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EDITORIAL COMMENT

Approximate Truth*

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In this issue of the *Journal*, 2 papers report on assessing physiological severity of coronary stenosis (1,2). Although diverse in their aims, methods, and conclusions, we editorialists see a commonality with 3 important themes for clinical physiology driving management of coronary artery disease.

SEE PAGES 3077 AND 3088

First, both papers address by different methodologies the physiological severity of coronary stenosis for guiding interventions. Second, they both derive from concepts of coronary physiology (3) and fluid dynamic equations (4) proven 40 years ago that still reveal essential lessons on approximations, limitations, and trade-offs of their methodologies having potentially suboptimal benefit for patients. Third, the basic commonality of these papers is "approximate truth," a concept essential for understanding, using, comparing, and advancing diagnostic or interventional procedures in cardiovascular medicine.

RESTING CORONARY PRESSURE GRADIENT AND INSTANTANEOUS WAVE-FREE RATIO

Fractional flow reserve (FFR) is a measure of relative hyperemic coronary flow reserve (CFR) flow determined by intracoronary pressure wire as the ratio of pressure distal to a stenosis (Pd) divided by the aortic pressure (Pa) during maximal coronary flow (5). The randomized FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation Trial) using FFR-guided percutaneous coronary intervention demonstrated physiological assessment of coronary stenosis to be superior to angiography or medical treatment for evidence-based interventions (6).

As FFR became the invasive standard of physiological severity, "shortcuts" were proposed to avoid pharmacologic stress despite its widespread acceptance and safety. Instantaneous wave-free ratio (iFR) was reported as a diastolic resting pressure measurement depending on proprietary software that claimed superiority over resting average coronary/aortic pressure (Pd/Pa) (1).

The basis for iFR assumed a purported diastolic "wave-free period" and its constant minimum microvascular resistance, subsequently proven to fall after adenosine. These assumptions were overturned by several reports showing no difference between iFR and resting Pd/Pa as shown in **Figures 1A** (7) **and 1B** (8). The important, meticulous study by van't Veer et al. (1) definitively demonstrates no benefit of the proprietary iFR over resting coronary Pd/Pa for any part of diastole, whole diastole, or whole heart cycle (**Figure 1C**).

The report by van't Veer et al. (1) incurs 3 physiological lessons. The first is that pressure wave analysis shows no diastolic wave-free period, as illustrated in **Figure 2** (9). Wave intensity analysis is the first time derivative of aortic forward and reflected backward pressure waves. Because this first derivative highlights rapidly changing pressure waves, the slowly changing diastolic pressure waves make this derivative lower during diastole than systole, but sufficiently large to reconstitute the original pressure on integration thereby proving the absence of a diastolic wave-free period.

The second lesson is that "the truth will come out" through peer-reviewed publications by objective studies without proprietary bias (7–9). The third and most interesting lesson addresses the increasing use of indirect physiological "approximations" of severity, here illustrated by resting Pd/Pa as a "shortcut approximation" in common with the second paper of this editorial.

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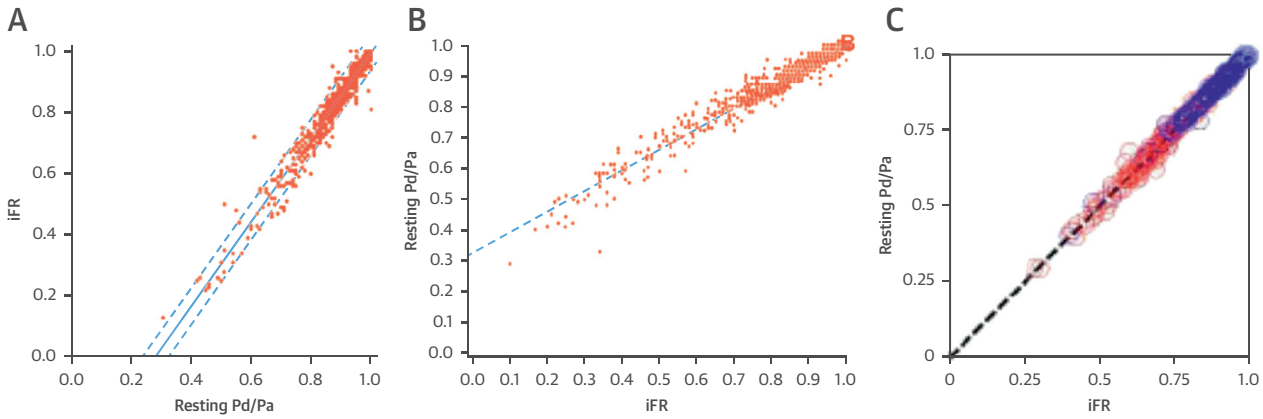
FIGURE 1 **Reported Correlations of iFR With Resting Pd/Pa**



Systematic studies show that nonproprietary resting Pd/Pa tightly correlates with the proprietary iFR with no additional information or benefit of iFR over resting Pd/Pa. Reproduced with permission from **(A)** Johnson et al. (7), **(B)** Jeremias et al. (8), and **(C)** van't Veer et al. (1). iFR = instantaneous wave-free ratio; Pa = aortic pressure; Pd = pressure distal to stenosis.

QFR OR FFR ANGIOGRAM

Xu et al. (2) used quantitative coronary angiography in 2 views to reconstruct 3-dimensional coronary anatomy with resting mean volumetric flow by TIMI (Thrombolysis In Myocardial Infarction) frame count for fluid dynamic equations to simulate FFR, called QFR. The correlation with and diagnostic accuracy of modeled QFR compared with actual FFR is reasonable, shown in **Figure 3B** (adapted from Xu et al. [2]) with 1 SD that is approximately one-half the SD reported for FFR based on computed tomographic (CT) computational fluid dynamics shown in **Figure 3C** (10) that is likely due to superior resolution of invasive angiography. The inaccuracy of these anatomically derived approximations becomes proportionately larger with progressively severe physiological severity as shown by the dashed red lines of **Figures 3B and 3C**. For example, at a measured threshold of 0.8, the QFR SD of ±0.13 constitutes a ±16% uncertainty compared with a QFR uncertainty of 22% for an FFR of 0.6 and a corresponding FFR based on CT computational fluid dynamics uncertainty of 30% and 40%, respectively.

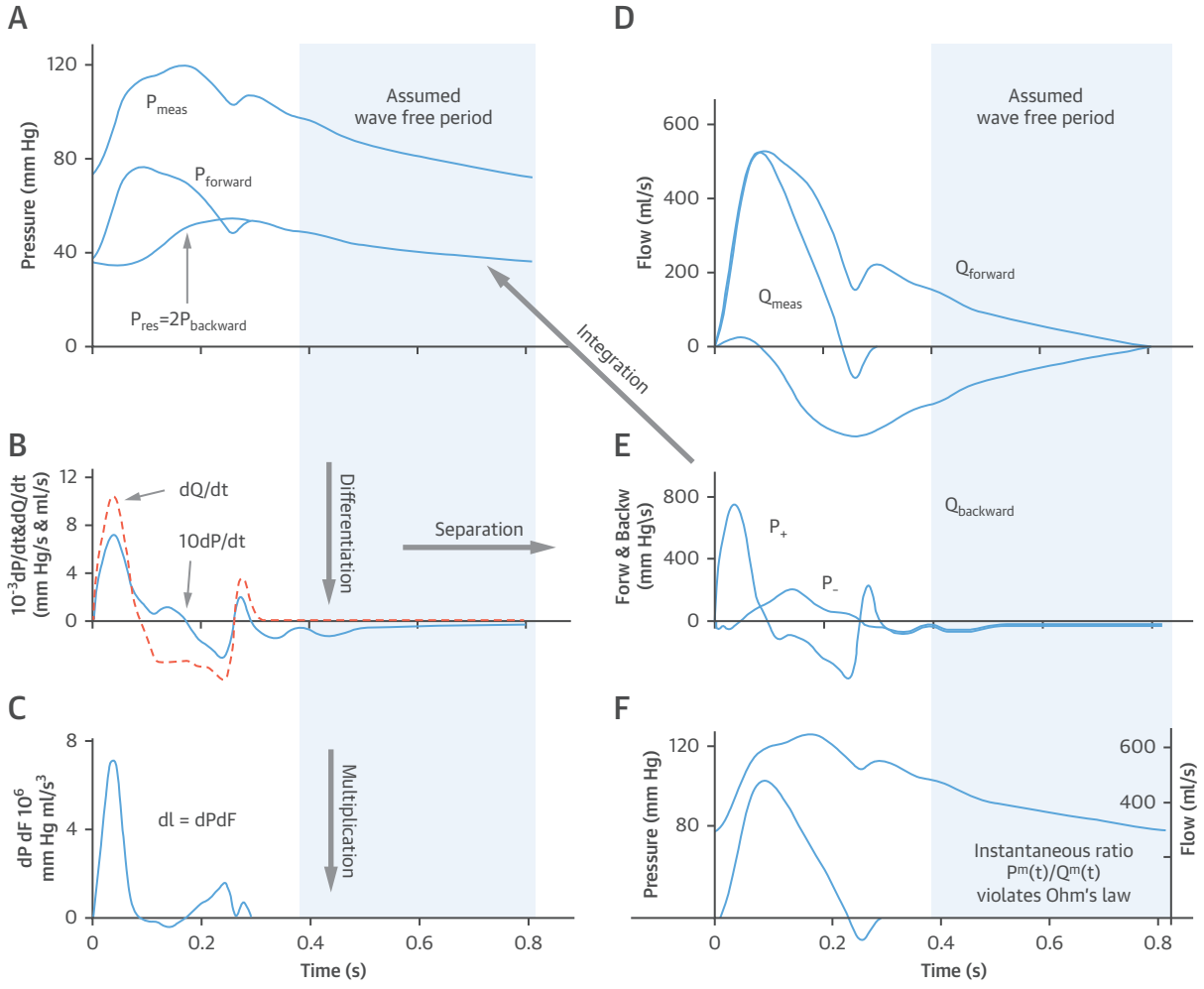
As predictably expected from extensive publications on limitations of percentage of diameter stenosis, QFR was more accurate than percentage of stenosis because quantitative coronary angiography in this study did not integrate all angiographic dimensions with the same fluid dynamic equations as used for QFR. The correlations and SD for QFR in 2017 are the same as for the first reported angiographic predicted relative CFR in 1990 for experimental stenosis by quantitative coronary angiography of complete, integrated, angiographic multidimensional geometry in **Figure 3A** (11). This parallel indicates the innate limitations of anatomy for predicting physiology even with modern angiography.

Xu et al. (2) concluded that QFR increases "overall feasibility of functional lesion assessment" when compared with pressure-based FFR due to "excessive pressure drift often encountered, warranting repeated pressure calibration and wire manipulation to achieve a reliable FFR measurement." On the other hand, the investigators claimed greater accuracy than the originators of QFR (12) due to "acquisition guide obtaining 2 good angiographic runs with minimal foreshortening and overlap" and "consensus on the position by the operators," which is "of particular importance for tandem lesions or diffuse disease." Because the SD for repeated FFR is 2% (0.02/1.0) versus 12% (0.12/1.0) for QFR, one might conclude that both techniques require meticulous attention during measurements depending on personal preferences for details.

THE PHYSIOLOGICAL LESSON FROM BOTH REPORTS

All current methodologies for assessing physiological severity of coronary artery disease derive from

FIGURE 2 **Wave Intensity Analysis**

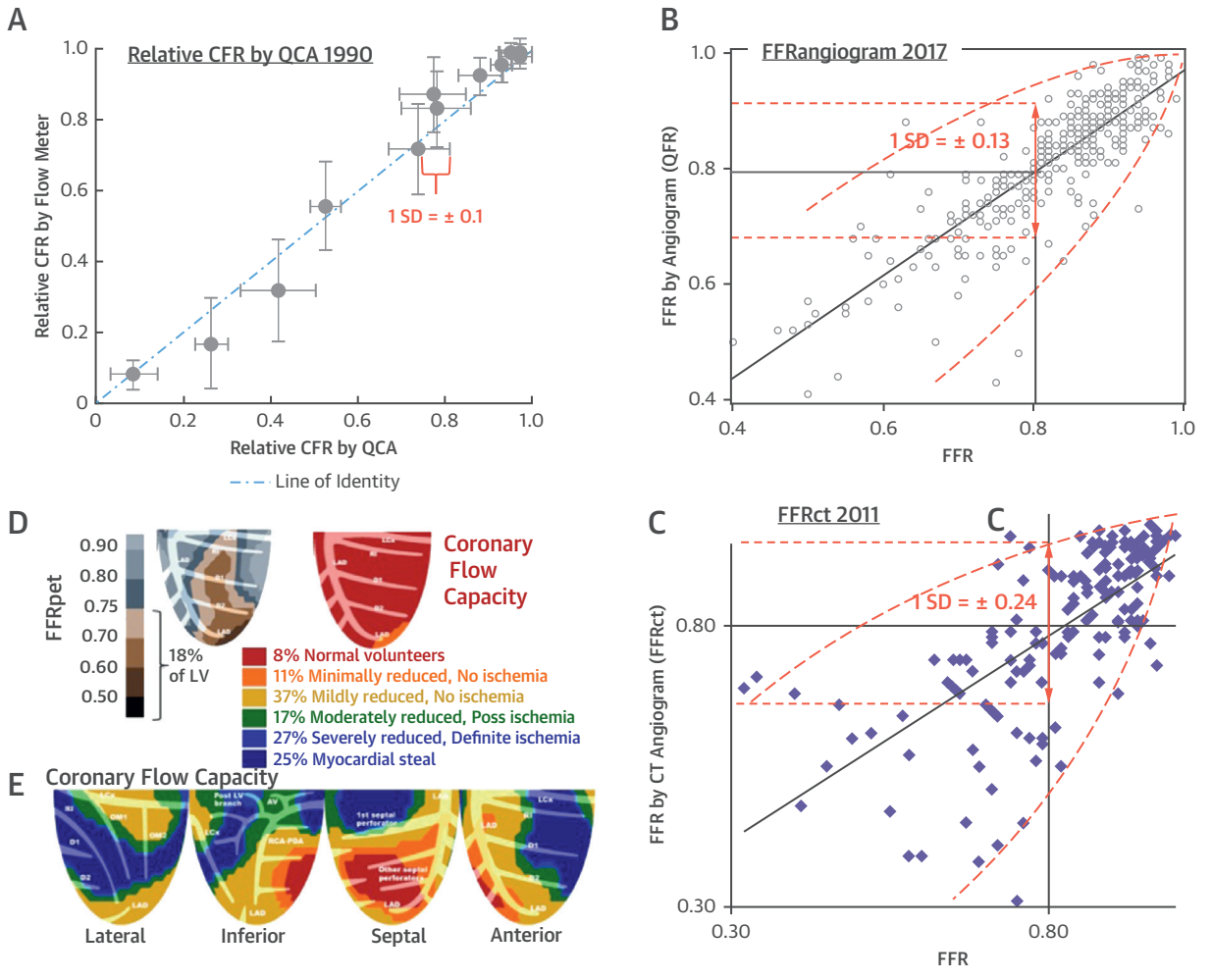


(A) Measured pressure wave (P_{meas}) compared to the pressure wave reconstituted ($P_{forward}$) by integrating the derivative of the forward pressure waves (P+) and backward pressure waves (P-) with respect to time in **E**. P_{res} is the theoretical Windkessel component of the reconstituted pressure wave ($P_{forward}$). **(B)** The derivatives of pressure (dP/dt) and flow (dQ/dt) with respect to time and a constant of 10 for scaling on the same graph. **(C)** The wave intensity term dI = dPdF = the abbreviated expression of dI = [dP(t)/dt]x[dQ(t)/dt]. **(D)** Measured forward flow (Q_{meas}) and the theoretical reconstituted forward ($Q_{forward}$) and backward ($Q_{backward}$) flow waves derived from the wave intensity term dI of **C** that comprise or add up to Q_{meas}. **(E)** The derivative of P+ and P- with respect to time that on integration reconstitute the P_{meas} of **A**. **(F)** The instantaneous wave-free ratio (iFR) measured as P(t)/Q(t) or instantaneous pressure divided by flow at time t. The assumed wave-free period **(grey zone of C)** is based on wave intensity analysis using the pressure derivative with respect to time reflecting primarily rapid pressure changes. Therefore, it fails to account for slower changing diastolic pressure waves clearly present throughout diastole as proven by their integration reconstituting the measured pressure. Therefore, there is no wave-free period as required for the validity of iFR thereby violating Ohms' Law that discredits the basis for iFR. Reproduced with permission from Westerhof et al. (9).

concepts of CFR and fluid dynamic equations relating integrated anatomy to pressure and absolute coronary flow (3,4,11) used here synonymously with perfusion. All indirect measures by pressure wire or angiographic anatomy provide approximations, not absolute quantitative perfusion at rest and stress or their epicardial-to-endocardial distribution or transmural maldistribution due to coronary artery disease.

In the past, physiological assessment of coronary stenosis had little clinical impact due to complex physiology and technology for their measurements with great variability not readily adapted to binary, anatomically driven management decisions. The FFR trials led a scientifically driven profound change from anatomy to physiology for revascularization over the 25 years since its introduction (5). With this sea change came a host of shortcuts, approximations, and adaptations of anatomic technology to ride the physiology wave.

FIGURE 3 Quantitative Coronary Angiography to Predict Relative Flow Reserve



(A) Correlation of relative coronary flow reserve (CFR) by flow meter to quantitative coronary angiography (QCA) integrating angiographic anatomy in experimental coronary stenosis. **(B, C)** Correlation of QFR, fractional flow reserve based on angiogram (FFRangiogram), and FFR based on computed tomography (CT) (FFRct) to FFR pressure, all of which are relative CFR measurements. **(D)** Stress perfusion in cc/min/g displayed as a relative map (FFR based on positron emission tomography [FFRpet]) with 18% of the left ventricle (LV) reduced to <0.75 **(brown)** but with high coronary flow capacity that is comparable with coronary flow capacity of healthy young athletes without ischemia **(red). (E)** Severely reduced coronary flow capacity in complex coronary artery disease beyond assessment by angiogram or pressure (see text). **(A)** Reproduced with permission from Gould et al. (11). **(B)** Adapted with permission from Xu et al. (2). **(C)** Reproduced with permission from Johnson et al. (10). AV = atrioventricular; D = distal; LAD = left anterior descending; LCx = left circumflex; OM = obtuse marginal; PDA = posterior descending artery; R = right; RCA = right coronary artery.

However, approximations incur tolerance for measurement error balanced against consequent adverse outcomes. Tolerance for making jet engines is very narrow due to disastrous outcomes for engine failure. For coronary interventions, the tools of the visually interpreted angiogram, exercise testing and stress single-photon emission CT, are indirectly approximately related to coronary flow with great imprecision, hence there are wide measurement tolerances that have failed to guide interventions in randomized trials to reduce hard endpoints.

Are approximations of coronary physiology "good enough" for optimal patient benefit of medical versus interventional management? Prior trials based on "belief in angiogram anatomy" that failed to reduce myocardial infarction or death provoke reasonable skepticism about improved event-free survival after revascularization guided by approximations of physiological severity or approximate truth. Approximate severity tests in low risk, mild to moderate coronary artery disease may lead to "iatrogenesis fulminans" (13,14) or unnecessary,

low-benefit procedures having risks as great as or greater than the disease.

All pressure or anatomic physiological approximations derive from absolute perfusion or flow, hence their reference or "truth." **Figure 3** illustrates this truth for 2 different cases over a wide range of CFR and stress perfusion combined as coronary flow capacity that angiographic or pressure measurements cannot match for interventional decisions.

The first case in single anterior views is a 59-year-old asymptomatic woman after percutaneous coronary intervention for ST-segment elevation myocardial infarction with nonculprit diagonal lesion (**Figure 3D**). Relative absolute stress perfusion in cc/min/g (FFR based on positron emission tomography) was reduced to <0.75 (brown) for 18% of the left ventricle. However, her very high coronary flow capacity (red) is comparable to that of young healthy athletes with no ischemia, just very high flow with a relative stress defect that needs no procedure.

The second case is a 69-year-old man with a patent left internal mammary artery to left anterior descending artery, recurrent severe angina, fall in ejection fraction from 41% at rest to 36% with stress due to ischemic stunning. The angiographic chronic total occlusion of right coronary artery and left circumflex artery have no visible vessels beyond the occlusion. The coronary flow capacity map shows the patent left internal mammary artery to left anterior descending artery and a severe stress defect in a dominant viable left circumflex distribution as the appropriate target for percutaneous coronary intervention, not the small distribution of the right coronary artery (**Figure 3E**). Although absolute perfusion is the most precise "gatekeeper" for quantitative ranges of severity to guide invasive procedures (**Figure 3D**), its greatest power of is defining true physiology of complex coronary artery disease for interventional guidance that angiogram, epicardial pressure, or CT measurements cannot provide (**Figure 3E**).

CONCLUSIONS

Although we recognize that physiological "approximations" are inherent in cardiology practice, we suggest that these approximations and indirect measures of physiological severity incur trade-offs of convenience versus optimal accuracy and benefit for individual patients. At a threshold of high-risk physiologically severe disease for which revascularization may reduce adverse events (15), quantitative myocardial perfusion itself may be a better guide than the imprecision of approximate truth illustrated by these 2 well-conducted studies on evolving clinical coronary physiology.

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KEY WORDS coronary flow reserve, fractional flow reserve, instantaneous wave free ratio, quantitative angiographic fractional flow reserve