

Assessment of Coronary Flow Reserve by Adenosine Transthoracic Echocardiography: Validation with Intracoronary Doppler

Hildick-Smith, David J. R. MD; Maryan, Richard MD; Shapiro, Leonard M. MD

Objective: Data on the accuracy of transthoracic echocardiographic (TTE) analysis of coronary flow reserve are scarce. We compared coronary flow reserve measurements assessed using TTE with those achieved using the gold standard of intracoronary Doppler. Methods: Twenty-one patients admitted for elective coronary angioplasty to the circumflex or left anterior descending (LAD) coronary artery underwent TTE immediately before angioplasty, both at rest and during intravenous administration of adenosine 140 μ g/kg/min. Transthoracic images of distal LAD coronary diameter and coronary flow were obtained in 14 patients (66%). These patients then underwent intracoronary Doppler analysis of coronary flow reserve in the distal LAD coronary artery. In 1 patient with a proximal LAD artery lesion, the narrowing could not be crossed with the Doppler guidewire. Paired data on coronary flow reserve were therefore available in 13 patients. Results: Patients were aged 61.7 \pm 8.3 years. Ten were men. Body mass index was 26.3 \pm 4.6 kg/m². Resting distal LAD artery blood flow was 18.4 \pm 9.0 mL/min assessed by TTE versus 17.6 \pm 8.1 mL/min by intracoronary Doppler. Hyperemic flow was 36.3 \pm 23.4 versus 33.1 \pm 19.2 mL/min, respectively. Coronary flow reserve was therefore 1.89 \pm 0.66 by TTE compared with 1.83 \pm 0.62 by intracoronary Doppler. Limits of agreement for coronary flow reserve were -0.28 to +0.44, well within boundaries of clinical acceptability. Conclusion: Transthoracic echocardiography is capable of providing accurate data on coronary flow reserve in the distal LAD coronary artery. As a truly noninvasive modality, this technique offers advantages over traditional invasive procedures.

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Left Ventricular Systolic Unloading and Augmentation of Intracoronary Pressure and Doppler Flow During Enhanced External Counterpulsation.

Michaels, Andrew D. MD; Accad, Michel MD; Ports, Thomas A. MD; Grossman, William MD

Background: Enhanced external counterpulsation (EECP) is a noninvasive, pneumatic technique that provides beneficial effects for patients with chronic, symptomatic angina pectoris. However, the physiological effects of EECP have not been studied directly. We examined intracoronary and left ventricular hemodynamics in the cardiac catheterization laboratory during EECP. Methods and Results: Ten patients referred for diagnostic evaluation underwent left heart catheterization and coronary angiography from the radial artery. At baseline and then during EECP, central aortic pressure, intracoronary pressure, and intracoronary Doppler flow velocity were measured using a coronary catheter, a sensor-tipped high-fidelity pressure guidewire, and a Doppler flow guidewire, respectively. Similar to changes in aortic pressure, EECP resulted in a dramatic increase in diastolic (71 \pm 10 mm Hg at baseline to 137 \pm 21 mm Hg during EECP; +93P <0.0001) and mean intracoronary pressures (88 \pm 9 to 102 \pm 16 mm Hg; +16P =0.006) with a decrease in systolic pressure (116 \pm 20 to 99 \pm 26 mm Hg; -15P =0.002). The intracoronary Doppler measure of average peak velocity increased from 11 \pm 5 cm/s at baseline to 23 \pm 5 cm/s during EECP (+109P =0.001). The TIMI frame count, a quantitative angiographic measure of coronary flow, showed a 28% increase in coronary flow during EECP compared with baseline (P =0.001). Conclusions: EECP unequivocally and significantly increases diastolic and mean pressures and reduces systolic pressure in the central aorta and the coronary artery. Coronary artery flow, determined by both Doppler and angiographic techniques, is increased during EECP. The combined effects of systolic unloading and increased coronary perfusion pressure provide evidence that EECP may serve as a potential mechanical assist device.

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Normal Coronary Flow Reserve After Arterial Switch Operation for Transposition of the Great Arteries: An Intracoronary Doppler Guidewire Study.

Oskarsson, Gylfi MD; Pesonen, Erkki MD, PhD; Munkhammar, Peter MD; Sandstrom, Staffan MD; Jogi, Peeter MD

Background: Recent studies performed with positron emission tomography have suggested that coronary flow reserve (CFR) is moderately to severely reduced after the arterial switch operation (ASO). These findings are of great concern but have not been confirmed by other methods. Methods and Results: Eleven symptom-free children were studied between 4 and 11 (median 6.0) years after the ASO. Flow velocity in the left anterior descending (LAD) and right coronary arteries (RCA) was measured with a 0.014-inch Doppler FloWire (Cardiometrics) before and after intracoronary injection of adenosine (0.5 [μ]g/kg) and nitroglycerin (5 [μ]g/kg). CFR was defined as the ratio of hyperemic to basal average peak velocity (APV). The median (range) CFR in the LAD was 3.7 (3.0 to 4.8) and 3.4 (2.9 to 4.8) in the RCA. The increase in APV after intracoronary injection of nitroglycerin was 300% (240% to 420%) in the LAD and 260% (190% to 460%) in the RCA. APV at rest was 15.0 (14.0 to 21.0) cm/s in the LAD and 16.0 (9.6 to 30.0) cm/s in the RCA. A linear relation was found between right ventricular systolic pressure and resting APV in the RCA ($r = 0.77$, $P = 0.0056$), and between resting APV and CFR ($r = -0.61$, $P < 0.05$) in the RCA. Conclusions: The CFR and coronary vasoreactivity to nitroglycerin in children treated for transposition of the great arteries with the ASO was within normal limits. Increased right ventricular pressure and myocardial hypertrophy can cause increased resting coronary flow velocity in the RCA and affect CFR negatively.

Noninvasive Assessment of Coronary Flow Velocity and Coronary Flow Velocity Reserve in the Right Coronary Artery by Transthoracic Doppler Echocardiography: Comparison with Intracoronary Doppler Guidewire.

Ueno, Yoshiki MD; Nakamura, Yasuyuki MD; Takashima, Hiroyuki MD; Kinoshita, Masahiko MD; Soma, Akira MD

The aim of this study was to evaluate whether coronary flow velocity (CFV) and coronary flow velocity reserve (CFVR) in the posterior descending right coronary artery can be reliably measured by transthoracic Doppler echocardiography (TTDE). In 17 patients, CFV in the posterior descending right coronary artery was measured with TTDE at the time of Doppler guidewire examination. CFV was measured by both methods at baseline and under hyperemic conditions. TTDE data were obtained for 12 patients. CFV and CFVR by TTDE show a good correlation with those obtained by the Doppler guidewire method (average diastolic peak velocity: $r = 0.98$, $y = 0.85x + 5.26$; diastolic peak velocity: $r = 0.97$, $y = 0.94x + 3.39$; CFVR: $r = 0.97$, $y = 0.87x + 0.56$). CFV and CFVR in the posterior descending right coronary artery obtained noninvasively by TTDE accurately reflect these values obtained by the invasive Doppler guidewire method. (J Am Soc Echocardiogr 2002;15:1074-9.)

Transthoracic Doppler assessment of coronary flow velocity reserve in children with Kawasaki disease: comparison with coronary angiography and thallium-201 imaging.

Hiraishi S, Hirota H, Horiguchi Y, Takeda N, Fujino N, Ogawa N, Nakahata Y.

OBJECTIVES: The purpose of this study was to determine the feasibility of coronary flow velocity reserve (CFVR) measurement by transthoracic Doppler echocardiography (TTDE) in children with Kawasaki disease (KD). **B**ACKGROUND: Doppler-derived CFVR is a reliable marker predicting the presence of myocardial ischemia. **M**ETHODS: We studied 49 patients (median age 11 years) with KD. The CFVR was calculated as the ratio of hyperemic to basal peak (peak CFVR) and mean (mean CFVR) diastolic flow velocities in the posterior descending coronary artery (PD) and left anterior descending coronary artery (LAD). The CFVR measurements by TTDE were compared with the results of coronary angiography, thallium-201 (TI-201) single-photon emission computed tomography (SPECT), and intracoronary Doppler study. **R**ESULTS: The CFVR measurements by TTDE were obtained in 92 (94%) of 98 vessels of the PD and LAD in 49 study patients. Both peak and mean CFVRs for 21 stenotic vessels were significantly smaller than those for 35 normal vessels and for 20 vessels with aneurysmal lesions ($p < 0.0001$). Peak and mean CFVR < 2.0 predicted significant coronary stenosis, as determined by coronary angiography, with sensitivities and specificities of 89% and 96% and 89% and 97%, respectively. Also, both peak and mean CFVRs were correlated with reversible perfusion defects on TI-201 SPECT (agreement 80 kappa 0.4). The correlation between peak and mean CFVRs determined by the TTDE and intracoronary Doppler studies in 36 vessels of 23 patients were 0.76 and 0.80, respectively. **C**ONCLUSIONS: The CFVR measured by TTDE predicts the presence of significant coronary stenosis of either the right coronary artery or LAD, as well as myocardial ischemia of these territories in children with KD.

Coronary Doppler measurements do not predict progression of cardiac allograft vasculopathy: analysis by serial intracoronary Doppler, dobutamine stress echocardiography, and intracoronary ultrasound.

Konig A, Spes CH, Schiele TM, Rieber J, Stempfle HU, Meiser B, Theisen K, Mudra H, Reichart B, Klauss V.

Coronary flow velocity reserve (CFVR) (maximum/baseline flow velocity, 16 microg adenosine) was compared with dobutamine stress echocardiography (DSE) (5 to 40 microg/kg/min) to assess the progression of angiographically silent cardiac allograft vasculopathy (CAV). As a reference for the morphologic assessment of CAV, serial intracoronary ultrasound (ICUS) measurements were performed. An increase in CFVR could be observed in all transplant patients despite morphologic or functional progression of CAV or non-progressive CAV as assessed by ICUS or DSE. Thus, serial intracoronary Doppler flow analysis is not useful to predict morphologic or functional progression of CAV.

Catheter Cardiovasc Interv 2002 Feb;55(2):255-9

Simultaneous intracoronary pressure and Doppler guidewires to assess coronary stenosis: if one is enough, are two too much?

Ruiz-Salmeron RJ, Goicolea J, Sanmartin M, Mantilla R, Sterling J, Romeo D.

We report a potential source of erroneous estimation of stenosis severity by pressure guidewire assessment. Simultaneous introduction of pressure and Doppler guidewires can lead to an overestimation of stenosis pressure gradient in the evaluation of intermediate stenosis.

Can adenosine triphosphate induce maximal hyperemic response in patients with impaired coronary microcirculation?: comparison of hyperemic response to adenosine triphosphate administered by intravenous and by intracoronary injection using Doppler guide wire

Yanagi S, Hirota K, Nagae K, Abe Y, Hasegawa T, Okada M, Ota T, Yoshikawa J.

OBJECTIVES: This study compared the hyperemic responses to adenosine triphosphate (ATP) administered by intravenous and by intracoronary injection in patients with impaired coronary microcirculation. **METHODS:** The hyperemic responses to intravenous and intracoronary administration of ATP in 107 patients (mean age 63 +/- 10 years, 77 males, 30 females) with impaired coronary circulation [including myocardial infarction (n = 68), cardiomyopath (n = 20) and diabetes mellitus (n = 11)] were compared by measurement of coronary flow reserve (CFR) using the Doppler guide wire. Patients with chest pain syndrome were used as the normal controls. The coronary blood flow velocity was measured at rest and during peak hyperemic responses to intravenous infusion (150 micrograms/kg/min) and intracoronary infusion of ATP (50 micrograms in the left coronary artery, 25 micrograms in the right coronary artery). The CFR was calculated as the ratio of averaged peak velocity during hyperemia to baseline averaged peak velocity. **RESULTS:** The CFR after intravenous administration of ATP (CFR_{i.v.}) was well correlated with CFR by intracoronary administration of ATP (CFR_{ic}) (r = 0.77, p < 0.001). However, the CFR_{i.v.} was also inversely correlated with the ratio of CFR_{ic} to CFR_{i.v.} (CFR_{ic/i.v.}) (r = -0.36, p < 0.001). There were no relationships between the changes of hemodynamic parameters (blood pressure and heart rate) induced by ATP and CFR_{ic/i.v.} A lower CFR_{i.v.} of less than 2.0 provided significantly greater CFR_{ic/i.v.} than that of CFR_{i.v.} greater than 2.0. **CONCLUSIONS:** The maximal hyperemic response of coronary artery was not always induced by conventional intravenous administration of ATP, especially in patients with lower CFR than 2.0. High dose of intravenous ATP and/or intracoronary ATP should be administered in patients with lower CFR to attain maximum hyperemia in the impaired coronary circulation

Measurement of fractional and coronary flow reserve using dual sensor guide wire

Shindo N, Tanaka N, Takeda K, Hiraide D, Amaya K, Kobori Y, Takazawa K, Yamashina A.

OBJECTIVES: Fractional flow reserve and coronary flow reserve (CFR) are indices of the severity of coronary artery stenosis influenced by both epicardial and microcirculatory dysfunction. The CFR was measured using the new pressure guide wire with thermal sensor (dual sensor guide wire) on the basis of the thermodilution principle (CFR-thermo), and compared to the CFR as measured by the Doppler method (CFR-Doppler), and the relationships were evaluated between CFR-thermo, fractional flow reserve and stress myocardial scintigraphy. **METHODS AND RESULTS:** CFR-thermo and CFR-Doppler were measured in 14 patients (20 vessels) by the dual sensor guide wire and Doppler guide wire, respectively. A significant positive correlation was found between CFR-Doppler and CFR-thermo ($y = 0.80x + 0.10$, $r = 0.70$, $p < 0.0001$). Stress myocardial perfusion single photon emission computed tomography (SPECT) was performed before coronary angiography in 56 patients (70 vessels), and then fractional flow reserve and CFR-thermo were measured using the dual sensor guide wire. CFR-thermo and fractional flow reserve were significantly lower in coronary segments with positive SPECT image ($n = 32$) than in coronary segments with negative SPECT image ($n = 38$) (1.29 ± 0.24 vs 1.96 ± 0.69 , $p < 0.0001$; 0.61 ± 0.13 vs 0.85 ± 0.09 , $p < 0.0001$). The cut-off values of CFR-thermo and fractional flow reserve for detection of ischemic segments demonstrated by SPECT image were 1.47 and 0.76, respectively. The sensitivity and specificity for detecting ischemia were 78% and 84% for CFR-thermo, 88% and 92% for fractional flow reserve, respectively. **CONCLUSIONS:** A significant correlation was found between CFR-thermo measured by the thermodilution principle using the dual sensor guide wire and CFR measured by the Doppler method. CFR-thermo measured by the dual sensor guide wire may be useful to detect myocardial ischemia.

Direct assessment of coronary steal and associated changes of collateral hemodynamics in chronic total coronary occlusions.

Werner GS, Figulla HR.

BACKGROUND: Coronary steal can occur in collateral-dependent myocardium during pharmacologically induced vasodilation. This study assessed coronary steal invasively in chronic total coronary occlusions (TCOs). **METHODS AND RESULTS:** In 35 consecutive patients with a percutaneous transluminal coronary angioplasty of a TCO (duration >4 weeks), coronary flow velocity (APV) by a Doppler wire and distal pressure (P(D)) by a pressure wire were assessed in the collateral-dependent vascular bed before dilatation. Indexes of peripheral resistance (R(P)) and for the collateral pathway, including the donor artery segment (R(CP)), were calculated. Changes of these parameters were assessed during intravenous adenosine (140 microg x kg(-1) x min(-1)). Adenosine caused a decrease of APV, ie, coronary steal, in 13 patients (37%; group S), an increase in 11 patients (group R), and no change in 11 patients (group N). Angiographic analysis of collateral pathways showed no difference between the groups, except that in group S all collateral connections were continuously visible but no large collaterals (>0.5 mm) were found. In group N, collaterals were least developed. The increase of APV in group R was associated with a decrease of R(P), whereas R(CP) remained unchanged. In contrast, group S showed no change in R(P) but a significant increase of R(CP), indicating an increased resistance of the donor segment. **CONCLUSIONS:** Coronary steal is observed in about one third of TCOs and is associated with specific hemodynamic changes of R(P) and R(CP). Steal occurred only with well-developed angiographically visible collaterals but not with very large collaterals.

The diastolic flow -pressure gradient relation in coronary stenoses in humans.

Marques KM, Spruijt HJ, Boer C, Westerhof N, Visser CA, Visser FC.

OBJECTIVES: We assessed the feasibility and reproducibility of the instantaneous diastolic coronary flow velocity-pressure gradient relation to characterize different degrees of coronary stenoses. **B**ACKGROUND: Assessment of the hemodynamic significance of coronary stenoses can be difficult. Using sensor-tipped guidewires, various physiologic indexes can be determined in the catheterization laboratory. Each of the current methods, however, has limitations. **M**ETHODS: After positioning a Doppler flow wire and a pressure wire distal of a coronary stenosis, the flow velocity signals and the proximal and distal pressure were sampled simultaneously, at baseline and after intracoronary administration of adenosine. The instantaneous diastolic flow velocity and pressure gradient of single cardiac cycles at baseline, at maximal and intermediate hyperemia were plotted. Data were fitted with a regression line using the equation: $\Delta P = 0 + kv + Sv(2)$. Measurements were performed in 11 normal coronary arteries, 20 intermediate stenoses and in 7 severe stenoses before and after percutaneous transluminal coronary angioplasty plus stenting. **R**ESULTS: We found significant differences between normal coronary arteries, intermediate and severe stenoses. Percutaneous transluminal coronary angioplasty nearly normalized the highly abnormal flow-pressure gradient relation in the severe stenoses. A high degree of reproducibility was observed. In 3% of the measurements, analysis was not possible due to the occurrence of pressure drift or bad flow velocity signals. **C**ONCLUSIONS: It is feasible to assess the diastolic flow velocity-pressure gradient relation over a wide range of stenoses. It characterizes the hemodynamics of epicardial coronary stenoses and allows discrimination between normal coronary arteries, intermediate and severe stenoses.

IC DOPPLER and PRESSURE

1. Assessment of Coronary Flow Reserve by Adenosine Transthoracic Echocardiography: Validation with Intracoronary Doppler. [Article]

Hildick-Smith, David J. R. MD; Maryan, Richard MD; Shapiro, Leonard M. MD

J Am Soc Echocardiogr 2002;15:984-90.

2. Left Ventricular Systolic Unloading and Augmentation of Intracoronary Pressure and Doppler Flow During Enhanced External Counterpulsation. [Report]

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Journal of the American Society of Echocardiography. 15(10 (Part 1)):1074-1079, October 2002.

5. Transthoracic Doppler assessment of coronary flow velocity reserve in children with Kawasaki disease: comparison with coronary angiography and thallium-201 imaging.

Hiraishi S, Hirota H, Horiguchi Y, Takeda N, Fujino N, Ogawa N, Nakahata Y.

J Am Coll Cardiol 2002 Nov 20;40(10):1816-24

6. Coronary Doppler measurements do not predict progression of cardiac allograft vasculopathy: analysis by serial intracoronary Doppler, dobutamine stress echocardiography, and intracoronary ultrasound.

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J Heart Lung Transplant 2002 Aug;21(8):902-5

7. Simultaneous intracoronary pressure and Doppler guidewires to assess coronary stenosis: if one is enough, are two too much?

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8. Can adenosine triphosphate induce maximal hyperemic response in patients with impaired coronary microcirculation?: comparison of hyperemic response to adenosine triphosphate administered by intravenous and by intracoronary injection using Doppler guide wire.

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J Cardiol 2002 Jan;39(1):1-10

9. Measurement of fractional and coronary flow reserve using dual sensor guide wire

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J Cardiol 2002 Nov;40(5):189-97

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Werner GS, Figulla HR.

Circulation 2002 Jul 23;106(4):435-40

11. The diastolic flow-pressure gradient relation in coronary stenoses in humans.

Marques KM, Spruijt HJ, Boer C, Westerhof N, Visser CA, Visser FC.

J Am Coll Cardiol 2002 May 15;39(10):1630-6

Am Coll Cardiol , 2001;37(5):1359-66

Effects of mental stress on coronary epicardial vasomotion and flow velocity in coronary artery disease: relationship with hemodynamic stress responses.

Kop WJ, Krantz DS, Howell RH, Ferguson MA, Papademetriou V, Lu D, Popma JJ, Quigley JF, Vernalis M, Gottdiener JS.

OBJECTIVES: This study examines the prevalence and hemodynamic determinants of mental stress-induced coronary vasoconstriction in patients undergoing diagnostic coronary angiography. **BACKGROUND:** Decreased myocardial supply is involved in myocardial ischemia triggered by mental stress, but the determinants of stress-induced coronary constriction and flow velocity responses are not well understood. **METHODS:** Coronary vasomotion was assessed in 76 patients (average age 59.9 +/- 10.4 years; eight women). Coronary flow velocity responses were assessed in 20 of the 76 patients using intracoronary Doppler flow. Repeated angiograms were obtained after a baseline control period, a 3-min mental arithmetic task and administration of 200 microg intracoronary nitroglycerin. Arterial blood pressure (BP) and heart rate assessments were made throughout the procedure. **RESULTS:** Mental stress resulted in significant BP and heart rate increases ($p < 0.001$). Coronary constriction (>0.15 mm) was observed in 11 of 59 patients with coronary

artery disease (CAD) (18.6%). Higher mental stress pressor responses were associated with more constriction in diseased segments ($r_{\Delta SBP} = -0.26$, $r_{\Delta DBP} = -0.30$, $r_{\Delta MAP} = -0.29$; $p < 0.05$) but not with responses in nonstenotic segments. The overall constriction of diseased segments was not significant ($p > 0.10$), whereas a small but significant constriction occurred in nonstenotic segments ($p = 0.04$). Coronary flow velocity increased in patients without CAD (32.2%; $p = 0.008$), but not in patients with CAD (6.4%; $p = ns$). Cardiovascular risk factors were not predictive of stress-induced vasomotion in patients with CAD. CONCLUSIONS: Coronary vasoconstriction in angiographically diseased arteries varies with hemodynamic responses to mental arousal. Coronary flow responses are attenuated in CAD patients. Thus, combined increases in cardiac demand and concomitant reduced myocardial blood supply may contribute to myocardial ischemia with mental stress.

J Am Coll Cardiol 2001 May;37(6):1565-70

Bradykinin stimulates the release of tissue plasminogen activator in human coronary circulation: effects of angiotensin-converting enzyme inhibitors.

Minai K, Matsumoto T, Horie H, Ohira N, Takashima H, Yokohama H, Kinoshita M.

OBJECTIVES: The goal of this study was to determine: 1) whether bradykinin (BK) directly stimulates tissue plasminogen activator (tPA) secretion in human coronary circulation, and 2) whether angiotensin-converting enzyme (ACE) inhibition favorably alters the fibrinolytic balance regulated by BK. **BACKGROUND:** Bradykinin is a potent stimulator of tPA secretion in endothelial cells; however, the effect of BK on tPA release in the human coronary circulation has not been studied. **METHODS:** Fifty-six patients with atypical chest pain were randomly assigned to two groups: 25 patients were treated with the ACE inhibitor enalapril (ACE inhibitor group), and 31 were not treated with ACE inhibitors (non-ACE inhibitor group). Graded doses of BK (0.2, 0.6, 2.0 microg/min), acetylcholine (ACh) (30 microg/min) and papaverine (PA) (12 mg) were administered into the left coronary artery. Coronary blood flow (CBF) was evaluated by Doppler flow velocity measurement. Blood samples were taken from the aorta (Ao) and the coronary sinus (CS). **RESULTS:** Bradykinin induced similar increases in CBF in both groups. The net tPA release induced by BK was dose-dependently increased in both groups, and the extent of that increase in the ACE inhibitor group was greater than that in the non-ACE inhibitor group. Bradykinin did not alter plasminogen activator inhibitor-1 (PAI-1) levels in the Ao or CS in either group. Neither ACh nor PA altered tPA levels or PAI-1 levels in either group. **CONCLUSIONS:** Intracoronary infusion of BK stimulates tPA release without causing any change in PAI-1 levels in the human

coronary circulation. In addition, this effect of BK is augmented by an ACE inhibitor.

Circulation, 2001;103(19):2339-45

Abnormal coronary flow velocity reserve after coronary intervention is associated with cardiac marker elevation.

Herrmann J, Haude M, Lerman A, Schulz R, Volbracht L, Ge J, Schmermund A, Wieneke H, von Birgelen C, Eggebrecht H, Baumgart D, Heusch G, Erbel R.

BACKGROUND: Residual reduction of relative coronary flow velocity reserve (rCVR) after successful coronary intervention has been related to microvascular impairment. However, the incidence of cardiac enzyme elevation as a surrogate marker of an underlying embolic myocardial injury in these cases has not been studied. **METHODS AND RESULTS:** A series of 55 consecutive patients with successful coronary stenting, periprocedural intracoronary Doppler analysis, and determination of creatine kinase (CK; upper limit of normal [ULN] for women 70 IU/L, for men 80 IU/L) and cardiac troponin T (cTnT; bedside test, threshold 0.1 ng/mL) before and 6, 12, and 24 hours after intervention were studied. Postprocedural rCVR was the only intracoronary Doppler parameter that independently correlated with cTnT ($r=-0.498$, $P<0.001$) and CK outcome ($r=-0.406$, $P=0.002$). Receiver operating characteristic analysis identified a postprocedural rCVR of 0.78 as the best discriminating value, with a sensitivity of 83.3% and 69.2% and a specificity of 79.1% and 76.2% for detection of cTnT and CK elevation, respectively. Stratified according to this cutoff value, the incidence of cTnT elevation was 52.6% in patients with ($n=19$) and 5.6% in patients without ($n=36$) a postprocedural rCVR <0.78 ($P<0.001$), associated with a CK elevation >1 times the ULN in 36.8% and 5.6% ($P=0.005$) of patients, respectively. **CONCLUSIONS:** Cardiac marker elevation can frequently be found after coronary procedures that are associated with a persistent reduction of rCVR, indicating procedural embolization of atherothrombotic debris with microvascular impairment and myocardial injury as a potential underlying mechanism.

J Am Coll Cardiol 2001;38(1):155-62

Assessment of flow velocity reserve by transthoracic Doppler echocardiography and venous adenosine

infusion before and after left anterior descending coronary artery stenting.

Pizzuto F, Voci P, Mariano E, Puddu PE, Sardella G, Nigri A.

OBJECTIVES: We sought to evaluate whether coronary flow velocity reserve (CFR) (the ratio between hyperemic and baseline peak flow velocity), as measured by transthoracic Doppler echocardiography during adenosine infusion, allows detection of flow changes in the left anterior descending coronary artery (LAD) before and after stenting. **BACKGROUND:** The immediate post-stenting evaluation of CFR by intracoronary Doppler has shown mixed results, due to reactive hyperemia and microvascular stunning. Noninvasive coronary Doppler echocardiography may be a more reliable measure than intracoronary Doppler. **METHODS:** Transthoracic Doppler echocardiography during 90-s venous adenosine infusion (140 microg/kg body weight per min) was used to measure CFR of the LAD in 45 patients before and 3.7 +/- 2 days after successful stenting, as well as in 25 subjects with an angiographically normal LAD (control group). **RESULTS:** Adequate Doppler spectra were obtained in 96% of the patients. Pre-stent CFR was significantly lower in patients than in control subjects (diastolic CFR: 1.45 +/- 0.5 vs. 2.72 +/- 0.71, $p < 0.01$; systolic CFR: 1.61 +/- 1.02 vs. 2.41 +/- 0.68, $p < 0.01$) and increased toward the normal range after stenting (diastolic CFR: 2.58 +/- 0.7 vs. 2.72 +/- 0.75, $p = \text{NS}$; systolic CFR: 2.43 +/- 1.01 vs. 2.41 +/- 0.52, $p = \text{NS}$). Diastolic CFR was often damped, suggesting coronary steal in patients with $>$ or $=90\%$ versus $<90\%$ LAD stenosis (0.86 +/- 0.23 vs. 1.69 +/- 0.43, $p < 0.01$). Coronary stenting normalized diastolic CFR in these two groups (2.45 +/- 0.77 and 2.64 +/- 0.69, respectively, $p = \text{NS}$), even though impaired diastolic CFR persisted in three of four patients with $>$ or $=90\%$ stenosis. Stenosis of the LAD was better discriminated by diastolic ($F = 49.30$) than systolic ($F = 12.20$) CFR (both $p < 0.01$). **CONCLUSIONS:** Coronary flow reserve, as measured by transthoracic Doppler echocardiography, is impaired in LAD disease; it may identify patients with $>$ or $=90\%$ stenosis; and it normalizes early after stenting, even in patients with $>$ or $=90\%$ stenosis.

Am Heart J , 2001;142(1):81-6

Value of coronary stenotic flow velocity acceleration on the prediction of long-term improvement in functional status after angioplasty.

Albertal M, Regar E, Piek JJ, Van Langenhove G, Carlier SG, Thury A, Sianos G, Boersma E, de Bruyne B, di Mario C, Serruys PW; Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) Study Group.

BACKGROUND: The coronary flow velocity acceleration at the stenotic site (SVA), defined as a $\geq 50\%$ increase in resting stenotic velocity when compared with the reference segment, has been shown to be highly sensitive and specific for the diagnosis of a hemodynamically significant stenosis. In this study, we describe the value of postprocedural SVA for the prediction of a lack of improvement in functional activity at long-term follow-up balloon angioplasty (BA). **METHODS:** We investigated the improvement in functional activity in patients undergoing single native vessel angioplasty and intracoronary Doppler (before BA, after BA, and again at 6-month follow-up) as part of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) I trial. Lack of improvement was defined as no change in Duke Activity Status Index (DASI) at 6-month follow-up, whereas SVA was defined as $\geq 50\%$ elevation in resting velocity at the treated area compared with the distal measurement. **RESULTS:** SVA was found more frequently in patients without improvement in DASI (45% vs 31%, $P = .03$). Similar percent diameter stenosis and coronary flow velocity reserve were observed in patients with and those without improvement in DASI at follow-up. By multivariate regression analysis, the presence of SVA ($P = .029$; odds ratio, 1.97; 95% confidence interval, 1.07 to 3.63) and an elevated DASI at baseline ($P < .001$; odds ratio, 1.05; 95% confidence interval, 1.03 to 1.07) were associated with a lack of improvement at follow-up. **CONCLUSIONS:** The detection of SVA was associated with failure of improvement in functional activity at follow-up after coronary intervention.

J Am Coll Cardiol , 2001;38(2):493-8

Tetrahydrobiopterin improves endothelial dysfunction in coronary microcirculation in patients without epicardial coronary artery disease.

Setoguchi S, Mohri M, Shimokawa H, Takeshita A.

OBJECTIVES: We aimed to determine whether intracoronary supplementation with nitric oxide (NO) synthase co-factor tetrahydrobiopterin (BH4) improves NO-dependent coronary microvascular dilation in patients with coronary risk factors but no significant organic stenosis. **BACKGROUND:** Impaired coronary microvascular dilator reserve attributable to endothelial dysfunction plays an important role in the regulation of coronary blood flow (CBF). **METHODS:** Fifteen patients were measured for CBF (Doppler-wire and quantitative

coronary angiography). Stimulated release of NO in the coronary microcirculation was evaluated by percent increase in CBF (%ACBF) at graded doses of intracoronary acetylcholine (1, 3, 10 and 30 microg/min). Measurements were repeated after intracoronary co-infusion of BH4 (4 mg/min) and acetylcholine. RESULTS: The patients were divided into two groups on the basis of CBF responses to acetylcholine: those with ?iminished?(%deltaCBF <300%, n = 8) and ?ormal?(%deltaCBF >300%, n = 7) flow responses. Tetrahydrobiopterin significantly ($p < 0.0001$) improved acetylcholine-induced increases in CBF in patients with diminished flow responses, but exerted no effect in those with normal flow responses. Among the 15 studied patients, the magnitude of flow improvement by BH4 was inversely correlated with baseline flow responses ($p < 0.02$). Microvascular dilator response to direct NO donor (isosorbide dinitrate) was not affected by BH4. CONCLUSIONS: We demonstrated for the first time that intracoronary BH4 improved acetylcholine-induced microvascular dilator responses in patients with endothelial dysfunction in vivo. Thus, supplementation with BH4 may be a novel therapeutic means to increase NO availability for patients with coronary microvascular disease

Catheter Cardiovasc Interv, 2001;53(4):459-63

Assessing coronary blood flow dynamics with the TIMI frame count method: comparison with simultaneous intracoronary Doppler and ultrasound.

Tanedo JS, Kelly RF, Marquez M, Burns DE, Klein LW, Costanzo MR, Parrillo JE, Hollenberg SM.

This study compared the TIMI frame count (TFC), which has been proposed as a method for quantifying coronary blood flow, with coronary flow and microvascular function measured with intracoronary Doppler and intracoronary ultrasound. Coronary blood flow volume was calculated from coronary blood velocity (by intracoronary Doppler) and lumen area (by intracoronary ultrasound) in the LAD in 46 post-heart transplant patients at baseline and after intracoronary adenosine. TFC correlated significantly with average peak coronary blood velocity ($r = -0.42$; $P = 0.004$) and coronary lumen area ($r = 0.39$; $P = 0.008$), but not with coronary blood flow volume ($r = -0.01$; $P = 0.96$) or the coronary flow reserve response to adenosine ($r = 0.09$; $P = 0.58$). In conclusion, TFC is a simple method of assessing coronary blood velocity but not volumetric flow. While TFC does not predict coronary flow reserve, as a measure of velocity it does provide an assessment of basal microvascular tone, information that is complementary to that afforded by flow reserve measurements.

Am Heart J , 2001;142(4):691-7

Increased heterogeneity of coronary perfusion in patients with early coronary atherosclerosis.

Wieneke H, Schmermund A, Ge J, Altmann C, Haude M, Von Birgelen C, Baumgart D, Dirsch O, Erbel R.

BACKGROUND: In patients with typical angina but angiographically normal coronary arteries, abnormal vasomotor function is assumed to be a major underlying cause. However, data on this issue are conflicting, and recent studies suggest that fluid dynamic abnormalities exist in these patients. The aim of the study was to evaluate whether early stages of atherosclerosis are characterized by alterations of baseline coronary hemodynamics and endothelium-independent vasomotion. Besides established intracoronary Doppler parameters, heterogeneity of perfusion was assessed and related to early signs of atherosclerosis as determined by electron-beam computed tomography (EBCT). **METHODS:** In 59 patients with typical angina and angiographically normal or near-normal coronary arteries, intracoronary Doppler measurements were performed in all 3 major coronary arteries. Baseline average peak velocity (bAPV) and hyperemic average peak velocity (hAPV) in response to intracoronary injection of adenosine were measured, and coronary flow velocity reserve (CFVR) was calculated. Heterogeneity was assessed as variability of bAPV, hAPV, and CFVR and was calculated as (STD/MEAN). 100. Doppler data were analyzed according to tertiles of the EBCT-derived Agatston calcium score (ie, score 0-1 [lowest tertile], 2-28 [medium tertile], and >28 [highest tertile]). **RESULTS:** The mean EBCT-derived Agatston calcium score was 49 +/- 107. No coronary calcium was observed in 17 (29%) patients. The mean values of bAPV, hAPV, and CFVR were not different between the calcium score tertiles. However, patients in the highest tertile had a significantly increased variability index of bAPV (29.6% +/- 11.6%) compared with patients in the lowest tertile (13.4% +/- 7.3%, $P < .0001$). Variability of CFVR was also increased in these patients (15.5% +/- 11.7% vs 10.5% +/- 4.0%, $P = .03$). **CONCLUSION:** These results indicate that early stages of atherosclerosis are characterized by microvascular abnormalities that do not uniformly affect the myocardium but are heterogeneous. The high variability of baseline coronary flow velocity with increasing coronary calcium suggests that in patients with early stages of atherosclerosis fluid dynamic effects may play a crucial role even in the absence of angiographically appreciable epicardial stenoses.

J Am Coll Cardiol, 2001 ;38(7):1866-71

Do beta-adrenergic blocking agents increase coronary flow reserve?

Billinger M, Seiler C, Fleisch M, Eberli FR, Meier B, Hess OM.

BACKGROUND: Beta-adrenergic blocking agents are the cornerstone in the treatment of coronary artery disease (CAD). The exact pathophysiologic mechanism is not clear but depends largely on the oxygen-sparing effect of the drug. Thus, the effect of metoprolol on coronary flow reserve and coronary flow velocity reserve (CFVR) was determined in patients with CAD. **METHODS:** Coronary blood flow velocity was measured with the Doppler flow wire in 23 patients (age: 56 +/- 10) undergoing percutaneous transluminal coronary angioplasty for therapeutic reasons. Measurements were carried out at rest, after 1-min vessel occlusion (postischemic CFVR) as well as after intracoronary adenosine (pharmacologic CFVR) before and after 5 mg intravenous metoprolol. In a subgroup (n = 15), absolute flow was measured from coronary flow velocity multiplied by coronary cross-sectional area. **RESULTS:** Rate-pressure product decreased after metoprolol from 9.1 to 8.0 x 10(3) mm Hg/min (p < 0.001). Pharmacologic CFVR was 2.1 at rest and increased after metoprolol to 2.7 (p = 0.002). Likewise, postischemic CFVR increased from 2.6 to 3.3 (p < 0.001). Postischemic CFVR was significantly higher than pharmacologic CFVR before as well as after metoprolol. Coronary vascular resistance decreased after metoprolol from 3.4 +/- 2.0 to 2.3 +/- 0.7 mm Hg x s/cm (p < 0.02). **CONCLUSIONS:** The following conclusions were drawn from this study. Metoprolol is associated with a significant increase in postischemic and pharmacologic CFVR. However, postischemic CFVR is significantly higher than pharmacologic CFVR. The increase in CFVR by metoprolol can be explained by a reduction in vascular resistance. The increase in CFVR (= increased supply) and the reduction in oxygen consumption (= decreased demand) after metoprolol explain the beneficial effect of this beta-blocker in patients with CAD.

Circulation , 2001;104(16):1917-22

Related Articles, Books, LinkOut

Fractional flow reserve compared with intravascular ultrasound guidance for optimizing stent deployment.

Fearon WF, Luna J, Samady H, Powers ER, Feldman T, Dib N, Tuzcu EM, Cleman MW, Chou TM, Cohen DJ, Ragosta M, Takagi A, Jeremias A, Fitzgerald PJ, Yeung AC, Kern MJ, Yock PG.

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BACKGROUND: Determination of fractional flow reserve (FFR) has been proposed as a means to assess stent deployment. In this prospective, multicenter trial, we evaluate the use of FFR to optimize stenting by comparing it with standard intravascular ultrasound (IVUS) criteria. **METHODS AND RESULTS:** Eighty-four stable patients with isolated coronary lesions underwent coronary stent deployment starting at 10 atm and increased serially by 2 atm until the FFR was ≥ 0.94 or 16 atm was achieved. IVUS was then performed. FFR was measured with a coronary pressure wire with intracoronary adenosine to induce hyperemia. The diagnostic characteristics of an FFR < 0.94 to predict suboptimal stent expansion by IVUS, defined in both absolute and relative terms, were calculated. Over a range of IVUS criteria, the highest sensitivity, specificity, and predictive accuracy of FFR were 80%, 30%, and 42%, respectively. Receiver operator characteristic analysis defined an optimal FFR cut point at ≥ 0.96 ; at this threshold, the sensitivity, specificity, and predictive accuracy of FFR were 75%, 58%, and 62%, respectively (P=0.03 for comparison of predictive accuracy, P=0.01 for concordance between FFR and IVUS). The negative predictive value was 88%. Significantly better diagnostic performance was achieved in a subgroup that received higher doses (>30 microgram) of intracoronary adenosine during pressure measurements, suggesting that FFR might be overestimated in the other group. **CONCLUSIONS:** A fractional flow reserve < 0.96 , measured after stent deployment, predicts a suboptimal result based on validated intravascular ultrasound criteria; however, an FFR ≥ 0.96 does not reliably predict an optimal stent result. Higher doses of intracoronary adenosine than previously used to measure FFR improve these results.

Journal of the American College of Cardiology, 1998;32:1272-1279

Coronary collateral quantitation in patients with coronary artery disease using intravascular flow velocity or pressure measurements

Christian Seiler, Martin Fleisch, Ali Garachemani, Bernhard Meier

Objectives. This study evaluated two methods for the quantitative measurement of collaterals using intracoronary (IC) blood flow velocity or pressure measurements.

Background. The extent of myocardial necrosis after coronary artery occlusion is substantially influenced by

the collateral circulation. So far, qualitative methods have been available to assess the human coronary collateral circulation, thus restraining the conclusive investigation of, for example, therapies to promote collateral development.

Methods. Fifty-one patients with a coronary artery stenosis to be treated by percutaneous transluminal coronary angioplasty (PTCA) were investigated using IC PTCA guidewire-based Doppler and pressure sensors positioned distal to the stenosis. Simultaneous measurements of aortic pressure, IC velocity and pressure distal to the stenosis during and after PTCA provided the variables for calculating collateral flow indices (CFI_v and CFI_p) that express collateral flow as a fraction of flow via the patent vessel. Both CFI_v and CFI_p were compared with conventional methods for collateral assessment, among them ST-segment changes >1 mm on IC and surface electrocardiogram (ECG) at PTCA. Also, CFI_v and CFI_p were compared with each other.

Results. In 11 patients without ECG signs of ischemia during PTCA (sufficient collaterals), relative collateral flow amounted to 46% as determined by Doppler and pressure wire. Patients with insufficient collaterals (n = 40) had relative collateral flow values of 18%. Using a threshold of CFI = 30%, sufficient and insufficient collaterals could be diagnosed with 100% sensitivity and 93% specificity by IC Doppler, and 75% sensitivity and 92% specificity by IC pressure measurements. The agreement between Doppler and pressure measurements was good: $CFI_v = 0.08 + 0.8 CFI_p$, $r = 0.80$, $p = 0.0001$.

Conclusions. Intracoronary flow velocity or pressure measurements during routine PTCA represent an accurate and, at last, quantitative method for assessing the coronary collateral circulation in humans.

Journal of the American College of Cardiology, 2000;35:1835-1841

Coronary flow velocity immediately after primary coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction

Tetsuzo Wakatsuki, Masato Nakamura, Taro Tsunoda, Hiroko Toma, Toshiyuki Degawa, Takashi Oki, Tetsu Yamaguchi

OBJECTIVES

The purpose of this study was to examine the relationship between the pattern of coronary blood flow velocity immediately after successful primary stenting and the recovery of left ventricular (LV) wall motion in patients with acute myocardial infarction (AMI).

BACKGROUND

It is difficult to predict the recovery of LV wall motion immediately after direct angioplasty in AMI. Recent reports indicate that dysfunctional coronary microcirculation is an important determinant of prognosis for AMI patients after successful reperfusion.

METHODS

We measured left anterior descending coronary flow velocity variables using a Doppler guide wire immediately after successful primary stenting in 31 patients with their first anterior AMI. The patients were divided into two groups: those with and those without early systolic reverse flow (ESRF). Changes in LV regional wall motion (RWM) and ejection fraction (EF) at admission and at discharge were compared between the two groups. Coronary flow velocity variables immediately after primary stenting were compared with changes in left ventriculographic indexes.

RESULTS

The change in RWM was significantly greater in the non-ESRF group than it was in the ESRF group (0.9 ± 0.7 vs. -0.1 ± 0.3 standard deviation/chord, respectively, $p < 0.001$). The change in EF was also significantly greater in the non-ESRF group than it was in the ESRF group (10 ± 10 vs. $1 \pm 6\%$, respectively, $p < 0.05$). In the non-ESRF group (diastolic to systolic velocity ratio [DSVR] < 3.0), the DSVR correlated positively with the change in RWM ($r = 0.60$, $p < 0.005$, $n = 24$) and the change in EF ($r = 0.52$, $p < 0.01$).

CONCLUSIONS

The coronary flow velocity pattern measured immediately after successful primary stenting is predictive of the recovery of regional and global LV function in patients with AMI.

Circulation, 1998 ;98: 2133-2140

Immediate and Long-Term Effect of Balloon Angioplasty or Stent Implantation on the Absolute and Relative Coronary Blood Flow Velocity Reserve

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Background-There is controversy regarding the immediate and long-term effects of PTCA on the coronary flow reserve.

Methods and Results-A total of 54 patients with 1-vessel disease and normal left ventricular function were studied after balloon angioplasty ($n=34$) or stent implantation ($n=20$). Distal coronary blood flow velocity reserve (CFR) was defined as the ratio of adenosine-induced hyperemic versus baseline blood flow velocity

with a 0.014-in Doppler guidewire. The relative CFR was defined as the ratio of the distal CFR and the reference CFR measured in the normal adjacent coronary artery. Hemodynamic and angiographic measurements were performed before and directly after balloon angioplasty or stent implantation and at 6-month follow-up. CFR after PTCA ≤ 2.5 was defined as an impaired CFR. Immediately after PTCA, CFR improved toward the range of the reference artery CFR. In both the balloon-treated and the stent-treated groups, initial high CFR values decreased and impaired CFR values increased at follow-up toward the values of the reference CFR in patients without restenosis. Impaired CFR after balloon angioplasty (33%) or stent implantation (58%) in patients without restenosis was related to an increased baseline flow velocity that normalized at follow-up. Patients with an increase of CFR after stenting were characterized by an unaltered baseline flow velocity and an increased adenosine-induced hyperemic flow velocity.

Conclusions-An impaired CFR (≤ 2.5) is a frequent finding after balloon angioplasty or stent implantation as a result of a high baseline flow velocity. Normalization of impaired CFR at follow-up in patients without restenosis was associated with a decline of the baseline flow velocity after both balloon angioplasty and stent implantation, supporting the contention that this phenomenon relates to a slow recovery of autoregulation of the microvascular bed.

J Am Coll Cardiol ,1998;31:526-33

Which Variable of Stenosis Severity Best Describes the Significance of an Isolated Left Anterior Descending Coronary Artery Lesion? : Correlation Between Quantitative Coronary Angiography, Intracoronary Doppler Measurements and High Dose Dipyridamole Echocardiography

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Objectives. This study sought to investigate the angiographic or intracoronary Doppler variables of stenosis severity that best correlate with the results of dipyridamole echocardiography.

Background. Quantitative coronary angiography and intracoronary Doppler flow velocity assessments are the commonly used techniques for the objective identification of significant coronary artery stenosis.

Methods. Thirty patients with an isolated lesion of the left anterior descending coronary artery (LAD) were studied by means of on-line quantitative coronary arteriography, intracoronary Doppler flow velocity measurements and dipyridamole echocardiography 6 months after percutaneous transluminal coronary

angioplasty. The quantitative arteriographic analyses were performed on-line; post-stenotic Doppler flow velocities were measured at baseline and after adenosine infusion. Angiographic and Doppler measurements were compared with the corresponding dipyridamole echocardiographic data and analyzed by discriminant analysis.

Results. The dipyridamole echocardiographic response was positive in 11 patients (37%). The best cutoff values for predicting an abnormal echocardiographic response were 1) stenotic flow reserve of 2.8 ($p = 0.0001$); 2) 59% diameter stenosis ($p = 0.0001$); 3) minimal lumen diameter of 1.35 mm ($p = 0.001$); 4) coronary flow reserve of 2.0 ($p = 0.0002$); and 5) maximal peak velocity of 60 cm/s during hyperemia ($p = 0.04$). Multivariate analysis identified stenotic flow reserve as the only independent predictor of ischemia during dipyridamole echocardiography.

Conclusions. Stenotic flow reserve is the variable that best describes the functional significance of an isolated LAD lesion, and a value of 2.8 is the best predictor of a positive dipyridamole echocardiographic response. Furthermore, angiographic variables of stenosis severity relate to echocardiographic test results better than intracoronary Doppler variables.

Summary

Circulation. 1998;98:40-46

Improved Assessment of Coronary Stenosis Severity Using the Relative Flow Velocity Reserve

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Background-Myocardial fractional flow reserve (FFR) is based on pressure measurements. We have now sought to establish a Doppler-based concept of relative flow velocity reserve (RFVR) for the functional assessment of stenosis severity in epicardial coronary arteries. A clear threshold value to discriminate the functional severity of a coronary stenosis does not exist for coronary flow velocity reserve (CVR) based on intracoronary Doppler measurements. In contrast, the concept of FFR, which is based on intracoronary pressure measurements, has been extensively validated. An FFR value below 0.75 reliably indicates a significant stenosis.

Methods and Results-RFVR is calculated as the ratio between distal CVR in the stenosed target vessel and distal

CVR in a nonstenotic reference vessel. In 21 patients, RFVR was determined in 24 target vessels by use of intracoronary adenosine and correlated to the FFR, determined as the ratio of mean poststenotic to aortic pressures, in the target vessel. Stenosis severity was classified according to quantitative coronary angiography analysis. Reference diameter was 3.0 ± 0.4 mm (mean \pm SD), and area stenosis was $74 \pm 15\%$ (range, 40% to 95%). CVRs in the target and reference vessels were 2.1 ± 0.5 and 2.6 ± 0.7 , respectively. FFR ranged from 0.49 to 0.99 (mean, 0.81 ± 0.15) and RFVR from 0.53 to 1.0 (mean, 0.82 ± 0.13). Poststenotic CVR did not correlate with either percent area stenosis ($r=0.27$, $P=NS$) or FFR ($r=0.33$, $P=NS$). In contrast, FFR as well as RFVR showed a curvilinear relation to percent area stenosis ($r=0.89$, $P<0.0001$ and $r=0.79$, $P<0.0001$, respectively). There was a close linear correlation between FFR and RFVR ($r=0.91$, $P<0.0001$).

Conclusions-RFVR correlates closely to FFR and to percent area stenosis, whereas the correlation of CVR with FFR and percent area stenosis is rather poor. RFVR is a promising new concept for assessment of coronary stenosis severity and clinical decision making based on Doppler measurements.

Summary

1. Poststenotic CVR - not correlate with either percent area stenosis ($r=0.27$, $P=NS$) or FFR ($r=0.33$, $P=NS$).
2. FFR and RFVR - curvilinear relation to percent area stenosis ($r=0.89$, $P<0.0001$ and $r=0.79$, $P<0.0001$, respectively).
3. Close linear correlation between FFR and RFVR ($r=0.91$, $P<0.0001$).

Circulation,102(19):2365-2370, 2000

Diastolic Fractional Flow Reserve to Assess the Functional Severity of Moderate Coronary Artery Stenoses: Comparison With Fractional Flow Reserve and Coronary Flow Velocity Reserve.

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Background: Coronary blood flow occurs mainly during the diastolic phase of each cardiac cycle and is mainly dependent on diastolic driving pressure, especially in the left anterior descending coronary artery (LAD). We hypothesized that calculation of the ratio of the diastolic driving pressure of a stenotic LAD to its normal value, namely diastolic FFR (d-FFR), might provide precise insight into the mechanism of FFR for assessment of the functional severity of the stenosis. We compared d-FFR with FFR, coronary flow reserve (CFR), and exercise myocardial thallium scintigraphy in an lesion of intermediate severity.

Methods and Results: The study population consisted of 46 consecutive patients with a moderate stenosis in the LAD in whom simultaneous measurements of aortic pressure, left ventricular pressure, and coronary pressure distal to the stenosis were obtained. Coronary flow velocity was successfully measured with a Doppler guidewire in 37 of the 46 patients. Values for FFR, d-FFR, and CFR in the noninvasive test-positive group were significantly lower than those in the negative group. With cutoff values of 0.75, 0.76, and 2.0 for FFR, d-FFR, and CFR, sensitivities were 83.3%, 95.8%, and 88.2% and specificities were 100%, 100%, and 95.0%, respectively.

Conclusions: The close similarity of the sensitivity and specificity of FFR and d-FFR, around almost identical cutoff values (0.75 versus 0.76), confirms the physiological validity of FFR as a clinical standard. In clinical practice, FFR remains the index of choice for assessment of the functional severity of moderate coronary artery stenoses.

Figure 5. ROC curves for FFR, d-FFR, and CFR used to discriminate noninvasive test-positive and -negative results

American Journal of Cardiology, 87(2):136-141, 2001

Intravascular Ultrasound Criteria for the Assessment of the Functional Significance of Intermediate Coronary Artery Stenoses and Comparison With Fractional Flow Reserve.

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The functional significance of coronary artery stenoses of intermediate severity is important in determining strategy in patient care. Intravascular ultrasound (IVUS) is often used to evaluate coronary stenosis severity. However, at present, few data are available about the role IVUS in the assessment of functional significance of intermediate lesions. Myocardial fractional flow reserve (FFR) <0.75 is a reliable index of a functionally severe coronary stenosis. In 53 lesions we assessed (1) by pressure wire: FFR (index of functional significance), and (2) by IVUS: minimal lumen cross-sectional area (MLA, square millimeters), minimal lumen diameter (MLD, millimeters), lesion length (millimeters), and percent area stenosis at the lesion site. By regression analysis, percent area stenosis and lesion length had a significant inverse correlation with FFR ($r = -0.58$, $p < 0.001$, $r = -0.41$, $p < 0.004$, respectively). MLD and MLA showed a significant positive relation with FFR ($r = 0.51$, $p < 0.001$, $r = 0.41$, $p < 0.004$, respectively). By using a receiver operating characteristic (ROC) curve, we identified a percent area stenosis $>70\%$ (sensitivity 100%, specificity 68%), a MLD ≤ 1.8 mm (sensitivity 100%, specificity 66%), a MLA ≤ 4.0 mm² (sensitivity 92%, specificity 56%), and a lesion length of > 10 mm (sensitivity 41%, specificity 80%) to be the best cut-off values to fit with a FFR <0.75 . The combined evaluation of both percent area stenosis

and MLD made the IVUS examination more specific (sensitivity 100%, specificity 76%). In 53 intermediate coronary lesions found by angiography, IVUS area stenosis >70%, MLD ≤1.8 mm, MLA ≤4.0 mm², and lesion length >10 mm reliably identified functionally critical intermediate coronary stenoses.

Circulation, 102(24):2959-2965, 2000.

Immediate Changes of Collateral Function After Successful Recanalization of Chronic Total Coronary Occlusions

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Background-: Coronary collaterals are essential to maintain myocardial function in chronic total coronary occlusions (TCOs). The aim of the present study was to assess the collateral circulation in TCOs before coronary angioplasty and to determine the recruitable collateral perfusion after recanalization by use of intracoronary Doppler flow velocimetry.

Methods and Results-: In 21 patients with TCOs (duration >4 weeks), Doppler recordings of basal collateral flow were obtained before the first balloon inflation. Angioplasty was performed with stent implantation in all lesions. At the end of the procedure, recruitable collateral flow was measured during a repeat balloon inflation. The collateral flow index (CFI) was calculated from the velocity integral during the occlusion/velocity integral of antegrade flow. In 17 of 21 patients, angiography was repeated after 24 hours, and CFI was reassessed. Average peak velocity of collateral flow was 10.95.6 cm/s with a predominantly systolic flow (diastolic/systolic velocity ratio <0.5) compared with antegrade flow (diastolic/systolic velocity ratio >1.5). After recanalization, the average peak velocity of recruitable collateral flow dropped by >50% to 4.72.5 cm/s. CFI fell from 0.480.25 to 0.210.16 (P <0.001). There was no further change of CFI during the following 24 hours. CFI was higher in patients with preserved regional ventricular function than in those with akinetic myocardium (0.570.23 versus 0.380.12, P <0.05).

Conclusions-: Collateral circulation in TCO provided 50% of antegrade coronary flow. A considerable fraction of collateral flow was immediately lost after recanalization, indicating that TCO may not remain protected from future ischemic events by a well-developed collateral function.

Figure 5. CFI at baseline, after recanalization, and at day 1. There was increase from day 0 to day 1 in only 1 patient with tachyarrhythmia.

Figure 6. CFI in patients with akinetic (day 0, n=10; day 1, n=7) and with normal or hypokinetic (day 0, n=11; day 1, n=10) regional wall motion. Mean±SEM values are shown. * P <0.05.

Circulation, 102(24):2938-2944, 2000

Randomized Comparison of Elective Stent Implantation and Coronary Balloon Angioplasty Guided by Online Quantitative Angiography and Intracoronary Doppler.

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Background-: The purpose of this study was to compare long-term outcomes of coronary stenting in all lesions (elective stenting) or only in lesions with inadequate morphological and functional results after balloon angioplasty (guided PTCA).

Methods and Results-: Treatment of multivessel disease, with any lesion length and vessel size, was allowed provided that all lesions were suitable for stent implantation. Patients were randomized to elective stent implantation (n=370) or guided PTCA (n=365). An optimal PTCA result (residual diameter stenosis ≤35%, coronary flow reserve measured with a Doppler guidewire >2.0, absence of threatening dissections) was achieved in 166 lesions (43%). The remaining 218 lesions underwent stent implantation (provisional stenting). Final residual diameter stenosis was lower in the elective and provisional stent groups (9.3% and 10.2%) than in the optimal PTCA group (24.8%, P <0.00001). On an intention-to-treat analysis, the probability of ≥1 major adverse cardiac event at 12 months was 17.8% in the elective stenting group and 18.9% in the guided PTCA group (20.1% for optimal PTCA and 18.0% for the provisional stenting subgroup, P =NS). The incidence of repeat target lesion revascularization at 1 year was 14.9% in the elective stent group and 15.6% in the guided PTCA group (17.6% for optimal PTCA and 14.1% for the provisional stenting subgroup, P =NS).

Conclusions-: When balloon angioplasty is guided by online quantitative angiography and Doppler-derived coronary flow reserve, with provisional stenting reserved for suboptimal results, early and late clinical outcomes are comparable to those achieved by elective stenting of all patients

Table 4. Frequency of Primary Clinical End Points at Follow-Up MI indicates myocardial infarction; TLR, target lesion revascularization; MACE, major adverse cardiac event; ES, elective stenting; and GP, guided PTCA.

Circulation, 102(24):2930-2937, 2000.

Randomized Comparison of Primary Stenting and Provisional Balloon Angioplasty Guided by Flow Velocity Measurement.

Serruys, Patrick W. MD; de Bruyne, Bernard MD; Carlier, Stephane MD; Eduardo Sousa, Jose MD; Piek, Jan MD; Muramatsu, Toshiya MD; Vrints, Chris MD; Probst, Peter MD; Seabra-Gomes, Ricardo MD; Simpson, Ian MD; Voudris, Vasilis MD; Gurne, Olivier MD; Pijls, Nico MD; Belardi, Jorge MD; van Es, Gerrit-Anne PhD; Boersma, Eric PhD; Morel, Marie-Angele MS; van Hout, Ben PhD; on behalf of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II Study Group

Background-: Coronary stenting improves outcomes compared with balloon angioplasty, but it is costly and may have other disadvantages. Limiting stent use to patients with a suboptimal result after angioplasty (provisional angioplasty) may be as effective and less expensive.

Methods and Results-: To analyze the cost-effectiveness of provisional angioplasty, patients scheduled for single-vessel angioplasty were first randomized to receive primary stenting (97 patients) or balloon angioplasty guided by Doppler flow velocity and angiography (523 patients). Patients in the latter group were further randomized after optimization to either additional stenting or termination of the procedure to further investigate what is "optimal." An optimal result was defined as a flow reserve >2.5 and a diameter stenosis $<36\%$. Bailout stenting was needed in 129 patients (25%) who were randomized to balloon angioplasty, and an optimal result was obtained in 184 of the 523 patients (35%). There was no significant difference in event-free survival at 1 year between primary stenting (86.6%) and provisional angioplasty (85.6%). Costs after 1 year were significantly higher for provisional angioplasty (EUR 6573 versus EUR 5885; $P = 0.014$). Results after the second randomization showed that stenting was also more effective after optimal balloon angioplasty (1-year event free survival, 93.5% versus 84.1%; $P = 0.066$).

Conclusions-: After 1 year of follow-up, provisional angioplasty was more expensive and without clinical

benefit. The beneficial value of stenting is not limited to patients with a suboptimal result after balloon angioplasty

Figure 3. Event-free survival (Kaplan-Meier curves) at 12 months. Patients with suboptimal and optimal balloon angioplasty were randomized to additional stenting or no further treatment. OS indicates optimal stenting (n=77); SOS, suboptimal stenting (n=112); OB, optimal balloon angioplasty (n=107); SOB, suboptimal balloon angioplasty (n=86); FE, Fisher's exact test; and LR, log-rank test. For definitions of optimal and suboptimal, see text.

Figure 4. Event-free survival (Kaplan-Meier curves) at 12 months in patients who had primary stenting (PRIM; n=97) or provisional angioplasty (PROV; n=523).

Circulation, 102(19):2371-2377, 2000.

Coronary Pressure Measurement to Assess the Hemodynamic Significance of Serial Stenoses Within One Coronary Artery: Validation in Humans.

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Background: When several stenoses are present within 1 coronary artery, the hemodynamic significance of each stenosis is influenced by the presence of the other(s), and the calculation of coronary and fractional flow reserve (CFR and FFR) for each individual stenosis is confounded. Recently, we developed and experimentally validated a method to determine the true FFR of each stenosis as it would be after the removal of the other stenosis; the true FFR can be reliably predicted by coronary pressures measured before treatment at specific locations within the coronary artery using equations accounting for stenosis interaction. The aim of the present study was to test the validity of these equations in humans.

Methods and Results: In this study of 32 patients with 2 serial stenoses in 1 coronary artery, relevant pressures were measured before the intervention, after the treatment of 1 stenosis, and after the treatment of both stenoses. The true FFR of each stenosis (FFR_{true}) was directly measured after the elimination of the other stenosis and compared with the value predicted (FFR_{pred}) from the initial pressure measurements before treatment. Although the hyperemic gradient across 1 stenosis increased significantly (from 10 \pm 7 to 19 \pm 11 mm Hg after treatment of the other stenosis), FFR_{pred} was close to FFR_{true} in all patients (0.78 \pm 0.12 versus 0.78 \pm 0.11 mm Hg; r =0.92; [DELTA]% =4 \pm 0%). Without accounting for stenosis interaction, the value of FFR

for each stenosis would have been significantly overestimated (0.85±0.08;P <0.01).

Conclusions: Coronary pressure measurements made by a pressure wire at maximum hyperemia provide a simple, practical method for assessing the individual hemodynamic significance of multiple stenoses within the same artery.

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Safety of intracoronary Doppler flow measurement.

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Background: With the introduction of Doppler-tipped guide wires, intracoronary Doppler flow measurement has been increasingly accepted as an additional diagnostic approach in the catheterization laboratory. However, the safety of intracoronary Doppler flow measurement has not been well-investigated. The purpose of our study was to evaluate the safety of intracoronary Doppler flow measurement using the Doppler FloWire (Cardiometrics, Mountain View, Calif).

Methods and Results: A total of 906 patients were examined by intracoronary Doppler with a 0.014-inch or an 0.018-inch Doppler FloWire. For coronary flow reserve measurement, intracoronary injection of adenosine or papaverine was used. Of the patients studied, 77 were cardiac transplant recipients and 829 were patients who had not received a transplant, of whom 617 had undergone diagnostic coronary procedures and 212 had coronary interventions. In 27 (2.98%) of 906 patients adverse cardiac events were observed. Fifteen (1.66%) of 906 patients had severe transient bradycardia develop (asystole or second- to third-degree atrioventricular block) after intracoronary administration of adenosine, 14 of which occurred in the right coronary artery and 1 in the left anterior descending artery. Nine (0.99%) of 906 patients had coronary spasm during the passage of the Doppler wire (5 in the right coronary artery, 4 in the left anterior descending artery). Two (0.22%) of 906 patients had ventricular fibrillation during the procedure. Hypotension with bradycardia and ventricular extrasystole each occurred in 1 (0.11%) of 906 patients. The incidence of complication was significantly higher in transplant recipients than in patients who underwent either diagnostic or interventional procedures (12.99% vs 2.43% vs 0.94%, P < .001). The Doppler measurements in the right coronary artery were associated with a higher incidence of complications, especially bradycardia, compared with the left anterior descending and the left circumflex arteries (right coronary, 5.87% vs left anterior descending, 1.05% vs left circumflex, 0.17%;P

< .001). All complications were cured medically.

Conclusion: Intracoronary Doppler flow measurement with Doppler wires and intracoronary administration of adenosine is a safe method. However, severe complications such as bradycardia and coronary spasm can occur. Attention should be paid to the examination of the right coronary artery, especially in heart transplant recipients.

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Angiographic and Clinical Outcome of Mild to Moderate Nonocclusive Unstented Coronary Artery Dissection and the Influence on Coronary Flow Velocity Reserve.

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Limited data are available regarding the angiographic healing rate and physiologic impact of coronary artery dissections. Therefore, we studied the impact of coronary dissections on coronary flow velocity and outcome as well as their healing rate at 6-month follow-up balloon angioplasty. Of 297 patients who underwent balloon angioplasty, 225 underwent intracoronary Doppler measurements and 184 had Doppler and angiographic assessment at 6-month follow-up. Dissections were scored by an independent core lab (Cardialysis BV) and divided in 4 groups: mild (types A to B), moderate (type C), severe (D to F), and patients without dissections. Severe dissections (types D to F) were excluded from the analysis. Clinical, angiographic, and Doppler data were compared among the remaining 3 patient groups. From the 67 dissections detected after balloon angioplasty, only 3 (4.5%) remained unhealed at follow-up. Immediately after balloon angioplasty, the moderate dissection group was associated with a lower coronary flow velocity reserve than the patients with mild (2.16 ± 0.60 vs 2.82 ± 1.00 , $p = 0.037$) or no dissections (2.16 ± 0.60 vs 2.71 ± 0.88 , $p = 0.046$), respectively. In addition, higher recurrence of angina at 30 days was observed in the moderate group rather than in the mild group (5 [50%] vs 8 [16%], $p = 0.0160$) and in the patients without dissections (11 [12%], $p = 0.007$). After standard balloon angioplasty, the occurrence of unhealed dissections is a rare phenomenon. An impaired coronary flow reserve was observed after the development of nonocclusive type C dissections, which was associated with a worse short-term outcome.

TABLE III Clinical and Angiographic Outcome at Six-Month Follow-Up

TABLE IV Procedural and Follow-Up Angiographic and Doppler Flow Data

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Coronary Artery Flow Velocity Is Related To Lumen Area and Regional Left Ventricular Mass.

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Background: Coronary flow velocity varies widely between individuals, even at rest. Because of this variation, indices with less apparent deviation, such as the ratio of hyperemic to resting velocity (coronary flow reserve), have been more commonly studied. We tested the hypothesis that the flow continuity principle could be used to model resting coronary flow, and we examined the resulting velocity relationship.

Methods and Results: We studied coronary velocity in 59 patients using a Doppler wire to measure resting and hyperemic average peak velocities in the left anterior descending artery. Quantitative techniques were used to calculate lumen cross-sectional area and the lengths of all distal coronary branches. Branch lengths were used to estimate regional left ventricular mass. We then calculated the ratio of lumen area to regional mass (A/m). Regional perfusion was estimated from the double product of heart rate and systolic blood pressure. Resting velocity (V) varied inversely with A/m ratio [$V=46.5/(A/m)$; $r =0.68$, $P <0.001$]. Disease in the left anterior descending artery was categorized as none or luminal irregularities only (n=22), mild (n=15), or moderate (n=22). The A/m ratio declined across these groups (8.7+/-4.0, 8.5+/-6.2, and 5.6+/-3.0 mm²/100 g, respectively; $P <0.04$), and the resting average peak velocity increased (27+/-16, 33+/-11, and 37+/-20 cm/s, respectively; $P =0.06$).

Conclusions: Resting coronary artery flow velocity is inversely related to the ratio of lumen area to regional left ventricular mass. Higher resting velocities are found when insufficient lumen size exists for the distal myocardial bed, as occurs with diffuse mild or moderate coronary atherosclerosis.

Figure 4. Relationship between velocity (V) and A/m ratio. A significant correlation was found ($r =0.68$, $P <0.001$). The theoretical curves that would result with myocardial perfusion rates of 50 and 100 mL/min per 100 g are also shown (lower and upper dashed curves, respectively).

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Relation of Phasic Coronary Flow Velocity Characteristics With TIMI Perfusion Grade and Myocardial Recovery After Primary Percutaneous Transluminal Coronary Angioplasty and Rescue Stenting.

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Background: A residual stenosis and/or microvascular damage have been proposed as mechanisms of TIMI 2 flow for acute myocardial infarction. Coronary flow dynamics were assessed in patients with TIMI 2 flow to predict whether additional intervention would improve TIMI grade.

Methods and Results: In 35 patients who had a successfully recanalized anterior acute myocardial infarction using angioplasty or rescue stenting, coronary flow patterns were compared with corresponding TIMI grade and regional left ventricular wall motion (LVWM) 1 month after the intervention. After angioplasty, the time-averaged peak velocity (APV) was lower in patients with TIMI 2 flow (n=22) than in those with TIMI 3 flow (n=13; 7.9 ± 3.9 versus 20.6 ± 5.1 cm/s; $P < 0.001$). Two different flow patterns were recorded in patients with TIMI 2 flow (versus TIMI 3, $P < 0.001$); patients with type 1 TIMI 2 flow (n=15) had a reduced diastolic APV (8.3 ± 4.8 versus 24.2 ± 7.4 cm/s), prolonged diastolic deceleration time (1176 ± 455 versus 728 ± 205 ms), and a small diastolic/systolic APV ratio (1.3 ± 0.6 versus 2.1 ± 0.7); patients with type 2 TIMI 2 flow (n=7) had systolic flow reversal (systolic APV, -7.9 ± 4.6 versus 11.7 ± 4.5 cm/s), a rapid diastolic deceleration time (221 ± 84 versus 728 ± 205 ms), and a negative diastolic/systolic APV ratio (-2.1 ± 1.4 versus 2.1 ± 0.7). A significantly lower mean chord LVWM (-3.0 ± 0.2 versus -1.9 ± 0.8 ; $P < 0.001$) and a greater number of chords $< -2SD$ (50 ± 2 versus 28 ± 18 ; $P < 0.001$) were present in patients with type 2 versus type 1 TIMI 2 flow. Stenting increased TIMI 2 flow to TIMI 3 flow more in patients with type 1 than type 2 flow (67% versus 0%; $P = 0.003$). Patients with TIMI 2 flow after stenting continued to demonstrate a type 2 pattern, and they had poor LVWM recovery.

Conclusions: The differentiation between 2 types of TIMI 2 flow can predict the improvement of TIMI grade and LVWM recovery after additional stenting.

Table 2. Phasic Coronary Flow Velocity Patterns and Regional LVWM in Patients With TIMI 2 Flow After PTCACFVR indicates coronary flow velocity reserve; DAPV, diastolic time-averaged peak velocity; DcT, deceleration time of diastolic velocity; DPV, diastolic peak velocity; SAPV, systolic time-averaged peak velocity; and SPV, systolic peak velocity.*P <0.001 vs TIMI 3 flow.

Figure 4. APVs, systolic APVs (SPVs), diastolic deceleration times (DcT), and DSVR of patients with TIMI 2 and TIMI 3 flow before and after angioplasty (PTCA) and after stent implantation. ? indicates TIMI 2 flow, and [white circle] demonstrates TIMI 3 flow; [white up pointing small triangle] indicates patients with TIMI 3 flow who obtained angiographic end point without stenting.

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Effects of Intravenous and Intracoronary Adenosine 5'-Triphosphate as Compared With Adenosine on Coronary Flow and Pressure Dynamics.

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Background: Measurements of Doppler derived coronary flow reserve (CFR) and pressure derived fractional flow reserve (FFR) for coronary stenosis assessment depend on the induction of maximal hyperemia. Adenosine is the most widely used pharmacological agent but is expensive and poorly tolerated by some patients.

Methods and Results: The objective of this study was to test the equivalency of adenosine 5'-triphosphate (ATP) to adenosine in their ability to cause maximal hyperemia as compared with the hyperemic response of complete coronary occlusion in 6 canines. Intracoronary administration of either ATP or adenosine resulted in a significant increase in CFR (2.790.64 and 2.220.7 for 10 [mu]g versus 4.651.22 and 4.250.78 for 100 [mu]g for ATP and adenosine, respectively, P for trend <0.001) but not reaching the level of coronary occlusion (6.352.26).

Additionally, FFR and CFR were measured in 35 different stenoses using ATP, adenosine, and coronary occlusion. There was an excellent linear correlation between ATP and adenosine for both CFR ($R = 0.934$, $P < 0.001$) and FFR ($R = 0.985$, $P < 0.001$). However, hyperemia with either ATP or adenosine was less than postocclusion hyperemia, resulting in significantly different reserve measurements (CFR: 1.930.66 and 2.080.81 versus 2.350.97, $P < 0.001$; FFR: 0.620.24 and 0.630.23 versus 0.580.2, $P < 0.001$).

Conclusions: 1) Step up in dosage of ATP and adenosine beyond currently recommended clinical doses resulted in a significant increase in coronary hyperemia; 2) ATP was equivalent to adenosine for both CFR and FFR; and 3) complete coronary occlusion yielded a better hyperemic response than either drug, indicating that maximal hyperemia was not achieved by either pharmacological stimulus.

Figure 4. Linear regression analysis of CFR and FFR measurements performed with intracoronary ATP and adenosine at a dose of 40 μg (top). Agreement between the 2 sets of measurements is shown in bottom panels according to the statistical approach proposed by Bland and Altman. Difference between measurements with ATP and adenosine has been plotted against their mean.

Intracoronary Doppler and pressure wire

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