Hemostatic Markers in Patients at Risk of Cerebral Ischemia

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Background—Increased levels of markers of hemostasis may assist in the determination of the extent of carotid occlusive disease and the identification of neurologically intact individuals at increased risk of ischemic events.

Methods—We conducted a prospective study of 304 subjects, including 82 with a recent (≤7 days) transient ischemic attack (TIA), 157 asymptomatic individuals with a cervical bruit, and 65 control subjects. Baseline evaluation included a neurological assessment, ECG, cervical ultrasonography, and cerebral CT and/or MRI. Levels of markers of coagulation and fibrinolytic activity were also determined. Results were analyzed in relation to the degree of carotid disease and the subsequent occurrence of cerebral and cardiac ischemic events.

Results—Over a mean follow-up period of 2.8 years (SD, 1.3 years), 114 ischemic events occurred. Survival analyses showed that prothrombin fragment 1.2 (F 1.2 ) was a predictor of time to cerebral and cardiac ischemic events in the combined TIA and asymptomatic bruit group (relative risk [RR], 1.46; 95% CI, 1.18 to 1.81) as well as in the asymptomatic bruit group separately (RR, 1.70; 95% CI, 1.14 to 2.53). In the TIA group, both F1.2 (RR, 2.36; 95% CI, 1.19 to 4.68) and severe (≥80%) carotid stenosis (RR, 3.53; 95% CI, 1.19 to 10.51) were predictive of time to ischemic stroke, myocardial infarction, or vascular death.

Conclusions—In patients with TIAs and in asymptomatic individuals with cervical bruits, F 1.2 levels were found to be independent predictors of subsequent cerebral and cardiac ischemic events. Our results are consistent with an active role of the coagulation system through upregulation of thrombin in carotid disease progression and in the pathogenesis of ischemic events in patients at risk. (Stroke. 2000;31:1856-1862.)

Key words: cerebral ischemia ■ diagnosis ■ hemostasis ■ prognosis ■ stenosis

Altered hemostasis has been reported to occur in different clinical conditions, ranging from ischemic coronary disease and peripheral vascular insufficiency to acute ischemic stroke and reversible cerebral ischemia.1–11 To date, most studies reporting abnormalities of hemostasis in cerebrovascular conditions have focused on patients with ischemic strokes, a condition that may, in itself, lead to a spurious elevation of markers secondary to a breakdown of the blood-brain barrier and release of procoagulants from necrotic cerebral tissue.7 The precise role of these markers has yet to be clarified, especially in nondisabled individuals who are at higher risk of cerebral infarction or other serious vascular events. Current prognostic models that use traditional risk factors have limited potential and have not had a major practical impact at the individual level.12

In the present study, we examined the diagnostic and prognostic role of several of these markers that reflect either activation of the coagulation system or decreased activity of the fibrinolytic process in neurologically intact subjects at various risks for ischemic vascular events. This was justified by the fact that hemostatic markers play an active role in the atherothrombotic process, which, in most cases, leads to the occurrence of ischemic events. Individuals were grouped according to the presence of recognized vascular risk factors, the presence and degree of asymptomatic carotid disease, and the occurrence of recent transient ischemic attacks (TIAs). Abnormalities in hemostatic marker profiles reflecting increased thrombotic activity might allow identification of higher-risk subgroups, which may lead to investigational and therapeutic changes, ultimately decreasing their risk of disabling deficits. A similar approach has recently been suggested in other groups of patients at high risk for stroke and other cardiovascular events.13

Subjects and Methods
From July 1993 to September 1996, all patients seen at either the Montreal General Hospital or l’Enfant Jésus Hospital with a diagnosis of recent TIA (≤7 days) in either the carotid or vertebrobasilar...
territory were approached for participation. TIA was defined as a sudden episode of focal neurological deficit believed to be vascular in nature with complete resolution within 24 hours. During the same period, all neurologically asymptomatic patients with a cervical bruit referred from the community or recruited from specialty clinics were also approached and formed the asymptomatic carotid bruit (ACB) group. A healthy control group consisted of spouses of patients, patients with nonneurovascular problems, or patients from other specialty clinics. For all subjects, enrollment was conditional on informed consent. Information on medical history and vascular risk factors was obtained directly from the individuals and review of hospital charts. All participants underwent a complete neurological evaluation at baseline. Determination of the presence of vascular risk factors was based on previously published criteria.15

We excluded patients <50 years of age, those with an ischemic lesion on either CT or MRI of the brain, patients taking oral anticoagulants, and those with potential causes of TIA other than atherosclerosis or conditions that could affect hemostasis, such as liver disease, coagulopathy, congestive heart failure, or arrhythmia, including atrial fibrillation, venous thromboembolic disorders, malignancy, surgery, or any invasive procedure in the previous 3 months. In addition, patients with a recent myocardial infarction (<6 months) or angina (<2 weeks) were excluded because these conditions have been shown to be associated with abnormal marker levels.3

All groups had blood drawn at baseline for measurement of complete blood count, platelets, prothrombin time, international normalized ratio, partial thromboplastin time, and liver, renal, and lipid profiles. Levels of the following markers were also determined: fibrinopeptide A (FPA), thrombin-antithrombin complexes (TAT), prothrombin fragment F 1.2(F1.2), d-imer, plasminogen activator inhibitor-1 (PAI-1), and plasmin-α2-antiplasmin complexes (PAP). Venous blood was obtained atracurially from tubes with sodium citrate for measurement of d-imer, TAT, F1.2, PAI-1, and PAP; blood was also collected into sodium citrate with added anticoagulants as supplied with the kit for measurement of FPA. Platelet-free plasma was obtained by centrifuging the blood immediately in a refrigerated centrifuge at 3000 rpm for 15 minutes. Plasma was placed in aliquots and kept at −70°C until testing. d-imer and FPA were quantified by ELISA with kits from Murex Diagnostics, Canada. The laboratory reference range for d-imer is 33 to 341 ng/mL; for FPA, 0.5 to 1.7 ng/mL. F1.2, TAT, and PAI-1 were measured by ELISA with kits from Behring Diagnostics Canada Inc. Laboratory reference ranges are as follows: F1.2, 0.2 to 2 nmol/L; TAT, 0.8 to 2.6 μL/L; and PAP, 161 to 503 μL/L. PAI-1 was assayed by ELISA with a kit from Biopool, Canada. All tests were carried out according to manufacturer’s suggestions. The PAI-1 reference range is 0 to 13.9 ng/mL.

Except for the control group, all individuals were scheduled for a 12-lead resting ECG and a cervical duplex ultrasound. The results of the ultrasound study were categorized as a reduction in luminal diameter in the following 6 categories: (1) no stenosis, (2) 1% to 15% stenosis, (3) 16% to 49% stenosis, (4) 50% to 79% stenosis, (5) 80% to 99% stenosis, and (6) occlusion. This method was validated previously at both institutions.16 In addition, all patients in the TIA group were scheduled for a CT scan of the brain within 1 month of the qualifying event and a cerebral MRI to exclude a recent cerebral infarction that could act as a trigger for a spurious increase in marker levels. The TIA patients were treated medically or surgically as judged appropriate and according to accepted standards of care.14 At initial assessment, 73% of the patients in the TIA group were already receiving either acetylsalicylic acid or another antiplatelet compared with only 32% (P = 0.001) in the ACB group.

For patients who required anticoagulant therapy or surgery during the course of the study, only blood samples drawn before these interventions were included in the analysis; in addition, these patients were censored from further follow-up starting at the time of the intervention. All patients were assessed every 6 months in the neurovascular clinics to document any new or further vascular events, such as TIA, stroke, new-onset angina, unstable angina, myocardial infarction, or vascular or nonvascular death. Clinical staff were blinded to the results of the hemostatic marker levels.

Statistical Analysis

In the first step, the clinical and demographic characteristics of the patient groups were compared with the use of ANOVA for age and marker levels. Multiple comparisons of means, adjusting the probability value for the number of comparisons, were done using Tukey’s Studentized Range Test. We used χ² tests to compare groups on categorical variables (eg, sex, presence of diabetes mellitus). All analyses were performed with SAS software.11 For some analyses, marker concentrations were categorized into terciles and quartiles. To assess the impact of inclusion of extreme values of FPA, which may reflect a traumatic puncture16 (ie, FPA > 22 ng/mL), analyses were performed with all subjects and subjects with FPA levels ≤22 ng/mL. Results were similar with both approaches.

The diagnostic potential of the markers was investigated through logistic regression, in which the outcome was defined as membership in the TIA group versus membership in the ACB group, excluding control subjects (n = 239), and degree of carotid stenosis defined as ≥50% or ≥80%. The prognostic value of markers and clinical variables to predict future events was assessed in the TIA/ACB groups combined, as well as for a higher-risk group that consisted of the TIA group and those patients from the ACB group with ≥50% stenosis in ≥1 carotid. This was done with logistic regression and survival analysis using the Cox proportional-hazards model.16 Adjusted odds ratios (ORs) and 95% CIs are reported for the logistic regression models; adjusted relative risks (RRs) and 95% CIs are reported for the Cox proportional-hazards models.

Two additional outcomes were defined: time to first ischemic event (ie, TIA, stroke, myocardial infarction, new-onset angina, and vascular death) and time to first serious vascular event (ie, myocardial infarction, stroke, and vascular death). Survival analysis was used for both types of outcomes, and for the first outcome, subjects who had not experienced any of these ischemic events by the end of follow-up were considered censored at their last date of follow-up. Similarly, for the second, more restrictive outcome, those subjects who had not experienced a myocardial infarction or stroke or had died from vascular causes were considered censored at the date of the last follow-up. Annualized rates of these 2 outcomes were also obtained for the TIA/ACB and high-risk groups. A value of P < 0.05 was considered statistically significant.

Results

Levels of markers were determined in 304 subjects, 82 presenting with an acute TIA, 157 from the ACB group, and 65 control subjects. Table 1 displays the distribution of the demographic characteristics and the vascular risk factors across groups. Age and sex were not significantly different between groups; however, hypertension and heart disease were more common in the TIA and ACB groups, as expected. Table 2 shows the mean levels of the markers across groups. The mean levels of both d-imer and PAP were significantly higher in the TIA group compared with the control group (P < 0.01 for both comparisons). The mean levels of F1.2 were also slightly higher in the TIA group compared with control subjects but did not reach statistical significance (0.05 < P < 0.1). In comparisons of the ACB and control groups, significant differences were also found, with higher mean levels in the ACB group for d-imer (P < 0.01), PAI-1 (P < 0.01), and PAP (P < 0.05). No significant differences in marker levels were found between the TIA and ACB groups.

Logistic regression analyses were performed to determine which variables were predictive of either group membership (TIA or ACB) or degree of carotid stenosis. Analyses categorizing FPA above or below the 75th percentile (FPA
Results of cervical ultrasonography were available for all 82 patients in the TIA group and for 155 patients (99%) in the ACB group. The proportion of patients with ≥1 carotid stenosis ≥50% was significantly higher in the ACB group (56%) than in the TIA group (41%) (P=0.032). Logistic regression analyses of the combined TIA/ACB group showed that upper quartile values of F1.2 (OR, 2.04; 95% CI, 1.10 to 3.78), presence of ischemic heart disease (OR, 2.04; 95% CI, 1.14 to 3.64), and hypercholesterolemia (OR, 1.92; 95% CI, 1.11 to 3.32) were all predictors of carotid stenosis (≥50%) on ultrasonography. In addition, the presence of peripheral vascular disease was found to be a strong predictor of severe (≥80%) carotid stenosis (OR, 2.74; 95% CI, 1.41 to 5.33). In the TIA group only, upper quartile levels of F1.2 (OR, 4.26; 95% CI, 1.44 to 12.61) and presence of ischemic heart disease (OR, 1.92; 95% CI, 1.11 to 3.32) were all predictors of carotid stenosis (≥50%) on ultrasonography. In addition, the presence of peripheral vascular disease was found to be a strong predictor of severe (≥80%) carotid stenosis (OR, 2.74; 95% CI, 1.41 to 5.33).

The mean follow-up period for the combined TIA and ACB group was 2.83 years (SD, 1.35 years); during this time, a total of 128 clinical events occurred, of which 89% were vascular. As expected, the proportion who experienced ≥1 event in the TIA group (48.7%) was significantly higher than the proportion in the ACB group (24.4%) (P=0.001). The mean follow-up in the former group was 2.51 years (SD, 1.26 years) compared with 2.99 years (SD, 1.36 years) in the ACB group (P=0.01). For both groups, most events were neurological and occurred primarily in the first 2 years of follow-up. Table 3 lists the first clinical events for both groups.

We also focused on patients who experienced a greater number of ischemic events during follow-up by grouping those patients from the TIA and ACB groups who had ≥2 ischemic events (n=27) and comparing them with patients with either no or only 1 ischemic event (n=207). The 2 groups were comparable with respect to age, sex, length of follow-up, and presence of known vascular risk factors. Significant increases in the mean levels of 2 of the markers in the multiple event group, F1.2 (2.3 versus 1.7 nmol/L, P=0.0002) and TAT (42.9 versus 5.5 μL, P=0.0056), were identified.

Using Cox proportional hazards analyses, we assessed the relationship between vascular risk factors, marker levels, and the time to occurrence of clinical events in all patients. F1.2 was found to be an independent predictor for all ischemic events, including TIA, ischemic stroke, new-onset angina, myocardial infarction, and vascular death, in the combined group of TIA and ACB patients (RR, 1.46; 95% CI, 1.18 to 1.81), as well as in the ACB group only (RR, 1.70; 95% CI, 1.14 to 2.53). In the TIA group, F1.2 (RR, 2.36; 95% CI, 1.19 to 4.68) and severe degree (≥80%) of carotid stenosis (RR, 3.53; 95% CI, 1.19 to 10.51) were independently predictive of more serious vascular events, such as myocardial infarction, ischemic stroke, and vascular death.

Prognostic survival analyses were also performed in the group of patients (n=171) composed of the TIA group and subjects from the ACB group with a carotid stenosis of ≥50%, representing a higher-risk subgroup. In this group, both F1.2 (RR, 1.46; 95% CI, 1.16 to 1.85) and peripheral

### Table 2. Mean Values of Markers Across Groups

<table>
<thead>
<tr>
<th>Markers</th>
<th>TIA Group (n=82) Mean (SD)</th>
<th>ACB Group (n=157) Mean (SD)</th>
<th>Control Subjects (n=65) Mean (SD)</th>
<th>Overall P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Dimer (n=301), ng/ml</td>
<td>657 (453)</td>
<td>609 (645)</td>
<td>367 (200)</td>
<td>0.002</td>
</tr>
<tr>
<td>TAT (n=302), ng/L</td>
<td>18.1 (111)</td>
<td>5.3 (6.7)</td>
<td>4.3 (5.3)</td>
<td>0.219</td>
</tr>
<tr>
<td>F1.2 (n=303), nmol/L</td>
<td>1.9 (1.1)</td>
<td>1.7 (0.7)</td>
<td>1.6 (0.6)</td>
<td>0.093</td>
</tr>
<tr>
<td>PAI-1 (n=302), ng/ml</td>
<td>19.5 (12.4)</td>
<td>22.2 (13.8)</td>
<td>18.4 (9.6)</td>
<td>0.080</td>
</tr>
<tr>
<td>PAP (n=302), ng/L</td>
<td>597 (243)</td>
<td>559 (265)</td>
<td>462 (190)</td>
<td>0.003</td>
</tr>
<tr>
<td>FPA (n=259), ng/ml</td>
<td>3.4 (4.0)</td>
<td>2.6 (3.2)</td>
<td>3.4 (4.3)</td>
<td>0.201</td>
</tr>
</tbody>
</table>

*From ANOVA.
†Values of FPA >22 ng/mL excluded.
Using Tukey’s Studentized Range Test for multiple comparisons; ‡P<0.01 vs control group; §P<0.05 when compared to control group.
vascular disease (RR, 2.06; 95% CI, 1.15 to 3.71) were independent predictors for any ischemic event. F1.2 remained an independent predictor (RR, 1.70; 95% CI, 1.29 to 2.23) of myocardial infarction, ischemic stroke, and vascular death.

Table 4 shows the estimated RRs for different vascular events in 3 subgroups of F1.2, defined by terciles, both in the combined TIA/ACB group and in the high-risk group. With the lowest tercile as the reference group, RR increases with increasing levels of F1.2. Annualized event rates for all vascular events were estimated on the basis of the lower and upper terciles for both the TIA/ACB combined group and the high-risk group. In the TIA/ACB group, the annual event rate was 5.12% in the lower F1.2 tercile compared with 17.01% in the upper tercile (P<0.01). In the high-risk group, the annual rates were 7.54% for the lower tercile compared with 21.37% in the upper tercile (P<0.01). Figures 1 and 2 show the relationship between time to first ischemic event and F1.2 levels in relation to carotid stenosis (Figure 1) and peripheral vascular disease (Figure 2). In the combined TIA/ACB group, subjects with F1.2 levels below the 33rd percentile were more likely to be event free by the end of follow-up regardless of the level of carotid stenosis. In a similar vein, a lower level of F1.2 in the high-risk group was predictive of being event free during follow-up regardless of the presence or absence of peripheral vascular disease.

**Discussion**

This study was designed to assess both the diagnostic and prognostic potential of selected markers of hemostasis in individuals at increased risk for cerebral and cardiac ischemic events. FPA proved to be directly and independently correlated with the recent occurrence of a TIA. F1.2 was correlated with a more severe degree of carotid stenosis and was found to be a predictor of future ischemic events.

As expected, several indicators of arterial disease, including severity of carotid stenosis, and the presence of peripheral vascular disease were also found to be independently related to outcome, and others, such as heart disease and hypercholesterolemia, were positively associated with the extent of carotid disease. Higher concentrations of F1.2 were significantly associated with more severe carotid stenosis in the combined TIA/ACB group. Previous studies in different populations have also reported a positive association between hemostatic factors and degree of carotid disease. In the present study, 2 of the markers that reflect thrombin generation, namely F1.2 and TAT, were significantly elevated at baseline in patients who suffered multiple ischemic events during their follow-up. This suggests an active pathophysiological role for thrombin in the recurrence of ischemic events in these patients. These results are in keeping with pathological findings that support a role for plaque instability and thrombus formation in symptomatic cerebral and cardiac disease.

Although several studies have reported hemostatic abnormalities in the context of ischemic coronary syndromes and cerebral infarction, few have prospectively studied the potential value of these hemostatic factors in neurologically intact individuals harboring various degrees of carotid atheroma. Our results are in accordance with these previous reports that showed a correlation between marker levels and outcome. The diagnostic and prognostic value of F1.2 is also supported by 2 recent studies; the first reported that high levels of F1.2 were independent predictors of myocardial infarction in asymptomatic hypertensive men, and the second showed that F1.2 was positively associated with the extent of coronary atherosclerosis in patients with established cardiac disease.

We found that concentrations of F1.2 identified different levels of risk for vascular events, as shown in Table 4, similar to what has been reported for other markers of coagulation in patients with angina. The up-to-5-fold increase in risk of ischemic events with increasing concentrations of F1.2 suggests that increased thrombin generation precedes vascular events in our population. The magnitude of risk might actually be underestimated because a substantial proportion of patients at baseline were taking aspirin, which can itself decrease levels of F1.2.

**Table 3. Types of First Clinical Event During Follow-Up**

<table>
<thead>
<tr>
<th>Events</th>
<th>TIA Group, n (%)</th>
<th>ACB Group, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>24 (30.8)</td>
<td>12 (7.7)</td>
</tr>
<tr>
<td>New-onset angina</td>
<td>2 (2.6)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>CVA</td>
<td>5 (6.4)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>MI</td>
<td>2 (2.6)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>2 (2.6)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Nonvascular death</td>
<td>3 (3.8)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>No event</td>
<td>40 (51.3)</td>
<td>118 (75.6)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (100)</td>
<td>156 (100)</td>
</tr>
</tbody>
</table>

CVA indicates cerebral vascular accident; MI, myocardial infarction.

**Table 4. RR of Events According to Concentration of F1.2**

<table>
<thead>
<tr>
<th>Tercile</th>
<th>Lower (95% CI)</th>
<th>Middle (95% CI)</th>
<th>Upper (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined TIA/ACB group (n=232)</td>
<td>1.0</td>
<td>3.542 (0.938–13.375)</td>
<td>4.272 (1.242–14.695)</td>
</tr>
<tr>
<td>High-risk group (n=164)</td>
<td>1.0</td>
<td>4.243 (0.838–21.486)</td>
<td>5.557 (1.257–24.565)</td>
</tr>
<tr>
<td>All Ischemic Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined TIA/ACB group (n=231)</td>
<td>1.0</td>
<td>2.639 (1.180–5.900)</td>
<td>3.116 (1.438–6.751)</td>
</tr>
<tr>
<td>High-risk group (n=164)</td>
<td>1.0</td>
<td>2.590 (1.079–6.214)</td>
<td>2.929 (1.282–6.690)</td>
</tr>
</tbody>
</table>

*RRs have been adjusted for confounding factors.
For both the TIA/ACB and high-risk groups, annual ischemic event rates were 3 times higher in patients with F1.2 levels in the upper tercile compared with those in the lower tercile. We also found that higher levels of FPA, a marker of thrombin-mediated conversion of fibrinogen to fibrin, were positively correlated with the TIA group, consistent with previous reports showing similar results in patients with either acute TIAs or acute reversible coronary syndromes.3,4

Elevated levels of hemostatic markers have also been reported in patients with nonvalvular atrial fibrillation.33–35

Figure 1. Time to first ischemic event in relation to F1.2 levels and carotid stenosis, TIA and ACB groups. □ Indicates stenosis <80% and F1.2 below 33rd percentile; ○, stenosis <80% and F1.2 above 33rd percentile; ●, stenosis ≥80% and F1.2 below 33rd percentile; and ○, stenosis ≥80% and F1.2 above 33rd percentile.

Figure 2. Time to first ischemic event in relation to F1.2 levels and peripheral vascular disease, TIA and high-blockage asymptomatics (high-risk group). □ Indicates no PVD and F1.2 below 33rd percentile; ○, no PVD and F1.2 above 33rd percentile; ●, PVD and F1.2 below 33rd percentile; and ○, PVD and F1.2 above 33rd percentile.
and are thought to reflect activation of the coagulation system, which contributes to the increased risk of ischemic stroke seen in this condition. To the best of our knowledge, no previous studies have reported on a potential role for activation of the coagulation system in individuals at risk for ischemic cerebral events in the absence of an established cardioembolic source. Some patients who present with higher levels of markers, such as F1.2, may be at increased risk for ischemic events and may respond better to anticoagulants rather than to antiplatelet therapy because treatment with warfarin decreases the levels of F1.2 more markedly than does aspirin.36,37 An approach that suggests the use of biological markers as therapeutic indicators has already been proposed, with determination of F1.2 levels to monitor anticoagulant treatment and response to therapy in patients with nonvalvular atrial fibrillation.38,39 A study of an ongoing randomized trial40 is also currently looking at the potential value of F1.2 and confirming these results, and ultimately only randomized clinical trials will be able to establish the precise value of F1.2 and other markers in the selection of more optimal preventive strategies in these patients.

Our results suggest that F1.2 may identify patients with TIA or asymptomatic carotid disease who are at increased risk for stroke and other ischemic events. This could accelerate patient investigation and may lead to more effective therapeutic interventions. Further studies, however, are needed to confirm these results, and ultimately only randomized clinical trials will be able to establish the precise value of F1.2 and other markers in the selection of more optimal preventive strategies in these patients.

Acknowledgments

This work was supported by the Quebec Heart and Stroke Foundation. We wish to thank Sandy Lavigne for her excellent secretarial work.

References


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Stroke. 2000;31:1856-1862
doi: 10.1161/01.STR.31.8.1856

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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