Thrombogenicity of Radiofrequency Lesions: Results With Serial D-Dimer Determinations

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Objectives. By measuring plasma levels of D-dimer, a product of fibrin degradation, we sought to investigate whether the application of radiofrequency (RF) energy might activate endogenous thrombotic mechanisms.

Background. Quantitative determination of D-dimer, a biochemical marker of thrombus formation and reactive fibrinolysis, helps to diagnose activation of the coagulation system. It remains controversial whether endocardial lesions produced during RF catheter ablation of arrhythmogenic foci have a thrombogenic effect, and the issue of the need for antithrombotic therapy after RF ablation is still unresolved.

Methods. We made serial determinations of plasma D-dimer levels by enzyme immunoassay before insertion of catheters, after completion of electrophysiologic study (EPS) but before RF ablation, immediately after RF ablation and before discharge (at 48 h) from the hospital in 37 patients undergoing RF ablation (22 men, 15 women; mean [±SD] age 37 ± 18 years, range 12 to 74; 16 ± 16 lesions produced) of accessory (n = 17) or slow (n = 12) pathways, atrial (n = 4) or ventricular foci (n = 3) or the atrioventricular node (n = 1). D-dimer levels were also measured in 26 age-matched control subjects undergoing EPS only.

Results. In the RF ablation group, the mean D-dimer levels increased from a baseline value of 29 ± 28 to 62 ± 56 μg/liter after EPS (p < 0.0001). However, after RF ablation, D-dimer levels increased to much higher levels (188 ± 138 μg/liter, p < 0.0001). There was no correlation of D-dimer levels with the number of RF lesions produced or the duration of the procedure. At 48 h after the procedure, D-dimer levels decreased (75 ± 67 μg/liter) but still remained significantly elevated compared with baseline values (p = 0.0001). There were no significant differences in baseline (25 ± 21 μg/liter) and post-EPS (51 ± 50 μg/liter) measurements between control subjects and patients. During RF ablation, intravenous heparin was given to nine patients who still demonstrated high plasma D-dimer levels after RF ablation.

Conclusions. As reflected by elevated plasma D-dimer levels, RF ablation has a thrombogenic effect that persists through 48 h after the procedure. This effect needs to be taken into account when considering antithrombotic therapy in patients undergoing RF ablation.

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The use of radiofrequency (RF) ablation has rapidly expanded over the past few years, and the method has become standard therapy for certain, mostly supraventricular, arrhythmias (1–10). Potential thrombogenicity of RF lesions has remained an issue over the years because of echocardiographic observations of endocardiac thrombi and reports of clinical thromboembolic events complicating the procedure (11–14). However, there have been no systematic efforts to study the thrombogenic potential of these endocardial lesions, and recommendations are lacking regarding antithrombotic or anticoagulant therapy during or after the procedure (3). Information regarding activation of the coagulation and fibrinolytic systems can be obtained by measurement of a biochemical marker such as

D-dimer, a product of fibrin degradation that is mediated by plasmin, which provides an index of thrombus formation and reactive fibrinolysis (15). Thus, the purpose of the present study was to investigate, by measuring plasma D-dimer levels, whether the application of RF energy might activate endogenous thrombotic mechanisms having important implications for the consideration of future antithrombotic measures.

Methods

Patients. Over 20 months, 37 consecutive patients undergoing RF ablation (22 men, 15 women; mean [±SD] age 37 ± 18 years, range 12 to 74) of accessory (n = 17) or slow (n = 12) pathways, atrial (n = 4) or ventricular (n = 3) foci or the atrioventricular (AV) node (n = 1) were included in the study. All patients had symptomatic tachyarrhythmias and were diagnosed as having Wolff-Parkinson-White syndrome (n = 13) or arrhythmias related to a concealed accessory pathway (n = 4), AV node reentrant tachycardia (n = 12), atrial tachycardia (n = 2) or flutter (n = 2), atrial fibrillation (n = 1) or

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Abbreviations and Acronyms

AV = atrioventricular
EPS = electrophysiologic study
RF = radiofrequency

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idiopathic ventricular tachycardia (n = 3). Electrophysiologic testing and mapping were always part of the ablation procedure and routinely preceded the production of RF lesions.

The study also included 26 patients (age-matched control subjects) undergoing electrophysiologic study (EPS) without RF ablation (16 men, 10 women; mean age 42 ± 22 years, range 13 to 70). All patients gave written informed consent for the procedures.

Electrophysiologic study. Diagnostic EPS was performed in the fasting state after all antiarrhythmic agents had been discontinued for a period of at least 5 drug-elimination half-lives. Routinely, three 6F quadripolar electrode catheters were introduced from the femoral vein and positioned under fluoroscopy at the high right atrium, across the tricuspid valve for His bundle recording and at the right ventricular apex. A 6F quadripolar or a steerable quadripolar catheter was placed in the coronary sinus from either the femoral or left subclavian vein. Previously described standard recording methods, programmed stimulation techniques, protocols and definitions were used (1,4–9). During the initial part of diagnostic EPS, the electrophysiologic variables, including conduction and refractoriness of the atrium, AV node, ventricle and accessory pathway were determined, the mechanism of inducible arrhythmias was defined, and the arrhythmia focus was localized.

Ablation procedure. After the approximate location of the arrhythmia focus had been determined during the initial part of the procedure, a 7F steerable quadripolar deflectable-tip catheter with a 4-mm distal electrode and 2-5-2-mm interelectrode spacing (Mansfield-Webster, or EP Technologies) was used for precise mapping and subsequent ablation with delivery of RF current. Access to the left heart was obtained using the transseptal approach for ablation of left-sided accessory pathways (6) or of left atrial foci and the transaortic technique for ablation of left-sided ventricular tachycardia foci. Only patients undergoing ablation of a left-sided arrhythmia focus received anticoagulation with heparin while the activated clotting time was being monitored and maintained ≥300 s during the procedure.

The RF current was generated at a frequency of 500 kHz by a conventional and commercially available electrosurgical unit (Osypka 200S) and was delivered between the distal electrode and a cutaneous indifferent dispersive pad positioned on the posterior thorax. Once the target site was identified, 20 to 50 W of RF energy was delivered through the ablation catheter. If loss of pre-excitation (in case of manifest accessory pathways), termination of the tachycardia (in case of concealed accessory pathways or atrial or ventricular tachycardias), accelerated junctional rhythm (in case of slow pathway ablation in patients

with AV node tachycardias) or complete heart block (in the case of AV node/His bundle ablation) occurred within 5 to 15 s, RF application was continued for 30 s, otherwise it was stopped, and attempts at mapping and ablation were continued. If impedance increased during ablation, RF application was interrupted, the catheter was removed and cleaned before reinsertion. At 30 min to 1 h after ablation, programmed stimulation was performed to confirm the efficacy of ablation. All vascular sheaths were removed at the end of the procedure. The patients were then monitored for 48 h before discharge from the hospital. During this period, serial electrocardiograms were obtained to evaluate for recurring arrhythmia, and echocardiography was performed to determine the presence of cardiac complications, including the presence of endocardiac thrombi. Intravenous heparin for those who underwent ablation in the left heart was continued for 24 h after the ablation procedure.

Blood sample collection and D-dimer assay. Blood samples were obtained from venous sheaths and introduced into tube collectors containing citrate buffer solution or sodium citrate solution. One part of the solution was carefully mixed with nine parts of venous blood, avoiding the formation of foam. Within 1 h it was centrifuged for 10 min at ~3,000 rpm, and the supernatant plasma was removed and kept at −20°C until the assay was performed.

Plasma D-dimer levels were determined by a sandwich enzyme immunoassay method (Enzygnost D-Dimer micro, Behring, Germany). All measurements were performed in duplicate. Hemolytic, lipemic and rheumatoid factor–containing plasmas do not interfere with the determination. In healthy subjects the reference range is 4 to 78 μg/liter (median 12 μg/liter). The measurement range extends from 10 to 600 μg/liter. With regard to specificity, the test does not react with fibrinogen or non–cross-linked fibrin(ogen) degradation products. The intraassay coefficient of variation falls between 6% to 13%, whereas the interassay coefficient of variation from day to day falls between 4% to 18%.

From each patient undergoing RF ablation, four blood samples were taken for D-dimer measurement. Initially, blood samples were obtained immediately after insertion of the venous sheaths and before introduction of the electrode catheters (baseline measurements). Subsequently, blood samples were taken on completion of EPS and mapping, just before production of the first RF lesion (post-EPS measurements). The third sample was taken after completion of the RF procedure (post-RF measurements) and before sheath removal. At 40 to 48 h later and before discharge from the hospital, a fourth blood sample was obtained.

Plasma D-dimer levels were also determined in 26 patients (age-matched control subjects) undergoing EPS without RF ablation. In this group of patients, blood samples were similarly obtained at baseline and on completion of EPS. In a smaller number (n = 13) of the control group, a third sample was taken at 24 h later (before discharge).

Patient follow-up and statistics. After discharge from the hospital, patients were to be followed up at our arrhythmia
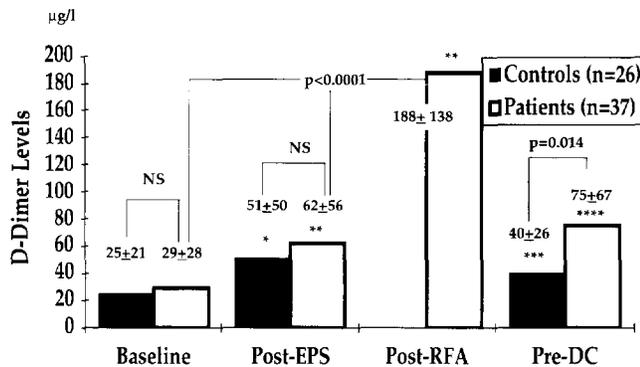
Figure 1. Plasma D-dimer levels in 37 patients undergoing EPS followed by RF ablation and 26 control subjects with EPS alone. Predischarge (pre-DC) measurements were obtained at 48 h and were available for all patients, whereas those taken at 24 h were available for only 13 control subjects. *p = 0.004, **p < 0.0001, ***p = 0.0504, ****p = 0.0001 versus baseline.

clinic or by their referring cardiologists every 3 to 6 months for the first year and annually thereafter. All patients who had an RF ablation procedure received one aspirin (325 mg) tablet daily for 3 months.

Results are expressed as mean value ± SD. Statistical comparisons were performed using analysis of variance with Bonferroni correction and paired or unpaired t tests as appropriate for normal distributions and the Friedman and Wilcoxon tests for nonnormal distributions. Correlations between procedural variables and plasma D-dimer levels were performed using linear and multiple regression analysis and the Spearman rank correlation (Statview 4.01 program). A p value <0.05 was considered significant.

Results

Procedural data. Thirty-seven patients undergoing RF ablation and 26 control subjects undergoing EPS alone were included in the study. All procedures were successfully completed without the occurrence of any complications. Three to four catheters were used in the control group and four to five in the ablation group. The total duration of RF ablation in the 37 patients averaged 3.3 ± 2.1 h, whereas that of EPS in the 26 control subjects was 2.7 ± 0.5 h (p = NS). In the RF ablation group, the mean number of RF lesions produced was 16 ± 16. Left-sided foci were ablated in nine patients who received intravenous heparin during the procedure.

D-dimer levels in ablation group. In the ablation group of the 37 patients, the mean D-dimer level at baseline was 29 ± 28 μg/liter (Fig. 1). After the EPS and before RF ablation, D-dimer levels increased to 62 ± 56 μg/liter (p < 0.0001 by paired t test, but p = NS by analysis of variance). However, after RF ablation was completed, D-dimer levels increased to very high levels (188 ± 138 μg/liter, p < 0.0001). There was no correlation of D-dimer levels with number of RF lesions produced (r = 0.23, p = NS) or duration of the procedure (r =

0.31, p = NS), as determined by linear regression analysis. At 48 h after the procedure and before hospital discharge, D-dimer levels decreased significantly (75 ± 67 μg/liter compared with peak levels immediately after ablation but still remained significantly elevated compared with baseline values (p = 0.0001).

There were no significant differences in baseline and post-EPS measurements between patients and control subjects. The highest levels of D-dimer (188 ± 138 μg/liter) were noted immediately after the procedure in patients undergoing RF ablation. Among the nine patients receiving heparin, similarly high D-dimer levels were observed (178 ± 150 μg/liter).

D-dimer levels in control group. In the control group of 26 patients undergoing EPS without RF ablation, baseline D-dimer levels averaged 25 ± 21 μg/liter. On completion of EPS, D-dimer levels rose to 51 ± 50 μg/liter (p = 0.004), values similar to those in the RF ablation group as measured after EPS but before RF ablation, even though the duration of EPS in the ablation group was shorter (2.0 ± 0.5 vs. 2.7 ± 0.5 h, p < 0.05). In a smaller number (n = 13) of control subjects, predischarge measurements of D-dimer levels (40 ± 26 μg/liter) were available at 24 h after the procedure, having a borderline difference from the baseline values (p = 0.0504).

Postprocedural data and follow-up. Echocardiograms obtained after the procedure failed to detect any intracardiac thrombi. No patient in the RF ablation or control group had any thromboembolic events during the hospital period, nor was any thromboembolism reported during later follow-up among the patients who underwent RF ablation. Patients in the latter group were maintained on aspirin (325 mg daily) for 3 months after the ablation procedure.

Discussion

D-dimer levels and RF ablation procedures. The present study demonstrates that plasma levels of D-dimer are increased during performance of catheter procedures for managing cardiac arrhythmias, such as diagnostic EPS and therapeutic RF catheter ablation. Manipulation of catheters during the diagnostic part of the procedure (EPS) appeared to be responsible for a moderate increase in D-dimer levels (double the baseline measurements), but RF ablation itself induced a marked increase (greater than sixfold increase above baseline values) in the plasma levels of this biochemical marker of thrombogenesis. Clearly this was not just the result of a longer RF ablation procedure because the control group had catheters in place for a similar duration (mean 2.7 vs. 3.3 h, control vs. RF group, p = NS), whereas there was no correlation between degree of D-dimer elevation and duration of the procedure. Interestingly, D-dimer values were still elevated (albeit at lower levels) at 48 h after the procedure (Fig. 1).

Thromboembolic complications of RF ablation. Although RF catheter ablation has been established as a safe and effective technique that offers a cure to patients with a variety of symptomatic supraventricular and ventricular tachyarrhyth-

mias (1–10), the thromboembolic potential of the procedure has long been recognized (11), but only recently have serious concerns been raised (13,14). Thromboembolic complications have been reported (12–14) both during the perioperative period and during follow-up (at 3 months). In this setting, the mechanism of thrombogenesis has not been elucidated, but endothelial disruption at the site of application of RF current might provide the nidus for thrombus formation and subsequent embolization. The results of our study indicate that RF ablation activates fibrin generation and lysis to a much greater degree than does simple electrode catheter manipulation during the diagnostic (EPS) part of the procedure. The degree of D-dimer level elevation could not be merely attributed to the large number of RF applications or the long duration of the procedure because plasma D-dimer levels were not found to correlate particularly with either the number of RF applications or the duration of the procedure, nor was there any influence observed by the administration of heparin. However, the latter observation is good evidence that the tissue injury is causing the thrombogenesis rather than the RF heating of blood itself despite the observed lack of correlation between number of RF applications and D-dimer levels. Apparently, the number of RF applications did not correlate with the extent of injured myocardial tissue in the present study because not all RF applications probably resulted in effective lesion formation, either due to unstable catheter position or our practice of interrupting unsuccessful RF applications within 5 to 15 s, or both. Also, the direct effects of heating generated by the RF energy on other clotting factors of the coagulation cascade, such as fibrinogen, should not be ignored, and future studies need to further explore this possibility.

Antithrombotic measures. The present study does not provide data to explain the lack of clinical thromboembolism in this group of patients despite (indirect) indexes of intense thrombogenesis. Heparin apparently did not provide any protection against the specific type of thrombogenicity. That some embolic events may remain subclinical or unrecognized, especially in patients undergoing right-sided procedures (in the absence of right to left shunting) can be appreciated. Furthermore, all our patients received antithrombotic therapy with daily aspirin for the apparently critical period of 3 months after ablation (12), but whether this measure was protective remains highly speculative. Further prospective studies are required to specifically address these daunting issues and evaluate specific antithrombotic measures.

Study limitations. The problem of thromboembolism is certainly multifaceted and cannot be fully studied with the determination of plasma levels of only one particular biochemical marker of thrombosis or thrombolysis. Further studies assessing a variety of such coagulation markers (15,16) will be needed to identify particular aspects of intravascular thrombophilia that appears to be induced by the application of RF current to endocardial sites. The present study included a heterogeneous cohort in terms of varying underlying arrhythmia substrates and therefore different approaches to catheter

ablation. This fact may or may not have any importance in leading to a better understanding of the mechanism by which thrombogenicity is incurred. Although no relation was found between D-dimer elevation and the number of RF applications, procedure duration or heparin use, one cannot exclude that this lack was due to the size of the study sample. However, a more plausible explanation for the lack of correlation between number of RF applications and D-dimer levels would be our inability to differentiate between effective and ineffective lesions; in future studies, this drawback may be circumvented by temperature-guided ablation. Finally, therapeutic measures, not evaluated in the present study, that will prevent activation of thrombosis and minimize the thromboembolic potential of the procedure need to be investigated (15).

Clinical implications. The present study offers a new approach to studying activation of the coagulation cascade during catheter ablation. It suggests that subclinical thrombosis may be ubiquitous after catheter ablation, as evidenced by the D-dimer elevation in patients undergoing these procedures. Further insight into the mechanism of such thrombogenicity needs to be obtained in properly designed studies. Preliminary data from our laboratory (17) indicate that certain antithrombotic regimens can mitigate the degree of D-dimer elevation and thus confer a lower thrombogenic potential and may be worth exploring in future clinical studies.

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