The β-thalassemias constitute a group of inherited disorders of hemoglobin synthesis primarily existing in the low- or middle-income countries of the tropical belt stretching from sub-Saharan Africa, through the Mediterranean region and the Middle East, to South and Southeast Asia. Continued migration has also greatly expanded the reach of these diseases into large, multiethnic cities in Europe and North America, thus making such disorders a global public health concern.1

Distinction of the various forms of β-thalassemia relies on clinical grounds. Patients with β-thalassemia major present to medical attention in early childhood with severe anemia requiring life-long transfusion and iron chelation therapy for survival.2 Conversely, patients with β-thalassemia intermedia present later in childhood with milder anemia and remain largely transfusion-independent.3 Such variation in phenotype has been attributed to several environmental and genetic factors that alter the α/β-chain imbalance and subsequent ineffective erythropoiesis and peripheral hemolysis, the hallmarks of disease process in β-thalassemia.4

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Among the sequelae associated with a diagnosis of β-thalassemia, pulmonary arterial hypertension (PAH) has received great attention in recent years.5 Prevalence...
rates exceeded 50% in some studies. Although the exact mechanisms implicated in the pathogenesis of PAH in β-thalassemia remain unclear, its association with several risk factors and with subsequent right-sided heart failure have been illustrated. The main concern is that most available studies that evaluated PAH in patients with β-thalassemia established the diagnosis solely based on echocardiographic criteria, without systematic confirmation on right heart catheterization, a procedure that is recommended in international guidelines as the standard of care. More importantly, recent evidence from patients with sickle cell disease (SCD) echoed earlier studies in other conditions which established that the use of echocardiography alone results in a considerable number of false positive diagnoses that are not confirmed on right heart catheterization. Hence, the true prevalence of PAH in patients with β-thalassemia remains unidentified. Such information not only has implications on health care use measures, but will also aid in proper interpretation of available studies highlighting risk factors and outcomes associated with PAH in this patient population. In this line, we aimed to evaluate the prevalence of PAH in a large group of patients with β-thalassemia using standard diagnostic criteria involving confirmatory right heart catheterization. The role of several risk factors was also evaluated.

Methods

Participants

This was a multicenter, cross-sectional study of β-thalassemia patients followed at 8 thalassemia comprehensive care centers taking part of the Italian Webthal project. Webthal is a computerized clinical record network for all thalassemia patients attending the participating centers and is commonly used for collaborative research studies. We included all adult (≥18 years) patients with a diagnosis of β-thalassemia major or intermedia defined as per standard criteria5 (n=1530), and excluded patients with chronic restrictive lung disease or a left ventricular ejection fraction of ≤50% on last echocardiography in whom pulmonary hypertension, if confirmed, would not be classified as PAH but would be attributed to left heart or lung disease (n=21). A total of 1309 patients were eligible for the study. The study was conducted over a 12-month period (January 20, 2012 through January 20, 2013). The institutional review boards at all participating centers approved the study protocol and all participants signed a written informed consent before inclusion (ClinicalTrials.gov Identifier: NCT01496963).

Study Design and Measurements

For all eligible patients, data were retrieved for demographics (age and sex), splenectomy status, as well as mean hemoglobin (pre-transfusional in transfused patients) and serum ferritin levels over the previous 10 years. Measurements were then conducted over 2 phases. During the first 6 months, all eligible patients underwent a screening transthoracic echocardiography as part of their standard phlebotomy and management. We used continuous-wave Doppler sampling of the peak tricuspid-valve regurgitant jet velocity (TRV) to calculate the pulmonary arterial systolic pressure (sPAP), as described previously. The echocardiographic acquisitions in transfusion-dependent patients were performed in the early post-transfusional period. Accordingly, patients were divided into 3 groups according to the European Society of Cardiology guidelines for the diagnosis of pulmonary hypertension (PH), with minor modification owing to the chronic anemia associated with β-thalassemia that may lead to overestimation of values: Group A, sPAP ≤36 mm Hg or TRV ≤3.0 m/s (PH unlikely); Group B, sPAP ≥40 mm Hg or TRV ≥3.2 m/s (PH likely); and Group C, sPAP >3.6 and <40 mm Hg or TRV >3.0 and <3.2 m/s (PH possible).

In the second phase of the study, patients in Groups B and C underwent a second transthoracic echocardiography and patients confirmed to belong to Group B further underwent a computed tomography angiography scanning. At this stage, patients in Group B were reevaluated for clinical and instrumental (echocardiography and computed tomography findings) evidence of left heart disease, chronic restrictive lung disease, and pulmonary embolism to exclude patients with evidence of chronic cardiopulmonary disease in whom pulmonary hypertension, if confirmed, would not be classified as PAH but would be attributed to left heart, lung, or chronic thrombembolic disease. Patients unfit for an invasive procedure were also excluded. The remaining patients underwent right heart catheterization to confirm the diagnosis of PH as per European Society of Cardiology guidelines. PH was established with a mean pulmonary arterial pressure (mPAP) of ≥25 mm Hg and PAH was confirmed with a pulmonary capillary wedge pressure ≤15 mm Hg (precapillary PH). In patients with confirmed PAH, we also retrieved values for cardiac index, pulmonary vascular resistance, vasoreactivity (a positive acute response was defined as a reduction of mPAP of 10 mm Hg to reach an absolute value of 40 mm Hg with an increased or unchanged cardiac output), and assessed patients functionality using the New York Heart Association Functional Classification and a 6-minute walk test.

Statistical Analysis

Descriptive statistics are presented as means±standard deviation (SD), medians and interquartile range, or percentages. Bivariate comparisons between groups were carried out using the independent samples t test or Mann–Whitney U test for continuous variables and the χ² test for categorical variables. Correlations between sPAP values were made using the Pearson’s correlation coefficient (r). A multivariate logistic regression model was constructed to establish the independent role of risk factors on the outcome of confirmed PAH by calculating the odds ratios (OR) and 95% confidence intervals (95% CI). All risk factors with a significant association with the outcome on univariate analysis were entered into the model. Regression models were adjusted for the confounding effect of the center at which the patient is treated by creating and adjusting for a variable with categories pertaining to each participating centre. This information was added to the statistical analysis section. All P values were 2-sided with the level of significance set at 0.05.

Results

Patients’ Characteristics

A total of 1309 patients were recruited in this study. The mean age was 36.4±9.3 years (range, 18–80) including 602 (46%) men. A total of 977 (74.6%) patients had β-thalassemia major, whereas 332 (25.4%) had β-thalassemia intermedia. Some 633 (48.4%) patients were splenectomized. The mean hemoglobin level was 9.3±0.7 g/dl (range, 6.0–13.4), whereas the median serum ferritin level was 1072.8 (interquartile range, 574–1868; min: 5, max: 14 142). Patients with β-thalassemia intermedia were older, more commonly splenectomized, and had lower hemoglobin and serum ferritin levels than patients with β-thalassemia major (Table 1).

Prevalence of Pulmonary Arterial Hypertension

The study flow chart is illustrated in Figure 1. Upon echocardiographic testing, the distribution of patients according to predefined criteria was: 1234 (94.3%) patients in Group A (PH unlikely, TRV ≤3.0 m/s), 47 (3.6%) in Group B (PH likely, TRV ≥3.2 m/s), and 28 (2.1%) patients in Group C (PH possible, TRV >3.0 and <3.2 m/s). Thus, relying solely on echocardiographic criteria the estimated prevalence of PH in the
study group would be 5.7% (95% CI, 4.6–7.1; β-thalassemia major: 3.2%; 95% CI, 2.2–4.5; β-thalassemia intermedia: 13.3%; 95% CI, 10.0–17.3) if the TRV >3.0 m/s threshold is considered to be diagnostic of PH and 3.6% (95% CI, 2.7–4.7; β-thalassemia major: 1.6%; 95% CI, 1.0–2.6; β-thalassemia intermedia: 9.3%; 95% CI, 6.7–12.6) if the TRV ≥3.2 threshold m/s is considered to be diagnostic of PH.

Among the 33 patients from Group B who further underw ent right heart catheterization, 31 (2.4%) had PH (mPAP ≥25 mm Hg) and 27 had confirmed PAH (precapillary PH with pulmonary capillary wedge pressure ≤15 mm Hg), giving a PAH prevalence of 2.1% (95% CI, 1.4–3.0). The PAH prevalence was higher in β-thalassemia intermedia (4.8%; 95% CI, 3.0–7.7) than β-thalassemia major (1.1%; 95% CI, 0.6–2.0), OR for intermedia over major: 4.78 (95% CI, 2.19–10.41). Hemodynamic and functional characteristics of these 27 patients are summarized in Table 2.

![Study flow chart](https://circ.ahajournals.org/)

**Figure 1.** Study flow chart. PAH indicates pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; TI, β-thalassemia intermedia; TM, β-thalassemia major; and TRV, tricuspid-valve regurgitant jet velocity.
There was a modestly good correlation between sPAP estimated on transthoracic echocardiography and measured on right heart catheterization (Figure 2). The positive predictive value for the TRV ≥ 3.2 m/s threshold for the diagnosis of PH was 93.9%.

**Risk Factors for Pulmonary Arterial Hypertension**

Compared to patients in Group A (PH unlikely on echocardiography), patients with right heart catheterization confirmed PAH were older, more likely to be β-thalassemia intermedia than major, and more commonly splenectomized (Table 3). Similar observations were made when patients who were likely (Group B) and possibly or likely (Groups B & C) to have PH on echocardiography were compared with Group A patients, although a role for low hemoglobin level was also apparent in this comparison (Table 3).

On multivariate logistic regression analysis including significant variables at the univariate level (age, β-thalassemia phenotype, and splenectomy status) the only independent significant risk factors for having confirmed PAH were age (OR, 1.102 per 1-year increase; 95% CI, 1.06–1.15; Figure 3) and splenectomy (OR, 9.31; 95% CI, 2.57–33.7). The OR for confirmed PAH in β-thalassemia intermedia compared with β-thalassemia major dropped from 4.78 (95% CI, 2.19–10.41) in unadjusted analysis to 1.84 (95% CI, 0.70–4.86) on age adjustment and to 4.10 (95% CI, 1.87–9.01) on splenectomy status adjustment, individually. This indicated that the marked increase in confirmed PAH risk in β-thalassemia intermedia compared with β-thalassemia major was primarily confounded by older age and only minimally mediated through an increased propensity for splenectomy (see Table 1). Upon adjustment for both factors (age and splenectomy status), a nearly 2-fold nonsignificant yet independent increase in confirmed PAH risk is noted in β-thalassemia intermedia compared with β-thalassemia major (OR, 1.80; 95% CI, 0.71–4.57).

**Discussion**

This is the first large study to evaluate the prevalence of PAH in patients with β-thalassemia using standard guidelines and confirmatory right heart catheterization. Previous studies relying solely on echocardiographic parameters reported prevalence rates ranging between 10% and 78.8% (averaging ≈ 30%).16–33 The diagnosis was usually established based on a TRV exceeding 2.5–2.8 m/s corresponding to an sPAP exceeding 30–35 mm Hg, with some studies including symptomatology within the definition.16,18,20,22,24,26–29,31–33 In our
study, the prevalence of PAH was considerably lower when more strict echocardiographic criteria and confirmatory right heart catheterization were used. Owing to the systematic approach undertaken in our study, we believe that estimates presented in this report are more likely representative of the true PAH prevalence in patients with β-thalassemia. Our study echoed previous reports demonstrating that the prevalence of PAH is higher in β-thalassemia intermedia than β-thalassemia major\(^{16-33}\) but did not observe the previously reported female predominance.\(^{34,35}\)

The correlation between sPAP as estimated on echocardiography and as measured on right heart catheterization was only moderately good in our study. There may be several reasons for the discrepancy between these 2 methods, including the imprecision of the echocardiographic measurement, inherent physiological variations in pulmonary hemodynamics, as well as the interval between echocardiography and right heart catheterization.\(^{10}\) When a threshold TRV of 3.2 m/s is used to define PH, the positive predictive value of echocardiography was as high as 93.3%. However, we could not determine the false negative rate of this threshold nor the predictive power of lower thresholds (2.5 or 2.8 m/s) used in other studies, because such patients did not undergo right heart catheterization in our study which followed the European Society of Cardiology guidelines for the diagnosis of PH, used higher TRV thresholds in light of the chronic severe anemia in thalassemia patients, and considered it inappropriate to perform an invasive procedure for asymptomatic patients with lower TRV thresholds, especially considering the findings of a high false positive rate in the recent study from patients with SCD.\(^{10}\) Thus, although we can confirm that relying on such a threshold to diagnose PH is justified, we cannot exclude that several patients with PH would not be detected with such a threshold.

Similar to patients with SCD and other chronic hemolytic anemias, pulmonary hypertension in β-thalassemia patients would be classified as PH (Class 1) in international guidelines, which is characterized by the presence of precapillary pulmonary hypertension in the absence of left-sided heart disease (Class 2), lung disease (Class 3), or chronic thromboembolism (Class 4).\(^{7,8,36}\) Although pulmonary hypertension can occur in β-thalassemia patients in the setting of siderotic left-ventricular dysfunction, pulmonary hemosiderosis and subsequent fibrosis,\(^{37}\) and chronic thromboembolic disease,\(^{22,38,39}\) these remain less commonly reported pulmonary hypertension settings (classes) and such patients would have been excluded from our study which exclusively aimed to evaluate PAH. Nonetheless, and similar to patients with Class 4 pulmonary hypertension attributed to chronic thromboembolic disease, hypercoagulability can play a major role in the cause of PAH, where thrombi may be present in both the small distal pulmonary arteries and the proximal elastic pulmonary arteries.\(^{7}\)

The association of splenectomy and older age with increased PAH risk in our study echoes previous reports\(^{18,19,22,24,25,33,35,39-41}\) and further supports the latter hypothesis. Abnormalities of platelets and hemolyzed red blood cells are believed to be the key factors causing hypercoagulability and subsequent thrombotic events in β-thalassemia; especially older, splenectomized, β-thalassemia intermedia patients.\(^{42}\) The association of thrombocytosis, increased platelet activation, increased levels of nucleated red blood cells, and other markers of hypercoagulability with PAH in patients with β-thalassemia (mostly

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Table 3. Risk Factor Analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Echo PH Unlikely (Group A)</th>
<th>Echo PH Possible or Likely (Groups B &amp; C)</th>
<th>Echo PH Likely (Group B)</th>
<th>PAH Confirmed by Right Heart Catheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1234</td>
<td>n=75</td>
<td>n=47</td>
<td>n=27</td>
</tr>
<tr>
<td>β-Thalassemia phenotype, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>946 (76.7)</td>
<td>31 (41.3)***</td>
<td>16 (34)***</td>
<td>11 (40.7)***</td>
</tr>
<tr>
<td>Intermedia</td>
<td>288 (23.3)</td>
<td>44 (58.7)***</td>
<td>31 (66)***</td>
<td>16 (59.3)***</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>35.8 (8.9)</td>
<td>46.2 (10.3)***</td>
<td>48.2 (11.1)***</td>
<td>47.7 (11.1)***</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>573 (46.4)</td>
<td>29 (38.7)</td>
<td>18 (38.3)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Splenectomized, n (%)</td>
<td>572 (46.4)</td>
<td>61 (81.3)***</td>
<td>40 (85.1)***</td>
<td>24 (88.9)***</td>
</tr>
<tr>
<td>Hemoglobin level in g/dl, mean (SD)</td>
<td>9.4 (0.7)</td>
<td>9.0 (1.0)***</td>
<td>8.9 (1.1)**</td>
<td>9.3 (1.1)</td>
</tr>
<tr>
<td>Serum ferritin level in ng/ml, median (IQR)</td>
<td>1099 (580.6–1889.1)</td>
<td>814 (500–1250.9)*</td>
<td>962.2 (472–1500)</td>
<td>694 (442.2–1249.1)</td>
</tr>
</tbody>
</table>

Comparisons were made against Group A patients. IQR indicates interquartile range; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and SD, standard deviation.

\(^*P<0.05, **P<0.01, ***P<0.001.\)

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Figure 3. Probability of having pulmonary arterial hypertension (PAH) confirmed on right heart catheterization as a function of age in all patients as well as according to splenectomy status. Probability formula was derived from the logistic regression equation using the following equation: Probability of PAH = \(\exp(Z\text{-value})/[1+\exp(Z\text{-value})]\) where Z-value is derived from the logistic regression model.
intermedia) have been reported, even in patients with no evidence or history of pulmonary embolic disease.\textsuperscript{19,24,25,34,39,43}

Other factors are also suggested to cause PAH in β-thalassemia. Associations between lower hemoglobin levels and increased markers of hemolysis with this morbidity have been reported.\textsuperscript{22,25,34,35} The process of hemolysis disables the arginine–nitric oxide pathway through the simultaneous release of erythrocyte arginine and cell-free hemoglobin. Both nitric oxide and its obligate substrate arginine are rapidly consumed. The biological consequences of hemolysis on nitric oxide bioavailability ultimately translate into pulmonary vasoconstriction and the clinical manifestations of PAH.\textsuperscript{6,44} The causal association of this pathway with PAH in patients with SCD, however, has been challenged.\textsuperscript{45} PAH is also associated with increased expression of endothelin receptors in pulmonary microvascular endothelial cells and monocytes, as a result of intrinsic high levels of placenta growth factor in patients with SCD and β-thalassemia.\textsuperscript{46} An association between iron overload (or absence of chelation therapy) and PAH has also been observed in patients with β-thalassemia.\textsuperscript{17,22,31,39,47–49} Iron is implicated in the pathogenesis of several vascular disorders including atherosclerosis, arterial thrombosis, microangiopathic hemolytic anemia, vasculitis, and reperfusion injury in nonthalassemic populations.\textsuperscript{50}

The presence of non–transferrin-bound iron in the sera of β-thalassemia patients can cause oxidative vessel injury and endothelial activation.\textsuperscript{51} Moreover, iron overload could lead to hepatic disease and subsequent alterations in coagulation factor levels, thus worsening the hypercoagulable state implicated in these patients.\textsuperscript{42,52} However, we did not observe a role for iron overload in this study. Patients with β-thalassemia receiving regular transfusions may also be at risk of PAH because of transfusion-related HIV infection.\textsuperscript{53} The cause of PAH in β-thalassemia is thus most likely multifactorial, involving a complex interaction of platelets, the coagulation system, erythrocytes, and endothelial cells along with inflammatory and vascular mediators.\textsuperscript{6,44,54}

β-Thalassemia patients with confirmed PAH in this report had a more marked increase in mPAP and pulmonary vascular resistance than what has been reported in patients with SCD.\textsuperscript{10} They also have a similarly high rate of functional limitation (New York Heart Association Functional Classification) and considerable decrease in the 6-minute walk distance.\textsuperscript{10} This parallels studies confirming that PAH in β-thalassemia is a serious morbidity associated with subsequent right ventricular dysfunction,\textsuperscript{28,30,38,49,55–57} and warranting prompt diagnosis and treatment. The higher prevalence of PAH in β-thalassemia intermedia compared with β-thalassemia major patients suggests a protective role for transfusion therapy in this setting. Even in patients with β-thalassemia intermedia, the administration of transfusion therapy is associated with lower PAH rates.\textsuperscript{59} Transfusions not only improve anemia and hemolysis, but may also have a role in ameliorating the hypercoagulable state in this disease.\textsuperscript{26,42,58} Similar effects may be attained with hydroxycarbamide (fetal hemoglobin inducer)\textsuperscript{59} therapy, and a role of this agent in PAH prevention has been observed.\textsuperscript{23,39,60,61} Sildenafil citrate, a potent inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase-5 and a selective smooth muscle relaxant, has shown promising results for the management of PAH in small studies in β-thalassemia patients.\textsuperscript{62–64} More recently, a large multicenter trial on patients with thalassemia showed that sildenafil therapy may improve cardiopulmonary hemodynamics in patients at risk for PAH (TRV $>2.5$ m/s).\textsuperscript{65} Bosentan (endothelin receptor antagonist) and epoprostenol (prostacyclin) were also reported to be effective in some patients.\textsuperscript{66,67} Results from ongoing and future clinical trials will help structure management guidelines for PAH in β-thalassemia, which have not yet been established.\textsuperscript{5}

In conclusion, our study provides the first right heart catherization confirmed prevalence estimate for PAH in β-thalassemia patients. We confirmed a higher PAH prevalence in patients with β-thalassemia intermedia than major, and identified a role for advancing age and previous splenectomy on increasing PAH risk in these patients. Understanding the pathogenesis, diagnostic options, prevention, and treatment strategies for such serious morbidity is critical for clinicians caring for β-thalassemia patients.

Acknowledgments
We thank Dr Silvia Caviglia and Dr Carla Tardito (Galliera Hospital, Genoa, Italy) for their contributions to data management. Author Contributions: Study conception and design: G.D. and G.L.F. Data collection: G.D., R.G., P.B., M.D.C., A.P., M.E.L., A.Q., G.C., S.P., V.P., G.L.F. Statistical analysis: K.M.M. Review and interpretation of results: G.D., R.G., P.B., M.D.C., A.P., M.E.L., A.Q., G.C., S.P., K.M.M., V.P., G.L.F. Manuscript drafting: K.M.M. Manuscript review for important intellectual content: G.D., R.G., P.B., M.D.C., A.P., M.E.L., A.Q., G.C., S.P., V.P., G.L.F. All authors approved the manuscript before submission. G.L.F. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Remaining Webthal Pulmonary Arterial Hypertension Group members (alphabetical order): Manuela Balocco, MD (Galliera Hospital, Genoa), Elena Cassinerino, MD (University of Milan, Milan), Carlo Dessi, MD (University of Cagliari, Cagliari), Franco Della Rovere, MD (Galliera Hospital, Genoa), Giuditta Marianna (University of Milan, Milan), Marco Melis, MD (S. Francesco Hospital, Nuoro), Pierluigi Merella, MD (S. Francesco Hospital, Nuoro), Gianni Quarta, MD (Ferrino Hospital, Brindisi), Simona Roggero, MD (University of Turin, Turin), Alessandra Spiga, MD (University of Cagliari, Cagliari), Immacolata Tartaglione, MD (Seconda University, Naples); all in Italy.

Sources of Funding
The study was partially sponsored by an educational grant from “Associazione Ligure Talassemici Onlus” (ALT). The sponsors had no role in the conduct of this study, in the analysis or the interpretation of the data, or in the preparation, review, or approval of the article.

Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

The pathophysiology β-thalassemia, an inherited disorder of hemoglobin synthesis, involves chronic anemia and hemolysis, iron overload, hypercoagulability, and vascular abnormalities, all placing patients at higher risk of vascular morbidity including pulmonary arterial hypertension (PAH). The prevalence of PAH confirmed by right heart catheterization in patients with β-thalassemia has remained so far unknown. Such information remains essential as it carries screening and diagnostic considerations, and future perspectives.
Prevalence and Risk Factors for Pulmonary Arterial Hypertension in a Large Group of β-Thalassemia Patients Using Right Heart Catheterization: A Webthal Study
Giorgio Derchi, Renzo Galanello, Patrizio Bina, Maria Domenica Cappellini, Antonio Piga, Maria-Eliana Lai, Antonella Quarta, Gavino Casu, Silverio Perrotta, Valeria Pinto, Khaled M. Musallam and Gian Luca Forni
on behalf of the Webthal Pulmonary Arterial Hypertension Group*

Circulation. 2014;129:338-345; originally published online September 30, 2013;
doi: 10.1161/CIRCULATIONAHA.113.002124
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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