Microvascular Tone in a Skeletal Muscle of Spontaneously Hypertensive Rats

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SUMMARY We studied the degree of arteriolar smooth muscle constriction in the spinotrapezius muscle microcirculation of spontaneously hypertensive rats and their normotensive controls, Wistar-Kyoto rats. The constriction was expressed in the form of a nondimensional tone as the difference between steady state and dilated diameter (after papaverine treatment) divided by the dilated diameter. Both animal strains showed on average a progressive increase of tone toward the more distal arterioles, with a peak tone being reached in the transverse arterioles. Tone values in the hypertensive animals were consistently elevated. The number of arterioles that had more than 5% tone (so-called responder arterioles) was higher in the hypertensive animals. These studies suggest that, besides the anatomical adjustments documented earlier in our laboratory in the arteriolar network of this muscle, functional adjustments in the form of an elevated microvascular tone are associated with the elevated resistance in spontaneously hypertensive rats. (Hypertension 9: 164–171, 1987)

KEY WORDS • tone • arteriole • spontaneous hypertension • microcirculation • skeletal muscle

O UR earlier studies of the microcirculation dealing with the spontaneous form of hypertension in rats showed that resistance is increased across the hierarchy of precapillary arterioles, as evidenced by the altered pressure-flow relationships in consecutive segments of the spinotrapezius muscle bed. There are, however, insufficient data concerning the factors responsible for such alterations. Previous workers advanced the so-called rarefaction concept of hypertension when they found that there was no statistically significant decrease in the diameter of comparable arterioles in order to account for the above-normal microvascular resistances in spontaneously hypertensive rats (SHR). Experimental data in support of arteriolar rarefaction have been advanced for the cremaster and anterior gracilis muscle preparations of SHR and for the renal form of hypertension.

Few of the studies in the literature have estimated microvascular resistance levels on the basis of direct measurements of pressure and flow in the various sections of the network. Our own studies of the problem in SHR indicate that arterioles in the microcirculation of the spinotrapezius muscle can have a more than two-fold increase in vascular resistance. The elevated resistance appears to be related to two different mechanisms, structural adaptations and functional adaptation.

We have previously investigated in detail the structural microvascular adjustments in the spinotrapezius muscle of SHR and Wistar-Kyoto rats (WKY) by examining dilated, ink-filled, and fully reconstructed networks. These dilated specimens provide evidence for a number of structural adjustments in SHR, such as a denser arcade arteriolar network and a small but significant reduction in the diameters of dilated arcade arterioles. However, this small diameter reduction is insufficient by itself to explain the measured increase of the hemodynamic resistance. Averaged values for the dilated diameters of the transverse arterioles and their precapillary branches show no significant differences between preparations from SHR and WKY. The possibility remains that a functional adjustment serving to increase arteriolar tone may contribute to the elevation of microvascular resistance in SHR at this level of the arteriolar network.

Although whole organ perfusion experiments have given evidence that, in addition to structural adaptations, arteriolar tone is also elevated in SHR, few reports have been concerned with the question of the actual degree of arteriolar contraction and its distribu-
tion in the microcirculation. Thus, the present study attempted to ascertain the degree of smooth muscle contraction along arteriolar pathways in the spinotrapezius muscle of SHR and their normotensive controls, the WKY, under normal perfusion conditions.

Materials and Methods

Microvascular changes were assessed in 31 SHR (Charles River Breeding Laboratories, Wilmington, MA, USA) between 14 to 16 weeks of age. Control values were obtained in a group of 32 age-matched WKY. About 1 hour before operation and general anesthesia, a femoral catheter was inserted with the rats under local anesthesia (4% lidocaine [Xylocaine], injected subcutaneously) and mean and pulsatile components of the arterial pressure were measured continuously for about 45 minutes. All animal procedures were previously reviewed and approved by the university animal subject committee. Mean pressures before general anesthesia were, on average, 126 mm Hg in WKY and 163 mm Hg in SHR.

In contrast to our previous experiments, in which anesthesia was maintained by different mixtures of chloralose urethane, general anesthesia was maintained in the current study by a bolus dose of about 10 mg/kg i.v. of alfaxalone (Alfathesin; Glaxovet, Boronia, Australia), a short-acting steroid-type agent, and thereafter by a continuous infusion of the drug to deliver 7.5 to 10 mg/kg/hr through an intravenous catheter. Under such conditions, systemic blood pressure was maintained at a mean level of 100–108 mm Hg in WKY and 150–160 mm Hg in SHR. By providing 1.0 to 1.5 ml of normal saline per hour, the infusion served also to restore the potential fluid deficits for such experimental preparations.

The spinotrapezius muscle along the back side of the animal was prepared for direct visualization using a previously established procedure. The exteriorized muscle was continuously suffused with a balanced electrolyte solution saturated in the reservoir with a 95% N₂, 5% CO₂ gas mixture maintained at a pH of 7.4 and a temperature of 36°C. The O₂ saturation in the effluent was kept at 0%. At the surface of the muscle the Po₂ is typically between 0 and 5 mm Hg. The animal was placed on a heating pad and covered by a plastic sheet to keep its body temperature at 37°C.

For comparison purposes, the transverse arterioles were identified and, in turn, their respective parent branches (arcading arterioles) and the precapillary branches (Figure 1). In each case, the particular network was photographed with a Polaroid camera (Leitz, Wetzlar, West Germany) to identify the precise location of the vessel in the network. Micropressure measurements were made with the servo-null micropipette procedures developed by Wiederhielm et al. and updated by Intaglietta and Tompkins. Vessel diameter was recorded along successive portions of the arterioles under optical magnification (200 ×) using an electronic image-shearing procedure that allowed continuous tracking of the inner luminal endothelial surface. All diameters reported in the study refer to inner lumen diameter; no corrections were made for noncircular cross-sections. In addition to steady state measurements, each microvessel was studied after the local application of a vasodilator (papaverine, 1.0 mg/ml, in normal saline). The dose applied was sufficient to eliminate active tone in the arterioles, since only vessel dilation, not narrowing at constant pressure, was observed in the presence of papaverine.

In a series of pilot experiments, the degree of vasodilation with papaverine was compared with that following dibenzyline and nitroprusside (see Results). Measurements before and after application of the drug provided steady state diameters (d₀) and maximal diameters (dₘₐₓ). The tone (T) was computed as T = (dₘₐₓ - d₀)/dₘₐₓ. Tone is a nondimensional measure for the degree of active smooth muscle constriction, which assumes tone to equal 0% in dilated vessels and to equal 100% in fully constricted and occluded vessels. Vessels that exhibited vasomotion were observed for several minutes, and the steady state diameter (d₀), was computed as the time average during at least 10 vasomotor cycles. Data were acquired for about 2 hours, at which time the intravital experiment was terminated, since thereafter tone values could be observed to decrease spontaneously in individual microvessels.

Blood pressure, vasomotor pattern, and colloid oncotic pressure were stable during this period of experimentation. On average, four to five transverse arterioles and their dependent branchings could be characterized completely in a given muscle (see the section "Arteriolar Diameter" in Results). They were selected in the same thin region of each muscle away from the edges. The analog signals from central blood pressure, micropressure, and diameter were fed into
the analog-to-digital converter of a laboratory computer (PDP-11/23; Digital Equipment, Maynard, MA, USA) at a sweep rate of 100 Hz. Each signal was calibrated, and all computations were performed on the computer.

Statistical analysis included the frequency distribution of all variables and determination of means and standard deviation or, for skewed distributions, computation of medians. Statistical comparison between SHR and WKY was performed with the Student’s t test for distributions with equal mean and median and otherwise with the Mann-Whitney U test for comparison of medians. For example, microvascular diameters are often close to a gaussian distribution, whereas tone usually exhibits nonsymmetrical frequency distributions. Whenever other procedures were used, they are described in the text. Statistical significance was assumed at a p level less than 0.05.

Results

Choice of Vasodilator Agent for Tone Test

The degree of vasodilation observed with papaverine was compared with that produced by two other vasodilators, dibenzyline (1.0 mg/kg i.v.) and nitroprusside (10 μg/ml in the superfusion solution). In both SHR and WKY, the greatest diameter increase was observed after papaverine application. The arcade and transverse arterioles in WKY did not dilate as much after dibenzyline treatment, remaining 39% (n = 9, p < 0.05) and 5% (n = 5, NS) narrower, respectively, in comparison with the diameters after papaverine treatment. After nitroprusside treatment the diameter remained 40% (n = 9, p < 0.05) narrower in arcades and 16% (n = 5, NS) narrower in transverse arterioles compared with the papaverine treatment. Similar values were found in the SHR. In this type of experiment a factor to be considered with respect to these diameter differences after vasodilation is the drop of the central blood pressure observed with the intravenous administration of dibenzyline or the topical application of sodium nitroprusside. Topical nitroprusside is absorbed rapidly into the circulation and lowers blood pressure. In both cases, typical central blood pressure reductions of 30 to 50 mm Hg are observed, a feature associated with an elastic recoil of blood pressure reductions of 30 to 50 mm Hg are observed. There is a tendency for the local blood pressure in the arcade arterioles to rise by about 2 to 4 mm Hg during application of the dilator. The majority of histograms were symmetrical with similar mean and median values, and there was no statistically significant difference for either median or mean values between WKY and SHR. These values were not statistically different in the two strains.

Arteriolar Diameter

Figure 2 shows diameter histograms for the three classes of arterioles (arcading, root of transverse arterioles, and precapillaries) in WKY and SHR at steady state and after vasodilation with papaverine. The corresponding local micropressures (listed in the legend for Figure 2) were not significantly different under these conditions between SHR and WKY. During application of papaverine, no significant change of central blood pressure was observed. There is a tendency for the local blood pressure in the arcade arterioles to rise by about 2 to 4 mm Hg during application of the dilator. The majority of histograms were symmetrical with similar mean and median values, and there was no statistically significant difference for either median or mean values between WKY and SHR. Diameter distributions for transverse arterioles and precapillaries in the dilated state were similar to those obtained for another set of diameter measurements in a fixed muscle preparation (dilated, carbon-filled, and optically cleared specimens). The data for the arcade arterioles in SHR were, however, at variance with the previous measurements. The basis for this discrepancy is of special interest and is discussed below.

Arteriolar Tone

Microvascular tone can be influenced by an array of parameters. The data presented on tone are based on in vivo measurements with minimal disturbance. One important intervention that may influence the tone is...
the anesthetic dose. Figure 3 shows the influence of the administered anesthetic dose of alfaxalone (Alfathe- sin) on the tone, as measured on single arteriolar vessels. The individual curves, shown in Figure 3, were normalized by the tone at a dose of 7.5 mg/kg/hr and then plotted as a function of the anesthetic dose (data not shown). After passing a linear correlation through these curves, it could be determined that between a dose of 7.5 and 30 mg/kg/hr there was on average a 14% increase of tone in arcading arterioles and a 9% decrease in transverse arterioles. The tone values showed no significant correlation with the micropressures. These results indicate that alfaxalone causes no significant variation of tone within the dosages used for general anesthesia (7.5–10 mg/kg/hr).

Microvascular tone was increased from the feeding arterioles toward the smaller arcading arterioles and roots of transverse arterioles. This feature is illustrated in Figure 4 and is common for the normotensive and hypertensive strains. In these graphs a cubic spline fit was performed to detect the trend in the data points. Comparison of values for WKY and SHR in Figure 4 suggests that the SHR may have higher tone values. To determine whether the difference is statistically significant, the data set was divided into the three classes of arterioles and a histogram was drawn for each class (Figure 5). Means and medians were compared with the Student's t test and the Mann-Whitney U test, respectively. Median values in each class were significantly higher in SHR (p<0.05).

Close inspection of this data set (e.g., in Figure 4) shows another feature of tone in these two animal strains: the number of arterioles with unusually low values of tone was higher in the normotensive animals.

Responders and Nonresponders

To illustrate this difference in tone, the vessels were divided into responders (tone > 5%) and nonresponders (tone ≤ 5%). Responders are vessels that show a contraction of more than 5% of their reference diameter (dmax). Table 1 summarizes the different classes of arterioles. When all arterioles are considered, the SHR have a larger number of responders. If one computes the tone for the responding population of arterioles only, the mean and median values show a statistically significant difference in the precapillary arterioles but not in arcading arterioles or their transverse arteriolar offshoots (Table 2). This observation suggests that the elevation of the tone in SHR may be due in part to fewer nonresponsive arterioles.

Figure 6 shows microvascular tone values along individual pathways of the arteriolar network. In spite of the carefully controlled experimental protocol, considerable heterogeneity existed in tone values. The pathways can be subdivided into various combinations of responding and nonresponding vessels. The majority of pathways in the spinotrapezius muscle of SHR show that either all three arterioles (Figure 6A) or at least the transverse and precapillary arteriole (Figure 6B) are responders, whereas along arteriolar pathways in WKY there is an 84% chance that at least one will be a nonresponsive arteriole. The combination of a responding arcading arteriole and a nonresponsive transverse and precapillary arteriole (Figure 6C) was rare in both strains, indicating that tone tends to be higher in the more distal arterioles and not vice versa. Among the pathways with responders only (see Figure 6A), about 41% of this group in SHR showed a progressively increasing tone toward the precapillaries, whereas
TABLE 1. Responding and Nonresponding Arterioles in the Rat Spinotrapezius Muscle

<table>
<thead>
<tr>
<th>Vessel type</th>
<th>Tone (%)</th>
<th>WKY</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arcading arteriole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>34</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>66</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Root of transverse arteriole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>56</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>44</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Precapillary arteriole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>66</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>34</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

R = responder (arterioles with tone >5%); N = nonresponder (arterioles with tone ≤5%).

TABLE 2. The Tone in Responding Arterioles*

<table>
<thead>
<tr>
<th>Vessel type</th>
<th>Strain</th>
<th>Tone (%)</th>
<th>No. of vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arcading arteriole</td>
<td>WKY</td>
<td>14.4±10.1 (9.9)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>12.9±6.9 (12.2)</td>
<td>29</td>
</tr>
<tr>
<td>Root of transverse arteriole</td>
<td>WKY</td>
<td>25.3±13.7 (27.5)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>24.8±14.8 (20.4)</td>
<td>45</td>
</tr>
<tr>
<td>Precapillary arteriole</td>
<td>WKY</td>
<td>14.5±5.6 (15.2)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>23.1±11.41 (19.2)</td>
<td>46</td>
</tr>
</tbody>
</table>

Values are means ± SD. Median values are shown in parentheses.
*Responding arterioles are defined by having more than 5% tone.

FIGURE 5. Histograms of the arteriolar tone for three classes of arterioles. The mean ± SD and the median value are given in each panel. The mean and median values were compared statistically by means of the Student's t test and Mann-Whitney U test, respectively. The number of observations in each histogram is 50.

Discussion

The mean vascular tone in the microcirculation of muscle rises toward the distal arterioles. Average tone reaches a maximum in the transverse arterioles of WKY, while in SHR it reaches its maximum in both the transverse arterioles and precapillaries. 2) Median values of vascular tone are higher in all arterioles of SHR. 3) In WKY, a significant number of arterioles exhibit a low tone in the spinotrapezius muscle preparation. Such vessels are less frequent in the SHR. These results indicate that a functional change leading to an increase in vascular tone may contribute to the elevated arteriolar resistance of SHR in this organ.

Previous Studies

Hutchins et al. have reported measurements on the degree of arteriolar constriction employing a slightly different definition of tone: \( T' = (d^4_{max} - d^4)/d^4_{max} \). By using the fourth power of the diameter, the value of \( T' \) represents a measure of the local vessel resistance increase due to smooth muscle contraction. These investigators also found an elevation of this tone measure, \( T' \), in SHR, even though they were unable to detect a difference in the steady state mean diameters for the same vessels. Similar findings are reported in the present study. No statistically significant difference was found for average diameters of a heterogeneous population of arterioles between preparations from SHR and WKY (see Figure 2). When the tone values for individual vessels were compared, however, significant differences became apparent.

Studies on cremaster muscle provided evidence for elevation of arteriolar tone in SHR after vasodilation with adenosine. Lombard et al. also found the greatest dilation in the region of the third-order (A3) arterioles (which are close to the transverse arterioles in our terminology) and attributed the effect to a higher neural transmission and more vigorous responses to oxygen. These observations are compatible with the greater density of nerve plexes in arterioles of SHR and an elevated central sympathetic nerve activity.

The fact that the degree of vascular tone varies considerably along individual pathways in the arterioles may suggest that such an elevated nerve activity is not transmitted uniformly along the arteriolar tree. Marshall has observed that short-term stimulation of sympathetic perivascular nerve fibers leads to a uniform contraction of arcade arterioles. In contrast, the transverse arterioles may escape such a stimulus and respond to local autoregulatory factors in the face of continued nerve stimulation. Comparable studies cur-
Fig. 6. Vascular tone in the spinotrapezius muscle along individual pathways from arcading arterioles (AA) to the root of the transverse arterioles (TA) and the precapillary arterioles (PA). The pathways are divided into individual groups according to the arrangement of responders (R) and nonresponders (N). For example, Panel A shows a pathway with all three responders (R, R, R), Panel B has only two responders (N, R, R), etc. Panel G shows one responder with two nonresponders (R, N, N). The number in each panel shows the percentage of pathways in each category. The number of pathways where all three vessels show no response (N, N, N) was 0% in the SHR and 16% in the WKY. The total number of pathways studied was 50.

Currently are not available in SHR. The higher tone in the arterioles of SHR may be the result of a long-term local autoregulatory adjustment.

Diameter Measurements

Histograms for diameters measured under these in vivo conditions in the transverse and precapillary arterioles showed no significant differences between SHR and WKY in the steady state or after dilation. Furthermore, if we compare the histograms, means, standard deviations, and median values for these vessels with another set of measurements obtained in fixed preparations, also after vasodilation in the same muscle, we note agreement within measurement error for transverse or precapillary arterioles in SHR and WKY and the arcade arterioles of WKY. However, mean values for the entire population of arcading arterioles in SHR were significantly narrower; the mean value was 36.1 μm as compared with the mean in this study of 52.7 μm (see Figure 2). A difference of 16 μm is outside the measurement error. The diameter measurements in both studies were performed after dilation in the same strain of animals, at the same age, and in the same muscle. Thus, the question arises: How could such a discrepancy exist in otherwise carefully controlled data selection, and why can it only be detected in the arcading arterioles of SHR and not in any other vessel of either animal strain?

Closer examination of this question shows that one of the problems may be the visibility of the fine arterioles during intravital microscopy. Engelson et al. visualized the entire arterial network by filling vessels with carbon after dilation and minimizing light diffraction in the tissue by infiltration with glycerol. Diameter histograms were derived from muscle specimens after a complete reconstruction from branch point to branch point of the arcading arterioles was performed. Engelson et al. noted that, on the basis of length per muscle volume, the arcading arteriolar network in SHR is about 50% denser, largely through the presence of a larger number of relatively narrow arterioles. For example, in the range of 20 to 30 μm, the percentage of arcading arterioles after carbon filling was 28% in the study of Engelson et al., whereas in the present study only 12% were found with intravital microscopy (see Figure 2). Such data suggest, since in vivo intravital microscopy deals with a more circumscribed area, that many of these vessels are not detectable; these vessels are narrow, carry few red blood cells, and are embedded deeply between several muscle fibers. There currently are no in vivo methods to overcome the limited visibility. We have experimented with fluorescent microscopy using a high molecular weight (150,000) dextran as a marker. Since this marker rapidly leaves the vasculature in SHR, there is insufficient time with images of sufficient contrast to reconstruct portions of the arteriolar network; most contrast disappears within about 30 seconds. We expect that inclusion of these narrow, “hidden” arterioles would further elevate the values for tone in the arcade arterioles of SHR, since these arterioles are more frequent in SHR than in WKY. The in vivo diameters were derived only from a subpopulation of arterioles that is visible in such a muscle preparation.

The question that may then be raised is whether such a problem of visibility also may exist for transverse and precapillary arterioles. In both animal strains this class of vessel can be visualized in vivo only in the thinnest regions of the muscle (with 2–3 muscle fibers), and in the current experiments, only a selected set of no more than two to three transverse arterioles per muscle was suitable for data collection. Such a
selection of vessels does not appear to constitute a bias toward a specialized class of transverse arterioles, since their size in thin regions is typical for any transverse arteriole anywhere in the muscle, as seen in the carbon-filled and optically cleared specimen. The limitations that prevent the full visualization of all arterioles may also explain why arteriolar rarefaction has been reported in skeletal muscle of SHR despite the absence of a measurable reduction in diameter. Arterioles that are not visible during steady state become visible after vasodilation and filling with red blood cells. In the spinotrapezius microcirculation, arteriolar rarefaction appears to be largely "functional," with less evidence for anatomical rarefaction.

**Arteriolar Resistance**

If we combine the evidence obtained in the present in vivo study on SHR with the evidence for arteriolar structural adjustments in injected and fixed spinotrapezius muscle obtained previously, the following picture emerges. The structural adjustments, as measured in vasodilated vessels at 100 mm Hg transmural pressure, are of multiple origin, so that several mechanisms may contribute to the elevation of resistance in SHR. One of the key parameters, however, is the vessel diameter. In the dilated state, the average diameters for the population of transverse arterioles and precapillary arterioles were not significantly different, although the tone for these vessels was elevated considerably. In contrast, the larger arterioles among the arcades appeared to have a significant structural narrowing in SHR, as well as a slightly elevated tone. The extent to which resistance is elevated in individual SHR arterioles can be estimated if we combine both the average functional and structural narrowing. Such an estimate can be obtained if we add the percentage of structural narrowing found by Engelson et al. to the percentage narrowing caused by tone in this study (see Figure 5). Diameters in SHR would be reduced by 25%, 13%, and 16% in arcade arterioles, at the root of transverse, and precapillary arterioles, respectively. Diameter reductions of this magnitude are substantial and, according to Poiseuille's equation, respectively cause a 3.1-fold, 1.7-fold, and twofold increase in arteriolar resistance. These resistance values are of the same order of magnitude as those estimated by direct in vivo experiments. In view of the fact that the arterioles may have noncircular cross-sections and that numerous other network adjustments are found in SHR, these values represent only an order of magnitude. A more precise picture of the impact of the structural and functional adjustments will require a complete network analysis. It is clear, however, that elevation of vascular tone represents an important facet of the elevation of vascular resistance in SHR.

**The Nonresponders**

In the present study the presence of arterioles in normotensive animals with low tone values was a common feature (see Figures 5 and 6), which we have also observed in other muscles besides the spinotrapezius muscle and in other animal species. Such vessels exhibit little vasomotion, and they may be located in an arteriolar network between vessels with higher tone, particularly if they are located in the arcade arterioles. They occur in the precapillary arterioles of both strains with relative low probability, and they are virtually absent in the SHR. The cause for this may be multifactorial, since under the experimental conditions neither a strong pressure nor a strong metabolic stimulus appeared to be present. It is possible that a differential anesthetic response of WKY and SHR may influence the occurrence of nonresponders. The surgical procedure, in turn, may have less of a differential effect, since it was performed in an identical manner in the two strains. The inability of the microcirculation of SHR to operate with such relaxed arterioles may be a fundamental defect that must be clarified in order to define the mechanism of hemodynamic resistance elevation.

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Hypertension. 1987;9:164-171
doi: 10.1161/01.HYP.9.2.164

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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