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Technical Note

Limitations of the Zero Crossing Detector in the Analysis of Intracoronary Doppler: A Comparison With Fast Fourier Transform Analysis of Basal, Hyperemic, and Transstenotic Blood Flow Velocity Measurements in Patients With Coronary Artery Disease

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The current clinical standard for the analysis of intracoronary Doppler signals is the application of a zero-crossing (ZC) detector. However, the accuracy of the method is questionable, especially in areas of disturbed flow, as confirmed by in vitro studies, animal experiments, and intraoperative observations. The aim of this study is the comparison of a conventional ZC detector and a custom-designed spectral analyzer (fast Fourier transform, FFT) in the analysis of intracoronary Doppler signals obtained in 19 patients undergoing coronary angioplasty.

A 3F catheter with an end-mounted Doppler ceramic crystal was placed over an 0.014″ guidewire in a normal or near-normal segment proximal to the lesion to be dilated. The Doppler signal was recorded before and after intracoronary infusion of 12.5 mg of papaverine. In 9 patients high flow velocities could be recorded when the catheter was advanced across the stenosis.

The blood flow velocity measurements obtained with ZC were significantly lower than the maximal FFT flow velocity measurements (16±12 cm/s vs. 29±18 cm/s, $p < .001$). In all the conditions of Doppler signal acquisition (baseline, hyperemia, stenosis) a large scattering of the signed differences between corresponding measurements was observed. The standard deviation of the difference ZC-FFT was ±11 cm/s and ±5 cm/s for the maximal and mean FFT flow velocity, corresponding in both cases to ±37% of the mean of the ZC and FFT measurements. Large differences were also observed in the values of coronary flow reserve (CFR) calculated as the ratio between ZC and FFT flow velocity measurements 30 s after papaverine intracoronary and at baseline. The standard deviation of the difference ZC-FFT based CFR was ±1.3 and ±1.2 for the values derived from the maximal and mean FFT flow velocities (percent difference ±32% and ±37%, respectively).

In conclusion, the measurements obtained from the same intracoronary Doppler signal analyzed with a ZC detector and an FFT technique showed large differences in various conditions of flow and also in the assessment of relative flow velocity derived indices such as CFR. Spectral analysis should replace the current use of a ZC detector for the evaluation of coronary Doppler signals, even for the assessment of relative flow velocity changes.

Key words: blood flow velocity, Doppler ultrasound, coronary stenosis, coronary flow reserve

INTRODUCTION

Spectral analysis has replaced the use of zero-crossing (ZC) detectors in most applications of Doppler ultrasound in cardiology. With a ZC detector the Doppler shift is measured from the interval between each pair of adjacent ZCs of the same polarity. Although this technique is adequate for a simple sinusoidal signal, only a rough approximation of the mean frequency is obtained

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when ZC is used for the analysis of composite Doppler signals induced by the presence of scatterers of different velocity in the Doppler sample volume [1,2]. The main advantages of the analysis of the full frequency spectrum of the Doppler signal are the detection of the maximal Doppler frequency and the more accurate calculation of the mean Doppler frequency from the weighted intensity of the signal for each frequency. Furthermore, the presence of noise can be more easily detected and distinguished from the physiologic signal. Despite these advantages of spectral analysis, ZC detectors are almost invariably used in recent reports applying intracoronary Doppler [3–5]. The small sample volume of most intracoronary Doppler probes and the use of relative rather than absolute measurements are possible arguments supporting the use of a ZC detector for the analysis of intracoronary signals [6].

Aim of this study is the comparison of a conventional ZC detector and a custom-designed spectral analyzer using a fast Fourier transform (FFT) algorithm for the analysis of intracoronary Doppler recordings. To this purpose intracoronary Doppler signals have been recorded and simultaneously analyzed with the two techniques in baseline conditions, during pharmacologically induced hyperemia, and in areas of disturbed flow (stenosis) in 19 patients undergoing coronary angioplasty.

MATERIALS AND METHODS

Patients

The Doppler studies were performed in 19 patients (age 57 ± 12 years, 11 men and 8 women) undergoing percutaneous treatment of symptomatic high-grade coronary stenosis (14 balloon angioplasty, 5 directional atherectomy). The protocol was approved by the Ethics Committee Erasmus University/Dijkzigt Hospital (protocol #104.975/1990/55). Written informed consent was obtained in all cases. The treated vessel was the left anterior descending artery in 8 cases, the right coronary artery in 6 patients, and the left circumflex artery in 5 patients.

Catheterization Procedure

The Doppler transducer consisted of a 20 MHz annular piezoelectric crystal [7] mounted at the tip of a 3F (diameter = 1 mm) intracoronary catheter (Schneider, Zürich, Switzerland). After systemic heparinization with 10,000 I.U. and intracoronary injection of 2–3 mg of isosorbide-dinitrate, the Doppler catheter was inserted into the proximal coronary artery through the guiding catheter and along an 0.014″ guidewire (Monorail technique). The position of the Doppler probe was optimized in order to obtain stable recordings in basal conditions. Afterwards, 12.5 mg of papaverine was injected intracoronarily through the guiding catheter and a new recording was obtained after 30 s [8,9]. The guiding catheter was withdrawn from the coronary ostium to avoid limitations of flow during hyperemia. Based on clinical conditions and severity and characteristics of the stenosis an attempt to advance the Doppler catheter across the stenosis was performed in 14 cases before angioplasty and in 4 cases after angioplasty. In 3 cases the severity of the lesion precluded the passage of the Doppler catheter. No complications related to the use of the Doppler catheters occurred. The entire procedure of acquisition of the Doppler tracings, from insertion to withdrawal of the Doppler catheter, had a mean duration of 12 min (range 7–31 min).

Doppler Recording and Analysis

The Doppler catheter was activated with an MVD pulsed Doppler velocimeter (Millar Instruments, Houston, TX, USA) with a carrier frequency of 20 Mhz and a pulse repetition frequency of 62.5 kHz. The gate control (sample volume of 0.46 mm in depth, movable from 1 to 10 mm from the catheter tip) was adjusted from 2 to 4 mm to optimize the signal intensity and characteristics. Low frequencies (<200 Hz) were partially removed using a high-pass filter. The quadrature audio signal was simultaneously analyzed with an internal ZC detector and transmitted to a spectral analyzer. This system uses an ADSP-2100A signal processor provided with two analog/digital converters (AD 1332). The FFT analysis was performed on 256 samples every 10 ms and transmitted across a parallel interface to an Olivetti M250 PC. With both systems the Doppler frequencies (kHz) were transformed in velocity (cm/s) by multiplying the frequency shift by 3.75 times according to the Doppler equation. After the recording of a calibration signal, the phasic and time-averaged ("mean") ZC velocities were continuously recorded on a strip-chart recorder. When a stable signal was obtained in basal conditions, across the stenosis and 30 s after papaverine injection, the ZC velocities were recorded at 25 mm/s simultaneously to the acquisition and storage of 10 s of signal processed with the FFT analyzer (Fig. 1). The time-averaged ("mean") ZC flow velocity was compared with the time-averaged maximal and mean FFT simultaneously acquired flow velocities automatically calculated as the 90th and 50th percentile of the flow velocity spectrum distribution, respectively.

Coronary flow reserve (CFR) was calculated as the ratio between coronary velocity 30 s after intracoronary papaverine infusion and at baseline (Fig. 2).

Statistical Analysis

The statistical significance of the difference between simultaneously acquired time-averaged ZC and maximal

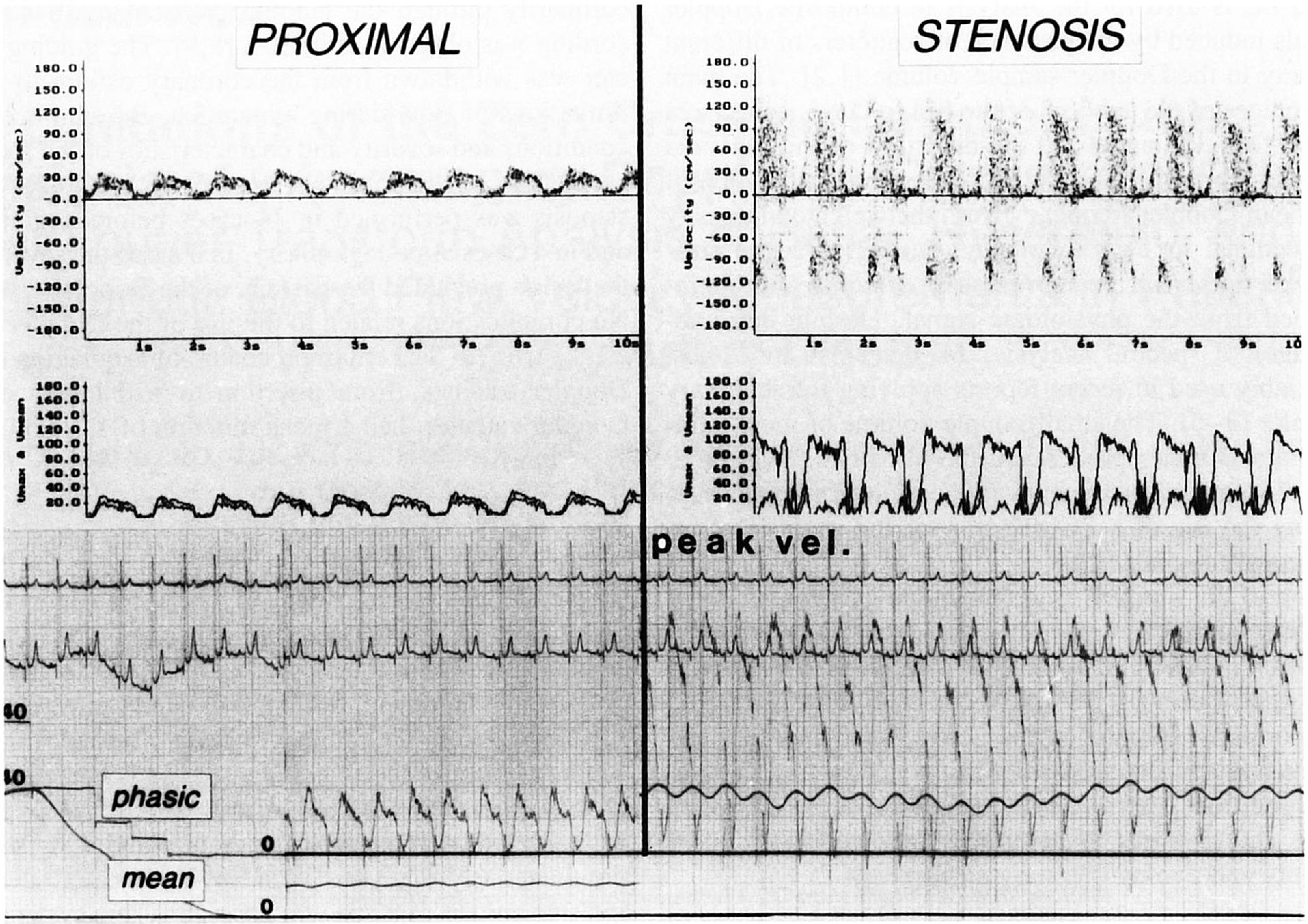

Fig. 1. Example of Doppler blood flow velocity recording in the proximal (PROXIMAL) left anterior descending coronary artery and with the Doppler catheter advanced across the stenosis (STENOSIS). Note that in the right upper tracing, recorded across the stenosis and analyzed with the FFT technique, the flow velocities higher than 120 cm/s are shown as negative because of frequency aliasing. Consequently, the algorithms automatically applied for calculation of maximal (Vmax) and mean (Vmean) blood flow velocity underestimated the true flow velocity. In the ZC tracing (lower part of the illustration, with the calibration signals for both phasic and time-averaged ("mean") flow velocity shown on the left) no clear evidence of the presence of frequency aliasing indicated that the ZC flow velocity measurement was falsely low.

and mean FFT measurements and derived CFRs was evaluated using Student's t-test. The time-averaged ("mean") ZC flow velocity was compared with the corresponding maximal and mean FFT velocities using linear regression analysis. The regression equation was separately calculated for the measurements at baseline, during hyperemia, and across the stenosis. Subsequently, according to the method described by Bland and Altman for the assessment of the agreement between different methods of measurement [10], the signed differences of the corresponding measurements were plotted against the mean of the measurements.

RESULTS

Forty-eight Doppler recordings were available for comparison (23 recordings in baseline conditions, 16 at peak papaverine effect, 9 across the stenosis). Papaverine injection was not performed in 3 patients. In 4 patients the measurements during hyperemia were impossible because of frequency aliasing (2 cases) and of signal deterioration after papaverine infusion (2 cases). In 3 of the 15 recordings across the stenosis a complete obstruction was induced by the Doppler catheter, with the development in 2 cases (excluded from this comparative study) of collateral circulation (reversed flow with very low negative flow velocity). In 3 cases frequency aliasing precluded the analysis of the tracings (Fig. 1). In 4 of the remaining 9 recordings mean FFT velocities could not be measured because of the impossibility to correctly analyze the flow velocity signal in the presence of prominent artifacts from vessel wall movements.

Comparison Between ZC and FFT Flow Velocity Measurements

The blood flow velocities measured with the ZC detector were significantly lower than the maximal FFT velocities (16±12 vs. 29±18 cm/s, $p < .001$). No sig-

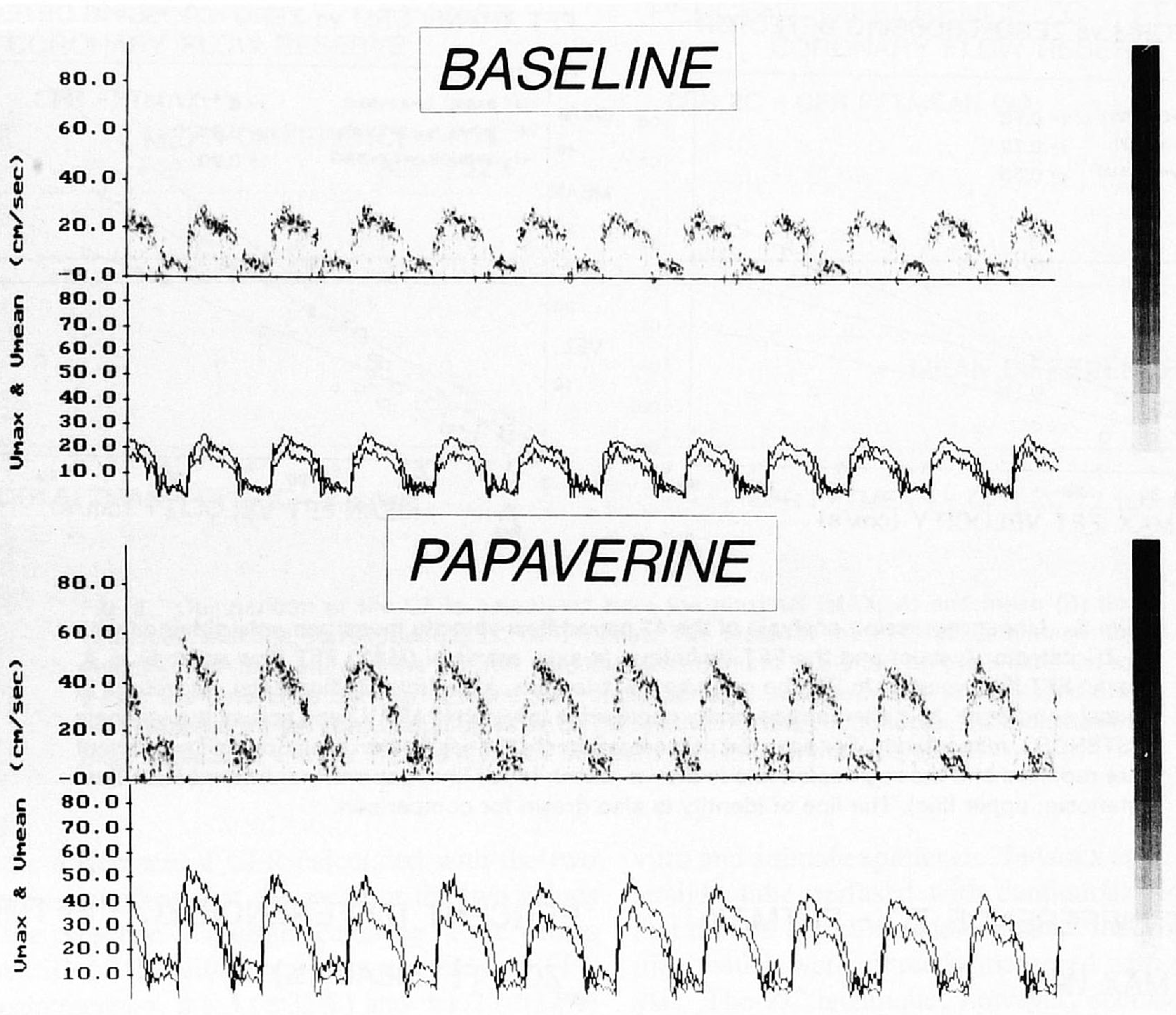

Fig. 2. Example of flow velocity measurement with the FFT analysis system used at the Thoraxcenter. The upper tracing (BASELINE) shows the spectral analysis of 10 s of Doppler flow velocity recording in the left anterior descending artery in basal conditions. The lower lines indicate the automatically calculated maximal flow velocity (Vmax) and mean flow velocity (Vmean). In the lower tracing (PAPAVERINE) the blood flow velocity increase 30 s after intracoronary injection of 12.5 mg of papaverine is shown in the same patient and with the same catheter position.

nificant differences were observed between ZC and mean FFT flow velocity measurements (16±12 vs. 15±9 cm/s, NS).

In Figure 3 linear regression analysis was used to compare ZC flow velocity measurements with the corresponding maximal (A) and mean (B) FFT flow velocity measurements. As evident from the comparison in Figure 3A of the three regression lines with the line of identity (slope of the regression line for the three series of measurement = 0.55), the blood flow velocity measurements obtained with ZC, a technique based on the averaging of the Doppler signal, were lower than the maximal FFT coronary blood flow velocities. The overall regression coefficient for the three series of measurements was 0.80. A better correlation was observed when ZC and mean FFT measurements were compared (Fig. 3B), with a slope of the cumulative regression line of 1.06 and an r value of 0.89.

In Figure 4 the signed percent differences of the corresponding ZC and FFT measurements are plotted against their mean value. As predicted from the principle of analysis of the ZC detector, negative differences were observed in the comparison with the maximal FFT blood flow velocity (mean −58%) while the mean difference with the mean FFT flow velocity measurements was −4%. With both techniques, however, a large scattering of the signed differences was observed (sd of the ZC/FFT difference = ±11 and ±5 cm/s for maximal and mean FFT velocities, equal to 37% of the mean of the ZC + FFT flow velocity measurements in both cases).

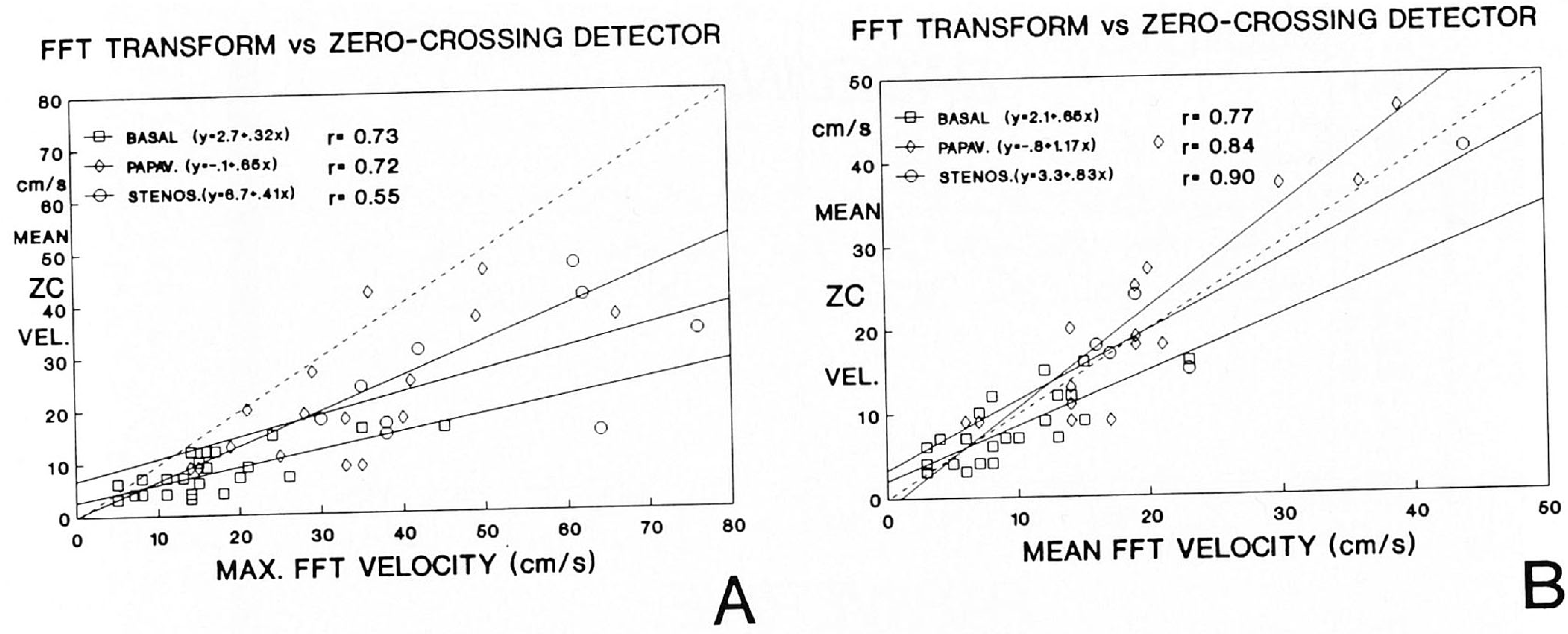

Fig. 3. Linear regression analysis of the 43 paired flow velocity measurements obtained with a ZC detector (y-axis) and the FFT technique (x-axis, maximal (MAX) FFT flow velocity in A, mean FFT flow velocity in B). The open boxes, triangles, and circles indicate the recordings in basal conditions, 30 s after intracoronary papaverine infusion (PAPAV.) and across the stenosis (STENOS.), respectively. For each set of measurements the regression equation and coefficient are reported and the regression line is drawn (basal: lower line; papaverine: intermediate line; stenosis: upper line). The line of identity is also drawn for comparison.

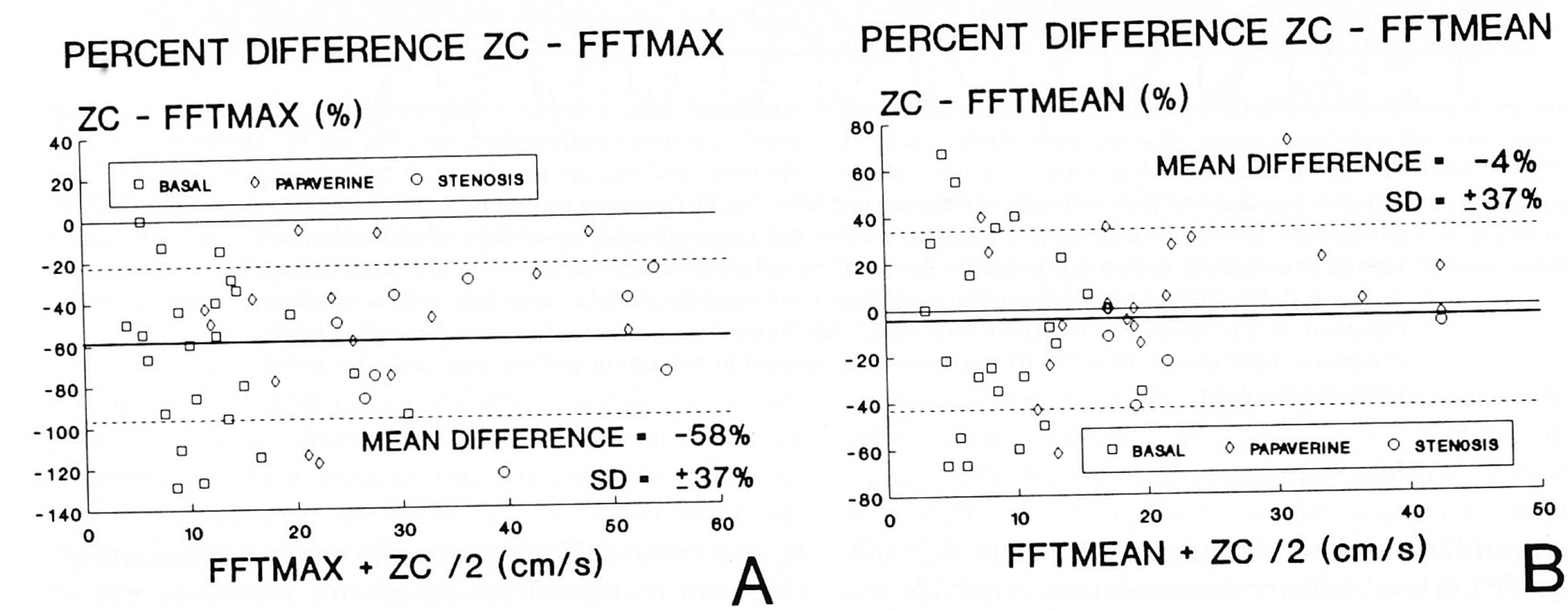

Fig. 4. Comparison of the FFT maximal (MAX, A) and mean (B) flow velocities with the corresponding ZC measurements. The mean of the FFT maximal/mean flow velocity measurement and the ZC flow velocity measurement is plotted on the x-axis. On the y-axis the signed difference between ZC and FFT paired measurements is plotted after normalization for the corresponding value on the x-axis (percent value). The thick continuous line indicates the mean difference and the dashed lines the standard deviation of the difference. Note the underestimation of the maximal FFT velocities and the large scattering of the data-points (SD= ±37% for both maximal and mean FFT velocities) over the wide range of explored velocities and in conditions of basal and hyperemic flow as well as in the recordings across the stenosis.

Comparison of ZC vs. FFT Analysis: Coronary Flow Reserve

Higher values of CFR were calculated from the ZC flow velocity measurements than from the FFT measurements (3.2±3.1 vs. 2.4±1.4 and 3.2±3.1 vs. 2.3±1.4 for maximal and mean FFT CFR measurements, respectively). Both differences, however, were not statistically significant.

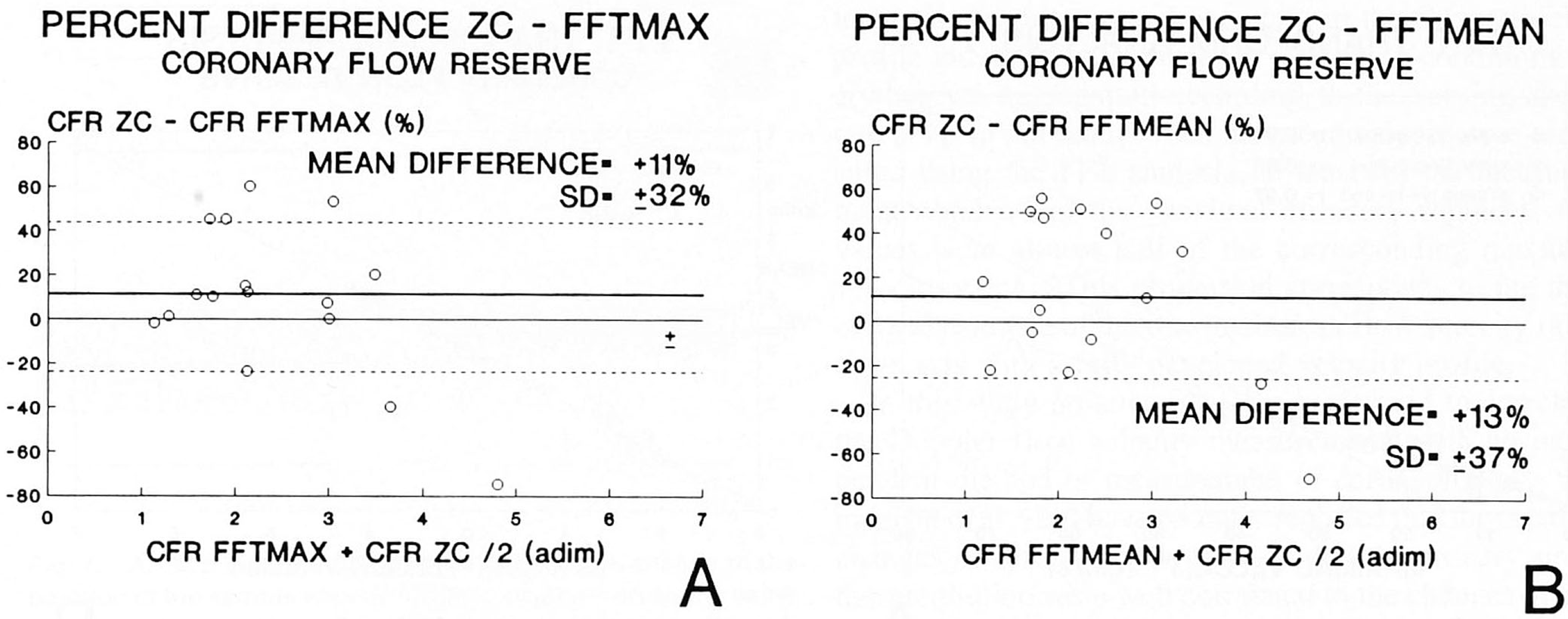

Fig. 5. Comparison of the CFRs calculated from the maximal (MAX, A) and mean (B) flow velocities with the corresponding ZC CFR values. The mean of the FFT maximal/mean flow velocity measurement and the ZC flow velocity measurement is plotted on the x-axis. On the y-axis the difference between ZC and FFT corresponding measurements is displayed after normalization for the corresponding value on the x-axis. The thick continuous line indicates the mean difference and the dashed lines the standard deviation of the difference.

When the difference of CFR calculated with the two techniques is plotted against the mean of the two values (Fig. 5), the presence of a large scattering of the values is evident (SD of the difference between ZC and FFT CFR measurements= ±1.3 (±32%) and ±1.2 (±37%) for maximal and mean FFT CFR measurements, respectively).

Maximal Vs. Mean Fast Fourier Transform Flow Velocities

The mean FFT flow velocity was obviously smaller than the maximal FFT flow velocity (15±9 vs. 29±18 cm/s, $p < .001$).

In Figure 6A linear regression analysis shows that the relation between the paired mean and maximal FFT measurements in basal and hyperemic conditions was defined by a regression equation with an intercept almost equal to 0 and a slope close to 0.5.

Similar values of CFR were calculated from maximal and mean FFT flow velocity measurements (2.4±1.4 vs. 2.3±1.4, NS).

As evident from the linear regression analysis of these data (Fig. 6B), maximal and mean FFT CFR values were highly correlated (r= 0.95), with a regression line almost superimposed to the line of identity.

DISCUSSION

The usefulness of the FFT analysis in the evaluation of intravascular Doppler signals is supported by previous in vitro and animal experience. Tadaoka et al. [11], using a straight tube perfused with continuous flow, observed that the ZC detector underestimated the true flow velocities, which were correctly measured with the FFT analysis. The ZC technique, however, seemed to be sufficiently reliable for the evaluation of relative flow velocity changes. Kajiya et al. [12] have reported that the flow velocity measured with a ZC detector is consistently different from the mean flow velocity detected with the FFT method in stenotic canine femoral arteries. In a canine model of adjustable coronary flow, Yock et al. [13] reported that the absolute flow measured with an electromagnetic flowmeter could be successfully estimated using the maximal velocities measured with the FFT but was poorly correlated to the flow velocities measured with a ZC detector. The same group in a separate experiment used stenosis phantoms of known diameter placed in canine coronary arteries and reported that the maximal FFT velocity proximal and across the stenosis gave the best estimate of the true cross-sectional area of the stenosis based on the continuity equation [14]. On the contrary, the corresponding flow velocities measured with a conventional ZC detector were poorly correlated with the cross-sectional areas where the sample volume was located. Tanouchi et al. [15] reported that the flow velocity measured in the left anterior descending coronary artery with the FFT spectral analysis correlated well with those estimated by electromagnetic flowmeter (y = .88x + 9.7, r = .93), whereas the velocities measured with a ZC detector significantly un-

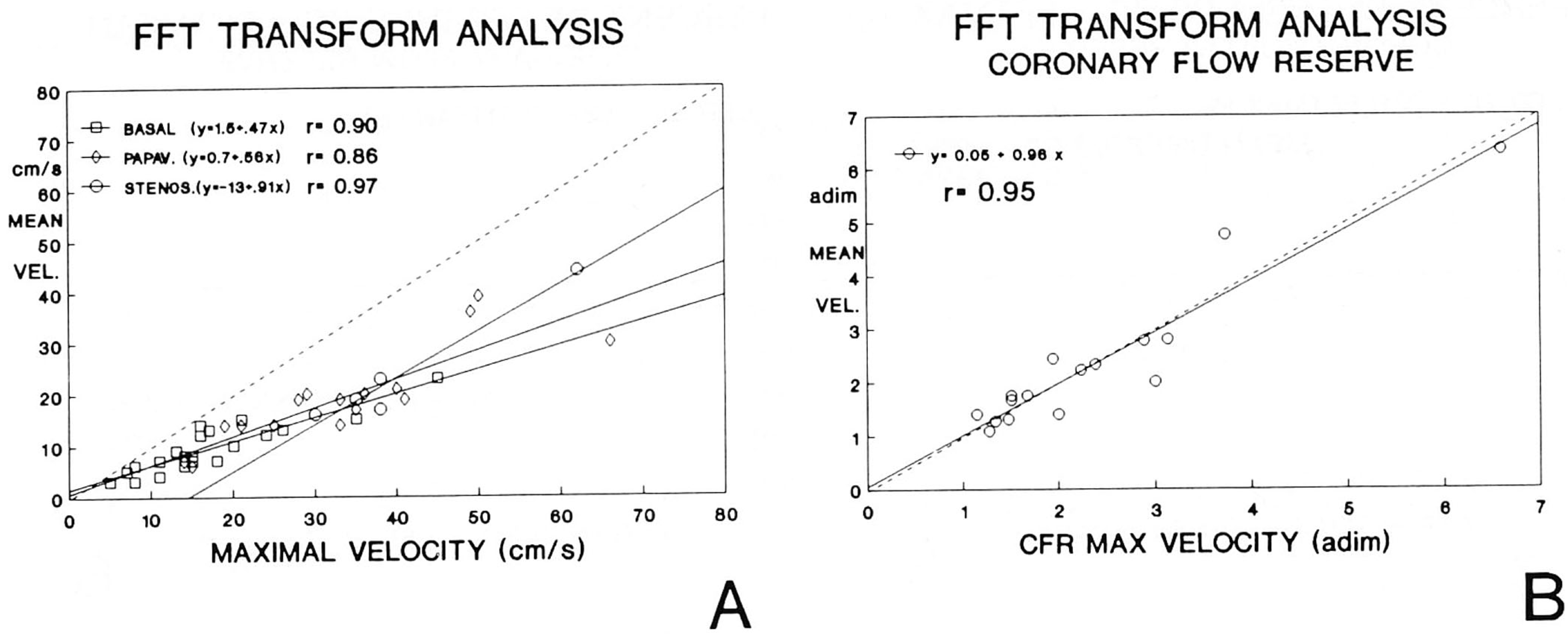

Fig. 6. A: Linear regression analysis of the mean FFT (y-axis) vs. maximal FFT (x-axis) flow velocity measurements. Symbols as in Figure 3. B: Linear regression analysis of the CFR calculated from the mean FFT (y-axis) and the maximal (MAX, X-axis) flow velocity measurements. The regression line (continuous line) is almost superimposed to the line of identity (dashed line).

derestimated those by electromagnetic flowmeter (y = .23x + 1.6, r = .82). Our study confirms that the agreement between ZC and FFT flow velocity measurements is too poor to allow the use of these techniques interchangeably for the analysis of the coronary signal. In principle ZC is an adequate technique for the assessment of a laminar flow containing only scatterers of the same velocity. In most of our FFT tracings, however, broad velocity spectra were recorded suggesting that the sample volume, despite the relatively small dimensions (longitudinal depth of the three-dimensional volume of 0.46 mm), included various blood flow lamina within the velocity profile of the vessel. Furthermore, the sample volume should be considered not as a spatially well demarcated region outside which no signal is received from the ultrasound transducer but rather as the area of greatest sensitivity [1].

Although a high pass filter was used in all cases, the Doppler signal was often disturbed by the presence of low velocity/high intensity signals induced by the movement of the coronary wall, a condition that further increases the complexity of the recorded Doppler signal. Experienced users of the ZC detector can adjust the position of the probe in order to improve the quality of the Doppler signal based on the careful evaluation of the audio feedback and the absence of ''spiking'' in the recording. With the use of spectral analysis the wall thumps are clearly distinguished from the flow velocity signal and their presence does not influence the measurements of maximal flow velocity. The ZC tracing, on the contrary, does not directly display these non-flow related signals which are averaged with the blood flow signal resulting in a misinterpretation of the true flow velocity.

The presence of disturbed flow or turbulence is a condition known to greatly impair the accuracy of the ZC detector, as shown by previously reported animal experiences [12]. In this study the scattering of the differences between corresponding ZC and FFT measurements was similar for the signals acquired across the stenosis and in the proximal artery probably because the Doppler system that we used was unable to record the true transstenotic maximal velocity. The relatively large dimensions of the catheter in comparison with the stenosis diameter induced partial or complete obstruction to flow and the high frequency and the pulse repetition rate of the system precluded a reliable measurement of flow velocities > 120 cm/s. The corresponding phasic ZC tracings (Fig. 1) showed no clear changes warning that frequency aliasing had occurred, inducing a falsely low flow velocity measurement.

An argument used to justify the use of the ZC detector is that intracoronary Doppler is a technique already confined to the assessment of relative flow velocity changes, for instance to study the effects of acute infusions of drugs or of coronary interventions, because of its well-known limitations for the measurement of absolute flow velocities (malalignment of the catheter with the maximal flow velocity, inclusion of a limited area of the velocity profile in the sample volume, presence of non-flow related disturbing signals) [16,17]. Our findings,

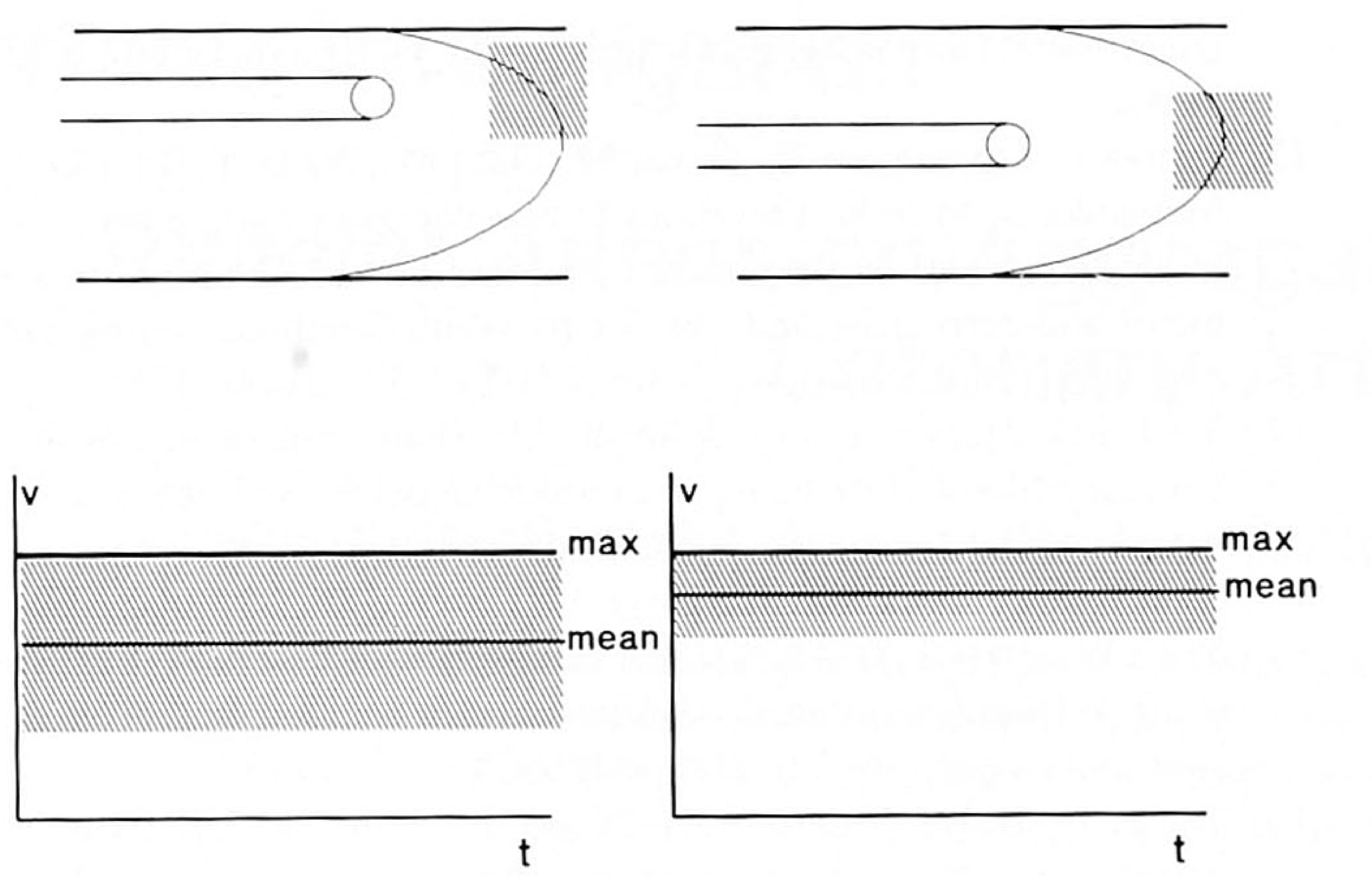

Fig. 7. Artist's representation of the effects of a change of the position of the sample volume (dashed square) across the same parabolic flow profile. A large difference is present in the calculated mean velocity while no changes are observed when the maximal velocity is considered. t = time; v = velocity.

however, do not corroborate the applicability of a ZC detector even for this simple purpose. As previously reported, Tadaoka et al. [11] found ZC reliable for the assessment of relative flow changes. The in vitro conditions of the study, in the presence of a continuous flow and of a stable catheter position, are very different from the more complex in vivo coronary application. In this latter situation the rough averaging process performed by the ZC detector is less likely to be linearly correlated to the true blood flow velocity changes.

The maximal blood flow velocity is detectable only using techniques of spectral analysis. The lower flow velocity measurements obtained with ZC are a predictable result because this technique measures a mean of all the Doppler shifts at a certain time. The use of the maximal flow velocity, however, gives substantial advantages over the Doppler measurements based on signal averaging, including the spectral mean velocity [18]. The average of the flow velocity signal can be modified by the presence of noise or artifacts that frequently occur during the acquisition of intracoronary Doppler recordings due to coronary wall motion and insufficient insulation of the Doppler catheter. The maximal velocity is less influenced by the presence of noise. The use of the maximal velocity, moreover, can partially obviate one of the most important limitations of intracoronary Doppler, the extreme space-dependency of the technique. As shown in Figure 7 changes of the position of the catheter in the vessel and, consequently, of the sample volume across the flow velocity profile can largely modify the measured mean velocity. The maximal velocity, however, does not change as long as the centerline of maximal flow is included in the sample volume. Another disadvantage of the use of averaged Doppler measurements is the different echogenicity in the flow velocity profile induced by the presence of varying conditions of erythrocyte aggregation according to the varying shear rate [19]. In our study when the mean velocity was measured using the FFT analysis, at least for the measurement obtained in the proximal coronary segment, the values were almost half of the corresponding maximal velocity values. This proportion corresponds to the theoretical estimate of the maximal/mean flow velocity ratio in vessels with a fully developed velocity profile.

In this study no attempts were performed to correlate the Doppler flow velocity measurements with an independent method of measurement of coronary flow. Yamagishi et al. [20] have recently reported that the relative changes of coronary flow measured with coronary sinus thermodilution were well correlated to the changes of the measured diastolic Doppler flow velocities measured with an FFT spectral analyzer.

CONCLUSIONS

The results of the analysis of intracoronary Doppler signals recorded in various conditions of flow with a conventional ZC detector and the FFT technique of spectral analysis showed a poor agreement between the two techniques, even in the assessment of relative flow velocity changes. Based on these findings and on the well-known principles of operation of the two techniques, we suggest that spectral analysis should replace the current use of ZC detectors for the analysis of intracoronary Doppler tracings because of its unique capability to detect the maximal flow velocity and more accurately measure mean flow velocity and of the easier detection of frequency aliasing, wall motion artifacts, and other noise components precluding a meaningful interpretation of the Doppler recording or requiring a readjustment of the probe position.

ACKNOWLEDGMENTS

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REFERENCES

1. Hatle L, Angelsen B: Blood flow velocity measurements using the Doppler effect on backscattered ultrasound. In Hatle L, An-

gelsen B (eds): "Doppler Ultrasound in Cardiology." Philadelphia: Lea and Febiger, 1982, pp 32–70.

2. Lunt MJ: Accuracy and limitations of the ultrasonic Doppler blood flow velocimeter and zero crossing detector. Ultrasound Med Biol 2:1–10, 1975.
3. Wilson RF, Wyche K, Christensen BV, Laxson DD: Effects of adenosine on human coronary arterial circulation. Circulation 82: 1595–1606, 1990.
4. Golino P, Piscione F, Willerson JT, Cappelli-Bigazzi M, Focaccio A, Villari B, Condorelli M, Chiariello M: Divergent effects of serotonin on coronary artery dimensions and blood flow in patients with coronary atherosclerosis and control patients. N Engl J Med 324:641–648, 1991.
5. Zeiher AM, Drexler H, Wollschläger H, Just H: Endothelial dysfunction of the coronary microvasculature is associated with impaired coronary blood flow regulation in patients with early atherosclerosis. Circulation 84:1984–1992, 1991.
6. Wilson RF, Laughlin DE, Ackell PH, Chilian WM, Holids MD, Hartley CJ, Armstrong ML, Marcus ML, White CW: Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 72:82–92, 1985.
7. Sibley DH, Millar HD, Hartley CJ, Whitlow PL: Subselective measurement of coronary blood flow velocity using a steerable Doppler catheter. J Am Coll Cardiol 8:1332–1340, 1986.
8. Wilson RF, White CW: Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation 73:444–451, 1986.
9. Zijlstra F, Juillière Y, Serruys PW, Roelandt JRTC: Value and limitations of intracoronary adenosine for the assessment of coronary flow reserve. Cathet Cardiovasc Diagn 15:76–80, 1988.
10. Bland MJ, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 8: 307–309, 1986.
11. Tadaoka S, Kagiyama M, Hiramatsu O, Ogasawara Y, Tsujioka K, Wada Y, Sawayama T, Kajiya F: Accuracy of 20 MHz Doppler catheter coronary artery velocimetry for measurement of coronary blood flow velocity. Cathet Cardiovasc Diagn 19:205–213, 1990.
12. Kajiya F, Ogasawora Y, Nakai M, Goto M, Wada Y, Tadoka S, Matsuoka S, Mito K, Fuwruora T: Evaluation of human coronary blood flow with an 80 channel 20 MHz pulsed Doppler velocimeter and zero-cross and Fourier transform methods during cardiac surgery. Circulation 74(Suppl III):III-53–III-60, 1986.
13. Yock PG, Hargrave VK, Johnson EI: Measurement of absolute coronary blood flow using a Doppler catheter. Validation in an animal model (abstract). J Am Coll Cardiol 11:45A, 1988.
14. Johnson EL, Yock PG, Hargrave VK, Srebro JP, Manubens SM, Seitz W, Ports TA: Assessment of severity of coronary stenoses using a Doppler catheter. Validation of a method based on the continuity equation. Circulation 80:625–635, 1989.
15. Tanouchi J, Kitabatake A, Ishihara K, Fujii K, Uematsu M, Yoshida Y, Doi Y: Experimental validation of Doppler catheter technique using fast Fourier spectrum analysis for measuring coronary flow velocity. Circulation 80(Suppl II):II-566, 1989.
16. Serruys PW, Hermans WRM, Zijlstra F, De Feyter PJ: Coronary Doppler. In Topol EJ (ed): "Textbook of Interventional Cardiology." Boston: W.B. Saunders Company, 1990, pp 768–798.
17. Serruys PW, Julliere Y, Zijlstra, Roelandt JRTC: Coronary blood flow velocity during PTCA: a guide-line for assessment of functional results. Am J Cardiol 61:253–259, 1988.
18. Evans DH, Schlindwein FS, Levene MI: The relationship between time averaged intensity weighted mean velocity and time averaged maximum velocity in neonatal cerebral arteries. Ultrasound Med Biol 15:429–435, 1989.
19. De Kroon MGM, Slager CJ, Gussenhoven WJ, Serruys PW, Roelandt JRTC, Bom N: Cyclic changes of blood echogenicity in high frequency ultrasound. Ultrasound Med Biol 17:723–728, 1991.
20. Yamagishi M, Hotta D, Tamai J, Nakatani S, Miyatake K, Validity of catheter-tip Doppler technique in assessment of coronary flow velocity and application of spectrum analysis method. Am J Cardiol 67:758–762, 1991.

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Basic Investigation

Platelet Adhesion/Aggregation in an In Vitro Model of Coronary Artery Stenosis

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Platelet adhesion/aggregation (PAA) at a site of coronary artery stenosis is believed to be a process strongly modulated by local shear rates and the functional state of neighboring endothelium. One purpose of the present work, therefore, is to describe an in vitro model for the direct imaging of such PAA. Another is to apply the model to the question as to whether the use of nonionic vs. ionic contrast media (CM) in the presence of vascular endothelium contributes to PAA at the stenosis site. Toward these ends, we utilized a special flow chamber which incorporates a monolayer of endothelial cells (ECs), a step 66% flowpath constriction at a site preadsorbed with microfibrillar collagen, and arterial shear rates. By epifluorescence microscopy and digital image analysis of video recordings, PAA was found to be greater with dysfunctional ECs (pretreated with lysine acetylsalicylate) than with normal ECs, thereby confirming a modulatory role in PAA of functionally intact ECs. When nonionic (iohexol) or ionic (ioxaglate, diatrizoate) CM was added to the flowing blood at a concentration of 20% by non-red cell volume, PAA was inhibited in the order diatrizoate > ioxaglate > iohexol > saline control. No inhibition by any CM was seen, however, when chamber prefill culture medium containing 20% by volume CM was displaced by CM-free blood, in simulation of bolus administration of CM. In terms of inhibition of PAA during percutaneous transluminal coronary angioplasty (PTCA), therefore, our model provides a conceptual basis by which one may anticipate in flowing blood no clear benefit of ionic over nonionic CM. This is because the greater antiplatelet effects of the ionic CM are lost with hemodilution by CM-free blood, while a greater anti-EC effect is likely to persist.

Key words: contrast media, flowing blood, endothelial cells, videomicroscopy

INTRODUCTION

Only a very few animal and in vitro models of stenotic lesions exist which may shed light on the true pathophysiology of coronary artery thrombosis under dynamic flow conditions [1–3]. One purpose of the present communication is to describe a new in vitro model which incorporates controlled blood flow, vascular endothelium, a specified local stenosis geometry, and imaging of platelet adhesion/aggregation (PAA) at the microscopic level. A second purpose is to apply the model to the question as to whether the use of nonionic vs ionic contrast media during percutaneous transluminal coronary angioplasty (PTCA) contributes to platelet adhesion/aggregation at the stenosis site and, therefore, to a reported 0.23% incidence of death, myocardial infarction, or cerebrovascular accident during PTCA [4–6]. The presence of flowing blood is to be contrasted with the lack of throughflow and effects of hemodilution in Born–O'Brien platelet aggregometry [7], with which nonionic and ionic contrast media have both been shown to have antiplatelet effects [8,9]. Toward this end we studied and compared the nonionic contrast agent iohexol, as Omnipaque® 350 (Winthrop Pharmaceuticals, Inc., New York, NY), and the ionic agents sodium methylglucamine diatrizoate, as Renografin-76® (E.R. Squibb and Sons, Princeton, NJ), and ioxaglate, as Hexabrix 320 (Mallinkrodt, St. Louis, MO). Contrast media and saline as control were either mixed with blood or added to culture medium bathing endothelial cell monolayers prior to onset of blood flow.

MATERIALS AND METHODS

In Vitro Model

The key to our approach is the in vitro simulation of a stenotic coronary artery utilizing a flow chamber (Fig. 1) mounted on a microscope stage (see below). One surface

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