supported by a latter-day retrospective study showing that danaparoid sodium for isolated HIT received in low prophylactic doses is associated with a high failure rate compared with patients received lepirudin in APTT-adjusted doses. This speaks in favour of the use of therapeutic-dose danaparoid in both isolated HIT and HIT with PE. 

Our recent clinical practice has registered nine successfully treated patients diagnosed with PE caused by HIT II. Initial danaparoid sodium (four patients) or lepirudin (three patients) treatment was successful in seven patients. The remaining two fell into the category of full therapeutic-dose danaparoid sodium resistant cases. One of these patients responded positively only upon lepirudin introduction, whereas in the other patient, no effect was produced even by therapeutic lepirudin doses where the remission was achieved only after plasmapheresis. Thus, it has not escaped our notice that the management of patients resistant to initial non-heparin anticoagulants was absolutely neglected, not only in the Guidelines themselves but also in other principal reference sources, though such cases account for a considerable proportion of HIT II patients treated with danaparoid sodium or lepirudin as non-heparin anticoagulants of similar efficacy (9.4% thrombosis rate with danaparoid vs. 7.9% thrombosis rate with lepirudin). 

Administration of new anticoagulants of bivaluridin and fondaparinux type may even favor the use of therapeutic-dose danaparoid sodium for patients received lepirudin doses where the remission was no effect was produced even by therapeutic doses is associated with a high failure rate compared with patients received lepirudin in APTT-adjusted doses. This speaks in favour of the use of therapeutic-dose danaparoid in both isolated HIT and HIT with PE. 

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doi:10.1093/eurheartj/ehi611
Online publish-ahead-of print 13 October 2005

The influence of the percutaneous closure of atrial septal defect on the occurrence of migraine

We have read with great interest the data presented by Mortelmans et al. on the prevalence of migraine before and after closure of ASD type secundum with an Amplatzer ASD closing device. As expected, the prevalence of migraine before closure was higher in these ASD patients than in the normal population, whereas after closure, in patients who suffered from migraine before closure, migraine was clearly reduced through a reduction in its prevalence and its frequency, similar to what is seen following PFO treatment. Surprisingly, however, several de novo cases of migraine were observed after ASD closure, becoming more apparent with the bigger devices. 

Re-analysing our own data in a group of patients (n:25) who underwent ASD Type II closure either by using a Starflex closing device (n:14) or by surgical closure (n:11), the observed prevalence of migraine before closure was similar to the Mortelmans’ study. Also similar was the drastic reduction in prevalence, frequency, and severity of the migraine attacks after ASD closure. Unlike the Mortelmans’ results, however, and regardless of ASD size, we did not see de novo cases of migraine following closure. We, therefore, suggest that the occurrence of de novo post-closure migraine in their study may perhaps not be caused by the abrupt haemodynamic change post-closure; instead, we suggest that the type of the device used could be an alternative explanation.

The Amplatzer device is composed entirely of Nitinol, an alloy of nickel, and titanium. The toxicity of the first element has been well studied and headache is a typical symptom of nickel intoxication. Because of the high nickel content of Nitinol, it is theoretically possible that nickel may dissolve from the material due to corrosion and cause unfavourable effects. Surface layers of nickel–titanium arch wires have been found to have irregular features characterized by lengthy island-like structures, from which selective dissolution of nickel may occur. Ni ion release was three times higher for Nitinol than for austenitic stainless steels when evaluated in physiological simulating fluids. It has recently been shown that allergy to nickel occurs in 12.5% (in other studies up to 20%) of a woman population who also complained of headache occurring in periodical patterns.

As there are no sufficient data available on Nitinol biocompatibility in vivo, and no studies on the prevalence of headache after Nitinol implants, further investigation is required.

Prospective studies should evaluate the evolution of migraine after ASD Type II closure. These studies should focus on the morbidity correlated to migraine rather than on the prevalence of migraine per se. As explained earlier, the chemical components of the devices as well as their biocompatibility should be taken into consideration.

References

Left ventricular hypertrophy, apoptosis, and progression to heart failure in severe aortic stenosis

We read with great interest the article by Kupari et al. 1 supporting the concept that left ventricular (LV) hypertrophy in severe aortic stenosis is a predisposing factor rather than a protective one against the development of systolic dysfunction and heart failure. The authors discuss in detail the relationship between hypertrophy and progression through failure from a clinical/instrumental point of view, but fail to indicate a pathophysiological mechanism responsible for such transition. Indeed, evidence is accumulating that a common molecular pathway mediates both hypertrophy and myocardocyte apoptosis. The upregulation of local angiotensin-converting enzyme and of norepinephrine release have been revealed in animal models of chronic pressure overload. The same factors are well-established promoters of apoptosis. The upregulation of p38 MAPK pathway has been suggested as the link between (i) angiotensin II/norepinephrine and (ii) alterations of gene expression profile associated to both hypertrophy and apoptosis. 2 In animal model of chronic pressure overload, apoptosis has revealed as a pivotal trait of myocardial damage together with overproduction of extracellular matrix. 2 In the same model, the role of angiotensin system in promoting apoptosis has been demonstrated by the ex adiuvantibus criterion. Furthermore, in our recent study, 4 we have for the first time disclosed an inverse correlation between indices of myocardial perfusion and myocardocyte apoptosis in the hypertrophied human heart with severe aortic stenosis. Demand ischaemia is a key feature of severe hypertrophy and a well-established stimulus to apoptosis. Given the analogy in inclusion criteria between the study by Kupari et al. 5 and our own, we believe that the results of these two investigations may be complementary and that taken together they support the hypothesis of myocardial apoptosis as a key element of histological damage and a main determinant of clinical course in these patients.

Moreover, the finding that no surgical variable (i.e. the size of implanted prosthesis) influences the degree of LV mass regression after aortic valve replacement, 5 but that the determinants of such regression are medical (i.e. co-existence of hypertension and pre-operative LV mass index), suggests that (i) the cause-effect link between pressure overload and hypertrophy is more complex and recognizes more co-factors than a direct linear relationship; (ii) the structural deterioration of the myocardium occurs first of all at a cellular/molecular level; (iii) a threshold in myocardial derangement exists beyond which the hypertrophy process is not reversible. These elements are compatible with the hypothesis of the 'apoapotic cardiomyopathy' in chronic pressure overload. The sudden development of symptoms and failure in unoperated aortic stenosis should mark the moment in which myocardic loss reaches a critical threshold; the same hypothesis can explain why late valvular replacement when failure has developed is unable to revert the unfavourable evolution of the disease.

References