Prevalence of thrombophilia in patients undergoing closure of patent foramen ovale

Philipp Wagdi, Manfred Ritter, Frank Salzer
HerzZentrum Hirslanden, Zurich, Switzerland

Summary

Objectives: One of the less controversial indications for percutaneous closure (C) of a patent foramen ovale (PFO) may be reduction of recurrent cerebral thromboembolic events, although these may sometimes recur after PFO-C. Hypercoagulable states are among the less well understood causes of cryptogenic stroke (CS). The reported prevalence of coagulopathies in patients with PFO varies widely and there is no consensus concerning their role.

Methods and results: This single centre observational study examined the prevalence of coagulopathies in 49 consecutive patients below 65 years of age in whom PFO-C was performed. Heterozygous mutation of factor V (Leiden) gene was detected in 6 patients (12%), prothrombin gene mutation in 3 patients (6%), protein S deficiency in 1 (2%), antiphospholipid antibodies in 1 (2%), and antithrombin III deficiency in 1 (2%). In all, a coagulopathy was detected in 11 patients (22.5%). During the follow-up period of 13 ± 5.5 months no cerebrovascular or other thromboembolic event occurred.

Conclusion: Heterozygous forms of inherited coagulopathies may be more frequent in patients with PFO and CS than in the general population, thus potentially contributing to the original event of paradoxical embolisation. Data from larger centres and meta-analysis of existing data may help to clarify the role of coagulopathies further.

Key words: thrombophilia; coagulation disorders; patent foramen ovale; stroke

Introduction

The actuarial risk of recurrent thromboembolic events after percutaneous closure of patent foramen ovale (PFO) has been reported as approx. 1.9 to 2.7% [1–3]. In patients aged over 65 the most common causes of stroke are extra- or intracranial atherosclerotic cerebrovascular disease and atrial fibrillation. In younger subjects the aetiology of stroke sometimes eludes diagnosis and is referred to as being "cryptogenic". Possible factors leading to recurrent stroke after PFO closure may be paradoxical embolism due to a residual shunt after closure [3] or to a previously undetected thrombotic or embolic cause (intermittent atrial fibrillation, aortic arch plaque, extra- or intracranial atherosclerosis, mural intraventricular thrombi, etc. Data are scarce concerning the prevalence of hypercoagulable states – both hereditary and acquired – in patients with PFO, and even more so on their clinical significance in patients in whom PFO has been closed [4–6]. This may be of special interest, as hypercoagulability may predispose to deep venous thrombosis and paradoxical embolisation until complete closure of the residual shunt. It is conceivable that a hypercoagulable state may have an influence on thrombus formation, especially before endothelialisation of both atrial surfaces of the device. Right-sided thrombi may again embolise paradoxically, and left-sided ones directly. Lastly, and unrelated to PFO-C, homozygous hereditary coagulation disorders may be a cause of arterio-arterial thromboembolism, for example intracerebrally. An overview of the most important coagulopathies, and the associated risk of thromboembolic events, is presented in table 1. A "normal" thrombophilic status is assigned a relative risk for a venous thromboembolic event of 1. Use of oral contraceptives (without concomitant coagulopathies) increases the relative risk fourfold. The reported relative risk of venous thromboembolic events shown in table 1 pertains to heterozygous forms of the coagulopathies mentioned. As a general rule, homozygous forms manifest themselves via severe thromboembolic disease at birth. Homozygous forms are thus excluded from the present discussion. It should also be mentioned that use of oral contraceptives in a patient with a heterozygous coagulopathy markedly increases the relative risk of venous thromboembolic events (fifteenfold in combination with prothrombin gene mutation and up to thirtyfold with factor V Leiden deficiency).

None of the authors has any conflict of interest to report.

Correspondence:
Philipp Wagdi
HerzZentrum Hirslanden
CH-8008 Zurich
Switzerland
wagdi@herzzentrum.ch

Table 1
Overview of the most important coagulopathies and associated thromboembolic risk (modified and adapted from [7–10]).

Thrombophilic status and prothrombotic mechanism	Prevalence in the general population	RR of venous thromboembolic events
*** Factor V Leiden** Factor V is resistant to inactivation by protein C (hence the name activated protein C resistance), increasing coagulability (see Protein C deficiency)	4–7%	5–7
*** Prothrombin gene mutation** Increased amounts of thrombin and prothrombin in blood	1–2%	3
*** Protein C deficiency** (Functional or quantitative) decrease in protein C, thus reduced inactivation of factor Va and VIIIa	0.2%	7
*** Protein S deficiency** Decreased level of protein S (co-factor for protein C) and decreased degradation of factor Va and VIIIa	1–5%	6
*** Antithrombin III deficiency** (Functional or quantitative) deficiency of AT, with decreased inhibition of factors Xa, IXa, IIa, XIIa, Xia and VIIa	0.02–1.1%	5
Antiphospholipid antibody Antibody subtypes: – Antibeta 2 glycoprotein (IgG / IgM) – Anticardiolipin (IgG / IgM) – Lupus anticoagulant Primary and secondary (underlying autoimmune disease)	2–4%	Consensus is that risk is increased, more precise figures lacking
Hyperhomocysteinaemia Deficiency of: – Methylenetetrahydrofolate reductase (MTHFR, more common and clinically relevant) – Less relevant clinically: cystathionine beta-synthase (CBS) or methionine synthase (MS) leads to increased homocysteine levels (role in hypercoagulability not entirely clear)	30–40% (MTHFR)	2–4% (controversial)

A "normal" thrombophilic status is assigned a relative risk of a venous thromboembolic event of 1. Use of oral contraceptives (without concomitant coagulopathies) increases the relative risk fourfold.
* The reported relative risk (RR) of venous thromboembolic events is shown for heterozygous forms of the coagulopathies mentioned. As a general rule, homozygous forms manifest themselves via severe thromboembolic disease at birth. Homozygous forms are thus excluded from the present discussion.

Methods

49 patients aged under 65 underwent PFO-C from January 2006 to December 2008. Patients over 65 and those with an atrial septal defect were excluded from the study since the role of paradoxical embolisation in this subset of patients is less well established and also controversial.
Prior to PFO closure, the following parameters, in addition to routine clinical chemistry and haematology, were determined: G 20210A prothrombin gene mutation, factor V Leiden gene mutation, activated protein C resistance, protein C and S deficiency, antithrombin III deficiency, antiphospholipid antibodies (anticardiolipin antibody Ig and IgM, antibeta 2 glycoprotein IgG and IgM, and lupus anticoagulant) and hyperhomocysteinaemia as previously reported [11]. As a part of preinterventional patient information, all patients were informed of the additional blood tests and had the right to refuse them. All patients had undergone a clinical and imaging workup by a neurologist prior to referral for PFO-C. Patients were followed up for 13 ± 5.5 months. Patients were seen by the cardiologist one (transthoracic echocardiography) and 6 months (transoesophageal echocardiography) after device implantation. All patients were asked to report symptoms potentially attributable to neurological events. No such events were reported by either patients or attending physicians. At discharge after PFO-C patients and their physicians were informed of the coagulopathy and briefed on self-administration of low molecular weight heparin in special situations (e.g., long flights, car drives, sitting at work, convalescence after operations, etc.). All patients were instructed to use clopidogrel for three months and acetylsalicylic acid for at least one year after PFO-C.

Results

Of the 49 patients included (aged 49 years ± 12.8, 24–64 years; 27 males), 11 (7 males) had at least one coagulopathy (22.5%), 2 patients each had 2 coagulopathies (table 2). Six patients exhibited a factor V Leiden mutation (12%), 3 a prothrombin gene mutation (6%), and one each (2%) a protein S deficiency, an antithrombin III deficiency, an antiphospholipid syndrome and a hyperhomocysteinaemia due to a MTHFR mutation. Clinically, no patient experienced any form of cerebrovascular event during follow-up. No symptoms reflecting thrombosis or embolism in any part of the circulation were reported. Neither transthoracic nor transoesophageal echocardiography showed any thrombus formation either on the left- or the right-sided discs.

Table 2
Clinical characteristics of patients with PFO-C and detected coagulopathies.

	Gender	Age 50 ± 11.3 years	Coagulopathy	Event before PFO-C	Device	FU (13 ± 5.5 months)	NE after PFO-C
1	M	51	Protein S deficiency AT III deficiency	Recurrent TIA	A	22	–
2	F	29	Heterozygous prothrombin gene mutation	Irreversible amaurosis fugax (thromboembolic)	P	21	–
3	F	57	Heterozygous factor V mutation, APC resistance	MRI documented minor stroke	A	18	–
4	M	47	Heterozygous factor V mutation, APC resistance	MRI documented minor stroke	F	10	–
5	F	56	Heterozygous factor V mutation, APC resistance	MRI documented minor stroke	A	13	–
6	F	61	Hyperhomocysteinaemia, MTHF mutation	MRI documented minor strokes	F	13	–
7	M	58	Heterozygous factor V mutation, APC resistance	MRI documented minor strokes	F	11	–
8	M	31	Heterozygous prothrombin gene mutation and antiphospholipid antibodies	MRI documented minor strokes	S	9	
9	M	58	Heterozygous factor V mutation, APC resistance	MRI documented minor stroke	S	6	–
10	M	54	Heterozygous prothrombin gene mutation	TIA	C	6	–
11	M	61	Heterozygous factor V mutation, APC resistance	MRI documented stroke	S	6	–

A = Amplatzer® device; C = Cardia Atriasept® device; F = Figulla® device; FU = Follow-up; NE = Neurological event; P = Premere® device; PFO-C = Closure of patent foramen ovale; S = Solysafe® device; TIA = Transient ischaemic attack, documented by a neurologist.

Discussion

The prevalence of coagulopathies in the general population is fairly well documented [7–10]. Their role – especially that of the heterozygous forms – in clinically manifest arterial and venous thromboembolic events, and the ensuing therapeutic consequences, is more or less clear. To the best of our knowledge only sparse data are available on the prevalence of coagulopathies in patients with PFO who had at least one thromboembolic event with subsequent percutaneous closure of the defect. A large-scale study reporting the incidence of thrombus formation after PFO-C investigated the role of thrombophilia only partially [5]. A smaller study [4] describes a prevalence of thrombophilia in PFO-C patients of 27%. Lastly, a case report describes device thrombosis 3 years after PFO-C [6]. The potential importance of a more precise knowledge of the prevalence of coagulopathies in patients undergoing PFO-C is twofold. First, a recurrent cerebrovascular event after closure of a PFO usually prejudices the patient both physically and psychologically, in addition to being diagnostically challenging to the physician. Since the commoner causes of cardioembolic events (atrial fibrillation, intracardiac thrombi, atherosclerosis of extra- and intracranial vessels, intracardiac mural thrombi, etc.) have usually been ruled out prior to PFO closure, the renewed search may end inconclusively again. The incidence of the heterozygous form of some of the coagulopathies in the general population is reported to be

as follows [10]: factor V Leiden 4–7%, prothrombin gene mutation 1–2%, protein S deficiency 1–5%, antiphospholipid antibody syndrome 2–4%. In our series the prevalence of both APC resistance and prothrombin gene mutation was higher, i.e., 10% and 6%. Some – albeit small – studies have specifically addressed the question of prevalence of coagulation disorders in the patient population with a PFO [12–14]. Here again the situation is confusing: Carod Artal et al. [12] and Sastry et al. [13] report that coagulopathies are not an additional factor for clinically relevant events (stroke and myocardial infarction). On the other hand, Karttunen and coworkers [14] imply that prothrombin gene mutation and factor V Leiden may predispose to paradoxical embolism in patients with patent foramen ovale. Our data are in line with this intuitive conclusion, although we concede that our numbers are small. Yet if we bear in mind that in our population subset 12% of patients showed factor V Leiden activated protein C resistance compared to the reported 7% (at best) in the general population, and that 6% of our patients had a prothrombin gene mutation (again compared to 2% in the general population), the question has to be raised again. Obviously our data do not allow meaningful statistics, which is why we urge a pooling and meta-analysis of data of the large Swiss centres, if available.

Whereas a greatly increased incidence of venous thromboembolic events in patients with heterozygous forms of coagulopathies is clearly documented [10], arterio-arterial events are not. This may be an argument for the paradoxical embolisation theory in our patients, all of whom had documented neurological events prior to PFO-C. Again, until dedicated large-scale studies with significant statistical power have addressed the issue, pooling the data available from smaller observational studies such as ours will help clarify this relevant issue. Always bearing in mind the small study size, the fact that none of our patients experienced a venous thromboembolic adverse event after PFO-C may have been due in part to our recommendation to patients to administer low molecular weight heparin in risk situations. To the best of our knowledge, no data are available regarding possible increased thrombogenicity on the arterial side (left atrial disc) in patients with coagulopathies [6], although no such increase is documented in the natural course of the heterozygote forms (with no interatrial septal device).

References

1 Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical emboli: a systematic review. Ann Intern Med. 2003;139:753–60.
2 Schwerzmann M, Windecker S, Wahl A, Mehta H, Nedeltchev K, Mattle H, et al. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart. 2004;90:186–90.
3 Wahl A, Kunz M, Moschovitis A, Nageh T, Schwerzmann M, Seiler C, et al. Long-term results after fluoroscopy-guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. Heart. 2008;94:336–41.
4 Giardini A, Donti A, Formigari R, Bronzetti G, Prandstraller D, Bonvicini M, et al. Comparison of results of percutaneous closure of patent foramen ovale for paradoxical embolism in patients with versus without thrombophilia. Am J Cardiol. 2004;94:1012–6.
5 Krumsdorf U, Ostermayer S, Billinger K, Trepels T, Zaden E, Horvath K, Sievert H. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1000 consecutive patients. J Am Coll Cardiol. 2004;93:426–31.
6 Ruge H, Wildhirt SM, Libera P, Vogt M, Holper K, Lange R. Left atrial thrombus on atrial septal defect closure device as a source of cerebral emboli 3 years after implantation. Circulation. 2005;112:e130–e131.
7 Hansson PO, Eriksson E, Welin L, Eriksson H. Prevalence of APC resistance and its relationship to arterial and venous thromboembolism in a general population sample of elderly Swedish men. J Internal Med. 1999;245:593–600.
8 Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol. 2001;37:215–8.
9 Greaves M, Cohen H, Machin SJ, Mackie I. Guidelines on the investigation and management of the antiphospholipid syndrome. Br J Haematol. 2000;109:704–15.
10 University of Illinois, Carle Cancer Center, Hematology Resource Page. www.med.uiuc.edu/hematology.
11 Wagdi Ph, Ritter M. Patient radiation dose during percutaneous interventional closure of interatrial communications. J Cardiol. 2009;53:368–73.
12 Carod Artal FJ, Vilela Nunes S, Portugal D. Thrombophilia and patent foramen ovale in young stroke patients. Neurologia. 2006;21:710–6.
13 Sastry S, Riding G, Tabemer D, Cherry N, Heagerty A, McCollum C. Young adult myocardial infarction and ischemic stroke. J Am Coll Cardiol. 2008;48:686–91.
14 Karttunen V, Hiltunen L, Rasi V, Vahtera E, Hilbom M. Factor V Leiden and prothrombin gene mutation may predispose to paradoxical embolism in subjects with patent foramen ovale. Blood Coagul Fibrinolysis. 2003;14:261–8.