EDITORIAL

Prophylactic anticoagulation following the Fontan operation

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Heart 2005;**91**:854–856. doi: 10.1136/hrt.2004.039073

Is it possible to advise either for or against prophylactic anticoagulation in patients following Fontan surgery?

The Fontan procedure was first successfully performed in 1971 in a patient with tricuspid atresia,[1] and has become the preferred approach for surgical palliation in patients in whom a biventricular circulation is not possible. The underlying principle is to divert the systemic venous return directly to the pulmonary arteries, thereby reducing volume overload of the single ventricle and increasing systemic oxygenation. The initial operation utilised a Glenn anastomosis with placement of valved conduits between the right atrium and ventricle and the right ventricle and pulmonary artery. The technique has undergone many modifications attempting to reduce early mortality and morbidity.

A modification that is still encountered frequently in adult patients is the connection of the right atrium to the pulmonary artery either directly or via a conduit. It had been assumed that incorporation of the pulsatile atrial chamber into the circuit would assist flow into the pulmonary circulation. In reality, atrial contraction is not essential to the maintenance of pulmonary blood flow and this approach has been shown to result in progressive atrial dilatation with increased turbulence and even flow reversal. The resultant energy loss may actually hinder flow through the Fontan pathway.[2] Further, right atrial dilatation leads to additional problems such as increased thrombus formation, arrhythmias, and pulmonary vein compression.

More recent modifications have attempted to preserve laminar flow within the Fontan circuit by routing systemic venous blood either through a lateral intra-atrial tunnel to the pulmonary artery, or by direct anastomosis of the venae cava to the pulmonary artery utilising a conduit placed externally to the heart to achieve continuity with the inferior vena cava.[3] These later approaches are also referred to as a total cavopulmonary circulation.

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LATE MORBIDITY AND MORTALITY

The low early postoperative mortality achieved following current Fontan surgery has led to a growing interest in late morbidity and mortality. Together with arrhythmias, systemic ventricular dysfunction, atrioventricular valve regurgitation, and protein losing enteropathy, thromboembolic complications have a major impact on long term prognosis. Survival following thromboembolic complications appears to be very poor, with mortality rates as high as 25% in paediatric series[4] and up to 38% in adult series.[5] The poor prognosis is further compounded by controversy surrounding the management of thromboembolism in these patients, with reports of surgical embolectomy, thrombolysis, and oral anticoagulation all appearing in the literature. As a result, some cardiologists advocate routine prophylactic anticoagulation for all patients following Fontan surgery.[6] This approach has to be weighed against the absence of randomised, controlled, prospective trials, the significant risk of bleeding estimated at 3.9 events per 100 patient years,[7] and the real compliance problems associated with a largely adolescent and young adult population. Given the lack of adequate trial data, it is inevitable that recommendations based upon the available evidence will be weakened. Additionally, the bulk of evidence is based on paediatric series with relatively short follow up time. Extrapolation to the emerging population of long term survivors to adulthood is fraught with difficulty.

INTRACARDIAC THROMBUS

There is no doubt that intracardiac thrombus is a major problem following Fontan surgery. The prevalence detected using primarily transthoracic echocardiography in a large cross sectional survey of 592 patients was 9%[8] with a median time from surgery of 22 months. Of the 52 patients with thrombus in this retrospective study, 24 were on low dose aspirin (because of an atrial fenestration), whereas six "high risk" patients were on warfarin. Far from being exclusively found within the systemic venous atrium (48%), thromboses were observed to almost the same extent in the pulmonary venous chamber (44%), with a much smaller proportion in other locations such as the ligated pulmonary artery stump or hypoplastic ventricular chamber. Screening with transoesophageal echocardiography resulted in the detection of intracardiac thrombus in 33% of a subsequent study population,[9] emphasising the need to consider this approach particularly if transthoracic imaging is either poor or yields equivocal results. In these studies, none of the thromboses had been associated with symptomatic embolism at the time of detection. However, the possibility of clinically silent embolism is very real with evidence of "silent" pulmonary emboli in 17% of adult patients following Fontan surgery.[10] In this study oral anticoagulation appeared to protect against thromboembolism.

THROMBOEMBOLIC COMPLICATIONS

Thromboembolic complications following Fontan operation give rise to significant morbidity and mortality. Thrombus located within the Fontan

circuit may result in obstruction to the pathway or chronic pulmonary embolic disease with ventilation/perfusion mismatch or elevation of pulmonary vascular resistance, all of which may seriously interfere with Fontan physiology. Thrombus located on the systemic side may result in stroke and death as may paradoxical embolism in the presence of right to left shunts—for example, fenestration. Incidences of venous thromboembolism between 3–16%, and of stroke or arterial thrombi between 3–19%, have been quoted in analyses of the data with a tendency to higher rates in more recent studies.[4] Many of these series were based on paediatric populations and the increased incidence in more recent studies probably reflects longer postoperative survival together with a greater awareness and better detection rates. In keeping with this, a recent study of Fontan patients reaching adulthood an average 15 years following surgery documented thromboembolic events in 25%.[5] This high incidence occurred despite more than 50% achieving adequate levels of anticoagulation with warfarin. The authors propose that adult patients may require a higher target INR or addition of antiplatelet agents, particularly since the mortality after an event in this series was 38%. The higher mortality than that observed in paediatric studies suggests that adult patients cope less well with the additional insult from thromboembolism, perhaps due to more advanced ventricular dysfunction.

Overall, there is no consensus from the available evidence regarding the benefit of anticoagulation or aspirin in patients following Fontan surgery. Aspirin or warfarin did not appear to be protective in any of the foregoing studies. A recent retrospective analysis of 101 patients divided into three groups according to the prescription of aspirin, warfarin, or neither concluded that the lowest incidence of thromboembolism occurred in association with warfarin treatment.[11] In contrast, another series of 72 patients routinely administered aspirin postoperatively failed to demonstrate any thromboembolic events over an average follow up of 40 months.[12] These are small series, but it is interesting to note that in the second study great care was taken at the time of surgery to minimise the potential for distortion and disruption of smooth endothelial surfaces in the venous pathways. This raises the possibility that surgical technique may have contributed at least in part to the favourable outcome in the latter study.

EXCESS RISK OF INTRACARDIAC THROMBUS

The evidence so far suggests that there is an excess risk of intracardiac thrombus formation in patients following Fontan surgery that is associated with a high chance of symptomatic thromboembolism, and that does not appear to be eradicated either by warfarin or aspirin therapy alone. Furthermore, the use of prophylactic anticoagulation raises other issues that need to be addressed, such as the timing of treatment after surgery and subsequent duration. Are there clues from the literature suggesting periods of particularly high risk? There does not appear to be any consistent pattern. Some authors have detected thrombus most commonly in the first year after surgery, with a plateau after 3.5 years followed by a second peak after 10 years.[6 13] The late peak in risk would be of particular concern in the long term survivors following Fontan surgery and might suggest a high risk group for prophylactic treatment. However, other authors observed the increased initial risk but a continued risk thereafter,[8] while no association with time after surgery could also be found.[7] Is there an association with age at surgery? The literature is divided on this issue.

In the absence of a consistent temporal pattern of thromboembolism, are there any other risk factors identifying a group that would benefit from prophylactic anticoagulation? It has been speculated that the type of surgery may relate to thrombotic risk. Early analyses have demonstrated a low risk of thromboembolism associated with the extracardiac Fontan utilising homograft or pericardial conduit.[7] In contrast, the atriopulmonary Fontan operation is considered to be of greater risk for thrombus formation, due to right atrial dilatation, with the attendant risks of arrhythmias and venous stasis. However, it has not been possible to document consistently an association between thrombus formation and type of surgery,[8 9] although this may be partly due to the confounding factor introduced by the different lengths of follow up between the older atriopulmonary and the newer cavopulmonary approaches. Other suggested risks related to the surgery include persistent right-to-left shunts,[7] presence of fenestration,[14] type of conduit material,[7] use of valved or non-valved conduits,[7] presence of a conduit diverting hepatic venous drainage in azygos continuation of the inferior vena cava,[15] and prior history of pulmonary artery banding.[16]

ATRIAL ARRHYTHMIA

Although no relation between arrhythmias and thrombus formation has been documented in the literature,[9] atrial arrhythmia has been consistently proposed as a major risk factor for thrombus formation. Furthermore, atrial arrhythmia relates to right atrial dilatation,[17] which is itself prothrombotic. Anecdotal experience suggests that thrombus formation may occur rapidly following a change in atrial rhythm in these patients, irrespective of haemodynamic compromise, and it is our practice to anticoagulate and attempt to restore sinus rhythm as quickly as possible in these patients. This often necessitates DC cardioversion preceded by transoesophageal echocardiography to exclude the presence of new intracardiac thrombus. Despite the lack of evidence, a history of atrial arrhythmias is considered by many to be a good indication for anticoagulation in this patient group.

An underlying prothrombotic tendency contributing to the excess risk of thromboembolism in patients following Fontan surgery has often been cited in the literature.[18] Interestingly, this may relate to preoperative coagulation abnormalities associated with single ventricle physiology. In a comparison of infants with and without single ventricle cardiac defects, concentrations of several anticoagulation factors were significantly lower in affected infants.[19] Similar derangements in concentrations of coagulation factors have also been observed following Fontan surgery and appear to persist for many years.[20 21] The most frequent prothrombotic observations are deficiencies of the anticoagulant factors antithrombin III, proteins C and S,[18 20–23] together with an increase in the procoagulant factor VIII.[21 22] However, an anticoagulant state is also suggested by deficiencies of several procoagulant factors and a prolonged prothrombin time.[20 24] It would appear that there is a dynamic balance between procoagulant and anticoagulant states with a high risk of thrombosis associated with an imbalance in favour of coagulation.

To complicate the picture further, the coagulation profile has also been observed to vary with time following surgery.[25] The aetiology of coagulation factor deficiencies is thought to relate to abnormal haemodynamics. The absence of a right sided pumping chamber may predispose to subclinical hepatic dysfunction through chronically elevated systemic venous pressure, leading to selective disturbances of protein synthesis. In support of this view, a higher superior vena cava pressure predicts the elevation in factor VIII[20] and correlations have also been observed between liver transaminases, right atrial pressure, and various coagulation parameters and factor concentrations.[26] Hepatic dysfunction may also help to explain why patients following Fontan surgery appear to

require lower doses of warfarin than the general population.[27] Although it has been proposed that coagulation factor abnormalities could be used to define a population at high risk of thrombosis,[19 25] no prospective studies of anticoagulation have yet addressed this hypothesis.

SUMMARY

Is it possible to advise either for or against prophylactic anticoagulation in patients following Fontan surgery? Certainly, the evidence suggests that thromboembolism is a major risk factor and it may therefore be considered reasonable to anticoagulate all patients. However, key information is missing regarding the safety and benefit from aspirin and warfarin treatment, as well as target international normalised ratio (INR) levels and timing of therapy. Consequently, if we are to subscribe to an evidence based approach, a blanket recommendation cannot be given. Nevertheless, if a high risk group is to be identified, patients with progressive right atrial dilatation and/or a history of atrial arrhythmia would appear, albeit anecdotally, to present the strongest case for prophylactic anticoagulation. Clearly, prospective controlled studies are required before definitive recommendations can be made.

ACKNOWLEDGEMENTS

MAG and the Royal Bromptom Adult Congenital Heart Programme are supported by the British Heart Foundation.

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