The article by Tarkin et al1 in this issue of Circulation: Cardiovascular Interventions adds interesting details to the extensive, well-established basis for assessing stenosis severity at maximal coronary flow induced by pharmacological vasodilatation. As the authors state, all the major clinical trials of fractional flow reserve (FFR) as the basis for percutaneous coronary angioplasty were made under conditions of stable hyperemia as defined in the original protocol. Their data in this article reinforce that requirement by showing the errors in FFR if measured during initial hemodynamic changes of the systemic and coronary circulation after intravenous adenosine before stable hyperemia is reached.

The authors display 7 arbitrarily chosen patterns of aortic (P_a) and distal coronary pressures (P_d) all showing larger peak stenosis gradient than the steady-state hyperemic gradient. P_d and the ratio P_a/P_d after adenosine (FFR) were related to but did not exactly parallel the stenosis gradient. Moreover, FFR paralleled to some extent P_d reflecting systemic hemodynamics as well as stenosis fluid dynamics, thereby raising the question of which provides the truth about stenosis severity. The answer is that stenosis gradient, P_a and P_d all tell the truth but respond to different questions. The stenosis gradient reflects the fluid dynamic characteristics of the stenosis depending on flow. P_d reflects pressure that the myocardial bed experiences at that flow, and FFR is the ratio P_a/P_d for normalizing P_d to aortic pressure at maximal steady-state hyperemia. It is used as an indirect marker of severity and inferred ischemia—indirect and inferred in that P_d and FFR do not quantify low flow causing ischemia. For clinical decisions, the truth of each measurement is defined by outcomes after treatment based on that measurement.2-4

Significance and Mechanisms of Early Pressure Changes
During the first seconds of adenosine infusion, P_a and P_d may fall and rise but to different extents. The factors that cause the directional or phase differences in P_a and P_d patterns of Figure 2 are complex and not identifiable from the data reported. The apparently simple disparate changes in P_a, P_d stenosis gradient, and FFR reflect diverse, interacting, cumulative, nonlinear, and rapidly changing mechanisms. They include transient systemic and coronary neural reflexes, circulating catecholamines, endothelial function, pressure rate product affecting myocardial flow, myocardial contractility and compression, changes in intrathoracic pressure related to the central action of adenosine, vasoactive medications, β-blockers, caffeine, physical conditioning, left ventricular hypertrophy, diastolic dysfunction, diabetes mellitus, hypertension, all different for different patients with differential time changes among all of these factors.

Moreover, the fall in P_d with falling P_a is not necessarily a physiological false or misleading signal about stenosis severity or myocardial ischemia. Decreased P_d also indicates decreased work and flow demand so that the parallel fall in P_d is physiological. Moreover, myocardial contractility in an experimental model remains normal with P_d that is, only 43% of aortic pressure if coronary flow is maintained.5

In addition, as the authors point out, different coronary arteries in the same patient may also behave differently because of heterogeneity of coronary vasomotor controls. To further complicate the net effects of an intravenous infusion of adenosine on P_a and P_d, different densities in adenosine receptors in different organs6 induce various, often opposite, physiological effects when stimulated. For example, while in the coronary vasculature adenosine induces vasodilation through prevailing A_2 receptors in the kidney, where A_1 receptors are predominant, adenosine infusion is paralleled by a vasocostriction leading to ischemia and stimulation of the sympathetic system and the renin–angiotensin system.

Finally, and probably most importantly, the effects of adenosine occur out of phase. From the infusion point, adenosine first travels through the pulmonary circulation, often inducing a short-lasting reflex peripheral vasoconstriction, and then reaches the left heart, the coronary and the peripheral circulations.

Consequently, the early variations of P_a and P_d imply no specific physiological mechanisms or clinical information other than emphasizing the necessity of steady-state hyperemia for assessing stenosis severity.

A Need for Standardization
A practical take-home message of Tarkin et al’s study1 is that, for the calculation of FFR, the physicians should take into account the raw pressure data rather than the numeric values produced by the pressure wire consoles. These softwares compute the P_a/P_d ratio at the time of the largest difference between the 2 signals whether it is in the early phase of the infusion of adenosine, in steady state, or related to a

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Standardized Hyperemic Stress for Fractional Flow Reserve

Bernard De Bruyne, MD; K. Lance Gould, MD

The article by Tarkin et al in this issue of Circulation: Cardiovascular Interventions adds interesting details to the extensive, well-established basis for assessing stenosis severity at maximal coronary flow induced by pharmacological vasodilatation. As the authors state, all the major clinical trials of fractional flow reserve (FFR) as the basis for percutaneous coronary angioplasty were made under conditions of stable hyperemia as defined in the original protocol. Their data in this article reinforce that requirement by showing the errors in FFR if measured during initial hemodynamic changes of the systemic and coronary circulation after intravenous adenosine before stable hyperemia is reached.

The authors display 7 arbitrarily chosen patterns of aortic (P_a) and distal coronary pressures (P_d) all showing larger peak stenosis gradient than the steady-state hyperemic gradient. P_d and the ratio P_a/P_d after adenosine (FFR) were related to but did not exactly parallel the stenosis gradient. Moreover, P_d and FFR paralleled to some extent P_d reflecting systemic hemodynamics as well as stenosis fluid dynamics, thereby raising the question of which provides the truth about stenosis severity. The answer is that stenosis gradient, P_a and P_d all tell the truth but respond to different questions. The stenosis gradient reflects the fluid dynamic characteristics of the stenosis depending on flow. P_d reflects pressure that the myocardial bed experiences at that flow, and FFR is the ratio P_a/P_d for normalizing P_d to aortic pressure at maximal steady-state hyperemia. It is used as an indirect marker of severity and inferred ischemia—indirect and inferred in that P_d and FFR do not quantify low flow causing ischemia. For clinical decisions, the truth of each measurement is defined by outcomes after treatment based on that measurement.

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pressure artifact. In this retrospective analysis of pressure tracings obtained in all comers undergoing FFR measurements for clinical decision making in intermediate stenoses, some noise in the pressure recordings likely contributed to the changes in measured $P_a - P_r$ and their respective fluctuations over time.

Accordingly, the data presented by Tarkin et al strongly support standardization of measuring FFR as originally reported, whether with intravenous or intracoronary administration of hyperemic stimuli. The growing use of FFR for individual clinical decision making, as a basis for randomization in clinical trials, and its analysis by core laboratories require a uniform data acquisition and interpretation of FFR measurements.

Conclusions
In this article, the authors properly state “Using intravenous adenosine via a central venous line maintains a steady state, stabilizing hemodynamic conditions and creates the optimal conditions for physiological lesion assessment.” The senior author of this article has frequently invoked the quote. The first step of scientific progress is both accepted knowledge and continual, instantaneous willingness to admit that what we believed true earlier was wrong and needing replacement by a view more consistent with new data. After substantial experience with resting diastolic stenosis gradients, the authors seem to have evolved in the respected scientific tradition of this quote by replacing their prior views with “optimal conditions for physiological lesion assessment,” thereby adding significantly to the massive scientific literature defining stenosis severity at maximal coronary flow.

Disclosures
The Cardiovascular Research Center Aalst receives institutional consultancy fees from St Jude Medical Systems for Dr De Bruyne. Dr Gould received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis, the 510(k) applicant for cfQuant approved by the Food and Drug Administration, and he has arranged that all his royalties permanently go to a University of Texas (UT) scholarship fund. UT has a commercial nonexclusive agreement with Positron Corporation to distribute and market cfQuant in exchange for royalties; however, Dr Gould retains the ability to distribute cost-free versions to selected collaborators for research. In addition, Dr Gould has signed a nonfinancial, mutual nondisclosure agreement with Volcano Corporation (maker of FFR pressure wires) to discuss coronary physiology projects.

References

Key Words: Editorials ■ adenosine ■ angiography ■ blood pressure ■ hemodynamics