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The role of hemostatic markers as venous stenosis or occlusion predictors following first transvenous cardiac device implantation

Andrzej Cacko[1], Eliza Kozyra-Pydyś[2], Monika Gawałko[2],
Grzegorz Opolski[2], Marcin Grabowski[2]

[1]Department of Medical Informatics and Telemedicine, Medical University of Warsaw, Poland
[2]1st Department of Cardiology, Medical University of Warsaw, Poland

Abstract

Background: *Among patients with an implanted cardiac implantable electronic device (CIED), ipsilateral upper extremity vein stenosis or occlusion (VSO) is observed more frequently than in the general population. However, there are no data available concerning the relationship between hemostatic markers (and their dynamics) and the occurrence of VSO. The aim of this study was to assess the predictive value of beta-thromboglobulin, the von Willebrand factor (vWF), fibrynogen and D-dimer for VSO development among first time CIED recipients.*

Methods: *This is a single-center, prospective study of consecutive first time CIED recipients without upper extremity VSO in baseline ultrasound examination. Biochemical data were collected from all the patients before CIED implantation (first measuring), up to 7 days subsequent (second measuring) and 6 months after the operation (third measuring). Primary endpoint was defined as the presence of upper extremity VSO at the implantation site during the ultrasound examination 6 months after the operation.*

Results: *The study included 71 patients (mean age 73.1 ± 10.5 years; 39 [55%] male). The incidence of VSO within 6-months follow up was 21.1%. Average concentrations of hemostatic markers increased significantly in all patients immediately after CIED implantation. Serial hemostatic marker concentrations were similar in patients who met or did not meet the primary endpoint, apart from vWF. The mean concentration was significantly elevated in the group of 15 patients who reached the primary endpoint (p = 0.032).*

Conclusions: *A significant increase in vWF concentration at 6 months post implantation may be a marker for VSO occurrence.* (Cardiol J 2021; 28, 5: 690–696)

Key words: cardiac implanted electronic devices, vein stenosis or occlusion, hemostatic markers

Introduction

Among patients implanted with a cardiac implantable electronic device (CIED), ipsilateral upper extremity vein stenosis or occlusion (VSO) is observed more frequently than in the general population and occurs in 14–64% of patients with CIED [1–3]. Although VSO is usually asymptomatic it can lead to upper extremity edema, paresthesia or pain and limits CIED upgrade.

Currently, several mechanisms of VSO formation are suggested. The most frequently mentioned one is the thromboembolic mechanism [4, 5]. The postulated thromboembolic mechanism of VSO

formation prompts the search for biochemical indicators of pro-thrombotic activity, which would correlate with the risk of VSO.

The concentration of D-dimers is a biochemical marker of the thromboembolic process. The precursor of D-dimers is fibrinogen: one of the coagulation system proteins. It seems that among patients after CIED implantation, the concentration of D-dimers and fibrinogen should be higher in patients with VSO [6]. Platelet activation results in secretion of many clotting activators, including beta-thromboglobulin (beta-TG). The von Willebrand factor (vWF), a glycoprotein involved in the hemostasis process, prevents the degradation of factor VIII of the coagulation pathway, promoting the formation of connections between collagen fibers, glycoproteins of the intercellular matrix and endothelial cells and blood platelets.

However, there are no specific data available concerning relationship between concentrations of the aforementioned hemostatic markers (and their dynamic) and the occurrence of VSO after CIED implantation. The aim of this study was to assess the predictive value of beta-TG, vWF, fibrynogen and D-dimer concentrations for VSO occurrence among first-time CIED recipients.

Methods

Study population

A single-center, prospective study was performed of consecutive first-time CIED recipients hospitalized in the documented department.

Patients included were those with:
— qualification for first-time intravenous implantation of the CIED system;
— written, informed consent to participate in the study.

Patients excluded were those with:
— upper extremity, shoulder girdle or jugular vein stenosis confirmed by preoperative imaging;
— venous compression syndromes of the upper extremity (thoracic outlet syndrome, cervical rib, compressive soft tissue tumors);
— thrombophilia;
— previous intervention on venous system at the intended implantation site.

Clinical assessment and follow-up

Each patient underwent an ultrasound examination to assess the condition of the venous system of the upper extremity, shoulder girdle and jugular veins before the planned operation and 6 months after the operation. The assessment of jugular veins and veins of shoulder girdle were performed in the supine position, while radiopaque and axillary veins were additionally assessed in the sitting position. A duplex Doppler mode consisting of a real-time B-mode image with a color-flow Doppler overlay was used for assessing the morphology and venous flow. All ultrasound examinations were carried out by experienced echocardiographers (all certified with the second-degree accreditation in echocardiography of the Echocardiography Working Group of the Polish Cardiac Society) using the Philips EnVisor C (Philips Electronics NV, Netherlands). The tests were examined using a 5–13 Mega-Hertz array transducer in both longitudinal and transverse sections.

All clinical conditions analyzed in the study, like diabetes or prediabetes, chronic heart failure, arterial hypertension, atrial fibrillation or atrial flutter, cancer, previous stroke or transient ischemic attack, were assessed based on subject medical history and in accordance with current guidelines.

The procedure of CIED implantation was performed in a reference cardiology unit by an expected electrophysiologist. For each subject the first-choice procedure to gain vascular access was venesection of cephalic vein. If this was unsuccessful, a subclavian vein puncture under ultrasound imaging was performed. Patient characteristics due to the number of implanted leads and type of vascular access was presented in a previous paper [7].

The concentrations of beta-TG, vWF, fibrynogen and D-dimer were measured before CIED implantation (first measuring), up to 7 days subsequent (second measuring) and 6 months after the operation (third measuring). Manual EIA kits were used to measure beta-TG and vWF (Shanghai Sunred Biological Technology Co, Shanghai, China). Roche Diagnostics laboratory kits were used in order to conduct D-dimer and fibrynogen tests using Cobas 6000 analyzer.

Study endpoints

Primary endpoint was defined as the presence of VSO in the vein system of the upper extremity, shoulder girdle or jugular vein at the implantation site during the ultrasound examination 6 months after the operation. For veins accessible to direct insonation, the criteria of noncompressibility, visualization of echogenic intravascular mass, and the absence of respiratory variation were used (subclavian vein). For veins inaccessible to direct insonation, the criterion of monophasic flow at the stenosis site with no retrograde wave or no

Table 1. The mean concentrations of biochemical markers measured at 1st, 2nd and 3rd measuring point in the whole study group.

Hemostatic marker	Mean ± SD	Median (IQR)
Fibrynogen [mg/dL]		
1st measuring	351.5 ± 81.8	343 (86–530)
2nd measuring	424.3 ± 95.5	408 (178–627)
3rd measuring	404.2 ± 98	391 (212–619)
D–dimer [mg/dL]		
1st measuring	723.5 ± 664	458 (170–3210)
2nd measuring	1252.1 ± 1068.3	875 (326–6586)
3rd measuring	1021.4 ± 778.5	766 (230–3890)
von Willebrand factor [μg/L]		
1st measuring	13.26 ± 5.55	12.25 (3.78–27.56)
2nd measuring	18.35 ± 9.29	16.64 (5.37–66.55)
3rd measuring	19.56 ± 11.11	17.38 (0.32–56.86)
Beta–thromboglobulin [μg/L]		
1st measuring	14.24 ± 5.77	13.43 (3.42–30.37)
2nd measuring	18.12 ± 6.93	18.18 (2.21–34.18)
3rd measuring	17.86 ± 6.5	10.06 (5.61–32.7)

Continuous and ordinal variables are shown as median (interquartile range [IQR]) and as mean ± standard deviation (SD).

color signal or flow in the vessel lumen was used (middle part of subclavian, brachiocephalic vein) to detect VSO [8, 9].

Statistical analysis

Statistical analysis was performed using Statistica v. 12. Quantitative variables are expressed as mean ± standard deviation and median (interquartile range). Categorical variables are presented as an exact number and percentage of patients. Differences between two groups for continuous variables were tested by the Mann-Whitney U-test. The comparisons of categorical variables were analyzed using the χ^2 independence test. Two-way tables were assessed with the χ^2 test with double-sided Fisher exact test due to a limited number of patients. A p value < 0.05 was defined as statistically significant. The dynamics of biochemical marker changes were assessed using the Friedman test. Post hoc analysis with the Wilcoxon signed ranks test was performed using the Bonferroni correction for multiple comparisons (1 vs. 2, 2 vs. 3, 1 vs. 3 measuring point), resulting in a significance level set at p < 0.017.

Results

The study population consisted of 71 patients (mean age 73.1 ± 10.5 years; 39 [55%] male).

Detailed patient characteristics were summarized in Supplemental Content (**Suppl. Table S1**). Implanted device systems comprised: cardioverter-defibrillator (n = 26), single-chamber or dual-chamber pacemakers (n = 34) and cardiac resynchronization therapy (n = 11). The incidence of VSO within 6-month follow up was 15 (21.1%) patients.

The mean concentrations of biochemical markers and their dynamics assessed at the 1st, 2nd and 3rd measuring points in the whole study group are presented in Table 1 and Figure 1. The average concentration of each biochemical marker increased significantly between the 1st and the 2nd measuring points.

The average values of biochemical markers at all measuring points were similar among patients who met or did not meet primary endpoint, except for vWF concentrations at the 3rd measuring point. The average concentration of the vWF 6 months after the CIED implantation was significantly greater in the group of patients with VSO than in the other subjects (p = 0.03). It was due to an additional increase of vWF concentration between the 2nd and 3rd measuring point observed only among patients with VSO (Fig. 2). The mean concentrations of biochemical markers and their dynamics in subgroups with and without primary endpoint were presented in Table 2 and Figure 2.
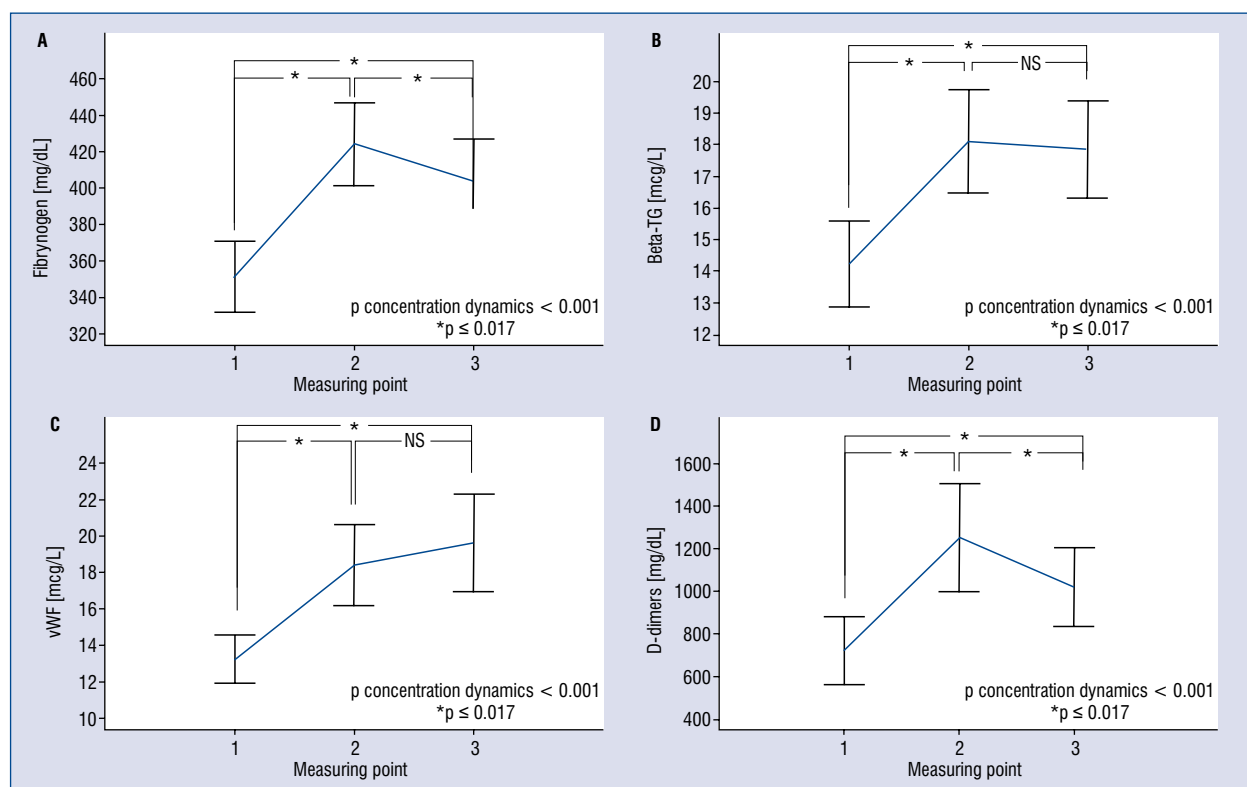
Figure 1. The mean concentrations of biochemical markers measured at 1st, 2nd and 3rd measuring point in the whole study group; beta-TG — beta-thromboglobulin; vWF — the von Willebrand factor; NS — non-significant.

Table 2. The mean concentrations of biochemical markers measured at 1st, 2nd and 3rd measuring point among patients who met or did not meet the primary endpoint.

Hemostatic marker	Endpoint		Non-endpoint		p
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Fibrynogen [mg/dL]					
1st measuring	347 ± 87.5	313 (244–530)	352.7 ± 81	352 (86–481)	0.61
2nd measuring	410.7 ± 91.3	388 (264–564)	427.9 ± 97	413.5 (178–627)	0.54
3rd measuring	398 ± 100.6	376 (234–591)	405.9 ± 98.2	396.5 (212–619)	0.82
D-dimer [mg/dL]					
1st measuring	762.9 ± 864.6	424 (170–3210)	712.9 ± 608.5	458.5 (170–2908)	0.58
2nd measuring	1247.3 ± 1132.6	825 (357–4506)	1253.4 ± 1061.1	929 (326–6586)	0.71
3rd measuring	1091.1 ± 949.7	736 (400–3890)	1002.8 ± 734.8	766 (230–3148)	0.92
Von Willebrand factor [µg/L]					
1st measuring	14.62 ± 5.77	15.29 (4.9–23.3)	12.89 ± 5.49	11.7 (3.78–27.56)	0.31
2nd measuring	16.54 ± 6.85	15.7 (8.63–30.6)	18.83 ± 9.84	16.92 (5.37–66.56)	0.41
3rd measuring	23.71 ± 10.14	18.79 (14.67–42.5)	18.45 ± 11.19	16.47 (0.32–56.86)	0.32
Beta-thromboglobulin [µg/L]					
1st measuring	16.2 ± 8.58	13.42 (3.42–30.37)	13.72 ± 4.72	13.52 (4.09–25.75)	0.64
2nd measuring	18.31 ± 8	19.01 (2.21–34.18)	18.07 ± 6.7	17.59 (3.03–34.14)	0.77
3rd measuring	18.11 ± 6.63	17.07 (7.95–30.63)	17.79 ± 6.53	17.04 (5.61–32.7)	0.91

Continuous variables are shown as median (interquartile range [IQR]) and as mean ± standard deviation (SD). P values are given for differences between the patients with and without primary endpoint.
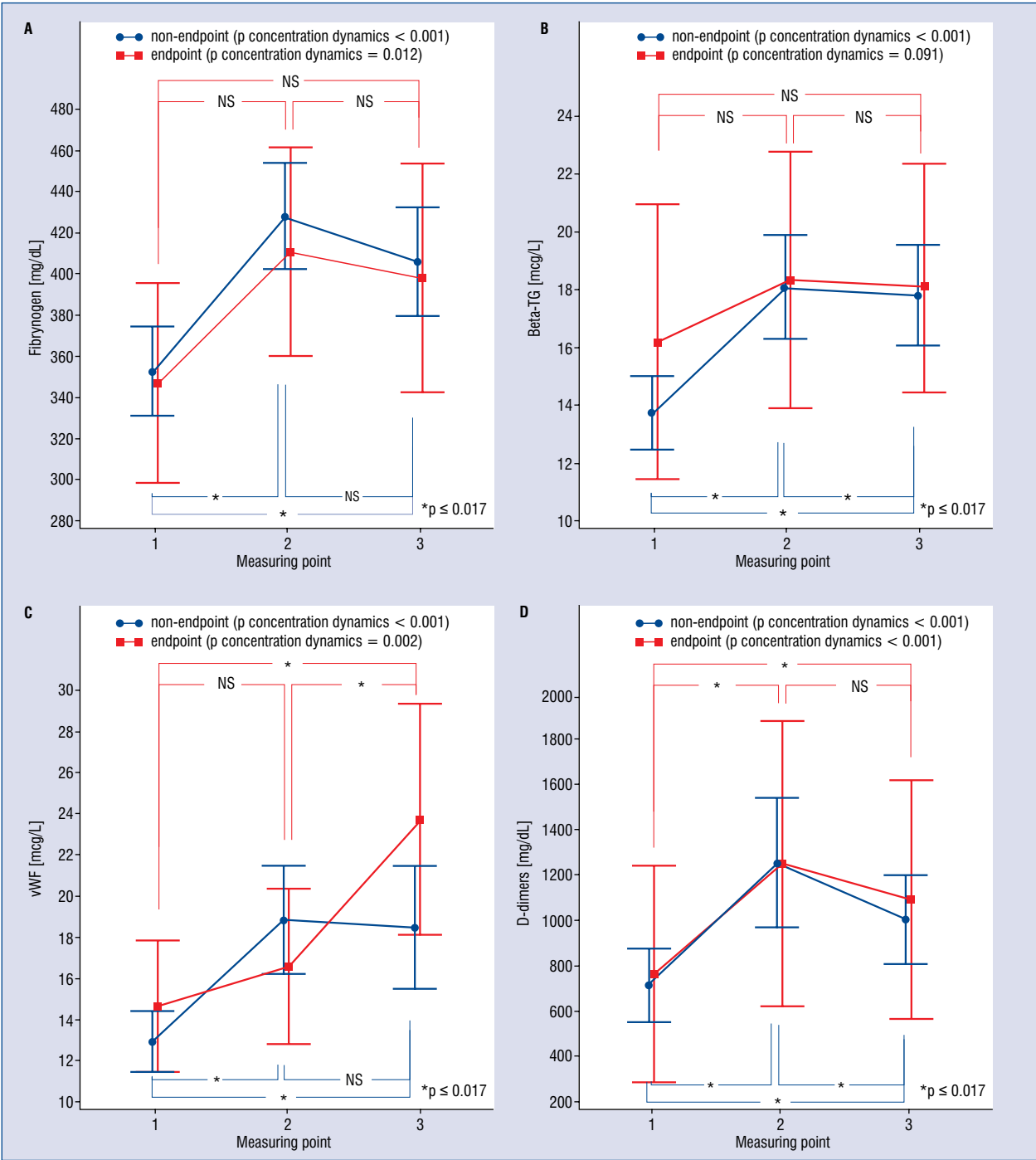
Figure 2. The mean concentrations of biochemical markers measured at the 1st, 2nd and 3rd measuring point among patients who met or did not meet the primary endpoint; beta-TG — beta-thromboglobulin; vWF — the von Willebrand factor; NS — non-significant.

The observation that anticoagulation therapy or presence of cancer was not associated with an increased risk for primary endpoint occurrence as described in a previous publication [7].

Discussion

The present paper was focused on simultaneous analysis of the dynamics of concentrations

of biochemical markers of inflammation (fibrinogen), coagulation activity (D-dimers) and platelet activation (vWF and beta-TG), in the population of first-time CIED recipients. According to available research, this is the first report describing dynamics of hemostatic markers among first-time CIED recipients followed-up by up to 6 months and their relationship with VSO, one of the most common complications of the lead placement into the vascular system. It should be emphasized that this report is important with regard to ensuring a better understanding of the mechanism of VSO occurrence and its prediction after CIED implantation.

Nevertheless, in starting the discussion, readers may be kindly forwarded to a previous paper presenting results of comparisons between subjects with and without study endpoints [6]. As it is a real-life population of first time CIED recipients, patients were included who had clinical conditions like atrial fibrillation, arterial hypertension, chronic heart failure, previous stroke or cancer. Though, during the follow up neither antithrombotic or anticoagulant treatment nor any of these conditions significantly increased the prevalence of VSO. Moreover, the presence of diabetes or prediabetes reduced the risk of VSO supporting the thesis of the inductive influence of inflammation. Reported observations built a multivariable prognostic model for VSO occurrence in the previously mentioned paper [7].

The procedure of CIED implantation, with intervention in the vascular system, initiated a significant increase in the concentration of biochemical markers. This is understandable considering the intervention itself (incision or puncture of a large venous vessel and preparation of the device pocket). However, only the vWF concentration, measured six months after the CIED implantation was significantly increased among patients who reached the primary endpoint. Moreover, the only marker that its concentration increased between the 2nd and 3rd measuring point among patients with VSO was vWF. It is worth mentioning that VSO occurrence is mostly associated with vessel trauma and subsequent inflammation [10]. This is consistent with the literature as vWF is synthesized in endothelium and is realized due to cell injury [11]. Moreover, inflammatory leukocytes release oxidizing agents that can render vWF more stable, with enhanced platelet binding, explaining higher concentrations of vWF among patients with VSO [12].

Results of this study propose possible clinical implantation of serial vWF measurement in a screening for VSO among first-time CIED recipients. Significant increases of vWF concentration between 7th day and 6th month follow-up from CIED implantation may identify patients with VSO. Still, as this is a pilot prospective study, additional observations in this field are required.

The fibrinogen and D-dimer concentrations have significantly decreased between 2nd and 3rd measuring points regardless of the occurrence of VSO. Also, the beta-TG concentration was reduced within 6 months (but not significantly). It is an important finding considering a conviction that promoted hemostasis and thrombosis should result in increase of fibrin-degradation-product concentration.

Finally, it is worth exploring the role of beta-TG. This protein is stored in alpha-granules of platelets and is released in large amounts after platelet activation. It acts as a megakaryocyte maturation factor and helps in regulating platelet production, thus it has been recognized as a marker for activated platelets. Current studies suggest that an increased level of activated platelets, measured by higher plasma levels of beta-TG, is associated with increased risk of incidence of cardiovascular disease [13, 14]. For instance, the Plicner et al. [15] study included 108 consecutive patients undergoing coronary artery bypass grafting, demonstrated that increased platelet activation contributes to the occurrence of perioperative myocardial infarction in an early postoperative period. However, Kubota et al. [16], a study with 746 participants, do not support the hypothesis that higher concentrations of beta-TG reflect an increased risk of cardiovascular endpoints in the general population.

Limitations of the study

The present study is single-centered and nonrandomized. The size of the study population was the result of the test methodology (the study group encompassed only a population of first time CIED recipients) and the cost of biochemical markers and limited funding. Moreover, the study population is homogeneous as all of patients who underwent their first cardiac device implantation and were assessed exactly at 6 months postoperatively. Another limitation of this study is the single image approach to diagnose VSO. However, color Doppler ultrasonography is a non-invasive method with high sensitivity (80%) and a specificity (90–100%) for detecting VSO [17, 18]. Another limitation is the fact that no attempt was made to study the ratio between the caliber of the vein and number of leads inserted.

Conclusions

All biochemical hemostatic marker levels increased significantly in response to transvenous CIED insertion and the presence of electrodes in the venous system. A significant increase in vWF level at 6 months post implantation may be a marker of VSO occurrence.

Conflict of interest: None declared

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