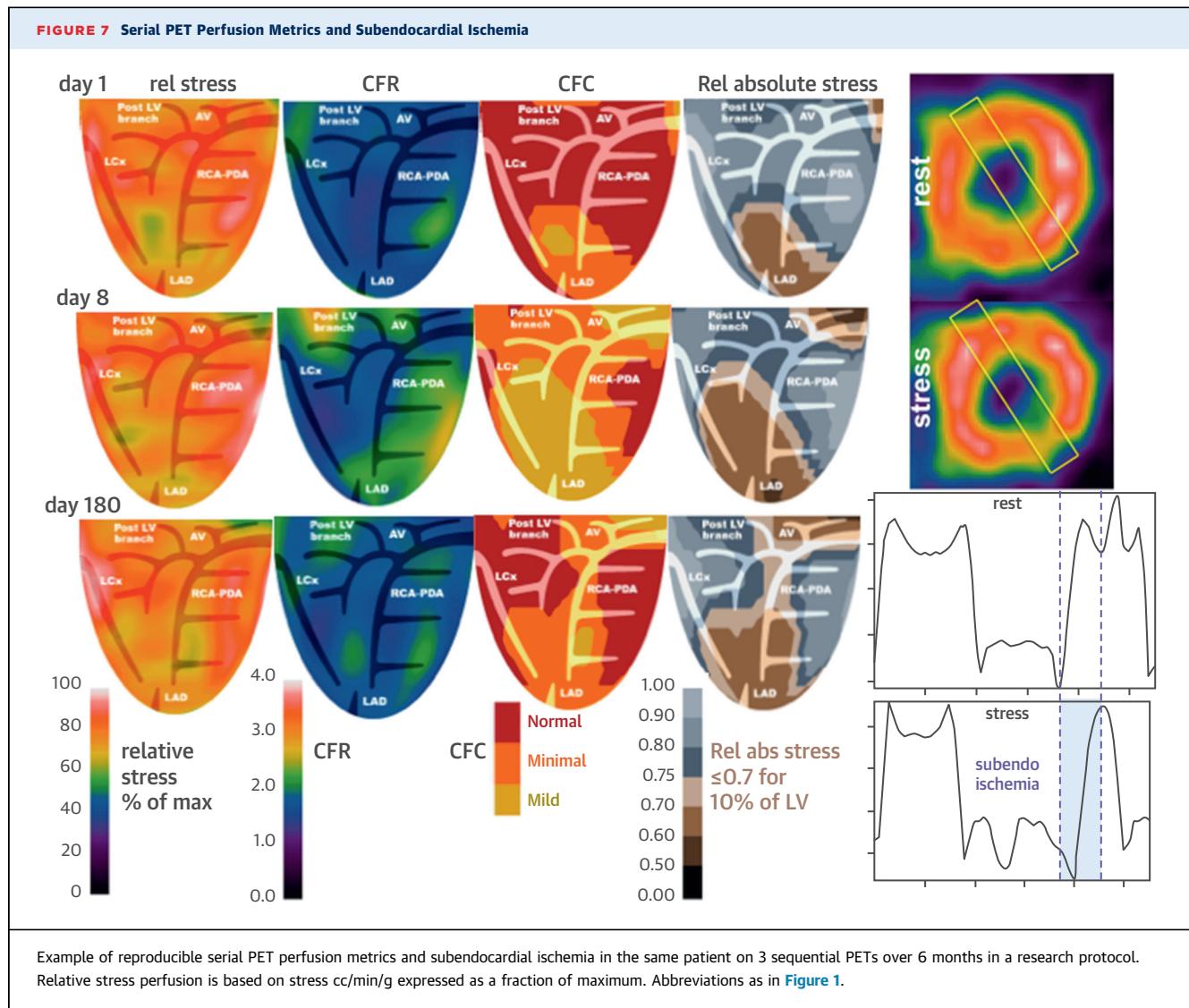
Subendocardial ischemia during vasodilator stress indicates adequate microvascular function sufficient to increase coronary blood flow in diffusely or focally narrowed arteries that reduces distal coronary pressure causing subendocardial ischemia. Therefore, despite increased mean transmural perfusion during vasodilator stress, subendocardial ischemia is common due to reduced pressure and subendocardial perfusion, a phenomenon called transmural steal or subendocardial/subepicardial steal. The view that vasodilatory stress causes “surplus perfusion” and hence no ischemia fails to recognize this fundamental common physiological mechanism.

PRECISION PHYSIOLOGY ESSENTIAL FOR DIAGNOSIS AND MANAGEMENT

For optimal diagnosis and management, comprehensive perfusion metrics must be repeatable with quantified test/retest precision. In serial repeated rest and stress perfusion images in the same subject, our

flow precision is $\pm 10\%$ with comparable matching CFC histogram distributions (25).

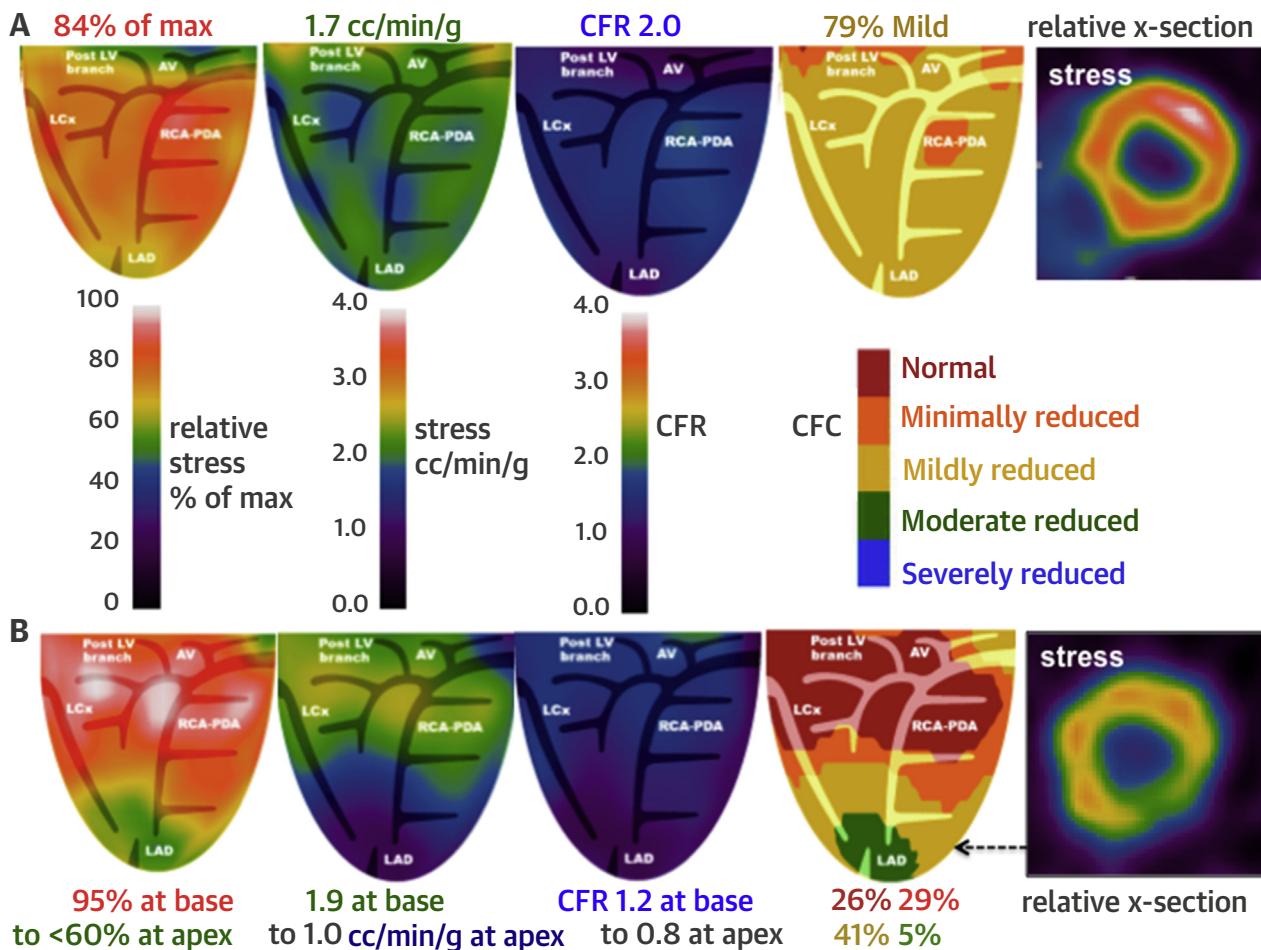
Figure 7 shows serial single inferior views of a 51-year-old active, asymptomatic, male volunteer with dyslipidemia, hypertension, family history of premature CAD, and coronary calcification. Relative uptake images were normal, with resting perfusion elevated to 1.4 ml/min/g due to an elevated pressure-rate product of $12,008 \text{ mm Hg/min}$. Stress flow remained excellent at 2.5 ml/min/g but with a CFR of 1.7 due solely to high resting perfusion. CFC showed normal high flow capacity (red and orange), indicating a good response to dipyridamole stress paralleling the excellent stress perfusion. Relative stress perfusion based on stress perfusion in ml/ml/g as a fraction of the maximum was 0.7 for 10% of the LV in the distal inferior distribution of the distal RCA, indicating low subendocardial perfusion shown by the blue hatched region on the activity profile plots. Repeat protocol PETs at 8 and 180 days later showed comparable images.



Example of reproducible serial PET perfusion metrics and subendocardial ischemia in the same patient on 3 sequential PETs over 6 months in a research protocol. Relative stress perfusion is based on stress cc/min/g expressed as a fraction of maximum. Abbreviations as in Figure 1.

Notably, the patient had definite moderate angina during dipyridamole reversed by aminophylline. The excellent stress perfusion of the surrounding LV and adequate inferior subepicardium excludes microvascular disease as a cause of his dipyridamole-induced angina. In this case, relative tomographic slices showed adequate subepicardial perfusion on the tomograms and on the activity profile plots. However, subendocardial perfusion was reduced in the distal inferior wall delineated by green subendocardial layer on tomograms and the blue-shaded region of the stress activity profile. Thus, mild subendocardial ischemia in the distal inferior distribution during dipyridamole was due to mild narrowing of the RCA. Without comprehensive integrated perfusion metrics, the angina might be erroneously attributed to microvascular disease.

In addition to essential distinction between global and regional CFR shown in the preceding text, global CFR may also reflect unrecognized inadequate methodology that precludes reliable regional perfusion measurements. Not only are global CFR measurements insufficient for making revascularization decisions that demand artery-specific flow quantification, but quantitative measurement must be obtainable in almost all patients for consistent clinical reliability. Prior published reports indicating failed quantitative flow data in 12% of cardiac PETs (22) are not optimal for clinical purposes. By contrast, in our 5,900 sequential clinical PETs with routinely quantified myocardial perfusion, only 0.7% of all studies had suboptimal flow data, due primarily to scanner failure or venous abnormalities precluding arterial input.

FIGURE 8 Microvascular Angina Versus Diffuse Epicardial Coronary Narrowing

(A) Diffuse regional and transmural microvascular impairment reducing all perfusion metrics with no transmural gradient. (B) Regional basal good CFC tapering in a longitudinal base-to-apex perfusion gradient characteristic of adequate microvascular function sufficient to increase basal coronary blood flow that is limited by diffuse epicardial narrowing along the length of the artery to its apex where the tomographic inset shows low subendocardial perfusion. Abbreviations as in Figure 1.

MICROVASCULAR ANGINA VERSUS SUBENDOCARDIAL ISCHEMIA: MECHANISMS AND IMAGING

Primary microvascular disease is illustrated in Figure 8A. This patient is a 78-year-old woman with an 11-year history of chest, arm, and jaw pain with severe dyspnea on mild exercise, also at rest with numerous risk factors including dyslipidemia, hypertension, and family history of CAD. She had undergone several equivocal stress SPECT scans and 5 “normal” coronary angiograms. CT showed no coronary calcium. Resting blood pressure was 114/65 mm Hg, heart rate 62 beats/min, and relative dipyridamole stress perfusion images were normal

without regional perfusion defects, angina, significant ST-segment changes during vasodilatory stress, or detectable blood caffeine.

Because all quadrants are homogeneously similar, only inferior quadrants are shown. Rest perfusion was 0.84; stress perfusion of 1.7 ml/min/g was mildly reduced below the threshold of 2.17 for healthy, young volunteers but well above the ischemic threshold of 0.83 ml/min/g; CFR of 2.0 was moderately reduced below 4.9 of healthy volunteers but well above the ischemic threshold of 1.2 (FDA 510(k) number 171303). CFC was therefore mildly reduced diffusely (yellow) but above low-flow ischemic thresholds (green or blue). Relative tomographic slices showed adequate subendocardial perfusion,

indicating adequate coronary pressure during adenosine vasodilator stress.

This CFR and CFC perfusion pattern is characteristic of microvascular impairment as a manifestation of risk factors causing endothelial dysfunction associated with risk factors hypertensive, other vasculopathy, or microvascular spasm also associated with risk factors. Combined high-dose long-acting nitrates, calcium blockers, renin-angiotensin antagonists, and statins eliminated her symptoms throughout 6 years follow-up.

Other similar cases may have angina and ST-segment depression due to low average transmural stress perfusion even without reduced subendocardial/subepicardial ratio on tomographic images. In this circumstance, ischemia may be caused by increased subendocardial oxygen demands due to high subendocardial wall stress in the face of maximum subendocardial capillary recruitment and arteriolar vasodilation (5).

By contrast, **Figure 8B** shows a 77-year-old woman with a history of an acute myocardial infarction (MI) during cholecystectomy, yet coronary angiography showed no significant stenosis. Risk factors included hypertension, dyslipidemia, diabetes treated with oral medications, and a family history of strokes and heart attacks. Chest CT showed a dense, 1-cm-long calcified plaque in the proximal LAD. Dipyridamole stress cause severe angina with 2-mm ST-segment depression requiring aminophylline reversal. Rest perfusion images were normal without scar (not shown). Relative stress perfusion images showed a graded, longitudinal, base-to-apex relative gradient characteristic of diffuse epicardial narrowing (5,24,35-37).

Stress perfusion was good at 2.6 ml/min/g at the base of the heart, tapering severely to 1.0 ml/min/g at the apex. CFR was 1.8 at the base, tapering severely to 0.8 at the apex indicating myocardial “branch steal” reported for severe, diffuse, epicardial atherosclerotic disease (35,36). Similarly, CFC was excellent at the base of the heart (red) but tapered to the apex (green). Tomographic views across the distal third of the LV showed reduced subendocardial perfusion causing her angina and ECG changes during dipyridamole stress.

This perfusion pattern characterizes diffuse, epicardial coronary atherosclerotic disease associated with a falling pressure gradient along the length of the artery due to viscous friction energy loss at high coronary blood flow during adenosine stress (5,24,35-37). This pressure gradient along the narrowed arterial length caused subendocardial ischemia shown in

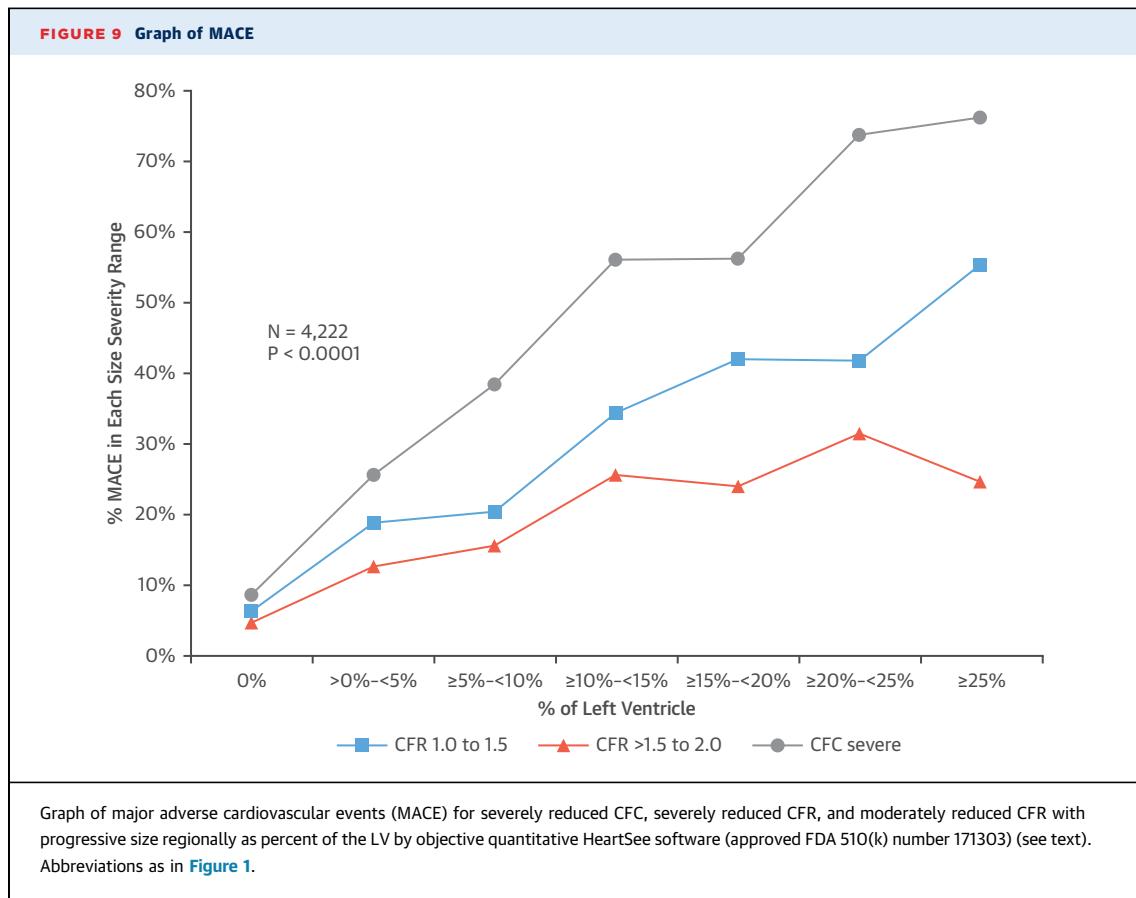
the relative tomographic image. Therefore, microvascular function was adequate enough to increase coronary blood flow sufficiently to produce the coronary pressure gradient necessary to lower subendocardial perfusion in the distal left ventricle, as quantified in size and severity by relative stress perfusion and moderately reduced CFC (green) at the apex.

MECHANISM FOR SUBENDOCARDIAL PERFUSION DURING VASODILATOR STRESS

The mechanism for angina with high CFC in **Figures 5 to 8** (case B) is based on well-established coronary physiology as illustrated in **Figure 4**. Good microvascular function with high coronary blood flow during vasodilator stress causes a pressure gradient along the length of diffuse, mildly narrowed coronary arteries that appear normal on angiography (5,24,35-37). As coronary blood flow increases due to good microvascular function, the pressure gradient increases proportionately for whatever mild diffuse narrowing exists. The low coronary perfusion pressure impairs subendocardial perfusion despite high epicardial perfusion with resulting low subendocardial/subepicardial ratio that is directly related to perfusion pressure. Such subendocardial ischemia due to high stress perfusion or high CFR is generally not considered, recognized, or imaged due to limited image quality or conceptual misunderstanding.

However, even with normal stress coronary perfusion pressure, subendocardial ischemia may occur due to extreme hypertrophy with thickened ventricular walls that slow subendocardial perfusion after systole (9), particularly during tachycardia causing angina in aortic stenosis (38). Marked hypertrophy or small vessel occlusion, intimal or medial hyperplasia, or destruction from inflammatory disease may increase intercapillary distances enough to impair adequate oxygen diffusion (5,7,24) during high oxygen demands with resulting transmural ischemia as well as reduced CFC but without transmural perfusion gradients.

A common erroneous concept views vasodilator stress as causing “surplus perfusion,” hence, no ischemia, only a relative defect. That view fails to recognize that even small increases of subepicardial flow may cause a severe perfusion gradient due to diffuse or focal epicardial narrowing leading to a transmural perfusion gradient and subendocardial ischemia, termed transmural or subendocardial/subepicardial steal.



PRECISION PHYSIOLOGY: CFR VERSUS CFC FOR MICROVASCULAR ANGINA AND MAJOR ADVERSE CARDIOVASCULAR EVENTS

Differentiating primarily microvascular dysfunction from primarily diffuse or focal epicardial artery narrowing requires comprehensive perfusion metrics as illustrated in prior examples. In addition to illustrating physiology and imaging of these cases, the predictive or prognostic power of CFR compared with CFC is an important measure of their diagnostic differentiation. Although many patients have differing proportions of both these pathophysiologies, the prevalence of these primary alternatives and their mix is essential for our understanding, diagnosing, and optimally managing patients.

Accordingly, Figure 9 shows data that were critically and rigorously reviewed using advanced statistical analysis specified and required by the Food and Drug Administration over the 5 years from 2012 to 2017 as the basis for FDA validating and approving the CFC maps presented here (510K 171303). The data of Figure 9 are based on 4,222 routine serial PETs with

no measurable blood caffeine levels confirmed for every patient (7% with measurable blood caffeine were excluded from analysis, leaving 4,222 cases). With 95% follow-up out to 9 years post-PET, there were 656 major adverse cardiovascular events (MACE) defined as percutaneous coronary intervention or coronary artery bypass grafting (406) and death, MI, or stroke (250). Severely reduced CFR (blue line) associated with very high MACE increasing with size as a percentage of the LV. MACE also increased with size of severely reduced regional CFR 1.0 to 1.5 (green line) or CFR moderately reduced to 1.5 to 2.0 (orange line). However, the predictive power of CFR was substantially lower than CFC. By logistic regression analysis, all groups in Figure 9 are significantly different with $p < 0.0001$.

Thus, the concept of CFC has been validated in the published reports (23–26,39) and by rigorous FDA review as the basis for FDA validation and approval. Although originally developed using noninvasive imaging, CFC has also been validated by invasive pressure and Doppler flow velocity (27), attesting to its broad physiological insights. Finally, as recently

reported, severely reduced CFC, but not severely reduced CFR, predicts a significant 54% reduction in death, MI, and stroke after revascularization compared with medical treatment or less severe perfusion abnormalities (39). It therefore provides an optimal basis for differentiating primarily microvascular disease from primarily focal or diffuse epicardial artery narrowing in the large cohort analysis and outcomes shown subsequently in **Table 1**.

PRECISION PERfusion FOR ANGINA WITHOUT ANGIOGRAPHIC STENOSIS

The **Central Illustration** summarizes the comprehensive perfusion metrics for understanding, diagnosing, classifying, and managing microvascular angina. It also summarizes several methodology flaws or issues that mimic microvascular dysfunction (false positive) despite good microvascular function, or failure to detect it despite homogeneously reduced CFC (false negative). As shown by case examples, and statistically confirmed subsequently in **Table 1**, these false positives and false negatives are due to incomplete or suboptimal perfusion metrics. The **Central Illustration** illustrates these methodological issues for assessing microvascular disease including global CFR, perfusion heterogeneity, subendocardial ischemia, overlooked CAD, caffeine, and nonischemic mechanisms for angina during high transmural perfusion, all summarized for the **Central Illustration** as follows:

Global CFR fails to account for regional stenosis or perfusion heterogeneity due to endothelial dysfunction compared with regional CFR and compared with the more comprehensive CFC (**Central Illustration**, panel A) as detailed in prior sections and **Figures 1 to 3**. Heterogeneous resting perfusion causes substantial regional variation of CFR suggesting regional flow-limiting stenosis that masks diffusely reduced microvascular function thereby causing a falsely negative CFR for microvascular disease. Alternatively, elevated homogeneous resting perfusion due to anxiety, or hypertension with adequate stress flow may substantially reduce CFR homogeneously, thereby suggesting microvascular disease that is not present, hence a falsely positive CFR for microvascular disease. Global CFR precludes the synthesis of regional CFR and stress perfusion together into CFC, which overcomes the problem of resting perfusion heterogeneity leading to corresponding heterogeneous CFR and false positives or false negatives for microvascular dysfunction.

Subendocardial ischemia may be caused by diffuse epicardial CAD or mild “insignificant stenosis” with good microvascular response to vasodilator stress

TABLE 1 Mixed Pathophysiologies of Microvascular Angina and Function in 5,900 PETs

	Criteria for Microvascular Angina*			
	CFR ≤2.2*	CFR ≤2.2†	CFR >2.2‡	High CFC§
Cases	21 (0.4)	83 (1.4)	167 (2.8)	174 (3)
Average maximum pixel CFR	2.27 ± 0.5	2.48 ± 0.5	3.91 ± 1.1	3.74 ± 1.2
Microvascular function	Impaired	Impaired	Good	Good
Rel str per <0.7 for >10% LV	9/21 (43)	45/84 (54)	53/167 (32)	43/174 (25)
Female	62	39	35	48
Risk factors or coronary Ca¶	Yes	Yes	Yes	Yes
MI or death over 9 yrs#	2/21 (9.5)	8/83 (9.6)	9/167 (5.4)	6/174 (3.5)
Approximate MI or death/yr	1%/yr	0.8%/yr	0.6%/yr	0.4%/yr

Values are n (%), mean ± SD, n/N (%), or %, unless otherwise indicated. *Angina, no known CAD, global CFR ≤2.2, and no stress-induced relative defects defined as rest-to-stress change of >5% of LV with ≤60% of maximum activity. †Angina, known CAD by angiogram, procedures, or events, but no stress-induced relative defects as defined in the preceding text. #Angina, global CFR >2.2, no stress induced relative defects as defined in the preceding text, includes no known CAD and known CAD by angiogram, procedures, or events, but no stress-induced relative defects as defined in the preceding text. §Angina, high CFC >70% of the LV normal or minimally reduced CFC (CFR >2.4 and stress >1.8 ml/min/g). ||Fractional flow reserve as relative absolute stress perfusion PET reflecting low subendocardial perfusion. Rel str per = relative distribution of stress in ml/min/g expressed as a fraction of the maximum. ¶MESA risk score >7%. #Median follow-up 3.2 years.

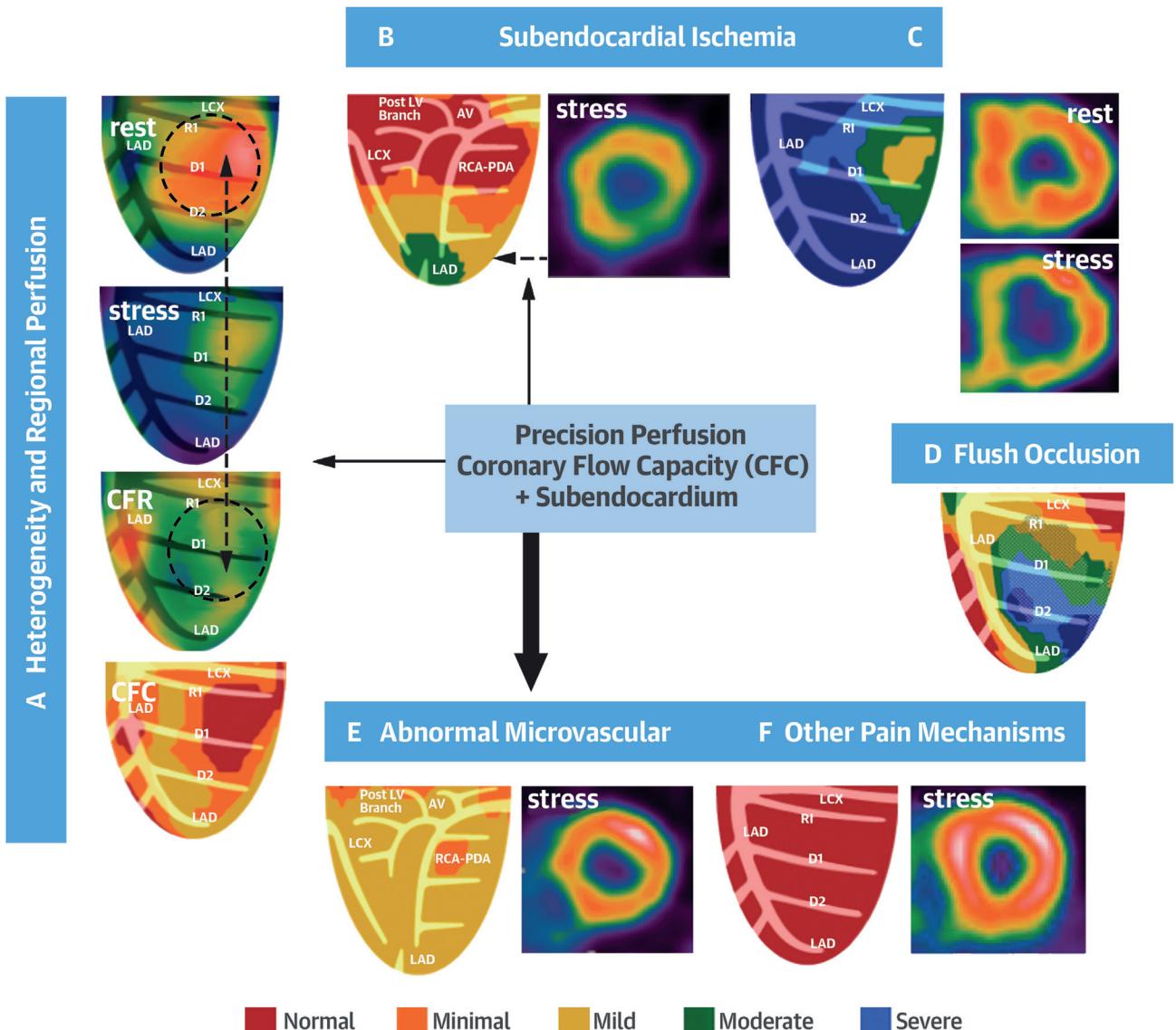
CAD = coronary artery disease; CFC = coronary flow capacity; CFR = coronary flow reserve; LV = left ventricular; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; PET = positron emission tomography.

producing a pressure gradient, low coronary pressure, and subendocardial ischemia associated with a base-to-apex longitudinal perfusion gradient. Subendocardial ischemia may be mild, small, and cause angina but with low risk of MI or death (**Central Illustration**, panel B) or severe and high risk (**Central Illustration**, panel C).

Overlooked stenosis is not uncommon due to flush occlusion not apparent on angiogram showing no stenosis (**Central Illustration**, panels C and D) or due to stent-caged branches that is increasingly common. The patient in panel C had risk factors, mildly progressing angina, with repeat angiogram by his cardiologist reportedly showing no significant stenosis, thereby suggesting microvascular angina. At routine PET on a research protocol 2 months after this angiogram, adenosine stress caused severe angina, 5-mm ST-segment depression, and hypotension.

Relative stress images were mildly abnormal, but CFC was severely abnormal in septal, anterior, and lateral LV involving over 70% of the LV. Relative tomographic slices of stress perfusion showed diffusely severely reduced subendocardial perfusion or “shelling out” of normal resting wall thickness. Activity profile plots showed severe subendocardial ischemia, in septal, anterior, and anterolateral regions.

These PET results are characteristic of severe left main stenosis, not microvascular disease. Review of the outside angiogram confirmed 2 frames with 75% diameter ostial left main stenosis not appreciated earlier. After PET-guided repeat angiography to

CENTRAL ILLUSTRATION Coronary Flow Reserve and Microvascular Angina

Gould, K.L. et al. J Am Coll Cardiol. 2018;72(21):2642-62.

(A) Global CFR fails to account for regional stenosis or perfusion heterogeneity compared with regional CFR and compared with the more comprehensive CFC. (B) Mild regional subendocardial ischemia causing angina and ST-segment depression. (C) Global subendocardial ischemia due to left main and LAD stenosis. (D) PET indicating an occluded collateralized first diagonal branch not seen on angiogram due to flush occlusion leading to percutaneous coronary intervention of the chronic total occlusion. (E) Characteristic primarily microvascular dysfunction with diffuse homogeneously mildly reduced CFC (yellow) without a transmural perfusion gradient. (F) Angina during high transmural perfusion mediated by non-ischemic mechanisms. AV = aortic valve; CFC = coronary flow capacity; CFR = coronary flow reserve; D1/2 = first/second diagonal branch; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LV = left ventricular; PDA = posterior descending coronary artery; PET = positron emission tomography; RCA = right coronary artery; RI = ramus intermedius coronary artery.

define left main stenosis, successful bypass surgery was done with relief of angina.

The patient in panel D of the **Central Illustration** had PET due to angina with an angiogram showing no stenosis. PET shows a large severe stress defect

in a large D1 with a flush occlusion at its origin with myocardial steal associated with collateralization. Once identified by PET, the occluded D1 was successfully opened and stented with relief of angina.

Primary microvascular dysfunction typically shows regionally homogeneously reduced stress perfusion, CFR and CFC with no subepicardial-to-subendocardial perfusion gradient because there is no epicardial artery narrowing to cause the pressure gradient necessary for subendocardial hypoperfusion (**Central Illustration**, panel E) as also illustrated in **Figure 8A**; angina and ECG changes for such patients may be due to diffuse transmural ischemia with exercise demands exceeding capacity for increasing flow without a subepicardial-to-subendocardial perfusion gradient.

Caffeine inhibition of vasodilator stress causes abnormally low stress perfusion, CFR and CFC, mimicking microvascular dysfunction that would also look like panel E of the **Central Illustration**. Systematic testing for caffeine identifies its presence in 7% (25,40) to 20% (41) of patients undergoing vasodilator stress testing despite instructions to avoid relevant drinks, food, and medications, and due in part to genetic slow caffeine metabolism.

Nonischemic mechanisms for cardiac pain with angina during high transmural perfusion may be mediated by aberrant or chimeric adenosine A1/A2 receptors (**Central Illustration**, panel F) for uncommon patients with high transmural stress perfusion, no microvascular dysfunction, and no subendocardial ischemia as in this 66-year-old woman with recurrent chest pain inconsistently related to exertion over 10 years. She had 3 normal coronary angiograms, total cholesterol around 400 mg/dl, a strong family history of premature CAD, and intolerance to statins. Dipyridamole stress caused moderately severe angina relieved by aminophylline, but no significant ST-segment change. CT at PET showed mild coronary calcium. Regional and global quantitative perfusion was normal with excellent stress perfusion at 3.3 ml/min/g, CFR 2.9, and excellent CFC all comparable to healthy young volunteers. Relative tomographic images showed no subendocardial hypoperfusion.

Cardiac pain is reportedly mediated by adenosine A1 receptors, whereas coronary arteriolar vasodilation and perfusion after pharmacological stress is mediated by adenosine A2 receptors (42,43). In most patients without CAD, vasodilator stress increases A2 receptor-mediated myocardial perfusion without triggering A1 receptor-mediated angina except in rare cases like in panel F in the **Central Illustration**. A1 receptor blockade reportedly reduces angina in stable CAD (44). As a potential mechanism of angina, chimeric adenosine A1/A2 receptors may respond to vasodilator stress with A1 receptor-mediated pain in addition to A2 receptor-mediated hyperemia.

Although such adenosine A1/A2 receptor chimeras are reported (45,46), to our knowledge, no reports have addressed their potential role in angina during coronary vasodilator stress with high transmural coronary flow. Finally, cardiac neuropathy, as in diabetes, and variable pain perception further complicate assessment of angina with or without microvascular dysfunction.

PHYSIOLOGICAL CLASSIFICATION OF NO STENOSIS ANGINA

Based on coronary pathophysiology reviewed here, the term *microvascular angina* might more correctly be called “no stenosis angina” with several physiologically diverse, evidence-based subcategories or “primary” prototypes quantified objectively from the most prevalent due to CAD with effective treatment, to least common with uncertain treatment as follows:

1. *Subendocardial ischemia* associated with diffuse epicardial narrowing and adequate microvascular function that is not recognized by standard imaging or may be associated with physiologically impaired subendocardial perfusion due to aortic stenosis or left ventricular hypertrophy and shortened diastolic perfusion time of tachycardia.
2. *Overlooked stenosis*, particularly flush origin occlusions of secondary arterial branches not seen on angiogram, increasingly common for stent-caged branches.
3. *Diffuse microvascular dysfunction* with low CFR and CFC associated with risk factors, subclinical coronary atherosclerosis, endothelial dysfunction, or microvasculopathy from diverse causes such as hypertension, inflammatory disease, sarcoid, etc.
4. *Nonischemic cardiac pain mechanisms* with angina at very high regional and transmural perfusion mediated by aberrant adenosine A1 receptors or other nonischemic mechanisms for cardiac pain.

PREVALENCE AND CLINICAL OUTCOMES

Some patients considered to have microvascular angina with no significant stenosis have differing mixes of both diffuse epicardial and small vessel disease. In order to obtain a systematic view, **Table 1** shows prevalence of strictly defined microvascular angina in our prospective database of 5,900 sequential diagnostic PETs meeting the following criteria: anginal chest pain, no known CAD, global CFR ≤ 2.2 , and no stress-induced relative defects (defined as no rest-to-stress change $>5\%$ of LV with $\leq 60\%$ of maximum activity). Such strictly defined cases are uncommon, found in only 21 cases

(0.4%), with females comprising 62% of the 21 cases, all with risk factors including coronary calcification and with abnormal quantitative PET perfusion images. This CFR threshold of 2.2 was chosen as a compromise between reported thresholds of 2.32 by Doppler wire (10) and 2.0 by PET (14) for microvascular angina as compared with CFR of 4.2 ± 0.8 for 125 healthy, young volunteers in our lab (5,21,23-26,39,40).

If the aforementioned criteria are expanded to include established CAD by angiography, procedures, or clinical events, but still with no relative stress defects as defined in the preceding text, prevalence is somewhat greater, 83 of 5,900 (1.4%) with 39% female. Approximately one-half had relative stress perfusion <0.7 for $>10\%$ of the LV, reflecting reduced relative subendocardial perfusion consistent with a fall in coronary pressure due to sufficient microvascular function to increase perfusion through mild, diffuse, epicardial coronary atherosclerosis with corresponding fall in coronary pressure. Over a span of up to 9 years follow-up, there were 8 MIs or deaths of the 83 cases (9.6%, or approximately 1.0%/year), consistent with treated risk factors. These observations from our large cohort expand prior limited reports on strictly defined microvascular syndromes with a similar, low prevalence and relatively low risk (4,11). By comparison, severely reduced CFC associates with a 30% prevalence of MI, death, or stroke during a comparable period (39).

AN UNEXPECTED BUT OBJECTIVE TRUTH

By contrast, we also examined the prevalence of the same strictly defined microvascular dysfunction except no angina as follows: no anginal chest pain, global CFR ≤ 2.2 , and no stress-induced relative defects defined as previously. Such cases are common, 734 of 5,900 (12.4%) with females comprising 39%, and 96% having risk factors or coronary calcium. Over 9 years follow-up, there were 20 MIs or deaths of the 734 (2.7%, or approximately 0.3%/year) consistent with treated risk factors.

Thus, microvascular dysfunction defined in the preceding text is common without angina, comparably prevalent in men and women, nearly always associated with risk factors, coronary calcium, or subclinical CAD, with relatively low risk of MI or death for treated risk factors.

Frequent microvascular dysfunction without angina might be expected because common microvasculopathies due to hypertension, diabetes, inflammatory disease, and cardiac transplantation

usually do not cause angina. Although sometimes seen with these syndromes, angina without angiographic stenosis is most commonly caused by subendocardial ischemia due to diffuse epicardial atherosclerosis and adequate microvascular function for increased coronary flow sufficient to lower coronary perfusion pressure responsible for the low subendocardial perfusion.

In order to find potential microvascular dysfunction in the absence of risk factors or clinically apparent cause, we determined the number of PETs with CFR ≤ 2.2 and no stress defect as defined in the preceding text, no blood caffeine, no CAD, no coronary calcium, no risk factors, no ventricular hypertrophy, no neurological stimulant or recreational drugs, no radiation or cancer treatment, no renal failure, no amyloid, sarcoid, systemic inflammatory or thrombotic disease, and no technical imaging failure.

Only 7 PETs of 5,900 met these criteria; 5 of the 7 had high resting perfusion, 1.7 ± 0.3 ml/min/g, and very high stress perfusion, 3.2 ml/min/g, thereby ruling out microvascular disease and implying that the CFR represented a false positive for microvascular dysfunction. The remaining 2 cases had CFR of 1.9 and 2.0 with stress perfusion of 2.0 ml/min/g, well above the ischemic threshold of 0.83 ml/min/g associated in other patients with angina and ST-segment changes (FDA 510(k) number 171393). All 7 cases had $\geq 70\%$ of the LV with high CFC, no angina, and no significant ECG changes either clinically or with dipyridamole stress. Four were under 50 years of age, and 3 were over 50 years of age.

Our findings suggest that microvascular angina and dysfunction nearly always have quantifiable perfusion abnormalities beyond CFR and nearly always an identifiable cause, by far the commonest being risk factors for or diffuse subclinical atherosclerosis (47-49).

NO STENOSIS ANGINA WITH HIGH CORONARY STRESS FLOW

We also examined the prevalence of angina associated with no known CAD, global CFR > 2.2 , and no stress-induced relative defects (Table 1). Angina in patients with adequate or high CFR was not uncommon, 167 (2.8%) of the 5,900 PET cases. Approximately one-third were female, one-third had relative stress perfusion <0.7 for $>10\%$ of the LV, consistent with reduced subendocardial stress perfusion and risk of adverse events comparable to treated risk factors.

In view of the limitations of using CFR alone, we separately analyzed angina associated with high CFC defined as definite clinical angina or during vasodilatory stress requiring termination of stress, and CFC >70% of the LV as normal (red or orange in our color scheme). Angina during high coronary flow and good CFC occurred in 174 of 5,900 cases (3.0%) with females comprising 48% of the 174 cases, 85% of the 174 cases with coronary calcium, all 174 cases with risk factors. For these cases, microvascular function is excellent with the majority having high transmural perfusion. A minority of 25% had relative stress perfusion <0.7 for >10% of the LV, suggesting reduced relative subendocardial perfusion. Over up to 9 years follow-up, there were 6 MIs or deaths in the 174 (3.4%, or approximately 0.4%/year) consistent with treated risk factors. These cases with high stress perfusion, no relative stress defect, and no subendocardial/subepicardial gradient may suggest aberrant cardiac pain mechanisms.

SUMMARY AND CONCLUSIONS

Angina with no angiographic stenosis is commonly labeled microvascular angina, assumed due to impaired microvascular function and reduced CFR, but with widely conflicted published reports. However, comprehensive quantitative perfusion beyond overly simplistic CFR integrates absolute and relative stress flow and CFR into CFC regionally as a

percentage of the LV with qualitative subendocardial gradients on relative tomographic images. This integrated precision perfusion provides new objective diagnosis, quantitative physiological classification, and potential treatment.

Based on precise quantitative myocardial perfusion, microvascular angina might more correctly be called “no stenosis angina” with 4 physiologically diverse, evidence-based subcategories or “primary” prototypes quantified objectively as follows: subendocardial ischemia due to diffuse epicardial atherosclerosis (most common), overlooked epicardial stenosis, diffuse microvascular dysfunction or microvasculopathies and nonischemic cardiac pain mechanisms (rare), or a mix of these prototypes, over 95% of which are associated with risk factors, and subclinical or clinically manifest coronary atherosclerosis needing vigorous risk factor treatment. Clinical application of these concepts requires ongoing research within the objective, quantitative, evidence-based, physiological framework reviewed here wherein coronary physiology trumps coronary anatomy (5,21,23,39).

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REFERENCES

- Scopus database. Available at: <https://www.scopus.com/>. Accessed March 12, 2018.
- Turgeon RD, Pearson GJ, Graham MM. Pharmacologic treatment of patients with myocardial ischemia with no obstructive coronary artery disease. *Am J Cardiol* 2018;121:888–95.
- Jennette JC, Stone JR. Chapter 11: diseases of medium-sized and small vessels. In: Willis MS, Homeister JW, Stone JR, editors. *Cellular and Molecular Pathobiology of Cardiovascular Disease*. Washington, DC: Academic Press, 2014:197–219.
- Lee BK, Lim HS, Fearon WF, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015;131:1054–60.
- Gould KL, Gewirtz H, Narula J. Chapter 34, coronary blood flow and myocardial ischemia. In: Fuster V, Harrington RA, Narula J, Eapen ZJ, editors. *Hurst's the Heart*. 14th edition. New York, NY: McGraw Hill, 2017:893–922.
- El-Tamini H, Mansour M, Wargovich TJ, et al. Constrictor and dilator responses to intracoronary acetylcholine in adjacent segments of the same coronary artery in patients with coronary artery disease. *Endothelial function revisited*. *Circulation* 1994;89:45–51.
- Honig CR. *Modern Cardiovascular Physiology*. Boston, MA: Little, Brown and Company, 1981.
- Lipscomb K, Gould KL. Mechanism of the effect of coronary artery stenosis on coronary flow in the dog. *Am Heart J* 1975;89:60–7.
- Downey HF, Crystal GJ, Bashour FA. Asynchronous transmural perfusion during coronary reactive hyperemia. *Cardiovasc Res* 1983;17:200–6.
- Pepine CJ, Anderson D, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcomes in women evaluated for suspected ischemia: results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation Study). *J Am Coll Cardiol* 2010;55:2825–32.
- Lanza GA, Filice M, De Vita A, et al. Primary stable microvascular angina: a long term follow-up study. *Circulation* 2017;135:1982–4.
- Bugiarini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease. A study of women with chest pain and normal coronary angiograms. *Circulation* 2004;109:2518–23.
- Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002;106:653–8.
- Murthy VL, Naya MN, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;129:2518–27.
- Stenstrom I, Maanitity T, Uusitalo V, et al. Frequency and angiographic characteristics of coronary microvascular dysfunction in stable angina: a hybrid imaging study. *Eur Heart J CV Imaging* 2017;18:1206–13.
- Kobayashi Y, Fearon WF, Honda Y, et al. Effect of sex differences on invasive measures of coronary microvascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. *J Am Coll Cardiol Intv* 2015;8:1433–41.
- Jaarsma C, Vink H, van Haarre J, et al. Non-invasive assessment of microvascular dysfunction in patients with microvascular angina. *Int J Cardiol* 2017;248:433–9.
- Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac

- syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948-53.
- 19.** Geltman EM, Henes CG, Sennett MJ, Sobel BE, Bergmann SR. Increased myocardial perfusion at rest and diminished perfusion reserve in patients with angina and angiographically normal coronary arteries. *J Am Coll Cardiol* 1990;16:586-95.
- 20.** Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* 1974;33:87-94.
- 21.** Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol* 2013;62:1639-53.
- 22.** Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated non-invasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. *Circulation* 2017;136:2325-36.
- 23.** Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiologic severity. *J Am Coll Cardiol Img* 2012;5:430-40.
- 24.** Gould KL, Schelbert H, Narula J. Chapter 19, positron emission tomography in heart disease. In: Fuster V, Harrington RA, Narula J, Eapen ZJ, editors. *Hurst's the Heart*. 14th edition. New York, NY: McGraw Hill; 2017:553-605.
- 25.** Kitkungvan D, Johnson NP, Roby AE, Patel MB, Kirkeeide R, Gould KL. Routine clinical quantitative rest stress myocardial perfusion for managing coronary artery disease: clinical relevance of test-retest variability. *J Am Coll Cardiol Img* 2017;10:565-77.
- 26.** Johnson NP, Gould KL. Physiologic basis for angina and ST change: PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. *J Am Coll Cardiol Img* 2011;4:990-8.
- 27.** Van de Hoef TP, vanLavieren MA, Damman P, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv* 2014;7:301-11.
- 28.** Danad I, Rajmakers PG, Harms HJ, et al. Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a ^{15}O -H₂O PET study. *Eur Heart J* 2014;35:2094-105.
- 29.** Gould KL. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. IV. limits of stenosis detection by idealized, experimental, cross-sectional myocardial imaging. *Am J Cardiol* 1978;42:761-8.
- 30.** Hoffman JIE, Buckberg GD. The myocardial oxygen supply:demand index revisited. *J Am Heart Assoc* 2014;3:e000285.
- 31.** Smalling RW, Kelley K, Kirkeeide RL, Fisher DJ. Regional myocardial function is not affected by severe coronary depressurization provided coronary blood flow is maintained. *J Am Coll Cardiol* 1985;5:948-55.
- 32.** Seiler C. *Collateral Circulation of the Heart*. Dordrecht, the Netherlands: Springer, 2009.
- 33.** Traupe T, Gloekler S, de Marchi SF, Werner GS, Seiler C. Assessment of the human coronary collateral circulation. *Circulation* 2010;122:1210-20.
- 34.** Meier P, Gloekler S, Zbinden R, et al. Beneficial effects of recruitable collaterals: a 10 year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. *Circulation* 2007;116:975-83.
- 35.** Gould KL, Kirkeeide R, Johnson NP. Coronary branch steal: experimental validation and clinical implications of interacting stenosis in branching coronary arteries. *Circ Cardiovasc Imaging* 2010;3:701-9.
- 36.** Gould KL, Nakagawa Y, Nakagawa N, et al. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base to apex, myocardial perfusion abnormalities by non-invasive positron emission tomography. *Circulation* 2000;101:1931-9.
- 37.** DeBruyne B, Hersbach F, Pijls NHJ, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "normal" coronary angiography. *Circulation* 2001;104:2401-6.
- 38.** Rajappan K, Rimoldi OE, Dutka DP, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. *Circulation* 2002;105:470-6.
- 39.** Gould KL, Johnson NP, Roby AE, et al. Regional artery specific thresholds of quantitative myocardial perfusion by PET associated with reduced MI and death after revascularization in stable CAD. *J Nucl Med* 2018 Aug 16 [E-pub ahead of print].
- 40.** Sdringola S, Johnson NP, Kirkeeide RL, Cid E, Gould KL. Impact of unexpected factors on quantitative myocardial perfusion and coronary flow reserve in young, asymptomatic volunteers. *J Am Coll Cardiol Img* 2011;4:402-12.
- 41.** Banko LT, Haq SA, Rainaldi DA, et al. Incidence of caffeine in serum of patients undergoing dipyridamole myocardial perfusion stress test by an intensive versus routine caffeine history screening. *Am J Cardiol* 2010;105:1474-9.
- 42.** Sylvén C. Mechanisms of pain in angina pectoris: a critical review of the adenosine hypothesis. *Cardiovasc Drugs Ther* 1993;7:745-59.
- 43.** Gaspardone A, Crea F, Tomai F, et al. Muscular and cardiac adenosine-induced pain is mediated by A1 receptors. *J Am Coll Cardiol* 1995;25:251-7.
- 44.** Tendera M, Gaszewska-Zurek E, Parma Z, et al. The new oral adenosine A1 receptor agonist capadenoson in male patients with stable angina. *Clin Res Cardiol* 2012;101:585-91.
- 45.** Rivkees SA, Lasbury ME, Barbhaiya H. Identification of domains of the human A1 adenosine receptor that are important for binding receptor subtype-selective ligands using chimeric A1/A2 adenosine receptors. *J Bio Chem* 1995;270:20485-90.
- 46.** Olah ME. Identification of A2a adenosine receptor domains involved in selective coupling to Gs: analysis of chimeric A1/A2 adenosine receptors. *J Bio Chem* 1997;272:337-44.
- 47.** Pepine CJ. Multiple causes for ischemia without obstructive coronary artery disease. *Circulation* 2015;131:1044-6.
- 48.** Pepine CJ, Ferdinand KC, Shaw LJ, et al. emergence of nonobstructive coronary artery disease. *J Am Coll Cardiol* 2015;66:1918-33.
- 49.** Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging microvascular dysfunction and mechanisms for female male differences in coronary artery disease. *J Am Coll Cardiol Img* 2016;9:465-82.

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