Effects of U74006F on Multifocal Cerebral Blood Flow and Metabolism After Cardiac Arrest in Dogs

Fritz Sterz, MD; Peter Safar, MD; David W. Johnson, MD; Ken-Ichi Oku, MD; and Samuel A. Tisherman, MD

Lipid peroxidation reactions during reperfusion after cardiac arrest may contribute to postischemic cerebral hypoperfusion, which in turn can contribute to permanent neurological dysfunction. We designed this study to determine whether the aminosteroid U74006F, a putative inhibitor of lipid peroxidation, mitigates cerebral multifocal hypoperfusion after cardiac arrest.

We used our established dog model of ventricular fibrillation cardiac arrest (no blood flow) of 12.5 minutes, reperfusion by cardiopulmonary bypass of ≤5 minutes, and control of extracerebral variables during 4 hours postarrest. Cerebral blood flow was monitored by the stable xenon computed tomography method. Changes in cerebral oxygen consumption were obtained from mean blood flow values of coronal slices and the cerebral arteriovenous (sagittal sinus) oxygen content difference. A treatment group (n=5) received U74006F starting with reperfusion (1.5 mg/kg i.a. plus 1.5 mg/kg i.v.) and three additional (graded) doses over 4 hours (total dose 4.5, 7.5, or 14.5 mg/kg). The U74006F-treated group showed the same postarrest transient hyperemia and protracted hypoperfusion in terms of global (computed tomography slice), regional, and local (multifocal) cerebral blood flow values and the same global cerebral oxygen consumption pattern as a concurrent control group (n=5). At 1–4 hours postarrest, in both groups there was mismatching of global cerebral oxygen consumption, which reached baseline values, in relation to global cerebral blood flow and oxygen delivery, which remained at 50% of baseline. We conclude that treatment with U74006F after prolonged cardiac arrest causes no deleterious side effects and does not seem to alter multifocal postarrest cerebral blood flow and oxygen consumption. (Stroke 1991;22:889–895)
study followed previous studies with the Xe-CT method of postarrest CBF after external CPR, open-crest CPR, or cardiopulmonary bypass (as in this study) and with postarrest hypertension and hemodilution.

**Materials and Methods**

This project was approved by the Animal Use Committee of the University of Pittsburgh. We used 22 healthy, custom-bred male coon hounds from the same breeding colony, mean age 10 (range 8–12) months and mean weight 19 (range 18–24) kg.

First, we conducted pilot studies in two dogs without cardiac arrest to rule out side effects of U74006F. Therapeutic intravenous doses in the above-mentioned studies seem to be 1–3 mg/kg. One normal, unanesthetized, unmonitored, spontaneously breathing dog received 1 mg/kg/min i.v. U74006F for 30 minutes (total dose 30 mg/kg). This infusion of an overdose resulted in no abnormal behavior, no overall functional changes, and no other side effects. Another normal dog was anesthetized with 50%:50% nitrous oxide:oxygen (N₂O:O₂) plus 0.5% halothane and paralyzed with pancuronium in a steady state with intermittent positive-pressure ventilation and invasive monitoring without cardiac arrest. Again, 1 mg/kg/min i.v. U74006F was administered for 30 minutes (total dose 30 mg/kg). This infusion resulted in no change from baseline of mean arterial blood pressure (MAP) or other monitored cardiovascular, pulmonary, or metabolic variables (see subsequent protocol), except that cardiac output increased from 4.5 l before to 7.6 l at 2 hours after U74006F infusion.

We then conducted the CBF study in 10 dogs, using our established model of ventricular fibrillation cardiac arrest (no blood flow) of 12.5 minutes with reperfusion by cardiopulmonary bypass for ≤5 minutes postarrest and intermittent positive-pressure ventilation to 4 hours. The five control dogs (group I) also served other studies and therefore were not placebo controlled. The five U74006F-treated dogs (group II) were, however, treated by the same team concurrent with the control dogs.

Anesthesia was induced with ketamine and maintained with 50%:50% N₂O:O₂ plus halothane by endotracheal intermittent positive-pressure ventilation. We continuously monitored the electrocardiogram, heart rate, MABP, central venous pressure, end-tidal CO₂, and central venous (core) temperature (Tc). We intermittently monitored arterial blood gases and hematocrit (Hct). We controlled MABP at 100±10 mm Hg (mean±SD) by adjusting the halothane concentration before and by using norepinephrine or trimethaphan after cardiac arrest, central venous pressure at 5–15 mm Hg, Tc at 37.5±0.5°C, PaO₂ at ≥100 mm Hg, PaCO₂ at 30–35 mm Hg, base excess at ±7 meq/l, and blood glucose concentration at 100–175 mg/dl before arrest. In preparation for the insult and during paralysis with pancuronium and intermittent positive-pressure ventilation, inhalation anesthesia was reduced with external transthoracic electric shock. At the end of ventricular fibrillation of 12.5 minutes, resuscitation was begun with 0.0125 mg/kg i.a. epinephrine and cardiopulmonary bypass (resuscitation time 0–10 minutes). Two minutes later, external countershocks were started and repeated until defibrillation and restoration of a spontaneous heartbeat. All dogs were weaned from cardiopulmonary bypass after 5 minutes. Intermittent positive-pressure ventilation and control of physiological variables (above) were continued to 4 hours.

In group II dogs, 1.5 mg/kg U74006F was infused into the arterial cannula of the bypass circuit at 0–5 minutes. Three additional bolus intravenous injections of U74006F were given—one (1.5 mg/kg) at 5 minutes, one (1.5 mg/kg) at 2.5 hours, and one at 4 hours of reperfusion. The latter was 0 mg/kg in one dog (total dose 4.5 mg/kg), 3 mg/kg in three dogs

**Table 1. Physiological Variables Measured at Baseline and After Cardiac Arrest in Dogs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>10 min</th>
<th>30 min</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong> (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tm (°C)</td>
<td>37.8±0.6</td>
<td>36.8±0.2</td>
<td>36.8±0.2</td>
<td>37.1±0.2</td>
<td>37.9±0.0</td>
<td>37.9±0.5</td>
<td>38.0±0.2</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>101±8</td>
<td>110±8</td>
<td>110±12</td>
<td>126±4</td>
<td>121±7</td>
<td>119±7</td>
<td>113±9</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.36±0.03</td>
<td>7.34±0.04</td>
<td>7.30±0.05</td>
<td>7.35±0.02</td>
<td>7.38±0.03</td>
<td>7.38±0.05</td>
<td>7.38±0.03</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>35.4±1.5</td>
<td>34.7±5.0</td>
<td>34.7±5.0</td>
<td>34.2±1.9</td>
<td>34.6±3.5</td>
<td>37.3±3.7</td>
<td>35.6±3.8</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>42±3</td>
<td>38±8</td>
<td>32±6</td>
<td>32±6</td>
<td>34±4</td>
<td>36±3</td>
<td>39±4</td>
</tr>
<tr>
<td><strong>U74006F-treated group</strong> (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tm (°C)</td>
<td>37.5±0.1</td>
<td>36.5±0.2</td>
<td>36.5±0.2</td>
<td>37.2±0.4</td>
<td>37.8±0.4</td>
<td>38.0±0.3</td>
<td>37.8±0.4</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>107±4</td>
<td>120±9</td>
<td>120±9</td>
<td>125±8</td>
<td>123±4</td>
<td>124±6</td>
<td>118±8</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.38±0.01</td>
<td>7.38±0.05</td>
<td>7.38±0.05</td>
<td>7.37±0.02</td>
<td>7.42±0.03</td>
<td>7.41±0.04</td>
<td>7.41±0.03</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>34.7±2.7</td>
<td>30.9±3.9</td>
<td>30.9±3.9</td>
<td>33.5±3.3</td>
<td>31.8±2.5</td>
<td>32.8±1.1</td>
<td>32.9±1.0</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>43±3</td>
<td>34±1</td>
<td>34±1</td>
<td>36±5</td>
<td>39±4</td>
<td>41±5</td>
<td>43±5</td>
</tr>
</tbody>
</table>

Values are mean±SD.

Tm, central venous (core) temperature; MABP, mean arterial blood pressure; Hct, hematocrit.

No group differences with p<0.05.
TABLE 2. Global CBF and Local CBF Ranges Before and After Cardiac Arrest in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hr</td>
<td>30 min</td>
</tr>
<tr>
<td>Control group (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>Mean±SD</td>
<td>50±7</td>
</tr>
<tr>
<td>% of baseline</td>
<td>...</td>
<td>100</td>
</tr>
<tr>
<td>Local</td>
<td>No flow</td>
<td>0.5±0.5</td>
</tr>
<tr>
<td></td>
<td>Trickle flow</td>
<td>1.5±0.8</td>
</tr>
<tr>
<td></td>
<td>Low flow</td>
<td>5.8±2.9</td>
</tr>
<tr>
<td>Normal for WM</td>
<td>29.6±7.1</td>
<td>30.8±6.4</td>
</tr>
<tr>
<td>Normal for GM</td>
<td>61.5±9.9</td>
<td>59.1±10.2</td>
</tr>
<tr>
<td>Hyperemic</td>
<td>10.9±0.9</td>
<td>0.1±0.6</td>
</tr>
</tbody>
</table>

U74006F-treated group (n=5)

|              | Mean±SD |        |        |        |        |        |        |        |        |
|              |         | 47±8   | 49±10  | 83±29  | 43±13  | 27±9   | 26±6   | 25±4   | 26±6   | 26±6   |
| % of baseline| ...     | 100    | 171    | 87     | 55     | 54     | 51     | 53     | 53     |        |
| Local        | No flow | 0.1±0.1 | 1.6±1.6 | 0.1±0.0 | 1.0±1.6 | 4.3±3.7 | 3.4±2.3 | 3.1±2.1 | 2.8±2.2 | 3.4±2.6 |
|              | Trickle flow | 0.9±0.9 | 1.3±1.0 | 0.4±0.5 | 3.2±3.8 | 11.8±6.1 | 11.1±5.8 | 9.7±2.7 | 10.1±4.5 | 10.7±4.8 |
|              | Low flow | 5.9±2.8 | 4.9±3.9 | 3.2±3.4 | 13.0±8.4 | 26.0±10.3 | 27.2±8.3 | 31.2±5.4 | 29.5±8.0 | 28.5±8.0 |
| Normal for WM| 30.6±18.4 | 30.9±12.0 | 18.3±5.4 | 37.9±10.8 | 48.0±5.6 | 42.8±2.8 | 40.6±3.3 | 43.0±3.8 |        |
| Normal for GM| 58.0±16.5 | 61.0±15.6 | 52.4±16.1 | 42.8±18.4 | 19.9±18.1 | 17.5±11.5 | 14.0±6.9 | 17.0±11.8 | 17.1±12.1 |
| Hyperemic    | 0.1±0.1 | 0.3±0.5 | 25.7±21.8 | 2.1±3.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |        |

Values are mean±SD ml/100 cm3/min for global, percentage area for local from posterior coronal slice 5 mm thick. Values from anterior slice were similar.

CBF, cerebral blood flow; WM, white matter; GM, gray matter.
No group differences with p<0.05.

The CBF was determined with the novel noninvasive Xe-CT method, adapted to cardiac arrest experiments with dogs. All CBF values were obtained from a computerized analysis of CT voxel density changes during Xe washin over 4.5 minutes and are expressed as milliliters per 100 cm3 (or gram) brain tissue per minute. The Xe washin technique is based on the Fick principle, using the CT scanner as a densitometer. Six Xe-enhanced images were obtained, beginning 30–40 seconds after the start of Xe inhalation. Constancy of the CT slices was ascertained by the consistent position of bony landmarks. Resolution in monkeys and humans seems to be ≥5×5×5=125 mm3. With the dog's head rigidly immobilized, we studied global CBF for the tissue volumes of two 5-mm-thick coronal slices located 10 mm apart. The anterior slice included the hippocampus and thalamus, and the posterior slice included the brain stem. Computer programs provided one CBF value for each voxel of 1×1×5=5 mm3. The CBF values of all voxels in each slice and in each selected anatomic region (each ≥5×5×5=125 mm3) were averaged to determine global and regional CBF, respectively. We calculated local CBF as the percentage of voxels in each CT slice (percentage area) having specific CBF ranges: no flow, 0–5 ml/100 cm3/min; trickle flow, 6–10 ml/100 cm3/min; low flow, 11–20 ml/100 cm3/min; normal flow for white matter, 21–40 ml/100 cm3/min; normal flow for gray matter, 41–120 ml/100 cm3/min; and hyperemic flow, >120 ml/100 cm3/min. We arbitrarily considered gray matter with a local CBF of <20 ml/100 cm3/min as having inadequate CBF.

Because it interferes with Xe monitoring, N2O was replaced by N2 and the analgesic effect was replaced by fentanyl given as a continuous intravenous infusion of 10 µg/kg/hr. Halothane (0.1–0.5%) was used before cardiac arrest for baseline anesthesia and MABP control. No halothane was given during CBF measurements or after cardiac arrest. The inhaled gas delivered contained 67% O2, the balance being N2, which was switched to 33% Xe during CBF measurements. Two baseline CBF studies were performed before cardiac arrest. Additional CBF studies were performed at 10 and 30 minutes and 1, 1.5, 2, 3, and 4 hours after reperfusion. Before each CBF measurement, MABP, PaO2, PaCO2, arterial pH, base excess, Hct, and TW were measured and controlled.

The CMRO2 was determined in three dogs of group I and four dogs of group II. Via a sterile 2-cm craniotomy, a PE50 nonocclusive catheter was inserted into the sagittal sinus with the catheter tip placed 1 cm rostral to the confluence of the sinuses. For each CMRO2 determination, the catheter dead.
space was cleared and arterial and sagittal sinus blood samples were drawn at a constant slow rate into heparinized syringes, cooled, and analyzed within 2 hours by a co-oximeter for O₂ content. Samples for arterial and sagittal sinus O₂ contents (CaO₂ and CssO₂, respectively) were taken just before each Xe inhalation. Global CMRO₂ was calculated as the posterior CT slice global CBF×cerebral arteriovenous O₂ content gradient [i.e., global CBF×(CaO₂−CssO₂)]. The cerebral O₂ utilization coefficient was calculated as global CMRO₂/arterial O₂ transport [i.e., global CBF×cerebral arteriovenous O₂ content gradient/global CBF×CaO₂, or (CaO₂−CssO₂)/CaO₂]. Although global CBF was calculated from only one CT slice and CaO₂−CssO₂ from the entire cerebrum, relative changes of CMRO₂ were considered valid.

All data were analyzed for group differences within times and for the time×group interaction using a univariate repeated-measures analysis of variance. Scheffé’s post hoc procedure was used for analyzing changes within each group over time (baseline versus postarrest). The CMRO₂ data were not statistically analyzed because of small numbers. Results are reported as mean±SD.

**Results**

All 10 dogs in which CBF was measured followed the life support protocol. There was no difference between groups in physiological variables before or after cardiac arrest (Table 1). Spontaneous normotension was restored within 2–3 minutes after the start of cardiopulmonary bypass. Immediately after restoration of the heartbeat, three of five dogs in each group developed brief episodes of hypertension (to peak MABP values of 130–190 mm Hg), and the others had normotensive reperfusion. Mild hemodilution caused by cardiopulmonary bypass was transient; near-baseline Hct was restored by 2–4 hours in both groups. Postarrest fentanyl and trimethaphan requirements were brief, minimal, and similar in both groups. For MABP control, dogs in group I required minimal norepinephrine at resuscitation time 0–15 minutes, while group II dogs required no norepinephrine.

In each dog, the two baseline global CBF measurements were similar (approximately 50 ml/100 cm³/min); there was a small standard deviation within each group and no significant difference between groups (Table 2, Figure 1). The first postarrest CBF measurement showed diffuse hyperemia in both groups, with especially no voxels with no or trickle flow and fewer voxels with low flow than at baseline (i.e., there was no evidence of a prolonged no-reflow phenomenon). At 30 minutes, global CBF had returned to baseline values in both groups and the percentage of voxels with a local CBF of <20 ml/100 cm³/min had increased above that at baseline. During the delayed protracted hypoperfusion phase at 1–4 hours postarrest, mean global CBF was 55% of baseline in group I and 53% of baseline in group II (Table 2). At 1–4 hours, the percentage of voxels with a local CBF of <20 ml/100 cm³/min was about 40% in both groups, significantly higher than the baseline value of about 7% in both groups (p<0.01).

There was no difference between groups (Table 2).

Regional CBF values (Figure 1) followed global CBF values (Table 2). No region showed a significant difference between groups. The initial transient hyperemia was greatest and most prolonged in the midbrain and thalamus in both groups. During 1–4 hours postarrest, regional CBF values were about 50% of baseline values in both groups. All regional CBF values (except for the white matter) were >20 ml/100 cm³/min in both groups.

The CaO₂ and CssO₂ values (Table 3) varied considerably between animals within times but followed a consistent pattern within dogs over time. PaO₂ remained ≥100 mm Hg throughout (PaO₂ not shown in table). A transient decrease in CaO₂ immediately after cardiac arrest was the result of hemodilution. CaO₂ reached near-baseline values by 4 hours. CaO₂−CssO₂ values (Table 3) were about 5–10 ml/dl
The two dogs without cardiac arrest showed that similar in the two groups. The model to 4 hours output was not monitored, but the U74006F-treated cardiac output without causing hypertension. After cardiac arrest, MABP was controlled and cardiac output was not monitored, but the U74006F-treated group required no norepinephrine while the control group did. Postarrest arrhythmias were transient and similar in the two groups. The model to 4 hours postarrest was appropriate. The same model, when life support was prolonged to 96 hours, resulted consistently in the same outcome—survival with severe brain damage—and mild hypothermia before or after arrest improved cerebral outcome. Postarrest patterns of global, regional, and local CBF and CMRO2 were the same in both groups. CBF followed the known hyperemia–hypoperfusion sequence. We used the stable Xe-CT method for CBF measurements because it is noninvasive and provides data for small regions, even regions deep within brain tissue. Verification of the Xe-CT method with autoradiography and microsphere methods in baboons has shown that regional CBF values of foci \( \geq 5 \times 5 \times 5 \) mm\(^3\) are real. The local CBF values of 1x1x5-mm\(^3\) voxels could partly be by chance due to systemic noise and possible computational and physical limitations of the method with low blood flows.

The negative CBF results with use of U74006F immediately after ventricular fibrillation suggest that factors other than lipid peroxidation cascades are responsible, at least in part, for the multifocal postarrest hypoperfusion. CBF values did not change when we gave 3 mg/kg i.v. U74006F in an additional dog at 4 hours postarrest. However, acidification with acetazolamide increased CBF. Thus, the hypoperfusion is not due to fixed obstruction. We have shown that deferoxamine and superoxide dismutase following asphyxiation cardiac arrest in dogs can mitigate the transient hyperemia and delayed hypoperfusion. Hemodilution to a Hct of 20% improved hypothermia before or after arrest improved cerebral outcome. Postarrest patterns of global, regional, and local CBF and CMRO2 were the same in both groups. CBF followed the known hyperemia–hypoperfusion sequence. We used the stable Xe-CT method for CBF measurements because it is noninvasive and provides data for small regions, even regions deep within brain tissue. Verification of the Xe-CT method with autoradiography and microsphere methods in baboons has shown that regional CBF values of foci \( \geq 5 \times 5 \times 5 \) mm\(^3\) are real. The local CBF values of 1x1x5-mm\(^3\) voxels could partly be by chance due to systemic noise and possible computational and physical limitations of the method with low blood flows.

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The CMRO₂ data are preliminary because of the few dogs investigated. Although for global CMRO₂ determinations we used CBF for one CT slice and arteriovenous O₂ content gradients for the entire cerebrum, the relative changes of these values are valid and baseline values were similar to those reported for the entire cerebrum. Postarrest reduction of CBF to 50% of baseline might worsen outcome only if arterial O₂ delivery is reduced below a critical level in relation to O₂ need (i.e., CMRO₂) and in multiple foci. In both groups, at 2 and 4 hours postarrest, approximately 50% CBF (Table 2) and 100% CMRO₂ (Table 3) suggest mismatching, as we reported before. This mismatching was missed in a recent study by Michenfelder and Milde, since they reported no mismatching in dogs only up to 1 hour after cerebrospinal fluid compression ischemia. The only published outcome study of U74006F after cardiac arrest in dogs does not meet our model requirements. Those investigators measured U74006F plasma levels to be 20 μg/ml immediately after a 1.5 mg/kg i.v. bolus and 0.1 μg/ml during a continued infusion of 0.25 mg/kg/hr. We did not measure plasma U74006F levels but infused more of the drug for longer periods. The optimal dosing and timing of U74006F are not known. After temporary, complete global brain ischemia induced by cerebrospinal fluid compression, protective pretreatment with U74006F showed benefit. We conducted four pilot experiments with larger doses of U74006F, given before and/or after ventricular fibrillation of 12.5 minutes' duration in our canine outcome model; by 24–96 hours postarrest, all four dogs had a best overall performance category of 3 or 4 (severe deficit or coma), as in historic controls. Outcome studies should be reexamined for life support factors that have been found to influence cerebral outcome, such as slight differences in brain temperature before or after the insult or differences in perfusion pressure. We conclude that U74006F, even in massive overdose, is well tolerated by the healthy organism. The established delayed postcardiac arrest cerebral hypoperfusion, mismatched by CMRO₂ returning to baseline values, does not seem to be influenced by the immediate postarrest administration of U74006F. The ability of U74006F administration after cardiac arrest to improve outcome remains to be documented with dose–response studies. If it does, it might be due to mechanisms other than improved O₂ need/O₂ delivery relations.

Acknowledgments

Edward Hall, PhD, and Eugene Means, MD, of the Upjohn Laboratories, Kalamazoo, Mich., provided supplies of U74006F and valuable advice. Stephen Hecht, MD, Robert Tarr, MD, and Ann Radosky, DVM, PhD, helped with CBF imaging. David Gur, PhD, Walter Good, PhD, Walter Obrist, PhD, Sidney Wolfson, MD, and Howard Yonas, MD, gave advice on CBF calculations. Janine E. Janosky, PhD, helped with statistical analysis. Yuval Leonov, MD, helped Dr. Sterz with team leadership. Mr. William Stezoski and Mr. Henry Alexander coordinated life support. Alan Abraham, Scott Nagel, Annette Pastula, and Mark Ritchey helped with the experiments. Teresa Adams, Pat Colorito, Franca Defelice, Vickie Mavrikas, William Wigginton, and Donna Wojciechowski were radiotechnologists. Lisa Cohn provided editorial assistance, and Gale Foster helped with preparation of the manuscript.

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KEY WORDS • cerebral blood flow • lipid peroxidation • resuscitation • dogs
Effects of U74006F on multifocal cerebral blood flow and metabolism after cardiac arrest in dogs.
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doi: 10.1161/01.STR.22.7.889

_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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