Case Report

Pacemaker Lead Thrombosis and Disseminated Intravascular Coagulation Following Warfarin Therapy: Case Report and Review of the Literature

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A 54-year-old male with a permanent pacemaker was admitted to the intensive care unit due to a stroke. This occurred six days following the initiation of warfarin therapy for paroxysmal atrial fibrillation. The patient presented with profuse bleeding through the sites of venipuncture and laboratory evidence of disseminated intravascular coagulation. Echocardiography revealed multiple thrombi adjacent to the pacemaker leads. Underlying thrombophilia and/or any other systemic disorders were excluded. Thereafter, he exhibited multiple organ failure and despite all therapeutic efforts he expired. In the absence of any thrombophilia, the rare patient with a preexisting intracardiac device, in whom warfarin is prescribed, might experience thrombotic events. The latter could be linked with the preexisting device and/or could be triggered by the initiation of warfarin treatment, but this is merely a hypothesis.

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The initiation of warfarin therapy may paradoxically increase the risk of thrombosis.[1] However, thrombotic complications are rare and are usually associated with an underlying thrombophilic disorder.[1] A common clinical manifestation of this hypercoagulable state is skin necrosis, appearing 3 to 6 days after initiation of coumadin derivatives.[2] Herein, we present a patient with a permanent pacemaker, who manifested devastating disseminated intravascular coagulation with associated massive intravascular thrombosis adjacent to the pacemaker leads six days after the initiation of warfarin therapy. The right cardiac chambers, innominate (RIV) and subclavian (RSCV) veins, in which the pacemaker leads were placed, as well as the neighboring internal jugular vein (RIJV) were found to carry thrombotic material on ultrasound evaluation.

Case presentation

A 54-year-old Caucasian male presented with a left hemiparesis of acute onset; soon after he was intubated due to coma and admitted to the intensive care unit (ICU). The patient had a history of hypertension, while a dual-chamber right-sided pacemaker had been implanted due to sinus nodal dysfunction two years previously. Six days before the patient's admission to the ICU, warfarin therapy was initiated for asymptomatic self-limited paroxysmal atrial fibrillation (AF), as documented by 24-hour Holter rhythm readings. At that time, echocardiography could not detect any pathology. Warfarin was started at 5

mg on the first day and then 2 mg/day; anticoagulation therapy with heparin was not co-administered, and prothrombin time (PT) or international normalized ratio (INR) were not determined during this 6-day period. The brain computed tomography (CT) scan upon admission was normal (Figure 1A), but another one performed 48 hours later depicted a large infarct in the area of the right middle cerebral artery.

Upon admission, the patient exhibited severe bleeding diathesis. Laboratory examinations revealed prolongation of INR >7 (normal range 0.8-1.2) and of PT >180 s (normal range 25-39), thrombocytopenia (platelet count=27,000 /μl, normal range 150,000-400,000), decreased fibrinogen (0.08 g/L, normal range 0.18-0.38) and increased D-dimer (6 μg/ml, normal values <0.3 μg/ml) serum levels. Because of the continued active bleeding through the sites of venipuncture and the oro-nasal mucosa, vitamin K, fresh frozen plasma (FFP) and platelet transfusions were prescribed. Nevertheless, 24 hours following admission he developed multiple organ failure; thus, he was supported with vasopressors and continuous venous-to-venous hemodiafiltration.

A thorough transthoracic (TTE) and transesophageael (TEE) echocardiographic study was performed. However, neither a source of emboli in the left sided cardiac chambers (including left atrial appendage) nor a patent *foramen ovale* was found. TTE revealed a large mobile mass within the right atrium. TEE confirmed the presence of this material, which showed typical thrombus morphology. It extended to the superior *vena cava* and was attached to the pacemaker leads (Figure 1B and 1C). A triplex study of the carotid system was normal, while thrombi within the RIV and the RSCV, following the path of the pacemaker leads, as well as within the RIJV, were evident (Figure 1D and 1E). No previous attempts to cannulate these veins were recorded. Thereafter, continuous infusion of unfractionated heparin (UFH) in a weight adjusted dose (10 iu/kg/h) was initiated.

During his hospitalization, a series of laboratory tests failed to detect any underlying thrombophilia or any other systemic disorder. Thus the diagnosis of disseminated intravascular coagulation (DIC) was established and other possible causes of his bleeding diathesis (i.e. sepsis, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, autoimmune disorders) were ruled out. In particular, plasma tests for protein C, protein S, von Willebrand and antithrombin III activity, activated protein C resistance, serum levels of tissue plasminogen activator, plasminogen activator inhibitor-1, homocysteine and serum ADAMTS 13 activity, were found to be normal. Additionally, a lupus anticoagulant test was negative, and serum levels of IgG and IgM antibodies against cardiolipins were found to be within the normal limits. Repeated blood cultures were not indicative of endocarditis.

Follow-up imaging studies revealed neither any other site of thrombosis nor any other pathology. Four days following admission, another brain CT scan showed that the infarct underwent hemorrhagic transformation, while new ischemic infarcts and severe cerebral edemas were depicted (Figure 1F); hence, the infusion of UFH was discontinued, and a decompressive craniectomy was performed. Blood clotting tests and platelet concentrations remained vertically abnormal throughout the period of hospitalization. Unfortunately, the patient expired due to multiple organ failure one month following admission.

Discussion

Hypertension is a major predictor of stroke in the setting of AF. Our hypertensive patient was at intermediate risk for thromboembolism according to the revised international guidelines; hence thromboprophylaxis was recommended with an oral vitamin K antagonist (Grade 1A).[3] However, warfarin may paradoxically exert a short-term prothrombotic effect when first administered. Warfarin decreases the production of the vitamin K-dependent coagulation factors (factors II [prothrombin], VII, IX and X), but also of protein C, an endogenous anticoagulant factor; thus, during the first days of therapy a transient hypercoagulable state may be generated, as the levels of anticoagulant protein C may decline faster than the vitamin K-dependent coagulation factors.[1] The early elevation of PT-INR may be misleading at this stage, as it may reflect the depletion of only the factor VII, which has a half life of about six hours, whereas factor II has a half life of approximately five days.[1] Nevertheless, thrombotic complications are rare during warfarin therapy and are commonly related either to underlying thrombophilic disorders (such as protein C and/or S deficiency) or to high loading doses.[1] The hypercoagulable state may be manifested as skin necrosis that occurs 3 to 6 days after the initiation of coumadin derivatives.[2,4] Rarely, major thrombotic complications— such as thrombosis of the abdominal aorta, as well as DIC, especially in patients with

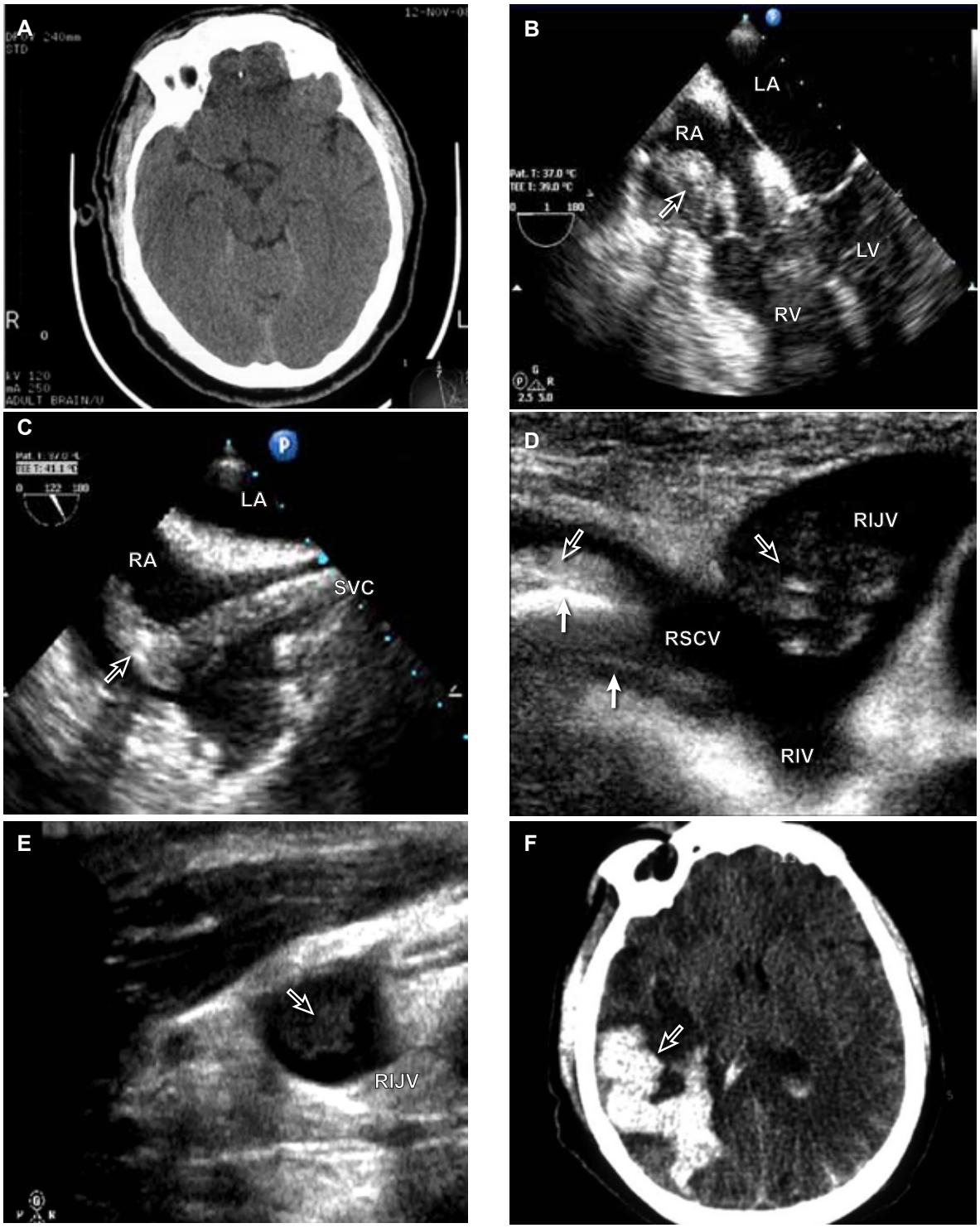

Figure 1. A) Cerebral infarcts or hemorrhagic lesions were not identified in the initial brain CT scan. B) Thrombotic material (open arrow) attached to the pacemaker leads depicted by transesophageal echocardiography (mid-esophageal four chamber view) C) A mid-esophageal bicaval view indicating the thrombotic substance (open arrow) following the path of the pacemaker leads from the right atrium towards the superior vena cava. D) Ultrasound view demonstrating the right subclavian and right internal jugular veins at the level they form the right innominate vein. Observe the thrombi (open arrows) in the right subclavian vein attached to the pacemaker leads (white arrows) as well as in the right internal jugular vein. E) Vascular ultrasonography revealing a thrombosed (open arrow), non-compressible, partially obstructed right internal jugular vein at the upper neck level. F) Follow-up brain computed tomography scan depicting a hemorrhagic transformation of the right middle cerebral artery infarct (open arrow), as well as diffuse cerebral ischemic lesions. RA – right atrium; RV – right ventricle; LA – left atrium; LV – left ventricle; SVC – superior *vena cava*; RSCV – right subclavian vein; RIJV – right internal jugular vein; RIV – right innominate vein.

thrombophilia or occult cancer – may be documented following warfarin treatment.[5-7] In our case, no evidence of thrombophilia or any other systemic disorder was documented. We speculated that the administration of warfarin and the subsequent hypercoagulable state might have been involved in the pathogenesis of the intravascular thrombotic events, including cerebral infarcts and pacemaker lead thrombosis. The presence of clots in the circulation may be a stimulus for the development of DIC;[8-11] hence we hypothesized that the localized venous thrombosis adjacent to pacemaker leads might have played a role in the development and/or the maintenance of DIC.

Permanent intravascular devices, such as pacemakers and defibrillators, have been associated with the development of local vascular stenosis and thrombosis.[12] This may be attributed to the presence of multiple pacemaker leads, the presence of a temporary wire before implantation and the use of dual-coil leads.[12] The localized detection of thrombosis, in our case, resembles localized intravascular coagulopathy (LIC) in the setting of venous malformations,[9] in which the local formation of clots and the consumption of components of the coagulation process (platelets, clotting factors) may result in bleeding complications and DIC. In our patient, the hypercoagulable state might have triggered the development of an LIC-like process within the area of the pacemaker lead. However, the pathogenetic role of the latter in the development of the thrombotic process is an unproven hypothesis.

DIC *per se* may provoke ischemic strokes, especially in patients with underlying malignancies.[13] Thus, recurrent cerebral infarcts in our patient were considered to be a manifestation of the devastating DIC process rather than embolic in origin; in fact, repeated TEE studies to monitor the development of thrombosis failed to detect any thrombi in the left atrial appendage.

There is no evidence that infusion of FFP stimulates the activation of coagulation, yet many clinicians suggest that this may aggravate a hypercoagulable state in the setting of DIC. However, the active bleeding from the oro-nasal mucosa and the sites of venipuncture made the transfusion of FFP necessary in our case.[14] If thrombosis predominates in DIC, therapeutic doses of UFH should be considered;[14] however, the hemorrhagic transformation of the cerebral infarct prompted us to discontinue the administration of UFH.

Treatment with oral anticoagulants is the mainstay of therapy in patients with AF who are at intermediate or high risk of embolic events.[3] Exclusion of thrombophilia before the initiation of warfarin therapy is not considered a cost-efficient strategy. However, we wish to underline that patients with intracardiac devices should begin therapy with low doses of warfarin and adjunctive low molecular weight heparin to minimize the risk of thrombosis.[1] Also, a careful echocardiographic examination should be performed to exclude possible localized thrombosis, especially in the presence of DIC. Further studies are clearly required to investigate the possible thrombotic risk following the initiation of warfarin therapy, especially in the presence of intracardiac devices.

Summary

Anticoagulation therapy is the mainstay of management in patients with AF. In the absence of any thrombophilia, the rare patient with a preexisting intracardiac device, in whom warfarin is prescribed, might experience thrombotic events. The latter could be linked with the preexisting device and/or could be triggered by the initiation of warfarin treatment, but this is merely a hypothesis. Adjunctive treatment with low molecular weight heparin for the first few days of warfarin therapy could be a wise strategy.[1] Finally, patients with permanent pacemakers who develop DIC should always be thoroughly studied for possible thrombosis of the pacemaker leads.

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