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Comparative long-term effects of coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty on regional coronary flow reserve

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ABSTRACT To evaluate the relative long-term improvement in coronary artery hemodynamics after revascularization by coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA), regional coronary flow reserve (CFR) was measured, by digital computer analysis of 35 mm cine film, in 50 men undergoing cardiac catheterization. CFR (mean \pm SEM) in 12 atherosclerotic arteries before revascularization was 1.02 ± 0.05 . Mean CFR in 29 normal arteries of men with normal coronary arteriograms was significantly higher (2.59 ± 0.11) than that in 16 atherosclerotic arteries of patients revascularized by CABG (2.02 ± 0.17 , $p < .01$) or in 14 atherosclerotic arteries of those revascularized by PTCA (1.97 ± 0.12 , $p < .01$). No difference in CFR between the CABG and PTCA groups was found and variables known to influence CFR were similar between groups. Equivalent and significant long-term improvement in coronary artery hemodynamics is provided by CABG or PTCA. We postulate that the difference in CFR in the men with normal arteries and those who underwent revascularization was related to the effects of the general atherosclerotic process, which remain despite successful treatment by these techniques.

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MYOCARDIAL REVASCULARIZATION can now be accomplished by either coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).¹⁻⁴ Although symptomatic, metabolic, hemodynamic, and functional improvement has been demonstrated with each technique,⁵⁻¹⁵ little data exist comparing the two.^{16, 17} One difficulty in undertaking comparative studies resides in the clinical disparities in groups of patients undergoing these procedures. While patients who undergo CABG are more likely to have chronic symptoms, a history of myocardial infarction, and multivessel disease, those treated by PTCA characteristically have recent onset of symptoms, normal ventricular function, and single-vessel disease. More importantly, the lack of a generally available clinical test sensitive enough to evaluate

subtle regional differences in coronary blood flow or myocardial function due to either technique has inhibited investigation.

The coronary reactive hyperemic response is an important, reproducible physiologic parameter.^{18, 19} It can be measured by determining the ratio of maximal coronary blood flow to resting flow. Increasingly significant obstructive coronary artery disease progressively exhausts this coronary flow reserve (CFR) by reducing peak flow.^{20, 21} Three techniques have recently been developed that allow the measurement of regional CFR in man. The first uses a pulsed Doppler coronary artery catheter, which can measure proximal coronary flow velocity in the catheterization laboratory.²² The second uses a Doppler velocity probe, which can be applied directly to selected epicardial coronary arteries at the time of open heart surgery to measure the reactive hyperemic response to transient arterial occlusion.²³ The third is a digital radiographic technique performed during routine cardiac catheterization that measures the myocardial reactive hyperemic response to intracoronary injection of contrast medium.^{24, 25}

The present study, in which we used the third tech-

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nique, was designed to evaluate the relative improvement in long-term regional CFR after myocardial revascularization by CABG or PTCA.

Methods

Patient population. The patient population consisted of 50 men undergoing coronary arteriography. These patients were divided into four groups for analysis. Group I was composed of 10 patients with symptomatic coronary artery disease (a total of 12 diseased arteries) who subsequently underwent revascularization by CABG or PTCA. Eleven patients with 16 arteries previously treated by CABG formed group II, and 13 patients with 14 arteries previously treated by PTCA formed group III; these patients were studied to evaluate postrevascularization vessel patency. In group II patients all grafts were patent and nonstenotic, and in those in group III there was a residual translesional pressure gradient of 20 mm Hg or less at the time of angioplasty and no angiographic evidence of restenosis at follow-up. Twenty-nine arteries in 16 patients with atypical chest pain and normal coronary arteriograms formed group IV and served as the normal control group. Patients were excluded if they had valvular heart disease, electrocardiographic evidence of left ventricular hypertrophy, more than mild hypokinesis documented on the contrast ventriculogram, or angiographically visible coronary collateral vessels. Data from 15% of arterial distributions were excluded from analysis because of use of an inadequate contrast injection technique, motion artifact, poor visualization of the perfusion bed, or failure of the angiographer to acquire arteriographic data suitable for digital processing.

Prescribed medication regimens were not followed the morning of the cardiac catheterization. Patients were premedicated with 10 mg diazepam and 50 mg diphenhydramine. This study was approved by the institutional committees on human research and informed consent was obtained from each patient.

Arteriographic technique. To obtain images for digital processing, the following arteriographic technique was used. Standard left ventriculography and multiple-view selective coronary arteriography were performed by the Judkins technique. Arteriography for subsequent functional image digital processing was obtained in the left anterior oblique projection on 35 mm cine film. Fixed parameter (kV, mA, and pulse width) cineradiography at 30 frames/sec was used. Patients were required to cease respiration and remain motionless during filming. Vein grafts and coronary arteries were opacified by a fixed dose of 5 to 8 ml of sodium meglumine diatrizoate (Renografin-76) injected by an electrocardiographically triggered power injector gated to the R wave of the electrocardiogram. Reflux of contrast medium into the aorta was considered proof that a maximal bolus of contrast was delivered to the artery and that the catheter was not impeding coronary blood flow. Baseline studies were performed at least 3 min after the previous injection of contrast. Studies under hyperemic conditions were performed 10 sec after intracoronary injection of an identical dose of contrast medium. Cineradiography was initiated at least one full cardiac cycle before injection of contrast. A density step wedge was imaged and checked densitometrically after film processing to ensure that the film gray scale was kept constant on a day-to-day basis.

Digital processing of the functional image. Digital image processing was performed by a technique similar to that previously described.²⁴⁻²⁷ Three general operations were required: digitization, mask-mode subtraction, and functional image generation. Arteriograms were displayed on a cine film projector (Vanguard Corporation, XR-35) equipped with a primary beam splitter coupled to a fixed-gain video camera and a video

analog-to-digital converter. Five to seven end-diastolic frames from consecutive cardiac cycles were chosen, with use of the criterion of closest duplication of arterial position, beginning with the end-diastolic frame just before injection of contrast medium. These frames were digitized into $512 \times 512 \times 8$ -bit matrixes. Video-amplified gain and projector light levels were adjusted to provide a linear correspondence between contrast x-ray absorption and digital scale. The digital images were stored in the disk memory of a digital radiographic computer (DPS-4100C, ADAC Labs, Edenvalle, CA) for subsequent processing.

Image enhancement was performed by standard mask-mode subtraction with use of the end-diastolic frame before injection of contrast as the mask. A single contrast intensity and appearance time-modulated functional image was then generated from each set of enhanced frames (figure 1).²⁵ The intensity value of each pixel corresponded to the maximum contrast density reached during each acquisition, while the appearance time of contrast in the pixel was color modulated, with a different color assigned to each postinjection cardiac cycle (red for the first cycle, yellow for the second, etc.). Only pixels with an intensity above a preset threshold appeared on the final functional image. This threshold was manually set at a level that excluded most of the background noise intensity. Acquisition and processing were identical for each pair of basal and hyperemic images so that each set was technically comparable.

Analysis of functional images. Mean myocardial contrast density and appearance were determined by a computer program that averaged pixel values in a region of interest defined by the operator in the basal images and in the same area of the hyperemic images (figure 1). Large epicardial coronary arteries and areas that overlapped with the aortic root, diaphragm, or coronary sinus were excluded from analysis. Since contrast density is directly related to the volume of distribution in the myocardium and flow is inversely related to myocardial contrast appearance time, digital estimation of coronary blood flow was calculated as

$$Q \propto \text{volume/time} \propto \text{CD}/\text{AT}$$

where Q = mean regional coronary flow; CD = mean maximal contrast density; and AT = mean contrast appearance time. CFR, the ratio of hyperemic (H) flow to basal (B) flow, corrected for heart rate (HR), was calculated as

$$\text{CFR} = Q_H/Q_B = \text{CD}_H/\text{CD}_B \times \text{AT}_B/\text{AT}_H \times \text{HR}_H/\text{HR}_B$$

Studies in dogs have demonstrated an excellent correlation between CFR measured by electromagnetic flow probe and the ratio CD/AT measured by digital subtraction angiography ($r = .92$). The digital measurements were accurate (regression slope = .90), reproducible ($\pm 13\%$), and had low interobserver ($r = .99$) and intraobserver ($r = .98$) variability.²⁵

Data analysis. Data are expressed as mean \pm SEM. Statistical comparisons between groups were obtained with the two-tailed, unpaired t test. Significant differences were assumed when confidence limits exceeded 95% ($p < .05$).

Results

Clinical characteristics. The clinical characteristics of the patients groups are listed in table 1. Nine of 11 patients in group II (CABG) had triple-vessel disease, while nine of 13 patients in group III (PTCA) had single-vessel disease. Forty-two of the 48 diseased arteries in group II and III patients were successfully revascularized. Two patients each in groups II and III

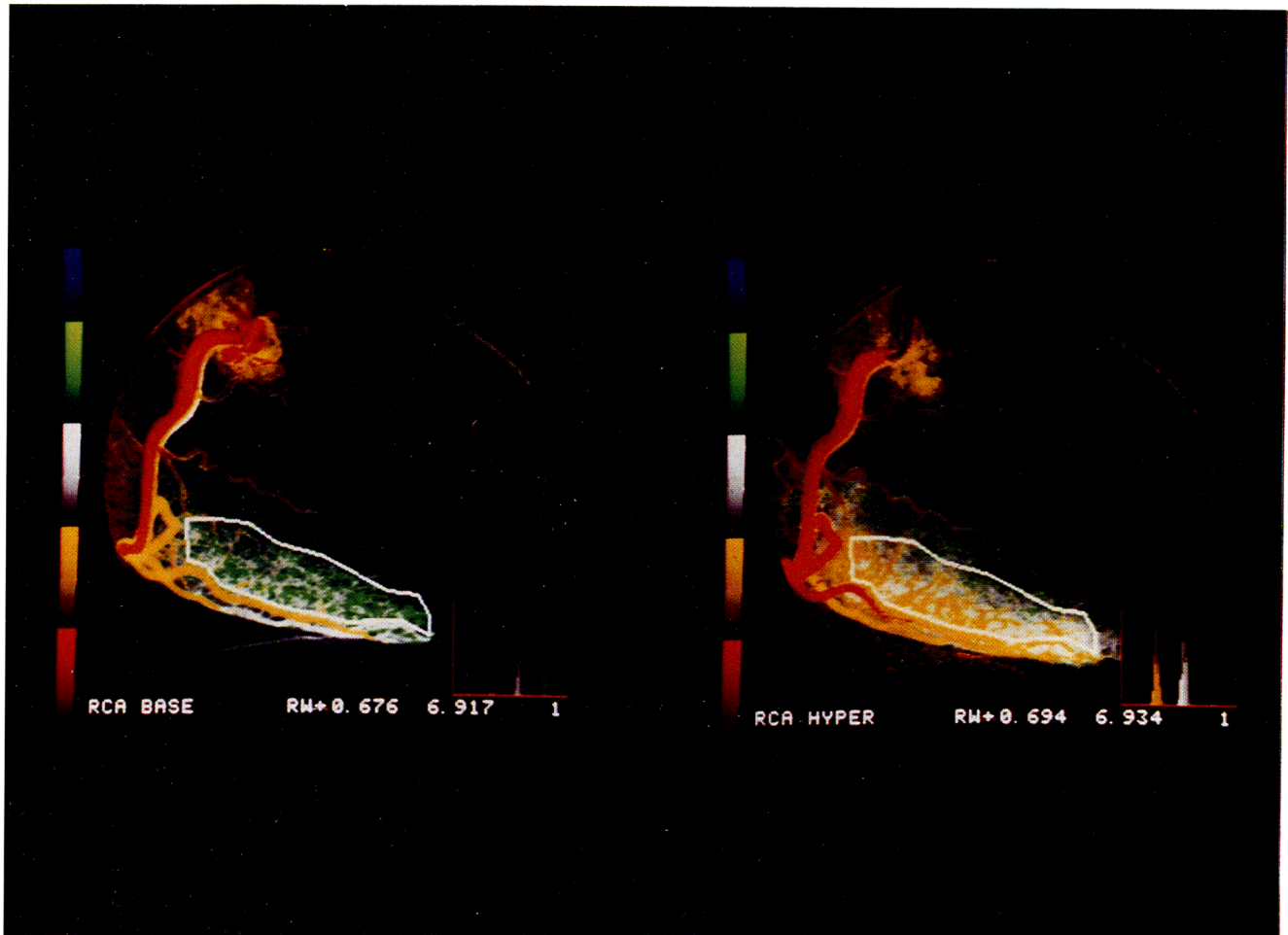


FIGURE 1. Contrast medium appearance pictures of a normal right coronary artery in the right anterior oblique projections at baseline (*left*) and under hyperemic (*right*) conditions. CFR was calculated to be 2.49 in the region of interest.

still had exertional chest pain; the others were pain free. The hemoglobin averaged 14.9 ± 0.7 g/dl in group II and 15.0 ± 0.3 g/dl in group III and the interval between revascularization and catheterization in these two groups was 15.4 ± 2.0 and 32.6 ± 4.2 weeks, respectively.

Cardiac catheterization. Data obtained at cardiac catheterization for the four patient groups are listed in table 2. There were no significant differences in heart rate, mean aortic pressure, or pressure-rate product between groups. Although group III patients had a significantly lower left ventricular ejection fraction than the men with normal arteries (group IV) ($p < .01$), the value was not statistically different from that in group II, and was well within normal physiologic limits. No difference in left ventricular end-diastolic pressures existed. Percent luminal stenosis of arteries was $80 \pm 4\%$ in group I and $17 \pm 3\%$ in group III.

CFR. Individual values for CFR for each group are plotted in figure 2. CFR in five patients who subse-

quently underwent CABG and in five patients who subsequently underwent PTCA are grouped together in group I because they were equivalent (1.10 ± 0.05 vs 0.95 ± 0.06). Mean values for CFR for groups I, II, III, and IV were 1.02 ± 0.05 , 2.02 ± 0.17 , 1.97 ± 0.12 , and 2.59 ± 0.11 , respectively. While CFR in patients with atherosclerotic arteries revascularized by CABG or PTCA was significantly higher than in those with arteries not revascularized ($p < .0001$), it was significantly lower than CFR in men with normal arteries ($p < .01$). No difference in CFR in groups II and III was found.

Discussion

Autoregulatory changes maintain basal coronary blood flow in arteries with flow-limiting stenoses by decreasing distal coronary resistance, but this limits potential further increases in flow. In arteries with high-grade stenoses suitable for revascularization by CABG or PTCA, CFR is exhausted. An improvement

TABLE 1
Characteristics of the 50 study patients

	Group I (n = 10)	Group II (n = 11)	Group III (n = 13)	Group IV (n = 16)
Age (yr) ^A	56 ± 3	57 ± 2	55 ± 3	48 ± 2
No. of diseased vessels	19	31	17	0
No. of vessels revascularized	18	27	15	0
No. of vessels studied	12	16	14	29
LAD	7	5	6	9
Diagonal branch	0	3	0	0
Left circumflex	2	6	2	8
RCA	3	2	6	12
Medications before testing				
Nitrates	10	3	3	10
β-blockers	2	9	0	11
Ca ⁺⁺ -blockers	6	2	9	3

LAD = left anterior descending artery; RCA = right coronary artery.

^AMean ± SEM.

in individual arterial CFR several months after CABG and immediately after PTCA, as measured by coronary radiography, has been demonstrated previously.^{26, 27} We have since modified our image analysis algorithm and use contrast density information to reflect regional vascular volume and the CD/AT ratio to more accurately estimate coronary blood flow.²⁵ While the CFR values found for vessels without severe obstruction are higher when CD/AT ratios than when AT ratios are used,²⁴⁻²⁷ findings with both methods indicate that CFR is absent in vessels with high-grade stenoses suitable for revascularization. In this report, the long-term effects of revascularization as determined by these two techniques were compared with this refined image algorithm. Equivalent and significant long-term improvements in regional CFR were found in arteries revascularized by either CABG or PTCA. Additionally, even though revascularization was quite successful in each artery, normal CFR was not restored.

Clinical implications. CABG has been the most popular means of restoring regional myocardial blood flow to perfusion beds distal to coronary stenoses for 15

years. More recently, PTCA has emerged as an alternative revascularization treatment for single-vessel obstructive coronary artery disease. It has clearly been demonstrated that successful revascularization by CABG or PTCA produces symptomatic, metabolic, hemodynamic, and functional improvement.⁵⁻¹⁵ The current investigation is the first to suggest that equivalent improvement in individual coronary artery hemodynamics is achieved by the two techniques and further justifies the use of revascularization by CABG or PTCA in properly selected patients.

Theoretical implications. The failure of successful revascularization to restore normal CFR to atherosclerotic coronary arteries is probably the most interesting finding of this study and one for which an explanation is not readily apparent. The patients in each group had equivalent basal oxygen demands, as estimated by pressure-rate product, and normal global left ventricular function. Patients with severe regional wall motion abnormalities, collateral blood flow, or left ventricular hypertrophy were excluded because these factors can have an effect on CFR independent of that of coronary

TABLE 2
Cardiac catheterization data

	Group I (n = 10)	Group II (n = 11)	Group III (n = 13)	Group IV (n = 16)
Heart rate (beats/min)	75 ± 2	75 ± 3	74 ± 3	71 ± 3
Mean aortic pressure (mm Hg)	92 ± 3	95 ± 4	97 ± 3	93 ± 3
Pressure-rate product (× 10 ⁻²)	99 ± 4	96 ± 5	98 ± 5	90 ± 6
Left ventricular ejection fraction (%)	65 ± 4	67 ± 3	59 ± 3 ^A	73 ± 3
Left ventricular end-diastolic pressure (mm Hg)	13 ± 2	10 ± 2	14 ± 2	13 ± 1

Data expressed as mean ± SEM.

^Ap < .01, as compared with the control group (group IV).

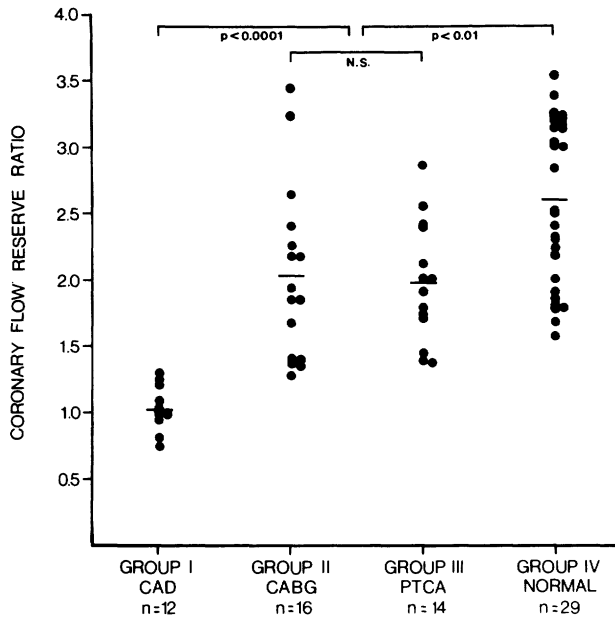


FIGURE 2. Long-term CFR values for the patient groups as determined by digital coronary radiography. CAD = coronary artery disease.

stenoses.²⁸⁻³¹ By using contrast medium as a direct vasodilator stimulus, rather than depending on the ischemic stimulation of vessel occlusion often used in the operating room, we avoided measurement of any influence dual blood supply may have had on determinations of graft CFR. Also, the arteries subjected to PTCA had very mild residual luminal stenoses and would thus not be expected to be associated with limitations of peak coronary blood flow.^{20, 21} In the early postrevascularization period patients were receiving antianginal medications prescribed by their referring physicians for prophylactic reasons, not because of persistent ischemia; none received antianginal medications on the day of the catheterization.

It is unlikely that use of a saphenous vein graft as the proximal conduit for coronary blood flow influences coronary artery hemodynamics. No change in timing of the resting pulse wave, pressure contour, or distal blood flow was found by Kakos et al.³² in bypassed normal canine coronary arteries. Others have shown graft CFR to be normal in the canine model.³³ Likewise, Brandt et al.³⁴ have demonstrated restoration of normal CFR by CABG in a nonatherosclerotic human right coronary artery originating from the left sinus of Valsalva.

It is postulated that the difference in CFR in men with normal arteries and those who underwent revascularization is related to the atherosclerotic disease process. First, although obstructive coronary artery disease, as defined by the coronary arteriogram, is

often detected as discrete proximal luminal stenoses treatable by CABG or PTCA, anatomic descriptions have repeatedly demonstrated the diffuse nature of atherosclerotic plaque in diseased epicardial coronary arteries.³⁵⁻³⁷ Secondly, local vasomotor reactivity may not be normal in atherosclerotic arteries. Neovascularization in the region of atherosclerotic plaque has been visualized by cinematography after silicone polymer injections into the arteries of isolated human hearts.³⁸ These transmural vascular networks potentially provide higher concentrations of vasoconstrictor substances and the proliferation of autonomic nerve terminals known to accompany neovascularization may enhance local catecholamine levels.³⁸ Also, endothelial damage due to mechanical injury or atherogenesis has been shown to inhibit arterial smooth muscle relaxation.^{39, 40} Finally, vascular reactivity at the arteriolar level may be affected by the atherosclerotic disease process through intimal thickening and fibrosis,⁴¹ altered α -adrenergic tone,⁴² or chronic microembolization of platelet aggregates.⁴³

The effect of experimental atherosclerosis on CFR has been studied in the cynomolgus monkey.⁴⁴ After an atherogenic diet was given to induce lesions producing an average of 60% luminal stenosis, a normal diet was given for a regression period of 18 months. While the degree of stenosis was reduced to 25%, intimal fibrosis was increased and CFR was only partially restored. The authors concluded that intimal fibrosis substantially limited arterial hemodynamic improvement.

Study limitations. The limitations of the digital radiographic technique we used have been previously summarized and include those related to specific hardware requirements, motion artifact, use of contrast medium as the hyperemic stimulus, and the mathematic assumptions necessary for calculation of blood flow.^{24-27, 45} Despite these difficulties, a good correlation between electromagnetic flowmeter and digital radiographic determinations of relative regional CFR has been demonstrated.²⁵ Also of concern is the fact that about a quarter of the normal CFR values were less than 2. We have recently shown that patients with chest pain, normal coronary arteriograms, and low regional CFR frequently have associated regional abnormalities on radionuclide exercise tests.⁴⁶ These patients probably have ischemic heart disease without epicardial coronary stenoses.^{47, 48} Since this normal group was defined only by the arteriogram, without radionuclide exercise test data, it is likely that the difference in CFR in the group with normal arteries and the group undergoing revascularization is larger than stated.⁴⁹ The wide range of CFR values found in

each patient group probably reflects the multiplicity of factors that can influence arterial CFR.^{49, 50}

In summary, revascularization by CABG or PTCA restores equivalent CFR to individual coronary arteries. Although normal CFR is not achieved, this improvement in coronary arterial hemodynamics is sufficient to reverse clinically detectable myocardial ischemia. The difference in CFR in normal and revascularized arteries requires further evaluation. Confirmation that physiologic perturbations accompany the previously documented anatomic changes caused by the presence of coronary atherosclerosis, despite successful revascularization of angiographically visible proximal stenoses, would be of importance in understanding the pathophysiology of obstructive coronary disease.

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References

- Favaloro RG: Saphenous vein graft in the surgical treatment of coronary artery disease. Operative technique. *J Thorac Cardiovasc Surg* **59**: 178, 1969
- Favaloro RG: Direct myocardial revascularization: A ten year journey. Myths and realities. Louis F. Bishop Lecture. *Am J Cardiol* **43**: 109, 1979
- Gruentzig AR, Senning A, Siegenthaler WE: Nonoperative dilatation of coronary artery stenosis: Percutaneous transluminal coronary angioplasty. *N Engl J Med* **301**: 61, 1979
- Gruentzig AR: Percutaneous transluminal coronary angioplasty: six years' experience. *Am Heart J* **107**: 818, 1984
- Peduzzi P, Hultgren HN: Effect of medical vs surgical treatment on symptoms in stable angina pectoris. The Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. *Circulation* **60**: 888, 1979
- Kent KM, Bentivoglio LG, Block PC, Cowley MJ, Dorros G, Gosselin AJ, Gruentzig A, Myler RK, Stertzer SH, Williams DO, Fisher L, Gillespie MJ, Dettre K, Kelsey S, Mullin SM, Mock MD: Percutaneous transluminal coronary angioplasty: report from the Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* **49**: 2011, 1982
- Kloster FE, Kremkau EL, Ritzmann LW, Rahimtoola SH, Rosch J, Kanarek PH: Coronary bypass for stable angina: a prospective randomized study. *N Engl J Med* **300**: 149, 1979
- Williams DO, Riley RS, Singh AK, Most AS: Restoration of normal coronary hemodynamics and myocardial metabolism after percutaneous transluminal coronary angioplasty. *Circulation* **62**: 653, 1980
- Barry WH, Pfeiffer JF, Lipton MJ, Tilkian AG, Hultgren HN: Effects of coronary artery bypass grafting on resting and exercise hemodynamics in patients with stable angina pectoris: a prospective randomized study. *Am J Cardiol* **37**: 823, 1976
- Rothman MT, Baim DS, Simpson JB, Harrison DC: Coronary hemodynamics during percutaneous transluminal coronary angioplasty. *Am J Cardiol* **49**: 1615, 1982
- Rahimtoola SH: Postoperative exercise response in the evaluation of the physiologic status after coronary bypass surgery. *Circulation* **65**(suppl II): II-106, 1982
- Ritchie JL, Narahara KA, Trobaugh GB, Williams DL, Hamilton GW: Thallium-201 myocardial imaging before and after coronary revascularization. Assessment of regional myocardial blood flow and graft patency. *Circulation* **56**: 830, 1977
- Scholl JM, Chaitman BR, David PR, Dupras G, Brevers G, Val PG, Crepeau J, Lesperance J, Bourassa MG: Exercise electrocardiography and myocardial scintigraphy in the serial evaluation of the results of percutaneous transluminal coronary angioplasty. *Circulation* **66**: 380, 1982
- Kent KM, Borer JS, Green MV, Bachrach SL, McIntosh CL, Conkle DM, Epstein SE: Effects of coronary artery bypass on global and regional left ventricular function during exercise. *N Engl J Med* **298**: 1434, 1978
- Kent KM, Bonow RO, Rosing DR, Ewels CJ, Lipson LC, McIntosh CL, Bachrach S, Green M, Epstein SE: Improved myocardial function during exercise after successful percutaneous transluminal coronary angioplasty. *N Engl J Med* **306**: 441, 1982
- Williams D, Singh A, Most A: Sustained efficacy of coronary angioplasty documented by stress testing at one year. *J Am Coll Cardiol* **1**: 644, 1983 (abst)
- Meier B, Gruentzig AR, Siegenthaler WE, Schlumpf M: Long-term exercise performance after percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. *Circulation* **68**: 796, 1983
- Coffman JD, Gregg DE: Reactive hyperemia characteristics of the myocardium. *Am J Physiol* **199**: 1143, 1960
- Olsson RA, Gregg DE: Myocardial reactive hyperemia in the unanesthetized dog. *Am J Physiol* **208**: 224, 1965
- Gould KL, Lipscomb K, Hamilton GW: Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measure of coronary flow reserve. *Am J Cardiol* **33**: 87, 1974
- Gould KL, Lipscomb K: Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* **34**: 48, 1974
- Cole JS, Hartley CJ: The pulsed Doppler coronary artery catheter. Preliminary report of a new technique for measuring rapid changes in coronary flow velocity in man. *Circulation* **56**: 18, 1977
- Marcus M, Wright C, Doty D, Eastham C, Laughlin D, Krumm P, Fastenow C, Brody M: Measurements of coronary velocity and reactive hyperemia in the coronary circulation of humans. *Circ Res* **49**: 877, 1981
- Vogel RA, LeFree MT, Bates ER, O'Neill WW, Foster RK, Kirilin PC, Smith D, Pitt B: Application of digital techniques to selective coronary arteriography: Use of myocardial contrast appearance time to measure coronary flow reserve. *Am Heart J* **107**: 153, 1984
- Hodgson JMcB, LeGrand V, Bates ER, Mancini GBJ, Aueron FM, O'Neill WW, Simon SB, Beaman GJ, LeFree MT, Vogel RA: Validation in dogs of a rapid angiographic technique to measure relative coronary blood flow during routine cardiac catheterization. *Am J Cardiol* **55**: 188, 1985
- O'Neill WW, Walton JA, Bates ER, Colfer HT, Aueron FM, LeFree MT, Pitt B, Vogel RA: Criteria for successful coronary angioplasty, as assessed by alterations in coronary vasodilator reserve. *J Am Coll Cardiol* **3**: 1382, 1984
- Bates ER, Vogel RA, LeFree MT, Kirilin PC, O'Neill WW, Pitt B: The chronic coronary flow reserve provided by saphenous vein bypass grafts as determined by digital coronary radiography. *Am Heart J* **108**: 462, 1984
- Pichard AD, Gorlin R, Smith H, Ambrose J, Meller J: Coronary flow studies in patients with left ventricular hypertrophy of the hypertensive type. Evidence for an impaired coronary vascular reserve. *Am J Cardiol* **47**: 547, 1981
- Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL: Decreased coronary reserve: A mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. *N Engl J Med* **307**: 1362, 1982
- Pichard AD, Smith H, Holt J, Meller J, Gorlin R: Coronary vascular reserve in left ventricular hypertrophy secondary to chronic aortic regurgitation. *Am J Cardiol* **51**: 315, 1983
- White CW, Wright CB, Doty DB, Hiratzka LF, Eastham CL, Harrison DG, Marcus ML: Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* **310**: 819, 1984
- Kakos GS, Oldham HN, Dixon SH, Davis RW, Haggren P-O, Sabiston DC: Coronary artery hemodynamics after aorto-coronary artery vein bypass. *J Thorac Cardiovasc Surg* **63**: 849, 1972
- Folts JD, Kahn DR, Bittar N, Rowe GG: Effects of partial obstruction on phasic flow in aortocoronary grafts. *Circulation* **51**(suppl I): I-148, 1975
- Brandt B, Martins JB, Marcus ML: Anomalous origin of the right coronary artery from the left sinus of Valsalva. *N Engl J Med* **309**: 596, 1982

35. Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackersstein H, Roberts WC: Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med* **91**: 350, 1979
36. Roberts WC, Jones AA: Quantitation of coronary arterial narrowing at necropsy in sudden coronary death: analysis of 31 patients and comparison with 25 control subjects. *Am J Cardiol* **44**: 39, 1978
37. Roberts WC, Jones AA: Quantification of coronary arterial narrowing at necropsy in acute transmural myocardial infarction: analysis and comparison of findings in 27 patients and 22 controls. *Circulation* **61**: 786, 1980
38. Barger AC, Beeuwkes R, Lainey LL, Silverman KJ: Hypothesis: vasa vasorum and neovascularization of human coronary arteries. A possible role in the pathophysiology of atherosclerosis. *N Engl J Med* **310**: 175, 1984
39. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* **288**: 373, 1980
40. Habib JB, Wells SL, Williams CL, Henry PD: Atherosclerosis impairs endothelium-dependent arterial relaxation. *Circulation* **70** (suppl II): II-123, 1984 (abst)
41. Saphir O, Ohringer L, Wong R: Changes in the intramuscular coronary branches in coronary arteriosclerosis. *Arch Pathol* **62**: 159, 1956
42. Cannon RO, Watson RM, Rosing DR, Epstein SE: Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* **1**: 1359, 1983
43. Folts JD, Crowell EB, Rowe GG: Platelet aggregation in partially obstructed vessels and its elimination with aspirin. *Circulation* **54**: 365, 1976
44. Armstrong ML, Heistad DD, Marcus ML, Piegors DJ, Aboud FM: Hemodynamic sequelae of regression of experimental atherosclerosis. *J Clin Invest* **71**: 104, 1983
45. Vogel RA: The radiographic assessment of coronary blood flow parameters. *Circulation* **72**: ?, 1985
46. LeGrand V, Hodgson JMcB, Bates ER, Auerson FM, Mancini GBJ, Smith JS, Vogel RA: Abnormal coronary flow reserve and abnormal radionuclide exercise tests in patients with normal coronary angiograms. *J Am Coll Cardiol* **5**: 531, 1985 (abst)
47. Opherk D, Zebe H, Weihe E, Mall G, Durr C, Gravert B, Mehmehl HC, Schwarz F, Kubler W: Reduced coronary dilatory capacity and ultrastructure changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation* **63**: 817, 1981
48. Berger HJ, Sands MJ, Davies RA, Wackers FJ, Alexander J, Lachman AS, Williams BW, Zaret BL: Exercise left ventricular performance in patients with chest pain, ischemic-appearing exercise electrocardiograms, and angiographically normal coronary arteries. *Ann Intern Med* **94**: 186, 1981
49. Rozanski A, Diamond GA, Forrester JS, Berman DS, Morris D, Swan HJC: Alternative referent standards for cardiac normality. Implications for diagnostic testing. *Ann Intern Med* **101**: 164, 1984
50. Hoffman JIE: Maximal coronary flow and the concept of vascular reserve. *Circulation* **70**: 153, 1984