Point of view

Oral anticoagulation in patients with mechanical valve prostheses: evolving protocols with new generation devices

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The evolution of anticoagulation

The introduction of the Starr-Edwards prosthesis represented a benchmark for heart surgery. Its structural and functional characteristics have been conditioning the aggressive protocols of anticoagulant prophylaxis for about four decades. The Starr prosthesis, introduced in trade in 1960 and withdrawn in 2002, was unfortunately characterized in international series[1], as well as in ours[2], by high thrombogenicity (annual rate of thromboembolic events: 1.36% patients/year in the first 10 years of implantation, 1.61% patients/year after the tenth year). These rates accounted for the high intensity of anticoagulation with coumarin derivatives in the recommended protocols: the target therapeutic values of the international normalized ratio (INR) ranged between 3 and 4.5 (National Heart, Lung, and Blood Institute guidelines, 1989)[3]. Hemorrhagic complications have concomitantly been frequent and severe for many years, with a reported incidence reaching 3.6% patients/year[4]. As a consequence, soon after the introduction of biological valve substitutes, their very low thrombogenicity, implying no need for long-term anticoagulation, constituted the concept inspiring the spreading of an incriminating opinion against mechanical devices.

Supported by the results of an active participation of manufacturing industries in the scientific research on this topic, the advantages of biological valves have been progressively overestimated, although this was based on *in vitro* data generating hopeful expectations, rather than on their actual clinical benefits. The international cardiologic and surgical community has been impressed by the good short-term overall results initially forwarded, almost neglecting the potential of newly introduced mechanical prostheses (i.e. second and third generation) in terms of anticoagulation intensity reduction, allowed by lower thromboembolic risk[5]: the consequent corrections in anticoagulation protocols have definitely come late.

In the meanwhile, the differences in thromboembolic risk between different implant sites, as well as the role of cardiac disease and co-morbidities in determining the need for anticoagulation, irrespective of the type of prosthesis implanted, have been addressed with increasing interest[6]. Anticoagulation has been shown to be needed in 33% of patients with aortic bioprostheses[7] and in 57% of those with mitral bioprostheses, due to baseline cardiac conditions (most frequently atrial fibrillation, atrial or ventricular dilation). Implanting a biological valve substitute today does not equate certain freedom from the need for anticoagulation and this has to be taken into account when proposing the best option for the single patient in everyday practice.

In the aortic position, the thromboembolic risk with bileaflet mechanical prostheses has been reported to be very low, allowing for lower intensity anticoagulation protocols, maintaining the INR between 2.0 and 3.0[6]. In mitral position, the risk associated with a bileaflet valve is lower (up

to 0.66% patients/year[8]) than with a tilting-disk model (0.81% patients/year[8]) and thrombosis, most commonly involving only one leaflet, is less frequently a lethal condition. Changing trends in mitral valve disease epidemiology (the conclusion of the endemic phase of rheumatic disease, today reduced to sporadic cases) and in surgical management of mitral regurgitation (with the spreading of reparative techniques addressing more and more complex anatomical conditions)[9], have reduced the number of patients requiring prosthetic implantation in mitral position. As a consequence, the problem of mechanical prosthesis implantation and subsequent anticoagulation is today moving to concern predominantly the setting of aortic position.

At our Institution the current protocols imply anticoagulation regimens tailored to the patient's conditions, mostly in accordance with the latest guidelines issued by the American College of Chest Physicians (ACCP)[10]:

a) patients with bileaflet aortic prosthesis in sinus rhythm with ejection fraction > 45% and left atrium < 4.5 cm: target INR 2.5 (range 2-3);

b) patients with bileaflet aortic prosthesis in atrial fibrillation, with ejection fraction < 45% or left atrium > 4.5 cm: target INR 3 (range 2.5-3.5);

c) patients with bileaflet mitral prosthesis: target INR 3 (range 2.5-3.5).

As recommended, we use aspirin (100 mg/day) adjunction to warfarin in patients experiencing thromboembolism while on adequate oral anticoagulation, unless contraindicated by conditions of high gastrointestinal hemorrhagic risk[10]. Indeed an advantage of adding antiplatelet therapy has been supposed, but most trials comparing this strategy to a more intense warfarin anticoagulation either did not acknowledge the degree of control of INR or were characterized by generally poor INR control[11,12]. In any case, we prescribe more frequent INR assessments in higher-risk patients. It has been demonstrated that an important determinant for thromboembolic and bleeding complications, as well as for long-term survival, is the time-within-the-range factor[13,14]. In this perspective it is important to follow up patients in dedicated Anticoagulation Centers, as we do at our Institution, rather than rely on the management by general practitioners.

A randomized trial has been going on at our Institution for 11 months in patients with 21 to 25 mm aortic mechanical valve prostheses implanted at least 1 year before enrolment, who were in sinus rhythm, had ejection fraction > 45% and left atrium < 4.5 cm, without other cardiac diseases. The study population included 120 patients, divided into two groups: group A comprised 60 patients in whom an anticoagulation regimen with target INR between 1.5 and 2.5 was adopted; in group B (60 patients) the protocol implied an INR range of 2 to 3. All study patients were followed up in our Anticoagulation Outpatient Clinic; follow-up controls including INR assessment were performed once every 2 weeks. The two groups were similar with regard to age, body surface area, cardiac disease and risk factors. Follow-up results (100% complete) have evidenced only one cerebral thromboembolic event and one bleeding event (hemopericardium), both occurring in group B. These results should be regarded as preliminary, since deriving from a small population. However, if confirmed in larger series, they could support low-intensity anticoagulation in well selected patients. The importance of patient selection must be stressed. A large meta-analysis by Vink et al.[15] led to opposite considerations, claiming the superiority of more intense (target INR > 3) anticoagulation, in terms of reduction of adverse event rates. However, that meta-analysis included also series with older generation prosthetic models, therefore our results are advising to consider the new possibilities provided by modern bileaflet designs and how their introduction has changed the issue of anticoagulant therapy.

Examples of the previous attitude to incriminate mechanical prostheses are represented by the widespread information that anticoagulation is contraindicated in the elderly[16] and that coumarin derivatives absolutely should not be administered to pregnant women[17].

Anticoagulation in the elderly

A retrospective study performed at our Institution reported clinical results after isolated aortic valve replacement with bileaflet prostheses in patients ageing > 70 years compared to patients < 50 years undergoing the same procedure[18]. A total of 118 over-septuagenarians (group A) were compared to 122 young patients (group B) operated on in a concurrent period. Patients with associated diseases such as coronary artery disease, mitral valve disease, aortic dissection, infective endocarditis, were excluded from the study. Preoperative clinical data, hospital and late mortality, valve-related and anticoagulation-related complications were compared. Hospital mortality resulted significantly lower in group B (2.45%) than in group A (9.3%, p = 0.022). Mean follow-up time was 50.98 ± 2.23 months. The 12-year survival was significantly lower in group A (69.6 ± 0.08%) than in group B (94.4 ± 0.02%, p < 0.001. The mean INR was 2.17 ± 0.1 in group A and 2.15 ± 0.1 in group B (p = NS). No statistically significant difference was found as regards valve-related and anticoagulation-related complications: one episode of retinic embolism in group A and one ischemic stroke in group B occurred; hemorrhagic complications were 1 in group A (0.9%) and 5 (4.2%) in group B, with an actuarial 12-year freedom from major bleeding of 97.4 ± 0.009% in group A vs 91 ± 0.05% in group B. The higher incidence of hemorrhagic complications in group B was consistent with the greater timeliness of the elder patients to more frequent scheduled control dates,

maybe due to the lower level of social activity and therefore greater compliance to prescriptions. Limitedly to the instance of aortic position, bileaflet valves have shown in our experience not to expose selected elderly patients to higher risks of anticoagulation-related complications when compared to younger ones. This could have been importantly affected by the exclusion of elderly patients with associated coronary artery disease, in whom atherosclerosis itself predisposes to embolic events. However, atrial fibrillation is quite common in elderly patients with heart valve disease, requiring anticoagulation irrespective of the valve substitute implanted (tissue or mechanical). In the absence of other co-morbidities, the prolonged mean life expectancy allows, today, for possible bioprosthetic degeneration even in elderly patients, in whom the inherent risk of a reoperation for prosthetic valve replacement could overwhelm that of a low intensity, accurately followed up anticoagulant therapy. The most recent guidelines[10] include the suggestion to maintain an INR of 1.8-2.5 in these patients, as already reported by other authors[19] with satisfactory results.

Anticoagulation in pregnancy

Anticoagulation with coumarin derivatives during pregnancy has represented another field of interest in our research activity, that started after the observation of 5 cases of prosthetic thrombosis in pregnant patients who had withdrawn warfarin according to the general practitioner's suggestions, substituting it with unfractionated heparin at the beginning of gestation. Today the hypothesis is gaining favor that unfractionated heparin failure in these patients could depend on altered pharmacokinetics, entailing the need for a dose increase and strict monitoring of the activated partial thromboplastin time or anti-Xa heparin level[10,13-20]. However reports of this approach with adjusted higher dose unfractionated heparin are still lacking, and the concern about both hemorrhagic and embryonic risk remains. The results of our experience, published in 1999[21] and thereafter updated in 2002[22], pointed out that the risk of fetal complications in patients with mechanical prostheses continuing warfarin anticoagulation throughout pregnancy varies according to the mean daily dose of warfarin assumed, especially in the first trimester. Between January 1987 and January 2000, 52 patients with mechanical valve prostheses under warfarin anticoagulation during the whole pregnancy experienced 71 pregnancies. Warfarin was withdrawn only 48 hours before and 24 hours after a scheduled cesarean delivery by the end of the 37th week of pregnancy. INR ranged between 2.25 and 4.0 according to the type of prosthesis and site of implantation, with a mean value of 2.5. No maternal complication was observed, while in 30 pregnancies (42%) fetal complications occurred: 23 spontaneous abortions, 5 stillbirths and 2 embryopathies in full-term infants (one case of nasal hypoplasia and one ventricular septal defect).

Dividing the population according to the mean warfarin daily dose, we noted that only three complications occurred in 30 pregnancies (10%) in women averagely taking < 5 mg/day. At multivariate analysis a mean warfarin daily dose > 5 mg/day was the only independent predictor of fetal complication, with an odds ratio of 49.4.

We strongly feel the need, after the analysis of our experience, for a thorough conversation with female patients with previous valve replacement willing to get pregnant as well as with women in childbearing age scheduled for heart valve replacement. Our protocols of anticoagulation imply that patients with a mechanical prosthesis undertaking pregnancy and averagely keeping INR within the therapeutic range with the assumption of < 5 mg of warfarin daily are advised to carry out their pregnancy under warfarin and to deliver by cesarean section according to the above scheme. Patients that must take > 5 mg of warfarin daily in order to maintain INR within the therapeutic range are informed about the risks that pregnancy carries about, and in particular they are made aware that continuing warfarin anticoagulation exposes the fetus to the risk of embryopathy or abortion, while warfarin withdrawal and substitution with heparin, regardless of the way of administration, carries high risk of prosthetic thrombosis and as a consequence also of fetal mortality. When informed, many women, especially if already having one or more children, choose to interrupt pregnancy. If a young woman needs valve replacement, she undergoes a period of preliminary warfarin anticoagulation for the determination of the mean daily dose of warfarin needed to reach the therapeutic INR range: if it is < 5 mg she is suggested to choose a mechanical prosthesis, while if it is > 5 mg then she is suggested to receive a bioprosthesis, informing her about the possibility of a more rapid structural valve deterioration and calcification in pregnancy. Five years after our first publication on warfarin anticoagulation throughout pregnancy the evidence of the dose-dependent fetotoxicity of coumarin derivatives and the option of warfarin continuation have been quoted in an extensive "clinician update review" published in *Circulation* in 2003[23]. More recently, the ACCP recommendations[20] have included the option of low-molecular-weight heparin (LMWH) administration throughout pregnancy or just in the first 12 weeks at high dosages, adjusted to comply with the changes in LMWH pharmacokinetics accompanying pregnancy. In fact studies published so far adopting conventional LMWH doses have reported unacceptable maternal outcomes[24-26]. The ACCP authors themselves acknowledged[20] that currently no randomized trial has been published that proves the efficacy of LMWH in preventing thromboembolic events in this condition and their concluding recommendations are not supported so far by adequate evidence. The aversion of Amer-

ican authors for warfarin admittedly derives from medical-legal concerns[20], since the package insert generically states that it is contraindicated in pregnancy. However in 2004 also the manufacturer of enoxaparin has issued a warning on its safety in pregnancy with mechanical valves and the package insert states that it is not indicated for prosthetic heart valve patients, pregnant patients, or pregnant patients with heart valves[10,13-20]. Again, from our point of view, it is crucial to extensively inform the patients, and this can include the report of those preliminary and incomplete experiences with LMWH, but so far no cardiac surgeon could provide conclusive information to his patients on this approach.

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