International Journal of Cardiology 153 (2011) 4–9

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Does patent foramen ovale closure have an anti-arrhythmic effect? A meta-analysis ☆

Omar A. Jarral [a], Srdjan Saso [a,*], Joshua A. Vecht [a], Leanne Harling [a], Christopher Rao [a], Kamran Ahmed [a], Michael A. Gatzoulis [b], Iqbal S. Malik [c], Thanos Athanasiou [d]

[a] Surgical Epidemiology Unit, Department of Biosurgery and Surgical Technology, Imperial College London, 10th Floor QEQM Building, St Mary's Hospital, London W2 1NY, United Kingdom
[b] Royal Brompton Hospital National Heart and Lung Institute, Imperial College London, Sydney Street, London SW3 6NP, United Kingdom
[c] Cardiovascular Sciences and the Renal Unit, Imperial College Healthcare NHS Trust, London, Hammersmith Hospital Site, Du Cane Road, London W12 0NN, United Kingdom
[d] Department of Cardiothoracic Surgery, National Heart and Lung Institute, Imperial College London, The Hammersmith Hospital, Du Cane Road, London W12 0NN, United Kingdom

ARTICLE INFO

Article history:
Received 25 November 2010
Received in revised form 16 January 2011
Accepted 7 February 2011
Available online 21 March 2011

Keywords:
Patent foramen ovale
Transcatheter closure
Atrial tachyarrhythmia

ABSTRACT

Background: Atrial tachyarrhythmias are associated with patent foramen ovale. The objective was to determine the anti-arrhythmic effect of patent foramen ovale closure on pre-existing atrial tachyarrhythmias.
Methods: Medline, EMBASE, Cochrane Library, and Google Scholar databases were searched between 1967 and 2010. The search was expanded using the 'related articles' function and reference lists of key studies. All studies reporting pre- and post-closure incidence (or prevalence) of atrial tachyarrhythmia in the same patient population were included. Random and fixed effect meta-analyses were used to aggregate the data.
Results: Six studies were identified including 2570 patients who underwent percutaneous closure. Atrial fibrillation was in fact the only AT reported in all studies. Meta-analysis using a fixed effects model demonstrated a significant reduction in the prevalence of atrial fibrillation with an OR of 0.43 (95% CI 0.26–0.71). When using the random-effects model, OR was 0.44 (95% CI 0.18–1.04) with a statistically significant trend demonstrated (test for overall effect: $Z = 1.87$, $p = 0.06$).
Conclusion: Closure of a patent foramen ovale may be associated with reduction in the prevalence of atrial fibrillation.

1. Introduction

Patent foramen ovale (PFO) is a common finding, present in 20–34% of the normal adult population [1] and in up to half of those suffering from cryptogenic stroke [2–6]. In these patients, the association appears more than chance, and may be explained by unknown haematological problems, the presence of atrial arrhythmias, or the presence of thrombus in the PFO tract. However, paradoxical embolism is often considered the main mechanism behind cerebral ischaemia. The management of these patients is aimed towards reducing the risk of recurrent neurological events with antiplatelet therapy, anticoagulation or consideration of percutaneous/surgical closure of the defect.

Even when anticoagulation or antiplatelet therapy is administered, the yearly recurrence rate of neurological events is estimated at between 3.8 and 5.5% [7–10]. Some studies have shown a significant reduction in recurrence associated with transcatheter closure [11–15] and these results, along with the drawbacks of conventional surgery (cardiopulmonary bypass with median sternotomy), have led to increasing numbers of percutaneous closures being performed worldwide. First introduced in the 1970s for atrial septal defects (ASDs), the technique has been demonstrated to be safe and effective in the management of PFO [14–20].

Although atrial tachyarrhythmias (AT) are most commonly associated with ASDs [21], there is also evidence that PFO may lead to 'atrial vulnerability' to arrhythmias [22]. Previous studies have investigated the effect of ASD closure on AT, showing that closure may lead to new AT or eliminate pre-existing AT [23]. A meta-analysis conducted by our own group, comprising twenty six studies and 2786 patients showed that both surgical and percutaneous ASD closures are associated with a reduction in pre-existing AT in the short to medium term [24]. A number of studies have also looked at the development of new-onset AT following percutaneous PFO closure, but no large trials have specifically investigated the effect of PFO closure on patients with pre-existing AT to identify any anti-arrhythmic effect. Any potential reduction in pre-existing AT post PFO closure is beneficial in that it may play a part in the reduction of recurrence of neurological events.

Therefore, the specific aims of the study were to: 1) determine whether PFO closure reduces prevalence of pre-existing AT, 2) determine whether these changes are maintained during the follow-up period.

☆ This work was supported by the National Institute of Health Research Biomedical Research Centre and British Heart Foundation (RG05/009).

* Corresponding author at: Department of Biosurgery and Surgical Technology, 10th Floor, QEQM Wing, St Mary's Hospital, London W2 1NY, United Kingdom. Tel.: +44 208 886 7630.
E-mail address: srdjan.saso@imperial.ac.uk (S. Saso).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.02.027

2. Materials and methods

2.1. Search strategy

A literature search was performed using Medline (PubMed interface), EMBASE, Cochrane Library, and Google Scholar databases for studies up until July 2010 using the search terms described in Appendix A.

The search was widened using reference lists from key articles and the 'related articles' function. Abstracts from The Journal of American Heart Association between 2003 and 2009 were also searched.

2.2. Outcome

The primary outcome of concern was change in prevalence of any form of pre-existing AT (as demonstrated by the above search terms) following PFO closure.

2.3. Inclusion and exclusion criteria

All studies reporting the incidence or prevalence of pre-existing AT before and after PFO closure in an adult population were included. Studies describing interatrial communications other than PFO, those not written in English and those not clearly differentiating between new-onset AT, persistent AT and eliminated AT were excluded.

2.4. Data extraction

Two reviewers (OJ and SS) independently screened papers obtained from the search strategy above for inclusion/exclusion by reading titles and abstracts of the studies. At this stage from the initial 248 papers, 181 were excluded because they were not experimental studies examining outcomes after PFO closure. Two reviewers (OJ and SS) then read the full text of the remaining 67 studies and included trials that met the inclusion criteria listed above (Fig. 1). Results from this were compared and any discrepancies resolved by consensus. The following data was extracted: study design, number of patients, mean age, type of closure/device used, and AT prevalence pre- and post-procedures.

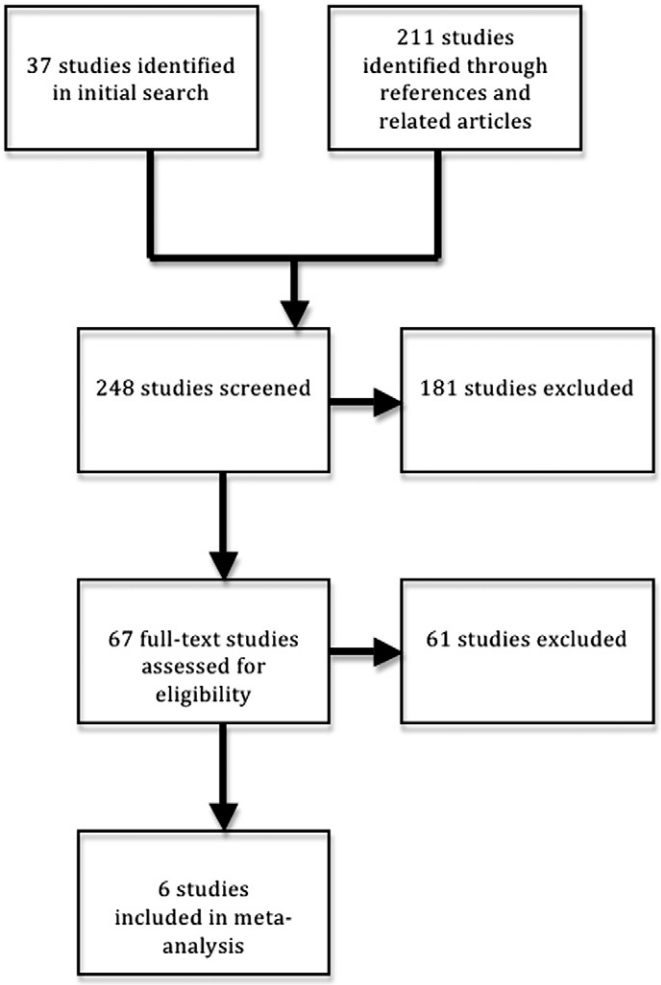

Fig. 1. Search strategy and selection of studies.

2.5. Quality scoring

A quality score was produced for each trial and was split into two sections: variables known to predispose surgical patients to atrial fibrillation (AFIB): age, gender, hypertension, diabetes, ejection fraction, chronic obstructive pulmonary disease and coronary artery disease and variables known to positively affect the incidence of post PFO closure AT in patients with AT: left atrial dilatation, right atrial dilatation, right ventricular dilatation and pulmonary hypertension [25,26]. The distribution of these risk factors is summarised in Table 1 and inclusion/exclusion criteria utilised by the studies are shown in Appendix B.

2.6. Statistical analysis

Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-Analyses guidelines for reporting of meta-analyses [27,28]. For categorical variables, we used odds ratio (OR) as the summary statistic. This ratio represents the odds of an adverse event occurring in the pre-closure group compared with the post-closure group. An OR of less than one favours the post-closure group, and the point estimate of the OR is considered statistically significant at the $p<0.05$ level if the 95% confidence interval (CI) does not include the value one.

Aggregation of the overall rates of the outcomes of interest was performed with the Mantel–Haenszel method [29]. Yate's correction was used for those studies that contained a zero in one cell for the number of events of interest in one of the two groups [29,30]. These 'zero cells' create problems with the computation of ratio measure and its standard error of the treatment effect. This can be resolved by adding the value 0.5 in each cell of the 2×2 table for the study in question, and if there are no events for both pre-closure and post-closure groups, the study should be discarded from the meta-analysis.

In this study, we used both fixed- and random-effect models. In a fixed-effect model, it is assumed that the treatment effect in each study is the same, whereas in a random-effect model it is assumed that there is variation between studies and the calculated OR thus has a more conservative value [31,32].

In the analysis of our results (Figs. 2 and 3), squares indicate point estimates of treatment effect (OR), with the size of the square representing the weight attributed to each study and 95% CI indicated by horizontal bars. The diamond represents the summary OR from the pooled studies with 95% CI.

Three different strategies employing quantitative and graphical comparisons were used to assess heterogeneity. These were:

1. Statistical analysis using random and fixed-effect models.
2. Graphical exploration using funnel plots to evaluate publication bias [33,34]
3. Sensitivity analysis through quality scoring of the study.

To quantify the study quality, we devised a scoring system as described above. We attributed a point to each study when compliant with 11 specified factors (Table 1). This generated a median of 5. The range was then divided into thirds which were scored from 1 to 3. Five studies qualified for the 'top' third ($\geq$5 matched factors) and these studies were analysed separately.

3. Results

3.1. Selected studies

Literature search identified 248 manuscripts. On screening the abstracts 181 were excluded. A further 61 were excluded after full

Table 1
Distribution of risk factors for atrial tachyarrhythmia within patient groups.

Author	A	B	C	D	E	F	G	H	I	J	K	Total matched factors	Study score
Alaeddini et al. [39]	*	*	*	*	*		*	*	*			8	3
Bijl et al. [16]	*	*	*	*			*					5	3
Goel et al. [38]	*	*										2	2
Spies et al. [37]	*	*	*	*			*					5	3
Staubach et al. [36]	*	*	*	*			*					5	3
Taaffe et al. [35]	*	*	*	*			*					5	3

Variables predisposing to atrial tachyarrhythmia in surgical patients: A, age; B, male gender; C, hypertension; D, diabetes mellitus; E, ejection fraction; F, chronic obstructive pulmonary disease; and G, advanced coronary artery disease.
Variables that affect the incidence of post PFO closure atrial tachyarrhythmia in patients with diagnosed pre-closure atrial tachyarrhythmia: H, left atrial dimension/dilatation; I, right atrial dimension/dilatation; J, right ventricular dimension/dilatation; and K, pulmonary hypertension.
Study score: 1, matched for 0–1 factor; 2, matched for 2–3 factors; 3, matched for 4–5 factors.