Factors Determining Direct Arterial Pressure and Its Variability in Hypertensive Man

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SUMMARY Intra-arterial pressure was recorded continuously in 26 patients with uncomplicated essential hypertension under standardized conditions. Recordings were analyzed beat by beat to obtain mean pressures and variability, expressed as the standard deviation of the frequency histogram. The major factors influencing variability were the level of pressure and the intensity of physical activity; systolic variability increased with progressive impairment of sino-aortic baroreflexes. Diastolic pressure increased with the level of sympathetic activity as reflected by plasma norepinephrine levels. After allowance for the decrease of plasma renin activity (PRA) with age, direct relationships were observed between PRA (log values) and the level of pressure and systolic variability; plasma angiotensin II values did not correlate. Systolic variability increased with the systolic response to cold but was unrelated to the response to dynamic or isometric exercise. Variability also tended to increase with obesity and was unrelated to age, sex, or race. (Hypertension 2: 333-341, 1980)

KEY WORDS • angiotensin II • blood pressure • epinephrine • norepinephrine • pressoreceptors • renin

VARIATION in blood pressure with sleep, physical activity, and emotional stimulation has been recognized for many years.1-3 Average daytime variations of 36 and 55 mm Hg were observed by Mueller and Brown in normotensive and hypertensive subjects respectively.4 Use of continuous recordings of direct arterial pressure has confirmed the importance of sleep and physical activity in determining blood pressure5-8 and characterized the short-term changes during smoking,7 defecating,8 coitus, and emotional stimulation.6 A circadian rhythm of arterial pressure has been observed in free-ranging subjects,8 although others have been unable to confirm such changes independently of sleep and physical activity.6,10-12 Beat-by-beat analysis of blood pressure by computer provides a quantitative assessment of the changes in blood pressure integrated over many hours.5 These methods have provided insight into the role of the sino-aortic baroreflexes in the moment-to-moment control of the cardiovascular system in the dog;13 studies that clarify the factors determining variability of blood pressure in man are limited to those of Birkenhäuser and co-workers, who observed that variability, measured with an automatic cuff method, correlated directly with resting cardiac output and plasma renin concentration.14,15 We have measured direct arterial pressure and variability in hypertensive patients under standardized conditions and have examined the relationship of pressure and variability to age, time of day, sino-aortic baroreflex activity, biochemical indices of activity of the sympathetic nervous system and the renin-angiotensin system, and the responses to dynamic and isometric exercise and cold.

Patients and Methods

We studied 26 patients with average outpatient blood pressures of greater than 140 mm Hg systolic or 90 mm Hg diastolic on at least three occasions; mean age was 39 years (range 17-54); eight patients were female, and six of the males were black. No patient had evidence of target organ damage, defined as clinical evidence of ischemic heart disease or cerebrovascular disease, left ventricular hypertrophy, renal impairment, or accelerated hypertension. An underlying cause for hypertension was excluded after clinical examination and measurement of plasma electrolytes and creatinine, catecholamine excretion, and intravenous pyelography. Five patients had received previous hypotensive treatment but none within 4 weeks of the study. All patients gave informed consent to the investigations, which were approved by the Hospital Ethics Committee.
Ambulatory Intra-Arterial Blood Pressure

The ambulatory intra-arterial blood pressure was recorded from a 1 mm diameter cannula introduced percutaneously into the brachial artery, and connected to a miniature pressure transducer and perfusion device. The transducer signal was recorded on a portable analogue tape recorder (Oxford Medical Instruments) with electrocardiogram and an event marker. The resonant frequency of the catheter and transducer system was 18 Hz; the tape signal was recorded without attenuation up to 10 Hz. Calibration, repeated at least three times during 24 hours, was linear between 30 and 250 mm Hg and varied by 2 ± 0.3% (mean ± SEM). Zero drift was less than 4 mm Hg in 24 hours.

Blood pressure was analyzed beat by beat on a computer after conversion of the analogue trace, sampled every 20 msec real time, to digital form. Frequency histograms of systolic and diastolic pressures during 10-minute intervals were constructed, and histograms for longer periods obtained by summation. Damped beats with a slow rate of upstroke (dp/dt < 7 mm in 20 msec) were excluded from analysis; periods of damping or artefact were identified from the pressure trace played out on ultraviolet sensitive paper and on an oscilloscope and were also excluded.

Frequency histograms of pressure were Gaussian in every case; the mean and standard deviation of the histograms were used to measure mean systolic and diastolic pressure variability respectively. Computer and manual measurements of blood pressure agreed within ± 3%.

Conditions of Study

Patients were studied in an open hospital ward for 36 hours; times of meals and visiting were standardized. After admission and arterial cannulation between 10 and 12 a.m., arterial pressure was recorded continuously in all patients until they retired to bed after 10 p.m. In 14 patients, satisfactory pressure recordings were obtained throughout 24 hours; after sleeping, between 11 p.m. and 6 a.m., these patients awoke and remained in bed until 8:30 a.m. and were then ambulant about the ward until 10:00 a.m. The exact times of activity, sleeping, and waking were marked on tape and in a diary.

Patients were studied during a standardized sodium intake (no salt added to food for 3 days before admission and then 60 mEq daily); 24-hour urine and sodium excretion was measured by flame photometer.

Indices of Renin-Angiotensin System

Plasma renin activity (PRA) and angiotensin II (AI1) were measured in specimens obtained from a venous cannula after overnight rest, before arising from bed (n = 23), and after 40 minutes' ambulation (n = 26). The PRA was measured by radioimmunoassay by the method of Waite et al.14 Inter- and intra-assay coefficients of variation were 12%. The All was measured by radioimmunoassay by the method of Dusterdiek and McElwee.18 Inter- and intra-assay coefficients of variation were 8%.

Vascular Reflexes

The following tests were performed in a quiet laboratory on the patients' second day in the hospital. Arterial pressure and heart rate were recorded with a Mingograf 81 recorder using a Gaeltec 3 EA/a pressure transducer connected to the arterial cannula.

Handgrip

The response was measured after squeezing a calibrated handgrip dynamometer with the dominant hand at 30% of maximum voluntary contraction for 3 minutes, while the patient was sitting (n = 19).

Cold Pressor Test

The response was measured as the maximum increase in blood pressure and heart rate during immersion of the hand in ice water for 4 minutes (n = 18).

Bicycle Exercise

The response was measured as the average increase in blood pressure and heart rate during the last 3 minutes of an upright bicycle exercise test of 8 minutes duration (n = 25). The workload was constant and determined from a previous test to exhaustion as the load causing 85% of maximum heart rate.

Sino-Aortic Baroreflex Sensitivity

Sino-aortic baroreflex sensitivity was measured in 23 patients by the method of Smyth, Sleigh, and Pickering:19 bolus doses of phenylephrine (30-100 µg) were injected intravenously to produce a pressor response of 30 mm Hg and repeated three to seven times. Baroreflex sensitivity was measured as the average slope of the regression line of pulse interval on systolic blood pressure measured beat by beat; inspiratory beats were excluded.

Indices of Sympathetic Activity

A forearm venous cannula was inserted 4 hours before blood sampling. Specimens were placed in tubes containing glutathione and analyzed for norepinephrine and epinephrine by a radio-enzymatic method using rat liver catechol-o-methyl transferase (Cat-a-kit; Upjohn Diagnostics). Samples were obtained during the last minute of bicycle exercise (n = 12) and after resting supine for 40 minutes after exercise (n = 13). Inter- and intra-coefficients of variation were 10% and sensitivity was 0.05 µg/liter.

Data Analysis and Statistics

Values of daytime pressure and variability refer to observations recorded between 2 p.m. and 10 p.m. unless specified otherwise. The duration of recording...
varied between patients because of exclusion of periods with damping or artefact; the shortest recordings were of 4 hours' duration (approximately 15,000 beats). Daytime recordings between 10 a.m. and 10 p.m. were made in nine patients and throughout 24 hours in 14 patients.

Data are presented as mean values ± one standard error. Standard methods were used for Student's t-test, analysis of variance, correlation, and partial correlation.21

Results

Arterial Pressure and Variability

Mean waking intra-arterial pressure, 145 ± 4/93 ± 3 mm Hg, was significantly less (p < 0.001) than mean outpatient blood pressure, 163 ± 4/103 ± 1 mm Hg. Intra-arterial values were more than 10 mm Hg lower than outpatient values in 18 of 26 patients for systolic pressure and in 12 patients for diastolic pressure.

The distributions of values of systolic and diastolic variability during waking were Gaussian; mean systolic variability (the SD of the mean) was 13.7 ± 0.4 mm Hg (range 9.3 -17.3); mean diastolic variability was 10.6 ± 0.3 mm Hg (range 7.2-13.7) and was less than systolic variability in each patient. Mean values in males and females and white and nonwhite patients were similar.

During waking (2 p.m.–10 p.m.), systolic pressure and variability were significantly correlated (r = 0.64, p < 0.001); the relationship between diastolic variables was not significant (0.34, 0.05 < p < 0.1).

We have previously reported that blood pressure and variability progressively increased with activity from sleep to bed rest to ambulation in the 14 patients studied throughout 24 hours.22 During bed rest, a close relationship was observed between systolic pressure and variability (r = 0.73, p < 0.01; fig. 1); the relationship for diastolic variables was similar (r = 0.71, p < 0.01). During sleep and activity, the relationship between systolic pressure and variability remained significant (r = 0.56, p < 0.05) but that for diastolic pressure and variability did not (p > 0.1).

A similar relationship was also observed within each patient. When mean systolic pressure and variability during many 10-minute periods throughout 24 hours were plotted (fig. 2), a highly significant relationship was observed in each patient (p < 0.001).

Time of Day

The 12-hour recordings of waking pressure made in nine patients were divided into morning, afternoon, and evening periods, during which the levels of activity were comparable (table 1). Mean values of pressure and variability were similar and analysis of variance confirmed that there was no significant variation in pressure or variability with time of day during waking.

Age

Systolic variability increased with age (r = 0.42, p < 0.05). When allowance was made for the increase of pressure with age, no significant relationship was observed between either systolic or diastolic variability and age, independently of blood pressure (p > 0.1).

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Activity</th>
<th>Period</th>
<th>Systolic pressure (mm Hg)</th>
<th>Diastolic pressure (mm Hg)</th>
<th>Systolic variability (mm Hg)</th>
<th>Diastolic variability (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 a.m.</td>
<td>arterial cannulation</td>
<td>morning</td>
<td>145 ± 8</td>
<td>90 ± 5</td>
<td>13.8 ± 1.1</td>
<td>10.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>meal</td>
<td>145 ± 6</td>
<td>91 ± 4</td>
<td>13.0 ± 1.0</td>
<td>9.5 ± 0.9</td>
</tr>
<tr>
<td>2 p.m.</td>
<td>visitors</td>
<td>afternoon</td>
<td>144 ± 6</td>
<td>90 ± 3</td>
<td>13.5 ± 1.0</td>
<td>9.8 ± 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>meal</td>
<td>145 ± 6</td>
<td>91 ± 4</td>
<td>13.0 ± 1.0</td>
<td>9.5 ± 0.9</td>
</tr>
<tr>
<td>6 p.m.</td>
<td>visitors</td>
<td>evening</td>
<td>144 ± 6</td>
<td>90 ± 3</td>
<td>13.5 ± 1.0</td>
<td>9.8 ± 0.9</td>
</tr>
<tr>
<td>10 p.m.</td>
<td>bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1. Relationship between average systolic pressure and variability of pressure in 14 patients studied during bed rest (r = 0.73, p < 0.01).
Systolic variability mm Hg

10 110 120 130 140 150 160 170

FIGURE 2. Relationship between average systolic pressure and variability of pressure measured in a 34-year-old hypertensive woman throughout 24 hours. Each point represents observations averaged over a 10-minute period.

 Obesity

The leanness index, calculated as (height)²/weight, was used as an index of obesity, values decrease with increasing obesity. No significant relationship was observed between variability and the leanness index (p > 0.1). After allowance for the covariance of pressure and variability by partial correlation, a relationship of borderline statistical significance was observed (r = -0.34 and -0.31, p = 0.1 for systolic and diastolic variability respectively), indicating a tendency for variability to increase with obesity.

Sino-aortic Baroreflex Sensitivity

Mean baroreflex sensitivity was 8.2 ± 0.9 msec/mm Hg (range 2.4–17.3). The inverse relationship observed between systolic variability and baroreflex sensitivity (r = -0.65, p < 0.01; fig. 3) indicated greater variability in patients with impaired baroreflexes; it remained significant independently of systolic pressure (r = -0.42, p < 0.05) and age (r = -0.56, p < 0.01). The relationship between diastolic variability and baroreflex sensitivity was not significant (r = -0.33, p > 0.1).

Indices of the Renin-Angiotensin System

Values of PRA were log transformed to obtain a Gaussian distribution. Mean supine PRA was 6.4 ng/ml/hr (range 0.8–36) and mean supine AII was 30 ± 0.7 pg/ml; after ambulation, values increased significantly (p < 0.001) to 11.3 ng/ml/hr (range 1.2–53) for PRA and to 38 ± 0.7 pg/ml for AII. Individual values tended to decrease with age (p < 0.05); no relationship was observed with urinary sodium excretion (p > 0.1; mean value 83 ± 7 mEq sodium daily). The correlation coefficients between log PRA and AII were 0.64 supine (p < 0.01) and 0.68 ambulant (p < 0.001).

No significant relationship was observed between average pressure and log PRA (table 2); the correlation between log PRA (supine) and systolic variability was of borderline significance (r = 0.41; p = 0.05). After allowance for the tendency of PRA to decrease with age, significant direct correlations were observed between log PRA (supine) and systolic and diastolic

FIGURE 3. Relationship between sino-aortic baroreflex sensitivity and variability of systolic pressure during waking in 23 hypertensive patients (r = -0.65, p < 0.01).
pressure ($p < 0.05$); correlations with ambulant PRA were not significant; log PRA (supine and ambulant) also correlated significantly with systolic variability (fig. 4) but not with diastolic variability; the relationship between supine PRA and systolic variability remained significant independently of pressure ($r = 0.49$, $p < 0.05$). No significant relationships were observed between All and pressure or variability before or after allowance for age.

Indices of Sympathetic Activity

Mean plasma norepinephrine was $0.47 \pm 0.05$ μg/liter at rest and increased ($p < 0.01$) to $1.27 \pm 0.16$ μg/liter during exercise; mean plasma epinephrine was $0.07 \pm 0.01$ μg/liter at rest and increased ($p < 0.01$) to $0.16 \pm 0.03$ μg/liter during exercise. Significant correlations were observed (table 3) between diastolic pressure and plasma norepinephrine at rest (fig. 5) and during exercise, which remained significant independently of age; diastolic pressure also correlated with plasma epinephrine during exercise but not at rest. No significant relationships were observed between plasma catecholamines and systolic pressure or variability of pressure.

Response to Exercise

Blood pressure responses were $56 \pm 3/14 \pm 3$ and $29 \pm 4/18 \pm 6$ mm Hg during cycling and handgripping respectively; heart rate increased by $59 \pm 4$ and $13 \pm 2$ beats/minute respectively. Individual responses did not correlate significantly with arterial pressure or variability ($p > 0.1$).

Response to Cold

The mean pressor response was $32 \pm 5/17 \pm 2$ mm Hg; heart rate increased by $7 \pm 2$ beats/minute. The systolic response correlated significantly with systolic variability ($r = 0.53$, $p < 0.05$; fig. 5); the relationship between diastolic variables was less strong ($r = 0.45$, $p < 0.1 > 0.05$). There was no significant relationship between the pressor response to cold and average pressure ($p > 0.1$).

Table 2. Correlation Coefficients Between Average Arterial Pressure and Variability During Waking and Supine and Ambulant Plasma Renin Activity (PRA, Log Values)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Supine PRA (n = 23)</th>
<th>Ambulant PRA (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before age correction</td>
<td>After age correction</td>
</tr>
<tr>
<td>Average systolic pressure</td>
<td>0.13</td>
<td>0.53*</td>
</tr>
<tr>
<td>Average diastolic pressure</td>
<td>0.23</td>
<td>0.47*</td>
</tr>
<tr>
<td>Systolic variability</td>
<td>0.41</td>
<td>0.67†</td>
</tr>
<tr>
<td>Diastolic variability</td>
<td>0.16</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* $p < 0.05$.
† $p < 0.01$.
Hypertensive patients, aged less than 55 years and without clinical evidence of target organ damage, were selected to minimize the possible effects of secondary structural changes on blood pressure. Average intra-arterial pressures were lower than outpatient recordings in approximately half the patients, which confirm the observations of others who have recorded pressure over prolonged periods. This suggests that, in many patients, observations made after acclimatization to the hospital environment, in the absence of an observer, may be more representative of true blood pressure than casual outpatient recordings, though clearly more data are required in order to substantiate this interpretation.

It is emphasized that careful editing of recordings is important since inclusion of periods of damping or artefact could alter the frequency distribution of blood pressure; a common artefact that was easily recognized and excluded was due to activity of the peristaltic pump of the perfusion device. The frequency distribution of blood pressure approximated closely to a Gaussian distribution in all subjects during waking and sleeping. Comparison of individuals with recordings of different duration during waking was unlikely to introduce any systematic error, since values of mean pressures and variability during 4-hour periods in the morning, afternoon, and evening were closely similar.

We have previously reported that the level of physical activity has a major influence on both blood pressure and variability. This influence was minimized by studying patients in a uniform hospital environment, in the absence of visitors. In addition, an attempt was made to control an endogenous circadian rhythm, the level of physical activity must be controlled. This study shows that after appropriate standardization, circadian changes in blood pressure are minor in comparison with the effects of physical activity.

A direct relationship between the level of pressure and its variability was demonstrated in two ways. First, when many periods of 10-minute duration were examined in individual patients, a direct relationship between pressure and variability was observed in each case; this may reflect the tendency of pressure and variability to increase with activity. Second, when data from the hypertensive population were examined, a close relationship between systolic and diastolic pressure and variability was observed during bed rest; during sleep and ambulation, the relationship between systolic pressure and variability remained significant but that between diastolic variables did not. Others have reported a similar tendency; on the contrary, Birkenhager et al. defined variability as the ratio of the range of pressure to the maximum pressure expressed as a percentage. We preferred to express variability in absolute terms as the standard deviation of the frequency distribution of pressure since this utilizes all the observations made. Only the extreme observations are utilized in the range and these may not be representative of the majority of observations. We allowed for the relationship between pressure and variability by partial correlation since this reflects the relationship between pressure and variability observed in the study population; normalization as a percentage presupposes a relationship that may not exist in reality. If we had expressed variability as a percentage
of the average pressure, no relationship between pressure and variability was apparent.

An inverse relationship was observed between baroreflex sensitivity and variability of systolic pressure, which remained significant independently of the decrease in baroreflex sensitivity with pressure or age. The relationship between baroreflex sensitivity and diastolic variability was not significant. The greater systolic variability in patients with poor baroreflex activity suggests that the sino-aortic baroreflexes remain important in buffering moment-to-moment variations in pressure despite the impairment of the baroreflex sensitivity that is observed at an early stage in hypertension. Therefore; prolonged arterial pressure recordings were used only by Schalekamp and co-workers, who reported weaker relationships or no relationship between arterial pressure and plasma norepinephrine, measured at rest and during exercise, provide some justification for such comparisons. A similar relationship has been reported in studies in which plasma norepinephrine was measured after 3 days or 4 hours bed rest. Other studies that reported weaker relationships or no relationship between arterial pressure and plasma norepinephrine were made in patients after shorter periods of acclimatization to the hospital. Our observations support the hypothesis that the level of sympathetic activity, as reflected by plasma norepinephrine levels, is important in determining the elevation of pressure in essential hypertension; however, this relationship may become apparent only after control of the many environmental factors, particularly anxiety, that may influence arterial pressure and plasma catecholamines.

Variability was unrelated to plasma catecholamine levels; Clement and co-workers observed that variability, measured indirectly, was similar in hypertensives with high or low plasma norepinephrine. Although lability of pressure is a notable feature of essential hypertensives treated with converting enzyme inhibitors. Because the relationship of age and PRA complicates the interpretation of our data, further studies using prolonged pressure recordings in uncomplicated essential hypertensives within a narrow age range appear to be warranted; further investigation will be required to determine whether the relationships that we have observed between PRA and blood pressure and variability reflect dependence of blood pressure on the renin-angiotensin system, mutual dependence of pressure and PRA on sympathetic activity, or a compensatory renin response to pressure-mediated natriuresis and decreased plasma volume.

Changes in plasma norepinephrine levels reflect changes in sympathetic activity within individuals; however, comparison between individuals may be limited by the considerable interindividual variation in norepinephrine kinetics. The linear relationships observed between diastolic blood pressure and plasma norepinephrine, measured at rest and during exercise, provide some justification for such comparisons. A similar relationship has been reported in studies in which plasma norepinephrine was measured after 3 days or 4 hours bed rest. Other studies that reported weaker relationships or no relationship between arterial pressure and plasma norepinephrine were made in patients after shorter periods of acclimatization to the hospital. Our observations support the hypothesis that the level of sympathetic activity, as reflected by plasma norepinephrine levels, is important in determining the elevation of pressure in essential hypertension; however, this relationship may become apparent only after control of the many environmental factors, particularly anxiety, that may influence arterial pressure and plasma catecholamines.

Variability was unrelated to plasma catecholamine levels; Clement and co-workers observed that variability, measured indirectly, was similar in hypertensives with high or low plasma norepinephrine. Although lability of pressure is a notable feature of animal models of neurogenic hypertension, these observations suggest that this may not be so in man.

The pressor responses to exercise and cold were examined in order to determine whether either structural vascular changes or the response of the autonomic nervous system to exercise and cold were important in determining blood pressure variability. The pressor responses to exercise and cold were examined in order to determine whether either structural vascular changes or the response of the autonomic nervous system to exercise and cold were important in determining blood pressure variability.
nervous system are importantly related to variability of pressure. The cold pressor test has the advantage of providing a standard stimulus; the relationship between the systolic response and systolic variability provides limited support for either hypothesis. The derived correlation coefficient of the relationship, however, suggests that the response to cold is of limited use as a predictor of variability. No relationship was observed between the pressor response to exercise and variability. Although we standardized the exercise workload, this was only partly successful, since the diastolic response to handgrip was directly related to the workload ($p < 0.01$).

This analysis has depended heavily on correlations that cannot necessarily be taken to indicate a causal relationship; in some cases, these relationships have become apparent only after making allowance for the interaction of a third factor. This approach was necessary because we studied a selected group of hypertensives without target organ damage; investigation of a normal control group was not considered ethical. While these limitations are acknowledged, these observations emphasize that variability in blood pressure occurring within an individual may result in casual readings that are not truly representative of that individual. Therefore, the linear relationships observed between blood pressure and biochemical indices of activity of the renin-angiotensin and sympathetic nervous systems are of particular importance, because conflicting data from other sources have often relied on casual blood pressure recordings that may not be representative.

As with any other measure, it is important to be aware of the magnitude and origin of variability in blood pressure. These investigations indicate that blood pressure becomes more variable as the level of physical activity and level of blood pressure increase; progressive impairment of sino-aortic baroreflexes as in hypertension is associated with decreased ability to buffer blood pressure; PRA and the degree of obesity are of possible but lesser importance; however, age, sex, race, time of day, and plasma catecholamine levels were unrelated to blood pressure variability.

Finally, the application of continuous blood pressure recording methods has provided further evidence that the activity of the sympathetic nervous system and the renin-angiotensin system may be important in determining the elevation of pressure in essential hypertension.

Acknowledgments

Dr. S. Hill gave technical assistance, and A. Strong and S. Whitcomb secretarial help. Plasma catecholamines were measured by B-M Ericksson and PRA and AI by Dr. P. Gosling.

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Hypertension. 1980;2:333-341
doi: 10.1161/01.HYP.2.3.333

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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