Cardiac Magnetic Resonance Imaging and Transesophageal Echocardiography in Patients With Transcatheter Closure of Patent Foramen Ovale

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OBJECTIVES
We studied the value of cardiac magnetic resonance imaging (CMRI) before and after closure of patient foramen ovale (PFO) in patients with cryptogenic ischemic events.

BACKGROUND
Cardiac magnetic resonance imaging is a powerful noninvasive tool for detailed assessment of cardiac anatomy and function. The relevance of CMRI compared with transesophageal echocardiography (TEE) in patients undergoing transcatheter PFO closure has not been evaluated so far.

METHODS
Contrast-enhanced CMRI and TEE were performed in 75 patients before and after PFO closure. Twelve months after PFO closure, both imaging techniques were repeated in 61 patients with contrast application. To determine provokable atrial right-to-left shunting in CMRI, we applied a contrast-enhanced perfusion imaging technique. Detection of atrial septal aneurysm (ASA) was achieved by means of a high-resolution cine imaging technique.

RESULTS
Before PFO closure, ASA was seen with CMRI in 28 of 75 cases (37.3%), compared with 47 of 75 (62.7%) cases using TEE. There were a total of 211 CMRI studies with a corresponding TEE performed in 75 patients. No shunt was present in 107 of 211 studies with both techniques. Contrast-enhanced right-to-left shunting was detected by CMRI in 48 of 72 (66.6%) cases with moderate or severe shunts seen with TEE, but only in 6 of 32 (18.8%) studies with mild shunts with TEE. Anomalous venous returns were excluded in all patients. In two patients, coronary anomalies were seen.

CONCLUSIONS
The present CMRI technique is inferior to TEE in detection of contrast-enhanced right-to-left shunting and identification of ASA. (J Am Coll Cardiol 2006;48:322–9) © 2006 by the American College of Cardiology Foundation

In clinical routine, the diagnosis of patent foramen ovale (PFO) in patients with cryptogenic ischemic events and follow-up evaluation after closure by transcatheter device implantation is performed with transesophageal echocardiography (TEE). Cardiac magnetic resonance imaging (CMRI) is a powerful noninvasive diagnostic tool providing detailed information on cardiac anatomy and function and on hemodynamic values in patients with structural heart disease (1). Magnetic resonance imaging after transcatheter closure of PFO is feasible and enables evaluation of patients after interventional closure with a noninvasive imaging modality (2). Recently, in a small population of 20 patients, a 100% concordance with CMRI and TEE in detection of PFO and atrial septal aneurysm (ASA) was reported (3). The value of CMRI compared with TEE in patients undergoing transcatheter PFO closure has not been addressed so far.

METHODS
Patients. Between May 2001 and April 2004, 75 patients with transcatheter closure of PFO attributable to a cryptogenic ischemic event were studied by CMRI before and after PFO closure. If all other possible causes for an ischemic event, such as atherosclerotic plaques or stenoses of the carotid or vertebral arteries, aortal plaques, cardiac arrhythmias, prothrombotic coagulation disorders, and cardiac thrombi, were excluded, the ischemic event was classified as cryptogenic. All patients underwent a workup with 12-lead electrocardiography, Holter monitoring, Doppler sonography, transthoracic echocardiography, TEE, and coagulation blood tests. All patients were in sinus rhythm, and there was no indication for oral anticoagulation because of other disorders. The study was approved by the local ethics committee. All patients gave their written informed consent for the PFO closure as well as TEE and CMRI studies.

TEE. The TEE was performed with a multiplane phased array 4- to 7-MHz TEE probe on an ATL HDI 5000 CV (Philips Medical Systems, Best, the Netherlands). For contrast enhancement we administered repeatedly 10 ml of agitated hydroxyethyl starch solution into an antecubital vein with the patient performing a proper Valsalva maneuver (4). Provocable right-to-left shunt was graded according to the amount of bubbles crossing the interatrial septum: no shunt = 0, mild shunt = 1 to 9 bubbles, moderate shunt = 10 to 20 bubbles, and severe shunt >20 bubbles or opacified left atrium because of bright contrast. An ASA was defined as an excursion of the atrial septum >10 mm (5).
Magnetic resonance imaging. The CMRI was performed on a 1.5-T Intera CV whole-body MR Scanner (Philips Medical Systems). The scanner was equipped with a high-performance gradient system, providing a maximal gradient strength of 30 mT/m and a maximal slew rate of 150 mT/ms. All data were acquired using a dedicated five-element cardiac phased-array coil.

To determine left and right ventricular function, a retrospective electrocardiography-gated segmented k-space balanced turbo-field echo sequence (steady-state free precession [SSFP]) without view sharing was used in short-axis and long-axis views along the true heart axis. Depending on the required field of view, the spatial resolution was between $1.7 \times 1.7$ mm and $2.3 \times 1.8$ mm in-plane, with a slice thickness of 10 mm. Echo time TE and repetition time TR were chosen as $TE = 1.7$ ms and $TR = 3.4$ ms. The RR interval was separated into 32 equidistant phases, which resulted into an effective temporal resolution of $TRR/32$ ms per image, with $TRR$ being the average RR cycle length in milliseconds.

The atrial septum was scanned using similar short-axis cine images with a higher spatial resolution ($1.5 \times 1.7$ mm in-plane), 8-mm slice thickness, and 39 phases per RR cycle, resulting in an effective temporal resolution of $TRR/39$ ms. The membranous part and total atrial septum were measured in short-axis and long-axis views. The ASA in CMRI was defined as the maximal extent of oscillation of the atrial septum $> 10$ mm based on the definition of ASA in TEE (5).

To determine provokable atrial right-to-left shunting in CMRI, we performed two contrast-enhanced sequences in a short-axis view and a long-axis four-chamber view, chosen from the localization of the fossa ovalis in the cine studies. In all patients we used continuous perfusion imaging applying a SSFP sequence. To improve the contrast agent sensitivity of the sequence, a selective saturation recovery prepulse (delay 115 ms to k-space center coverage) was applied before the acquisition of each image. Image acquisition parameters were: repetition time $TR = 2.8$ ms, echo time $TE = 1.4$ ms, slice thickness 10 mm, matrix $176 \times 256$, in-plane-resolution $2.1 \times 2.6$ mm, and a reconstructed voxel size of $1.48 \times 1.48 \times 10$ mm. Further increase of the temporal resolution was achieved by parallel imaging techniques with a reduction factor of 2, by restriction of the data acquisition to the central 80% of k-space, and by using an 85% rectangular field of view. The acquisition time of a single image was 168 ms, which, in combination with the saturation prepulse, yielded an overall acquisition time of 200 ms per image. During visualization of the bolus, imaging was performed continuously at a frame rate of five images per second. A bolus of 0.1 mmol/kg body weight gadolinium-diyethyletriaminepentaacetate (Gd-DTPA) (Magnevist, Schering AG, Berlin, Germany) was injected into an antecubital vein by a power injector (Medrad Spectris, Volkach, Germany) at a rate of 4 ml/s flushed with 20 ml saline while patients performed a Valsalva maneuver identical to the TEE procedure. Two independent reviewers performed all analyses regarding assessment of contrast-enhanced right-to-left shunting. If both reviewers disagreed, a third reviewer was consulted and discussion was performed until consensus was achieved. All reviewers were blinded to the TEE data. Patients were classified to have a contrast-enhanced right-to-left shunt if there was a clear contrast passage seen in the perfusion scans and/or there was a clear peak in the left atrium at the same time as the peak in the right atrium was visible in the time-intensity curves (Fig. 1). The regions of interest were placed in the left atrium close to the atrial septum and in the right atrium and were manually fitted to every image.

Flow measurements in the main pulmonary artery and ascending aorta were performed by means of a conventional phase contrast technique retrospective gating with free breathing (field of view 300 mm, slice thickness 6 mm). Left and right ventricular function and volumetry as well as quantification of flow measurements were carried out on an EasyVision workstation (Philips Medical Systems). We carefully performed shunt quantification according to the method described in detail by Araoz et al. (6) using left and right ventricular volumetry as well as flow measurements. Cutoff for detectable shunts by CMRI was set to $\geq 5\%$ of cardiac output. For detection of pulmonary veins, we performed an electrocardiography-gated transversal stack of T2-weighted turbo spin echo sequences with a black-blood prepulse and a slice thickness of 5 mm (6).

PFO closure. The Cardia Star (Cardia, Inc., Burnsville, Minnesota) closure device was implanted in the catheter laboratory under fluoroscopic and TEE guidance as described by Braun (7). Procedures were performed in local anesthesia and facultative sedation with midazolam and propofol. After implantation of the device, contrast-enhanced TEE was performed to detect residual right-to-left shunting. All patients received a combined antiplatelet therapy with 100 mg acetylsalicylic acid and 75 mg clopidogrel per day for 6 months. For prophylaxis of endocarditis, cephazolin 2 g before the intervention and 6 h after closure were administered.

Follow-up. Patients were scheduled for clinical and TEE control 3 months after PFO closure. The CMRI and TEE were performed on the same day 12 months after device implantation.

Statistics. Data were analyzed using a chi-square test. To compare differences between means, the Student $t$ tests were applied. The Bonferroni correction was used to account for
type I error caused by multiple testing. Statistical analysis was done with Statistica version 6.0 (StatSoft Inc., Tulsa, Oklahoma). Values of \( p < 0.05 \) were considered statistically significant.

RESULTS

Patients. All patients had experienced cryptogenic ischemic events. Baseline characteristics are shown in Table 1. The CMRI was performed at a median of 1 day before (range 0 to 89 days) and 1 day after (range 0 to 13 days) PFO closure and was repeated in 64 (85.3%) patients after a median of 360 days (range 237 to 441 days). All patients received TEE before and after PFO closure. The TEE was repeated after 3 months in 73 (97.3%) patients and after 12 months in 63 (84%) patients. Three patients received only CMRI at 12-month follow-up refusing TEE. Two patients received only TEE at 12-month follow-up, refusing CMRI examination. A total of 66 of 75 patients received at least one imaging technique at 12-month follow-up. One patient underwent open-heart surgery. The remaining 8 patients received scheduled TEE control 3 months after device implantation but refused imaging evaluation at 12-month follow-up because of a clinically asymptomatic course.

TEE versus CMRI. Separation of septum primum and septum secundum was detected in all patients with TEE compared with 56 of 75 (74.7%) patients with CMRI (\( p < 0.0001 \)). An ASA was seen with CMRI in 28 of 75 (37.3%) patients compared with 62.7% (47 of 75) with TEE (\( p = 0.0019 \)). Figure 2 shows a series of SSFP sequences in a patient with PFO and ASA. Cine sequences showed a clear contrast-enhanced right-to-left shunt and ASA before closure. The corresponding time-intensity curves are shown in Figure 1 (for perfusion sequences and four-chamber view cine sequences before PFO closure and at 12 months, see Online Video 1 to 4). There was no multiple perforated atrial septum or additional atrial septal defect. Detection of PFO by contrast-enhanced right-to-left shunting during

![Figure 1](image-url)
Valsalva maneuver significantly differed between both imaging methods. Based on our inclusion criteria, all 75 patients had contrast-enhanced right-to-left shunting via PFO in TEE. In contrast, before intervention CMRI showed evidence of a provable right-to-left shunt in only 48 of 75 (64.0%) patients \( (p < 0.0001) \).

To exclude a potential clinical learning curve, we divided our study population into three equal subgroups (25 patients each). The first subgroup represents the patients recruited during the first 12.5 months of the inclusion period, the second subgroup consists of the patients included during the following 12.5 months, and the third subgroup is the patients recruited within the last 10 months. The CMRI showed contrast-enhanced right-to-left shunting in the first subgroup in 17 of 25 (68%) patients, in the second subgroup in 13 of 25 (52%) patients, and in the third subgroup in 18 of 25 (72%) of patients.

After PFO closure, residual contrast-enhanced right-to-left shunting was seen in 25.3% of patients (19 of 75) with TEE and in 6.7% of patients (5 of 75) with CMRI \( (p < 0.002) \). Both imaging techniques with contrast application were performed in 61 patients at follow-up. In these patients, a residual contrast-enhanced shunt was seen with TEE in 16.4% (10 of 61) and with CMRI in 1.6% (1 of 61; \( p < 0.0044 \)). The time course of residual contrast-enhanced right-to-left shunting seen with TEE is detailed in Figure 3.

There were a total of 211 CMRI investigations with their corresponding TEE before intervention, after intervention, or at 12-month follow-up with contrast application to assess

Figure 2. A series of steady-state free-precession sequences in a patient with patent foramen ovale and atrial septal aneurysm. (A) A four-chamber view and (B) a short-axis view before interventional closure. The two arrows indicate the separated atrial septum. The same patient at 12-month follow-up after transcatheter closure in (C) a four-chamber view and (D) a short-axis view. The arrows point at the closure device (for cine sequences, see Online Videos 1 to 4).
right-to-left shunting during Valsalva maneuver. In these 211 studies, TEE showed moderate or severe shunts in 72 studies and mild shunts in 32 studies. The CMRI detected 48 of 72 (66.6%) of these moderate or severe shunts seen with TEE, but only 6 of 32 (18.8%) of the mild shunts. No contrast-enhanced shunt was present in 107 cases with both imaging modalities.

**CMRI.** A visible left-to-right jet with CMRI cine sequences without contrast agent was only present in 2 of 75 (2.7%) patients before PFO closure. On flow measurements, aortic cardiac output was $5.7 \pm 1.1 \text{ l/min}$, pulmonary cardiac output was $5.9 \pm 1.1 \text{ l/min}$, aortic stroke volume was $86 \pm 17 \text{ ml}$, and pulmonary stroke volume was $88 \pm 17 \text{ ml}$. By careful shunt quantification, we were able to calculate systemic shunts before intervention in 18 of 75 (24.0%) patients with a mean shunt fraction of $7.6 \pm 2.3\%$ (range 5.0% to 13.0%) of cardiac output. We attributed this shunt fraction to the PFO because anomalous pulmonary venous return could be excluded in all patients by CMRI and TEE, and no evidence for other systemic intracardiac shunts was seen, neither with CMRI nor with TEE. After PFO closure, only in one patient did a 10.0% continuous shunt remain, disappearing until 12-month follow-up.

In two patients we assumed an anomalous origin of a coronary artery in the transversal stack of black-blood images. For a better assessment, we performed additional scans using targeted SSFP sequences for visualization of coronary arteries in CMRI and confirmed the anomalous origin by cardiac catheterization. One patient had a separate origin of the dominant right coronary artery next to the left sinus of Valsalva. In the other patient, the left main coronary artery arose from the right sinus of Valsalva with an interarterial course between the aorta and the pulmonary main vessel. Neither patient suffered from ischemic heart disease.

In CMRI, total atrial septum measured $46.6 \pm 8.8 \text{ mm}$ in four-chamber view and $41.0 \pm 8.6 \text{ mm}$ in short-axis view. The membranous portion measured $21.8 \pm 6.5 \text{ mm}$ in four-chamber view and $22.6 \pm 6.5 \text{ mm}$ in short-axis view. There was no statistical difference in hemodynamic values, left and right ventricular parameters between CMRI before PFO closure, and at 12-month follow-up (Table 2; 11 comparisons included in the Bonferroni adjustment). Subgroup analysis of patients with systemic shunts before

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<th>Table 2. Hemodynamic Values, Right and Left Ventricular Parameters Assessed by Cardiac Magnetic Resonance Imaging</th>
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<td><strong>n = 64</strong></td>
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Measurements are mean ± standard deviation.

CI = cardiac index; CO = cardiac output; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVESVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVI = left ventricular end-systolic volume index; PFO = patent foramen ovale; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume.
intervention also showed no change in these parameters at 12-month follow-up. The CMRI showed further information in two patients with severe complications during follow-up. Both complications were also visible in TEE. One patient underwent open-heart surgery for a dislocated spoke of the closure device that nearly perforated the aortic root (see Online Video 5). Another asymptomatic patient showed a new 60/80-mm structure cranial and lateral to the right atrium at 3-month control (Fig. 4). There was no contrast enhancement with any evidence of central perfusion, suggesting a large paracardial hematoma. At 25-month follow-up, the structure had totally dissolved. Both patients recovered completely without long-term sequelae.

DISCUSSION

This is the first large study to assess the value of CMRI in the detection of PFO and ASA in patients with transcatheter closure of PFO. In comparison with TEE, contrast-enhanced right-to-left shunting was detected significantly less frequent with CMRI. An ASA was significantly more frequently detected with TEE compared with CMRI before PFO closure. The CMRI revealed additional information on the size of left atrium, atrial septum, left and right ventricular parameters, and hemodynamic values. Anomalous venous return could be excluded in all patients with CMRI.

PFO. We included 75 patients with a total of 211 CMRI investigations. For each CMRI study, we performed its corresponding TEE study to detect contrast-enhanced right-to-left shunting. The CMRI is clearly inferior to TEE in the detection of contrast-enhanced right-to-left shunting. A mild shunt seen in TEE was detected with CMRI only in 19% of cases. Moderate or severe shunts with TEE were seen in 67% of cases with CMRI. Especially at follow-up after PFO closure, TEE revealed no moderate or severe shunts, limiting the diagnostic impact of CMRI. These results are probably based on a lower spatial and temporal resolution of CMRI perfusion sequences compared with TEE. The volumetric and hemodynamic data,
which were in the normal range for patients without structural heart disease (8), confirms our inclusion criteria of which were in the normal range for patients without cardiac anomalies.

There is only one other trial dealing with the detection of PFO with CMRI compared with TEE (3), showing a 100% concordance in the detection of PFO between both imaging techniques. This apparently perfect equivalence was based on only 20 corresponding CMRI and TEE studies, whereas our trial is based on 211 corresponding CMRI and TEE analyses performed in 75 patients. To detect a contrast-enhanced right-to-left shunt in patients with PFO, it is crucial to perform a proper Valsalva maneuver (4). We paid great attention to performing a proper Valsalva maneuver with the patient being in the MRI scanner. To do so, it is indispensable to precisely find the point in time at which the contrast agent reaches the right atrium to release the Valsalva maneuver. The pressure in the right atrium exceeds the pressure in the left atrium just after release of the Valsalva maneuver. There will be no detectable right-to-left shunt if the Valsalva maneuver is released too early, because the right atrium is not yet filled by the contrast agent. If the Valsalva maneuver is released too late, then the contrast agent filling the left atrium is already inflowing from the pulmonary veins (normal pulmonary circulation time, 4 to 6 s). Hence, there must be an acceptable temporal resolution to perform a proper Valsalva maneuver. We were able to attain a temporal resolution of 200 ms resulting in a frame rate of 5 images/s compared with Mohrs et al. (3) with 832 ms acquiring only one image every heartbeat. We did not compare the signal-time curves in the left atrium to that in the pulmonary vein as done by Mohrs et al. (3) because there are four pulmonary veins with differences in blood flow causing differences in contrast enhancement depending on which pulmonary vein is visualized. Mohrs et al. (3) did not optimize the axis of the perfusion sequences with respect to the localization of the pulmonary veins as the imaging technique was optimized for PFO. In case that the left atrium has already been contrasted because of a faster occurrence via the nonvisualized pulmonary veins, their results could be biased when finding the perfect correlation between TEE and CMRI. This could be an explanation of their results in patients with grade 1 or 2 shunts with TEE. Three of these five patients showed a higher PFO grade with CMRI compared with TEE. Indeed, there was one patient with a grade 1 shunt with TEE (3 to 9 bubbles) showing a grade 3 shunt with CMRI defined by a bright contrast enhancement in the left atrium before the contrast agent reached the pulmonary veins. The influence of their results by detection of contrast in the left atrium because of contrast filling via nonvisualized pulmonary veins is supported by their own data (3). In two patients of that control group with no PFO with TEE, the time to peak in the pulmonary veins was longer than the time to peak in the left atrium. Because PFO was excluded by TEE, the faster contrast filling of the left atrium before contrast filling of the pulmonary vein can only be explained by a more rapid filling of the left atrium via nonvisualized pulmonary veins.

ASA. The TEE allows continuous visual interpretation of the atrial septum with detection of ASA in 63% of our patients. In contrast, CMRI revealed ASA in 37% of patients. We used the best technique in both imaging studies to get the clinically important information on the presence or absence of an ASA. These techniques include Valsalva maneuver in TEE but not in CMRI studies. The performance of a Valsalva maneuver is basically possible with CMRI. However, the maximal oscillation of the atrial septum occurs after release of the Valsalva maneuver. To capture this extremely short moment, a high temporal resolution is necessary, and to visualize the atrial septum, a high spatial resolution is necessary. Real-time CMRI could provide the temporal but not the spatial resolution to visualize the oscillation of the atrial septum. High-resolution cine sequences provide the spatial resolution but are hampered by the acquisition over several heartbeat cycles and therefore do not allow one to detail the very short period of time after release of the Valsalva maneuver. Furthermore, in TEE studies the atrial septum was scanned in multiple planes, allowing selection of the maximal extent of oscillation, whereas in CMRI at first the atrial septum was scanned, and after image acquisition the maximal extent of oscillation was measured. There may be an advantage for CMRI in patients not tolerating the TEE probe with the subsequent need for deep sedation, which prevents the performance of a proper Valsalva maneuver. Nevertheless, this is an important limitation of CMRI because PFO with ASA is at present considered to be associated with a high risk for recurrent ischemic events (9,10).

Systemic shunts. The CMRI is the best technique for quantification of continuous systemic shunts (6,11). The TEE studies with color Doppler have shown continuous blood flow via the PFO shunting from the right to the left atrium and vice versa. We investigated whether in patients with PFO systemic shunts were measurable using CMRI. In patients with PFO we detected a continuous systemic shunt in 24% of patients, with a mean shunt fraction of 7.6%. Follow-up CMRI showed complete disappearance of these continuous shunts after successful transcatheter closure of PFO. These continuous systemic shunts are unlikely to have any relevant hemodynamic impact because our volumetric and hemodynamic data were within the normal range and did not change during follow-up.

Cardiac anomalies. According to present guidelines, CMRI is indicated to detect anomalous venous returns (12), which are often associated with atrial septal defects. The frequency of an association with PFO is generally not evaluated. The detection of an anomalous venous return in combination with a PFO after a cryptogenic ischemic event may favor surgical treatment. The CMRI is superior to X-ray angiography or transthoracic echocardiography in detection of anomalous venous returns (13). The assessment of pulmonary veins with modern multiplane TEE is more
Conclusions. We were able to detect four pulmonary veins returning to the left atrium in all 75 patients with both imaging modalities and equated this information with the exclusion of an anomalous venous return. Moreover, the absence of a measurable shunt after PFO closure excludes a significant accessory pulmonary vein.

In addition, due to all imaging acquisitions we assumed an anomalous origin of a coronary artery in 2 of our 75 patients. To confirm this diagnosis, we performed additional scans in these two patients using targeted SSFP sequences for visualization of coronary arteries in CMRI and confirmed these anomalies by cardiac catheterization. Usually PFO closure is performed without coronary angiography. The detection of an anomalous origin of coronary arteries with CMRI may be important because compression of the circumflex artery with an anomalous origin from the right coronary sinus after device closure of PFO has been described (15).

With CMRI we were able to gain additional information in both patients with severe complications. The two umbrellas of the occluder are expanded by nitinol wires. Although periprocedural TEE and fluoroscopy showed a correct position of both occluders during the implantation procedure, the stress of the nitinol wires on the atrial wall during cardiac contraction may have induced perforation of the atrium.

Study limitations. The study included patients with PFO and contrast-enhanced right-to-left shunting with TEE and indication for transcatheter PFO closure because of cryptogenic ischemic events. These inclusion criteria limit the potential value of CMRI because only patients with a positive TEE were included. We did not perform contrast-enhanced magnetic resonance angiography to exclude anomalous pulmonary venous returns, which would be superior to black-blood MRI, especially in detection of an accessory pulmonary vein. Nevertheless, the lack of left-to-right shunting after PFO closure can be used to exclude any significant shunt attributable to an accessory pulmonary vein.

Conclusions. The present CMRI technique is inferior to TEE in the detection of contrast-enhanced right-to-left shunting during Valsalva maneuver and identification of ASAs.

REFERENCES


APPENDIX

For accompanying videos, please see the online version of this article.