Improved Detection of Ischemia-Induced Increases in Coronary Sinus Adenosine in Patients with Coronary Artery Disease

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Attempts to monitor coronary sinus adenosine as a clinical marker of myocardial ischemia in humans have been disappointing. Accordingly, procedures have been developed for detecting adenosine in blood collected from the human coronary sinus. Collection involves using a double-lumen metabolic catheter, which allows blood to be mixed with a stop solution at the catheter tip, thereby minimizing adenosine formation and degradation. A five-component stop solution almost completely arrests adenosine formation and degradation. Adenosine analysis is improved by using both boronate and C18 Sep-Pak columns to purify and concentrate adenosine in human plasma before HPLC. Plasma adenosine in the coronary sinus of patients with and without coronary artery disease, measured before and during peak atrial pacing, showed a twofold atrial pacing-induced increase in adenosine in the patients with coronary artery disease (n = 9, P <0.001) but no change in the patients with normal epicardial coronary arteries (n = 6). These preliminary results indicate that coronary sinus adenosine may provide an index of myocardial ischemia in patients with coronary artery disease.

Additional Keyphrases: myocardial ischemia · metabolic catheter · chromatography, liquid

Adenosine has been proposed as a likely metabolic signal released by the hypoxic or ischemic myocardium to elicit an increase in coronary blood flow in response to a decrease in the oxygen supply/demand ratio (1). However, attempts to monitor coronary sinus adenosine as a clinical marker of myocardial ischemia in humans have been disappointing. An early report that adenosine is increased in the coronary sinus of patients with ischemic heart disease during pacing (2) was not reproduced in several subsequent studies in which more sensitive assay techniques were used (3-6). This may be because the half-life of adenosine in human blood is <1.5 s (7) and because a large fraction of adenosine is taken up by endothelial cells (8) and other cellular blood elements (9). Only when the adenosine transport inhibitor dipryridamole was systemically infused before pacing could Sollevi et al. (4, 5) demonstrate a pacing-induced increase in coronary sinus adenosine in patients with coronary artery disease.

We hypothesized that the inability to use blood adenosine concentrations as a metabolic marker of myocardial ischemia in patients might be due in part to methodological limitations. In current sampling techniques, catheters >100-cm long are used to draw blood from the coronary sinus. No solution to stop adenosine metabolism is included and therefore both degradation and artificial production of adenosine are likely to occur during transit in these long catheters. Our objective was to develop methodology capable of detecting ischemia-induced increases of coronary artery adenosine.

Materials and Methods

Sample Collection

We developed a double-lumen metabolic catheter (U.S. patent 5,090,634), which allows addition and mixing of a stop solution to blood entering the tip of the catheter. Figure 1A is a schematic diagram of the catheter, which has two lumens, consisting of an outer catheter (8F multipurpose) and an inner catheter (2.5F) ending 1 cm from the end of the outer catheter (Figure 1B). A prototype of this catheter was described previously (10). The outer and inner catheters are connected by a Y-adaptor. Blood and solution movement through the outer and inner catheters are coupled by a double-syringe device. The larger collection syringe holds 6 mL, whereas the smaller infusion syringe holds 3 mL. The smaller syringe, being half the cross-sectional area of the larger syringe, ensures equilibration of blood with the stop solution at the tip of the metabolic catheter. During patient studies, the plunger is pulled out of the collection syringe and blood flows into the outer catheter and the collection syringe. As the plunger in the collection syringe is being pulled out, the second plunger is pushed into the infusion syringe, infusing stop solution through the inner catheter so that mixing between the stop solution and blood occurs at the distal end of the metabolic catheter. Both catheters are primed with stop solution before the blood is withdrawn. The total volume of blood plus stop solution in the collection syringe is 4 mL.

The stop solution contains the adenosine uptake inhibitor dipripyridamole (0.2 mmol/L; Boehringer Ingelheim, Ridgefield, CT), the adenosine deaminase inhibitor erythro-9(2-hydroxy-3-nonyl)-adenine (EHNA, 5 µmol/L; Burroughs Wellcome, Research Triangle Park, NC), the 5'-nucleotidase inhibitors α,β-methylene-aden-
The inner nyl)-adenine; centrifuged at 55 °C, dried under N₂ in a Multiivap Analytical Evaporator (Organomation Associates, South Berlin, MA), and reconstituted with 400 μL of KH₂PO₄ (5 mmol/L, pH 3.6).

The HPLC column was used a 4.6 × 250 mm, 5-μm particle, 0.8-nm pore, C₁₈ column (Beckman Instruments, San Ramon, CA). The mobile phase was KH₂PO₄ (5 mmol/L, pH 3.6) in methanol (100 mL/L). Adenosine and the internal standard were eluted isocratically at a flow rate of 1.5 mL/min. The ultraviolet absorbance (254 nm) of the eluent was monitored continuously (0.002 absorbance units, full scale).

The amount of adenosine in each sample was determined by comparing the observed peak area with a standard curve. The amount of plasma assayed was calculated as follows:²

\[
\text{Plasma volume assayed} = \frac{1 \text{mL} \times (1 - \text{Hct})}{(4.44 - \text{Hct})}
\]

Because half of the sample was injected onto the HPLC column, this result was divided by 2. For a normal Hct of 0.40, the assayed plasma volume is 74 μL of plasma.

The concentration of adenosine in plasma was then calculated by dividing the amount of adenosine measured by the volume of plasma assayed, with correction for recovery of the internal standard, which ranged from 50% to 65%.

Assay Verification

**Coefficient of variation.** A 4-mL peripheral venous blood sample was collected from a volunteer into 12 mL of stop solution through a 2.5-cm, 19-gauge needle. The supernate was divided into seven 1-mL portions and processed as above. The mean, SD, and CV determined from these seven samples were 0.186 and 0.034 μmol/L and 18.3%, respectively. Because the CV was >10%, all results presented are the means of duplicate determinations.

**Recovery of adenosine and internal standard during sample preparation.** To verify that the recoveries of both adenosine and N⁶-methyladenosine were the same, we added 18.7 pmol of adenosine and 106 pmol of internal

- Nonstandard abbreviations: EHNA, erythro-9(2-hydroxy-3-nonyl)-adenine; AOPCP, α,β-methylene-adenosine diprophosphate; Re, Reynolds numbers; and Hct, hematocrit.

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² This equation was derived as follows: The total volume of blood/stop solution in the collection syringe is 4 mL, of which 0.2 mL is AOPCP/EHNA, 2.8 mL is stop solution, and 0.9 mL is blood. The plasma volume collected = 0.9 mL (1 - Hct). The total volume collected minus erythrocytes = 4 mL - (0.9 mL)(Hct). Therefore, each 1 mL of collected sample contains a volume of plasma given by 1 mL(0.9mL(1 - Hct)/(4 mL - (0.9mL)(Hct))).
standard to 1 mL of stop solution and processed and analyzed this sample as above. The chromatographic peak areas were compared with those for identical amounts of adenosine and internal standard injected directly onto the HPLC column. Duplicate samples were analyzed on three separate occasions (n = 6).

Linear recovery of adenosine added to plasma. We collected 4 mL of blood in 12 mL of stop solution as described above. The supernatant fluid from this sample was divided into six 1-mL portions, to which we added adenosine (0, 4.7, 9.4, 18.7, 28.1, and 37.4 pmol) and processed the samples as above. The amount of adenosine detected was plotted as a function of adenosine added.

Effect of adenosine deaminase on HPLC profiles. We collected blood as in the preceding section but divided the supernate into two portions. One portion was processed as described above. The second portion was processed similarly except that the dried samples were reconstituted with 200 μL of adenosine deaminase (2 kU/L added to HPLC-grade H2O; Sigma Chemical Co.). After letting the samples sit at room temperature for 20 min, we added 200 μL of KH2PO4 (10 mmol/L, pH 3.6) to each sample. The deaminase was inactivated by boiling for 3 min, and the sample was filtered as before and injected onto the HPLC column. We did not add internal standard to the sample to be deaminated because it was a substrate for the enzyme.

Stop-Solution Verification

To determine the extent to which adenosine breakdown is arrested by the metabolic catheter when dipyridamole, EDTA, and heparin are added at its tip and EHNA and AOFCP are added in the collection syringe, we performed the following experiment. Venous peripheral blood (3.6 mL) was drawn from a volunteer into heparin (25 kilo-int. units/L). The blood was immediately dispensed into 11.6 mL of dipyridamole and EDTA solution (at concentrations given in Sample Collection) containing 16 μL of [14C]adenosine (New England Nuclear, Boston, MA; specific activity 57.2 Ci/mmol; 58 159 dpm/mL in blood plus stop solution). At 9 and 60 s after withdrawal of blood from the volunteer, 0.8 mL of EHNA and AOFCP were added (9 s is the average transit time for blood in the metabolic catheter). Blood, five-component stop solution, and [14C]adenosine were centrifuged at 2500 × g for 1.5 min, and the supernate was removed.

We added 50 μL of trichloroacetic acid solution (final concentration in supernate, 50 g/L) to 950 μL of supernate and centrifuged at 2500 × g for 1 min. We then mixed 0.5 mL of this supernate with 0.5 mL of tri-n-octylamine (0.5 mmol/L) in Freon and centrifuged again at 2500 × g for 1 min. We injected 50 μL of the top (aqueous) layer into the HPLC column and continuously monitored the radioactivity with a Beckman 171 radioisotope detector. To determine the extent to which AMP is degraded, we substituted 483 μL of [14C(U)]AMP (specific activity 590 Ci/mmol; 71 713 dpm/mL in blood plus stop solution) for [14C]adenosine.

The metabolism of adenosine and AMP was markedly inhibited by the stop solution at 9 s. [14C]Adenosine and [14C]AMP were recovered in HPLC peaks corresponding to these purines at the following rates (mean ± SD): 98.5% ± 0.8% (n = 6) and 90.5% ± 1.5% (n = 8), respectively. At 60 s, although the metabolism of [14C]-adenosine was still markedly inhibited [95.5% ± 1.2% was still present (n = 2)], the metabolism of [14C]AMP was not: 1.2% ± 0.5% remained (n = 2).

Metabolic Catheter Verification

A model of the metabolic catheter was built to verify that the stop solution and blood are mixed at its tip. We used a precision-bore glass tube to simulate the outer catheter, to allow a direct microscopic view of flow at the tip. An inner catheter was inserted into the glass tube, and the coupled syringe system was connected to an infusion—withdrawal pump to control the flow rate. The open end of the glass tube was located in a small reservoir with a pressure of 1–3 cm of H2O (~100–300 Pa), simulating the coronary sinus. Dextran solutions with viscosities equal to those of blood at 37 °C and stop solution at 25 °C were used. The dextran stop solution also contained cresyl violet (20 g/L) to provide contrast for flow visualization. For all observations we used a microscope with a 3.5× Leitz long-working-distance objective and photographed the flow patterns for later analysis. The Reynolds numbers (Re) that indicated adequate mixing (II) were then determined. Flow rates of 0.045, 0.090, 0.180, 0.270, 0.315, and 0.405 mL/s were examined, corresponding to Re of 7.7, 15.5, 31.0, 46.5, 54.2, and 69.7, respectively. Analysis of flow data involved determination by digital densitometry of the black-and-white negative micrographs of the space between the glass model of the outer and inner catheters. A uniform absorbance (optical density) between these catheters was interpreted as adequate mixing. A gradation of optical densities was interpreted as indicating regions of laminar flow and inadequate mixing of simulated blood and stop solution.

Figure 2 shows micrographs of the flow patterns in the glass model of the outer catheter, at the location of the inner catheter tip. The black rectangular shapes are the tips of the inner catheters. The left and right boundaries of the micrographs are the inner walls of the glass model of the outer catheter. The dashed lines drawn on each micrograph indicate where the optical density was measured. Panels A–C show an unmixed (clear) region of simulated blood at the left wall of the outer catheter and a dark (blue dye) region of stop solution near the inner catheter body. This gradation of mixing is reflected in the optical density measurements, which show a continuous decrease from the inner catheter body to the wall of the outer catheter. In panel D the micrograph appears to show uniform mixing, but the optical density measurements show that a concentration gradient is still present. In panels E and F the optical density is uniform across the lumen of the outer catheter, indicating that complete mixing has been achieved. Thus, adequate mixing occurs at the tip of the metabolic catheter if Re are maintained at ≥54.2. This
corresponds to withdrawal of a 4-mL sample (of blood plus stop solution) in 12.7 s (0.315 mL/s). For all studies with patients, 4 mL of blood plus stop solution was withdrawn in 12 s, which exceeds the minimum flow rate required for adequate mixing.

Oxygen and Lactate Analysis

Oxygen saturation of blood samples was determined by an electrochemical fuel-cell method (Co-oximeter; Corning Medical, Medfield, MA) in the catheterization laboratory. Blood lactate concentrations were determined with the acx (E.I. du Pont de Nemours and Co., Wilmington, DE), by a modification of the Marbach and Weil method, which involves the oxidation of lactate to pyruvate. Lactate production was defined as coronary sinus lactate exceeding aortic lactate at peak pacing.

Studies with Patients

Fifteen patients with a history of stable angina pectoris or atypical chest pain were chosen from the elective cardiac catheterization schedule. Six of these patients were found to have normal epicardial coronary arteries and left ventriculography. The other nine had two- or three-vessel coronary artery disease, with at least one stenosis >70%. Patients were identified 18 h before catheterization and were approached for consent. All medications were stopped at this time.

We waited 30 min between the routine diagnostic catheterization and the research protocol. The atrial pacing stages were 100, 120, and 140 beats/min, each for 2 min, with a final stage of 160 beats/min for 5–7 min. We measured baseline and peak pacing coronary sinus adenosine, simultaneous coronary sinus and aortic lactate and oxygen saturation, heart rate, and blood pressure, and obtained a 12-lead electrocardiogram.

Results

Assay Verification

Recovery of adenosine and internal standard during sample preparation. In three paired samples (n = 6) the percentage recoveries for adenosine and N<sup>6</sup>-methyladenosine through all steps of the assay, from preparation for boronate column application to reconstitution in phosphate buffer, were 61.9 (SD 7.0)% and 61.1 (SD 5.5%), respectively (not significantly different).

Analytical recovery of adenosine added to plasma. The amount of adenosine detected by the assay was linearly related (r<sup>2</sup> = 0.97) to the amount of exogenous adenosine added to plasma. In addition, the slope of the regression line was near unity (0.973), and the sum of endogenous and added adenosine was close to the predicted value (y = 17.61 + 0.973x).

Effect of adenosine deaminase on HPLC profiles. Figure 3 depicts chromatograms for paired samples obtained from the same volunteer. One sample of each pair was incubated with adenosine deaminase; the other was not. Adenosine deaminase eliminated the adenosine peak, indicating that this peak was indeed adenosine. (We did not add internal standard to the sample to be deaminated because it was a substrate for the enzyme.)

![Fig. 3. Effect of adenosine deaminase on HPLC profiles for paired samples from the same volunteer, before (A) and after (B) treatment with adenosine deaminase](image)

Adenosine (black arrow) and internal standard (white arrow) were eluted at 9.7 and 28.8 min, respectively. Internal standard was not added to the sample to be deaminated.

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Studies with Patients

Patients' results are displayed in Table 1. There was no difference in baseline heart rates, but the normal group attained a higher peak heart rate during atrial pacing. There was no difference in the baseline or peak atrial pacing rate-pressure products between the normal and coronary artery disease groups. Seven of nine coronary artery disease patients had normal baseline electrocardiograms and developed >1.5 mm ST-segment depression. The other two patients also developed >1.5 mm ST-segment depression, but the electrocardiogram changes with atrial pacing were nondiagnostic because their baseline electrocardiograms were abnormal, with ST-segment depression. One of six normal patients with ST-segment depression at baseline developed >1.5 mm ST depression with atrial pacing. Eight of nine coronary artery disease patients developed reproduction of their typical angina with atrial pacing, whereas only one of six normal patients developed reproduction of their typical chest pain symptoms with pacing.

There was no difference at baseline or change with pacing in the aortocoronary sinus oxygen content difference between the coronary artery disease and normal groups. Only three of the nine patients with coronary artery disease had lactate production, defined as the myocardial lactate extraction fraction becoming negative, although the coronary artery disease group as a whole had a decrease in the extraction fraction. There was no change in the myocardial lactate extraction fraction for the normal group. There was no difference in the baseline coronary sinus adenosine concentration between the two groups; every patient in the coronary artery disease group had an increase in coronary sinus adenosine of >1.5-fold (Figure 4). There was no change in coronary sinus adenosine with atrial pacing in the normal group.

Discussion

These results suggest that adenosine in coronary sinus blood is consistently increased during myocardial ischemia. The equivocal results of previous studies in

<table>
<thead>
<tr>
<th>Table 1. Results of Patients' Studies (Mean ± SD)</th>
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<tr>
<td><strong>CAD (n=9)</strong></td>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>RPP, ×10⁶</td>
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<tr>
<td>ECG changes, no.</td>
</tr>
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<td>Angina score</td>
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<tr>
<td>Ao-CS O₂diff, mL/L</td>
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<tr>
<td>Lactate ExF</td>
</tr>
<tr>
<td>Adenosine₀₀₀, µmol/L</td>
</tr>
<tr>
<td><strong>Pacing</strong></td>
</tr>
<tr>
<td><strong>Change</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Pacing</strong></td>
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<tr>
<td><strong>Change</strong></td>
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<tr>
<td><strong>Normal (n=6)</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td><strong>Pacing</strong></td>
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<tr>
<td><strong>Change</strong></td>
</tr>
</tbody>
</table>

*P <0.05, baseline vs pacing.
#P <0.05, CAD vs normal.

CAD, coronary artery disease; normal, normal epicardial coronary arteries; pacing, peak pacing stage; RPP, rate-pressure product; ECG changes, pacing-induced ischemic electrocardiogram changes (>1.5 mm ST-segment depression); angina score, reproduction of typical symptoms on a scale of 0-10, 10 being severe discomfort; Ao-CS O₂diff, aortocoronary sinus oxygen content difference; lactate ExF, myocardial lactate extraction fraction; adenosine₀₀₀, coronary sinus adenosine.

Fig. 4. Coronary sinus adenosine concentrations (µmol/L) at baseline and peak atrial pacing for individual patients in the coronary artery disease (CAD) and normal groups.

Means ± SD are shown for each group. The increase in the CAD group was significant (*P <0.001)

which attempts were made to correlate blood adenosine with myocardial ischemia in patients may have been due to methodological limitations. We used a double-lumen metabolic catheter and a modified stop solution to prevent artifactual production of adenosine by the use of inhibitors of 5'-nucleotidase. Using these techniques, we obtained plasma samples that showed that nine of nine patients with coronary artery disease responded to pacing-induced ischemia with a >1.5-fold increase in coronary sinus adenosine, whereas only three of the nine had lactate production.

Adenosine has a half-life of <1.5 s in human blood (7). To detect increases in coronary sinus adenosine resulting from myocardial ischemia, one must quickly arrest
Adenosine metabolism. A double-syringe device was introduced by Ontyd and Schrader (12) to address this need. This device allowed stop solution to be added at the entrance of the syringe collecting blood. However, such a device will not arrest the adenosine metabolism that occurs as the blood travels through a catheter. Because long catheters must be used to sample blood from the human coronary sinus, the only practical way to arrest the metabolism of adenosine is by injecting metabolic inhibitors at the tip of the sampling catheter. The utility of such a metabolic catheter has been validated in vitro by Shryock et al. (10) and applied clinically in the present study. We built a model of the metabolic catheter to ensure that mixing of blood and stop solution occurs at its tip. Moreover, in all patients' studies, we used a flow rate at which adequate mixing occurred (0.33 mL/s). The use of this catheter may explain why this study demonstrates ischemia-induced increases in coronary sinus adenosine in the absence of systemic dipryridamole, even though no such changes could be detected in earlier studies (3–6).

The coronary sinus adenosine concentrations reported here are lower than in studies where inhibitors of 5'-nucleotidase were not incorporated into the stop solution (Table 2). Hamm et al. (6) did not use an adenosine deaminase inhibitor, which may have contributed to the low concentrations of adenosine they detected. The low concentrations of coronary sinus adenosine we detected here suggest that artificial production of adenosine is an important source of error in studies dealing with whole human blood. Studies in which the highest concentrations of coronary sinus adenosine were reported used stop solutions designed to prevent loss but not production of adenosine. The stop solutions in these studies included dipryridamole (3, 4, 13), EHNA (3, 4), or MnCl₂ (13) to prevent cellular uptake of adenosine or to inhibit adenosine deaminase. However, for accurate assessment of adenosine concentrations in blood, one must prevent adenosine formation. Because adenosine might be formed from adenine nucleotides released as a result of platelet aggregation (14), Sollevi et al. (4, 5) added indomethacin to prevent platelet aggregates. However, adenine nucleotides may also be derived from even slight lysis of erythrocytes, which may occur during collection of coronary sinus blood samples. The enzymes necessary to degrade adenine nucleotides to adenosine also are present in human blood (16). In the present study, we incorporated inhibitors of 5'-nucleotidase (AOPCP and EDTA) into the stop solution. Although, to ensure patient safety, we could place AOPCP only in the collection syringe, EDTA could be infused at the tip of the metabolic catheter.

Previous studies with HPLC were hampered by the presence in human plasma of several substances that are eluted near adenosine. Although some early reports quantified adenosine directly (16, 17), more recent investigators have used peak-shift methodology (10, 12). In the latter technique, an HPLC fraction containing adenosine is collected, deaminated, and injected for a second HPLC run; the amount of inosine is then quantified. McCann and Cathode (18) recently described preparing fluorescent etheno-derivatives of adenosine but still rechromatographed the human blood samples to remove interfering substances. If adenosine is to be used in patient care, simplification of methods for quantifying adenosine in human blood would be advantageous. We combined the use of boronate and C₁₈ Sep-Pak precolumns to partially purify and concentrate the adenosine in plasma before HPLC; thus, we could quantify the adenosine accurately as an overnight procedure with a single isocratic HPLC step. Although boronate (4, 17) and C₁₈ Sep-Pak columns (7, 19) have been used individually in assays of adenosine, their combined use was not previously reported.

An outgrowth of this study may be the physiological assessment of coronary artery disease at the time of cardiac catheterization. Clinical decisions regarding revascularization vs drug therapy are largely affected by the percentage of stenosis revealed by coronary angiography, currently the "gold standard" by which the functional severity of coronary disease is evaluated. Many studies, however, document marked variability in interpretations of the severity of a stenosis (20, 21), and autopsy studies have demonstrated a lack of correlation with arteriography (22). Thus new methods are needed for better physiological assessment of coronary artery stenoses.

There are several limitations to the methodology we have presented. First, we have not accounted for the effect of pacing-induced changes in arterial adenosine concentration or coronary sinus blood flow on the concentration of coronary sinus adenosine. Because pacing is associated with increased coronary sinus blood flow (23), the increase in adenosine plasma concentration in the coronary artery disease patients probably underestimates the true change in the magnitude of adenosine production. A second limitation is that we cannot distinguish between adenosine derived from ischemic myocardium and that from other sources such as the vascular endothelium (24, 25), blood cells (15), and nerves (26). Nonetheless, this study establishes adenosine as a marker of myocardial ischemia, regardless of the precise mechanism by which it is released. A third limitation is the inability of the metabolic catheter to

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**Table 2. Coronary Sinus Adenosine Concentration Compared with Other Studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Adenosine concn, μmol/L</th>
<th>Relative adenosine</th>
<th>Stop solution*</th>
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<tbody>
<tr>
<td>6*</td>
<td>0.106 ± 0.049</td>
<td>0.8</td>
<td>—</td>
</tr>
<tr>
<td>This study</td>
<td>0.132 ± 0.051</td>
<td>1.0</td>
<td>AOPCP, EDTA</td>
</tr>
<tr>
<td>4</td>
<td>0.22 ± 0.02</td>
<td>1.7</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>0.29</td>
<td>2.2</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>0.674 ± 0.333</td>
<td>5.1</td>
<td>—</td>
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</table>

*The only study in which an adenosine deaminase inhibitor was not used.

*Ratio of adenosine concentration reported in cited reference divided by that reported in this study.

*Inhibitors of artificial adenosine production were in the stop solution.
In summary, by using a double-lumen metabolic catheter, modified stop solution, and a simplified HPLC assay, we are able to detect an ischemia-induced twofold increase of coronary sinus adenosine in the absence of systemic dipyridamole. This is the first convincing demonstration that adenosine produced by ischemic myocardium in patients can escape from the interstitial space, cross the major metabolic endothelial barrier, and accumulate and be detected in coronary sinus blood.

We thank Dra. Rafael Rubio and George Beller for their advice, Jonquil Feldman for artwork, and the members of the cardiac catheterization staff for their support. Dr. Luis Belardinelli designed a prototype of the metabolic catheter used in this study. Supported by the Bayer Fund for Cardiovascular Research, Sterling Drug, New York, NY (M.D.F.); the American Heart Association, Virginia Affiliate, Grant-in-Aid (grant G800110) (M.D.F.); and the Cordis Corp., Miami, FL, which supplied components to build the metabolic catheter. Portions of this work were presented in abstract form at the 39th Annual Scientific Session of the American College of Cardiology, New Orleans, LA, March 18–22, 1990.

References