Failure of Thromboxane A\textsubscript{2} Blockade to Prevent Attacks of Vasospastic Angina

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SUMMARY Thromboxane A\textsubscript{2} (TxA\textsubscript{2}), a derivative of arachidonic acid, is mainly produced by platelets and actively released during platelet release reaction.\textsuperscript{1} TxA\textsubscript{2} is a powerful constrictor of vascular smooth muscle\textsuperscript{2} and may be a cause of coronary vasospasm.\textsuperscript{3,4} Increased levels of thromboxane B\textsubscript{2} (TXB\textsubscript{2}), the stable nonenzymatic metabolite of TxA\textsubscript{2}, have been found in the peripheral blood of patients with variant angina,\textsuperscript{1} a widely recognized hallmark of vasospastic ischemia.\textsuperscript{5,6} Whether high levels of TxA\textsubscript{2} play a primary role in precipitating coronary vasospasm or merely represent an epiphenomenon of transient myocardial ischemia, however, is still uncertain.

The present study was aimed at assessing the effects of a single, low, i.v. dose of aspirin, which blocks the release of platelet TxA\textsubscript{2},\textsuperscript{10} on the number, severity and duration of episodes of transient acute ischemia caused by coronary vasospasm.

Material and Methods

We studied seven consecutive male patients, ages 39–60 years (mean 52 years), who had frequent episodes of angina at rest. Transient ST-segment elevation was documented in six patients by serial 12-lead ECGs recorded in the coronary care unit during several anginal episodes; ST-segment depression was consistently observed in one patient (BU), in whom spasm was demonstrated angiographically. Every patient underwent continuous ECG monitoring/recording in the coronary care unit to assess objectively the frequency of ischemic episodes even if asymptomatic. The ECG lead showing the most evident ST-segment changes during the episode was selected for this purpose. All seven patients had 10 or more episodes of transient myocardial ischemia per day documented by typical transient ischemic changes.

Coronary arteriography, performed in all patients by the Judkins technique, showed variable degrees of atherosclerotic disease, from normal coronary arteries (one patient) to three-vessel disease (one patient). During angiography, a transient vasospasm of the left circumflex coronary artery in one patient and the right coronary artery in another occurred spontaneously. In one, the spasm completely occluded the vessel and was accompanied by ST-segment elevation in the inferior leads; in the other (BU), the spasm was not occlusive, marked by delayed distal filling and was accompanied by ST-segment depression in the inferolateral leads. In both patients, the spasm was promptly relieved by intracoronary nitrates. We no longer consider it essential to perform provocative tests in patients with electrocardiographically proved variant angina, particularly when the stress test is negative (three patients) or positive at a rather high work load only (four patients).
Protocol

Throughout the study, two ECG leads were continuously recorded on a dual-channel Holter monitor (Oxford Medilog II). Beat-by-beat analog printouts of the whole recording period were obtained on a six-channel U.V. recorder (San-ei Visigraph) as described elsewhere.\(^1\)\(^2\) The tracings were blindly analyzed by two separate observers. Ischemic episodes were identified by the appearance of transient positive or negative ST displacement (\(\geq 0.15 \text{ mV}\)) or pseudonormalization of inverted T waves lasting at least 30 seconds, regardless of the presence of anginal pain.\(^11\)\(^-\)\(^14\)

Antianginal treatment was discontinued 24 hours before the study, and only oral nitrates were given to relieve anginal attacks when required.

After a 48-hour control Holter recording (72 hours in two patients), a single dose of injectable aspirin (lysine salt of acetylsalicylic acid, 3.6 mg/kg, corresponding to 2 mg/kg of aspirin) was given intravenously. Holter monitoring was then continued for 48 hours in five patients and for 72 hours in two.

Whole blood samples were drawn from a peripheral vein every 12 hours before and after aspirin, immediately separated into 1-ml aliquots and allowed to clot in glass tubes (1 cm i.d.) at 37°C. After 1 hour, the serum was separated by centrifugation at 3000 rpm and stored at \(-20°C\). Within 1 week, the levels of TxB\(_2\) were assayed in triplicate by radioimmunoassay, as described by Patrono et al.\(^10\)

Results

The average control levels of platelet TxB\(_2\), 48 and 24 hours before aspirin were, respectively, 225 \(\pm\) 56 and 240 \(\pm\) 38 ng/ml (mean \(\pm\) sd). Twenty-four and 48 hours after aspirin, they fell to 4.6 \(\pm\) 6.5 and 9.7 \(\pm\) 12.3 ng/ml (fig. 1). Both the control TxB\(_2\) values and those obtained after aspirin were comparable to those in healthy volunteers treated with comparable i.v. doses by Patrono et al.\(^10\)

We recorded 275 ischemic episodes, 50 of which were accompanied by anginal pain. ST-segment elevation occurred in 194, ST-segment depression in 42 and pseudonormalization or peaking of inverted T waves in 39 (fig. 2). Five patients alternated different electrocardiographic changes on the same leads in different episodes (although the most frequent change was ST-segment elevation); one patient had only episodes with ST-segment elevation and one only episodes with ST-segment depression; in the latter patient, spasm was documented during arteriography.

FIGURE 1. Total number of ischemic episodes and platelet thromboxane B\(_2\) (TxB\(_2\)) levels in the 2 days before (left) and after (right) aspirin (ASA). The various cross-hatched and stippled segments represent the number of episodes for a single patient. Despite the dramatic decrease in platelet TxB\(_2\) after aspirin, no significant difference in the number of ischemic episodes is evident.

FIGURE 2. Average duration and relative distribution of ischemic episodes characterized by ST-segment elevation (ST \(\uparrow\)), ST-segment depression (ST \(\downarrow\)) and pseudonormalization of inverted or flat T waves (PNTW) before and after aspirin (ASA). Aspirin did not significantly affect either the duration or the severity of ischemic episodes.
There were 129 ischemic episodes before aspirin and 146 after (figs. 1 and 2). Of the episodes accompanied by pain, 26 occurred before aspirin and 32 after. During the control period, 87 ischemic episodes were characterized by ST-segment elevation, 18 by ST-segment depression and 24 by pseudonormalization of inverted T waves; after aspirin we recorded 107 ischemic episodes characterized by ST elevation, 24 by ST depression and 15 by pseudonormalization of inverted T waves (fig. 2). The differences were not statistically significant (t test). Similarly, the average duration of episodes and the incidence of chest pain were not affected by aspirin (fig. 2). In the two patients in whom TxB, and the ECG were monitored for 3 days before and after aspirin, there was no consistent difference in the number of ischemic episodes (fig. 3). Repeated Holter monitoring during treatment with high-dose nitrates and calcium antagonists showed that the number of ischemic episodes was reduced to less than 20% of that observed during the aspirin trial.

Discussion

The dramatic decrease in platelet TxA, in our patients after aspirin did not affect the number, severity and duration of episodes of transient ischemia caused by coronary vasospasm. This finding suggests that the release of the prostanoid from aggregating platelets is not a necessary step in the genesis of coronary vasospasm.

Acetylsalicylic acid prevents the production of platelet thromboxane A, through an acetylation of cyclooxygenase, the enzyme catalyzing the synthesis of cyclic endoperoxides from arachidonic acid. This effect is not limited to TxA; the formation of other prostanoids is also impaired in platelets and in other cells.

Inhibition of prostacyclin synthesis could be partially responsible for the negative results in our study. Miwa et al. observed a decreased threshold for exercise-induced coronary vasospasm after high-dose aspirin (4 gr/day), which they interpreted as a consequence of reduced prostacyclin production by the endothelial cells. Impairment of prostacyclin synthesis by human veins was documented up to 48 hours after 300 mg of aspirin had been given. However, cultured endothelial cells incubated with aspirin rapidly recovered their ability to synthesize prostacyclin. PGI, release induced in the human forearm by local ischemia was not affected by aspirin at the doses used in our study. Also, arterial tissue appears much less sensitive to the action of aspirin than venous tissue and platelets, and rapidly recovers the capability of producing PGI. Thus, it seems unlikely that aspirin at the doses used in our study significantly affected arterial PGI.

Whatever the effect of aspirin on PGI, production, the role of PGI, in preventing coronary vasospasm is still unsettled. We previously showed that i.v. infusion of exogenous prostacyclin did not prevent coronary vasospasm in eight of nine patients with variant angina.

In conclusion, although we cannot rule out that the local production of prostacyclin in the artery undergoing spasm was partially and temporarily impaired by aspirin in our patients, an almost complete blockade of TxA, failed to prevent acute myocardial ischemia due to coronary vasospasm. This finding indicates that TxA, probably does not initiate coronary spasm. Robertson et al. simultaneously reached similar conclusions.

References

Pathophysiology of Coronary Artery Spasm

Ben Freedman, M.B., David R. Richmond, M.B., and David T. Kelly, M.B.

SUMMARY Coronary arterial measurements were made from cineangiograms in patients with positive and negative ergonovine tests. In those with positive tests, normal segments of arteries adjacent to the site of spasm and arteries without spasm showed no greater sensitivity to ergonovine than arteries from control patients (20 ± 13% constriction vs 17 ± 12%, NS). In patients with positive and negative ergonovine tests, constriction was measured at lesion sites after ergonovine and compared with values predicted from a geometric theory. The measured constriction was always greater than predicted in patients with a positive ergonovine test, and frequently less than predicted in patients with a negative test. The increased sensitivity of arteries that show localized vasoconstriction at lesion sites after ergonovine administration is not explained by geometry alone.

CORONARY artery spasm may cause angina at rest, but its pathogenesis is unclear. Spasm is usually associated with atherosclerotic encroachment of the lumen, but this may be minimal.1,2 Whereas small doses of ergonovine given to patients with angina due to spontaneous coronary spasm usually produce spasm,3-7 larger doses given to normal controls or to patients with non-cardiac chest pain produce only a mild, generalized vasoconstriction.4,6 This difference suggests that the arteries of patients with spontaneous spasm are hypersensitive to ergonovine at the sites of atherosclerotic lesions. MacAlpine8 recently proposed that this hypersensitivity was due to the amplification of normal vasoconstriction at sites of atheromatous luminal encroachment, the degree of vasoconstriction being related to the severity of encroachment (geometric theory). We undertook the present study to determine whether this geometric theory could explain the hypersensitivity of arteries in patients with vasospastic angina.

Methods

Patient Selection

Eleven patients (seven men and four women, mean age 51 ± 8 years) with documented9 or clinically suspected8 variant angina formed the study population (group A). All patients had a positive ergonovine test in the cardiac catheterization laboratory. Coronary angiograms demonstrated normal findings in two patients and minor lesions in nine (2–52% luminal diameter reduction; mean 25%). Twenty-one patients (eight men and 13 women, mean age 49 ± 8 years) with chest pain atypical for myocardial ischemia and a negative ergonovine test were used as controls for com-
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