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Quality of life after percutaneous closure of patent foramen ovale in patients after cryptogenic stroke *compared to a normative sample*

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ABSTRACT

Aims: Despite the widespread use of percutaneous closure of patent foramen ovale (PFO) in patients after a cryptogenic stroke, little is known about its impact on health-related quality of life (HRQoL). The aim of this study was to assess HRQoL in these patients compared to PFO patients not considered candidates for percutaneous closure, and to a normal population.
Methods and results: A total of 402 patients with cryptogenic stroke or transient ischaemic attack (TIA) who had been referred to our center for PFO closure were invited to a long-term clinical follow-up (mean follow-up 5.5 years; range 3–13 years). HRQoL was assessed using the SF-36 Health Survey and data were compared with an age- and gender-matched reference group from the Swedish SF-36 normative database. Fifteen patients had died and 43 did not answer the SF-36. Of the remaining 344 patients, 208 had undergone PFO closure, and 136 had not. The closure group and reference group reported similar HRQoL levels. However, the non-closure group showed significantly lower HRQoL in role limitation – physical, vitality, general health, mental health ($p < 0.05$) and social functioning ($p = 0.05$) than the reference group and also had significantly lower scores than the closure group, correcting for age differences, on physical functioning, role limitation – physical, vitality and general health ($p < 0.05$).
Conclusions: Non-closure patients had lower HRQoL than their counterparts in the normal population and the closure group. Percutaneous PFO closure is associated with a favorable quality of life.

1. Introduction

Patent foramen ovale (PFO) is common in asymptomatic adults and is associated with cryptogenic stroke (CS), i.e. ischaemic stroke where the cause remains unidentified despite extensive evaluation [1–4]. Patients with CS or transient ischaemic attack (TIA) presumed to be related to PFO are at risk of recurrent cerebrovascular events, indicating the need for prevention [5–7]. Observational studies favour percutaneous closure of PFO over medical therapy for reducing the risk of recurrent stroke and mortality [8,9].

Initially three randomized trials of PFO closure did not show a significant reduction in stroke risk in their primary analysis; nonetheless an exploratory long-term follow up of the RESPECT trial and two randomized trials CLOSE and Gore REDUCE trial indicate a reduction in the risk of recurrent stroke of 50–75% [10–14]. However, all these trials recruited relatively young patients, with a very clear list of indications and contraindications. Many patients will fall outside of these eligibility criteria and local algorithms and decision aids have frequently been used, together with a multidisciplinary approach, to overcome these difficulties [20]. The effect of PFO-closure on the risk of recurrent events is less clear and patient preferences as well as potential side-effects of closure and health related quality of life, are increasingly important.

Pooled data from observational and randomized studies suggest a positive net clinical benefit (i.e. recurrent stroke and risk of bleeding) of PFO closure over medical therapy [15].

Percutaneous closure of patent foramen ovale, here abbreviated to PFO closure, is therefore widely used on the assumption that it may prevent recurrent cerebrovascular events in patients with PFO and CS. However, the impact of PFO closure on the health-related quality of life (HRQoL) of these patients is not well known. To date, two studies have assessed HRQL in patients who underwent PFO closure after CS. Cohen et al. [16] showed that patients had a high level of HRQoL after PFO closure. Evola et al. [17] found that PFO closure had a good impact on HRQoL six months after PFO closure compared to before closure. However, the long-term impact of PFO closure on HRQoL has not been reported.

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Table 1
Baseline characteristics of 344 PFO patients with ischaemic stroke or transient ischaemic attack (TIA).

	All patients	Closure Group	Non-closure Group	*P*-value
Total respondents, n	344	208	136	
Age, y (SD±)	52 (11.9)	49 (10.7)	57 (11.7)	<0.05
Gender, female, n (%)	129(37)	74 (36)	55 (40)	–
Hypertension, n (%)	82 (24)	34 (16)	48 (35)	0.318
Diabetes mellitus, n (%)	16 (5)	5 (2)	11 (8)	0.591
				0.062
Current smoker, n (%)	47 (14)	25 (13)	22 (16)	
Ex-smoker >3 months, n (%)	92 (27)	48 (23)	44 (32)	–
Never smoker	201 (58)	133 (64)	68 (50)	–
Hypercholesterolaemia, n (%)	73 (21)	38 (18)	35 (26)	0.355
Cerebrovascular index event[a] n (%)				
Ischaemic stroke	173 (65)	97 (47)	76 (55)	0.093
Transient ischaemic attack	80 (30)	33 (15)	47 (35)	<0.001
Previous cerebrovascular events n (%)				
Ischaemic stroke	49 (14)	35 (17)	14 (10)	0.625
Transient ischaemic attack	74 (22)	52 (25)	22 (16)	0.023

[a] Cerebrovascular index event refers to the event that triggered referral for assessment for PFO closure. Referrals 1997–2005 ($n = 78$) only registered cerebrovascular events. Referrals from 2006 onwards distinguished stroke and TIA.

The Gothenburg Centre for Adults with Grown-Up Congenital Heart Disease (GUCH) has performed PFO closure with the aim of reducing the risk of recurrent stroke in selected patients since 1997. According to our previous studies, the procedure was associated with very low risk of recurrent stroke and was suitable for most patients [18,19]. No mortality or long-term device-related complications were related to PFO closure. Long-term HRQoL follow-up would contribute to our understanding of the impact of the procedure from a patient perspective.

Faced with an increasing number of cases and the difficulties in defining clinically whether CS is present or not, we established in 2006 regular multi-disciplinary PFO conferences to harmonize clinical decision-making between doctors [20]. During the period 2006 to 2009, about half of the patients with CS and PFO who were referred to the centre underwent closure, the other half did not. Because we have carried out a long-term clinical follow-up in both groups, we have a unique opportunity to study the HRQoL of patients with PFO and stroke, both those who undergo PFO closure and those who do not.

Aims: To assess long-term HRQoL after PFO closure in patients with CS or TIA, compared with age- and gender-matched Swedish norms and with patients whose PFO was unclosed because their stroke or TIA was considered unrelated to PFO.

Table 2
Modified Rankin Scale of 344 PFO patients with ischaemic stroke or transient ischaemic attack at long-term follow-up.

	All patients	Closure group	Non-closure group	*P*-value
Total Respondents, n (%)	344	208	136	
Modified Rankin Scale				0.051
No symptoms at all	219 (66)	137 (66)	82 (60)	
No significant disability despite symptoms;	65 (19)	41 (20)	24 (18)	
Slight disability;	36 (11)	16 (8)	20 (15)	
Moderate disability;	7 (2)	5 (2.4)	2 (1.4)	
Moderately severe disability;	3 (0.9)	0	3 (2.2)	
Severe disability;	1 (0.3)	0	1 (0.7)	

The disability categories are ordered from 0 to 5, with 0 representing no symptoms at all and 5 representing severe disability.

2. Methods

All PFO patients with a suspected diagnosis of stroke or TIA referred to our centre for PFO closure between 1997 and 2009 were included in this study. In the period 1997 to 2005, the decision about PFO closure was made by one or two interventional cardiologists. Between 2006 and 2009, each patient's case was evaluated in a multidisciplinary PFO conference attended by specialists in neurology, cardiology, and internal medicine. They evaluated the patient's clinical data, stroke aetiology, and medical records, including trans-esophageal echocardiography (TEE), magnetic resonance imaging (MR), and/or computerized tomography (CT) imaging documenting the presence or absence of stroke or other cerebral pathology. All decisions were made by consensus. CS was defined when no cause of ischaemic stroke was identified despite an extensive evaluation. PFO was defined as TEE evidence of infused microbubbles in the left atrium within three cardiac cycles after their appearance in the right atrium, at rest or during Valsalva release.

A diagnosis of TIA was given by the treating neurologist if acute neurological deficits with a probable vascular (ischemic) cause completely resolved within 24 h regardless of any infarction shown on cerebral imaging. Ischemic stroke was defined as a sudden new focal neurological deficit lasting >24 h *regardless* evidence of brain damage on a CT scan or MRI.

Patients with CS or TIA most probably related to PFO underwent PFO closure, whereas those with stroke of known origin or a diagnosis other than stroke or TIA did not. All included patients were invited for a long-term clinical follow-up visit during the period 2012 to 2014.

At the clinical follow-up, HRQoL was assessed using the Swedish version of the Medical Outcomes Study Short Form 36 Health Survey (SF-36) [21]. The questionnaire was mailed to patients who were unable to attend the follow-up. An age- and gender-matched reference sample ($n = 344$) was randomly drawn from the Swedish SF-36 normative database ($n = 8930$). The SF-36 is a widely used 36-item generic questionnaire that measures HRQoL in eight domains: *physical functioning* (PF), *role limitation – physical* (RP), *bodily pain* (BP), *general health* (GH), *vitality* (VT), *social functioning* (SF), *role limitation – emotional* (RE), and *mental health* (MH). Item ratings are aggregated using a standard algorithm such that domain scores range from 0 to 100, where higher scores represent better HRQoL. The Swedish version of the SF-36 has been shown to have good reliability and validity [22,23].

Disability was assessed using the Modified Rankin Scale (MRS) [24]. MRS is commonly used to measure levels of disability and independence in performing daily activities after stroke, incorporating the WHO components of body function, activity, and participation. The disability categories are ordered from 0 to 5, with 0 representing no symptoms and 5 representing severe disability.

3. Ethics

The Regional Medical Research Ethics Committee of Gothenburg approved the study (DNR = 029–09). Informed written consent was obtained from all participants.

4. Statistical analyses

For descriptive purposes, means, medians, and interquartile ranges were used. Comparisons between patient groups (closure and non-closure) and reference values were performed using the parametric

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