Thrombogenicity of radiofrequency ablation procedures: what factors influence thrombin generation?

D. S. Y. Lee¹, P. Dorian¹, E. Downar², M. Burns¹, E. L. Yeo³, W. L. Gold³, M. Paquette¹, W. Lau¹ and D. M. Newman¹

¹St Michael’s Hospital, Division of Cardiology, ²Toronto General Hospital, Division of Cardiology, and ³Toronto General Hospital, Divisions of Hematology and Internal Medicine, University of Toronto, Toronto, Canada

Aims
Thromboembolic complications have been reported after radiofrequency ablation but the low incidence of overt clinical events has been a limitation to the study of factors affecting thrombogenic risk. The aim of this study was to determine whether radiofrequency ablation has a procoagulant effect and to examine variables that affect thrombin generation.

Methods and Results
Thirty-seven consecutive patients who underwent radiofrequency ablation were studied prospectively. Blood samples were assayed for thrombin-antithrombin III (TAT) and d-dimer (DD) at five different time points: (1) baseline; (2) after sheath insertion; (3) after electrophysiological study but before radiofrequency ablation; (4) at completion of the procedure; and (5) 24 h post-procedure.

TAT levels were within the normal range at baseline and increased significantly after sheath insertion from 2.1 ± 1.2 μg l⁻¹ to 13.3 ± 16.0 μg l⁻¹ (P<0.01). Levels increased further to 24.0 ± 19.9 μg l⁻¹ (P<0.01) after electrophysiological study but did not increase after radiofrequency ablation. TAT normalized at 24 h. DD remained elevated at 24 h. Procedure duration was the only variable that correlated with the relative increase in TAT and DD. The patients with the longest procedure durations had more catheters inserted, more radiofrequency applications and largely consisted of accessory bypass tract-mediated tachycardias. Heparin administration significantly blunted the relative increase in TAT after radiofrequency ablation (P=0.005).

Conclusion
Radiofrequency ablation procedures confer an increased risk of thrombosis. Catheterization and diagnostic study contribute largely to the thrombogenic stimulus. Thrombogenicity is increased in prolonged, complex procedures and is decreased in patients who have been administered heparin during the procedure.

Key Words: Radiofrequency ablation, thrombosis, heparin.

Introduction
Radiofrequency ablation procedures are used widely for the management of arrhythmias⁴. It is reported that complications occur infrequently⁴ but a number of thromboembolic complications has been reported in association with radiofrequency ablation⁵–⁷. Whereas systemic thromboembolic complications such as stroke
have been of concern, there are increasing numbers of recent reports of both fatal and non-fatal pulmonary embolism\[8–12\]. The factors that predispose to these risks have not been elucidated and thus strategies to administer anticoagulation to the subgroup of patients at greatest risk have not been devised. The empirical strategy that is typically employed to minimize thromboembolic complications may entail heparin and aspirin for left-sided ablations, and aspirin alone for rightsided ablations, which may sub-optimally prevent a potential worst-case scenario of fatal massive pulmonary embolism\[12\].

The potential mechanisms of thrombogenesis during ablation procedures are multiple and include endothelial disruption, coagulation necrosis, electroreporation injury, mechanical damage in the vessel wall, and heating of circulating blood elements by radiofrequency energy\[13–18\]. The above mechanisms can cause activation of the cascade of events that ultimately results in thrombin generation and platelet activation\[18\].

The primary objective of the current study was to determine whether radiofrequency ablation has an independent, incremental procoagulant effect by assessing biochemical markers of thrombogenicity. A secondary objective was to examine variables that influence these markers. The biochemical markers used in this study were direct measures of thrombin generation (thrombinantithrombin III, TAT) or fibrinolysis (d-dimer, DD). Thrombin is generated rapidly reaching peak levels within minutes after a thrombogenic stimulus\[19\]. TAT is formed by the irreversible interaction of antithrombin III and thrombin, after thrombin is cleaved from prothrombin. The formation of DD follows chronologically after thrombin is generated and reflects lysis of fibrin. The half-life of TAT is 15 min\[20\], which is shorter than the 8-h half-life of DD\[21\]. These markers are increased in plasma when thrombosis is present, but they are not site-specific and thus they may be elevated in both arterial and venous thrombosis at any level in the circulatory system\[22\].

### Methods

#### Patients

Consecutive patients undergoing electrophysiological study followed by radiofrequency ablation procedures were enrolled in this prospective study. Patients with an active thrombotic process, renal failure, previously identified coagulopathy or thrombocytopenia were excluded. Antiarrhythmic drugs were held prior to the study but patients who were previously taking aspirin continued it throughout the study period.

#### Catheterization laboratory procedure

Central venous access was obtained at the femoral vein and the internal jugular vein if necessary. Arterial access was obtained at the femoral artery. Standard aseptic techniques were employed using the Seldinger technique for vascular access. Indwelling 7 or 8 Fr vascular cannulae were employed, through which 7 Fr electrode catheters were positioned in the right ventricular apex, His position, high right atrium and coronary sinus as deemed clinically necessary. Procedures involving catheter manipulation and ablation in the left atrium and ventricle were performed by a retrograde aortic or transeptal approach. Patients who were anticoagulated received an unfractionated heparin bolus of 4000 units typically after entry into the systemic cardiac chambers. Stimulation protocols varied depending on the primary electrophysiological diagnosis. Upon completion of the diagnostic portion of the procedure, all patients underwent standard temperature-guided radiofrequency ablation with a quadrupolar ablation catheter (EP Technologies, Menlo Park, CA, U.S.A.). Radiofrequency energy was delivered via a standard commercial cardiac radiofrequency lesion generator (EP Technologies, Menlo Park, CA, U.S.A.) to a maximum power of 50 W to maintain a tissue temperature of 60°C.

Serial blood samples were drawn at five time points: (1) pre-procedure; (2) immediately post-sheath insertion; (3) upon completion of the diagnostic portion of the study but before any radiofrequency energy application; (4) at the conclusion of the procedure (approximately 15 min after the last radiofrequency application); and (5) 24 h post-procedure. Procedure duration was defined as the time from initial vascular access to the time of completion of the entire procedure and collection of blood sample 4. Blood samples 1 and 5 were drawn by experienced phlebotomists without a tourniquet and with minimal vessel trauma. Samples 2, 3 and 4 were drawn through the femoral venous sheath. The first 5 ml of blood was discarded from all samples. Blood samples were immediately centrifuged to separate plasma from whole blood and were stored at −70°C until assays were conducted.

#### Thrombin-antithrombin III and D-dimer quantitation

Quantitation was performed by a sandwich enzyme immunoassay (Enzygnost\[8\] TAT micro, Behring Diagnostics Inc., Westwood, MA, U.S.A.) for the determination of human TAT complex with a reference range of 1.0–4.1 μg l\(^{-1}\). DD quantitation was also performed by a commercial ELISA technique (Asserachrom\[8\] D-Di, Diagnostica Stago, Asnieres-Sur-Seine, France) with a normal value of less than 400 ng ml\(^{-1}\) and a lower limit of detection of 5 ng ml\(^{-1}\). Technicians performing the assays were blinded to patient identity and timing of the samples.

#### Statistical analysis

Statistical analyses were performed using SPSS and SAS software. Descriptive analyses are expressed as...
mean ± standard deviation. To determine differences in DD and TAT measures across time at the five sampling points, repeated measures analysis of variance was performed. Post hoc analysis using paired t tests and Hochberg correction for multiple comparisons was employed to determine if DD and TAT levels differed between pre-procedure and post-sheath insertion, post-sheath insertion and pre-radiofrequency ablation, pre- and post-radiofrequency ablation, and post-radiofrequency ablation and 24 h post-procedure. P values <0.05 associated with the time variable were considered statistically significant.

**Results**

Thirty-seven patients were enrolled (28 female, nine male). Mean age was 47 ± 19 years (range 18–82 years). Most of the ablation procedures were performed for the following indications: atrioventricular node re-entrant tachycardia (n=18), and accessory pathway-mediated tachycardia (n=12). The remainder of the procedures included the following: atrioventricular junction ablation for rate control of atrial fibrillation (n=4), atrial flutter ablation (n=2), and right ventricular outflow tract ventricular tachycardia (n=1). The number of venous and arterial catheters inserted was 3 ± 1 (range 2–5). Total number of radiofrequency applications was 6 ± 9 (range 1–55). Mean time to completion of the diagnostic electrophysiological study was 64 ± 35 min. Mean total procedure duration was 114 ± 60 min. There were no instances of impedance rise that might have suggested coagulum formation. There were no clinical thromboembolic complications.

**Thrombin-antithrombin III**

TAT level was within the normal range (2.1 ± 1.2 µg l⁻¹) at baseline and increased significantly after sheath insertion to 13.3 ± 6.0 µg l⁻¹ (P=0.008 vs baseline) as depicted in Fig. 1 (top panel). Levels increased further to 24 ± 19 µg l⁻¹ after mapping and catheter manipulation (P=0.006 vs sheath insertion) but did not increase after radiofrequency ablation. There was a nonsignificant decrease in TAT post-ablation to 22 ± 19 µg l⁻¹ (P=0.30 vs pre-ablation) which subsequently normalized to a near-baseline level of 2.6 ± 3 µg l⁻¹ at 24 h (P=0.14 vs baseline).

**D-dimer**

DD concentrations were within the normal range (230 ± 176 ng ml⁻¹) at baseline and increased significantly after sheath insertion to 285.4 ± 237.4 ng ml⁻¹ (P=0.019 vs baseline) as depicted in Fig. 1 (bottom panel). There was a significant further increase in DD after electrophysiological study but prior to radiofrequency ablation to 423.4 ± 324.3 ng ml⁻¹ (P=0.004 vs sheath insertion). DD increased modestly after ablation to 464.4 ± 307.4 ng ml⁻¹ (P=0.16 vs pre-ablation) and continued to increase at 24 h to 670.9 ± 500.4 ng ml⁻¹ (P=0.031 vs post-ablation).

**Variables increasing biochemical measures of thrombogenicity**

The primary biochemical index of interest was the relative increase in DD and TAT post-radiofrequency ablation compared with baseline levels (i.e. ratio of post-radiofrequency ablation to baseline levels). The relative increase in DD had a significant but modest correlation with procedure duration (R²=0.46, P=0.01), number of sheaths employed (R²=0.49, P<0.01) and number of radiofrequency applications (R²=0.52, P=0.02). Procedure duration was the only variable that correlated significantly with the relative increase in TAT (R²=0.38, P=0.01). Patient age influenced absolute marker levels after radiofrequency ablation. Nine patients were ≥60 years of age and they tended to have higher TAT levels than the younger cohort (33.8 ± 14.5 vs 19.4 ± 19.9 µg l⁻¹, P=0.07). DD for the older cohort
Figure 2 Plot of relative increase in thrombin-antithrombin III (TAT) compared with baseline levels according to heparin administration during the ablation procedure. TAT ratio [post-radiofrequency ablation (RFA)/baseline] was higher in the patients who were unanticoagulated (n=15). Patients who received heparin during the procedure (n=8) had low TAT ratios: 12·9±8·2 for heparin and 3·3±3·5 for non-heparin groups (P=0·005). Heparin administration attenuated the relative increase in thrombin generation in this comparison.

was significantly greater than their younger counterparts (750·0±337·9 vs 369·3±233·4 ng ml$^{-1}$, P=0·02).

Patients in the highest quartile of procedure durations exhibited procedural characteristics suggesting greater complexity in comparison with the three lower quartiles. The highest quartile had a mean procedure duration of 202·4±37·5 min (range 155–263 min) and consisted largely of patients with a re-entrant tachycardia involving an accessory pathway (seven of nine patients) or atrial flutter (one of nine patients). The number of radiofrequency applications was 12±17 (median 5) for the highest quartile vs 4±4 (median 3) for the remainder (P=0·032). The number of catheters inserted for the procedure was 4±1 (median 4) in the upper quartile vs 3±1 (median 3) for those cases with a shorter procedure duration (P<0·0001).

**Effect of heparin administration**

A pharmacological intervention that decreased the TAT ratio was intravenous heparin administration intraprocedurally. Heparin significantly attenuated the relative increase in TAT (Fig. 2). Patients who received heparin generally had less than a five-fold increase in post-ablation to baseline TAT ratio. In contrast, patients who did not receive heparin had more than a five-fold increase in post-ablation TAT compared with baseline (12 of 15 patients). The comparison of mean TAT ratios for unheparinized and heparinized groups was significantly different: 12·9±8·2 vs 3·3±3·5, respectively (P=0·005). This subgroup did not include patients who were receiving oral anticoagulants or antiplatelet agents. Of the patients who were taking aspirin prior to the study for indications unrelated to the ablation procedure, TAT levels post-ablation were not significantly different in those patients taking aspirin vs those not taking the drug (31·4±17·2 vs 21·6±19·9 µg l$^{-1}$, P=0·354). After 24 h, there was also no difference in TAT between aspirin users and non-users (2·7±1·4 vs 2·6±1·3 µg l$^{-1}$ respectively, P=0·85).

**Discussion**

This study evaluated two markers of thrombogenicity, DD and TAT, in radiofrequency ablation procedures, and confirms previous work suggesting that the coagulation and fibrinolytic cascade is activated by the procedure.$^{[23]}$ These data suggest that the relative contribution to thrombogenicity afforded by catheter insertion and diagnostic study appears to be greater than that related to radiofrequency energy delivery. The number of radiofrequency applications did not correlate with the relative increase in TAT and concentrations were not observed to increase after radiofrequency ablation as compared with pre-ablation levels, suggesting that thrombin is generated more in response to catheter manipulation than radiofrequency energy delivery. DD increased at a slightly later time relative to TAT, which is consistent with previous observations.$^{[24]}$ DD increased significantly after electrophysiological study and was still elevated at 24 h; this may have been due to ongoing fibrinolysis of thrombin and its relatively long elimination half-life.

**Clinical risk variables**

Risk factors that predispose to thromboembolism have not been fully characterized. Using relative and absolute levels of TAT and DD after radiofrequency ablation as a surrogate measure of clinical thromboembolism, it was found that procedure duration was a significant but modest predictor of thrombogenicity. Older age groups had a tendency towards higher absolute levels of both TAT and DD. These results are consistent with those of previous investigators who also found that procedure duration is an important determinant of activation of the coagulation cascade.$^{[25,26]}$

The findings in this study build upon previous observations because these results suggest that longer procedure duration is associated with greater procedural complexity. This study found that patients with longer procedure durations had more catheters inserted and more radiofrequency applications. The quartile with the longest procedure durations also represented a more complex substrate which included accessory pathway-mediated tachyarrhythmias and atrial flutter focus ablation. Longer procedure duration may partially
represent a global variable that encompasses other important factors that are not mutually exclusive (e.g., more radiofrequency applications will likely increase procedure time relative to fewer radiofrequency applications).

**Effect of anticoagulation**

TAT increases significantly after sheath insertion, catheter manipulation and mapping, and in comparison with baseline levels, a more robust thrombogenic response was observed if heparin was not administered during the procedure. Heparin has been employed clinically in an attempt to prevent thromboembolic complications after radiofrequency ablation.[27,30] Routine heparin administration, however, is not widely employed in all ablation procedures and the evidence for its use in procedures involving the systemic cardiac chambers but not in right-sided ablations is empirical. The American Heart Association/American College of Cardiology guidelines for the care of patients undergoing radiofrequency ablation does not address the routine use of heparin, even in cases involving ablation in the systemic cardiac chambers.[31] This study has demonstrated that a biological rationale that may justify the use of heparin during radiofrequency ablation may be to decrease thrombin generation. This study was not designed to assess the role of heparin in reducing clinical or subclinical events (e.g. pulmonary embolism), but rather generates a hypothesis that heparinization may have a role in preventing pulmonary embolism. The incremental benefits of heparin in exclusively right-sided ablations may be small, but the hypothesis may be raised that heparin may prevent potentially severe complications in procedures anticipated to be long or complex, where the risks of thrombosis are likely to be increased. Further study in this area is warranted to assess the risks and benefits of a strategy of selective anticoagulation, given the small but measurable risk of bleeding with anticoagulation.

**Limitations**

The primary objective of this study was to determine whether a procoagulant effect can result from radiofrequency ablation procedures. To reduce selection bias, consecutive patients with a range of electrophysiological diagnoses were included. A limitation of such a design is the resultant heterogeneity in the patient population with inclusion of different arrhythmogenic substrates and types of ablation. In particular, the study was limited by small numbers of some specific electrophysiological substrates such as atrial flutter and ventricular tachycardia ablation, which may have elicited an exaggerated thrombogenic response.

Unlike previous reports, this study did not employ patients who underwent diagnostic electrophysiological study without radiofrequency ablation as a control group.[32] The authors’ hypothesis was that procedure duration might be a significant determinant of thrombogenicity, and it would be unethical to control for differences in procedure duration by continued intravascular deployment of catheters, even after completion of a purely diagnostic study.

**Conclusions**

Radiofrequency ablation procedures confer an increased risk of thrombogenicity as reflected by accentuated thrombin generation and reactive fibrinolysis. Catheterization and catheter manipulation appear to contribute more significantly to the thrombogenic stimulus than radiofrequency current application in these procedures. Longer procedure duration was associated with an increase in both TAT and DD levels. Heparin administration attenuated the increase in thrombogenic markers and thus provides a biochemical rationale for anticoagulation in radiofrequency ablation procedures. Heparin administration may be warranted in procedures that are prolonged or complex even if the systemic cardiac chambers are not involved in the procedure. Further study in clinical datasets is warranted to elucidate the efficacy and optimum strategy of heparin administration.

We thank Edith Antonopoulos and Ileana Spanu for their expert technical assistance, and Andrea Snihura for editorial assistance. This study was supported by a research grant from the PSI Foundation, Canada.

**References**


Europace, Vol. 3, July 2001