LETTERS TO THE EDITOR

Risk of Thrombus Formation on Devices Used to Close Transcatheter Atrial Septal Defect and Patent Foramen Ovale

In a recent issue of the Journal, Krumsdorf et al. (1) discussed the incidence of thrombus formation on atrial septal defect (ASD) and patent foramen ovale (PFO) closure devices in 1,000 consecutive patients. The investigators report a group of 593 patients with PFO but only 235 patients had an embolic event. Closure of a PFO is usually indicated if there is a spontaneous or provokable right-to-left shunt during contrast transesophageal echocardiography (TEE) in a patient with clinical and/or radiologic evidence of an ischemic stroke, a transient ischemic attack, or an extracranial peripheral thromboembolic episode.

Most of the thrombi (14 out of 20) were detected at the four-week TEE study, but it is not clear whether the investigators excluded the presence of them immediately after the procedure. Krumsdorf et al. (1) described different protocols of anticoagulation during the procedure.

Regarding our experience (751 ASDs; 170 PFOs) we believe that the two most sensitive points are: 1) monitoring of the anticoagulation of the patient during the procedure using the activated clotting time, and 2) duration of antiplatelet therapy after transcatheter ASD closure.

This last point is not yet clarified; endothelialization of an ASD device is supposed to occur within a few months after implantation; this information is supported by animal studies (2). It is accepted that six months of antiaggregation (with one or two drugs) is a long enough period to prevent thrombus formation on the device (3,4). The researchers found three thrombi at the six-month TEE; this might indicate that the endothelialization could not be completed at that time. Therefore, a longer period of antiplatelet therapy may be useful.

Chessa Massimo, MD, PhD
Butera Gianfranco, MD, PhD
Carminati Mario, MD
Pediatric Cardiology Department and GUCH Unit
IPSD
Via Morandi, 30
20097 San Donato Milanese
Milan
Italy
E-mail: massimo.chessa@lycos.com


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Thrombus Formation on Intracardiac Devices: A Complex Issue

Recently, Krumsdorf et al. (1) reported on the incidence and risk factors of thrombus formation on atrial septal defect (ASD) and patent foramen ovale (PFO) closure devices. Data provided in their study indicate that among other risk factors the device design and/or materials affect the risk of thrombus formation, being higher in CardioSEAL/STARFlex (NMT Medical, Boston, Massachusetts) and PFO-Star (Applied Biometrics Inc., Burnsville, Minnesota) compared to Amplatzer (AGA Medical Corp., Golden Valley, Minnesota) implants. However, other studies including comparable numbers of CardioSEAL/STARFlex devices (2) or even larger numbers of PFO-Star occluders (3) yielded much lower incidences of thrombus formation. Moreover, early thrombus formation on Amplatzer devices has also been documented and described in this Journal (2) and elsewhere (4,5). Therefore, we do not agree with the conclusion drawn by Moore and Levi (6) in their accompanying editorial that routine transesophageal echocardiography (TEE) surveillance in patients with Amplatzer septal occluders (in contrast to other devices) should not be recommended. In our opinion, all intracardiac devices should undergo a thorough and routine follow-up, including adequate imaging of the implanted devices (TEE).

With regard to the early thrombus formation, the editorial underemphasizes, the observation by Krumsdorf et al. (1) that 19 of 20 thrombi described were found in patients antagonized with protamine at the end of the implantation procedure. We would strongly advise against this unusual approach, and the investigators have in fact abandoned it with apparently better results in subsequent patients.

Using a multiple regression analysis, Krumsdorf et al. (1) found age not to be a risk factor for thrombus formation on atrial septal occluders. This may hold for their predominantly adult study population. In our combined experience of more than 200 ASD closures in children and adolescents using both the Amplatzer and CardioSEAL/STARFlex devices, we have not observed any thrombus formation. Furthermore, to the best of our knowledge, thrombus formation after ASD closure in children has not yet been described in the published reports.
Finally, the editorial comment (6) addresses our work on bioengineered septal occluder devices (7). These devices showed rapid complete neo-endothelialization. The scaffold can be heparin-coated in order to decrease further the thrombogenicity of the implant surface. The basic concept of this evolving device, however, is its biodegradability. Especially in children with an expected implant persistence of some 80 years, the degradation of the implant after ingrowth and concurrent replacement by autologous host tissue might be a concept not only to minimize foreign-body reactions (such as perforations) but also to avoid the potential for yet unknown long-term sequelae.

Christian Jux, MD
Department of Pediatric Cardiology and Intensive Care Medicine
Georg-August University
Robert Koch Strasse 40
D 37099 Goettingen
Germany
E-mail: Dr.C.Jux@medizin.uni-goettingen.de

Harald Bertram, MD


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Transcatheter Intracardiac Device Implantation for Atrial Level Defects and Thrombosis:
A Call for Randomized, Controlled Data

In their review of transcatheter device implants for atrial septal defects (ASDs) and patent foramen ovale (PFO), Krumsdorf et al. (1) present an instructive example of how the cataloguing of non-standard indications for intervention, treatment techniques, and outcome assessment confounds the management of patients with congenital heart disease. Indeed, the lack of controlled data plagues the device arena and prevents us from making evidence-based treatment decisions in our patients with PFO and stroke. Unfortunately, the accompanying editorial by Moore and Levi (2) fails to call attention to the limitations of such nonrandomized, uncontrolled data. As a result we are concerned that erroneous conclusions will be drawn that can have a negative impact on patient recruitment in ongoing randomized, controlled clinical trials of device closure in patients with PFO.

The investigators present a large collection of patients but without a table of patient characteristics, making later analysis against their defined end point of device-related thrombosis all but impossible. The patient data that do exist lack a standardized preprocedural assessment of prothrombotic risks (including major serologic determinants of arterial and venous thrombosis such as antiphospholipid antibodies and homocysteine as well as external determinants such as cigarette and oral contraceptive use, thyroid or liver disease, blood dyscrasias, obesity or trauma, valvular heart disease, preprocedural palpitations, or atrial fibrillation). Those deficiencies, combined with non-standardized implant techniques, the use of postprocedural prothrombotic therapy (protamine), non-standard, periprocedural antiplatelet therapy, and variable device-specific follow-up protocols cloud the interpretation of the results.

The sensitivity and specificity of echocardiographically detected device-related thrombosis is not defined for any of the particular devices (each has different metallic composition and echocardiographic penetrance). In some cases, device characteristics may limit detection of the 3- to 5-mm thrombus that may be associated with neurologic events. Both intra- and interobserver variability in recognizing device-related thrombus are not discussed. Given the uncertainty about diagnostic accuracy, because very few occurrences were seen in the trial, correlation of outcome to causative factors becomes difficult at best.

Of particular concern is generalization from data obtained in a practice setting that the investigators themselves recognize is outside of current standards of care for device implants (namely, use of protamine at procedure termination in the first 813 patients): 19 of 20 thrombotic events occurred in this group. The applicability of such data for today’s patients, who receive implants without the use of postprocedure protamine, cannot be determined.

Moore and Levi (2) unfortunately generalize from the investigators’ unsupported conclusions to recommend care standards based upon differences in device design. In addition, the editorial comment does not place into context the additional recognized device-related complications such as cardiac erosion, death, valve interference, embolizations, fractures, and proarrhythmia. We are deeply concerned by these editorial recommendations. Clinical care standards should be established only through the performance and analysis of randomized controlled clinical trials and not through anecdotal data as offered by Krumsdorf et al. (1).