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Original Article

Effect of heart rate control on coagulation status in patients of rheumatic mitral stenosis with atrial fibrillation – A pilot study☆

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ABSTRACT

Background and aim of study: Systemic thromboembolism is a major complication in patients of mitral stenosis (MS) with atrial fibrillation (AF) due to induction of hypercoagulable state. The aim was to assess the relationship, if any, between control of ventricular rate and systemic coagulation factors.

Method: 70 patients of moderate to severe MS in AF were studied. 35 patients with average heart rate >100 beats/min over a 24 hour period assessed by Holter monitoring were considered as having a uncontrolled ventricular rate (Group A) and those with average heart rate ≤100 beats/min as controlled ventricular rate (Group B). 30 healthy volunteers acted as controls.

Results: Plasma concentration of prothrombin fragment 1 + 2 (PF1 + 2) 6600 pmol/ml [interquartile range (IQR) 5400.0–9500], thrombin antithrombin III 22.0 ng/ml [IQR 18.6–28.0], and plasminogen activator inhibitor 46.8 ng/ml [IQR 44.0–54.0] were elevated in Group A as compared to Group B (5400 pmol/ml [IQR 3600–7700] $p = 0.009$, 16.0 ng/ml [IQR 11.0–18.5] $p < 0.001$, and 25.8 ng/ml [IQR 20.9–34.4] $p < 0.001$), respectively. A significant correlation was found between heart rate and all three coagulation markers. Multivariate multiple regression analysis showed only heart rate to be an independent predictor of systemic coagulation activation and risk of thrombus formation.

Conclusion: Control of ventricular rate in subjects of MS with AF produces significant reduction in the activation of the coagulation system and may decrease risk of thrombosis.

☆ Read the Editorial to this manuscript: Hypercoagulable state in mitral stenosis with atrial fibrillation: Can strict rate control prevent thrombus formation?

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1. Introduction

Rheumatic heart disease (RHD) is a major health problem in our country. Mitral stenosis (MS) is the most common manifestation, and atrial fibrillation (AF) develops in 40% patients.[1] Though MS per se induces a hypercoagulable state,[2–5] development of AF is an indication for initiating oral anti-coagulant therapy to prevent systemic thromboembolism. However, risk of bleeding often prevents treating physicians of our country from prescribing vitamin K antagonist (VKA) in these patients. This is due to the fact that VKA therapy warrants regular assessment of International Normalized Ratio (INR) to monitor efficacy and safety of drug. However, in our country, RHD often afflicts subjects of poor socioeconomic status, in whom not only lack of facilities to monitor (INR) but also the cost involved makes them reluctant to use VKA. Studies have revealed that rate control strategy is not inferior to rhythm control strategy in preventing cardiovascular morbidity and mortality including risk of thromboembolism in patients of nonvalvular AF.[6,7] Hypothesizing that rate control per se may have a beneficial effect on systemic hypercoagulable state, Atak et al.[8] in a small interesting study had shown that control of ventricular rate per se with AV nodal blocking drugs produced significant decrease in systemic level of procoagulants in patients of MS with AF. However one the shortcoming of the study was that patients were considered to have controlled or uncontrolled ventricular rate on the basis of a single resting ECG showing ventricular rate ≤100/min and >100/min, respectively. As a result, the level of systemic procoagulants in patients with controlled ventricular rate was reported as similar to those in healthy controls. However, rate control per se is unlikely to decrease level of procoagulants in patients of MS with AF to that in normal subjects. Hence we decided to conduct a pilot study to restudy the systemic coagulation factors in patients with controlled ventricular rate verses uncontrolled ventricular rate (average heart rate ≤100/min or >100/min) assessed over 24 hour period by Holter monitoring. We felt that assessment of the procoagulants in patients with controlled ventricular rate over 24 hours would help to overcome the shortcoming of the previous study.

2. Clinical materials and methods

2.1. Patients

Patients were recruited for the study from the Cardiology Outpatient Department of our hospital, a tertiary care Centre between September 2013 and August 2014. Patients with clinical evidence of significant MS in AF not on any VKA therapy (either never prescribed by treating physician before referral or had stopped therapy for at least 3 weeks prior to presentation in the OPD) were considered for the study. A screening 2D Echo and resting 12 lead ECG was done to confirm the presence of significant MS (moderate to severe; MVA <1.5 cm^2) and AF without associated significant mitral regurgitation (MR) (moderate to severe) or aortic valve disease (moderate to severe aortic stenosis and/or aortic regurgitation). All patients underwent detailed Trans Thoracic Echocardiography (TTE) in order to evaluate valvular involvement in the study group and to exclude cardiac disease in control subjects using Philips iE33 fitted with a commercially available 5 MHz transducer. The mitral valve area (MVA) was calculated using both planimetry and pressure half-time methods. Mean transmitral diastolic gradients and pulmonary artery systolic pressure (PASP) were also measured by Doppler studies. All echocardiographic examinations were performed 5–10 times, as patients were in AF[9]; the mean values of the replicate measurements were calculated. Patients with moderate to severe MS (MVA <1.5 cm^2) with concomitant mild and/or absent MR were included in the study. Trans Esophageal Echocardiography was done in all cases to look for LA/LAA thrombus and left atrial spontaneous echo contrast (LASEC). Patients with LA/LAA thrombus and LASEC were excluded from study, as like LA thrombus,[10] presence of LASEC has also been shown to increase systemic levels of peptide byproducts of coagulation cascade like PF1 + 2.[11] Other exclusion criteria were coexistent left ventricular (LV) dysfunction (ejection fraction <45%), pregnancy, prolonged activated partial prothrombin time (aPTT) or INR, antiplatelet or anticoagulation therapy, diabetes mellitus, renal and hepatic dysfunction, overt malignancy, chronic inflammatory disease, history of systemic and/or pulmonary embolism, history of deep venous thrombosis, and NYHA class IV patients.

After preliminary evaluation, eligible patients were subjected to 24 hour Holter monitoring. We defined controlled ventricular rate as patients having average heart rate ≤100/min along with no individual rate >110% of maximum predicted heart rate for the age of the patient over a 24 hour period as was used in AFFIRM trial.[7] Based on the reports of the Holter, patients were accordingly stratified as either having controlled (≤100/min) or uncontrolled ventricular rate (>100/min).

We decided to study 100 subjects [70 cases and 30 controls] in this preliminary cross sectional pilot study to assess effect of heart rate on systemic coagulation factors (prothrombin fragment 1 + 2 (PF1 + 2), thrombin antithrombin III (TAT)) and plasminogen activator inhibitor (PAI-1) by ELISA. Accordingly, we recruited 35 patients, each with either controlled or uncontrolled ventricular rate (as defined in our study) and 30 healthy volunteers as control group for our study. The controls had no echocardiographic evidence of structural heart disease, were in sinus rhythm and had all other exclusion criteria identical to study patients. The study protocol was approved by the ethical committee of our institution, and informed consent was obtained from each subject included in the study.

2.2. Hematological investigation

Baseline laboratory tests [(hemogram, erythrocyte segmentation rate, renal function tests, liver function tests, PT (prothrombin time), aPTT, fibrinogen and platelet count)] were done in all subjects of our study (cases and controls). Peripheral venous samples of the study subjects for measuring levels of plasma coagulation parameters, including PAI-1, TAT and PF1 + 2 were drawn in the morning between 8 and 10 AM. Samples were taken using 21-G vacuum tube phlebotomy needles into 3.8% 1:9 trisodium citrate-containing tubes, without venous stasis. The plasma was immediately separated by centrifugation of blood (3000 × g for 15 min), and then stored in several aliquots at −70 °C until used for assay.