Thromboxane Release During Pacing-induced Angina Pectoris: Possible Vasoconstrictor Influence on the Coronary Vasculature

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SUMMARY We developed a radioimmunoassay for plasma thromboxane B₂, the metabolite of the coronary vasoconstrictor thromboxane A₂. To see if thromboxane A₂ is produced during myocardial ischemia, we used atrial pacing to study 14 patients with greater than 75% occlusive coronary artery disease. Paired samples were taken from the coronary sinus (CS) and an artery (A) for lactate and thromboxane B₂ analysis before pacing. During and after pacing at 140 beats/min, sampling was repeated. Before, during, immediately after and 10 minutes after pacing, percent myocardial lactate extractions (A–CS/A × 100) were 29.3 ± 3.7%, 21.1 ± 12.8%, −74.3 ± 20.3% and 25.1 ± 3.5%, respectively (all changes p < 0.01). Before pacing, five patients had detectable coronary sinus or arterial thromboxane levels. During pacing, 18% and 40% increases occurred in coronary sinus and arterial blood, respectively (0.8 ± 0.1 to 0.9 ± 0.2 pmol/ml, and 0.5 ± 0.2 to 0.7 ± 0.2 pmol/ml). Immediately after pacing, increases of 204% and 132% occurred in the coronary sinus and arterial blood (p < 0.05), respectively (2.3 ± 0.9 pmol/ml and 1.2 ± 0.4 pmol/ml). Ten minutes after pacing, thromboxane B₂ returned to prepacing levels. These data indicate that thromboxane A₂ is produced during pacing-induced myocardial ischemia and could alter regional coronary blood flow.

ATRIAL PACING coupled with coronary sinus blood sampling has been used extensively to study angina pectoris. During controlled tachycardia, induced myocardial ischemia is accompanied by increased concentrations of lactic acid, carbon dioxide, hydrogen ion, potassium and bradykinin. Fox et al. observed the release of adenosine from human hearts during angina induced by rapid atrial pacing. Subsequently, Berger et al., in a similar experimental setting, reported the release of prostaglandin F₃ from the coronary sinus during anginal provocation.

Hamberg, Svensson and Samuelsson described another prostaglandin, thromboxane A₂, which has been found to have potent coronary vasoconstricting and platelet-aggregating ability. Our development of a radioimmunoassay to measure thromboxane B₂, the stable but inactive metabolite of thromboxane A₂, led us to design an investigative protocol using rapid atrial pacing to determine if thromboxane release is involved in the cardiovascular response to ischemia. This study documents increases in both coronary sinus and arterial thromboxane B₂ concentrations during and after ischemia in patients with arteriographically proved, fixed coronary artery disease.

Materials and Methods

Fourteen patients with anginal syndrome admitted to Thomas Jefferson University Hospital from June to December of 1978 were studied by atrial pacing using a method previously reported, followed by coronary arteriography and ventriculography. Descriptions of these patients are shown in table 1. All were judged to have unstable or accelerating angina pectoris and were candidates for emergency myocardial revascularization. After informed consent was obtained, catheterization of the coronary sinus was performed by means of a #7 Gorlin pacing catheter. An 18-gauge Teflon cannula was inserted into the exposed brachial artery. The Gorlin catheter was positioned 2 cm beyond the orifice of the coronary sinus and the position was confirmed by injection of contrast material. Before pacing, blood samples were simultaneously obtained from the arterial cannula and coronary sinus catheter. The specimens were immediately transferred into a glass tube containing polyethylene glycol for lactate analysis as previously described, and into a 2-ml vacutainer (Becton-Dickinson) prefilled with 0.04 ml of a 7.5% solution of EDTA for thromboxane B₂ analysis. Repeated fluoroscopic observation confirmed the stability of the catheter position. Contrast material injected during the study has been shown in control patients not to affect thromboxane measurements.

Pacing was instituted at the rate of 110 beats/min and increased by 10 beats/min each 10 seconds up to 140 beats/min. This rate was then maintained for 5 minutes under constant electrocardiographic monitoring (standard lead III and V₅). No atrioventricular block was encountered and no atropine was required. Electrocardiographic leads were used primarily to confirm atrial pacing capture and to evaluate arrhythmias. Blood samples were collected again as described above beginning at 3 minutes of pacing until the end of 5 minutes. Immediately after pacing, a third set of specimens was collected. In three cases, samples were also obtained 10 minutes after pacing.

From the Cardeza Foundation for Hematologic Research, Division of Cardiology, and the Departments of Physiology and Pharmacology, Thomas Jefferson University, Philadelphia, Pennsylvania. Dr. Lewy was supported in part by grants HL-14980, HL-21239 and Training Grant AM-07084 from the USPHS. Address for correspondence: Robert I. Lewy, M.D., 1 Waverly Court, Houston, Texas 77005. Received July 9, 1979; revision accepted November 30, 1979. Circulation 61, No. 6, 1980.
TABLE 1. Thromboxane B₂ and Lactate Measurements in 14 Coronary Artery Disease Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Stage*</th>
<th>Coronary sinus TxB₂ (pmol/ml)</th>
<th>Arterial TxB₂ (pmol/ml)</th>
<th>Coronary sinus lactate (mg/dl)</th>
<th>Arterial lactate lactate (mg/dl)</th>
<th>Lactate extraction (%)</th>
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<tr>
<td>1</td>
<td>32</td>
<td>M</td>
<td>1</td>
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<td>4.2</td>
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<td>2</td>
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<td>&lt;0.5</td>
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<td>&lt;0.5</td>
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<td>5.4</td>
<td>+50.0</td>
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<tr>
<td>6</td>
<td>52</td>
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<td>6.2</td>
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<td>&lt;0.5</td>
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<td>3.6</td>
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<td>4.9</td>
<td>+46.9</td>
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</tbody>
</table>

*Stages: 1 = rest, 2 = paced, 3 = after pacing, and 4 = recovery (10 minutes).
†Percent (%) refers to maximal reduction in luminal diameter observed in one or more views.

Abbreviations: LAD = left anterior descending coronary artery; LMS = left main stem coronary artery; LCA = left circumflex coronary artery; RCA = right coronary artery; TxB₂ = thromboxane B₂.

Subsequent coronary arteriography was performed by the Sones technique. Each coronary artery was observed in 50° left anterior oblique and 30° right anterior oblique views. Angiograms were repeated, when possible, during chest pain. After the initial angiographic series, repeat views were obtained under the influence of sublingual nitroglycerin (0.4 mg). Fixed coronary occlusive disease was judged to be the
basis for angina pectoris because no dynamic change in coronary lesions was apparent despite repeated coronary visualizations. Significant coronary lesions were considered to be present if a major coronary artery was proximately obstructed by at least 50% of the luminal diameter in at least one radiographic view.

Unstable or accelerating angina pectoris was defined as anginal distress of recent onset (less than 1 month) or when angina was found to have changed from a chronic, stable pattern to attacks manifesting one or more of the following changes: 1) more than doubled in frequency, 2) increased to 15 minutes or more in duration, 3) recent onset of rest angina, 4) diminished response to nitrates or propranolol or

<table>
<thead>
<tr>
<th>Arteriography†</th>
<th>Brachial artery pressure (rest) (mm Hg)</th>
<th>Heart rate at rest (beats/min)</th>
<th>Chest pain</th>
<th>Chest pain during stage</th>
<th>Medications before study</th>
<th>Duration (minutes) at 140 beats/min</th>
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<td>90% LAD, 90% RCA</td>
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<td>85</td>
<td>Yes</td>
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<td>5</td>
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<tr>
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<td>62</td>
<td>No</td>
<td>—</td>
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<td>96</td>
<td>Yes</td>
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<td>Propranolol, procainamide, isosorbide dinitrate</td>
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<tr>
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<td>Yes</td>
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<td>None</td>
<td>3</td>
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<tr>
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<td>62</td>
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<td>55</td>
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<tr>
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<td>60</td>
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<td>2</td>
<td>None</td>
<td>5</td>
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<tr>
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<td>Nitroglycerin</td>
<td>4</td>
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<tr>
<td>100% LAD 80% LCA, 100% RCA</td>
<td>145/70</td>
<td>66</td>
<td>Yes</td>
<td>2</td>
<td>Propranolol, isosorbide dinitrate</td>
<td>5</td>
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</table>
both, 5) more easily provoked, and 6) unpredictable onset. Serial ECGs did not reveal new Q waves or persisting repolarization abnormalities, and cardiac enzyme determinations were normal during observation.

Patients were excluded or deferred from study until the influence of agents such as aspirin and steroidal and nonsteroidal antiinflammatory drugs were presumed negligible (48 hours). Propranolol, nitroglycerin and isosorbide dinitrate were not considered to be likely to influence these results. All patients received no medication for at least 12 hours before study. Observations in our laboratory do not support the possibility that these medications have an aspirin-like effect on thromboxane release in vivo.

**Thromboxane B₂ Radioimmunoassay**

Collected samples were prepared by centrifugation at 6000 g for 10 minutes at 4°C. Radioimmunoassays were performed by mixing either 0.1 ml of normal, platelet-free plasma (with or without known amounts of thromboxane B₂), or 0.1 ml of patient platelet-free plasma, with 0.15 ml of 1-H-thromboxane B₂ (4000 cpm) dissolved in 140-mM NaCl, 15-mM Tris-HCl (pH 7.4). The binding reaction was initiated by the addition of thromboxane B₂ antibodies (10 μl, 1.25 μg protein), was continued for 1 hour at 37°C and terminated by mixing with 0.25 ml of saturated ammonium sulphate. After centrifugation at 15,000 g for 2 minutes, 0.25 ml of the supernatant was transferred to 5 ml of the Bray’s Cocktail (New England Nuclear, Boston, Massachusetts) for liquid scintillation counting.¹⁶ As a control, 18 protocol specimens were collected into EDTA alone and EDTA containing 5 μl of 10-mM indomethacin. Measurements of thromboxane B₂ of the duplicates by radioimmunoassay were essentially identical. The coefficient of variation of this assay is less than 5%.

Lactate assays were performed by enzymatic analysis assay.¹⁷ The coefficient of variation of this assay is about 2%. Normal values in our laboratory for arterial lactate and the corresponding lactate extraction are: 5.9 ± 2.1 mg/dl (19.9 ± 3.0%) at rest, 5.5 ± 1.9 mg/dl (20.9 ± 3.2%) during pacing and 5.6 ± 1.5 mg/dl (20.6 ± 2.7%) after pacing.

We tested the following hypotheses: 1) Pacing-induced angina is associated with increased lactate production. 2) Pacing-induced angina is associated with increased thromboxane B₂ release in coronary sinus and peripheral blood. 3) There is a significant correlation between decreased lactate extraction and detection of thromboxane B₂ during or after pacing. 4) When pacing does not evoke lactate production, thromboxane B₂ is indetectable. These hypotheses were tested by the t test for paired data (a,d), the Fisher exact test (e), and descriptive comparison of means and variance (b).¹⁸

All 14 patients reported met the following criteria: presence of unstable angina, absence of lactate production at rest, development of lactate production during or after pacing and fixed occlusive coronary artery disease proved by coronary arteriography. This group was studied consecutively for thromboxane release. Thus, patients were excluded if resting lactate production was present, if pacing failed to induce lactate production or if coronary arteriography was not consistent with the diagnosis of fixed coronary obstruction.

Using the same procedure, we studied four additional patients for thromboxane release in whom pacing evoked no metabolic abnormalities (i.e., lactate production). Two had normal arteriograms and two had fixed obstructive coronary artery disease. These served as controls for the effect of pacing-induced cardiac work.

**Results**

Table 1 summarizes the individual results obtained for coronary sinus and brachial artery specimens analyzed for thromboxane B₂ and lactate, as well as the individual brachial artery pressures at rest, resting heart rate, occurrence of chest pain, stage of pacing during which chest pain occurred, medication before study, and minutes of pacing at 140 beats/min. Means and standard errors for these measurements before, during and after pacing are shown in table 2.

Because only concentrations of thromboxane B₂ greater than 0.5 pmol/ml were detectable, samples containing 0.5 pmol/ml or less were assigned a value of 0.5 pmol/ml, while samples with more than 0.5 pmol/ml were reported directly. This enabled us to evaluate means and variance before, during and after pacing (table 2) and permitted calculations of the effect of pacing expressed as percentage changes (fig. 1). Because levels of less than 0.5 pmol/ml could not be distinguished from the complete absence of thromboxane B₂, this analysis had the effect of minimizing the apparent increases in pacing-induced thromboxane release.

Pacing was accompanied by angina in 13 of 14 patients. In four patients, pacing was terminated before the 5-minute interval because of severe angina. Before pacing, lactate extraction was shown (fig. 1), while during pacing, lactate extraction fell significantly (p < 0.01) as coronary sinus lactate rose (p < 0.02). Immediately after pacing there was a further significant rise in coronary sinus blood lactate values (p < 0.001) and further decrease in extraction (p < 0.01). After 10 minutes, measurements in three unselected patients showed a return to levels similar to those before pacing, and the lactate extraction normalized (table 2). We have previously observed that coronary sinus and arterial lactate concentration vary greatly among patients during all phases of the pacing protocol. While resting lactate concentrations are not identical in patients reported, the effect of pacing and discontinuation of pacing on the mean lactate values is significant.

Coronary sinus thromboxane B₂ results showed increases from control values in four patients during pacing (with an increase of the mean of 18.0%). Three of these patients continued to have increases after pacing, and were joined by six patients who developed detectable levels only after pacing was discontinued (with an increase in the mean of 203% of control).
Arterial thromboxane B₂ results showed increases from control values in two patients during pacing (with an increase of the mean of 40%). Both patients continued to have further increases after pacing was stopped, and were joined by six patients in whom thromboxane B₂ became detectable only after pacing was discontinued (with an increase of the mean of 132% of control) \( (p < 0.05, \text{paired } t\text{ test}) \).

Thus, thromboxane B₂ was indetectable in only two patients. In the other 12 patients, arterial levels alone \( (n = 3) \), coronary sinus levels alone \( (n = 4) \) or levels from both sites \( (n = 5) \) were higher after pacing was stopped than before pacing.

The rise in coronary sinus and arterial lactate and thromboxane B₂ in patients after discontinuation of pacing probably represents a washout phenomenon from the ischemic zone. We have found this to be a reproducible observation with respect to lactate concentration.

After 10 minutes, mean coronary sinus and brachial artery thromboxane B₂ concentrations returned to levels observed before pacing or below. Contingency-table analysis for association between negative lactate extraction and a result of greater than 0.5 pmol/ml coronary sinus thromboxane B₂ detection in the post-pacing period yielded \( p = 0.027 \) (one-tailed Fisher exact test). Of the four patients studied separately in whom pacing did not evoke lactate production or decreased extraction, thromboxane B₂ was below detectable limits in all specimens in all phases of the protocol.

Only atrial pacing appeared to determine the degree of thromboxane released. Thus, the resting brachial artery pressure and heart rate or medications taken before study (table 1) did not appear to influence pacing-induced thromboxane release statistically. Contingency-table analysis also failed to show an association between the duration of pacing at 140 beats/min and the appearance of thromboxane B₂ in coronary sinus or arterial specimens.

**Discussion**

In the present study, we often found increases above control values of coronary sinus and arterial thromboxane B₂ concentrations after pacing-induced
ischemia and never found increases where ischemia was not evoked. These increases followed a similar time course to increased lactate production. Both substances returned to control levels within 10 minutes after cessation of cardiac pacing. Rapid clearance of circulating thromboxane B₂ has been shown recently in the monkey. In the same study it was also demonstrated that during this interval the majority of plasma thromboxane B₂ is not metabolized to compounds not detectable by the radioimmunoassay we used.

Lactate is supplied to the myocardium as a substrate in arterial blood, extracted by normal myocardium and produced by the myocardium in the presence of ischemia and anaerobic metabolism. Lactate production or decreased lactate extraction has been shown to be a reliable indicator of myocardial ischemia in angina patients. Accordingly, the observed thromboxane release during myocardial ischemia suggests that this substance may play a pathophysiologic role in the cardiac response to ischemia.

Our findings therefore suggest a more complex circulatory response to ischemia than vasodilation alone. To date, studies have shown release of adenosine, potassium, hydrogen ion and bradykinin during pacing-induced angina. These responses imply reduction in coronary vascular resistance. However, thromboxane A₂, a potent coronary vasoconstrictor in vitro and in experimental models, could competitively influence regional coronary flow during and after angina pectoris.

The concentration of thromboxane necessary locally to produce this competitive effect is not known. However, in a study reported elsewhere of patients with coronary artery spasm manifesting variant angina, we measured circulating levels of thromboxane B₂. While these levels were tenfold higher than those produced by pacing in the present study, this detection of thromboxane B₂ in another condition in which coronary blood flow is markedly reduced supports a possible vasoconstrictive effect during angina pectoris in the patients studied here.

Under conditions of prolonged total coronary occlusion, prostaglandin release from the heart has been observed in isolated heart preparations and in the intact, open-chest animal. Using an experimental protocol similar to our own, Berger et al. showed cardiac release of prostaglandin F in patients during myocardial ischemia induced by atrial pacing. In other studies, the compound prostaglandin F₂α, a member of the prostaglandin F series, was found to be released during myocardial ischemia induced by coronary occlusion. Although the preponderance of evidence favors a deleterious coronary vasoconstrictive effect after such thromboxane A₂ release, recent studies have shown a paradoxic decrease in coronary blood flow during vasodilation of the ischemic distal coronary bed. Hence, vasoconstriction resulting from thromboxane release could conceivably be beneficial: A vasoconstrictive response to transient myocardial ischemia could potentially prevent both a coronary steal and abrupt increases in stenotic resistance by maintaining appropriate distal coronary pressure.

Thromboxane A₂, by independently acting on circulating platelets, may lead to mechanical obstruction of this same distal coronary bed, further enhancing the intensity of ischemia. Indirect evidence suggests that the platelet-aggregating effect of thromboxane A₂ may play such a role in spontaneously occurring ischemia. Coronary sinus platelets are more aggregable to epinephrine and ADP stimulation in coronary artery disease patients than in control subjects. It has recently been observed that platelet counts are lower in coronary venous blood than in arterial blood in certain coronary artery disease patients. These observations during spontaneous angina are relevant to the present study, as platelets in either the ischemic zone or the coronary circulation are a likely source of the observed pacing-induced thromboxane.

Our findings that thromboxane is released during increased myocardial lactate production suggests that this compound, by its platelet-aggregating or coronary-vasoconstricting potential, could play a role in the response to regional myocardial ischemia. The final effect on coronary blood flow and salvage of jeopardized myocardium in the intact subject with fixed occlusive coronary artery disease and spontaneously occurring ischemia remains to be assessed.

Acknowledgment

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References

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