A Modified Anatomical-Functional-RoPE (AF-RoPE) Score Improves Patient Selection for Patent Foramen Ovale Closure

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Introduction
Although recent trials [1] and meta-analysis about transcatheter closure of patent foramen ovale (PFO) [2-7] have suggested that PFO closure is both an effective and cost-effective treatment for recurrent embolic stroke, the management of patients with symptomatic PFO is not yet completely clarified. Recently, the RoPE score calculator has been proposed [8] in order to stratify the patients in whom PFO may be considered not a confounding but presumably a causative factor. This score is mainly based on clinical criteria and it doesn’t include any anatomical or functional characteristics, such as permanent and/or large shunt, presence of atrial septum aneurysm (ASA) and long tunnelized PFO. Moreover, these PFO structural aspects have already been considered for both patient selection and clinical decision making.

Highlights
Background
The RoPE score calculator has been suggested to stratify patients in whom the patent foramen ovale (PFO) should be considered a causative factor for stroke.

Methods
We reviewed the medical and instrumental data of 1040 consecutive patients (mean age 47.3±17.1 years, females) prospectively enrolled in two centres over a 13 year period for management of PFO in order to select anatomic and functional parameters to be incorporated in a modified RoPE score. A scoring system (AF-RoPE) was built up and applied in a prospective blinded fashion to a cohort of 406 consecutive patients (mean age 43.6 ±17.5 years, 264 females) with cryptogenic stroke and PFO, comparing its performance with the standard RoPE.

Results
Multiple stepwise logistic regression analysis demonstrated that right-to-left (R-L) shunt at rest (OR 5.9), huge ASA (> 20 mm) (OR 3.9), long tunnelized PFO (> 12 mm) (OR 3.5), and massive R-L shunt (grade 5 by TCD) (OR 1.9) conferred the highest risk of recurrent stroke. The AF-RoPE score resulted in a more precise separation of patients with RoPE score 8-10. Patients with AF-RoPE score >11 had more stroke recurrences and more diffuse area of stroke on MRI in the medical history than those ranging from 10 to 7 or less (85.2 and 68.5 % respectively, p <0.01).

Conclusions
The AF-RoPE score discriminates cryptogenic stroke patients who are more likely to develop recurrent stroke compared with a RoPE score between 8-10. These highest risk patients may be more likely to benefit from PFO closure.

Keywords: patent foramen ovale; echocardiography; stroke; anatomy.

Citation:
process towards device-based closure or medical therapy. Our study assessed the potential role of a modified anatomic-functional RoPE score in guiding selection of patients with cryptogenic stroke (CS) for device closure or medical therapy.

Methods
We reviewed the medical and instrumental data of 1040 consecutive patients (mean age 47.3±17.1 years, 992 females) prospectively enrolled in two secondary referral centre registries, the Department of Cardiovascular Disease, Cittadella General Hospital, Padua, Italy, and the Cardiovascular Diagnostics and Endoluminal Interventions Unit, Rovigo General Hospital, Rovigo, Italy, over a 13 year period (February 1999 to February 2012) to select both anatomical and functional parameters that could be incorporated into a modified RoPE score. The same institutional protocol was used in both centres and all patients were screened with Transcranial Doppler (TDC) and transesophageal echocardiography (TEE) before any therapeutic decision. Patients records were reviewed for demographic, classic cardiovascular risk factors, clinical history, neuroimaging findings, TCD, transesophageal and intracardiac echocardiographic studies, in order to retrieve anatomical and functional characteristics of increased risk for recurrent paradoxical embolism. A score was developed and applied in a prospective blinded fashion to a cohort of 406 consecutive patients (mean age 43.6 ±17.5 years, 264 females, table 2) referred to the Cardiovascular Diagnosis and Endoluminal Interventions Unit, Rovigo General Hospital, Rovigo, Italy for management of cryptogenic stroke and PFO in the last 3 years, from February 2013 to February 2016. A comparison between the standard RoPE and the modified AF-RoPE score applied to the same population was performed. The study protocol was in accordance with ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee.

Echocardiography protocols
Transesophageal echocardiography
TEE was performed using a GE Vivid 7 (General Electric Corp., Norfolk, VI, USA) with contrast injection and Valsalva manoeuvre under local anaesthesia. Right-to-left shunting was defined as permanent, small, medium, and large following Homma et al[9], whereas PFO diameter was assessed measuring with an electronic caliper the maximum opening of the PFO in the end-diastolic frames[10]. Presence and severity of ASA were classified according to Olivares et al [11]. Long tunnel-type patent foramen ovale was defined as length >10 mm by intracardiac echocardiogram.

Transcranial Doppler
Transcranial Doppler was performed using an intravenous bubble study by an experienced neurologist, according to current standards [11] and using a Transcranial Doppler monitoring device (DWL, MultidopX, ScanMed Medical, UK). Both MCAs were simultaneously monitored through the temporal window by the use of 2-MHz probes. The contrast was obtained by mixing 100 cc of saline solution with 2-3 cc of Emagel and loading a 10 cc syringe with this mixture. The solution, agitated between two 10-cc syringes, connected by a 3-way stopcock, was immediately injected with a 20-gauge/32-mm catheter placed in the antecubital vein to obtain a bolus of air microbubbles. This procedure was performed 3 times during normal breathing and the same number of times during a Valsalva manoeuvre. The bolus of microbubbles was injected in 1 to 2 seconds when this 7-second period ended. We quantified the importance of right-to-left shunt by counting the number of signals in one mean cerebral artery within 7 seconds of the injection, as previously reported [13-14]: mild (<10 bubbles within three cardiac cycles), moderate (> 10 bubbles within three cardiac cycles) with shower effect (many bubbles but still countable), severe (> 10 bubbles within three cardiac cycles) with curtain effect (many bubbles but not countable). A distinct pattern of shunt occurs when bubbles are identifiable before the valsalva manoeuvre (basal or permanent shunt).

All the TEE and TDC studies were reviewed and analysed by two independent observers with extensive experience in echocardiography with an inter-observer agreement of 99.8%.

Statistical Methods
Chi-square, Student-t, and ANOVA tests were used to compare frequencies and continuous variables among groups. Stepwise logistic regression analysis was used to determine independent determinants of recurrent paradoxical embolism before closure. The analyzed variables were presence and grade of atrial septal aneurysm (ASA), presence of Eutachian valve (EV)/Chiari Network (CN) (EV/CN), permanent shunt on TCD and shunt grade on TEE. Correlation coefficient was employed to establish correlation between anatomical variables. Statistical analysis was performed using a statistical software package (SAS for Windows, version 8.2; SAS Institute; Cary, NC). A probability value of < 0.05 was considered to be statistically significant.

Results
Demographic and clinical data of the population enrolled is presented in Table 1. Multiple stepwise logistic regression analysis of considered anatomo-functional variables demonstrated that permanent right-to-left (R-L) shunt (OR 5.9, 1.8- 11 [95% CI], p < 0.001), ASA 3-5 LR or LR following Olivares et al classification (OR 3.9, 0.5- 8 [95% CI], p < 0.001), tunnel-like PFO (OR 3.5, 0.8- 6 [95% CI], p < 0.001), and curtain R-L shunt on TCD (OR 1.9, 0.3- 4 [95% CI], p < 0.001) conferred the highest risk of recurrent stroke. Assimilating for simplicity the scoring system of the RoPE score following the scheme (Table 3), 2 points was arbitrarily given to each of: permanent shunt, ASA 3 to 5 LR or LR, and tunnel-like PFO. One point was given to curtain R-L shunt (Figure 1, Panel B).

Figure 1. Panel A: Histograms representation of the comparison between 7,8-10and >11 AF-RoPE score about as multiple lesion on cerebral MRI and clinical stroke recurrences (see Table 4 for p-values). Panel B: AF-RoPE score composition.
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Discussion
Figure 1, Panel A.
68.5 %, respectively, p <0.01) as showed in Table 3 and 4 and
in the medical history than those ranging 10 to 7 or less (85.2 and
more stroke recurrences and more severe cerebral neuroimaging
standard RoPE score. Patients with AF-RoPE score > 11 had
selection of patients for transcatheter repair compared to the
disaggregation of patients with stroke and PFO, adding an
Functional RoPE score (AF-RoPE) resulted in a more precise
Applied on the prospective cohort, the modified Anatomo-
Variables
Table 1. Demographic and clinical data.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean or No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retrospective 1040 pts</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±10.9</td>
</tr>
<tr>
<td>Female</td>
<td>710 (68.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>630 (60.6%)</td>
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<tr>
<td>High blood pressure</td>
<td>312 (30.0%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>268 (25.7%)</td>
</tr>
<tr>
<td>Oral contraception</td>
<td>214 (20.6%)</td>
</tr>
<tr>
<td>Deficiency of anti-thrombin III, C, S</td>
<td>28 (2.7%)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>16 (1.5%)</td>
</tr>
<tr>
<td>Mutation MTHFR (homozygote)</td>
<td>258 (24.8%)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>112 (10.8%)</td>
</tr>
<tr>
<td>Antiphospholipid or antcardiolipin antibodies</td>
<td>24 (2.3%)</td>
</tr>
<tr>
<td>Patent foramen ovale mean diameter (mm)*</td>
<td>8.9±2.5</td>
</tr>
<tr>
<td>ASA &gt;3</td>
<td>200 (19.2%)</td>
</tr>
<tr>
<td>Permanent shunt on Transcranial Doppler</td>
<td>354 (34.0)</td>
</tr>
<tr>
<td>Shower Shunt pattern on Transcranial Doppler</td>
<td>462 (44.4%)</td>
</tr>
<tr>
<td>Curtain Shunt pattern on Transcranial Doppler</td>
<td>578 (55.6%)</td>
</tr>
<tr>
<td>Medium Shunt *</td>
<td>360 (34.0%)</td>
</tr>
<tr>
<td>Large Shunt*</td>
<td>680 (65.4%)</td>
</tr>
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</table>

Table 2. Distribution of RoPE score and AF-RoPE score in the prospective cohort of patients (n° of patients/%).
<table>
<thead>
<tr>
<th>Score</th>
<th>0-4</th>
<th>5-7</th>
<th>8-10</th>
<th>11-13</th>
<th>14-16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>RoPE</td>
<td>104/406 (25.6)</td>
<td>132/406 (32.5)</td>
<td>170/406 (41.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF-RoPE</td>
<td>106/406 (26.1)</td>
<td>130/406 (32.2)</td>
<td>62/406 (15.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.9</td>
<td>0.9</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3. Distribution of clinical variables in the prospective study population (number or %) depending on AF-RoPE score

Table 4. Distribution of AF-RoPE score in the prospective cohort of patients (n° of patients/%).
<table>
<thead>
<tr>
<th>Score</th>
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<td>-</td>
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<td>-</td>
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Applied on the prospective cohort, the modified Anatomo-
Functional RoPE score (AF-RoPE) resulted in a more precise
disaggregation of patients with stroke and PFO, adding an
anatomo-functional value which possibly better guided the
selection of patients for transcatheter repair compared to the
standard RoPE score. Patients with AF-RoPE score > 11 had
more stroke recurrences and more severe cerebral neuroimaging
in the medical history than those ranging 10 to 7 or less (85.2 and
68.5 %, respectively, p <0.01) as showed in Table 3 and 4 and
Figure 1, Panel A.

Discussion
Our small study suggests that the simple addition of few
anatomo-functional variables to the RoPE score may improve
its usefulness, facilitating the clinical decision-making process in
patients with PFO and CS, in order to expedite the identification of patients who can benefit from transcatheter PFO closure.
Moreover, it confirms previous studies which suggested the
relationships of permanent shunt, large ASA, tunnel-like anatomy,
and high grade shunt and risk of stroke recurrence [15-16].

While the relationships between PFO and paradoxical embolism has been well known since the 18th century, the demonstration of
a true increasing of risk of paradoxical embolism into the brain in patients with PFO is still controversial. Many reasons have been
claimed as confounding factors in the design and enrollment process of past negative or inconsistent trials [17-18], or of
some more recent studies such as the CODICIA study [19], the
TACET study [20], and the PC trial [21] which again suggested a
poor relationship between PFO and stroke and a poor protective
effect of closure. Fortunately, recently the RESPECT trial [1]
and its extended results [22] seem to give some more insights to
the view considering PFO closure an effective and protective
procedure. Despite the raw count the intent-to treat results showed a non-significant difference between the two arms, the
per-protocol and the as treated analysis demonstrated for the first time a reduction of recurrence of stroke of 63.4 and 72.7% with
a immediate, procedural and effective closure rate very
high at >93%. The analysis of the number needed to treat (NNT)
demonstrated that 24 patients would need to be treated with the
device in order to prevent 1 stroke over a 5-year period of time.
The extended results enhanced even more this trend in favour of transcatheter closure. Although the results are not widely
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RoPE score has been showed to successfully disaggregate stroke patients into a stratum with a PFO prevalence that matches the background population (23% RoPE score 0-3), which increases in a linear fashion to the highest RoPE scores with a very high prevalence of PFO (73% RoPE score 9-10). While it is surely useful for an initial stratification of patients with PFO and stroke, it seems less adequate for helping in the practical selection of patients to submit to device-closure therapy. Our study suggests that the AF-RoPE score is able to stratify with better accuracy the patients with RoPE score ranging from 8 to 10, those in whom the AF-RoPE score is able to stratify with better accuracy the population studies are needed to fully validate this score in respect of efficacy and long-term outcomes.

declaration of Interest

The authors declare no conflicts of interest.

Acknowledgements

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [23].

References