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Changes in the levels of factor X (FXA) and factor XII (FXIIA) in patients after permanent pacemaker implantation

Denislav Biserov [1, 2], Ivaneta Yoncheva [1, 2, *] and Mariya Negreva [3]

[1] *University Hospital, Burgas, Bulgaria.*
[2] *University Hospital "Virgin Mary" Burgas, Bulgaria.*
[3] *University Hosptal "St.Marina" Varna, Bulgaria.*

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Abstract

Introduction: There are considerable evidences for the activation of coagulation after implantation of medical devices. In addition, the categorical connection between PPM implantation and the development in time of CTEPH (chronic thromboembolic pulmonary hypertension) is proven.

Objectives: To examine the levels of FXa and FXIIa during dynamic in patients after PPM implantation.

Materials and methods: We examined the levels of FXa and FXIIa at the baseline, at 6 weeks, at 12 weeks and at 24 weeks after implantation of dual chamber PPM in 45 patients (25 men and 20 women – median age 72.18 ±9.08yrs.) and in 46 controls (22 women and 24 men – median age 71,96 ±8.75yrs.), corresponding in gender, age and BMI. The method of research was enzyme-linked immunosorbent assay.

Results: The values of FXa and FXIIa at the baseline were not different in patients and controls 92.88 pg/ml vs 98,87 pg/ml ($p>0.05$) and 95.41 pg/ml vs 100.31 pg/ml ($p>0.05$). At the 6 and 12 weeks follow up checks, the values of FXa and FXIIa increased significantly compared to those in controls $p<0.001$ (tabl.1). At 24 weeks, the absolute values were still higher than those in controls, as for FXa the difference did not reach significant meaning ($p>0.05$) (tabl.1) and the values of FXIIa remained at significantly higher level compared to the controls ($p<0.05$) (tabl.1).

Conclusion: Due to permanent maintenance of elevated levels of FXa and FXIIa, we believe it can be accepted that the implantation of PPM leads to a lasting procoagulant state.

Keywords: Coagulation; Cardiostimulation; Chronic Thromboembolism; Pulmonary Hypertension; Right Ventricle Pacing

1. Introduction

In modern cardiology, the treatment of a wide range of diseases is carried out with the implantation of various electronic devices – starting with the conventional pacemaker in bradycardias, the resynchronization therapy in LBBB and left ventricular dysfunction, ICD for primary and secondary prophylaxis of SCD, and to the experimental devices for pressure monitoring in the vascular system, new methods for treatment of heart failure and modulation of the sympathetic activity.

* Corresponding author: Ivaneta Yoncheva.

The implantation of PPM can lead to thromboembolic incidents in a variable period of time after the procedure. On one hand, the endothelial trauma due to the vascular access can provoke early or late onset of vein thrombosis, and on the other hand, the presence of endocardial electrodes can initiate the formation of microthrombi, which can embolize in the pulmonary vascular system [1,2].

Over the last two decades, there have been significant changes in the understanding of the blood coagulation process. The classic cascade model, introduced by Macfarlane, Davie and Ratnoff back in 1964, identifies two activation pathways: an extrinsic (initiated by tissue factor (TF) and an intrinsic pathway (initiated by coagulation factor XII (FXII), which function separately and are capable of independently inducing the formation of fibrin thrombi [3]. However, clinical observations have shown that this model does not accurately reflect *in vivo* hemocoagulation. Therefore, a new hypothesis has been proposed, in which a key point is a clear distinction between physiological activation and pathological thrombosis [4]. The two processes are defined as qualitatively different with different regulatory mechanisms. In healthy people, the coagulation cascade is constantly activated externally. Under the initiating action of the TF/FVIIa complex, low levels of activated coagulation factors are generated mainly outside the blood vessels, which impedes the completion of coagulation. However, in conditions of thrombosis, the internal coagulation pathway is activated by rule. The activated FXII (FXIIa) and FXI (FXIa) in *in vitro* conditions stimulate additional thrombin synthesis, which in turn provides for the propagation and stabilization of thrombi. Therefore, the modern model of hemocoagulation considers the simultaneous activation of both pathways of the coagulation cascade as an integral part of the thrombus formation.

Despite significant developments in the basic understanding of hemocoagulation, there is still uncertainty about the exact pathophysiological mechanisms that initiate the coagulation cascade in thrombotic conditions. After clinical studies have shown normal hemostatic capacity and absence of abnormal bleeding in congenital FXII deficiency, the involvement of FXII in *in vivo* coagulation remains controversial. In this sense, we can say that the intimate mechanisms that determine the tendency for hypercoagulability in patients with PPT remain unclear.

The aim of the study was to investigate the intimate mechanisms that initiate the coagulation cascade in patients with implanted PPM.

2. Materials and Methods

2.1. Study design

The study was conducted in the Cardiology Department at the Virgin Mary University Hospital, Burgas, Bulgaria for the period March 2019 – August 2021. The inclusion of patients and controls began after approval by the Research Ethics Committee at the Medical University of Varna, No 82, March 28th, 2019 and the Virgin Mary University Hospital, Burgas, No. 502, March 21st, 2019, in compliance with the requirements of the Declaration of Helsinki (The World Medical Association, Declaration of Helsinki, 2008). Participants over 18 years of age were included after prior explanation and signing of an informed consent to participate.

Two groups were formed, patients and controls. Selection of study participants was based on clearly formulated inclusion and exclusion criteria (see below).

The study was designed to equalise the demographic and clinical characteristics of both groups in order to minimise the possibility of selection bias and compare them objectively [5]. This contributed to the reliability of the conclusions, as well as the established cause-and-effect relationships. The control group was created similar to the patient group in terms of gender, age and comorbidities.

For the purpose of the study, peripheral venous blood was drawn from a cubital vein, and the levels of FX and FXII were examined in each participant.

Coagulation factors were determined four times in patients: immediately before PPM implantation (baseline value or visit 1 - V1), at 6 weeks (visit 2), at 12 weeks (visit 3 – V3) and 24 weeks (visit 4 – V4) after implantation. The same parameters were also examined only once in controls: at baseline (visit 1 - V1). Blood was centrifuged, and the resulting plasma was frozen and stored, according to the requirements of the assays used.

Indication for implantation in the patients included in the study was presence of complete AVB. After signing informed consent, they were implanted with a dual chamber pacemaker (PPM in DDDR mode), according to the requirements described in the EHRA (European Heart Rhythm Association) expert consensus for this type of procedure [6]. For the

purposes of the study all participants underwent transthoracic echocardiography on the day after implantation to assess LV pump parameters and rule out structural heart disease.

2.2. Study population

For the purpose of the study, 144 patients were screened from which 45 (25 men, 20 women, 72.18 ± 9.08 years) without serious cardiovascular disease (except arterial hypertension and conduction disorder, indication for the procedure) were selected. 99 were excluded from the study due to exclusion criteria (see below).

The control group was formed after screening 102 patients, and 46 (24 men, 22 women, 71.96 ± 8.75 years) were selected according to the set inclusion and exclusion criteria and included in the study after signing informed consent. The controls had no history and ECG evidence of current rhythm-conduction pathology. 39 of them had arterial hypertension as a comorbidity, which was optimally controlled with medications.

2.3. Inclusion criteria for the patient group

- Age≥18 years
- Written informed consent
- Presence of complete AVB as an indication for implantation of a dual chamber pacemaker.
- Eligible comorbidity: moderate arterial hypertension that was medically well-controlled.

2.4. Inclusion criteria for the control group

- Age≥18 years
- Written informed consent
- No history or ECG evidence of rhythm-conduction pathology.
- Eligible comorbidity: moderate arterial hypertension that was medically well-controlled.

2.5. Exclusion criteria:

- Presence of cardiovascular disease: Coronary artery disease (acute coronary syndrome; history of myocardial infarction, regardless of age; coronary revascularisation PCI/CABG; stable angina pectoris); heart failure with depressed pump function; uncontrolled hypertension; inflammatory heart disease: myocarditis, pericarditis, infective endocarditis; congenital heart disease; clinically significant acquired valvular heart disease; cardiomyopathies; thromboembolic events.
- Presence of other diseases: renal or liver failure; diseases of the central nervous system; inflammatory and/or infectious diseases in the last three months; neoplastic or autoimmune diseases; nutritional pulmonary disease; diseases of the endocrine system; surgical intervention in the last three months;
- 3.Presence of pregnancy, systemic intake of NSAIDs (Non-steroidal anti-inflammatory drugs) and antithrombotic drugs and mineralocorticoid antagonists.

2.6. Collection and storage of blood samples

Blood samples were obtained after puncture of the cubital vein (left or right) with a vacutainer system. Venous blood samples were centrifuged for 15 min at 3500 rpm. The separated plasma was frozen at -20 C and after 3 to 4 weeks transferred for storage at -80 C. The included patients had 4 blood samples taken as it follows: at baseline before pacemaker implantation, at 6, at 12 and at 24 weeks after implantation. In the control group, blood samples were tested once during selection for inclusion in the study.

2.7. Laboratory procedures

Factors tested:

- **F X: Act** (Factor X, activity) – determined by a standardized kinetic coagulometric test FII/FVII/FX deficient plasma immunads, Technoclone, Austria).
- **F XII: Act** (Factor XII, activity) – determined by a standardized kinetic coagulometric test FXI/FXII deficient plasma native, Technoclone, Austria)

2.8. Statistical analysis

All analyses were performed with STATISTICA 13.3.0, StatSoft Inc, USA.

Continuous variables were expressed as mean ± SD) and categorical variables were expressed as percentage of the total group. Two-tailed Student's t-test for independent samples was used to compare quantitative variables measured in controls and patients. Values $p<0.05$ were adopted for statistically significant.

3. Results

Table 1 Levels of FXa and FXIIa in patients after dual-chamber PPM implantation and controls. V1 – Visit 1- baseline; V2 – Visit 2-6 weeks after V1; V3 – Visit 3 - 12 weeks after V1, V4 – Visit 4 - 24 weeks after V1.

Indicator	Controls	Patient V1	p	Patient V2	p	Patient V3	p	Patient V4	p
FXa	98.88 ±32.47	92.88 ±33.56	P= 0.39	161.75 ±53.15	P< 0.001	161.73 ±66.13	P< 0.001	111.91 ±35.47	P=0.08
FXIIa	100.31 ±27.60	95.42 ±33.11	P= 0.45	154.20 ±40.49	P< 0.001	156.83 ±53.90	P< 0.001	117.19 ±33.39	P< 0.05

There were no statistical differences between patients and controls in terms of number, mean age, sex and BMI (P = N.S) as seen in Table 2.

Table 2 Demographic characteristics of patient and control groups

	Patients	Controls	P value
Number of participants	45	46	P = N.S
Mean age	72.18 ± 9.08	71.96 ± 8.75	P = N.S
Men/Women	25/20	24/22	P = N.S
BMI (kg/m^2)	27.45 ± 0.64	26.51 ± 0.49	P = N.S

According to the study design, the patient and control groups had no significant differences in comorbidities (P = N.S) and antihypertensive therapy (P = N.S) as seen in Table 3.

Table 3 Clinical characteristics of patient and control groups

	Patients (%)	Controls (%)	P value
Comorbidities			
Hypertensive disease	39 (86.66 %)	37 (80.43%)	P = N.S
Antihypertensive therapy			
Dopegit	23 (51.11%)	24 (52.17%)	P = N.S
Amlodipine	35 (77.78%)	33 (71.74%)	P = N.S
Hydrochlorothiazide	35 (77.78%)	35 (76.09%)	P = N.S

As it is seen in figure 1, the baseline levels of FX in the patient (patients V1) and control (controls V1c) group have no significant difference (92.88±33.56 vs 98.88±32.47, $p>0.05$). Following the results, it can be seen that at 6 (V2) and 12 (V3) weeks the values increase significantly compared to those in the control group (161.75±53.15 vs 98.88±32.47, $p<0.001$; 161.73±66.13 vs 98.88±32.47, $p<0.001$). At 24 weeks, they remain on a higher level compared to those in controls, but the difference does not reach significant meaning (111.91±35.47 vs 98.88±32.47, $p=0.08$).

In figure 2 it is seen that the baseline levels of FXII have no significant difference between patient and control group (95.42±33.11 vs 100.31±27.60, $p>0.05$). Following the results in patients, a statistically significant elevation of values

is established at 6 and 12 weeks (154.20±40.4 vs 100.31±27.60, p<0.001; 156.83±53.90 vs 100.31±27.60, p<0.001). At 24 weeks, the levels of FXII decrease, but remain on a significantly higher level compared to those in the control group (117.19±33.39 vs 100.31±27.60, p<0.05).

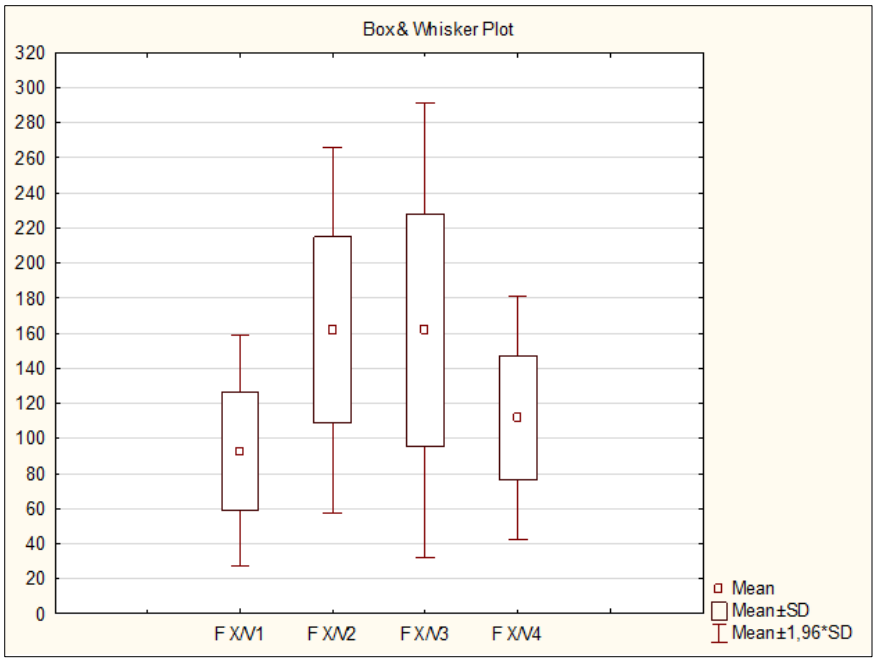

Figure 1 Levels of FX in control group FX/V1c and in patient group at baseline FX/V1, at 6 weeks FX/V2, at 12 weeks FX/V3 and at 24 weeks FX/V4.

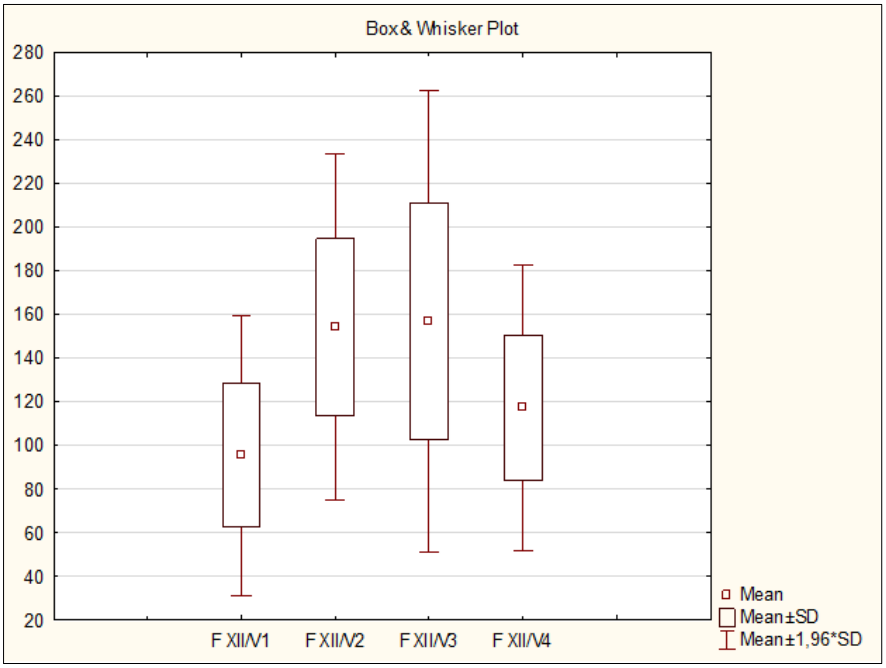

Figure 2 Levels of FXII in control group FXII/V1c and in patient group at baseline FXII/V1, at 6 weeks FXII/V2, at 12 weeks FXII/V3 and at 24 weeks FXII/V4

4. Discussion

Thromboembolism is one of the main causes for morbidity and mortality in the elderly population worldwide [7]. Regardless of etiology, the initial cause is thrombus formation and activation of the coagulation cascade in the body. For this reason, the intimate mechanisms of blood coagulation are the subject of research, both for scientific purposes and in the context of individual cases in clinical practice.

Factor X (FX) is a vitamin K-dependent serine protease zymogen, and it is the first of the final common pathway of coagulation. In the coagulation cascade, the activation of FX can occur via both the extrinsic and intrinsic pathways. Regardless of the mechanism, this is a cell-mediated process, occurring upon exposure of the TF/FVIIa complex to the cell membrane (extrinsic pathway) or upon exposure of the tenase complex on platelet, endothelial or monocyte surface (intrinsic pathway) [8]. Factor Xa also functions as a positive feedback element, activating FV, FVII and FVIII, and therefore fibrin synthesis.

Factor XII is a zymogen of the serine protease FXIIa. It is mainly formed in the liver and circulates in the plasma as a single-stranded polypeptide chain, and after contact activation, it is converted into a double-stranded chain [9]. *In vitro* studies prove that FXII, along with the other elements of the contact system, has an initiating role in the intrinsic coagulation pathway [10].

It turns out that mechanical valves provoke thrombin generation via the intrinsic coagulation pathway with the participation of FXII [11]. This is an example and a reason why FXII should not be neglected in prothrombotic conditions, despite the lack of clinically significant manifestation of the congenital deficiency of this factor. It is appropriate to examine FXII in any prothrombotic condition and assess its role in hemostatic imbalance [12]. In our study, FXII increased significantly even at 6 weeks (Figure 2; $p<0.001$) after PPM implantation and it remained elevated after 24 weeks (Figure 2; $p<0.05$). These results are extremely important from both a scientific and a clinical point of view. They show that FXII is involved in *the amplification of the coagulation signal and the realization of increased "basal coagulation".*

The activated FX, bounded to the non-enzymatic cofactor FVa in the framework of the prothrombinase complex amplificates the rate of prothrombin activation about 300,000 times and leads to explosive thrombin generation [13]. Factors Xa and Va have clearly defined procoagulant activity, determining the rate of thrombin synthesis. Thrombin (FIIa), in turn, has a central role in the coagulation cascade [14]. Factors Xa, Va and IIa are irrevocably responsible for formation of fibrin strands in the clot [15]. They finalize the coagulation cascade and their increased activity is directly associated with the presence of procoagulant conditions [16, 17].

Our results showed significantly higher values of FXa as early as 6 weeks after PPM implantation, and this elevation remains significant even at 12 weeks ($p<0.001$, Figure 1). At 24 weeks, a reduction is observed in the values of FX, as they remain higher compared to those in the control group, despite the fact that the difference does not reach significant meaning at limit value $p=0.08$. These deviations are *evidence of activation of the common pathway of the coagulation cascade as early as 6 weeks after PPM implantation*. They are a good prerequisite for propagation of the coagulation process and enhanced formation of fibrin. *A definite tendency for hypercoagulability occurring extremely early* in the follow-up period is seen.

5. Conclusion

Changes in hemocoagulation were observed even 6 weeks after PPM implantation. They suggest an early tendency for hypercoagulability in that group of patients, with the involvement of the extrinsic pathway.

Compliance with ethical standards

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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