Coronary flow regulation in patients with ischemic heart disease: release of purines and prostacyclin and the effect of inhibitors of prostaglandin formation

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ABSTRACT The present investigation was undertaken to study cardiac release of adenosine and prostacyclin (prostaglandin [PG] I₂) in patients with ischemic heart disease (IHD), and to assess coronary vascular resistance before and after inhibition of synthesis in such patients. In 48 patients with IHD, arterial and coronary sinus blood samples were taken at rest, during atrial pacing to angina, and after pacing. Levels of purines were determined by high-performance liquid chromatography and the PG₁₂ metabolite 6-keto-PGF₁α was measured with radioimmunoassay. Coronary sinus blood flow was determined with retrograde continuous thermodilution before and after oral administration of indomethacin, aspirin, naproxen, or ibuprofen. Atrial pacing induced myocardial ischemia, as evidenced by typical chest pain and arrested lactate extraction. Adenosine was extracted at rest, but during ischemia there was a significant release of its metabolite hypoxanthine, indicating increased myocardial breakdown of high-energy adenine nucleotides. Arterial and coronary sinus concentrations of 6-keto-PGF₁α were low and no significant differences between them were found. After administration of the PG-synthesis inhibitor indomethacin, coronary vascular resistance was elevated, as was the cardiac oxygen extraction. The three other PG-synthesis inhibitors (aspirin, naproxen, and ibuprofen) did not, however, induce any change in coronary vascular resistance or in the cardiac extraction of oxygen. On the basis of these data we suggest that in patients with IHD (1) cardiac ischemia results in increased myocardial production and release of purines, (2) cardiac ischemia does not elicit any detectable increase in coronary production of prostacyclin, and (3) the increased coronary resistance induced by indomethacin does not reflect the involvement of locally formed PG in the maintenance of coronary flow, but is rather a direct effect of the drug.


IN VIEW OF the vasodilating effect of adenosine and the increased formation of this substance in hearts from cats, dogs, and rats during hypoxia or ischemia, Berne and Gerlach et al. proposed that adenosine might be the major link that couples the coronary flow rate to the metabolic state of the heart. This hypothesis has been thoroughly investigated and is generally accepted at present. It has also been demonstrated in man that the release of purines from the heart is increased during ischemia. The formation of primary prostaglandins (PGs) in the heart has likewise been found to rise in conjunction with ischemia or hypoxia in animal experiments. After the discovery of prostacyclin (PGI₂), this vasodilator and antiaggregatory cyclooxygenase product was soon shown to be the major PG produced in animal hearts in response to oxygen deprivation. Recently we reported augmented cardiac formation of PGI₂ in humans during sustained and severe global ischemia (cardioplegia related to open heart surgery).
In view of its formation in the coronary vessels and its biological actions, PG12 has been proposed to be involved in the pathophysiologic control of the coronary circulation. This hypothesis was supported by the recent finding that inhibition of PG synthesis in man by indomethacin elicits an increased coronary vascular resistance.

The present investigation was undertaken to further characterize the possible roles of adenosine and PG12 in coronary flow regulation under pathophysiologic conditions. In patients with ischemic heart disease (IHD) we have determined the simultaneous cardiac efflux of purines and PG12, and have also studied the effect of some different inhibitors of PG synthesis on coronary flow regulation.

Methods

Subjects. Forty-eight male patients who were 28 to 69 years old and suffering from IHD were investigated. IHD was evidenced by severe effort-triggered angina pectoris and definite, typical electrocardiographic changes during a bicycle exercise test. Most of the patients had a history of myocardial infarction(s). They continued their medications as usual; most were taking B-blocking drugs and nitrates. All patients were carefully informed about the aim of the study before giving their voluntary consent to participate. The protocol was approved by the local human investigations committee.

Procedure. A catheter was introduced into the coronary sinus of each patient under fluoroscopic control, and its correct position was verified by analysis of blood oxygen saturation. The catheter contained an electrode for atrial pacing and a thermistor for flow determination with retrograde continuous thermodilution (Wilton-Webster). Another catheter was inserted in a brachial artery. Atrial pacing was started at a frequency of 90 or, in cases of high resting heart rate, 100 impulses/min. The frequency was increased by 10 impulses/min every minute until the patient experienced severe chest pain (rating of 6 to 7 on a 0 to 9 scale: 0 no pain, 9 maximal pain) or until a heart rate of 150 beats/min had been reached. Pacing was continued at that level for a few minutes, allowing time for collection of blood samples and determination of coronary flow. Simultaneous samples of blood from the arterial and coronary sinus catheters were obtained while patients were at rest, during atrial pacing at the highest heart rate reached in the individual patient, and 3 min after the end of pacing. Coronary sinus flow rates were determined in connection with all sampling times, and also during pacing at a frequency of 110 impulses/min.

Subsequently, 10 patients were given indomethacin (50 mg orally), five patients received naproxen (500 mg orally), six patients took aspirin (3 g orally), and 11 patients were given ibuprofen (1.2 g orally). After 60 min, the pacing and blood sampling procedures and flow determinations were repeated. The efficacy of the blockade of PG synthesis was regularly checked by testing the aggregability of platelets, induced by arachidonic acid, in platelet-rich plasma before and 60 min after administration of the different drugs. Blood samples were analyzed for content of oxygen, lactate, 6-keto-PGF1α, adenosine, inosine, and hypoxanthine. Arterial blood pressure and a one-lead electrocardiogram (ECG) were monitored continuously. All types of analyses were not performed in all investigations.

Analyses. Oxygen and lactate levels were determined in most of the subjects, by standard procedures. In the cases in which 6-keto-PGF1α content was determined (n = 26), blood was collected in tubes containing indomethacin and EDTA (final concentrations 0.3 and 10 mM, respectively) and immediately centrifuged at 600 g for 2 min. Plasma was separated and kept frozen (−80°C) until it was analyzed. Determinations of 6-keto-PGF1α were performed in duplicate, in unextracted samples diluted 1:15, by radioimmunoassay (RIA) with a detection limit of 7.5 pg/ml.

In the cases in which levels of adenosine, inosine, and hypoxanthine were determined (n = 23), blood was collected directly into a syringe containing an equal volume of chilled saline, 20 μM dipyridamole, and 10 μM erythro-9-(2-hydroxy-3-nonyl) adenine (to inhibit adenosine uptake into blood cells and plasma adenosine deaminase) as described by Sollevi et al. The sample was then immediately centrifuged at 10,000 g for 1 min at a temperature of 4°C. One milliliter of the supernatant was subsequently transferred to cooled Eppendorf tubes containing 100 μl of the internal standard N2,N7-dimethylguanosine (final concentration 0.5 μM) for the determination of adenosine. The samples were then deproteinized by perchloric acid at a final concentration of 0.4M. Another 20 μl of supernatant was removed for the determination of hypoxanthine. The nucleoside samples were centrifuged for 1 min (10,000 g), all supernatant was removed, and the sample was neutralized by 2.5M ammonium acetate (pH 9.5), giving a final sample pH of 8.8. Samples were then frozen (−20°C). Analytical procedures for adenosine and inosine determinations were performed as described by Fredholm and Sollevi in purified samples, with use of high-pressure liquid chromatography (HPLC) with absorbance detection. The measurements were corrected according to the individual recoveries (70% to 90%). Hypoxanthine was analyzed in the unpurified samples by HPLC as described by Schweinsberg and Loo. The detection limits were 0.02 μM for adenosine, 0.02 to 0.05 μM for inosine, and 0.16 μM for hypoxanthine.

When applicable, Student’s t test or Wilcoxon’s signed-rank test was used for statistical calculations. Numerical differences resulting in p values greater than .01 were not considered to be significant. Results are given as mean ± SEM, unless otherwise stated.

Results

Basal state. Mean coronary sinus blood flow, when the patients were resting on the examination table before drug administration and before atrial pacing, was 118 ml/min (table 1). The cardiac oxygen extraction was 133 ml/liter, implying a calculated oxygen consumption of 15 ml/min in the drained myocardium. Arterial mean blood pressure was 110 mm Hg. Assuming a mean right atrial pressure of 3 mm Hg, the coronary resistance was 0.99 mm Hg × min/ml (table 1). Myocardial net extraction of lactate was 25% (figure 1). Adenosine was extracted by the heart to a significant extent (table 2, figure 2). The arterial and coronary sinus concentrations of inosine were low, never exceeding 0.21 μM, and no difference was found between them. No significant uptake or release of hypoxanthine was noted (table 2). The arterial and coronary sinus levels of 6-keto-PGF1α were, with a few exceptions, low, and there was no significant difference between them (table 3).
TABLE 1
Coronary sinus flow (CSF), arterial–coronary sinus difference in oxygen content [d(A-CS)O₂], oxygen consumption by the drained myocardial area (M VO₂), mean arterial blood pressure (BP), and coronary vascular resistance (CVR)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Pace₁₀</th>
<th>Pace_max</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF ml/min</td>
<td>118 ± 8</td>
<td>176 ± 16</td>
<td>231 ± 19</td>
<td>181 ± 11</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>21</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>d(A-CS)O₂ ml/l</td>
<td>133 ± 3</td>
<td>131 ± 3</td>
<td>131 ± 3</td>
<td>131 ± 3</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>31</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>M VO₂ ml/min</td>
<td>15 ± 1</td>
<td>30 ± 1</td>
<td>17 ± 1</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>20</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>BP mm Hg</td>
<td>110 ± 3</td>
<td>116 ± 3</td>
<td>126 ± 5</td>
<td>114 ± 4</td>
</tr>
<tr>
<td>n</td>
<td>31</td>
<td>30</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>CVR× mm Hg × min/ml</td>
<td>0.99 ± 0.07</td>
<td>0.74 ± 0.06</td>
<td>0.61 ± 0.06</td>
<td>0.97 ± 0.11</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Pace₁₀ = data obtained during atrial pacing to a heart rate of 110 beats/min; Pace_max = data obtained during the highest atrial pacing frequency.

A=Calculated from CSF and BP, assuming a mean right atrial pressure of 3 mm Hg.

Atrial pacing. During atrial pacing all patients experienced chest pain; in some cases the pain was severe (subjective ratings 3 to 9 on a 0 to 9 scale according to Borg et al. 17). Most patients developed ST-T changes of the ischemic type on the one-lead ECG. Blood pressure and coronary sinus blood flow increased, and the coronary resistance fell (table 1). Cardiac oxygen extraction (arterial–coronary sinus difference) was not changed and consequently the calculated myocardial oxygen consumption increased (table 1). Lactate extraction in the heart was arrested during pacing compared with the basal state (figure 1).

During pacing the extraction of adenosine became insignificant (table 2, figure 2) and the arterial and coronary sinus concentrations of inosine remained low. A large amount of hypoxanthine was released during angina (table 2, figure 2). The arterial and coronary sinus levels of 6-keto-PGF₁α did not change in most cases (table 3).

Recovery. Within 3 min after the onset of the recovery following atrial pacing the majority of the patients were relieved of pain and the electrocardiographic changes were reversed. Mean arterial pressure, coronary sinus flow, and coronary resistance returned toward resting values (table 1). Cardiac oxygen extrac-

Effect of inhibition of PG synthesis. Administration of the PG-synthesis inhibitor indomethacin induced a decrease in coronary sinus flow, implying an increase in coronary resistance (figure 3). This effect of indomethacin was of the same magnitude in the basal state, during atrial pacing, and during recovery. This was further evidenced by the cardiac oxygen extraction (figure 4), which was markedly elevated. The calculated oxygen consumption was maintained at the same level as before drug administration. Arterial mean blood pressure was not affected.

After administration of the PG-synthesis inhibitor ibuprofen a minor and insignificant decrease in coronary sinus flow developed; the coronary resistance was unaltered (figure 3). Cardiac oxygen extraction (figure 4) and oxygen consumption were unaltered by ibupro-

FIGURE 1. Top. Arterial (●) and coronary sinus (○) concentrations of lactate in patients with IHD at rest, during atrial pacing to angina pectoris (Pace), and 3 min after the end of the pacing (Recovery). "Before Drug" refers to data obtained before administration of PG-synthesis inhibitors. "After Drug" refers to the pooled data obtained after the different PG-synthesis inhibitors. All values are mean ± SEM. Bottom. Fractional extraction of lactate, expressed as a percentage of the arterial concentration, in patients with IHD at rest, during atrial pacing to angina pectoris (Pace), and 3 min after the end of the pacing (Recovery). For explanation of "Before Drug" and "After Drug" see above.
fen. A slight decrease in mean arterial blood pressure was evident under all conditions.

The PG-synthesis inhibitors naproxen and aspirin also failed to induce any changes in the cardiac extraction of oxygen (figure 4), indicating an unaltered coronary sinus flow and resistance. Coronary flow determinations in these patients were not regularly performed. Both drugs elicited a slight decrease in systemic blood pressure.

None of the drugs elicited any change in subjective pain rating or in the net turnover of lactate (figure 1) or purines.

**Discussion**

In the present study patients with IHD displayed a normal net extraction of lactate in the basal state, indicating mainly aerobic cardiac metabolism. During atrial pacing myocardial ischemia developed, as evidenced by the simultaneous appearance of chest pain, electrocardiographic changes, and arrested uptake of lactate. Consequently, the coronary blood flow was insufficiently increased to meet the elevated metabolic demand of the heart during the atrial pacing. The pacing-induced ischemia was reversible and of short duration after cessation of pacing.

Adenosine is rapidly eliminated or degraded in biological tissues or fluids. In circulating blood the half-life of adenosine is less than 10 to 15 sec as a result of uptake into the vascular endothelium and blood cells and of degradation by deamination. In the present investigation the sampling procedure was designed to prevent further elimination, in the test tube, of adenosine and its metabolites. The observed levels of adenosine can therefore be assumed to fairly accurately reflect the true concentrations in arterial and coronary sinus plasma at the time of sampling (see below). No significant myocardial release of adenosine was detected, either at rest or during ischemia; there was in fact a myocardial extraction of the compound during basal conditions. This small net extraction of adenosine may to some extent have been due to the fact that the coronary sinus catheter was longer than the arterial catheter, since a longer sampling time allows for some additional elimination of adenosine. Fox et al. reported appearance of adenosine in coronary sinus blood from patients with IHD during pacing-induced ische-

**TABLE 2**
Concentrations (μM) of adenosine, inosine, and hypoxanthine and the total sum of these substances in arterial and coronary sinus blood at rest, during atrial pacing, and during recovery 3 min after pacing in patients with IHD

<table>
<thead>
<tr>
<th></th>
<th>Arterial</th>
<th>Coronary sinus</th>
<th>Arterial</th>
<th>Coronary sinus</th>
<th>Arterial</th>
<th>Coronary sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenosine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.28</td>
<td>0.29</td>
<td>0.30</td>
<td>0.28</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>Range</td>
<td>(0.03-0.92)</td>
<td>(0.05-0.55)</td>
<td>(0.05-1.07)</td>
<td>(0.04-0.78)</td>
<td>(0.06-1.09)</td>
<td>(0.05-1.26)</td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>19</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>p value*</td>
<td>p &lt; .005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Inosine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Range</td>
<td>(ND-0.15)</td>
<td>(ND-0.21)</td>
<td>(ND-0.12)</td>
<td>(ND-0.15)</td>
<td>(ND-0.19)</td>
<td>(ND-0.15)</td>
</tr>
<tr>
<td>n</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>17</td>
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<tr>
<td>p value*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
<td><strong>Hypoxanthine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.29</td>
<td>1.10</td>
<td>0.83</td>
<td>1.49</td>
<td>0.75</td>
<td>1.71</td>
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<tr>
<td>Range</td>
<td>(0.32-4.56)</td>
<td>(0.16-4.03)</td>
<td>(0.16-3.88)</td>
<td>(0.16-4.56)</td>
<td>(0.16-3.82)</td>
<td>(0.32-4.98)</td>
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<td>n</td>
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<td>17</td>
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</tr>
<tr>
<td>p value*</td>
<td>NS</td>
<td>p &lt; .005</td>
<td>p &lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.34</td>
<td>1.22</td>
<td>1.11</td>
<td>1.61</td>
<td>1.29</td>
<td>1.95</td>
</tr>
<tr>
<td>Range</td>
<td>(0.41-4.98)</td>
<td>(0.28-4.53)</td>
<td>(0.28-4.23)</td>
<td>(0.32-5.43)</td>
<td>(0.28-4.15)</td>
<td>(0.43-5.31)</td>
</tr>
<tr>
<td>n</td>
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<td>13</td>
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<tr>
<td>p value*</td>
<td>NS</td>
<td>p &lt; .001</td>
<td>p &lt; .005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND = not detected.

*By Wilcoxon nonparametric signed-rank test.

Although the median concentrations of adenosine in arterial and coronary sinus blood were not different, there was statistically significant extraction of the compound.
mia. However, their method for analysis was far less sensitive than that currently used, resulting in a majority of determinations below the detection limit. Nevertheless, in spite of the present sensitive method for determination of adenosine levels, we could not demonstrate enhanced adenosine formation, probably because of its rapid endogenous elimination before sampling. Inosine, the deaminated metabolite of adenosine, was present in very low concentrations that were in the vicinity of the detection limit for the method, and there was no difference between the arterial and coronary sinus concentrations. The breakdown product of inosine — hypoxanthine — was present in higher concentrations, with a nonsignificant cardiac extraction at rest. During ischemia, as well as 3 min after the end of pacing, there was a marked release of hypoxanthine — one far exceeding the small nonsignificant net extraction of adenosine. This indicates an ischemia-induced facilitated breakdown of energy-rich adenine nucleotides in the heart, with subsequently increased release of adenosine, which in turn was evidently (since no release of adenosine per se was detected) further metabolized to hypoxanthine before sampling. This is in accordance with previous findings by Remme et al.\(^8\)

Kugler\(^8\) primarily found a release of inosine, but in addition reported cessation of hypoxanthine extraction in patients with IHD during ischemia.

That myocardial ischemia in fact elicits a breakdown of energy-rich nucleotides is also evidenced by recent data obtained by analysis of purines in biopsy samples from more severely ischemic human hearts (during cardioplegia for open heart surgery); the data showed significant elevation of tissue concentrations of adenosine and its metabolites.\(^\ast\) These data on cardiac purine turnover in the basal state and during myocardial ischemia were all obtained in patients who were not pretreated with any investigational drug. When the study was repeated after administration of various PG-synthesis inhibitors no apparent change in cardiac purine turnover could be detected. This suggests that, under the conditions that prevailed, cardiac purine turnover and coronary arachidonate metabolism were not closely connected.

No cardiac release of 6-keto-PGF\(_{1\alpha}\) was detected, either in the basal state or during ischemia. This is in contrast to findings of previous studies, both in animals\(^9\) and in humans,\(^10\) in which cardiac ischemia was followed by a considerable production of PGI\(_2\). In the latter study, performed in cardioplegic hearts, the ischemia was severe, long-lasting, and probably global. In the present study the ischemia was less pronounced and brief, and may therefore have been insufficient to trigger production of PGI\(_2\). Also, in this study ischemia was probably limited spatially, which may have rendered generation of PGI\(_2\) difficult to detect due to dilution of the coronary sinus blood with that from non-ischemic myocardium. Such dilution would certainly have affected arterial-coronary sinus lactate and purine differences similarly. Since an effect of atrial pacing on lactate and purine turnover in the heart was in fact noted it can be assumed that regional formation of PGI\(_2\) was less facilitated, if at all, than the production of lactate and nucleosides. The arterial and coronary sinus levels of 6-keto-PGF\(_{1\alpha}\) measured in the present study are higher than previously reported concentrations in peripheral venous plasma.\(^9\) As recently demonstrated by Roy et al.,\(^25\) cardiac catheterization causes release of endogenous PGI\(_2\), as assessed by the urinary excretion of its major metabolite 2,3-dinor-6-keto-PGF\(_{1\alpha}\). The absolute values of 6-keto-PGF\(_{1\alpha}\) measured by RIA in the present study are remarkably similar to the aortic and coronary sinus concentrations measured by Roy et al.\(^25\) using gas chromatography/mass spectrometry in the negative ion–chemical ionization mode. Consistent with our present findings, no detectable difference was observed by these investigators between corresponding aortic and coronary sinus levels of 6-keto-PGF\(_{1\alpha}\), suggesting that procedure-related PGI\(_2\) release may obscure more subtle changes in PGI\(_2\) production induced by transient ischemia.

Normally myocardial oxygen extraction is high, leaving only small amounts of oxygen in the coronary sinus blood. Increased myocardial oxygen demands in response to increased cardiac work are therefore primarily met by changes in the coronary resistance and flow. The increased arterial-coronary sinus oxygen concentration difference that develops as a result during constant cardiac work (and hence also constant myocardial oxygen demand) is indicative of a decrease in coronary blood flow. The current results in IHD patients confirm the significance of changes in coronary flow as determinants of myocardial oxygen uptake; oxygen extraction was unchanged during pacing-induced ischemia and hence, even when oxygen supply was insufficient, the fractional extraction was not increased. In this connection it is important to stress that if myocardial ischemia is very localized, regional oxygen extraction may be increased, although this may not be detected in the mixed coronary sinus blood. However, it is also relevant to point out that in the nonatherosclerotic human heart, increased work produced by atrial pacing is met by a greater increase in coronary flow than in myocardial oxygen consumption, i.e., fractional oxygen extraction is lowered.\(^*\)

The unaltered fractional extraction in the majority of our patients would therefore indicate that a significant part of the heart muscle had restricted blood flow and locally increased fractional extraction.

Quantitation of coronary sinus blood flow is a delicate task, and even with very advanced equipment the technique is difficult. The possible sources of erroneous values connected to the currently applied method, i.e., thermodilution, come from thermistor “adherence” to the vessel wall, thermistor location just at the

inflow of a branch (causing inadequate mixing of the indicator and the blood), and unstable catheter position. The appearance of such difficulties could not always be avoided since a catheter position allowing adequate blood sampling was always given highest priority. The determination of oxygen concentration in arterial and coronary sinus blood allows some of these drawbacks to be avoided. Therefore, in this study the cardiac oxygen extraction was used as an indirect measure of changes in coronary flow induced by drugs when the investigational conditions, apart from the drug used, were comparable. Conclusions concerning changes in coronary resistance have therefore been made both from the oxygen extractions and from direct flow determinations.

Indomethacin caused an increase in coronary resistance, as evidenced by both direct measurements of flow and by increased oxygen extraction. This finding is in accordance with those of Friedman et al., who reported reduced basal coronary flow after administration of indomethacin in patients with IHD. However, three other inhibitors of PG synthesis — ibuprofen, naproxen, and aspirin — did not induce any change in coronary resistance, as evidenced by direct flow measurements (ibuprofen, figure 3) or by the unaltered oxygen extraction (all drugs, figure 4). This leads us to propose that the vasoconstrictor effect of indomethacin is not related to the drug’s inhibitory action on cyclooxygenase but is rather a direct effect on the coronary vessels, an alternative also proposed by Friedman et al.16

Our data consequently demonstrate that purines and prostacyclin are not released in any appreciable amounts in patients with IHD investigated under basal conditions. For reasons discussed above such lack of measurable global release does not rule out the possibility of local release of vasoactive concentrations of these compounds in certain regions of the heart. A global coronary flow-regulating role of purines or prostacyclin in these patients in the basal state does not, however, seem very likely. During ischemia, more complete degradation of ATP seems to develop, since the adenosine metabolite hypoxanthine is liberated in increased amounts. This increased nucleoside liberation is compatible with a flow-regulating role for

![FIGURE 3. Change in coronary vascular resistance (ΔCVR) induced by two inhibitors of PG synthesis, indomethacin (IND) and ibuprofen (IBU). Indomethacin caused an increased CVR that did not differ at rest, during atrial pacing to angina pectoris, or during recovery. The presented values represent the means of determinations under these various conditions.](http://circ.ahajournals.org/)

![FIGURE 4. Change in differences in oxygen content (arterial-coronary sinus) [Δd(A−CS)O2] induced by different PG-synthesis inhibitors (IND = indomethacin; IBU = ibuprofen; NAP = naproxen; ASP = aspirin) in patients with IHD. This change was of the same magnitude at rest, during atrial pacing to angina pectoris, and during recovery, and the presented values represent the means of determinations under these various conditions. Only indomethacin elicited a significant increase in Δd(A−CS)O2 and this increase was significantly different from the responses to the other drugs.](http://circ.ahajournals.org/)
EDLUND et al.

adrenosine during elevated coronary flow, local or regional. In contrast to the liberation of nucleoside, prostacyclin did not appear even during pacing to angina, indicating no more than a possibly local role for this arachidionate product in coronary flow regulation. This is further evidenced by the fact that inhibition of PG formation failed to affect lactate release, purine turnover, cardiac oxygen uptake, or the severity of chest pain during ischemia. Indomethacin elicits coronary vasoconstriction, but this is probably due to a direct effect on the coronary vessels and not related to inhibition of PG bioformation, since three other inhibitors of PG synthesis did not alter coronary resistance.

References

1120
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