The role of atrial septal abnormalities in cryptogenic stroke — still questionable?

During the last decade cardiovascular embolism has been recognized as the cause of otherwise unexplained stroke or transient ischaemic attack in a relevant number of adult patients below the age of 55 years. The wide range of prevalence from 12% to 41% mainly reflects the uncertainty of the diagnosis which can only be set up indirectly by excluding other causes. Even though imaging modalities such as computed tomography or magnetic resonance imaging are able to clearly define the diagnosis of cerebral ischaemic events, a causal relationship between a possible source of emboli and an embolic event in the individual patient can only be assumed to be more or less probable. Moreover, there is a variety of different ‘potential’ sources of emboli, which alone or in combination may coexist and cause an embolic event. The patent foramen ovale and the atrial septal aneurysm are considered as typical potential sources of emboli whose precise relation to embolic events is difficult to prove.

A patent foramen ovale is a persistent valvular-like connection between the right and left atrium which in the majority of subjects closes by fibrous adhesions between the septum primum and secundum during the first months of life. However, in some subjects an inter-atrial connection may persist which allows intermittent right to left shunting. Autopsy studies have demonstrated a prevalence of patent foramen ovale in the population in the range of 17% to 35%. After first anecdotal reports about the possible role of the patent foramen ovale as a gate for paradoxical embolism, a large number of studies have suggested a strong correlation between the presence of a patent foramen ovale on the one hand and of an embolic event on the other. Advances in the diagnosis of the patent foramen ovale by transoesophageal echocardiography as well as studies showing a correlation between the size of a patent foramen ovale and the risk for an embolic event supported the assumption that the mechanism of paradoxical embolism may be responsible for more arterial embolic events than previously realized. Meanwhile the presence of a patent foramen ovale is generally accepted to be a potential source of emboli in an otherwise unexplained transient ischaemic attack or stroke.

An atrial septal aneurysm consists of redundant atrial septal tissue bulging into the right or the left atrium, sometimes even oscillating between both atria. Different definitions for the cut-off point between a mobile and an aneurysmatic atrial septum have been used, which may partly contribute to the range of atrial septal aneurysm prevalence in various studies in recent years (2%-9%). However, there is general agreement in all definitions that the basal width of an atrial septal aneurysm should be more than 15 mm and the excursion of the aneurysm beyond the plane of the residual atrial septum should be at least 10 or 15 mm.

Atrial septal aneurysm has been found in about 1% of consecutive autopsies and in up to 4-9% of patients undergoing transoesophageal echocardiography for reasons other than a search for sources of embolism. In contrast, a large number of studies have described a significantly higher percentage of atrial septal aneurysm between 4% and 15% in pre-selected patient populations with otherwise unexplained transient ischaemic attack and stroke. Most of these studies assessing the potential role of atrial septal aneurysm as a source of emboli have compared the prevalence of atrial septal aneurysm in patients undergoing transoesophageal echocardiography after an embolic event with the frequency in patients in whom transoesophageal echocardiography was performed for other clinical indications. However, these highly selected control groups may have led to a bias and an over-estimation of the true prevalence of atrial septal aneurysm in an unselected population. A recent study from Agmon et al. similarly demonstrated a higher percentage of atrial septal aneurysm in patients with otherwise unclear cerebral embolism (7-9%) compared to the prevalence in a large matched population-based and thus not pre-selected control group (2-2% of subjects within the SPARC study).

In the present multicentre study Mattioli and co-workers analysed 245 patients with an otherwise unexplained cerebral event (transient ischaemic attack or stroke) and compared the prevalence of atrial septal anomalies to an age- and sex-matched control group of 316 subjects. The prevalence of atrial septal aneurysm both in the patient group (27.7%) and in the controls (9.9%) was nearly four times higher than in the latest study of Agmon...
atrial septal aneurysm. Most studies have shown a high correlation between patent foramen ovale and atrial septal aneurysm with atrial arrhythmias or atrial septal defects as well as mitral valve prolapse or atrial arrhythmias. Due to the fact that these abnormalities are also possible sources of cardiac emboli it is even more difficult to assess the embolic potential of an atrial septal aneurysm independently. A variety of pathogenetic mechanisms have been described to explain the well-known statistical association between atrial septal aneurysm and embolic events: paradoxical embolism via patent foramen ovale, thrombus formation within the aneurysmal sac or within the left atrium as a consequence of the association of atrial septal aneurysm with atrial arrhythmias or atrial fibrillation. The present paper found an increased thickness of the atrial septum in atrial septal aneurysm stroke patients compared with control patients with atrial septal aneurysm. The authors concluded that this may suggest another possible pathogenetic mechanism, namely the thrombus formation within the aneurysmal sac. This is in agreement with former anecdotal reports that described a thickened interatrial septum and possible thrombotic structures attached to the atrial septal aneurysm as diagnosed by transoesophageal echocardiography. However, this possible link between atrial septal aneurysm and embolism has only rarely been proven by autopsy or during surgery. Several multicentre studies have mentioned paradoxical embolism as only one among other possible mechanisms, but nearly all found a high correlation between patent foramen ovale and atrial septal aneurysm. Mügge and co-workers described an inter-atrial right-to-left shunt in 54% of all atrial septal aneurysm patients. A local thrombus formation attached to the inter-atrial septum was found in only a small subgroup, 1% of the atrial septal aneurysm patients. The French study group of Mas and co-workers has convincingly demonstrated a strong association between patent foramen ovale and atrial septal aneurysm, as well as the statistically higher risk for an embolic event of both abnormalities separately. They observed an additional synergistic effect of the combination of patent foramen ovale and atrial septal aneurysm with an even higher embolic risk. More recent studies stressed that paradoxical embolism is by far the most important mechanism for transient ischaemic attack and stroke in atrial septal aneurysm patients, although in most of these former studies (such as the present one) venous thrombus formation as the primary underlying cause was not evaluated systematically or reported.

In agreement with these results, Mattioli et al. not only demonstrated a statistical association of patent foramen ovale and atrial septal aneurysm, but also showed that both morphological abnormalities were independent predictors of embolic events in a multivariate analysis. The association between atrial septal aneurysm and patent foramen ovale was even stronger in a subgroup of patients below the age of 45 years, where 97% of atrial septal aneurysm patients also had a patent foramen ovale. However, the overall low frequency of patent foramen ovale compared to earlier studies, both in the patient group (22.8%) as well as in the control group (9.8%), may be due to patient selection and therefore makes an interpretation difficult.

The association of atrial septal aneurysm and patent foramen ovale is of even greater clinical importance because different therapeutic options have been used to avoid recurrent embolic events in patent foramen ovale patients and to circumvent the otherwise necessary life-long anticoagulation.

In conclusion, there seems to be striking evidence for a potential role of atrial septal aneurysm as a source of emboli, either as an isolated anomaly or in combination with other potential sources of emboli. However, as long as several other potential sources are not excluded, as in the present study population (such as mild carotid or aortic atherosclerosis) or cannot be excluded (such as a frequently coexisting patent foramen ovale), the truly ‘independent’ role of atrial septal aneurysm still remains — and perhaps always will remain — unclear.

**References**