Baroreflex Sensitivity, Clinical Correlates, and Cardiovascular Mortality Among Patients With a First Myocardial Infarction
A Prospective Study

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Experimental studies have shown that among dogs with a healed myocardial infarction, depressed baroreflex sensitivity (BRS) identifies a subgroup at higher risk for sudden death. We have examined the relation among BRS, several clinical cardiovascular variables, and subsequent mortality in 78 patients below the age of 65 years who have had a first myocardial infarction. BRS was assessed by calculating the regression line relating phenylephrine-induced increases in systolic blood pressure to the attendant changes in the RR interval. A reduced BRS primarily reflects an impairment in the vagal efferent component of the baroreceptor reflexes. The BRS of the entire population was 7.8±4.9 msec/mm Hg. BRS was lower among patients with an inferior myocardial infarction (6.1±3.3 vs. 8.9±5.8 msec/mm Hg, p=0.03), with a three- versus a one-vessel disease (4.8±2.7 vs. 7.1±3.1 msec/mm Hg, p=0.04), and with episodes of ventricular tachycardia (5.1±3.0 vs. 8.3±5.1, p=0.03). There was no correlation between BRS and left ventricular ejection fraction or with mean pulmonary capillary wedge pressure at peak exercise, but a correlation (r=0.35, p<0.001) was present with exercise tolerance. During the 24 months mean follow-up period, there were six cardiovascular deaths (7.6%), and four were sudden. The BRS of the deceased patients were strikingly lower than those of the survivors (2.4±1.7 vs. 8.2±4.8 msec/mm Hg, p=0.004), and mortality dramatically increased from 2.9% (two of 68) to 40% (four of 10) (p<0.001) in the presence of a markedly depressed BRS (<3.0 msec/mm Hg). Even among patients with depressed left ventricular function, mortality was associated with reduced BRS. This clinical prospective study suggests that analysis of baroreflex sensitivity in patients after myocardial infarction provides novel information on cardiovascular pathophysiology and may contribute to more accurate identification of individuals at high risk for subsequent mortality. (Circulation 1988;78:816–824)

Considerable progress has been made in risk stratification after myocardial infarction (MI)\textsuperscript{1,2}; however, the accurate identification of patients after MI at high risk for cardiovascular mortality and sudden cardiac death remains a challenging and important problem. In addition to the appreciation of left ventricular dysfunction,\textsuperscript{3,4} the extent of coronary atherosclerosis,\textsuperscript{5,6} and complex arrhythmias\textsuperscript{7–10} as risk factors, the importance of the autonomic nervous system has been increasingly understood.\textsuperscript{11–15}

It has been shown recently (among dogs after MI) that analysis of baroreflex sensitivity (BRS) can identify subgroups at both lower and higher risk for sudden death.\textsuperscript{16,17} Specifically, it had been found that depressed BRS, a marker of depressed vagal reflexes, is associated with a higher risk of developing ventricular fibrillation during transient acute myocardial ischemia.\textsuperscript{16}

Based on these notions, the present study was designed to evaluate if analysis of BRS among patients after MI might be of use for the identification of individuals at higher risk and to assess...
whether there is a relation between BRS and several clinical cardiovascular parameters.

Preliminary data have been presented.\textsuperscript{18,19}

\textbf{Patients and Methods}

\textit{Study Population}

The study population consisted of 78 consecutive male patients discharged from the coronary care unit after a first myocardial infarction diagnosed by classic criteria.

Patients were excluded from enrollment if they were older than 65 years, had coexisting significant valvular disease or cardiomyopathy, had arterial blood pressure of more than 160/90 mm Hg, had insulin-dependent diabetes, could not undergo exercise stress testing because of congestive heart failure or unstable angina, had atrial fibrillation or abnormal sinus node function, or had serious noncoronary disease that might have limited long-term follow-up (e.g., cancer or liver cirrhosis).

All patients were submitted to cardiac function assessment and autonomic control study 4 weeks after the acute myocardial infarction, after pharmacological washout (24-hour withdrawal from nitrates and nifedipine; 7 days withdrawal from \(\beta\)-blockers, verapamil and diltiazem). Patients did not receive digitalis or antiarrhythmic drugs.

All patients gave informed consent to participate in the study.

\textit{Ambulatory Electrocardiography}

Two-channel, 24-hour ambulatory electrocardiograms were evaluated for the presence of ventricular tachycardia with an Avionics 660 A high-speed scanner (Irvine, California). Final review was by a physician.

Ventricular tachycardia was defined as three or more consecutive ventricular premature complexes at a rate of more than 100 beats/min.

\textit{Exercise Protocol}

Maximal symptom-limited exercise tests were performed in upright position on a bicycle ergometer with an initial workload of 25 W with subsequent increments of 25 W every 3 minutes.

Exercise was terminated whenever angina, dyspnea, exertional hypotension, ventricular tachycardia, exhaustion, ST segment elevation, or depression equal to or more than 2 mm occurred.

Among the ergometric variables, maximal work capacity and the occurrence of ventricular tachycardia during exercise or during the recovery phase or both were considered.

Exercise hemodynamics were evaluated in 56 patients who underwent right-heart catheterization. With a percutaneous approach, a 7F Swan-Ganz thermodilution catheter was passed through the basilic or femoral vein into the right side of the heart and positioned in one of the pulmonary artery branches.

Phasic and mean pressure were recorded from the right atrium, pulmonary artery, and pulmonary wedge with a Hewlett-Packard 1290-A quartz transducer (Cupertino, California). These parameters were evaluated at rest and during exercise according to the stepwise procedure described above.

\textit{Coronary Angiography}

Selective coronary arteriograms were performed in 62 patients with either the Sones or Judkins technique within 2 months of the myocardial infarction. A significant coronary artery stenosis was defined as a decrease in luminal diameter equal to or more than 75\% (as judged by two independent

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Retouched computer printout of a phenylephrine test. Panels A and B: Beat-to-beat changes in systolic blood pressure (SBP) and in RR intervals compared with baseline values. Analysis is limited to the first major increase in blood pressure with the attendant changes in heart rate. These points are used (Panel C) for calculation of the regression line. In this patient, phenylephrine produced a 25 mm Hg increase in systolic blood pressure, which was accompanied by a marked increase in the RR intervals. Accordingly, the slope of the regression line expressing the baroreflex sensitivity (BRS) is rather high—19 msec/mm Hg.}
\end{figure}
FIGURE 2. Like in Figure 1. Heart rate in this patient did not change despite a clear-cut increase in systolic blood pressure (SBP). Accordingly, baroreflex sensitivity (BRS) is extremely depressed—0.5 msec/mm Hg (Panel C).

Baroreflex Sensitivity Assessment

Arterial baroreceptor function was evaluated by the administration of phenylephrine according to the method of Smyth et al.21 Studies were carried out with subjects in the supine position in the fasting state. Brachial or radial arterial pressure was obtained through a Teflon cannula (Abbocath-T 22G) connected to a Hewlett-Packard 1290-A quartz transducer. One electrocardiographic lead and systolic arterial pressure signal were continuously sampled, digitally converted (sampling frequency, 200 Hz; twelve-bit resolution) and fed into a Hewlett-Packard 1000 computer system. The data were also recorded on a multichannel oscillograph (Gould S 1000 Electrostatic, Ballainvilliers, France) at a paper speed of 25 mm/sec.

After catheterization, the patients were allowed to rest for 30–40 minutes during which time heart rate and blood pressure were continuously monitored on an oscilloscope and were recorded at a few minutes’ interval. When stable values were present for approximately 10 minutes, the continuous record-

FIGURE 3. Plot of relation between baroreflex sensitivity (BRS) and age.

ing on paper was initiated and phenylephrine HCl (Neo-Synephrine, Winthrop Laboratories, 2 µg/kg) was injected by an antecubital vein. Patients received a bolus injection to raise systolic arterial pressure more than 15 and less than 40 mm Hg. If blood pressure did not increase as desired, additional injections were made increasing the dosage of phenylephrine by increments of 25 µg to reach a maximum of 3.5 µg/kg. The bolus injection was repeated at least three times at the dosage found to induce the required blood pressure increase and at not less than 10 minutes’ interval. At random, patients received saline solutions to determine spontaneous variation of heart rate and blood pressure.

An off-line computer analysis provided accurate detection of all sinus QRS complexes (premature beats and the three subsequent sinus beats were excluded). Systolic blood pressure (mm Hg) and RR intervals were calculated as increments in respect to the baseline condition. The RR intervals were plotted against the preceding arterial pulse, and a linear regression analysis was performed for those points included between the beginning and the end of the first significant increase in systolic arterial pressure (Figures 1 and 2). Only regression lines with a correlation coefficient either more than 0.80 or statistically significant (p<0.05) were accepted for analysis. A final slope was obtained by calculating the mean value of at least three determinations. This value was then considered as representing BRS (msec/mm Hg). Throughout the text, BRS values below 3.0 msec/mm Hg will be considered to represent “markedly depressed baroreflex sensitivity.”

Statistical Analysis

One-way analysis of variance was used to assess the relation between BRS and different categories of variables, whereas for continuous variables, simple linear regression was fitted. Homogeneity of variances was assessed by Cochran’s C test. The χ² test was used to compare mortality in two groups of patients. Data are expressed as mean ± SD. Significance was accepted for values of p<0.05.
Results

The BRS of the entire population (n=78) was 7.8±4.9 msec/mm Hg (range, 0.7–25.3 msec/mm Hg). The mean age of the population under study was 51±8 years (range, 26–65 years). As expected, BRS progressively decreased with increasing age; Figure 3 shows the linear relation between BRS and age (r = -0.57, p<0.001).

No adverse effects were observed during or after the phenylephrine injection. Specifically, in no instance did signs or symptoms of acute myocardial ischemia become evident. A minor and quite rapidly transient headache was reported by very few patients (<5%).

During the 1st year after enrollment in the study, 19 patients were treated with nitrates, 14 with β-blockers, and 24 with calcium entry blockers; 21 patients received no therapy. Only three patients received in addition one antiarrhythmic drug.

Baroreflex Sensitivity and Myocardial Infarction

No correlation was present between BRS and extent of MI as assessed by the serum creatine kinase peak elevation during the intensive care unit period (r=0.11). As shown in Figure 4A, patients with Q wave MI (n=66) had a BRS not significantly different from that of patients with a non-Q wave MI (n=12) (7.4±4.9 vs. 9.8±4.8 msec/mm Hg, NS). Among patients with a Q wave MI, BRS was found to be higher among patients with an anterior MI (n=31) compared with that of patients (n=35) with an inferior MI (8.9±5.8 vs. 6.1±3.3 msec/mm Hg, p=0.03) (Figure 4B).

Baroreflex Sensitivity, Coronary Arteriography, and Ejection Fraction

One-vessel disease was present in 23 of 62 patients (37.1%), two-vessel disease in 25 patients (40.3%), and three-vessel disease in 10 patients (16.1%). Four patients (6.4%) had completely normal coronary arteries. The latter group had a BRS (12.9±4.9 msec/mm Hg) clearly higher than those of patients with varying degrees of coronary vessel involvement (Figure 5). Specifically, patients with three-vessel disease had the lowest BRS (4.8±2.7 msec/mm Hg). This was also signifi-
siderately lower than that of patients with a one-vessel disease ($7.1 \pm 3.1$ m/sec/mm Hg, $p = 0.04$).

The left ventricular ejection fraction in 60 patients ranged from 15% to 77%, and there was no significant correlation with BRS ($r = 0.07$, NS) as shown in Figure 6.

**Baroreflex Sensitivity and Exercise**

Exercise tolerance was significantly related to BRS even if the correlation coefficient was rather low ($r = 0.35$, $p < 0.001$), as shown in Figure 7. On the other hand, no correlation was present between mean pulmonary capillary wedge pressure at peak exercise and BRS ($r = -0.24$, NS) (Figure 8).

**Baroreflex Sensitivity and Ventricular Tachycardia**

Episodes of ventricular tachycardia (VT) were detected in 13 patients (17%); VT was observed during a 24-hour Holter recording in 12 patients and during the exercise stress test in one patient. As a group, patients with VT had a lower BRS compared with patients in whom VT was not documented ($5.1 \pm 3.0$ vs. $8.3 \pm 5.1$ m/sec/mm Hg, $p = 0.03$). Figure 9 documents the existence of a considerable overlap; nonetheless, it is of interest that all patients with VT had a BRS within the medium-to-low range of BRS.

**Baroreflex Sensitivity and Mortality**

During the 24-month follow-up period (range, 6–40 months), there were six deaths (this includes one patient who was resuscitated from a documented ventricular fibrillation that occurred 10 months after the MI). There were four sudden (within 1 hour from onset of symptoms) and two nonsudden deaths, the latter two patients developed cardiogenic shock after a reinfarction. The main clinical characteristics of these six patients are described in Table 1.

The BRS of these six patients (2.0, 1.3, 5.0, 1.0, 4.0, and 1.0 m/sec/mm Hg) was clearly in the lower portion of the distribution of the entire population (Figure 10) and was remarkably lower than that of the survivors (2.4±1.7 vs. 8.2±4.8 m/sec/mm Hg, $p = 0.004$). It was also significantly lower than that of those patients who had a reinfarction ($n = 5$) or who underwent coronary artery bypass surgery ($n = 6$) (9.5±6.4 and 10.1±4.5 m/sec/mm Hg, respectively).

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**Table 1. Characteristics of the Deceased Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>MI site</th>
<th>Angio</th>
<th>EF</th>
<th>VT</th>
<th>Fatal event</th>
<th>BRS</th>
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<tr>
<td>2</td>
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<td>...</td>
<td>0.35</td>
<td>No</td>
<td>Reinf</td>
<td>1.3</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>INF</td>
<td>3 V</td>
<td>0.25</td>
<td>No</td>
<td>Reinf</td>
<td>5.0</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>INF</td>
<td>2 V</td>
<td>0.67</td>
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<td>SD</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
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<td>2 V</td>
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<td>SD*</td>
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</tr>
<tr>
<td>6</td>
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<td>2 V</td>
<td>0.36</td>
<td>No</td>
<td>SD</td>
<td>1.0</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; EF, ejection fraction; VT, ventricular tachycardia; BRS, baroreflex sensitivity; INF, inferior; ANT, anterior; SD, sudden death; Reinf, reinfarcted.

*Resuscitated.
Baroreflex Sensitivity

The mortality, which for the entire group was 7.6%, had a striking correlation with BRS. To calculate the mortality risk in relation to BRS, an arbitrary cut-off point representing one standard deviation below the mean was chosen; this figure (2.9 msec/mm Hg) was then approximated for practical use to 3.0 msec/mm Hg. Whereas mortality for patients with BRS equal to or more than 3.0 msec/mm Hg was 2.9%, it dramatically increased to 40% for patients with markedly depressed BRS ($\chi^2 = 14.2, p<0.001$) (Table 2).

<table>
<thead>
<tr>
<th>BRS, Baroreflex sensitivity</th>
<th>n</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population</td>
<td>78</td>
<td>7.6%</td>
</tr>
<tr>
<td>BRS $\geq$ 3.0 msec/mm Hg</td>
<td>68</td>
<td>2.9%</td>
</tr>
<tr>
<td>BRS $&lt;3.0$ msec/mm Hg</td>
<td>10</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

The relation between BRS, ejection fraction, and mortality is shown in Figure 11. It is evident that for patients with a reduced ($<50\%$) ejection fraction, mortality increases from 10% (two of 20) to 50% (three of six) if BRS is also depressed.

Baroreflex Sensitivity and Test-Related Variables

To rule out potential effects on BRS of variables related to the phenylephrine test, several parameters were examined, and no significant correlation was found. This was true for basal heart rate ($r = 0.2, p = 0.08$), for systolic blood pressure ($r = -0.2, p = 0.08$), for dosage of phenylephrine ($r = -0.12, p = 0.3$), and for the attendant increase in systolic blood pressure ($r = -0.17, p = 0.13$), as shown in Figure 12. Also, the increase in systolic blood pressure and the dosage of phenylephrine were not correlated ($r = -0.17, p = 0.14$).

Discussion

This study, performed in patients with a first MI, examined the relation between BRS and clinical features of ischemic heart disease; it also showed a striking correlation between cardiovascular mortality and markedly depressed BRS. The present results on the reflex autonomic control in hearts with a healed MI provide an additional link between experimental pathophysiology and clinical reality.

Baroreflex Sensitivity Assessment

Different methods exist for the evaluation of baroreflex sensitivity. The bolus injection of phenylephrine, a well-accepted method already in use as a tool for clinical investigation, was chosen also because it had recently proven of value in assessing susceptibility to ventricular fibrillation in experimental studies.

Several characteristics of the vasoactive drug technique (with phenylephrine) have been described: the heart rate responses are neurally mediated, as shown by their absence in denervated hearts and by their reduction or abolition after section of the sinoaortic nerves; the stimulus acts similarly on all arterial baroreceptors, as it occurs physiologically; and the subjects are usually unaware of the stimulus, thus avoiding emotional responses.

The main limitation of this method is in the need for an arterial catheterization. The inability of the technique to measure baroreflex control of vascular resistance is not relevant to the goals of studies, like the present one, which address specifically the autonomic reflex control of the heart. Similarly, the reproducibility of this method reported to be limited over a few months' period in a small study is of minor relevance to the relation between BRS soon after an MI and subsequent events.

A weak and not statistically significant correlation was found between BRS and basal RR interval and between BRS and basal blood pressure. This finding, somewhat at variance with previous studies, may simply reflect the fact that the autonomic changes occurring during the initial period after an MI and indicating a transiently impaired vagal control have slightly altered the normal relation between these basal parameters and BRS.

It is worth noting the complete absence of significant side effects with this maneuver, even in patients recovering from an acute MI.

Baroreflex Sensitivity and Clinical Correlates

The presence of a negative correlation between BRS and age was expected and is in agreement with previous studies.
Largely based on the classic study by Pantridge’s group, one might have expected a more depressed BRS among patients with an anterior MI, which is usually associated with signs of increased sympathetic activity. The opposite was found; namely, those with the lower BRS were the patients with an inferior MI, even if considerable overlap was present. This seeming discrepancy may well depend on the fact that while that study was performed within the first hour of an MI, the present one was conducted 30 days after MI, clearly exploring a different situation. Another explanation involves the possibility of a greater destruction, secondary to the MI, of vagal sensory endings particularly abundant in the inferior portion of the ventricles. This would result in a reduced activation of vagal afferent fibers, which contribute to the baroreceptor reflex.

BRS was not related to the extent of creatine kinase release during the acute phase of MI, a widely used but relatively poor index of infarct size. On the other hand, there was an interesting trend for a better preserved BRS in non-Q wave MI.

An oversimplistic extrapolation from the well-known fact that patients with congestive heart failure have a depressed BRS might have predicted a direct correlation between BRS and indexes of left ventricular function. The absence, in this study, of patients with clinical signs of pump failure combined with a wide range of resting left ventricular ejection fraction made such a prediction less certain. As a matter of fact, no correlation was found between BRS and ejection fraction at rest or with pulmonary wedge pressure at peak exercise. Furthermore, preliminary data from a more thorough study of left ventricular function, including quantitative measures of systolic function and wall motion analysis, indicate complete lack of correlation with BRS.

The correlation between BRS and maximal work capacity, considered by some as an indirect index of left ventricular function, deserves a comment. Maximal work capacity is affected by several factors, such as age and appearance of ischemic changes or arrhythmias, which could bring to a premature end the exercise test independently of the pump function. Thus, there is no contrast between this finding and the observed lack of correlation between BRS and left ventricular function.

More extensive coronary artery disease, as evaluated by the number of coronary vessels with a critical stenosis, was associated with a more depressed BRS. Explanations for this are not immediately evident. One may speculate that such a condition could be associated with either a more widespread alteration in cardiac microgeometry or with multiple areas of underperfusion that could influence the discharge of sensory vagal and sympathetic mechanoreceptors, thus contributing to a reduction in BRS.

This study did not involve a comparison with healthy subjects. With a different technique, BRS of a control population had been found to be higher than that of a group of patients after MI (12.0 ± 2.6 vs. 8.2 ± 3.7 mvec/mm Hg, p = 0.0001).

Baroreflex Sensitivity, Arrhythmias, and Mortality

Electrical stability of the myocardium depends in part on the balance between the two limbs of the autonomic nervous system. The occurrence of MI tends to disrupt this equilibrium by decreasing parasympathetic tone, thus enhancing the effects of sympathetic activity. The finding that among patients after MI with ventricular tachycardia, BRS...
tends to be depressed, suggesting weak vagal reflexes, is in good agreement with this concept.

The 24-month mortality for the entire group was rather low—7.6%. This reflects some important characteristics of the population under study. Not only were all patients below age 65 and had had a first MI, but they had also been selected on the basis of the eligibility to perform a maximal exercise stress test in pharmacological washout; thus, they were already identified as a low-risk group. Nonetheless, analysis of BRS allowed the identification within this population of a subgroup at a very high risk.

The BRS of all six deceased patients was depressed and markedly so in four of them. Indeed, when mortality was calculated in respect to the absence or presence of a markedly depressed BRS (<3.0 msec/mm Hg), it was found to vary from 2.9% to 40%. Although the number of deceased patients and of patients with markedly depressed BRS is relatively small, the difference in mortality is large enough to make its dependence on the numbers involved unlikely. This interpretation is strongly supported by a study involving 192 dogs studied 1 month after MI wherein different levels of risk for subsequent sudden death, ranging from 12% to 96%, could be identified on the basis of BRS.39

Whereas five of the deceased patients had to be considered at risk on the basis of traditional clinical variables, such as depressed ejection fraction or multivessel disease, the sudden death of the sixth patient was totally unexpected based on the same considerations. Indeed, the combination of inferior MI, two-vessel disease, and a good ejection fraction is usually regarded as a marker of low risk. However, he also had an extremely depressed BRS (1.0 msec/mm Hg). This case is probably of more than mere anecdotal value because it suggests the possibility of identifying some individuals at high risk who might otherwise go unrecognized.

Furthermore, among patients with a reduced ejection fraction, mortality increases from 10% (two of 20) to 50% (three of six) according to the simultaneous absence or presence of a markedly reduced BRS.

Recently, it has been reported by Kleiger et al.40 that another index of vagal tone—heart rate variability—is inversely correlated with mortality, even among patients after MI with left ventricular dysfunction. Thus, there are now clinical data to support the concept that derangements in autonomic balance favoring a sympathetic dominance and largely secondary to impaired vagal activity (vagal tone in Kleiger’s study and vagal reflexes in the present study) are associated with increased mortality in patients after MI.41

In conclusion, this prospective study raises the possibility that the analysis of baroreceptive reflexes in patients after MI may contribute to a more accurate identification of individuals at high risk for subsequent mortality.

Acknowledgments

We express our gratitude to Dr. Gianni Pinna, bioengineer, for the development of the computerized program for the analysis of baroreflex sensitivity and for technical assistance throughout the study and to Dr. Michael R. Rosen, Columbia University, New York, for reviewing the manuscript and for helpful criticism.

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KEY WORDS • autonomic reflexes • phenylephrine • sudden death
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Circulation. 1988;78:816-824
doi: 10.1161/01.CIR.78.4.816

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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