wjpmr, 2020,6(2), 13-17

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

EARLY AND LATE VENOUS THROMBOSIS AFTER PACEMAKER IMPLANTATION

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Article Received on 01/12/2019 **Article Revised on 22/12/2019** **Article Accepted on 12/01/2020**

ABSTRACT

Both early and late complications associated with venous access have been repeatedly reported in scientific literature. Venous thrombosis and stenosis after permanent pacemaker implantation are probably more common than reported incidence in literature due to frequent asymptomatic course. Patients with this complication have a higher potential risk for thrombotic events. Therefore they should be actively screened and the pathogenetic causes for the complication should be clarified. According to the literature, a frequency of 20 to 30% of partial or total thrombosis of the vein used for electrode placement has been reported, and no specific risk factor has been identified for it. At present, the researchers are facing many unclear issues that have yet to be addressed in order to decide on a change in the therapeutic strategy for this group of patients.

KEYWORDS: Thrombosis; pacemaker; venous aaccess; venography.

INTRODUCTION

After the introduction of the transvenous route for pacemaker implantation in early 1965, it became the main route for endocardial electrode placment. Due to its easy access and low risk of complications, it has become the main method for cardiac stimulation, resynchronization and defibrillation.[1,2] Both early and late complications associated with venous access have been repeatedly reported in literature. Venous thrombosis and stenosis after permanent pacemaker implantation are probably more common than the reported incidence in literature due to the frequent asymptomatic course. Because the potential risk to the patient is not underestimated, early and late thrombotic complications associated with pacemaker electrodes should be actively sought. Patients with this complication have a higher potential risk for thrombotic events. Therefore they should be actively screened and the pathogenetic causes for the complication should be clarified.

In 1969, Robboy at al. reported an autopsy series of 7 patients who had undergone pacemaker implantation 5 to 18 months earlier.[3,4] They found focal phobrosis leading to adhesion of the electrode to the endothelium of VCS (vena cava superior) and RA (right atrium), proportional to the elapsed time since electrode placement. An analysis of published data for the period 1960-1991 by Daniel B. et al found post treatment syndromes in 34% of patients, pulmonary embolism (PE) in 9.4% (one half documented by lung scan or angiography) and fatal outcome in 1.2% (3 of 4 deaths due to PE).[15,16] Data from this analysis raise the question about the incidence of the thrombotic complications after pacemaker electrode implantation and their etiology.

In 1989, Antonelli et al. studied a series of 40 patients with implanted permanent pacemakers. Venography was performed at 1-6 months, 6-12 months, and 12-18 months after implantation.[5] The group was analyzed in terms of number of electrodes, type of electrode isolation and venous access. The venograms performed between 1 to 6 months were normal in 31 patients, in six patients they showed partial venous obstruction and in three patients total obstruction. The thromhotic obstructions were located in the subclavian vein, commonly proximal to the cephalic vein junction. At 6 months to 12 months, partial obstruction was observed in 5 patients with previously normal venogram. In patients with partial obstruction established during the first 6 months, there was no progression to total occlusion by the end of the study. Symptoms of venous thrombosis were found in only two patients in this group, manifested with upper extremity edema. No significant difference was found associated with access: cephalic vein or subclavian vein. Interestingly, in the cases of two placed electrodes, one through the cephalic and the other through the subclavian vein, there was no deviation in venogram.[6] These results are unusual since previous studies indicated that venous stenosis developed predominantly in patients with more than one electrode. No difference in incidence was found according to the type of insulation and polarity of the electrode.

This study clearly demonstrates that venous thrombosis can develop early after endocardial electrode placement. Cases of partial or total vein obstruction occurred in around 23% of cases in the early postoperative period, with the percentage approaching the number reported in other series of patients in the later post-implantation period. This indicates that venous thrombosis appears earlier than previously thought after permanent pacemaker implantation.[7,8]

Although transvenous access for placement of electrodes has been the main route for over 50 years, data from published studies so far do not indicate a clearly defined risk factor for the development of early or late venous thrombosis or stenosis.[9,10] There is no direct correlation between the type and insulation of the electrode, thickness and manufacturer. No correlation has been found between complication rate and type of venous access: cephalic, subclavian, or axillary. Several predisposing factors are highlighted: number of electrodes placed, use of hormone replacement therapy, history of prior venous thrombosis, placement of a temporary electrode before implantation, and others. However, anticoagulant therapy performed for other causes has a protective effect on such complications.

In 2012, Mandal S et al. published in PACE data from a study of 20 patients who were clinically registered with upper extremity deep vein thrombosis (DVT) for up to 6 months after pacemaker implantation. Total vein occlusion was found in 6 patients from the group, and partial obstruction in the remaining ones. Analysis of comorbidities showed that diabetes was the most frequent risk factor (present in 45%) followed by smoking (35%), hypertension (30%), obesity with body mass index ≥30 (30%), history of acute myocardial infarction (25%), chronic obstructive pulmonary disease (20%), and history of congestive cardiac failure (15%). Antiplatelets were not found protective against the development of this situation. After 6 months, warfarin anticoagulant treatment resulted in complete resolution of thrombotic complications.

In a study published in 2007 in Europace by Haghjoo M. at al., contrast venography was performed in 100 patients who were candidates for generator change, lead revision, or device upgrade.[17] Patients treated with aspirin (n = 50) and warfarin (n = 11) were included in the analysis, the indication for antiplatelet and anticoagulant therapy being a concomitant disease.

No pathological changes were found in 74%, while venous obstruction to varying degrees was observed in 26%, with 9% having total obstruction and 17% partial. Well-developed collateral circulation was observed in all patients with complete or partial obstruction. All patients were asymptomatic and no abnormalities were found on physical examination.

Numerous patient-related and device-related risk factors were investigated and compared between patients with and without venous complications.

There was no statistically significant differences in terms of age (P = 0.90), sex (P = 0.42), baseline rhythm (P = 0.79), indications for implantation (P = 0.17), left ventricular ejection fraction (P = 0.24), cardiothoracic ratio (P = 0.81), and hypertension (P = 0.08). Regression analysis of the data showed that only the number of leads (P = 0.039, OR: 2.22, and 95% CI: 1.03–4.76) and antiplatelet / anticoagulant therapy (P = 0.044, OR: 2.79, and 95% CI: 0.98– 7.96) were predictors of venous obstruction after transvenous device implantation.

Do carmo da costa et al study included 229 patients with indications of primary permanent pacemaker implantation.[18,19] Exclusion criteria were pulmonary embolism, lower or upper extremity deep venous thrombosis, previous use of central venous catheters, coagulation disturbances, and malignancy. Six months after implantation, contrast venography was performed on 202 patients. 36% had no abnormalities, while 64% had partial or tomplete vein occlusion. The presence of prior cardiac stimulation (P = 0.0001, OR = 4.260, CI = 2.133–8.465) and LVEF ≤40% (P = 0.0378, OR = 3.437, CI = 1.064–12.326) were considered as independent risk factors for the development of venous stenosis or thrombosis 6 months after permanent pacemaker implantation.

The pathogenesis of lead-induced venous thrombosis has not been clearly determined. There are several possible causes early thrombosis: extension of a thrombus from the ligated vein (mainly in cephalic access); electrode-induced endothelial injury, leading to local release of coagulation factors; hypercoagulation state provoked by surgery.[1]

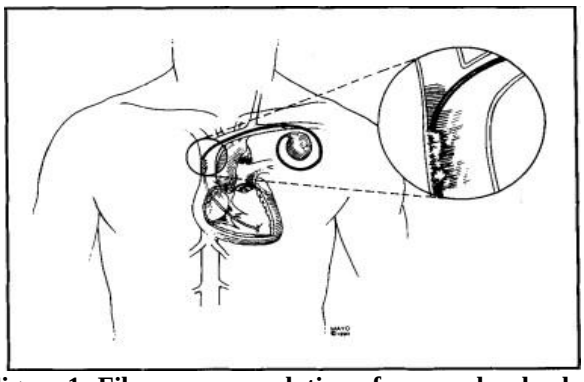

Figure 1: Fibrous encapsulation of pacemaker lead at the vena caval-right atrial junction.

Thrombosis without concomitant vein stenosis occurs relatively early, usually within 1 year after implantation. Symptomatic lead-induced thrombosis in the early post treatment period usually indicates an acute process and manifests itself before adequate collateral network is formed. Later, the symptomatology may be due to a

previous thrombosis that grows towards the axillary vein or occludes existing collaterals. The longer the period from lead implantation and their number being more than one, acts as a "foreign body" type, provoking a chronic fibro-inflammatory state, the blood flow is locally delayed, which can subsequently lead to thrombosis overlay.[20]

In 2004, Cornelis et al. examined 145 patients who had a permanent pacemaker implanted. They were all assessed for venous thrombosis risk factors and examined with Doppler imaging at 3, 6 and 12 months after implantation. Thrombosis was reported in 34 (23%) of patients. In 31 venous thrombosis did not cause clinical symptoms and in 3 it was reversible.[12] Similar results were obtained by Abu-El-Haija B. et al (2015) in a study of 212 patients after pacemaker implantation.[13] They found occlusion of the subclavian or axillary vein in 26% of the patient group (Figure 2). All of them had a well-developed collateral network, which minimized symptoms.

Figure 2: Venography demonstrating subclavian vein occlusion in a patient admitted for pulse generator re-implantation.

However, this data only provides information about the incidence of the examined events. No coagulation factors or other individual characteristics of the patients who have developed any complications were studied.

The relationship between patient procoagulant status and the development of thrombotic complication after implantation was examined in another prospective study of 150 patients by Korkeila P. et al. in 2010.[14] Contrast venography was performed before implantation and after 6 months. All patients underwent transthoracic echocardiography at baseline and at 6 months. In some patients (n = 66), transesophageal ultrasound was performed at 6 months to objectify probable thrombosis at upper vena caval level and the right atrium junction. Computed tomography was performed in the presence of clinical suspection for pulmonary embolism. The patient group included patients who developed lead-induced thrombosis, intracardiac thrombosis, pulmonary embolism, or venous obstruction. They were all associated with similar control patients in terms of age and sex.

To assess the prothrombotic condition, blood samples were examined before implantation and on the day after implantation. Prothrombin fragment 1+2 was examined to evaluate surgical trauma. D-dimer was used to evaluate fibrin formation and degradation. Von Willebrand factor (vWF) and soluble thrombmodulun have been identified as markers of endothelial vascular activation. Patients with thrombotic events were examined for thrombophilia.

There was no significant difference in the thrombosis and control groups in terms of known risk factors for prothrombotic conditions such as obesity, congestive heart failure, advanced age (over 75 years), previous PE, history of neoplastic disease, and hypertension.

The established study endpoints were

Major endpoints - TVO, pulmonary embolism with TVO, pulmonary embolism with lead thrombosis in TEE, pulmonary embolism alone, acute symptomatic upper extremity deep vein thrombosis (UEVDT).

Other endpoints - venographic stenosis, lead thrombus in TEE, venographic lead thrombus

Although no single VTE risk factor emerged as a major event predictor, the majority of the cases with an endpoint were found to have at least one VTE risk factor. As the number of risk factors increases, the rate of thrombotic events also increases (Figure 1/). (P = 0.036, linear dependence). As the number of risk factors increased, the rate of thrombotic events also increased (Figure 1/). (P = 0.036, linear association).

The changes in the investigated hemostatic parameters before and 24 hours after Implantation

Rise in DD levels in the majority (94%) of the patients, and a minimum of two-fold rise in 54%. Procedure-related changes in all of these parameters were, however, comparable in the cases with thrombotic endpoints and their controls

Plasma biomarker levels at baseline and on the first postoperative day indicate that:

- Plasma D-dimer levels increased significantly in both groups (P <0.001),
- The prothrombin fragment F1+2 also increased in both groups, with no significant difference between the groups. (P = 0.06).
- Von Willebrand factor also increased significantly, but with no difference between groups (P = 0.949).
- Thrombomodulin did not change.

Thrombophilia was detected in 2 out of 5 PE cases. It was not known before implantation and none had previous history of thrombotic events.

The data reported so far indicate that the development of venous obstruction, partial or total with or without thrombosis, is not a rare event after implantation of a pacemaker with transvenous access for electrode placement. These cases cannot be associated with the technical parameters of the electrodes or the type of surgery. On the other hand, the risk factors predisposing to thrombotic events are associated with the development of a subsequent complication. The examined hemostatic factors before and after the procedure indicate that surgery itself leads to activation of the coagulation system. However, this activation is transient and cannot explain the thrombotic events.

On the other hand, there are data from a number of studies that the use of antiplatelet agents or anticoagulants on other occasions leads to less thrombosis or stenosis of the vein, through which the electrodes were placed. However, these data are from small groups and are sometimes contradictory. A prospective randomized trial is needed to determine the need and effectiveness of anticoagulant administration as a prophylaxis of thrombotic complications, as well as to evaluate the risk of bleeding in this group of patients.

It is also appropriate to look for individual characteristics of the patient's coagulation system, which is the main factor for the risk of thrombotic events. This raises the question of whether the changes are only local or the placement of endocardial electrodes leads to a systemic procoagulation response in the affected patients. Although cardiostimulation has a decades-long history and there no evidence of a link between thrombotic events and a specific electrode covering material has been found, the question arises as to whether these complications are the result of "foreign body" type provocation or the result of an individual coagulation response. The individuals with an established prothrombotic condition need to be monitored dynamically to assess long-term prognosis. There are many unclear issues that need to be addressed in order to decide on a change in the treatment strategy of this group of patients.

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