Transesophageal versus intracoronary Doppler measurements for calculation of coronary flow reserve

Manfred Zehetgruber*, Gerold Porenta, Gerald Mundigler, Deddo Mörtl, Thomas Binder, Günter Christ, Peter Probst, Helmut Baumgartner, Gerald Maurer, Peter Siostrzonek

Department of Cardiology, University of Vienna, Währinger Gürtel 18-20 Vienna A-1090, Austria

Received 25 February 1997; accepted 29 May 1997

Abstract

Objective: The present study was performed to compare coronary flow reserve by transesophageal Doppler echocardiography and intracoronary Doppler flow wire measurements in patients with LAD disease. Methods: 17 patients with various degree of LAD stenosis were studied. Intracoronary LAD Doppler measurements were performed at baseline and after intracoronary injection of 18 μg adenosine. Transesophageal coronary sinus and LAD Doppler measurements were performed at baseline and after intravenous dipyridamole 0.6 mg/kg/5 min. Coronary flow reserve was calculated as the ratio of hyperemic to baseline average peak velocities. Results: Coronary flow reserve was 2.44 ± 0.62 and 2.19 ± 0.76 for proximal and distal intracoronary measurements and was 2.25 ± 0.64 and 1.74 ± 0.63 for transesophageal LAD- and coronary sinus measurements. Proximal intracoronary flow reserve significantly correlated with transesophageal coronary sinus (r = 0.73, p ≤ 0.001) and LAD (r = 0.70, p ≤ 0.005) measurements, whereas distal intracoronary flow reserve only correlated with transesophageal coronary sinus flow reserve (r = 0.56, p ≤ 0.02). Receiver operating characteristic curve analysis demonstrated similar diagnostic accuracy of all applied techniques for detection of a significant LAD stenosis. Conclusions: Coronary flow reserve by both transesophageal techniques correlated with intracoronary Doppler flow wire measurements, however considerable discrepancies may occur in the individual patient. © 1997 Elsevier Science B.V.

Keywords: Coronary flow reserve; Transesophageal echocardiography; Intracoronary Doppler flow wire; Human; Coronary artery disease

1. Introduction

The vasodilator capacity of the coronary circulation provides important diagnostic information in a variety of cardiac diseases [1–5]. Accordingly, coronary flow reserve measurements have been employed to assess the physiologic significance of coronary stenoses and to evaluate microcirculatory function in disorders such as syndrome X and left ventricular hypertrophy. Coronary flow reserve measurements are most commonly performed by invasive methods or by positron emission tomography, both techniques being limited in their large-scale applicability [6,7]. Recent reports suggest the use of non-invasive measurement of coronary flow reserve by transesophageal Doppler echocardiography. Several groups have demonstrated the feasibility of this method by either evaluating blood flow velocity of the proximal left anterior descending coronary (LAD) artery [8–12] or of the coronary sinus [13,14] before and after vasodilator administration. However, invasive validation of transesophageal Doppler echocardiography by intracoronary measurements has not been performed.

Thus, the present study sought to compare coronary flow reserve as obtained by transesophageal Doppler echocardiography with intracoronary Doppler flow wire measurements.

* Corresponding author. Tel.: +43-140-400-4614; fax: +43-140-81148.

1 This work was presented in part at the 68th Scientific Sessions of the American Heart Association in Anaheim, November 1995.

0008-6363/97/$17.00 © 1997 Elsevier Science B.V. All rights reserved.

PII S0008-6363(97)00166-1
2. Methods

2.1. Patients

17 patients with single vessel disease of the proximal LAD without previous Q-wave myocardial infarction were prospectively included in this study. Patients with angiographically visible collateral vessels, wall motion abnormalities at rest, uncontrolled hypertension, elevated right heart pressures, bradycardia and tachycardia were excluded from the study. The mean age of these patients (12 men and 5 women) was 59 ± 2 years. 11 patients had stable angina pectoris, 6 patients were referred for unstable angina pectoris. No patient had angina or ischemic ECG changes at rest.

The investigation conformed with the principles outlined in the Declaration of Helsinki and the study protocol was approved by the local human subjects committee. Written informed consent was obtained from all patients. All vasoactive medication with the exception of short-acting nitrates was discontinued on the study day. Intracoronary measurements and transesophageal studies were performed within 24 h. The echocardiographer was unaware of the results of the Doppler flow wire measurements.

2.2. Coronary angiography

Selective coronary angiography was performed with a 8F Judkins guiding catheter from the femoral artery. Two to three orthogonal projections of the target lesion were obtained using a biplane angiography system (HICOR, Siemens Inc.). Quantitative coronary angiography (QCA) was performed from 35 mm cine film using a commercially available second generation QCA system (CMS, Cardiovascular Measurement System; Medis). Two to three enddiastolic image frames were analysed to obtain percent luminal diameter reduction of the stenosis and the highest stenosis grade was included for further analysis.

2.3. Intracoronary velocity measurements (IC-LAD)

A 0.014 inch, 14 MHz Doppler guide wire (FloWire, Cardiometrics) was advanced into the proximal part of the LAD. Doppler velocity profiles were displayed and an automated tracking algorithm was used to detect the maximal instantaneous flow velocity and to compute average peak velocity over two heart cycles as an index of coronary flow. Once a stable Doppler signal was obtained baseline flow velocity was recorded 1–2 cm proximal to the stenosis. After intracoronary administration of 18 μg adenosine [15,16] hyperemic flow response was recorded for 90 s. The wire was then advanced to a position ≥ 2 cm distal to the stenosis and measurements were repeated at baseline and after adenosine. Doppler measurements were recorded twice at each location and the average of two measurements was used for further analysis. Coronary flow reserve was calculated as the ratio of the respective hyperemic to baseline average peak velocity.

2.4. Transesophageal velocity measurements

The study was performed with a VINGMED 800 system (Sonotron) using a multiplane 5 MHz transesophageal probe. Transesophageal echocardiography was performed without sedation using topical anesthesia to the oropharynx. Continuous ECG-recording was obtained and arterial blood pressure was measured noninvasively at baseline and after dipyridamole administration.

2.5. Recording of coronary sinus flow velocity (TEE-CS)

A modified four chamber view with dorsal angulation of the transducer was used to visualize the ostium of the coronary sinus. The position of the probe was optimized until the coronary sinus with its ostium into the right atrium could be visualized throughout the cardiac cycle. Coronary sinus flow velocity recordings were performed with the Doppler sample volume placed in the coronary sinus within a distance of no more than 10 mm from its ostium. In all patients, the angle between the Doppler beam and the long axis of the coronary sinus was less than 30°. Flow signals were recorded during expiration and were repeated until constant flow signals of adequate quality were obtained.

2.6. Recording of LAD flow velocity (TEE-LAD)

The proximal LAD was visualized by positioning the transducer in a short axis plane slightly superior to the aortic valve. In most patients anterior and lateral angulation of the transducer was necessary for optimal imaging. Flow velocity was recorded by placement of the Doppler sample volume in the proximal LAD. As with coronary sinus recordings attempts were made to minimize the angle between the long axis of the vessel and the ultrasound beam.

After coronary sinus and LAD recordings were obtained at baseline, dipyridamole was administered intravenously at a constant infusion rate of 0.6 mg/kg over a 5 min period. In patients with an inadequate increase of heart rate of less than 10% an additional dipyridamole infusion of 0.28 mg/kg was infused for 2 min. Two minutes after cessation of dipyridamole infusion, coronary sinus and LAD velocity recordings were repeated. In case of anginal pain during dipyridamole infusion, aminophylline (0.12–0.24 g) was administered intravenously. Flow velocity recordings of the LAD and coronary sinus were performed in random order to avoid method-related errors due to different time intervals between dipyridamole administration and the respective flow velocity recordings. Videotape recordings of three to five cardiac cycles with optimum
Table 1
Hemodynamic findings

<table>
<thead>
<tr>
<th></th>
<th>Intracoronary study</th>
<th>Transesophageal study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Adenosine</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68 ± 13</td>
<td>69 ± 13</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132 ± 24</td>
<td>133 ± 23</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 ± 11</td>
<td>78 ± 9</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>9228 ± 2264</td>
<td>9327 ± 2962</td>
</tr>
</tbody>
</table>

BP = blood pressure.

* *p ≤ 0.0002 as compared to baseline.

* *p < 0.05 as compared to intracoronary study.

Fig. 1. (A) Left coronary angiogram demonstrating a 59% diameter stenosis in the proximal LAD. (B) Intracoronary flow velocity recording proximal to the stenosis at baseline and after adenosine resulting in a coronary flow reserve of 1.5. (C) Intracoronary flow velocity recording distal to the stenosis at baseline and after adenosine resulting in a coronary flow reserve of 1.4. (D) Transesophageal Doppler flow velocity recording in the proximal LAD at baseline and after dipyridamole resulting in a coronary flow reserve of 1.9. (E) Transesophageal Doppler flow velocity recording in the coronary sinus at baseline and after dipyridamole resulting in a coronary flow reserve of 1.4.
quality before and after dipyridamole were analyzed [8,10,13]. For both coronary sinus and LAD recordings, coronary flow reserve was calculated as the ratio of hyperemic to baseline average peak velocity (hand-tracing).

2.7. Statistical analysis

Data are expressed as mean ± SD. Intra- and interobserver variability of transesophageal flow reserve measurements was assessed in 10 randomly assigned patients from video-tape recordings. Intraobserver variability was determined by having one observer reevaluate coronary flow reserve at least one month apart and interobserver variability was determined by having two independent observers blindly evaluate flow reserve. For intra- and interobserver variability differences between separate measurements were calculated and the mean difference as well as the standard deviation of the differences were expressed as percentage of the mean coronary flow reserve. An analysis of variance for repeated measures and the Scheffe’s F test were performed to compare data obtained by various methods and to compare data before and after vasodilator application. Results of different methods for coronary flow reserve calculation were compared by linear regression analysis as well as by agreement analysis as proposed by Bland and Altman [17]. Sensitivity, specificity and overall predictive value for diagnosing significant coronary lesions (stenosis-diameter ≥ 50%) [18] were evaluated for various methods of flow reserve calculation. Based on the calculated sensitivities and specificities for various threshold values receiver operating characteristic curves were developed. Additionally, on the basis of previous studies threshold values operating characteristic curves were developed. Additionally, on the basis of previous studies threshold values were chosen to differentiate normal and abnormal vasodilator capacity. Statistical significance was considered at a p value of < 0.05.

3. Results

3.1. Feasibility and reproducibility

Adequate transesophageal Doppler recordings were obtained by the coronary sinus method in all patients and by the LAD method in 15 of 17 patients. Acceptable flow velocity signals could not be obtained by intracoronary Doppler in one patient proximal and in two patients distal of the stenosis. Intraobserver variability was 2.1% (SD = 7.9%) for the transesophageal coronary sinus and 0.1% (SD = 11.2%) for the transesophageal LAD flow reserve. The respective interobserver variabilities were 6.1% (SD = 16.9%) and 1.2% (SD = 7.3%) for coronary sinus and LAD measurements.

3.2. Hemodynamic data

Hemodynamic data at rest and after vasodilator application are shown in Table 1. At rest blood pressure and heart rate were similar for both methods (p = n.s.), resulting in comparable rate-pressure products (p = n.s.). Heart rate remained unchanged after intracoronary adenosine but increased significantly after intravenous dipyridamole administration. Chest pain was present in one patient after dipyridamole but administration of aminophylline was not required.

3.3. Coronary flow reserve

An example of intracoronary and transesophageal Doppler flow velocity recordings in a patients with severe

Fig. 2. Left panels: Linear regression analysis between transesophageal LAD (TEE-LAD) (A): coronary sinus (TEE-CS) (B) and proximal (IC-prox) and distal (IC-dist) intracoronary flow reserve (CFR). Right panels: Analysis of an agreement plotting the difference between the respective methods against the mean of the two measurements.
LAD stenosis is presented in Fig. 1. For the total group of patients coronary reserve assessed by the flow wire was $2.44 \pm 0.62$ for proximal and $2.19 \pm 0.76$ for distal LAD measurements ($p = \text{n.s.}$), and was $2.25 \pm 0.64$ for transesophageal LAD and $1.74 \pm 0.63$ for transesophageal coronary sinus measurements. Compared to the results of all other techniques, flow reserve obtained by coronary sinus flow velocities was significantly lower ($p \leq 0.01$).

Results of linear regression and agreement analysis between the different methods are presented in Fig. 2. There was a significant correlation between proximal and distal intracoronary flow reserve measurements. A similar degree of correlation was found between proximal intracoronary flow reserve measurements and both transesophageal methods, whereas distal intracoronary flow reserve measurements only correlated with transesophageal coronary sinus flow reserve.

### 3.4. Coronary flow reserve and stenosis severity

Mean diameter stenosis as assessed by quantitative angiography was $47 \pm 17\%$ (range: $11\%–64\%$). 5 patients had diameter stenosis of $< 50\%$ and 12 patients of $\geq 50\%$. Receiver operating characteristic curves revealed similar diagnostic accuracy for detection of significant LAD stenosis for all applied methods (Fig. 3). Sensitivity, specificity and overall predictive value of the intracoronary flow wire technique and both transesophageal methods for prediction of significant stenosis are shown in Table 2.

### 4. Discussion

This study compares assessment of coronary flow reserve by transesophageal Doppler echocardiography with intracoronary Doppler flow wire measurements. It is demonstrated that coronary flow reserve determined by both transesophageal Doppler techniques significantly correlates with intracoronary flow reserve, however considerable discrepancies may occur in the individual patient.

The value of coronary flow reserve as a marker of the functional significance of a coronary stenosis has been previously reported. Several diagnostic techniques have already been validated for determination of coronary flow reserve [7,20,21] but their large-scale applicability is limited by the requirement of cardiac catheterization or of quantitative PET imaging. Recently, transesophageal flow reserve obtained by assessment of coronary flow reserve was reported [8–14]. However, this new approach has not yet been compared to more established methods such as intracoronary Doppler flow wire measurements.

#### 4.1. Comparison of transesophageal LAD with intracoronary Doppler flow wire measurements

After its introduction by Iliceto et al. [8], assessment of coronary flow reserve by transesophageal Doppler recordings in the proximal LAD has been applied in several clinical studies [8–12]. In these studies the method allowed separation of normal subjects from patients with significant LAD stenosis.

The present study demonstrated a significant correlation between flow reserve as assessed by the transesophageal LAD method and intracoronary flow wire measurements proximal to the stenosis. However, no correlation between transesophageal LAD and poststenotic intracoronary measurements could be observed. These discrepancies might be explained by various method-inherent limitations. Transesophageal Doppler recordings are usually limited to a small sampling site in the very proximal segment of the LAD. Therefore, side branching between the actual site of flow recordings and the stenosis might lead to overestimation of coronary flow reserve. Conversely, in patients with very proximal LAD stenoses transesophageal recordings are performed in the proximity of the stenosis, so that turbulent stenotic flow might impact on Doppler recordings. However, discordant coronary flow reserve values due to side branching may also occur with prestenotic intracoronary Doppler measurements and therefore, poststenotic measurements are generally considered superior to

---

Table 2

<table>
<thead>
<tr>
<th>Parameter (%)</th>
<th>IC-prox</th>
<th>IC-dist</th>
<th>TEE-LAD</th>
<th>TEE-CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>50</td>
<td>75</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>86</td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>OPV</td>
<td>75</td>
<td>80</td>
<td>73</td>
<td>76</td>
</tr>
</tbody>
</table>

IC-dist = distal intracoronary flow reserve; IC-prox = proximal intracoronary flow reserve; OPV = overall predictive value; TEE-CS = transesophageal coronary sinus flow reserve; TEE-LAD = transesophageal LAD flow reserve.
prestenotic recordings [22]. However, even intracoronary poststenotic measurements may be influenced by collateral flow and the inability to obtain stable and reproducible flow signals [23]. Nevertheless, the absence of correlation between poststenotic coronary flow reserve by intracoronary flow wire and prestenotic transesophageal measurements has to be considered a substantial limitation in the assessment of coronary stenoses by transesophageal echocardiography.

Despite significant correlations by prestenotic intracoronary and transesophageal measurements, discordant results may be obtained by the various techniques in the single patient (Fig. 2). According to the results obtained by agreement analysis, a coronary flow reserve of 2.5 by prestenotic intracoronary Doppler measurements could range anywhere between 1.6 and 3.4 by transesophageal LAD Doppler measurements. This is in line with a previous study, comparing coronary flow reserve by transesophageal Doppler measurements in the LAD and positron emission tomography with oxygen 15 water in healthy volunteers [24]. Similarly, a good linear correlation was observed between these two techniques although results also demonstrated some discordance in the individual patient. Nevertheless, it must be noted that agreement analysis has also shown considerable differences between other, more established methods which are routinely applied in clinical practice [25].

4.2. Comparison of transesophageal coronary sinus with intracoronary Doppler guide wire measurements

Recent studies demonstrated the feasibility of transesophageal coronary sinus flow velocity recordings for the assessment of coronary flow reserve. With this method flow reserve was found to be lower in patients with dilated cardiomyopathy and syndrome X as compared to normal subjects [13,14]. Although the coronary sinus technique may be considered particularly sensitive in patients with global reduction of coronary flow reserve, it has previously been found to be also reduced in the majority of patients with significant LAD disease [14]. Accordingly, the present study showed a significant correlation between coronary flow reserve as assessed by the transesophageal coronary sinus- and the intracoronary Doppler flow wire technique. In contrast to the transesophageal LAD method coronary sinus measurements also significantly correlated with poststenotic intracoronary flow reserve. This may be explained by the various aforementioned limitations of transesophageal LAD measurements, but might also indicate a closer representation of poststenotic flow by the coronary sinus technique.

Coronary flow reserve values were substantially lower by the transesophageal coronary sinus method as compared to all other techniques. Although the reason for this must remain unclear, it has to be noted that lower coronary flow reserve values were also reported for the coronary sinus thermodilution method, when compared to the results of intracoronary Doppler measurements [26].

4.3. Diagnostic accuracy of coronary flow reserve measurements

As shown by similar areas under the respective receiver operating characteristic curves, diagnostic accuracy for detection of a significant LAD stenosis was comparable between both transesophageal and pre- as well as poststenotic intracoronary Doppler flow wire measurements. Using predefined cut off values for diagnosis of severe LAD stenosis, concordant classification by both transesophageal methods was obtained in all but one patient. Discordant results were noticed in a single patient with severe LAD stenosis and a large prestenotic side branch. In this patient coronary flow reserve was 2.38 by transesophageal LAD and 1.22 by coronary sinus Doppler measurements. Accordingly, intracoronary prestenotic flow reserve was higher than poststenotic flow reserve (2.2 versus 1.2, respectively), illustrating the confounding influence of side branching on the assessment of prestenotic coronary flow reserve.

4.4. Study limitations

Transesophageal and intracoronary Doppler studies were not performed simultaneously for logistical reasons. Moreover, different vasodilators were used for each technique. Dipyridamole is commonly used for non-invasive assessment of coronary flow reserve, but due to its prolonged duration of action has only limited applicability in invasive studies. In contrast, adenosine is preferred for intracoronary administration because it enables repeated consecutive flow reserve measurements within a short period of time [27]. However, the dosages used in the present study were reported to produce comparable coronary hyperemia in the majority of patients [28,29].

Heart rate was similar for both methods at baseline but increased significantly only after dipyridamole administration. However, it is unlikely that this might have influenced our results, since hyperemic blood flow had been previously shown to be unrelated to the achieved rate-pressure product [30–32]. In addition, similar mean coronary flow reserve values were observed with transesophageal LAD and intracoronary Doppler measurements, suggesting comparable hyperemia with both pharmacological stimuli.

The present results were obtained in a highly selected patient group. All patients had single vessel disease with proximal stenosis of the LAD. It remains to be shown whether transesophageal Doppler techniques will also enable detection of more distal LAD stenoses. Furthermore, the transesophageal techniques cannot be applied for functional assessment of stenoses of the right coronary artery and feasibility of the coronary sinus technique in evaluating stenoses of the left circumflex coronary artery is unknown.
QCA was used as reference method for assessment of diagnostic accuracy of various techniques for coronary flow reserve measurements. Although the angiographic aspect of a stenosis is known to correlate poorly with its physiologic significance, quantitative angiography correlated closely with coronary flow reserve in patients with discrete single vessel disease [33].

4.5. Conclusion

Although transesophageal and intracoronary measurements of coronary flow reserve correlated significantly in a group of patients with LAD disease, considerable discrepancies between these methods may occur in the individual patient.

References