JACC Vol. 30, No. 3
September 1997:613–20

From Research to Clinical Practice: Current Role of Intracoronary Physiologically Based Decision Making in the Cardiac Catheterization Laboratory

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Decisions regarding coronary interventions should be combined with objective evidence of myocardial ischemia. The most common physiologic approach utilizes hospital facilities outside the catheterization laboratory, requiring additional time and cost. With the introduction of sensor-tipped angioplasty guide wires, distal coronary flow velocity and pressure can be obtained in the cardiac catheterization laboratory, facilitating physiologically based decisions regarding the need for intervention. In the catheterization laboratory, physiologically significant stenoses can be characterized as having impaired post-stenotic coronary flow reserve <2.0 and pressure-derived fractional flow reserve <0.75, both variables related strongly to positive ischemic perfusion imaging or stress testing results. Deferring coronary interventions on the basis of normal translesional physiology is safe and is associated with a low rate (<10%) of lesion progression over a 10-month follow-up period. Preliminary data indicate that excellent physiologic and anatomic end points after balloon angioplasty are associated with low (<20%) restenosis rates at 6-month follow-up. Clinically relevant relations of in-laboratory physiology support the insight that physiologic, as much as or more than anatomic variables, ultimately determine the functional status of a patient. Current data suggest that an intracoronary physiologic approach complements coronary lumenology and appears to have important clinical and economic implications for patients undergoing invasive evaluation and treatment of coronary artery disease.

(J Am Coll Cardiol 1997;30:613–20)

The Problem: Moving Beyond Lumenology

On January 31, 1996, the first training course on intracoronary diagnostic techniques, endorsed by the European Society of Cardiology, Working Group on Coronary Circulation, was convened in the Catharina Hospital, Eindhoven, The Netherlands. The course addressed three important questions that arise when treating patients with a coronary stenosis: as a physiologist, "What is the effect of this stenosis on coronary flow and myocardial function?"; as a clinician, "Is this lesion responsible for the patient's symptoms?"; and finally, as an interventionalist, "Will opening this artery improve the patient?" As discussed by Topol and Nissen (1), these critical questions cannot be adequately answered solely by anatomic examination of the coronary lumen ("lumenology") using angiographic or intravascular ultrasound anatomic imaging. In the most commonly encountered stenoses, those in the intermediate ranges, coronary lumenology does not provide sufficient functional information to support clinical decisions.

It is generally accepted that decisions regarding coronary interventions should be combined with some objective evidence of ischemia (2). This physiologic approach often utilizes hospital facilities outside of the catheterization laboratory and may require additional time and cost before the evaluation is concluded. Some patients may not undergo such an evaluation before proceeding with angioplasty (3). As an alternative approach for patients with stable chest pain (i.e., suspected ischemic) syndromes, some centers have adopted the use of coronary physiologic data obtained in the catheterization laboratory after diagnostic angiography or before angioplasty to facilitate clinical decisions (4–7).

The purpose of this article is to review the current status of coronary physiologic techniques in the catheterization laboratory. From the available data, intracoronary flow velocity and pressure measurements have extended in-laboratory coronary physiology from research to clinical practice, facilitating a rational alternative approach to decision making.

Development of Coronary Physiology for the Catheterization Laboratory

The hemodynamic significance of a given stenosis, determined by the pressure–flow relation (8), has not been incorporated into clinical practice because of cumbersome catheter techniques (9,10) and questionable or conflicting results from

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Manuscript received September 26, 1996; revised manuscript received May 27, 1997, accepted May 30, 1997.

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Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(97)00224-6

Abbreviations and Acronyms

CFR = coronary flow reserve
FFR = fractional flow reserve
FFRmyo = fractional flow reserve of myocardium

patients studies (11,12). Predictable relations between anatomic and physiologic variables demonstrated in experimental animal studies were often not present in patients (12–15). The reasons for this weak relation are not completely understood but include the limitations of coronary angiography as a standard of lesion severity (16,17) and complex, and at times, compromised physiologic measurement techniques (9–14). In addition, flow velocity measured proximal to a stenosis may differ from post-stenotic flow data, a phenomenon related to lower prelesional branch resistance directing flow away or around the stenosis (6,18–21). Application of translesional pressure measurements was hampered by catheter size and an incomplete interpretation using only absolute values instead of the related pressure response at maximal flow (refer to Fractional Flow Reserve in reference 5).

In catheterization laboratories today, distal coronary flow velocity and pressure data can be acquired safely and rapidly using sensor-tipped angioplasty guide wires (Fig. 1), which have overcome catheter limitations, can be easily incorporated into routine procedures and do not substantially interfere with blood flow across subcritical stenoses (22,23).

Intracoronary flow velocity can be measured with a Doppler-tipped angioplasty guide wire (24). The Doppler FloWire (Cardiometrics, Inc.) is a 175-cm long, 0.014- to 0.018-in. (0.035-l to 0.046-cm) diameter, flexible, steerable angioplasty guide wire with a piezoelectric ultrasound transducer integrated into the tip. The system is coupled to a real-time spectrum analyzer, videocassette recorder and thermal page printer. The Doppler signals are continuously displayed on a video monitor. Coronary flow reserve (CFR) is computed as the ratio of maximal hyperemic to basal mean coronary flow velocity.

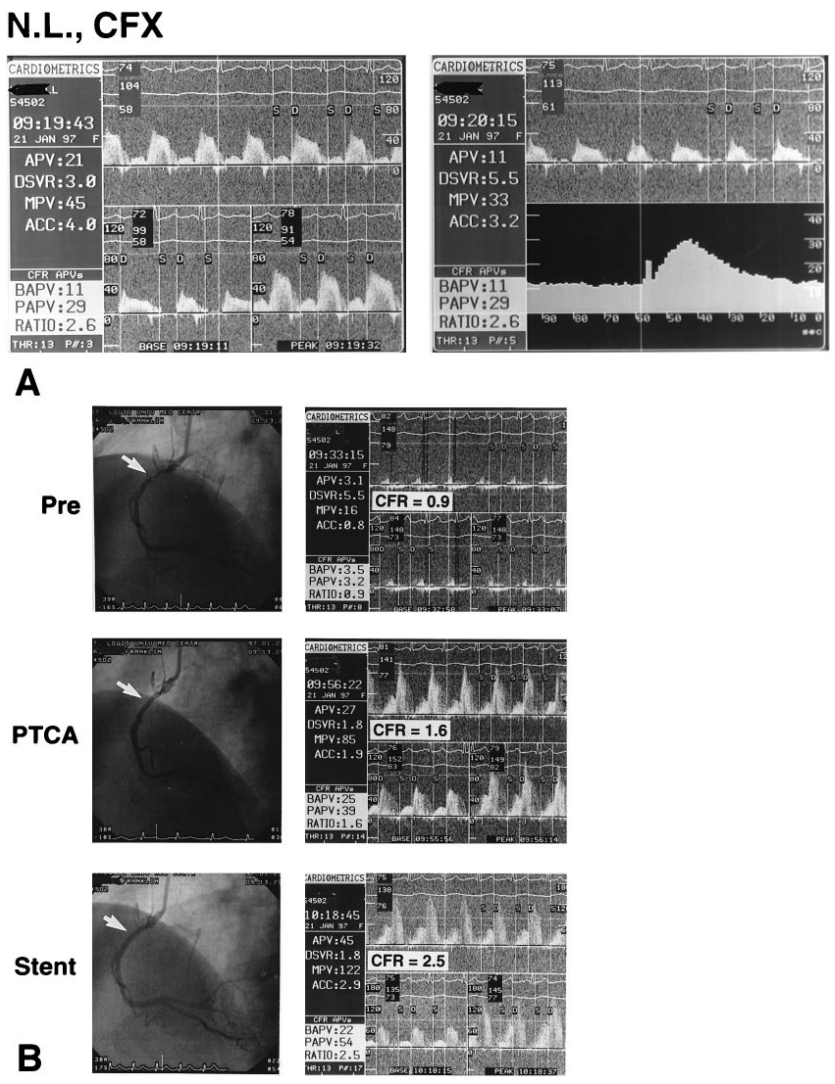

Figure 1. A (left panel), Coronary flow velocity signals obtained in a normal circumflex coronary artery (N.L., CFX) of a patient undergoing angioplasty of the right coronary artery (**B**). The screen is divided into top and bottom, and the bottom half divided into left and right panels. The top half represents continuous flow velocity signals in real time. The electrocardiogram, aortic pressure and spectral flow signals are provided from top to bottom. The scale is 0 to 120 cm/s. S and D = systolic and diastolic periods demarcated by the electrocardiogram, respectively. The **lower left panel** demonstrates basal flow velocity, and the **lower right panel** demonstrates the peak hyperemic velocity. **Right panel,** The trend plot of the continuous flow velocity measurement (average peak velocity [APV]) is shown in the right-hand panel on the lower tracing. After intracoronary adenosine administration, average peak velocity increased from 11 to 29 cm/s, producing a coronary flow ratio (CFR) of 2.6. The duration of hyperemia is 45 s. The trend velocity scale is 0 to 40 cm/s. The time base is 90 s. **B,** Angiography and coronary flow velocity signals before and after balloon angioplasty and after stent placement in the same patient as in **A.** The right coronary artery stenosis is narrowed >75% in diameter. **Left panels** show stenosis **(arrow)** before (Pre) and after angioplasty (PTCA) and after stenting (Stent). Before angioplasty **(top right),** distal flow velocity is 3.5 cm/s with impaired CFR (0.9 to 1.0). After angioplasty, basal average peak velocity increased to 25 cm/s with CFR 1.6. After stenting, CFR increased to normal (2.5). The value was similar to the reference coronary vasodilatory reserve (2.6). The relative coronary vasodilatory reserve after stenting was 0.96. Format as in **A.** ACC = acceleration; BAPV = base average peak velocity; DSVR = diastolic/systolic velocity ratio; MPV = maximal peak velocity; PAPV = peak average peak velocity; PTCA = percutaneous transluminal coronary angioplasty.

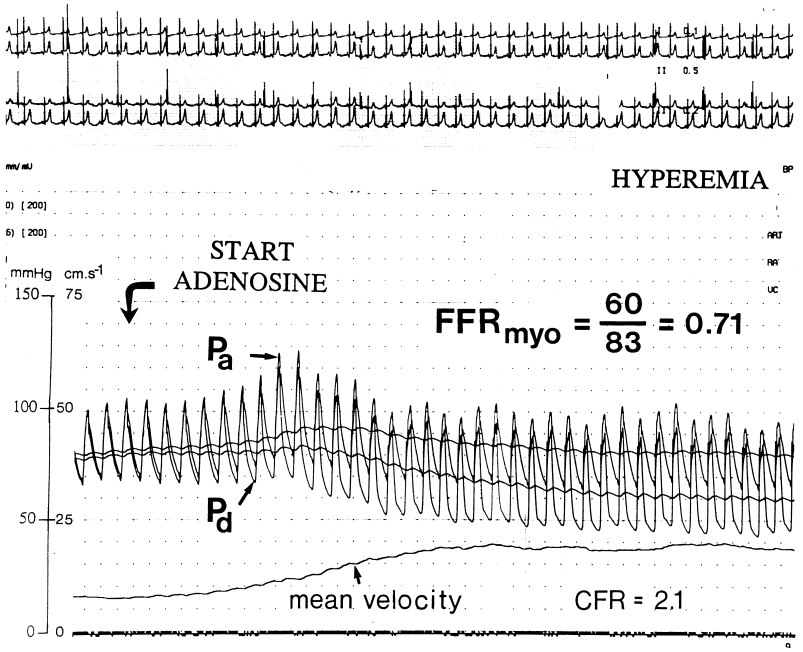

Figure 2. Translesional pressure measurements made with a fiber optic guide wire (Radi, Inc.) were used to compute FFRmyo. The initial translesional pressure gradient (aortic [Pa] − Distal coronary [Pd]) is <3 mm Hg **(left side)** before inducing hyperemia. During adenosine infusion, coronary mean flow velocity increases (CFR 2.1) and translesional pressure gradient increases. Distal coronary pressure falls to 60 mm Hg. Aortic pressure declines slightly to 83 mm Hg. The FFRmyo is calculated as Pd/Pa during maximal hyperemia—0.71—indicating a functionally significant stenosis. The pressure scale is 0 to 150 mm Hg.

Intracoronary pressure measurements can be made with two angioplasty guide wire devices currently available outside the United States. The Pressure Guide (Radi Medical Systems, Uppsala, Sweden) is a 0.014-in. (0.035-cm) relatively stiff guide wire with a fiberoptic capability to detect changes in reflected light from a mirror source deformed by pressure changes (25). The high fidelity signal produces phasic pressure waveforms equivalent to larger high fidelity catheters (Fig. 2). The second device is a fluid-filled, 0.014-in. (0.035-cm) diameter angioplasty guide wire (Schneider Corporation, Bulag, Switzerland) (23). This wire has the same overall characteristics as a conventional angioplasty guide wire and can be connected to any pressure transducer, but it produces a damped phasic pressure owing to its small inner lumen. In contrast to angioplasty balloon catheters, pressure guide wires produce useful pressure signals without the artifact of a catheter shaft or balloon material in the artery lumen (23).

From guide wire pressure measurements during hyperemia, a new concept for the determination of coronary blood flow—the fractional flow reserve of the myocardium (FFRmyo)—has emerged (5). The FFRmyo is defined as the ratio of maximal hyperemic flow in the stenotic artery to the theoretic maximal hyperemic flow in the same artery without a stenosis. The FFRmyo is computed as the ratio of distal mean coronary pressure and mean aortic pressure during maximal hyperemia and is a specific index to describe the influence of the coronary stenosis on maximal perfusion of the subtended myocardium. The FFRmyo is derived from the relations of flow and resistance across the myocardial bed (see Appendix) and represents the fraction of maximal blood flow that can still be attained despite the presence of the epicardial coronary lesion. The FFRmyo has an unequivocal value of 1.0 for every patient and every coronary artery. It is generally unaffected by changes in heart rate, blood pressure and contractility (26,27). A fractional flow reserve (FFR) value of 0.75 reliably distinguishes functionally significant coronary stenoses (27–30).

Safety, Reliability and Reproducibility

The sensor guide wire method for lesion assessment has an excellent safety record. In over 1,800 studies from the laboratories of the authors in normal, diseased and transplanted coronary vessels, only three patients had a sensor guide wire–related complication involving a severe coronary stenosis. As with angioplasty guide wires for severe stenoses, the Doppler guide wire has been used as a primary angioplasty crossing wire with >90% success for most coronary stenoses (21). In worldwide application, <20 cases of 45,000 uses have been reported to be associated with arterial injury reported to the manufacturer or the Food and Drug Administration, an incidence lower than that with diagnostic angiography alone.

Reproducibility of the pressure and velocity signals is generally excellent with interobserver and intraobserver variation: <12% and 9%, respectively (22–25). However, tip position alterations may result in different absolute velocity values without significant changes in the CFR ratio. Using the fiber optic pressure wire system, the coefficient of variation for duplicate measurements is <5% (27–30). Signal distortion due to arterial tortuosity has been improved with reduction in wire stiffness of the fiber optic system.

Clinical Considerations to Using Coronary Physiology in Patients With Coronary Artery Disease

Coronary flow velocity and pressure signals have been extensively validated (22–25,30) and the technical limitations

encountered in clinical situations well described (31,32). Flow velocity can be used as a surrogate for volumetric flow assuming a constant vessel cross-sectional area at the measurement site (33). Most clinical Doppler studies use nitroglycerin to pretreat the target vessels and have applied this assumption. Clinical investigators have accepted that a small degree of flow-mediated vasodilation during hyperemia would result in an underestimation of the true volumetric flow response (18,20,21,24,28,32–35).

The variability of coronary vasodilatory reserve in patients within the catheterization laboratory limits establishing a finite coronary vasodilatory reserve as true normal or abnormal. Biologic conditions impairing normal microvascular function exist in patients with diabetes mellitus, left ventricular hypertrophy, myocardial infarction, syndrome X and various hematologic and rheologic abnormalities in the absence of obstructive atherosclerotic coronary disease (36). The incidence of impaired coronary vasodilatory reserve <2.0 in 416 angiographically normal coronary arteries from 214 patients undergoing evaluation for chest pain or cardiac transplantation at follow-up angiography is $<12\%$ (34). To identify microvascular disease, a relative CFR ratio can be determined from the ratio of coronary vasodilatory reserve in an angiographically normal reference vessel to the target vessel CFR. The variation in coronary vasodilatory reserve among the coronary branch arteries is $<10\%$ (34,37), producing a normal relative CFR of 1.01 ± 0.2 (38).

Changes in systemic hemodynamic data can produce excessive variability in coronary vasodilatory reserve (39). For most stable patients, coronary vasodilatory reserve is reproducible during diagnostic or interventional studies. Unlike coronary vasodilatory reserve, the influence of systemic hemodynamic data is negligible on pressure-derived FFR because this index only uses hemodynamic responses during maximal hyperemia and includes mean aortic pressure in the determination of FFRmyo (26).

In a myocardial region with microvascular disease, insufficient maximal translesional flow will limit the hyperemic pressure response and theoretically yield a normal FFR. It should be emphasized that FFR is a specific index for epicardial stenosis, whereas CFR addresses both the conduit and microvascular circulation. Because each current physiologic method individually reflects only one aspect of the pressure–flow relation, borderline or ambiguous data, acquired by either pressure or flow velocity alone, can be theoretically confirmed using the complementary technique. A combined guide wire device with both pressure and flow could eliminate questions related to borderline values.

Clinical Studies: Translesional Hemodynamic Variables as a Surrogate for Ischemic Stress Testing

Several single-center studies (40–42) and one multicenter trial (43) have reported excellent correlations with myocardial perfusion imaging and post-stenotic coronary flow velocity reserve. An impaired distal hyperemic flow velocity reserve <2.0 corresponded to reversible myocardial perfusion imaging defects with high sensitivity (86% to 92%), specificity (89% to 100%), predictive accuracy (89% to 96%) and positive and negative predictive values (94% to 100% and 77% to 95%).

The FFRmyo has also been validated against myocardial perfusion using positron emission tomography (44), and normal range values (>0.75) can easily discriminate among stenoses responsible for positive exercise stress testing (27–29) with excellent specificity and sensitivity ($>90\%$) and high diagnostic accuracy (93%).

Pijls et al. (29) compared FFRmyo with a unique ischemic standard composed of four commonly used noninvasive tests to detect myocardial ischemia in 45 patients with moderate coronary stenosis and chest pain of uncertain origin. In all 21 patients with FFR <0.75, reversible myocardial ischemia was demonstrated unequivocally on at least one noninvasive test. After coronary revascularization, all positive results reverted to normal. In 21 of 24 patients with FFR ≥ 0.75, all tests were negative for reversible myocardial ischemia. No revascularization procedures were performed and no patient required further intervention over 14 months of follow-up.

Like most other diagnostic techniques, including exercise electrocardiography, stress echocardiography, perfusion scintigraphy, quantitative angiography and intravascular ultrasound imaging, coronary guide wire–based physiologic measurements provide only a single "snap-shot" in time and are unable to evaluate the dynamic nature of coronary artery disease. Physiologic information must be interpreted in the context of the clinical syndrome. Currently, in-laboratory physiologic data for a single target stenosis, unlike myocardial perfusion imaging and stress testing, has not yet produced long-term prognostic information (45). In addition, intracoronary flow velocity and pressure measurements do not account for stress-induced paradoxic vasoconstriction that may occur in patients with coronary atherosclerosis (46).

Translesional Hemodynamic Data and Clinical Outcomes

Diagnostic catheterization. A prospective study (47) determined the feasibility, safety and outcome of deferring elective angioplasty in patients with angiographically intermediate (40% to 70% diameter narrowing by quantitative coronary angiography) lesions with normal translesional physiology in 100 lesions from 88 patients with single-vessel ($n = 26$) and multivessel coronary artery stenoses ($n = 74$). Over the follow-up period (mean 10 ± 8 months, range 6 to 30), rehospitalization due to cardiac events (angina) occurred in 12 patients. No patient had a myocardial infarction or developed unstable angina. Two patients died unrelated to target lesion assessment or progression. Of the 10 patients requiring either coronary artery bypass graft surgery ($n = 6$) or coronary

angioplasty (n = 4), only six involved target arteries and four had lesions not present on initial assessment.

On the basis of physiologic normal criteria, postponing angioplasty had a satisfactory clinical outcome. Progression of target stenoses was <10%, 92% without the need for later revascularization. Although it is unknown if outcomes based on symptomatic treatment alone would have been equivalent, based on angiographic and clinical criteria, a majority of these patients would have had angioplasty with an expected restenosis rate in excess of that in the deferred angioplasty group. Similar safety and clinical outcomes of this deferral strategy have been reported from other centers using only coronary vasodilatory reserve (20) or FFRmyo (29).

In-laboratory translesional hemodynamic studies may not reflect all ischemia-producing conditions, especially those related to vasomotor changes that may occur with exercise or emotional stimuli (48). However, these dynamic conditions are generally responsive to medical therapy. Although the precise mechanisms for improvement or stabilization of symptoms in deferred angioplasty studies (47,49) are not known, it is unlikely that coronary angioplasty will improve preexisting normal translesional hemodynamic data, but may instead trigger intimal hyperplasia and lumen remodeling in some patients with an initially mild and stable stenosis.

Angioplasty. The question of whether translesional hemodynamic data are related to the outcome of coronary balloon angioplasty was addressed, in part, by a European, multicenter, prospective study (Doppler Endpoints Balloon Angioplasty Trial Europe [DEBATE] [50]) of 224 patients undergoing single-vessel angioplasty.

After angioplasty, there was no difference in the angiographic minimal lumen diameter between patients with early (30 days) events (n = 35) and asymptomatic patients (n = 189) (1.81 ± 0.39 vs. 1.79 ± 0.29 mm, respectively). However, the post-stenotic coronary vasodilatory reserve (2.73 ± 0.93 vs. 2.22 ± 0.64, $p < 0.05$) was higher in the asymptomatic compared with the early event group. Although the symptomatic group could be differentiated, the overlap of coronary vasodilatory reserve values diminishes the prognostic power. However, combining postprocedural CFR >2.5 with an optimal anatomic result (quantitative angiographic percent diameter stenosis <35%) identified 44 of 224 patients with a 16% rate of repeat angioplasty at 6 months, a value similar to restenosis rates in stent trials (51).

From this large, multicenter, preliminary report, the combined anatomic and functional data were better prognostic indices than either variable alone, and this combined value was strongly predictive of early and late clinical events. Prospective trials (DEBATE II, Doppler Endpoint Stent International Investigation Using CFR [DESTINI-CFR]) are under way to determine if physiologically guided decisions will further improve clinical outcome in patients who undergo angioplasty.

For nonballoon coronary interventional devices, only limited and anecdotal reports (52–54) are available. The physiology and physiologic end points for such procedures remain to be defined.

Physiologic Decision Making During Diagnostic Catheterization

The concepts of pressure and flow for determining coronary stenosis significance have remained unchanged for >20 years and are applicable to stable patients commonly encountered in the catheterization laboratory. Although once used to determine angioplasty end points when the angiogram could not be used with confidence (9), translesional pressure was then measured with inadequate devices under inadequate circumstances (i.e., not during maximal hyperemia) and was inadequately interpreted (i.e., rest gradients rather than FFRmyo). Despite better angiographic systems and smaller angioplasty catheters, the physiologic approach to angioplasty has renewed relevance in light of the intravascular ultrasound imaging data demonstrating the angiogram as an imprecise reflection of the coronary lumen.

Assuming no major technical or clinical problems, an in-laboratory physiologic evaluation may take an additional 10 min, time that can be balanced against the time that will be encumbered by the patient and hospital during testing over the subsequent days or weeks. The additional procedural time facilitates a critical decision that can be based on data rather than conjecture when objective information is not immediately available. Intracoronary hemodynamic criteria for lesion severity in patients have been derived from ischemic testing correlations (27–29,40–44) (Table 1). Like all clinical testing, borderline values will require interpretation and judgment for use within the clinical context.

Expense of Physiologic Data

The Doppler and pressure guide wires cost $350 to $450, with capital equipment expenses of $45,000 and $15,000 for Doppler and pressure signal analyzers, respectively. These costs can purportedly be justified by the reduction in additional hospital time ($200 to 500 per day) and stress testing ($250 to $1500 depending on the test). The potential cost savings of using an in-laboratory physiologic assessment strategy was examined in 53 patients with intermediate coronary stenoses randomized to CFR measurements in the catheterization laboratory or thallium stressing testing in the days after angiography. Stress thallium studies required 2.1 ± 0.8 additional hospital days, with direct costs of $1,914 ± 55 for the in-laboratory group (n = 29) and $2,718 ± 242 in the out-of-laboratory thallium testing group (n = 24) ($p < 0.05$) (55).

Most third-party reimbursement does not allow for decision making using nonangiographic methods of evaluating coronary stenoses. Although the clinical benefit is transmitted to the patient, these costs must be borne by the catheterization laboratory. This approach currently does not translate into a cost-neutral or cost-saving situation for the physician or catheterization laboratory. A system-wide savings can accrue to physicians and hospitals operating in a capitated structure, because decision time and facility utilization are reduced. Unnecessary interventional procedures as expenditures are

Table 1. Ischemic Testing and Translesional Pressure and Flow Values

Study (ref. no)	No. of Pts	Ischemic Test	CFR	Sens	Spec	PPV	NPV	Accuracy
Post-stenotic CFR								
Miller et al. (40)	33	Adeno/dipy MIBI	<2.0	82%	100%	100%	77%	89%
Joye et al. (41)	30	Ex Tl	<2.0	94%	95%	94%	95%	94%
Deychak et al. (42)	17	Ex Tl	<1.8	94%	94%	100%	91%	96%
FFRmyo								
Pijls et al. (29)	45	4-test standard	<0.75	88%	100%	100%	88%	93%
de Bruyne et al. (28)	60	Ex ECG	<0.72	100%	87%	—	—	—

Adeno = adenosine; CFR = coronary flow reserve; dipy MIBI = dipyridamole 2-methoxy isobutyl isonitrile; Ex ECG = exercise electrocardiogram; Ex T1 = exercise thallium; FFRmyo = fractional flow reserve of myocardium; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.

curtailed and appropriate higher cost interventions become justified by objective data.

The need for objective justification before performing ad hoc invasive coronary procedures appears to be offset, in part, by the highly favorable clinical outcome, the satisfaction of performing the procedure and the associated financial reward (56,57). From a practical perspective, the physiologic approach must overcome current practice patterns to use objective information that might potentially defer a patient in whom angioplasty would "ordinarily" be performed ad hoc at a cost to the catheterization laboratory budget without reimbursement. Nevertheless, the drive to perform ad hoc angioplasty should not overwhelm a thoughtful approach. It is known that the expense of equipment for important decisions is often trivial compared with the human expense of an unwarranted procedure and the rare associated complications.

Physiologically Guided Angioplasty

Despite a successful angiographic appearance, standard balloon angioplasty may not achieve a satisfactory physiologic result (58,59). Combined intravascular ultrasound imaging and flow velocity studies (60) demonstrated that increases in coronary vasodilatory reserve after stenting were often related to residual lumen area, rather than the previously hypothesized microvascular impairment (58,59). Similarly, in a preliminary study, stent implantation resulted in the absence of any hyperemic pressure decline across the stented segment (61). Coupled with data on angioplasty outcome (50), decisions for stent placement may be complemented by physiologic data acquired during the procedure (54,60–62).

Pressure Versus Flow

Refinements in guide wire sensor technology will facilitate an in-laboratory physiologic approach. Ambiguous values associated with coronary vasodilatory reserve can be reduced using a pressure-derived flow (FFRmyo) assessment as a more specific index of conduit narrowing. The superiority of one technique is not established, because pressure and flow represent the two sides of the same coin—that of coronary lesion flow resistance. The preference for one physiologic technique may come from advances in guide wire capabilities and handling characteristics, ease of signal interpretation and integration into the specific catheterization laboratory system. Situations where ambiguous values presented by use of one physiologic technique can be reduced or eliminated by coupling that response to the corresponding alternative methodology. From the physiologic point of view, both techniques are highly complementary.

Summary

Clinically relevant relations with in-laboratory physiology continue to support the insight that physiologic, as much or more than anatomic variables, ultimately determine the functional status and well being of a patient. Although technical improvements in equipment and more clinical studies are needed, the current experience appears to indicate that in-laboratory physiology is making the transition from research tool to clinical adjunct, especially with regard to myocardial perfusion and ischemic stress studies. Using coronary physiology, one might modify a widely practiced dictum, "When in doubt, dilate" to "When in doubt, measure and decide."

Intracoronary pressure and flow velocity measurements are useful in the 20% to 30% of the current angioplasty population with stable chest pain syndromes in whom evidence of ischemia is lacking and complaints are atypical or in whom additional intermediate lesions during multivessel angioplasty may require assessment. Although conclusive data for stent decision making is not yet available, a clinically useful relation exists between coronary hemodynamic data, clinical events and lumen enlargement after angioplasty. A physiologic approach complements lumenology and appears to have important clinical and economic implications for patients undergoing invasive evaluation and treatment of coronary artery disease.

We thank Patrick W. Serruys, MD for support and critical review and Donna Sander for manuscript preparation.

Appendix

*Pressure–Flow Equations**

The flow (Q) to the myocardium is determined by the pressure drop (ΔP) across the resistance (R) to flow. For a coronary stenosis, $\Delta P = P_d - P_v$, where P_d = mean distal coronary pressure at maximal hyperemia; and P_v = mean central venous pressure at maximal hyperemia.

Hence, $Q = P_d - P_v/R$, where R = myocardial resistance at maximal hyperemia. If the same artery did not have a stenosis, then $\Delta P = P_a - P_v$, where P_a = mean arterial pressure at maximal hyperemia; and $Q^N = P_a - P_v/R$, where Q^N = normal maximal myocardial blood flow. The fractional flow reserve (FFR) is defined as Q^S/Q^N, where Q^S = maximal flow through the stenotic vessel; therefore,

$$FFR = \frac{P_d - P_v/R}{P_a - P_v/R}.$$

If P_v is normal, it can be eliminated. Hence,

$$FFR_{myo} = \frac{P_d - P_v}{P_a - P_v} \approx \frac{P_d}{P_a}, \quad [A1]$$

where FFR_{myo} = myocardial fractional flow reserve;

$$FFR_{cor} = \frac{P_d - P_w}{P_a - P_w}, \quad [A2]$$

where FFR_{cor} = coronary fractional flow reserve; and P_w = mean distal coronary pressure at coronary artery occlusion; and

$$Q_c/Q^N = FFR_{myo} - FFR_{cor}, \quad [A3]$$

where Q_c/Q^N = fractional collateral flow, and Q_c = maximal flow through collateral channels.

*From Pijls et al. (5), with permission.

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