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AN ABNORMAL FLOW PROFILE OF INTERNAL JUGULAR VEIN IN PATIENTS IMPLANTED WITH PACEMAKER-LEADS

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Abstract

Background ; Pacemaker (PM)-lead-induced venous thrombosis is a rare but serious complication. Its early detection is diagnostic challenge. Lead-induced venous thrombosis causes internal jugular vein (IJV) engorgement, but little attention was given to the IJV blood flow pattern. Our aim was to characterize the IJV flow profile of patients with PM-leads, and to identify the risk factors of the lead-induced venous thrombosis by using IJV stasis as a surrogate marker. **Method & Results** ; 43 patients implanted with PM-leads were studied. Blood stasis of left IJV was found in 20 of 43 (47%), in which spontaneous echo contrast was observed in all patients with IVJ stasis. According to the ultrasound based IJV flow pattern, patients were classified into two groups ; no-stasis group and stasis group. Average number of implanted leads in stasis group was significantly higher than that in no-stasis group (2.39 ± 0.10 vs. 2.75 ± 0.12, $P = 0.0304$). Although Hb, D-dimer levels and right ventricular function were unrelated, the reduced left ventricular ejection fraction (LVEF) had an association with findings of IJV stasis. **Conclusions** ; The number of PM-leads relates to the occurrence of IJV stasis. Additionally, the reduced LVEF could be a causative factor for IJV stasis in patients with PM-lead.

Key words : pacemaker-leads, venous thrombosis, venous ultrasound, blood stasis, internal jugular vein

Introduction

During the past six decades, technology of implantable cardiac rhythm management devices has evolved from single-chamber and fixed-rate pacemakers (PMs) to multi-chamber and rate-responsive units capable of pacing and cardioversion or defibrillation, while reducing the pulse generator size and improving longevity. The number of patients with transvenous PM-leads currently has been dramatically increased. Pacemaker implantation (PMI) is complicated by major thrombotic event which is a rare[1] but serious complication. The underlying mechanism of the lead-induced venous obstruction is considered to be lead-induced mechanical stress triggering vascular wall inflammation, fibrosis, thrombosis, and ultimately obstruction. Lead-induced venous obstruction are most commonly asymptomatic and symptomatic cases are seen infrequently (1-3%)[2]. Therefore, reported incidence of PM-lead thrombosis is likely to be underestimated. The obstruction sometimes causes superior vena cava (SVC) syndrome. Although lead-induced SVC syndrome is rare, once it occur, the patient has serious condition. Since patients implanted with three PM-leads has been increasing as cardiac resynchronization therapy (CRT) become familiar, the increased risk of de-

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veloping the lead-induced venous obstruction is concerned. However, its early detection is diagnostic challenge. It is desirable to devise a novel assessment approach for SVC stenosis.

Venous ultrasound has recently received increased attention in the clinical setting. It is commonly used to search for blood clots, especially in the veins of the leg, in which spontaneous echo-contrast (SEC) appears on B-mode images as moving curls of smoke in the lumen of veins. This phenomenon is caused by increased ultrasonic backscattering from red blood cells. SVC obstruction causes internal jugular vein (IJV) engorgement and stasis, but little attention was given to the SEC of IJV in the patients implanted with PM-leads.

The purpose of this study was to characterize the IJV flow profile including SEC in patients implanted with PM-leads, and to identify the risk factors of the lead-induced venous obstruction by using IJV stasis as a surrogate marker.

Method

Study Population

This was a retrospective observational study using data extracted from our prospectively collected database. Between September 2015 and June 2018, 43 consecutive patients admitted to Akita University Hospital for their first pulse generator replacement or device upgrade were enrolled in the study. Twenty one men and 22 women with a mean age of 68±15 years (range 33-91) were included. Underlying diseases were coronary artery disease (24.3%), dilated cardiomyopathy (22.0%), hypertrophic cardiomyopathy (12.2%), hypertension (51.2%), diabetes (29.3%) and valvular heart disease (33.3%). There were 16 patients implanted with PMs, 13 with an implantable cardioverter-defibrillators (ICD) and 14 with cardiac resynchronization therapy (CRT) devices. Of all patients, transvers leads were implanted from left pectoral side by subclavian approach. Twenty one patients were implanted two PM-leads, and other 22 patients were implanted with three or more PM-leads. All leads were in place for an average of 79.5 months.

Blood investigation

In all patients, venous blood was drawn for laboratory evaluation of white blood cell (WBC), hemoglobin (Hb), hematocrit (Hct), platelet (Plt) and D-dimer.

Echocardiography

Cardiac function was evaluated by transthorasic echocardiography using a Philips iE33 Ultrasound Machine (Philips Medical Systems, Andover, MA, USA). The parameters analyzed are as follows : left ventricular ejection fraction (LVEF), left atrial dimension (LAD), LV end-diastolic dimension (LVDd), e' determined from spectral pulsed-wave tissue Doppler imaging, tricuspid annular plane systolic excursion (TAPSE), tricuspid Regurgitation Peak Gradient (TRPG) and diameter of inferior vena cava (IVC).

Venous ultrasound

Left IJV flow profile was evaluated at the dispensary or during their hospitalization. Venous ultrasound of IJV was performed for all patients in the supine position using a Philips iE33 Ultrasound Machine (Philips, Andover, MA, USA) equipped with an 11 MHz linear transducer, by an experienced sonographer. We tried to minimize changes of settings during insonation, although depth was adjusted according to subjects' condition. Ultrasound examination of IJVs included longitudinal and axial sections.

Statistical analysis

Continuous data are presented as mean±SD and ranged when appropriate. Continuous variables were compared by Student's *t*-test in case of normal distribution. Otherwise, the non-parametric test Mann-Whitney U was used. For categorical data, χ^2 analysis was used, and the Fisher exact test for cell count less than five. A P value 0.05 was defined as statistically significant. The software GraphPad Prism 7 was used for statistical analysis.

Results

Characterization of IJV flow pattern in patients with PM-leads

Blood stasis of left IJV was found in 20 of 43 (47%), in which SEC was observed in all patients with IVJ stasis. Enrolled subjects consisted of 21 patients with two PM-leads and 22 patients with three or more PM-leads. According to the left IJV flow pattern (Figure 1), we categorized patients having ante-grade flow without stasis as no-stasis group (n=23), and patients having stasis and/or reverse flow as stasis group (n=20).

Comparison of patient characteristics between no-stasis group and stasis group

Patient characteristics are summarized in Table 1. Patient-related and device-related risk factors were investigated and compared between no-stasis group and stasis group. There were no statistically significant differences in terms of age (P=0.205), sex (P=0.763), BSA (P=0.443), the use of diuretics therapy (P=0.544) and anticoagulant therapy (P=0.538). Also, no significant differences between no-stasis group and stasis group were observed in the type of device and the period from PMI (P=0.3132). However, average number of leads per patient in stasis group was significantly higher than that in no-stasis group (2.39±0.10 vs. 2.75±0.12, P=0.0304). A 42-year-old patient who was implanted with four leads due to the complication of lead breaking had a SVC occlusion and IJV stasis with thrombosis. CT and venography showed SVC obstruction (Figure 2A and B). Venous ultrasound revealed the enlargement and thrombus in left IJV (Figure 2 C and D).

Comparison of laboratory data between no-stasis group and stasis group

In laboratory analysis, there were no significant differences between no-stasis group and stasis group (Table 2). RBC, Hb and Hct in the stasis group slightly tended to be higher than those in stasis group. Although D-dimmer levels were slightly elevated above normal in both groups, there were no significant differences.

Assessment of LV and RV functions by echocardiography

To evaluate the cardiac function, echocardiography was conducted in all patients. There was no statistically significant difference in LVDd (P=0.179), LAD (P=0.357) and e' (P=0.426). Of note, echocardiographic variables of the study population showed that LVEF in the stasis group was significantly lower than that in no-stasis group (58.3%±3.7% vs. 43.4%±4.3%, P=0.0125). Right ventricular function indicated by TAPSE, TRPG and IVC diameter were not significantly different between no-stasis group and stasis group (Figure 3).

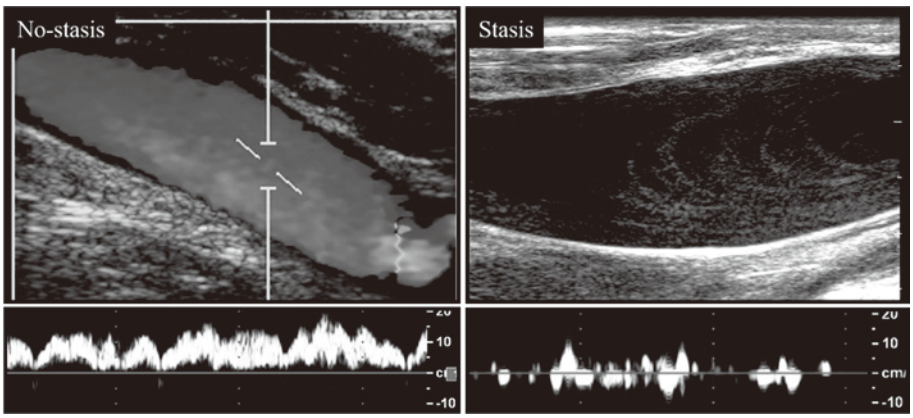

Figure 1. Two-dimensional and pulsed-wave Doppler ultrasound images of IJV
We categorized patients having ante-grade flow without stasis as no-stasis group (left side panels), and patients having stasis and/or reverse flow as stasis group (right side panels).

Table 1. Characteristics of the patients

	No-stasis	Stasis	Pvalue
Patients, *n*	23	20	
Age, years	70±3	65±3	0.2048
Men, *n* (%)	12 (52)	9 (45)	0.7626
Body surface area, m^2	1.60±0.05	1.66±0.06	0.4431
CRT, *n* (%)	6 (26)	8 (40)	0.5151
ICD, *n* (%)	9 (39)	4 (20)	0.2025
PM, *n* (%)	8 (34)	8 (40)	0.7611
Average number of lead per patient	2.39±0.10	2.75±0.12*	0.0304
The period from initial PMI (months)	94±20	68±15	0.3132
Anti-coagulant therapy, *n* (%)	11 (48)	7 (35)	0.5375
Diuretics, *n* (%)	11 (48)	12(60)	0.5435

Data are expressed as means ± SD or numbers (%). *$p < 0.05$; No-stasis vs. Stasis.
CRT ; cardiac resynchronization therapy, ICD ; implantable cardioverter-defibrillators, PM ; pacemaker.

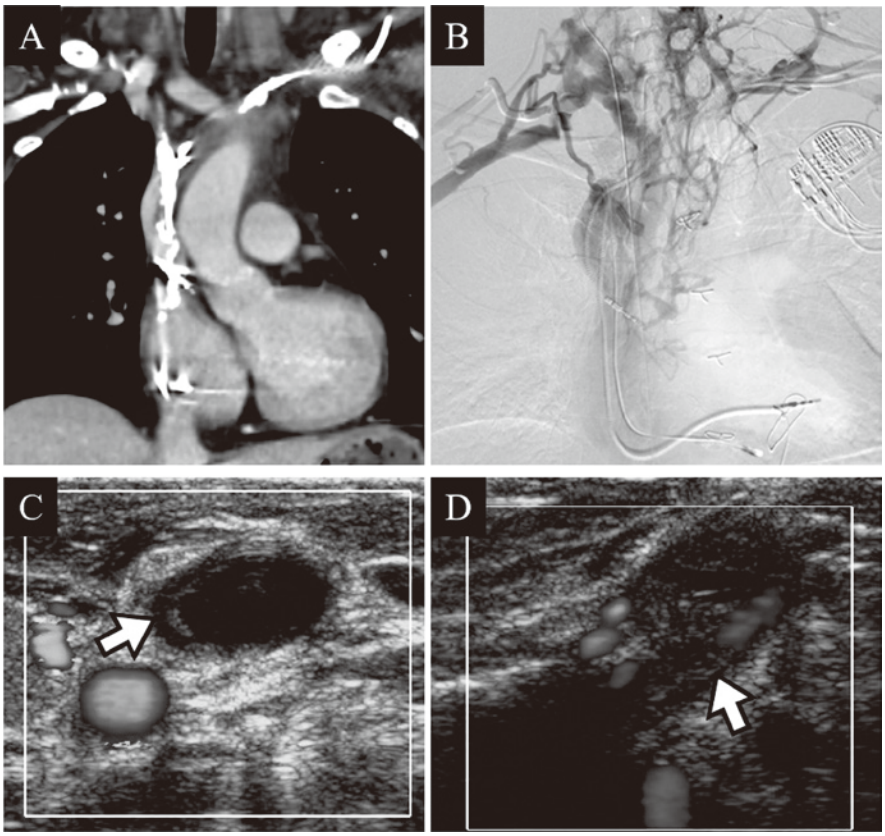

Figure 2. A representative case of leads-induced SVC syndrome and IJV thrombosis.
(A) Contrast-enhanced CT image. (B) Venography showed SVC occlusion with collaterals. Transverse (C) and longitudinal (D) power Doppler ultrasound images show the thrombus in the left IVJ (arrows).

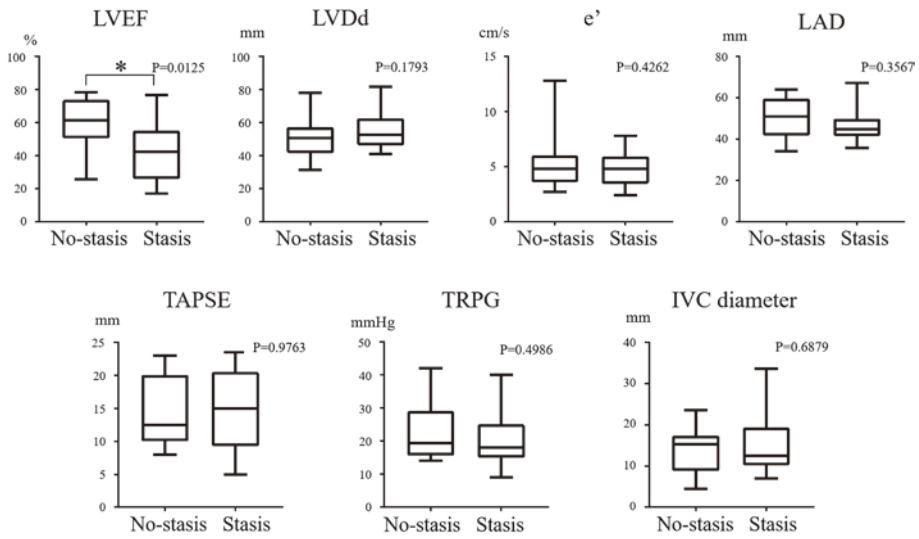

Figure 3. Comparison of echocardiographic variables between no-stasis and stasis group.
LVEF in the stasis group was significantly lower than that in no-stasis group. Data are expressed as means ± SD. $*p < 0.05$.

Discussion

The main findings of this study are as follows : (1) The number of lead was related with occurrence of IJV stasis. (2) LVEF in the stasis group was significantly lower than that in no-stasis group. (3) There were no significant difference in D-dimmer, RBC and Hb between no-stasis group and stasis group.

PM-lead-induced thrombus formation may be caused by multifactorial factors including all components of the classic Virchow's triad, i.e. injury to vessel walls, impairment of blood flow and hypercoagulability. Although a predictor of PM-lead-induced thrombus in transvenous systems has been an object of study for a long time, there is little agreement as to risk factors that lead to venous stenosis[3-8]. This is likely for two reasons. One is a rarity of patients with the lead-induced venous thrombosis. Thus, it is difficult to amass the data and extract parameters. Another reason is the difficulty to conduct experimental animal studies that pertain to the lead-induced venous thrombosis. In this study, we used IJV stasis as a surrogate marker of lead-induced thrombosis, which is considered to be a precursor state of thrombosis. To the best of our knowledge, the present study is the only ultrasound study to evaluate the IJV flow profile in patients with pacemaker leads who are more prone to the lead-related venous thrombosis.

Table 2. Laboratory data

	No-stasis	Stasis	*P* value
WBC, /μl	6,347±517	6,653±603	0.7014
RBC, × 10,000/μl	400±18	439±17	0.1402
Hb, g/dl	12.1±0.5	13.2±0.4	0.1300
Hct, %	36.3±1.4	39.4±1.4	0.1311
Pit, μg/ml	19.9±1.5	18.0±1.2	0.2831
D dimer, × 10,000/μl	2.0±0.4	2.1±0.5	0.9732

Data are expressed as means ± SD.

Our data showed that average number of leads in stasis group was significantly higher than that in no-stasis group (Table 1). Conversely, occurrence rate of an IJV blood stasis with SEC was significantly higher in patients implanted with three PM-leads compared with patients implanted with two PM-leads. These results imply that the implantation of multiple leads are associated with an increased risk of venous obstruction. Although the fuller study of cellular mechanisms of venous obstruction lies outside the scope of this paper, it is reasonable to

postulate that the implantation of multiple leads increases the propensity to endothelial injury and local inflammation. In addition, the almost cases with three PM-leads were implanted with CRT for the treatment of severe heart failure due to asynchronous and hypokinetic LV motion. As mentioned later, it is likely that low LVEF and subsequent prolong circulation time might increase blood viscosity.

Our data showed the lower LVEF in the stasis group compared with no-stasis group. In general, patients with low LVEF are characterized by low cardiac output and prolongation of circulation time. Blood is recognized as non-Newtonian fluid and its viscosity varies depending on the shear stress in blood vessel wall[9]. Hyperviscosity has a close relation with thrombus formation[11,12]. Therefore, it is likely that reduced LVEF is associated with IJV blood stasis with SEC.

Unexpectedly, in this study, no-stasis group as well as stasis group had high D-dimer levels (Table 2). As shown in Table 2, there was no difference in D-dimer levels between no-stasis group and stasis group. In the clinical setting, D-dimer is used as an initial screening test to diagnose patients who have signs, or symptoms suggestive of venous thromboembolism (VTE). All the guidelines agree that D-dimer testing can be used to rule out VTE in patients with a sufficiently low pretest probability of VTE[12-14]. However, D-dimer testing cannot be used in patients assessed to have a high pretest probability. Thus, patients with a negative D-dimer result can be ruled out, while patients with a positive D-dimer result need to have imaging performed for confirmatory diagnosis. Many factors are known to play a key role in changing the sensitivity and specificity of D-dimer testing, including the extent of thrombosis and fibrinolytic activity, anticoagulant therapy, comorbidity due to surgical or medical illnesses, inflammatory diseases, elderly age and cancer. The possibility remains that those factors influence D-dimer testing also in this study.

It is generally accepted that hemoconcentration could be a risk factor for thrombosis. Previous study by Sagesaka T, *et al.* showed that hemoconcentration could be a risk factor for thrombosis even within the normal range, especially beyond the boundary of $5.0\times10^6/mm^3$ of RBCs[15]. In our data, stasis group tended to have hemoconcentration, however, it could not achieve statistical significance (Table 2). Possible explanation for the difference between our results and Sagesaka's data might be attributed to small sample size in this study.

Limitation

The present study must be interpreted in the face of certain limitations. This study was a retrospective analysis and limited by the fact that the incidence of venous obstruction prior to implanting the leads was not been investigated. Moreover, the size of the study population was relatively small, and the study is a single center experience.

Conclusion

These results suggest that the number of lead relates to the occurrence of IJV stasis. Additionally, the reduced LVEF could be a causative factor for IJV stasis in patients with PM-leads.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

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