Exenatide Reduces Final Infarct Size in Patients With ST-Segment–Elevation Myocardial Infarction and Short-Duration of Ischemia

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Background—Exenatide has been demonstrated to be cardioprotective as an adjunct to primary percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction (STEMI). The aim of the post hoc analysis study was to evaluate the effect of exenatide in relation to system delay, defined as time from first medical contact to first balloon.

Methods and Results—Patients with STEMI and Thrombolysis In Myocardial Infarction flow 0/1 were randomly assigned to intravenous exenatide or placebo continuous infusion. Study treatment was commenced 15 minutes before intervention and maintained for 6 hours after the procedure. The patients were stratified according to median system delay (132 minutes). Final infarct size and myocardial area at risk were measured by cardiovascular magnetic resonance. Among patients with a system delay \( \leq 132 \) minutes \((n=74)\), treatment with exenatide resulted in a smaller infarct size (9 grams [interquartile range (IQR), 4–13] versus 13 grams [IQR, 8–24], \( P=0.008 \), corresponding to 8% [IQR, 4–12] versus 11% [IQR, 7–17] of the left ventricle, \( P=0.015 \)). In a regression analysis adjusting for myocardial area at risk the data points of the exenatide group lay significantly lower than for the placebo group \((P=0.006)\). In the patients with system delay \( >132 \) minutes \((n=74)\) no difference was observed in infarct size expressed as grams \((P=0.49)\) or percentage \((P=0.46)\). There was significant interaction between system delay (less than or equal to median versus greater than median) and treatment allocation in terms of infarct size \((P=0.018)\).

Conclusions—In this post hoc analysis, exenatide treatment was associated with a 30% decrease in final infarct size in patients with short system delay, whereas no cardioprotective effect in patients with long system delay was seen. However, this finding must be confirmed in larger studies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00835848.


Key Words: ST-segment–elevation myocardial infarction ■ exenatide ■ reperfusion injury ■ duration of ischemia ■ primary percutaneous coronary intervention
WHAT IS KNOWN

- Reperfusion injury after vessel recanalization is a determinant of infarct size in patients with STEMI.
- Ischemic preconditioning, cyclosporine, remote ischemic preconditioning, and cooling have been shown to be cardioprotective and limit reperfusion injury.
- Exenatide, a GLP-1 analog, decreased infarct size in experimental models of reperfusion injury.
- Exenatide increased myocardial salvage index in patients with STEMI undergoing primary PCI.

WHAT THE STUDY ADDS

- Treatment with exenatide before the onset of reperfusion with primary PCI decreased final infarct size by 30% in STEMI patients with TIMI flow 0/1 and a short duration of ischemia (≤132 minutes).
- Treatment with exenatide in STEMI patients with TIMI flow 0/1 and a long duration of ischemia (>132 minutes) was not found to be cardioprotective.
- The beneficial cardioprotective effects of exenatide are achieved only when the duration of ischemia before primary PCI is short (≤132 minutes). When given after this time, exenatide did not decrease infarct size significantly.

as a marker for duration of ischemia, but this is associated with many confounders. Accordingly, some previous studies did not find treatment delay to be related to infarct size and myocardial salvage, and a nearly horizontal association between treatment delay and mortality has been reported. In contrast, system delay defined as time from first medical contact to balloon treatment is more objective and also more strongly related to outcome. System delay may thus be a better surrogate marker for duration of ischemia than treatment delay. In the present post hoc analysis, we therefore hypothesized that the effect of exenatide is more pronounced in patients with short system delay.

Methods

The methodology of this randomized, double-blind, placebo-controlled trial has previously been described. Briefly, patients were eligible if they were 18 years or older and presented within 12 hours from the onset of symptoms and signs of STEMI to the catheterization laboratory. An ECG was obtained either in the ambulance or at the referring hospital. STEMI was defined as significant ST-segment elevation in the limb lead (I, II, III, aVL, and aVF) and V1-V6 and 2-mm ST-segment–elevation in the limb lead (I, II, III, aVL, and aVF) and V1-V6 and 2-mm ST-segment–elevation in V1-V5. In the present post hoc analysis, patients were excluded if thrombolysis in Myocardial Infarction (TIMI) flow grade was >1 before intervention. Patients with multivessel disease were not excluded from the present analysis.

Patients were randomly assigned to either placebo or exenatide, using a 1:1 computer-generated sequence. Patients assigned to exenatide were treated with an intravenous infusion of exenatide BYETTA (Amylin-Lilly) diluted in saline (25 µg exenatide in 250 mL saline). The infusion was commenced immediately after patient consent was obtained and at least 15 minutes before reopening of the culprit vessel with a flow rate of 72 mL/h (0.12 µg/min). After 15 minutes, the flow rate was reduced to 26 mL/h (0.043 µg/min), which was continued for 6 hours to maintain exenatide plasma concentration between 0.03 and 0.3 nmol/L. Patients in the control group were treated with continuous infusion of saline in equivalent velocities and durations.

In Denmark, the National Health Service provides tax-supported emergency medical service consisting of ambulances and physician-manned mobile units containing equipment for transmitting 12-lead ECGs. In the case of STEMI, the patient is transferred directly to the catheterization laboratory, bypassing the local hospital. This field triage was used during the entire inclusion period. The registration of the system delay was based on data registered by emergency medical service personnel in the ambulance files or in the physician-manned mobile unit files and/or data registered in hospital files. Time of ambulance call or first medical contact and time of first balloon were registered. System delay was defined as time from ambulance call or first contact with healthcare system (eg, local hospital) to first balloon inflation. The patients were stratified according to the median system delay.

Study End Points

The end points were final infarct size measured by late-enhancement cardiovascular magnetic resonance (CMR) after 3 months, final infarct size adjusted for area at risk, myocardial salvage index, peak plasma level of troponin T, and left ventricular (LV) ejection fraction (EF) determined by CMR after 3 months. In all randomly assigned patients without contraindications for CMR, an initial scan was performed during the index admission (within 1 week after primary PCI) to assess the myocardial area at risk using a T2-weighted short tau inversion recovery sequence. A second scan was performed 90±21 days later to assess the final infarct size in all randomly assigned patients using standard late-enhancement CMR. Final infarct size was expressed both as absolute values in grams and as a percentage of LV mass. The salvage index was calculated as follows: (area at risk minus infarct size)/area at risk. 

Results

Study Population

Figure 1 shows the trial profile. A total of 387 patients were randomly assigned to either exenatide or placebo. Sixty
patients, 29% of the eligible for inclusion, were lost to CMR. These patients were less likely to be male (65% versus 83%; P = 0.002) and had shorter system delay (115 versus 132 minutes; P = 0.010). Otherwise, there were no statistically significant difference between the patients included and the patients lost to CMR (data not shown). Importantly, no difference was observed between the patients lost to CMR and the included patients in terms of number of patients randomly assigned to exenatide (48% versus 52%; P = 0.55).

In the patients eligible for inclusion who had available CMR data for infarct size (n = 148), the median system delay was 132 minutes. Table 1 shows the baseline demographics and angiographic and procedural results according to random assignment for patients with system delay less than or equal to the median (132 minutes) and for the patients with system delay greater than the median (132 minutes). Fewer patients treated with exenatide had diabetes, otherwise, the treatment groups were well balanced in terms of baseline characteristics (Table 1), including the myocardial area at risk (Table 2).

In comparing patients with system delay less than or equal to the median with the patients with system delay greater than the median, no differences were observed in terms of baseline characteristics, except for age (P = 0.038) and treatment delay (P = 0.003) (data not shown).

Infarct Size and Myocardial Salvage Index

In patients with system delay less than or equal to median (n = 74), treatment with exenatide resulted in smaller infarct size expressed as grams (9 grams [interquartile range (IQR), 4–13] versus 13 grams [IQR, 8–24]; P = 0.008) in patients treated with placebo. The corresponding percentage of LV mass was 8% (IQR, 4% to 12%) versus 11% (IQR, 7% to 17%) (P = 0.015) (Table 2). Adjusting for area at risk in regression analyses showed that data points in the exenatide group were located significantly lower than for the placebo group (P = 0.006; Figure 2A), indicating that patients in the exenatide group developed significantly smaller infarcts for equivalent areas at risk. In addition, a larger myocardial salvage index was observed in the exenatide treatment group compared with the placebo group (P = 0.012, Table 2). Performing the analysis by excluding patients with multivessel disease, exenatide still reduced infarct size (8% [IQR, 3% to 14%] versus 13% [IQR, 8% to 17%]; P = 0.009) and increase myocardial salvage index (0.77 [IQR, 0.69–0.83] versus 0.63 [IQR, 0.50–0.73]; P = 0.002). Adjusting for a history of preinfarct angina, anterior infarct location, multivessel disease, and angiographically detected collaterals in a multivariable regression analysis, the difference in final infarct size and myocardial salvage index between treatment groups remained statistically significant (Table 3).

In patients with system delay greater than median (n = 74), no difference in infarct size expressed as grams (P = 0.49) or as percentage of the LV (P = 0.46) was observed between treatment groups (Table 2 and Figure 2B). Excluding patients with multivessel disease, no difference was observed between treatment groups in terms of infarct size (P = 0.13) or myocardial salvage index (P = 0.96) among patients with long system delay. In the analyses of covariance, a significant interaction between system delay (less than or equal to median versus greater than median) and treatment allocation in terms of final infarct size (grams) (P = 0.018) and myocardial salvage index (P = 0.021) was seen.

With regard to LVEF, no significant differences were observed between the treatment groups in both subgroups.
Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Less Than or Equal to Median System Delay (n=74)</th>
<th>Greater Than Median System Delay (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide (n=38)</td>
<td>Placebo (n=36)</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td>59±11</td>
</tr>
<tr>
<td>Male</td>
<td>33 (87)</td>
<td>31 (86)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (33)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (3)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (29)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16 (42)</td>
<td>23 (64)</td>
</tr>
<tr>
<td>Peirinfarct angina</td>
<td>4 (11)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Preinfarct medical treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>4 (11)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>3 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Statin</td>
<td>6 (16)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5 (13)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>System delay, min</td>
<td>101 (87–117)</td>
<td>99 (87–121)</td>
</tr>
<tr>
<td>Symptom-to-balloon time, minutes</td>
<td>141 (101–235)</td>
<td>173 (108–228)</td>
</tr>
<tr>
<td>Door-to-balloon, min</td>
<td>34 (23–58)</td>
<td>28 (21–43)</td>
</tr>
<tr>
<td>Anterior infarct</td>
<td>14 (37)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>Collateral flow, Rentrop grade 2/3</td>
<td>8 (21)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>7 (18)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Bifurcation treatment</td>
<td>2 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>TIMI grade 3 after procedure</td>
<td>35 (92)</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Thrombectomy/aspiration</td>
<td>25 (66)</td>
<td>24 (67)</td>
</tr>
<tr>
<td>Treatment with GP IIb/IIIa inhibitor</td>
<td>34 (89)</td>
<td>31 (86)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; GP, glycoprotein; TIMI, Thrombolysis In Myocardial Infarction; and GP, glycoprotein.

Data are presented as mean±SD, median (interquartile range), or n (%) unless otherwise indicated.

(Table 2). In patients with system delay less than or equal to median, peak troponin T was 4.0 (IQR, 2.4–8.) in the exenatide group and 4.6 (IQR, 2.5–9.0) in the placebo group (P=0.61).

Stratifying the patients according to system delay <90 minutes (n=39) there was a trend toward a difference in a final infarct size expressed in grams (P=0.07) and in myocardial salvage index (P=0.09). Among the patients with system delay <90 minutes, no differences in infarct size (P=0.71) or myocardial salvage index (P=0.21) were observed. Stratifying the patients according to system delay <150 minutes (n=110), exenatide resulted in a smaller final infarct size expressed in grams (P=0.008) and a larger myocardial salvage index (P=0.008). Among the patients with system delay >150 minutes, no differences in infarct size (P=0.40) or myocardial salvage index (P=0.60) were observed.

Discussion

The main finding of our post hoc analysis was that exenatide treatment decreased final infarct size with 30% and increased myocardial salvage index with 14% in STEMI patients with TIMI flow 0/1 and short system delay, whereas no effect of exenatide was observed in patients with long system delay, indicating an upper limit of ischemia duration for the cardioprotective effect exerted by exenatide during reperfusion.

Final infarct size was assessed by CMR, and the cardioprotective effect was observed regardless of whether infarct size was expressed as grams or percentage of LV mass. The results remained consistent when adjusting for area at risk, peirinfarct angina, anterior infarct location, multivessel disease, and angiographically detected collaterals in multivariable analyses.

To secure that no difference exists between treatment groups in the amount of myocardial tissue exposed to imminent cell death, it is important to measure the myocardial area at risk in addition to infarct size when studying reperfusion injury. In clinical settings, CMR is considered the method of choice to assess final infarct size, due to a superior reproducibility and better detection of myocardial infarction boundaries compared with single-photon emission computed tomography.19,20 In this study, area at risk was evaluated using the T2-weighted CMR technique, which is based on the visualization of edema in the ischemic myocardium caused by coronary artery occlusion,21 which is seen as hyperintensive areas on T2-weighted images.22–24 The size of these hyperintensive areas correlates with histopathologic defined areas at risk,16,22 and with areas at risk measured by single-photon emission computed tomography.25 However, T2-weighted images may be technically problematic and have a sufficient diagnostic quality in only 88% to 95% of patients with STEMI.26,27 Furthermore, the CMR scans are performed...
after reperfusion, and it may be speculated that exenatide or any other effective treatment modality per se leads to a decrease in edema and hence a smaller myocardial area at risk. In turn, this will result in an underestimation of salvage index and thus the effect of a given therapy. It is therefore important to notice that the myocardial areas at risk was of the same magnitude in the exenatide and placebo groups in the present study, and even more important that final infarct size in itself was significantly smaller in the exenatide group among patients with short system delay. Due to a larger difference in final infarct size in the present analysis, an augmented difference in myocardial salvage index would also have been expected. However, on the contrary infarct size the increase in myocardial salvage index was of the same magnitude in the present analysis as in the parent study.

In the original study, patients were included if they had TIMI flow 0/1 before intervention and no other stenosis >70% than the culprit lesion.5 Whereas preprocedural TIMI flow is well established as a pivotal determinant of reperfusion injury, the role of multivessel disease is more controversial.28 In the parent study, we chose to exclude patients with multivessel disease because these patients may inadvertently have been exposed to ischemic preconditioning in myocardium subtended by the stenotic vessels. However, despite the fact that multivessel disease may be an important predictor of the clinical outcome in patients with STEMI, the impact of

Table 2. Outcomes Evaluated With Cardiac Magnetic Resonance

<table>
<thead>
<tr>
<th>System delay less than or equal to median (≤132 min)*</th>
<th>n</th>
<th>Exenatide</th>
<th>n</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final infarct size, g</td>
<td>38</td>
<td>9 (4–13)</td>
<td>36</td>
<td>13 (8–24)</td>
<td>0.008</td>
</tr>
<tr>
<td>Final infarct size, %LV</td>
<td>38</td>
<td>8 (4–12)</td>
<td>36</td>
<td>11 (7–17)</td>
<td>0.015</td>
</tr>
<tr>
<td>Area at risk, %LV</td>
<td>35</td>
<td>30 (23–38)</td>
<td>31</td>
<td>32 (27–40)</td>
<td>0.25</td>
</tr>
<tr>
<td>Myocardial salvage index</td>
<td>35</td>
<td>0.75 (0.69–0.83)</td>
<td>31</td>
<td>0.66 (0.59–0.76)</td>
<td>0.012</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>38</td>
<td>117 (98–138)</td>
<td>36</td>
<td>127 (113–154)</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEF, 3 mo, %</td>
<td>38</td>
<td>56 (51–65)</td>
<td>36</td>
<td>57 (49–63)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

System delay greater than median (>132 min)*

| Final infarct size, g                                  | 39 | 15 (11–24) | 35 | 15 (10–22) | 0.49    |
| Final infarct size, %LV                                | 39 | 12 (9–20)  | 35 | 12 (8–15)  | 0.46    |
| Area at risk, %LV                                      | 34 | 34 (29–46) | 31 | 30 (25–36) | 0.05    |
| Myocardial salvage index                               | 34 | 0.67 (0.57–0.72) | 31 | 0.68 (0.53–0.73) | 0.84   |
| LV mass, g                                             | 39 | 126 (107–144) | 35 | 128 (96–152) | 0.99   |
| LVEF, 3 mo, %                                          | 39 | 53 (47–60)  | 35 | 55 (48–62)  | 0.41    |

LV indicates left ventricle; LVEF, left ventricular ejection fraction.

Data are presented as median (interquartile range).

*For interaction of system delay less than or equal to median with exenatide treatment, P=0.018 for final infarct size (%LV) and P=0.021 for myocardial salvage index.

Figure 2. Infarct size plotted against area at risk. Infarct size plotted against the myocardial area at risk measured by T2-weighted cardiac magnetic resonance techniques for patients with system delay ≤132 minutes (A) and >132 minutes expressed (B), respectively. A The line for the exenatide group lies significantly below the line for the placebo group (P=0.006). In both groups, the infarct size correlates with the area at risk (r=0.84 and r=0.72, P<0.001). B, The lines for the 2 treatments groups are not significantly different (P=0.75). In both groups, the infarct size correlates with the area at risk (r=0.75 and r=0.60, P<0.001).
multivessel disease per se on myocardial damage caused by STEMI seems to be negligible. Therefore, to increase the statistical power of the present analysis, patients with multivessel disease were not excluded. Importantly, neither excluding patients with multivessel disease nor adjusting for multivessel disease in a multivariable analysis affected the overall results.

We found that cardioprotection by exenatide depends on system delay, a surrogate marker for duration of ischemia. However, whether the same relationship is present between system delay and other cardioprotective modalities, such as ischemic postconditioning, cyclosporine A, and remote conditioning, remains unknown. The effect of 2 previously tested agents (FX06 a fibrin derivate and adenosine) seems to be more pronounced in patients with short treatment delay. In addition, the effect of ischemic preconditioning and postconditioning is diminished with longer duration of ischemia, at least in the experimental setting. Thus, the association between protection against reperfusion injury and system delay/duration of ischemia may be true with different cardioprotective strategies. The reason for the loss of cardioprotection with a longer duration of ischemia is not fully elucidated but may be related to that interventions generally are most effective in the first 2 to 3 hours after onset of ischemia. Patients with longer duration of ischemia have a relative larger irreversible myocardial damage caused by prolonged ischemia, leaving less cardiomyocytes exposed to reperfusion injury. Another explanation may be that longer duration of ischemia leads to changes in the cardiomyocytes or mitochondria, rendering them more resistant to cardioprotection. One such mechanism may be recovery of the mitochondrial membrane potential that is changed during ischemia and tends to recover after generation of flow. The ability of the membrane potential to recover depends on the duration of preceding ischemia. Furthermore, changes in the mitochondrial potential are related to the myocardial damage after ischemia-reperfusion. Future experimental and larger clinical studies are needed to clarify the relationship between reperfusion injury and cardioprotection on one side and time to reperfusion/duration of ischemia on the other. These studies also must address the relations between cardioprotection and comorbidity such as aging, LV hypertrophy, diabetes, and so forth.

If the findings of the present study can be confirmed, it may explain why results from many clinical studies on cardioprotection have been disappointing. Furthermore, it creates a paradox because patients with short system delay have good outcome already, and it may be difficult to improve the prognosis in these patients. In this study, only 1 patient had a system delay <60 minutes. Thus, most patients in the short system delay subgroup were at intermediary risk regarding system delay. Furthermore, in this proof-of-concept study analysis, the median system delay was used to differentiate between short and long duration of ischemia, but the exact system delay cutoff value is unknown. Using the median is a well-established and objective method that minimizes the risk of selection bias when splitting up a population into subgroups. An alternative could be to use 90 or 150 minutes as cutoff value. As demonstrated in this substudy, the 90-minute cutoff decreases the statistical power, whereas the 150 minutes cutoff leads to similar results and conclusion as using the median. Larger-scaled clinical studies are warranted to evaluate whether the cardioprotective effect of exenatide will translate into improved clinical outcome. These studies must take the relationship between exenatide and system delay into account. In the present analysis, the median system delay was higher than the European recommendations for transportation delays (120 minutes). However, the European recommendations are based on time from first medical contact to balloon, which is defined different from system delay. This may partly explain that the median system delay in the present analysis is >120 minutes. Furthermore, patients in this study also encompass patients not undergoing initial field triage, who have expected longer system delay. Because the diagnosis of STEMI must be affirmed before the choice of treatment (PCI or fibrinolysis) can be made and it takes additional time to establish fibrinolysis, the PCI-related delay is therefore significantly shorter than system delay. However, there seems to be the need for continuous optimization of the prehospital assessment, treatment, and transportation.

Limitations
The present study was performed as a post hoc analysis, and, due to the risk of selection bias, the results must be interpreted accordingly. In addition, a fairly high number of patients (29%) were lost to CMR for different but well-described reasons. These patients only differed from the included in terms of sex and system delay; thus, although a potential selection bias cannot be ruled out, it seems less likely that this could have affected the results.

It would have been more appropriate to include the present post hoc analysis in the parent study. However, looking into the effect of exenatide in relation to duration of ischemia was not a part of the original statistical analysis plan, but the hypothesis came to our attention after the parent study was published. The results and data within the present analysis do, however, provide important new knowledge to the effect of exenatide and the entire field of reperfusion injury and cardioprotection in clinical settings.
Conclusion
In the present post hoc analysis, exenatide treatment was associated with a 30% decrease in final infarct size in patients with short system delay (≤132 minutes), but no cardioprotective effect in patients with long system delay (>132 minutes) was found. However, this finding must be confirmed in larger studies.

Acknowledgments
We thank research study nurses Lene Kløvgaard, Bettina Løjmand, and Bente Andersen and the entire staffs of the Departments of Cardiology at Copenhagen University Hospital, Rigshospitalet and Arhus University Hospital, Skejby.

Sources of Funding
This study was supported by the Danish National Research Foundation for Heart Arrhythmia, the Novo Nordisk Foundation, Danielsen’s Foundation, Rigshospitalet’s Research Foundation, and the Danish Heart Foundation.

Disclosures
None.

References


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_Circ Cardiovasc Interv._ 2012;5:288-295; originally published online April 10, 2012; doi: 10.1161/CIRCINTERVENTIONS.112.968388

_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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