

Effect of Atrial Pacing on Intracoronary Thromboxane Production in Coronary Artery Disease

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The effect of atrial pacing on intracoronary thromboxane production was investigated in 35 patients with stable ($n = 19$) or unstable ($n = 16$) angina. Arterial and coronary sinus thromboxane B_2 , the stable metabolite of thromboxane A_2 , myocardial lactate extraction and thermodilution coronary sinus flow were measured before, during and immediately after atrial pacing until the onset of angina. Pacing did not significantly increase coronary sinus thromboxane B_2 (rest, 233 ± 107 pg/ml; pacing, 249 ± 154 pg/ml; postpacing, 330 ± 309 pg/ml) (mean \pm standard deviation) despite a moderate increase in arterial thromboxane B_2 (rest, 270 ± 170 pg/ml; pacing, 387 ± 364 pg/ml; postpacing, 446 ± 420 pg/ml) (all changes probability [p] < 0.05). A positive transmural thromboxane B_2 gradient, suggesting intracoronary thromboxane A_2 production, occurred in only five patients at rest (gradient = 60 ± 35 pg/ml). During pacing, a transmural thromboxane B_2 gradient was

not observed despite myocardial lactate production in 18 patients. A postpacing gradient was observed in eight patients (gradient = 284 ± 349 pg/ml). These gradients were significantly more frequent in patients who produced lactate during pacing (7 of 18) than in patients without lactate production (1 of 17) ($p < 0.05$). In patients with and without a postpacing gradient, coronary vascular resistance decreased with pacing and returned to rest levels immediately after pacing, suggesting that a postpacing thromboxane gradient does not significantly alter coronary tone.

These data suggest that: 1) pacing-induced angina is usually not associated with substantial intracoronary thromboxane A_2 production; 2) in a minority of patients who develop intracoronary thromboxane A_2 production, the amount is small and does not produce significant coronary vasoconstriction.

Thromboxane A_2 is an arachidonic acid metabolite produced by activated platelets that cause marked vasoconstriction of isolated coronary arteries (1-3) and myocardial ischemia (4-8) in experimental animals. Several recent studies (9-11) have demonstrated detectable circulating levels of thromboxane B_2 , the stable metabolite of thromboxane A_2 , in patients with coronary artery disease both at rest (12-16)

and during stress-induced angina (14-17). A positive transmural thromboxane B_2 gradient, suggesting intracoronary thromboxane A_2 production, has also been noted in some patients with coronary artery disease (12,14,16,17). Consequently, it has been postulated that intracoronary thromboxane A_2 production plays a role in the pathophysiology of angina pectoris. This study was undertaken to investigate this possibility by evaluating 1) the incidence of thromboxane A_2 production in the coronary and noncoronary circulations during pacing-induced angina; 2) the relation of thromboxane production to myocardial ischemia and the clinical pattern of angina; and 3) the relation of pacing-induced thromboxane production to changes in coronary hemodynamics.

Methods

Patient selection. Thirty-five patients (31 men and 4 women) with coronary artery disease undergoing cardiac catheterization for evaluation of chest pain were studied.

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The mean age was 55 ± 8 years. Nineteen patients had stable exertional angina without a change in their clinical status in the preceding month. Sixteen patients had unstable angina as defined by a recent change in anginal symptoms and at least one episode of rest pain in the preceding month. Seven of these patients had angina at rest associated with transient ST segment changes within 48 hours of catheterization; none experienced rest angina during the study. All of the patients had 75% or greater stenosis of one or both major vessels of the left coronary system and were receiving long-acting nitrates, or beta-adrenergic blocking agents, or a combination of both. These medications were withheld for 12 hours before the study. Patients were excluded if they had been treated with aspirin, dipyridamole or aspirin-containing compounds within 1 week of catheterization. The study was approved by our institution's Committee for Research Involving Human Subjects and written informed consent was obtained from each patient.

Catheterization protocol. Patients came to the cardiac catheterization laboratory in the postabsorptive state. A thermodilution coronary sinus catheter (Wilton-Webster) was inserted through the right basilic vein and advanced into the midcoronary sinus. Position was confirmed by injection of 5 ml of Renografin-76. The thermodilution catheter was equipped with an electrode tip for pacing and a lumen through which blood could be sampled. Arterial blood pressure was measured continuously by a catheter in the femoral or brachial artery. All six electrocardiographic limb leads and one or two precordial leads were monitored throughout the study.

Atrial pacing. Duplicate baseline measurements of coronary sinus flow and arterial pressure were recorded. Arterial and coronary sinus blood samples for thromboxane B_2 and lactate concentrations were obtained. The heart rate was then increased by coronary sinus pacing in increments of 20 beats/min every 2 minutes until the patient experienced anginal pain or a heart rate of 150 beats/min. At the end of each pacing period, coronary flow, arterial pressure and electrocardiograms were recorded. At the peak pacing rate, repeat arterial and coronary sinus samples for thromboxane B_2 and lactate concentration were obtained. Immediately after the termination of pacing, additional arterial and coronary sinus samples for thromboxane concentration were obtained. At 1 minute after pacing, coronary flow and arterial pressure were remeasured. The position of the coronary sinus flow catheter was checked by fluoroscopy at the time of each flow measurement to ensure a stable position.

Coronary sinus flow. Coronary sinus flow was determined using a continuous infusion of room temperature 5% dextrose in water at a rate of 38 ml/min, as previously utilized in our laboratory (18,19). Both indicator and dilution temperature were measured during infusion. Flow was calculated using the equation of Ganz et al. (20). Duplicate flow measurements varied by less than 10%. Coronary vascular resistance was calculated as mean arterial pressure divided by coronary sinus flow.

Assays. Thromboxane A_2 has a half-life of 30 seconds in aqueous solution and is rapidly converted to the inactive metabolite thromboxane B_2 (9-11). Thromboxane B_2 is metabolized and excreted over a period of hours, and consequently may be used to assess acute changes in thromboxane A_2 production (10,11).

Blood samples for thromboxane B_2 concentration were drawn through catheters and collected in plastic tubes containing 4.5 mM sodium ethylenediaminetetra-acetic acid (EDTA) and 10 μ M indomethacin (in final concentration). The samples were then centrifuged at 6,000 g at 4°C for 10 minutes. Thromboxane B_2 was measured by radioimmunoassay using a New England Nuclear Kit. Briefly, 0.1 ml of the patient's platelet free plasma was mixed with 0.1 ml of H_3 -thromboxane B_2 and 0.1 ml of thromboxane B_2 antibody and incubated overnight at 4°C. Dextran-coated charcoal was used to separate bound from free thromboxane B_2 , and the bound fraction was counted in a liquid scintillation counter. Standard curves were prepared in buffer and calculations were performed according to the manufacturer's recommendations. The sensitivity of this assay is 180 pg/ml (0.5 pmol/ml), and the coefficient of variation is 10%. The antibody employed has a low cross-reactivity with other prostaglandins (PG): 0.2% with PGE_2 , less than 0.2% with PGA_2 , less than 0.2% with $PGF_{2\alpha}$ and less than 0.2% with 6-keto $PGF_{1\alpha}$. Furthermore, our assay detected suppression of in vitro thromboxane B_2 production by aspirin.

To ensure that our sampling technique did not falsely elevate thromboxane B_2 , we obtained femoral venous samples in five patients by direct needle stick as well as through our arterial and coronary sinus catheters. Thromboxane was undetectable in all samples. Other investigators (21-23) have also reported that this method of sampling does not activate platelets or falsely elevate thromboxane B_2 levels.

Blood for lactate determination was deproteinized in iced 10% perchloric acid and assayed on the same day using a spectrophotometric technique (Sigma Chemical Company Kit). Lactate extraction in the myocardial bed was calculated as aortic - coronary sinus lactate concentration/aortic lactate concentration.

Statistical analysis. Blood samples containing undetectable levels of thromboxane B_2 were arbitrarily assigned a value of 180 pg/ml. Group concentrations were expressed as mean values \pm standard deviations. Group comparisons were made utilizing nonparametric methods (Wilcoxon signed rank and Mann-Whitney tests) for paired and nonpaired data, as appropriate. A probability (p) value less than 0.05 was considered significant.

Results

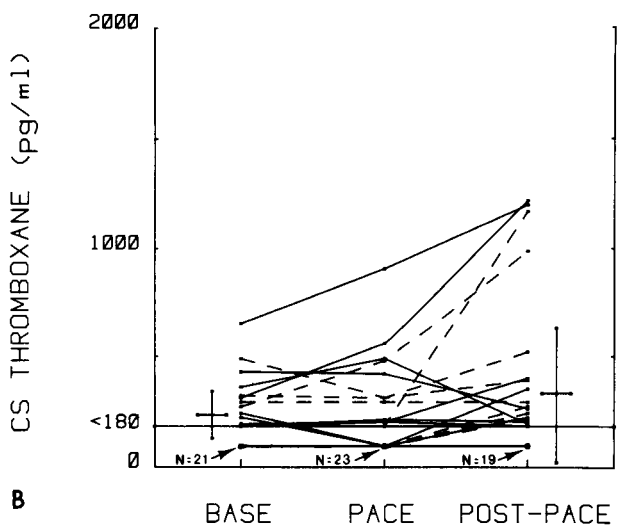
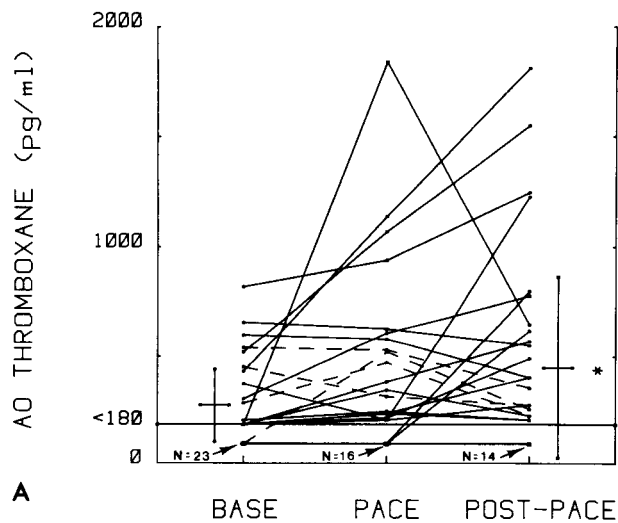
Atrial pacing increased the heart rate from 64 ± 10 to 123 ± 15 beats/min and the rate-pressure product from $8,750 \pm 1,800$ to $17,850 \pm 2,500$ mm Hg beats/min. Angina developed in 29 of the 35 patients.

Thromboxane measurements during pacing (Fig. 1 and 2). At rest, 17 (49%) of the 35 patients had detectable levels of thromboxane B₂ in arterial or coronary sinus blood, or both; mean arterial thromboxane was 270 ± 170 pg/ml and mean coronary sinus thromboxane was 233 ± 107 pg/ml. Five patients exhibited a small positive transmyocardial thromboxane gradient (60 ± 35 pg/ml; range, 40 to 120), suggesting intracoronary thromboxane production. Nine patients had a higher arterial concentration than coronary sinus concentration.

Pacing increased arterial thromboxane to 387 ± 364 pg/ml ($p < 0.05$ compared with base) but did not increase coronary sinus thromboxane (249 ± 154 pg/ml). No patient exhibited a positive transmyocardial thromboxane gradient during pacing.

Immediately after pacing, arterial thromboxane increased

Figure 1. Effect of pacing on arterial (AO) (A) and coronary sinus (CS) (B) thromboxane B₂ concentrations. Patients who developed a positive transmyocardial gradient after pacing are indicated by broken lines. The number of patients with undetectable thromboxane B₂ at each stage of pacing is indicated. * $p < 0.05$ versus base.



further to 446 ± 420 pg/ml ($p < 0.01$ compared with base), whereas coronary sinus thromboxane remained unchanged from basal values (330 ± 309 pg/ml). Eight (23%) of the 35 patients developed a positive transmyocardial thromboxane gradient with a mean postpacing coronary sinus thromboxane level of 510 ± 368 pg/ml (range, 210 to 1,170). Only one of these eight patients exhibited a rest gradient. The mean gradient (284 ± 349 pg/ml; range, 30 to 990) was significantly larger than those noted at rest ($p < 0.05$) but exceeded 100 pg/ml in only four patients. Eighteen patients had a higher arterial than coronary sinus concentration, suggesting noncoronary thromboxane production after pacing.

Thromboxane and lactate. During pacing, myocardial lactate production developed in 18 patients (lactate extraction: base, $10 \pm 24\%$; pacing, $-25 \pm 14\%$), whereas lactate extraction was noted in the other 17 patients (lactate extraction: base, $27 \pm 10\%$; pacing, $16 \pm 10\%$). A postpacing positive transmyocardial thromboxane gradient developed significantly more frequently in the 18 patients who produced lactate during pacing (7 of 18 patients) than in the 17 patients without lactate production (1 of 17 patients) ($p < 0.05$). In addition, the mean transmyocardial thromboxane gradient postpacing was significantly higher ($p < 0.05$) in the patients who developed lactate production than in patients without lactate production (Table 1).

Thromboxane and anginal pattern. Nineteen patients had stable angina and 16 patients had unstable angina. In these two groups, a positive transmyocardial thromboxane gradient occurred with equal frequency both at rest (stable group, 3 of 19 versus unstable group, 2 of 16; $p =$ not significant [NS]) and after pacing (stable group, 4 of 19 versus unstable group, 4 of 16; $p =$ NS). There was no

Figure 2. Effect of pacing on transmyocardial arterial-coronary sinus (AO-CS) thromboxane gradients. Patients who developed a positive transmyocardial gradient after pacing are indicated by broken lines.

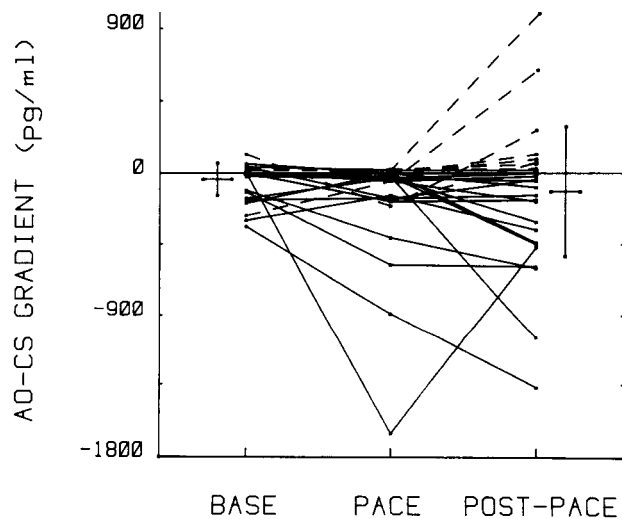


Table 1. Comparison of Thromboxane B₂ Concentrations (pg/ml) in Patients Who Developed Myocardial Lactate Production (n = 18) Versus Patients Who Continued to Extract Lactate (n = 17) During Pacing

	AO	CS	Transmyocardial Gradient (CS-AO)	CS > AO
Lactate production				
Base	292 ± 387	256 ± 174	-36 ± 170	3 of 18
Pacing	347 ± 478	277 ± 349	-97 ± 169	0 of 18
Postpacing	368 ± 300	389 ± 351	22 ± 409*	7 of 18*
Lactate extraction				
Base	251 ± 138	209 ± 66	-42 ± 103	2 of 17
Pacing	436 ± 473	219 ± 105	-224 ± 455	0 of 17
Postpacing	528 ± 515	267 ± 252	-262 ± 409	1 of 17

*p < 0.05 compared with patients with lactate extraction during pacing
AO = arterial, CS = coronary sinus.

difference between the two groups in the absolute arterial and coronary sinus thromboxane levels noted at rest, during pacing or after pacing (Table 2).

Seven of the 16 patients with unstable angina developed angina at rest associated with transient ST segment changes within 48 hours of catheterization. None of these patients exhibited a rest or postpacing positive transmyocardial thromboxane gradient. In addition, their absolute arterial and coronary sinus thromboxane concentrations throughout the study were comparable with those of patients with stable angina.

Thromboxane and coronary hemodynamics. To investigate the effect of pacing-induced thromboxane production on coronary vascular resistance, rest and postpacing coronary resistance were compared in three groups of patients: 1) patients with a postpacing positive transmyocardial thromboxane gradient (n = 8); 2) patients with detectable thromboxane in arterial or coronary sinus blood, or both, but without postpacing gradients (n = 18); and 3) patients with undetectable arterial and coronary sinus thromboxane levels throughout the study (n = 9). In all three groups, coronary resistance decreased with pacing and immediately returned to rest levels after the termination of pacing (Table

3). Coronary sinus blood flow after pacing did not decrease below rest levels in any of these groups.

Thromboxane and angina duration. Pacing produced angina in all 8 patients with a postpacing transmyocardial thromboxane gradient and also in 21 other patients. Angina abated spontaneously within 2 minutes after pacing in 7 of the 8 patients with a thromboxane gradient in contrast to 14 of the 21 patients without a gradient (p = NS).

Discussion

Thromboxane A₂ is an arachidonic acid metabolite that is synthesized by activated platelets (1), and has been detected in the coronary circulation of experimental animals during ischemia (7,24). Several observations suggest this prostanoid can exacerbate ischemia: 1) It produces vasoconstriction in isolated coronary arteries (1-3). 2) Administration of microsomal incubates containing thromboxane A₂ to guinea pigs and rabbits produces myocardial ischemia, subendocardial necrosis and occasionally ventricular fibrillation (4-6). 3) Blockade of thromboxane activity with pinane thromboxane A₂ reduces myocardial ischemia in dogs (25). Consequently, it has been postulated that the intracoronary production of thromboxane A₂ plays a role in the pathophysiology of stress-induced myocardial ischemia in human beings. Accordingly, we examined the incidence and degree of intracoronary thromboxane production during pacing-induced ischemia in patients with coronary artery disease.

Thromboxane during pacing. Substantial intracoronary production of thromboxane A₂ in ischemic myocardium would be expected to produce a positive transmyocardial gradient. In the present study, however, we observed small positive thromboxane gradients in five patients at rest and these gradients were not associated with lactate production. During pacing, none of the patients had a positive transmyocardial thromboxane gradient, and only eight exhibited a coronary sinus thromboxane level greater than 200 pg/ml. Eighteen patients exhibited myocardial lactate production.

Table 2. Comparison of Thromboxane B₂ Concentrations (pg/ml) and the Incidence of Positive Transmyocardial Gradients (CS > AO) in Patients With Stable or Unstable Angina*

	AO	CS	CS > AO
Stable angina (19 patients)			
Base	278 ± 157	248 ± 123	3 of 19
Pacing	419 ± 406	263 ± 180	0
Postpacing	365 ± 289	369 ± 348	4 of 19
Unstable angina (16 patients)			
Base	268 ± 187	221 ± 89	2 of 16
Pacing	349 ± 317	233 ± 119	0
Postpacing	542 ± 531	283 ± 258	4 of 16

*There was no significant difference between the two groups.
AO = arterial, CS = coronary sinus

Table 3. Relation of Postpacing Thromboxane B₂ Concentrations (pg/ml) to Changes in Coronary Vascular Resistance (mm Hg/ml·min⁻¹) During and After Pacing

Postpacing Thromboxane B ₂	Postpacing CS Thromboxane B ₂	Coronary Vascular Resistance		
		Base	Pacing	Postpacing
Undetectable (n = 9)	< 180	1.4 ± 0.6	1.0 ± 0.6	1.5 ± 0.7
AO > CS (n = 18)	329 ± 327	1.3 ± 0.6	0.9 ± 0.4	1.2 ± 0.6
CS > AO (n = 8)	510 ± 368*	1.2 ± 0.5	0.7 ± 0.2	1.2 ± 0.5

*p < 0.05 compared with patients without gradients.
AO = arterial; CS = coronary sinus

Thus, blood samples in these patients were clearly obtained from ischemic myocardium. These data, therefore, suggest that extensive intracoronary thromboxane production did not occur during pacing-induced ischemia, although production of small amounts of thromboxane A₂ in some regions could not be excluded.

After termination of pacing, a positive transmural gradient was noted in eight patients, but the gradient was greater than 200 pg/ml in only four. The development of a transmural gradient after pacing was related significantly to the development of myocardial lactate production during pacing, suggesting that thromboxane production occurs predominantly in ischemic myocardial beds. These postpacing gradients may have been due to small amounts of thromboxane A₂ production during pacing that were not detected until after pacing. Such delayed detection may occur because of a relative reduction of blood flow to the ischemic areas during pacing. Alternatively, thromboxane A₂ production may not occur until after the termination of pacing and may be caused by release of ischemic byproducts, mechanical events or other factors.

Although substantial intracoronary thromboxane production did not appear to occur during pacing, increases in arterial thromboxane were noted. This observation suggests that thromboxane production in the noncoronary circulation frequently occurs during pacing-induced angina. Several other studies (17,27,28) have also demonstrated a greater increase in arterial than in coronary sinus thromboxane levels during pacing. The source of this production is presently unclear, although platelet activation in the pulmonary or noncoronary systemic beds is possible.

Relation of thromboxane to coronary hemodynamics. The presence of intracoronary thromboxane production after pacing did not appear to be associated with substantial coronary vasoconstriction. Coronary resistance decreased during pacing and returned to rest levels after pacing in patients with and without a postpacing thromboxane gradient. In addition, angina was rapidly relieved by the termination of pacing. Previous studies (19,26) have demonstrated that thermodilution measurement of coronary sinus flow can detect changes in coronary resistance produced by the cold pressor test and by coronary spasm. Therefore, if persistent extensive changes in coronary resistance oc-

curred in myocardial beds producing thromboxane, it is likely that they would have been detected.

Because thromboxane A₂ has a short half-life, it is uncertain if thromboxane production in noncoronary vascular beds can affect coronary tone. The patients in this study with arterial thromboxane concentrations higher than coronary sinus concentrations after pacing had no detectable adverse coronary hemodynamic effects. After the termination of pacing, they had a prompt return of coronary vascular resistance to rest levels, as did patients without detectable circulating thromboxane.

Comparison with previous studies. Our observations that positive transmural thromboxane gradients did not occur during pacing but developed in some patients immediately after pacing are, in general, compatible with those of Lewy et al. (17). In a group of 14 patients with coronary disease, they observed a positive transmural thromboxane gradient in only 4 patients during pacing as opposed to 9 patients after pacing. In addition, Lewy et al. (17) and others (27,28) observed a greater increase in arterial than in coronary sinus thromboxane levels during pacing, as in our study. However, our findings suggest that the incidence of positive postpacing gradients may be less frequent than that noted in the study of Lewy et al. (17).

Our findings and those of Lewy et al. (17) differ from the findings of Tada et al. (16). These investigators noted intracoronary thromboxane production during pacing in 9 of 10 patients with stable exertional angina; an increase in arterial thromboxane concentrations was not observed. Differences in the patient population, particularly with regard to the extent of coronary and noncoronary vascular disease as well as pulmonary disease, may account for these discrepancies.

Our findings also differ from the observations of Hirsh et al. (12) concerning the relation of thromboxane production to anginal pattern. These investigators noted that rest transmural thromboxane gradients were frequent in patients with both unstable angina and pain within 48 hours. In a preliminary study (14), they also reported that patients with unstable angina develop transmural thromboxane gradients during stress whereas patients with exertional angina do not. Seven patients in our study developed angina at rest associated with transient ST segment changes within

48 hours of catheterization. None of these patients had rest transmural gradients. We also observed no relation between anginal pattern and stress-induced thromboxane production. Variation in the extent of coronary disease and the different types of stress employed by Hirsh et al. (12) may in part explain these discrepancies.

The studies of Tada et al. (16) and Hirsh et al. (12) also differ from both the present study and the study of Lewy et al. (17) with respect to assay techniques. These groups of investigators increased the sensitivity of their assay by extracting and concentrating thromboxanes before analysis. However, this alone cannot account for the differences in results because the thromboxane levels reported by Tada et al. (16) and Hirsh et al. (12) were within the range detectable by our assay.

Clinical implications. This study suggests that pacing-induced myocardial ischemia is not associated with substantial intracoronary thromboxane production in the majority of patients with coronary artery disease. Even in patients with intracoronary thromboxane production, the transmural concentration gradients were usually low and no evidence of major coronary vasoconstriction was noted. These observations suggest that intracoronary thromboxane production may not play a major role in the pathogenesis of stress-induced angina. This is consistent with recent observations (27,29) that specific thromboxane inhibitors have no significant effect on coronary flow or on the anginal threshold of patients with coronary disease.

Nevertheless, our data and those of others (14,16,17) demonstrate that intracoronary thromboxane production occurs in some patients with stress-induced ischemia, and may indicate an increased propensity for intracoronary platelet activation and thrombosis. Therefore, it is of interest to determine whether patients with stress-induced intracoronary thromboxane production have a more malignant clinical course than patients without such production and whether agents that inhibit thromboxane synthesis are useful in the treatment of these patients.

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