Stroke

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Articles

Platelet Activation and Lipid Peroxidation in Patients With Acute Ischemic Stroke

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Abstract

Background and Purpose Both platelet activation and lipid peroxidation are potential sources of vasoactive eicosanoids that can be produced via the cyclooxygenase pathway, ie, thromboxane (TX) A_2, or by free radical–catalyzed peroxidation of arachidonic acid, ie, isoprostanes. We investigated the biosynthesis of TXA_2 and F_2-isoprostanes, as reflected by the urinary excretion of 11-dehydro-TXB_2 and 8-epi-prostaglandin (PG) $F_{2\alpha}$, respectively, in 62 consecutive patients (30 men, 32 women; mean age, 67±14 years) with acute ischemic stroke.

Methods At least two consecutive 6-hour urine samples were obtained during the first 72 hours after onset of symptoms. Urinary eicosanoids were measured by previously described radioimmunoassays.

Results Repeated periods of enhanced thromboxane biosynthesis were found in 52% of patients. Urinary 11-dehydro-TXB_2 averaged 221±207 (mean±SD; n=197; range, 13 to 967) pmol/mmol creatinine in 30 patients treated with cyclooxygenase inhibitors (mostly aspirin) at the time of study versus 392±392 (n=186; range, 26 to 2533) in 32 untreated patients (P<.001). The corresponding values for 8-epi-$PGF_{2\alpha}$ excretion were 74±42 (range, 14 to 206) and 83±65 (range, 24 to 570) pmol/mmol creatinine (P>.05). The correlation between the two metabolites was moderate in both untreated patients (r=.41, P<.001) and patients with cyclooxygenase inhibitors (r=.31, P<.001). In a multiple regression analysis, increased thromboxane production was independently associated with severity of stroke on admission, atrial fibrillation, and treatment with cyclooxygenase-inhibiting drugs.

Conclusions We conclude that during the first few days after an acute ischemic stroke (1) platelet activation occurs repeatedly in a cyclooxygenase-dependent fashion; (2) platelet activation is not associated with concurrent changes in isoprostane biosynthesis; (3) platelet activation is independently associated with stroke severity and atrial fibrillation; and (4) isoprostane biosynthesis is largely independent of platelet cyclooxygenase activity.

Key Words: cerebral ischemia • lipid peroxidation • platelet activation • thromboxanes

Introduction

Both platelet activation and lipid peroxidation are potential sources of vasoactive eicosanoids that can be produced via the cyclooxygenase pathway, ie, TXA_2, or by free radical–catalyzed peroxidation of arachidonic acid, ie, isoprostanes. In previous studies we reported enhanced thromboxane biosynthesis, reflected by the urinary excretion of a major thromboxane metabolite, 11-dehydro-TXB_2, in patients with acute stroke.[1,2] Thromboxane production could be largely suppressed by low-dose aspirin, suggesting its cyclooxygenase-dependent formation in platelets. The F_2-isoprostanes, a family of prostaglandin isomers, are free radical–catalyzed products of arachidonic acid metabolism, of which in vivo formation in humans was first reported by Morrow et al.[3] They are initially formed in situ on phospholipids, from which they are subsequently released, preformed presumably by phospholipases.[4] They circulate in plasma and are excreted in urine.[5,6] Among the F_2-isoprostanes, 8-epi-$PGF_{2\alpha}$ is one of the most abundantly formed under physiological conditions.[5] It was shown to be a potent vasoconstrictive agent in animal models in both renal[3,7] and pulmonary vessels.[8,9] Furthermore, 8-epi-$PGF_{2\alpha}$ was found to cause platelet shape change but not aggregation.[10,11] Increased plasma levels of F_2-isoprostanes were found in smokers,[12] in patients with the hepatorenal syndrome,[13] and in patients with non–insulin-dependent diabetes mellitus.[14] Increased urinary 8-epi-$PGF_{2\alpha}$ levels were found in healthy smokers,[15] after acetaminophen overdose,[16] in patients treated with thrombolytic therapy for acute myocardial infarction,[16] and in hypercholesterolemia.[17] Since F_2-isoprostanes are formed by means of free radical–catalyzed peroxidation of arachidonic acid, it is suggested that an increased production may be a reflection of oxidative stress in these different clinical conditions. However, recent studies suggest that relatively small amounts of 8-epi-$PGF_{2\alpha}$ can also be formed in a cyclooxygenase-dependent manner.[16,18,19,20] It is not known to what extent urinary excretion of 8-epi-$PGF_{2\alpha}$ reflects biosynthesis in the vasculature, since no dose-response infusion studies have yet been performed to assess its fractional elimination. Moreover, the metabolism in humans has been only incompletely characterized.[21]

In patients with ischemic stroke, both activation of platelet and monocyte cyclooxygenases[20] and the free radical–catalyzed pathway are potential sources of 8-epi-$PGF_{2\alpha}$ formation. Moreover, by its potential effect on vessel walls and platelets, this eicosanoid may have a negative influence on stroke outcome.

To investigate the actual rate of 8-epi-$PGF_{2\alpha}$ biosynthesis in vivo, we studied the urinary excretion of this prostaglandin in patients with acute ischemic stroke. In addition, we related the production of 8-epi-$PGF_{2\alpha}$ to thromboxane biosynthesis, as reflected by urinary 11-dehydro-TXB_2 production. Finally, we evaluated the effect of cyclooxygenase inhibition on the production of both eicosanoids.

Subjects and Methods

Study Patients

We prospectively studied 62 consecutive patients (30 men and 32 women; mean age, 67±14 years) with acute ischemic stroke who were admitted to the Dijkzigt University Hospital Rotterdam and were included in the Rotterdam Stroke Databank between March and December 1994. The University Hospital Rotterdam is an area hospital serving an urban population. This center has no specific selection criteria for the admission of stroke patients; however, young stroke patients are referred more frequently to this center than to the nonacademic centers in the region.

All patients were screened according to a strict protocol consisting of a full neurological examination, standardized blood tests, at least one and usually two CT scans of the brain, duplex scanning of the carotid arteries, and a cardiac analysis that included standard 12-lead electrocardiography and, if indicated, 24-hour electrocardiographic monitoring and echocardiography. All patients were examined within 72 hours, and 42 of them were examined within 24 hours after onset of neurological symptoms. In patients with stroke in the carotid territory, the symptoms were further subdivided according to the presence of cortical signs (aphasia, dysgraphia, dyslexia, or hemianopia) or one of the following lacunar syndromes: pure motor hemiplegia, pure sensory stroke, or sensorimotor stroke.[22] The CT scans were reviewed by at least two neurologists without knowledge of the clinical features or the results of the biochemical studies. Cerebral infarctions were classified according to location and vascular territory.[23] Subcortical infarctions were further classified as small (≤15 mm) or large (>15 mm).

Apart from the neurological history, the following risk factors were recorded: smoking habits, hypercholesterolemia (history of hypercholesterolemia and/or fasting total cholesterol level >6.5 mmol/L),[24] hypertension (history of hypertension and/or systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg, treated or not), diabetes mellitus (history of diabetes mellitus type I or II and/or a random blood glucose of ≥8.0 mmol/L together with an HbA_{1c} level of ≥6.3%, treated or not),[25] atrial fibrillation (history of atrial fibrillation and/or atrial fibrillation on electrocardiogram), and a history of intermittent claudication, angina pectoris, prior myocardial infarction, or prior vascular surgery (carotid, coronary, aortic bifurcation, or peripheral vascular surgery). We carefully recorded the medication that was used in the days before the stroke and during the study period, distinguishing patients without antithrombotic or anticoagulant therapy and those using cyclooxygenase inhibitors, heparin, oral anticoagulant therapy, or a combination of these. Patients with atrial fibrillation were heparinized and received oral anticoagulant treatment. In patients with aspirin for secondary prevention after stroke or myocardial infarction, treatment was continued during the study period. The other patients were included in the IST and were randomized for treatment with aspirin, heparin, both, or neither.[26] Stroke severity was assessed by means of the modified Rankin scale[27] on admission, and functional outcome was assessed by means of this scale at 3-month follow-up.

The routine laboratory investigations included hemoglobin, hematocrit, leukocyte, erythrocyte and platelet counts, erythrocyte sedimentation rate, blood urea, creatinine, fasting cholesterol and glucose, and liver enzymes.

Exclusions
Patients were excluded if they required invasive investigations, in particular angiography, during the study period. Also excluded were patients with vasculitis, renal disease (creatinine >200 μmol/L), unstable angina pectoris (recent onset of class III to IV chest pain according to the Canadian Heart Association, in the absence of an increase in the MB fraction of plasma creatinine kinase), or macroscopic hematuria.

Urine Measurements
Two to eight 6-hour samples of urine were collected during the first 72 hours after the onset of symptoms, starting as soon as possible after admission to the hospital. The average delay between onset of symptoms and the start of urinary sampling was 14±12 hours. The volume of each urine sample was recorded, and the creatinine concentration was measured. Samples of 50 mL, containing 1 mmol/L 4-hydroxy-TEMPO as an antioxidant, were stored in the refrigerator until they were frozen every 6 hours and stored at -70°C until extraction. Analytical measurements related to eicosanoid biosynthesis were performed in a manner blinded to the pharmacological treatments.

Immunoreactive 11-dehydro-TXB_2 and 8-epi-$PGF_{2\alpha}$ were extracted from 10-mL aliquots of each coded urine sample (the pH was adjusted to 4.0 with formic acid) on SEP-PAK C18 cartridges (Waters Associates) and eluted with ethyl acetate. The eluates were subjected to silicic acid column chromatography and further eluted with benzene/ethyl acetate/methanol (60:40:30, vol/vol). The overall recovery averaged 74.5±5.1%. The eluates were dried, recovered with 5 mL of buffer, and assayed in the radioimmunoassay system at a final dilution ranging from 1:30 to 1:1000 for 11-dehydro-TXB_2 and 1:30 to 1:1000 for 8-epi-$PGF_{2\alpha}$.[28,29] The urinary excretion rate of 11-dehydro-TXB_2 and 8-epi-$PGF_{2\alpha}$ was expressed as picomoles per millimole of creatinine.

Validation of the 8-epi-$PGF_{2\alpha}$ assay in urine was provided by comparison of values obtained by thin-layer chromatography/enzyme immunoassay (with the same antibody used in the present study) with an independent analytical approach, negative ion chemical ionization–gas chromatography/mass spectrometry. An excellent correlation between the two methods was obtained: r=.99, n=9, P<.001, slope of regression line=1.01. Moreover, 12 urine samples were extracted and measured by radioimmunoassay with the use of two different antisera with different cross-reactivities toward 8-epi-PGE_2, and similar values were obtained (r=.99, n=12, P<.001).[29]

Statistical Analysis
Mean values between groups were compared with the use of Student's t test. Values of P<.05 were considered statistically significant. For time series analysis, all potential prognostic variables were dichotomized by their medians or trichotomized at the P33 and P67 when deemed appropriate. In an exploratory analysis, the relationship between the levels of 8-epi-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 in consecutive urine samples and these variables was analyzed with ANOVA for repeated measures with the use of the BMDP program 9d.[30] The difference between mean levels of 8-epi-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 for a certain variable was considered clinically meaningful when there was a statistically significant difference (P<.05; ANOVA) for at least two consecutive samples or for a total of four samples in the series in the same direction. In a logistic regression analysis with stepwise forward selection of variables, we identified those factors that

were independently related with repeatedly increased (ie, more than once) 11-dehydro-TXB_2 levels.

Results

In the majority of patients (42) sampling started within 24 hours after stroke onset, and in 28 sampling started within 12 hours. Two to eight consecutive 6-hour urinary samples were obtained during the first 48 hours after admission. Thirty patients were treated with cyclooxygenase inhibitors, 26 used aspirin, 1 aspirin and the NSAID indomethacin, and 3 NSAIDs only, of whom 1 used ibuprofen, 1 diclofenac, and 1 naproxen. Three patients with NSAIDs were using this drug before onset of stroke, and during the study it was continued. The patient on diclofenac started with this medication on admission. Of the 27 patients on aspirin, 13 were using it as secondary prevention before the onset of the current stroke, and it was continued during the study. Twelve patients started with aspirin at the beginning of the study, of whom 11 received it in accordance with the IST and 1 after denying consent for randomization in the IST. In 2 patients who had received aspirin from the general practitioner and who denied consent for randomization in the IST, the medication was discontinued during the sampling period. Thus, a total of 17 patients were using antiplatelet medication before the start of the study, which was continued in 15 and stopped in 2, and 13 patients started with antiplatelet medication at the beginning of the study. No difference was found in excretion levels of both eicosanoids between patients who were on antiplatelet medication before the beginning of the study and patients who started on admission, nor was a difference found between patients on aspirin and patients on NSAIDs. Therefore, all patients using cyclooxygenase inhibitors before and/or during the sampling period were compared with patients without cyclooxygenase inhibitors.

Compared with thromboxane excretion levels of control subjects from our previous study (mean+2 SD=251 pmol/mmol creatinine),[1] 40 patients (65%) had at least one sample with an increased excretion rate of 11-dehydro-TXB_2, while in 32 (52%) increased metabolite excretion was found repeatedly. For patients treated with cyclooxygenase inhibitors at the time of study, the corresponding percentages were 53% and 40%, respectively. In untreated patients these percentages were higher (P=.1), at 75% and 63%, respectively.

In 30 patients treated with cyclooxygenase inhibitors (most of whom were taking 300 mg of aspirin daily), 197 samples were obtained. Urinary 11-dehydro-TXB_2 averaged 221±207

pmol/mmol creatinine (mean±SD; range, 13 to 967) in these samples. In 186 samples of 32 untreated patients, 11-dehydro-TXB_2 averaged 392±392 (range, 26 to 2533). The difference was statistically significant (P<.001). No statistically significant difference was found in the levels of 8-epi-$PGF_{2\alpha}$, with mean values of 74±42 (range, 14 to 206) in patients on cyclooxygenase inhibitors and 83±65 (range, 24 to 570) in untreated patients.

Values of 8-epi-$PGF_{2\alpha}$ were only modestly correlated with 11-dehydro-TXB_2 excretion, with a coefficient of .40 (P<.001). The correlation coefficient was .35 in patients treated with cyclooxygenase inhibitors and .41 (P<.001) in untreated patients.

Fig 1 shows mean values and 95% confidence intervals of both eicosanoids of all patients for each time period. The level of 8-epi-$PGF_{2\alpha}$ fluctuated at approximately 80 pmol/mmol creatinine. No consistent pattern was found in its excretion over time. In contrast, excretion of 11-dehydro-TXB_2 was increased in the first period after stroke onset, with a subsequent decline thereafter. When medication was taken into account, most of this decline could be attributed to cyclooxygenase inhibition. As shown in Fig 2, patients treated with cyclooxygenase inhibitors had a swift and constant decrease in 11-dehydro-TXB_2 excretion to normal values in the first 24 hours after stroke onset. Metabolite excretion remained constant in the subsequent periods. In contrast, patients without cyclooxygenase inhibition had repeatedly increased values of 11-dehydro-TXB_2 excretion. No difference was found in 8-epi-$PGF_{2\alpha}$ excretion between patients with and without cyclooxygenase inhibitors.

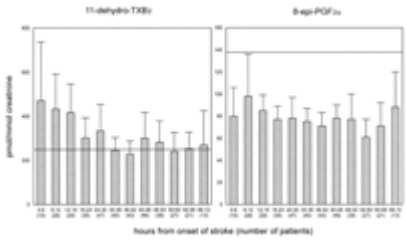

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Figure 1. Mean values and 95% confidence intervals of urinary excretion of 11-dehydro-TXB_2 and 8-epi-$PGF_{2\alpha}$ for each time period in hours after onset of stroke. Line indicates the mean+2 SD of control subjects.

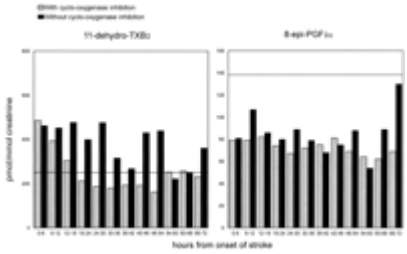

Figure 2. Mean values of urinary excretion of 11-dehydro-TXB_2 and 8-epi-$PGF_{2\alpha}$ for patients with and patients without cyclooxygenase inhibitors for each time period in hours after onset of stroke. Line indicates the mean+2 SD of control subjects.

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In a first approach to evaluate univariately the relationship between baseline characteristics, risk factors, stroke characteristics, and medication on the one hand and level of eicosanoids on the other, we explored differences in peak eicosanoid excretion. Table 1 shows the mean±SD value of peak eicosanoid excretion for demographic characteristics and cardiovascular risk factors. Higher values of 11-dehydro-TXB_2 were found in patients with atrial fibrillation and in patients with congestive heart failure. For 8-epi-$PGF_{2\alpha}$ no differences in excretion rates were found. Table 2 shows the mean±SD of peak eicosanoid excretion for stroke characteristics and medication. Patients with a cortical syndrome had higher peak values of 11-dehydro-TXB_2 than patients with a lacunar stroke or a stroke confined to the vertebrobasilar territory. Higher peak values of 11-dehydro-TXB_2 were also found in patients with severe strokes. Patients using cyclooxygenase-inhibiting drugs had significantly lower peak values of 11-dehydro-TXB_2. Again, for 8-epi-$PGF_{2\alpha}$ no differences in excretion rate were found.

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Table 1. Maximum 8-Epi-$PGF_{2\alpha}$ and 11-Dehydro-TXB_2 Production for Demographic Characteristics and Cardiovascular Risk Factors

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Table 2. Maximum 8-Epi-$PGF_{2\alpha}$ and 11-Dehydro-TXB_2 Production for Stroke Characteristics and Medication

As a second step, we performed the time series analysis described in "Subjects and Methods." In this analysis, 8-epi-$PGF_{2\alpha}$ levels were found to be elevated in patients with atrial fibrillation. Higher levels of 11-dehydro-TXB_2 were found in patients with a history of intermittent claudication, atrial fibrillation, cortical infarctions, severe strokes, and poor stroke outcome and in patients with a urinary catheter. Patients with a history of myocardial infarction and patients

using cyclooxygenase inhibitors had lower values of 11-dehydro-TXB_2. Because patients with a urinary catheter had increased 11-dehydro-TXB_2 levels, we examined whether this could be explained by urinary tract damage with subsequent hemorrhage and platelet activation. None of the patients had macroscopic hematuria. Furthermore, no relationship was found between level of microscopic hematuria and level of 11-dehydro-TXB_2.

In a multiple logistic regression analysis, repeatedly increased 11-dehydro-TXB_2 levels were related to severity of stroke on admission, presence of atrial fibrillation, and antiplatelet treatment. Coumarin and heparin treatment were not associated with repeatedly increased 11-dehydro-TXB_2 levels.

Finally, repeatedly increased thromboxane metabolite excretion was not a statistically significant independent prognostic factor for outcome when added to stroke syndrome or stroke severity in a multiple logistic regression model, probably because of the rather small size of this study.

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Discussion

In this study, 65% of patients with acute ischemic stroke had at least one period of enhanced thromboxane biosynthesis, while in half of the patients this occurred repeatedly. This is slightly less than the 85% and 61%, respectively, we found in our previous study.[2] However, in the current study almost half of the patients received cyclooxygenase inhibitors. For untreated patients the results were in accordance with our previous findings.

In contrast, levels of 8-epi-$PGF_{2\alpha}$ seemed rather low, with an average of approximately 80 pmol/mmol creatinine. Although no control subjects were used in this study, normal values of 8-epi-$PGF_{2\alpha}$ of 50.7±5.7 and 70.5±33.9 pmol/mmol creatinine were reported in other studies.[16] [29] We found only a weak correlation between levels of 11-dehydro-TXB_2 and 8-epi-$PGF_{2\alpha}$. Whereas levels of 11-dehydro-TXB_2 decreased in time in patients with cyclooxygenase-inhibiting drugs, no changes in urinary 8-epi-$PGF_{2\alpha}$ excretion were found in these patients. Although some studies suggest that 8-epi-$PGF_{2\alpha}$ can be formed in a cyclooxygenase-dependent fashion from human platelets,[16] [18] our results indicate that in a clinical condition in which platelets are clearly activated, there are no concurrent changes in 8-epi-$PGF_{2\alpha}$ formation and excretion. Moreover, no significant differences in 8-epi-$PGF_{2\alpha}$ were found between patients with and without cyclooxygenase-inhibiting drugs, again indicating that levels of 8-epi-$PGF_{2\alpha}$ found

in patients with acute ischemic stroke are probably not produced in a cyclooxygenase-dependent fashion. In univariate analysis, no factors that were found to be associated with 11-dehydro-TXB_2 production were also related to 8-epi-$PGF_{2\alpha}$ excretion. Only in patients with atrial fibrillation was 8-epi-$PGF_{2\alpha}$ found increased in two consecutive periods in the time series analysis.

Increased levels of 8-epi-$PGF_{2\alpha}$ excretion were found after thrombolytic therapy in patients with acute myocardial infarction.[16] These findings suggest that the source of 8-epi-$PGF_{2\alpha}$ under these conditions is free radical–catalyzed lipid peroxidation associated with occlusion/reperfusion. Enhanced formation of 8-epi-$PGF_{2\alpha}$ might be expected in patients with acute stroke, a condition in which formation of free radicals occurs. However, in our patients no evident peaks of 8-epi-$PGF_{2\alpha}$ excretion could be detected. In stroke patients it is difficult to predict if and when reperfusion occurs. Still, we should have detected significant changes in 8-epi-$PGF_{2\alpha}$ excretion if they occurred, since we collected 6-hour samples of urine during the time in which reperfusion might be expected in the majority of patients.[31] Alternatively, increased oxidant stress might occur as an early transient event, largely missed by the timing of our urine sampling, or else the signal-to-noise ratio might be too small to be detected at a distance from its source.

Increased 11-dehydro-TXB_2 excretion was univariately associated with a history of intermittent claudication or atrial fibrillation, the presence of a urinary catheter, cortical infarctions, severe strokes, and worse outcome. A urinary catheter may induce urinary tract damage with subsequent hemorrhage and possibly platelet activation. In our study a urinary catheter was indeed associated with enhanced 11-dehydro-TXB_2 level but also with stroke severity and outcome. In our ward, patients with severe strokes are always given a urinary catheter, which explains the relation to severity and outcome. None of the patients had macroscopic hematuria, and no association was found between the level of microscopic hematuria and the level of urinary 11-dehydro-TXB_2. Therefore, it is unlikely that urinary 11-dehydro-TXB_2 levels were the result of urinary tract damage. Data on the number of leukocytes and epithelial cells in the urine were incomplete, and therefore the contribution of these cells to urinary 11-dehydro-TXB_2 could not be evaluated.

The other factors associated with increased thromboxane production—ie, atrial fibrillation, large subcortical and cortical infarctions, stroke severity and outcome, and the absence of cyclooxygenase inhibitors—may reflect the fact that atrial fibrillation is more likely to cause large cortical infarctions that are mostly severe. Moreover, patients with atrial fibrillation usually receive heparin and coumarin treatment and not cyclooxygenase inhibitors. However, in a multiple logistic regression analysis, atrial fibrillation, stroke severity, and cyclooxygenase inhibition were independently related to the level of urinary 11-dehydro-TXB_2.

An important remaining question is whether a causal relationship exists between the extent and duration of platelet activation, as reflected by the level of 11-dehydro-TXB_2 excretion, and stroke severity and outcome. In this study repeatedly increased thromboxane production was not a statistically significant independent prognostic factor for outcome when added to stroke syndrome or stroke severity in a multiple logistic regression model, probably because of the rather small size of our study. However, the results of trials that evaluate the value of antiplatelet therapy in acute ischemic stroke, of which the IST[26] and the Chinese Acute Stroke Trial[32] are by far the largest, may contribute to define the role of platelet activation in this setting. Preliminary

results of these studies indicate that aspirin has a beneficial effect, albeit small, in acute ischemic stroke.[32] [33]

We conclude that during the first few days after an acute ischemic stroke (1) platelet activation occurs repeatedly in a cyclooxygenase-dependent fashion; (2) platelet activation is not associated with concurrent changes in F_2-isoprostane biosynthesis; (3) platelet activation is independently associated with stroke severity and atrial fibrillation; and (4) F_2-isoprostane biosynthesis is largely independent of platelet cyclooxygenase activity.

Selected Abbreviations and Acronyms

11-dehydro-TXB_2	=	11-dehydro-thromboxane B_2
8-epi-$PGF_{2\alpha}$	=	8-epi-prostaglandin $F_{2\alpha}$
IST	=	International Stroke Trial
NSAIDs	=	nonsteroidal anti-inflammatory drugs
TXA_2	=	thromboxane A_2

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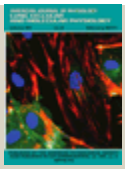

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