PULMONARY HYPERTENSION IN PATIENTS AFTER PERMANENT PACEMAKER IMPLANTATION

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Abstract

Permanent pacemaker (PPM) implantation can lead to thromboembolic events at different times after the procedure. According to literature, 1.7% of patients with pulmonary embolism have an implantable cardiac device. This frequency is higher than reported so far, from 0.16 to 0.47% of the total population.

The pathophysiologic mechanism of pulmonary embolism in chronic thromboembolic pulmonary hypertension (CTEPH) is multifactorial. Recently, there is evidence that not only the organisation of thrombotic deposits in the proximal pulmonary arterial vessels is important, but also the development of small vessel disease, which plays an important role in the evolution and progression of the disease. The role of thrombosis in medical devices in contact with blood flow, such as stents, vascular grafts, heart valves, has been well studied and documented in scientific literature on biomaterials. It is clear that implantable cardiac devices such as pacemakers, similarly to other foreign surfaces exposed to blood flow, promote blood clotting and complement activation. Numerous studies to date have addressed the potential risk of distal vascular involvement of pulmonary circulation in the presence of a pacemaker, but none has conclusively proven this hypothesis.

Over the last decade, there has been significant progress in the therapeutic potential of CTEPH. Pulmonary endarterectomy remains the only therapeutic method that can lead to lasting clinical improvement in these patients while achieving a good quality of life. This method is operational, with high financial value and is associated with the presence of a highly specialised team of specialists. This justifies the search for ways to prevent the onset of the disease rather than treat the consequences.

Keywords

pulmonary embolism • pacemaker electrodes • thromboembolism • endarterectomy • small vessel disease

Introduction

In modern cardiology, the treatment of a wide range of diseases is carried out by implantation of various electronic devices, from the conventional pacemaker for bradycardia, resynchronisation therapy in left bundle branch block and left ventricular dysfunction, implantable cardioverter-defibrillator (ICD) for primary and secondary prevention of sudden cardiac death (SCD), to experimental devices for monitoring vascular pressures, new methods for treating heart failure and modulating sympathetic activity. According to data from registers for implanted cardiac devices in European countries, we can see that with the increase in life expectancy, increases the number of implanted devices per million people [1]. More than 500 000 devices are implanted worldwide each year. Therefore, precision in the clinical approach to pacemaker patients is becoming increasingly important.

PPM implantation can lead to thromboembolic events at different times after the procedure. On the one hand, endothelial trauma in vascular access can provoke early or late venous thrombosis, and on the other hand, the presence of endocardial electrodes can initiate formation of microthrombi, leading to embolisms in the pulmonary vascular bed. According to protocols from pathoanatomical studies, thromboembolic complications (mainly asymptomatic pulmonary thromboembolism and electrode-associated thrombi) found in PPM patients are much more common than clinically established [2, 3].

The recently growing interest in the study and treatment of pulmonary vascular disease has led to increased research and improved diagnosis of patients with chronic thromboembolic pulmonary hypertension (CTEPH) [4].
CTEPH is defined if after 3 months of adequate anticoagulant treatment the following is established:

1. Mean pulmonary arterial pressure >25 mmHg in pulmonary capillary pressure <15 mmHg;
2. Pulmnoangiography data for reduced perfusion of one or more segments of the lung.

The number of patients with CTEPH is unclear. Until recently, it was defined by patients who experienced pulmonary embolism, in which the criteria for this diagnosis were established with a frequency of 0.1 to 5.1% in the course of follow-up.

CTEPH is a result of a single or recurrent pulmonary thromboembolism followed by incomplete thrombi resolution with subsequently developing fibrous organisation and remodelling of affected arteries and increased pulmonary artery resistance, progressive right ventricular failure and fatal outcome. Only 66% of patients with CTEPH have evidence of previous pulmonary thromboembolism, and for the rest, the cause is another pathophysiological process. Recurrent thromboembolism is also more common in men, while both sexes are equally affected by CTEPH, which means that pathogenesis here deviates from the classical pathway of thrombosis and thrombolysis [5, 6].

The discovery of clinical risk factors for CTEPH has shed light on new molecular mechanisms for the formation of thrombotic formations, their persistence in the vascular lumen and their fibrous transformation.

The pathophysiological mechanism of pulmonary hypertension in CTEPH is multifactorial. Recently, there is evidence that it is important not only to organise thrombotic deposits in the proximal pulmonary arteries, but also the development of small vessel disease, which plays an important role in the evolution and progression of the disease.

Risk factors for PE-associated CTEPH include: idiopathic form of embolism, recurrent episodes of embolism, a large perfusion defect, younger age, and mean pulmonary pressure above 50 mmHg at diagnosis [7, 8]. Some laboratory parameters are found in higher concentrations in CTEPH patients, such as factor VIII, lupus anticoagulant (LA), antiphospholipid antibodies, (APA) von Willebrand factor (vWF), plasminogen activator inhibitor type 1 (PAI-1) and fibrinogen.

A team of researchers from Bratislava, Bohacekova et al., analysed 81 patients (30 male and 51 female) with CTEPH, confirmed by cardiac catheterisation, half of them undergoing surgical treatment (endarterectomy) [9, 10]. All patients were screened for concomitant pathology. The team focused on the known established risk factors for CTEPH: idiopathic and recurrent PE, DVT, neoplastic disease, chronic inflammatory condition, presence of pacemaker electrodes, thyroid pathology, splenectomy, autoimmune disease, blood type other than 0. In both patients and controls, detailed studies of coagulation parameters, platelet aggregation (spontaneous aggregometry), serum Von Willebrand factor (vWF) and PAI-1 levels were performed to assess endothelial damage. Results showed that in 79% of cases there was previous PE, in 59.3% a known DVT, and in 19.8% an idiopathic PE. In addition, 19% had history of thyroid pathology, 71% had blood type other than 0, 6.2% had inflammatory bowel disease, and 2.5% had a pacemaker or splenectomy. From haematological risk factors, spontaneous platelet aggregation (SPA) was found to be significantly higher in the CTEPH group (10.9±4.3% vs. 8.4±6.2%), as well as vWF activity, fibrinogen and FVIII levels, but not significantly.

The results from this study show the importance of SPA and the change in haemostatic parameters in the development of CTEPH, as well as the need for additional studies.

**Discussion**

The discovery of the pathogenetic mechanisms and differentiation of high-risk CTEPH patients is the basis of many studies in this area. An analysis by Bonderman et al. of European CTEPH Registry data included 687 patients [11]. The study was retrospective and conducted in three major European Cardiovascular Research Centres: Medical University of Vienna (359 patients), Medical University of Prague (95 patients), Medical University of Homburg (233 patients). Results confirm the currently accepted risk factors, more commonly associated with CTEPH, such as infected pacemaker electrode, splenectomy, previous venous thrombosis, blood type other than 0, lupus anticoagulant and antiphospholipid antibodies. Thyroid pathology from replacement therapy and neoplastic disease are highlighted as additional risk factors.

Recent data from Rohith Nayak in JACC 2018 [12] show a clear link between CTEPH and implantable cardiac devices (ICD). CTEPH is a potentially treatable disease through pulmonary endarterectomy. They studied 982 CTEPH patients referred for this type of surgical treatment for the period January 2009 - December 2015 at the University of California, San Diego (UCSD). Results showed that 14 patients had implanted PPM before surgery and 3 had ICD (1.7% of the total). It was found that 12 out of 17 (70.6%) patients with PPM had distal vascular disease compared to 241 out of 933 (25.8%) patients without ICD (p = 0.0002). Venous thromboembolism was present in 50% of the PPM group and in 78.6% of non-PPM patients.

The established 1.7% incidence of pulmonary embolism in patients with ICD was higher than previously reported – 0.16-0.47% in the general population. Moreover, there was a prevalence of small vessel involvement and low association with previous venous thromboembolism. This suggests that
ICD electrodes can be a source of microthrombi that embolise distally and compromise pulmonary vascular circulation. This thesis is supported by data from the cardiovascular surgery team at UCSD. Medani et al. analysed and published data from 1500 pulmonary endarterectomies, performed in patients with symptomatic CTEPH for the period March 1999 – December 2010 [13, 14]. In those patients, pulmonary hypertension was associated with endocardial pacing electrodes and preoperative pulmonary angiography showed minimal peripheral thromboembolic involvement. However, intraoperatively, they established more severe involvement of peripheral vessels, which after endarterectomy led to normalisation of haemodynamic parameters.

The role of thrombosis in medical devices in contact with blood flow, such as stents, vascular grafts, heart valves, has been well studied and documented in scientific literature on biomaterials. It is clear that implantable cardiac devices such as pacemakers, similarly to other foreign surfaces exposed to blood flow, promote blood clotting and complement activation [15].

A population-based study by Pederson et al. found a 0.3% risk of venous thromboembolism at 3 months and a 1.9% risk at 5 years after ICD implantation [16, 17]. There is also abundant data on the study of endocardial electrodes and formation of thrombotic masses on their surface [18]. In a retrospective study by Supple et al. in patients with ICD who underwent intracardiac echocardiography in preparation for an ablation procedure, thrombosis was found in 30% of cases [19]. A similar incidence of intracardiac electrode thrombosis was also demonstrated by Novak et al. in an autopsy study of patients with a pacemaker or ICD, n=90 (33% in ventricular electrode and 48% in atrial electrode) [20]. Also in some cases there was simultaneous thrombosis, both intracardiac and in the vein used for access. Based on this, they conclude that pulmonary thromboembolism was direct cause of death in 4 patients. Also, 8 patients were diagnosed with non-massive thromboembolism, and according to medical records during their lifetime, they were oligosymptomatic.

Numerous studies to date have addressed the potential risk of distal vascular involvement of pulmonary circulation in the presence of a pacemaker, but none has conclusively proven this hypothesis. Novak's analysis found that patients with CTEPH and a pacemaker were more often associated with distal vascular pathology. This suggests that electrodes may be a source of thrombi, which embolise in segmental and subsegmental branches of the pulmonary artery.

Organised thrombi in these small vessels are more difficult to remove in surgical endarterectomy and may even be referred to as inoperable in some centres [21].

According to UCSD data, despite their higher risk profile, patients with CTEPH and presence of cardiovascular implantable electronic device (CIED) had comparable postoperative hemodynamic parameters and long-term prognosis to patients without a pacemaker. This shows that this group of affected individuals is indicated for surgery as well as explantation of the electronic device to avoid recurrence of symptoms [22, 23].

Development of risk scores and scales for predicting complications and selecting patients with indications for treatment is applied in a significant number of socially significant diseases. As early as 2001, the CHADS2 score was introduced as a predictor of ischemic stroke in patients with non-valvular atrial fibrillation (AF). After analyses and studies, this score was extended to CHA2DS2-VASc, increasing the accuracy of predicting the risk of ischemic events and included in the recommendations of the European Society of Cardiology from 2016. There are also data from literature on the predictive value of CHA2DS2-VASc for cardiac events in patients without AF [24]. A 2015 study by Podolecki et al. showed an association between CHA2DS2-VASc and increased in-hospital mortality in patients with acute myocardial infarction. Melgaard et al. obtained similar results [25]. They found that higher CHA2DS2-VASc was associated with increased risk of IMI and death in chronic heart failure patients with or without AF [26].

Several mechanisms may explain the predictive role of CHA2DS2-VASc in adult patients. All risk factors are associated with increased incidence of ischemic brain events, both in AF and non-AF patients. Diabetes mellitus, hypertension and congestive heart failure are accompanied by endothelial dysfunction, increased thrombosis, increased levels of some adhesion molecules and oxidative stress. All of these lead to a prothrombotic state. On the other hand, as the number of risk factors increases, so does the number of ischemic events.

By analogy, a risk scale for patients with ICD can be developed, where the use of antithrombotic drugs could prevent deposition of thrombotic masses and their microembolisation in the pulmonary vascular bed. Differentiating this group will not be easy. On the one hand, the definite connection between the prothrombotic state, formation of microthrombi, their embolisation and development of CTEPH must be proved. On the other hand, AF incidence increases with age. Data from ICD are used to register these paroxysms, which is an indication for initiating anticoagulant therapy as a prophylaxis of thromboembolic events. The target population for the study should consist of patients with dual-chamber pacemaker with no evidence of AF paroxysms, and the presence or absence of risk factors for thrombotic events is debatable.

In a population-based study mentioned above, Pederson et al. [16] looked for a link between venous thromboembolism and concomitant pathology in patients with ICD/CRT-D. Comorbidity was determined, based on data from the Danish National Patient Registry, using the Charlson Comorbidity
Index (CCI) score, which has been validated as an adequate tool for assessing prognostic assessment in patients with ICD. Results showed a 2.7-fold higher incidence of venous thromboembolism in patients with severe comorbidity compared to those without concomitant pathology [27].

**Conclusion**

The scientific community has the task to specify a risk scale for predicting those patients with implantable cardiac devices who would benefit from prophylactic treatment with an antithrombotic agent.

**Conflict of Interest Statement**

No conflict of interest is declared.

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