Neuraxial Modulation for Refractory Ventricular Arrhythmias
Value of Thoracic Epidural Anesthesia and Surgical Left Cardiac Sympathetic Denervation

Tara Bourke, MD; Marmar Vaseghi, MD; Yoav Michowitz, MD; Vineet Sankhla, MD; Mandar Shah, MD; Nalla Swapna, MD; Noel G. Boyle, MD, PhD; Aman Mahajan, MD, PhD; Calambur Narasimhan, MD, DM; Yash Lokhandwala, MD, DM; Kalyanam Shivkumar, MD, PhD

Background—Reducing sympathetic output to the heart from the neuraxis can protect against ventricular arrhythmias. The purpose of this study was to assess the value of thoracic epidural anesthesia (TEA) and left cardiac sympathetic denervation (LCSD) in the management of ventricular arrhythmias in patients with structural heart disease.

Methods and Results—Clinical data of 14 patients (25 to 75 years old, mean ± SD of 54.2 ± 16.6 years; 13 men) who underwent TEA, LCSD, or both to control ventricular tachycardia (VT) refractory to medical therapy and catheter ablation were reviewed. Twelve patients were in VT storm, and 2 experienced recurrent VT despite maximal medical therapy and catheter ablation procedures. The total number of therapies per patient before either procedure ranged from 5 to 202 (median of 24; 25th and 75th percentile, 5 and 56). Eight patients underwent TEA, and 9 underwent LCSD (3 patients had both procedures). No major procedural complications occurred. After initiation of TEA, 6 patients had a large (≥80%) decrease in VT burden. After LCSD, 3 patients had no further VT, 2 had recurrent VT that either resolved within 24 hours or responded to catheter ablation, and 4 continued to have recurrent VT. Nine of 14 patients survived to hospital discharge (2 TEA alone, 3 TEA/LCSD combined, and 4 LCSD alone), 1 of the TEA alone patients underwent an urgent cardiac transplantation.

Conclusions—Initiation of TEA and LCSD in patients with refractory VT was associated with a subsequent decrease in arrhythmia burden in 6 (75%) of 8 patients (68% confidence interval 51% to 91%) and 5 (56%) of 9 patients (68% confidence interval 34% to 75%), respectively. These data suggest that TEA and LCSD may be effective additions to the management of refractory ventricular arrhythmias in structural heart disease when other treatment modalities have failed or may serve as a bridge to more definitive therapy. (Circulation. 2010;121:2255-2262.)

Key Words: tachycardia ■ nervous system, sympathetic ■ nervous system, autonomic ■ ventricles

The autonomic nervous system plays a critical role in the genesis and maintenance of ventricular arrhythmias. Protection from ventricular arrhythmias by use of pharmacological antiadrenergic interventions such as β-blockers is well established.

Clinical Perspective on p 2262

Selective modulation of neuraxial efferents to the heart with thoracic epidural anesthesia (TEA) is a therapeutic option for arrhythmia management in humans. TEA has been used successfully in the management of electrical storm in a patient with ischemic cardiomyopathy. The antiarrhythmic effects of TEA have been demonstrated in animal studies and its effects include lengthening of repolarization and prolongation of refractory periods.

The protective effects of left cardiac sympathetic denervation (LCSD) have been demonstrated in patients with long-QT syndrome who continue to experience syncpe or cardiac arrest despite β-blockade and in small numbers of patients with catecholaminergic polymorphic ventricular tachycardia (VT). LCSD has been shown to lengthen ventricular refractoriness and raise the ventricular fibrillation threshold (by ~70%) without impairing cardiac contractility. Although it has been used primarily in the treatment of adrenergically driven arrhythmias in structurally normal hearts, LCSD has also been shown to contribute to a reduction in the incidence of sudden cardiac death among subgroups of post-myocardial infarction patients at high risk.
with a high mortality. The purpose of the present study was to review the effect of using 2 forms of neuraxial modulation (TEA and LCSD) in the management of malignant ventricular arrhythmias in the presence of structural heart disease (SHD).

Methods

Patient Population
We reviewed data from 14 patients from 3 medical centers between July 2005 and September 2009 who underwent neuraxial modulation with TEA or LCSD for the management of refractory ventricular arrhythmias. These patients were a subset of 154 patients who presented with “refractory” ventricular arrhythmias (over the 51-month period) to the centers involved in the present report. Stepwise arrhythmia management (with ablation in many cases) controlled arrhythmias for the vast majority; the patients who were selected for neuraxial modulation were refractory to all available treatments and were too unstable for any further treatment without arrhythmia control. We included 1 patient in the present series who was included in a previous report from our institution. Review of patient data was approved by the local institutional review boards of each of the medical centers.

Data Collection
The type, cause, and treatment of ventricular arrhythmias, neuraxial modulation used, immediate outcomes, procedural complications, and follow-up were noted in all patients. VT storm was defined as 3 or more sustained episodes of VT within a 24-hour period, each of which required termination by intervention. Incipient VT was defined as continuous sustained VT that recurred promptly despite repeated intervention for termination over several hours. When available, telemetry tracings and implantable cardioverter-defibrillator interrogation details were reviewed for each patient.

Arrhythmia Management
Ventricular arrhythmias were managed aggressively according to the standard clinical practice for management of ventricular arrhythmias at our centers. β-Blockers and antiarrhythmic drugs were given in sequence, devices were reprogrammed to minimize shocks, reversible causes (such as myocardial ischemia and electrolyte disturbances) were treated, deep sedation and intubation with induction of general anesthesia were considered, and catheter ablation was performed where feasible. When arrhythmias remained refractory despite these interventions, and when death was thought to be imminent, use of TEA or LCSD was considered to stabilize the patient before further interventions. The decision for TEA was individualized. If a surgeon who could perform emergent LCSD was not readily available or a patient was awaiting orthotopic heart transplant evaluation or catheter ablation, the patient underwent TEA. Otherwise, the patient underwent LCSD.

Procedural Details

Thoracic Epidural Anesthesia
Under an aseptic technique, with the patient in a left lateral decubitus position, a 17-gauge Tuohy needle (Baxter, Deerfield, Ill, and GPC Medical Ltd, New Delhi, India) was inserted via a paramedian approach into the T1–2 or T2–3 epidural interspace via a standard loss-of-resistance approach. A 19-gauge Flex-Tip Plus epidural catheter (Arrow International, Reading, Pa, and Chennai, India) was advanced 5 cm beyond the needle tip into the epidural space and was secured in a sterile manner. Lack of aspiration of blood and cerebrospinal fluid was determined to exclude intrathecal or intravascular catheter placement; the presence of paresthesia was confirmed, and 1 mL of 0.25% bupivacaine was injected, followed by an infusion at 2 mL/h, which was uptitrated according to the arrhythmic response.

LCSD: Operative Technique
A video-assisted thorascopic surgical approach was used. Under general anesthesia, with the use of a double-lumen endotracheal tube that allowed the ipsilateral lung to be deflated and nonventilated during the procedure, the pleural cavity was entered through three 1.5-cm incisions in the left subaxillary area. The left thoracic sympathetic chain was identified, and the lower half of the stellate ganglion, together with part or all of the T2–4 sympathetic chain, was dissected and resected. Histological confirmation was obtained intraoperatively (Figure 1). The chest drain was removed after confirmation of lung reexpansion.

Response to Neuraxial Modulation and Outcomes

Thoracic Epidural Anesthesia
With TEA, the antiarrhythmic effect is immediately evident; therefore, daily therapy rates before and during TEA were compared to determine the effects of the infusion on arrhythmia burden. An arrhythmia reduction of ≥80% was considered significant. Total therapies included successful antiarrhythmia pacing and cardioversion for patients with implantable cardioverter-defibrillators and represented the number of external cardioversions for patients without a device.

Left Cardiac Sympathetic Denervation
Response to LCSD was defined as follows: Complete response if no ventricular arrhythmias occurred within 1 week of the procedure, partial response if there was recurrence of ventricular arrhythmias that did not fulfill the definition of VT storm, and no response if VT storm or incessant VT occurred within the first week. Subsequent VT...
among the 10 patients with monomorphic VT, 7 had polymorphic VT, and 10 patients (71%) had monomorphic VT. Among the 10 patients with monomorphic VT, 7 had polymorphic VT, and 10 patients (71%) had monomorphic VT. Among the 10 patients with monomorphic VT, 7 had polymorphic VT, and 10 patients (71%) had monomorphic VT.

Clinical Characteristics
Clinical parameters of the patients are shown in Table 1. The group consisted of 13 men and 1 woman, with an age range from 25 to 75 years (54.2 ± 16.6 years). Twelve patients were in VT storm (4 were in incessant VT), and 2 experienced recurrent VT on maximal medical therapy despite having had 3 previous VT ablation procedures each. Four patients (29%) had active ischemia but had no targets for revascularization. The total number of therapies per patient before either procedure ranged from 5 to 202, with a median of 24 (25th and 75th percentile of 5 and 56). Twelve patients (86%) had an implantable cardioverter-defibrillator. Eleven patients (79%) had a history of VT, 8 (73%) of whom had previously undergone VT ablation.

Follow-Up
Hospitalizations, outpatient visits, and implantable cardioverter-defibrillator interrogation records were used to determine patients’ outcomes after their discharge from hospital.

Statistical Analysis
Continuous variables are summarized with mean±SD or median and quartiles as appropriate. Exact 68% confidence intervals are provided for outcome percentages. Computations were performed with StatXact (Cytel Inc, Cambridge, Mass).

Results
Clinical Characteristics
Clinical parameters of the patients are shown in Table 1. The group consisted of 13 men and 1 woman, with an age range from 25 to 75 years (54.2 ± 16.6 years). Twelve patients were in VT storm (4 were in incessant VT), and 2 experienced recurrent VT on maximal medical therapy despite having had 3 previous VT ablation procedures each. Four patients (29%) had polymorphic VT, and 10 patients (71%) had monomorphic VT. Among the 10 patients with monomorphic VT, 7 (70%) had more than 1 VT morphology; the mean±SD number of morphologies was 2.4 ± 0.9. Nine (64%) of 14 patients had an ejection fraction of 0.9. One patient (patient 4) had active ischemia but had no targets for revascularization. The total number of therapies per patient before either procedure ranged from 5 to 202, with a median of 24 (25th and 75th percentile of 5 and 56). Twelve patients (86%) had an implantable cardioverter-defibrillator. Eleven patients (79%) had a history of VT, 8 (73%) of whom had previously undergone VT ablation.

Treatment of Ventricular Arrhythmias
Treatment of VT and immediate response to neuraxial modulation are summarized in Table 2. β-Blockers were used in 12 of 14 patients but were contraindicated in 2 patients owing to cardiogenic shock and a history of severe bronchospasm. Antiarrhythmic drugs were used in all patients. Three patients were intubated to facilitate arrhythmia management.

VT Catheter Ablation Procedures
Six patients underwent VT ablation before neuraxial modulation, whereas 4 patients were too unstable to undergo a procedure (Table 2). Multiple VT morphologies precluded ablation in 2 patients, and 1 patient had unmappable VT. An ablation procedure was contraindicated in 1 patient because of the presence of severe thrombocytopenia. No patient underwent intra-aortic balloon pump implantation or insertion of a ventricular assist device before neuraxial modulation.

Response to Neuraxial Modulation: Immediate Outcome

TEA Group
Eight patients underwent TEA; a reduction of ≥ 80% in arrhythmia burden was seen in 6 patients (Table 2; Figure 2). Infusion duration in these 6 patients ranged from 48 to 96 hours (63 ± 19.3 hours). Patient 3 received 1 shock 17 hours after TEA was commenced; no further shocks occurred after uptitration of the bupivacaine infusion to 3 mL/h. After discontinuation of TEA owing to the development of sepsis, patient 2 received 2 shocks.
within 24 hours; the patient was reloaded with intravenous amiodarone but continued to receive shocks despite the addition of lidocaine, and he underwent urgent cardiac transplantation. Patient 4 received a shock within 10 minutes of epidural placement but had no further therapies for the duration of the infusion. Four patients received no shocks during TEA infusion; 1 of these patients received a shock within 4 hours of discontinuation of TEA and continued to receive 4 shocks per day until LCSD was performed 2 days later. A reduction of 17% in daily therapies was seen in 1 patient; catheter displacement occurred, and despite the catheter being repositioned and then replaced, uncertainty remained relative to the duration of medication delivery. An increase of 38% in the daily number of therapies was seen in 1 patient in whom a prior septal myectomy had failed to excise the arrhythmogenic focus. Three patients had LCSD performed after TEA.

**LCSD Group**

Nine patients underwent LCSD. Levels of denervation varied and were as follows: Lower half of left stellate ganglion to T4 (patients 9, 10, 12, and 14), lower half of left stellate ganglion to T2 (patients 6 and 8), and entire left stellate ganglion to T2 (patients 5, 7, and 13). Three patients had a complete response to LCSD, with no VT within 1 week of the procedure. Two patients had a partial response to LCSD, with recurrent VT within 1 week; the VT resolved within 24 hours in 1 patient and required VT ablation in the second. Four patients had no response to LCSD; VT storm persisted in 1 patient; 2 patients had a recurrence within 36 and 48 hours, respectively; and 1 patient with incessant VT unresponsive to drugs, pacing, or external defibrillation had resolution of arrhythmias for 72 hours, although VT storm recurred subsequently.

**Survival to Discharge**

**TEA Group**

Five patients had TEA alone; of these, 1 survived to hospital discharge, 1 received an urgent heart transplant, and 3 died.
(all had a protracted hospital course). The cause of death was pneumonia and asystolic cardiac arrest in patient 1; aspiration pneumonia, and cardiac and renal failure culminating in a pulseless electrical activity arrest in patient 4; and multiorgan failure in patient 11. The 3 patients who had TEA followed by LCSD all survived to hospital discharge.

**LCSD Group**

Of the 9 LCSD patients, 7 survived to hospital discharge. One patient (patient 10) died owing to a recurrence of VT storm 3 days after LCSD; a VT ablation procedure was not performed during this period because of the presence of pulmonary edema and biventricular thrombi. Patient 12 developed refractory VT storm 36 hours after LCSD that responded to intra-aortic balloon pump placement and repeat extensive epicardial ablation after thoracotomy; however, he later developed multiorgan failure, and support was withdrawn.

**Response to Intervention (Summary)**

Six of 8 patients who underwent TEA had a ≥80% reduction in arrhythmias; this included 3 of 3 patients with polymorphic VT and 3 of 5 with monomorphic VT (Table 3). The causes of the polymorphic VT were ischemic cardiomyopathy in 2 patients and arrhythmogenic right ventricular dysplasia in 1 patient. The causes of the monomorphic VT were ischemic cardiomyopathy in 2 patients and nonischemic cardiomyopathy in 1 patient. Of these 6 patients, 4 survived to discharge, 1 had TEA alone (and underwent urgent cardiac transplantation), and 3 had TEA followed by LCSD. One patient who did not respond to TEA survived to discharge.

Of the 9 patients who underwent LCSD, 5 had either a complete or partial response (Table 3). This included 1 patient with polymorphic VT due to arrhythmogenic right ventricular dysplasia and 4 patients with monomorphic VT due to ischemic cardiomyopathy, nonischemic cardiomyopathy, sarcoid cardiomyopathy, and arrhythmogenic right ventricular dysplasia (1 patient each). All 5 patients survived to discharge, as did 2 patients in whom no response to LCSD was seen.

**Follow-Up**

**TEA Group**

Of the 8 patients in this group, 5 survived. Patient 3 was alive and well 37 months after cardiac transplantation. Patient 2 presented to the emergency department with multiple implantable cardioverter-defibrillator firings 8 days after discharge and underwent cardiac transplantation; he was alive and well 31 months postoperatively. Patients 5, 6, and 13 underwent LCSD after TEA, and their follow-up is documented below.

**LCSD Group**

Seven of the 9 LCSD patients survived to discharge, including all 5 patients with complete or partial response. Duration of follow-up ranged from 1.5 to 15 months (6.2±4.6 months). Patient 6 had recurrence of VT storm after 1 month that was managed medically; he has been shock-free for 5 months since that time. Patient 7 had a recurrence of VT storm after 4 months that was treated with rescue ablation; he has been shock-free for 11 months. Patient 8 continued to have intermittent VT after LCSD and catheter ablation; he had another endocardial ablation followed by VT storm 2 months later, which was managed medically. Patient 9 was arrhythmia-free for 4 months before dying of decompensated heart failure. Three patients (5, 13, and 14) had been arrhythmia-free since discharge and had been followed up for 8, 2, and 1.5 months, respectively. All patients were maintained on antiarrhythmic therapy and β-blockade.

**Complications**

**TEA Group**

Patient 3 developed an elevated temperature and white cell count after 48 hours of TEA. The epidural catheter was removed because the source of infection was unclear; a respiratory cause was later identified. Cultures of the catheter tip were negative.

**LCSD Group**

Patient 7 developed Horner syndrome, which resolved after 6 months of follow-up. Patient 9 developed a small apical pneumothorax after LCSD; this was managed conservatively and resolved within 24 hours. This patient also developed anhydrosis of the left side of her face, which, in combination with a lack of postprocedure VT, served as objective evidence of effective denervation.

**Discussion**

**Major Findings**

These observational data suggest that the use of TEA and LCSD can be beneficial for the management of refractory ventricular arrhythmias in patients with SHD. Both procedures were well tolerated, which allowed stabilization of patients before a catheter ablation procedure was performed or acted as a bridge to definitive therapy.

**Thoracic Epidural Anesthesia**

TEA is a therapeutic option that selectively targets fibers that innervate the myocardium. Its immediate onset of action can interrupt the vicious circle of recurrent shocks that lead to elevation of catecholamine levels that in turn potentiate further arrhythmias, and it may avert the need for intubation. TEA tends to have minimal effects on hemodynamic parameters, including heart rate, mean arterial pressure, cardiac
Left Cardiac Sympathetic Denervation

After LCSD, a 90% reduction in cardiac events has been shown in high-risk patients with long-QT syndrome.\(^9\) A reduced number of cardiac events was also seen in a cohort of patients with long-QT syndrome and catecholaminergic polymorphic VT who received LCSD for secondary prevention.\(^11\)

LCSD interrupts the major source of norepinephrine release in the heart. The antiarrhythmic effects of LCSD, although present to some extent immediately after denervation, become more complete with chronic denervation. This may be due in part to the massive neuraxial activation at the moment of surgical resection.\(^22\) By our definition of “no response,” we may have excluded some patients in whom transient benefit from LCSD was seen. LCSD involves a preganglionic denervation with removal of synapses, and therefore, neural regeneration does not occur. Furthermore, there is a partial reduction of the catecholamine content of the ventricle, which reduces postdenervation supersensitivity.\(^23\)

LCSD is a more definitive treatment than TEA and has lasting effects. There is objective evidence of denervation after resection of the sympathetic chain, with histological confirmation of the presence of sympathetic chain and ganglia. Surgical LCSD requires general anesthesia and intubation, which alone may help control arrhythmias temporarily; however, hemodynamic instability may preclude this in the clinical setting.\(^25\)

Potential Clinical Strategy for Management of Ventricular Arrhythmia Storm

The present data strengthens the available data in the literature on the value of sympathetic blockade for the management of ventricular arrhythmias. The key strategies for management of VT storm include the following: (1) Early pharmacological sympathetic blockade; (2) antiarrhythmic drugs, especially amiodarone and lidocaine; (3) reprogramming of devices to minimize shocks; (4) management of reversible causes that are proarrrhythmic, which include electrolyte disturbances, fluid overload, and ischemia; (5) catheter ablation of the clinical arrhythmia if patients can be
transported safely to the laboratory; and (6) deep sedation or intubation with general anesthesia as an adjunct to sympathetic blockade in arrhythmia control, as well as for patient comfort. Of note, TEA can be instituted quickly and has the advantage of providing immediate effect while precipitants are addressed, cardiac transplant evaluation is performed, or surgery or assist device insertion is arranged, or when stabilization of the patient before ablation is required. TEA may also be used as a bridge to LCSD if this is not available emergently. LCSD provides long-lasting effects; it may be indicated if there are no reversible precipitants and no further surgical or ablative options exist, and it may be used as a bridge to nonurgent cardiac transplantation.

Study Limitations
Because of the retrospective observational nature of the present study, some (unavoidable) limitations must be considered. Patients were not randomized; VT storms sometimes do subside spontaneously, and the contribution of such remissions to the study findings cannot be delineated clearly. However, patients were treated unsuccessfully with aggressive medical therapy and catheter ablation (where feasible) before undergoing either procedure. In addition to the small size of the study, the causes of ventricular arrhythmias in the present study population were diverse, and the value of autonomic blockade may vary in cardiomyopathies of different origins.

LCSD procedures were performed by several operators, and levels of denervation differed. The fact that only 4 patients in the present series had complete denervation may have adversely impacted the LCSD outcomes. Of the 8 TEA patients, 3 were already intubated before commencement of TEA infusion, which may have modified the effects of the TEA. Although all 3 patients had arrhythmias despite general anesthesia, the addition of TEA abolished arrhythmias in 2 of 3 patients, which suggests an added beneficial effect.

There is also a referral bias in this study population, because all of the centers involved in the present study are specialized referral centers for catheter ablation of VT. Over the 51-month period of this study, 154 patients presented with refractory ventricular arrhythmias to the centers involved. Medical therapy (with ablation in many cases) controlled arrhythmias for the vast majority of these patients (140; 91%). Of the remaining 14 (9%) very-high-risk patients who underwent neuraxial modulation, 9 (64%) survived to hospital discharge. A 9% rate of nonresponse to conventional treatment for ventricular arrhythmias may be higher than would be expected in the general population of patients with VT.

Ventricular arrhythmias in patients with SHD typically tend to be macroreentrant; however, it is not known how often functional VTs due to triggered activity may play a role. Adrenergic modulation is thought to play a significant role in such cases of functional VT. Alteration in refractoriness and a reduction in ectopy/triggers may mechanistically account for the effect of either intervention. Myocardial refractoriness was not measured, and ectopy was not quantified before and after intervention. The present study does not allow examination of potential confounding factors such as prior episodes of VT storm, comorbidities, and pathogenesis.

Conclusions
Neuraxial modulation has the potential to reduce ventricular arrhythmias in patients with SHD. This form of treatment may be of value to control malignant ventricular arrhythmia when other treatment modalities have failed. Both TEA and LCSD may act as a bridge to definitive therapy such as catheter ablation, cardiac transplantation, or cardiac surgery. Larger prospective, randomized studies are needed to further define the clinical role of this therapeutic strategy. Prospective studies to evaluate sympathetic modulation in SHD are under way (http://www.clinicaltrials.gov/ct2/show/NCT01013714).

Acknowledgments
We thank Drs Satyanand Shastri, Narsaiah Bura, and Samuel Ahn for performing LCSD in patients from Holy Family Hospital, Mumbai, India, CARE Hospital, Hyderabad, India, and UCLA, respectively. We also thank the anesthesiology teams at these hospitals. We would also like to thank Dr Chi Lai (UCLA) for review of the pathology slide, Dr Jeffrey Gornbein (UCLA) for statistical assistance, and Dr Isaac Wiener (UCLA) for thoughtful review of the manuscript and comments.

Sources of Funding
This study was supported by the National Heart, Lung, and Blood Institute (R01HL084261 to Dr Shivkumar).

Disclosures
None.

References
Our findings are retrospective and will need further evaluation in prospective, randomized studies. Refractory ventricular arrhythmias represent a life-threatening acute-care emergency and pose a major therapeutic challenge. Our study reports the effect of modulating cardiac sympathetic output from the neurexia with thoracic epidural anesthesia and left cardiac sympathetic denervation for the management of refractory arrhythmias. Our observation suggests that control of serious arrhythmias can be approached in a stepwise fashion. The majority of patients presenting with malignant ventricular arrhythmias respond to a combination of β-blockade, antiarrhythmic drugs, and catheter ablation; however, in a subset of patients (such as the patients represented in this study), arrhythmias remain refractory. Additional therapeutic strategies such as thoracic epidural anesthesia and left cardiac sympathetic denervation could be considered in this setting. In our study, these procedures were well tolerated, without serious complications. Thoracic epidural anesthesia can be performed at the bedside; it can be used as a bridge to catheter ablation, cardiac transplantation, and left cardiac sympathetic denervation. Left cardiac sympathetic denervation can be performed in an acute setting if it is readily available when no further ablative or surgical options exist or as a bridge to nonurgent cardiac transplantation. Our findings are retrospective and will need further evaluation in prospective, randomized studies.
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_Circulation_. 2010;121:2255-2262; originally published online May 17, 2010;
doi: 10.1161/CIRCULATIONAHA.109.929703

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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