Improved Detection of Radiofrequency Current-Induced Minor Myocardial Injury by Cardiac Troponin T Measurement

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Abstract

Transcatheter radiofrequency current application in patients with cardiac arrhythmias was reported to be associated with a low rate of an increase in the activity of enzyme creatine kinase (CK) and CK-MB isoenzyme. As the novel heart-specific protein troponin T (cTnT) was shown to be superior to CK and CK-MB in detecting small damage to myocardial tissue in various clinical situations including unstable angina, a comparison of the diagnostic efficiency of these marker proteins to detect myocardial damage was made in 34 patients (mean age 38.3 ± 15.6 years) undergoing radiofrequency (RF) catheter ablation of accessory pathways (n = 17) and atrioventricular nodal reentrant tachycardia (n = 17). Serial measurements of total CK and CK-MB activity before and every 8 hours for 24 hours after ablative procedure were performed with enzymatic and immunoinhibition method, respectively, using automated chemical analyzer Hitachi 717. Serum concentration of cTnT was determined by one-step sandwich ELISA performed on ES 300 analyzer (Boehringer Mannheim).

With a median of 7.0 (range 1-39) RF current pulses only 12 (35%) and 10 (29%) of 34 patients showed an increase above the upper limit of normal CK and CK-MB activity, respectively. The peak activity of CK (mean peak = 285.8 ± 517.7 IU/L) occurred at a variable time that infrequently coincided with those of peak CK-MB activity (23.1 ± 8.0 IU/L). By contrast, all except 4 (88%) of 34 patients exhibited a distinct elevation of cTnT concentration (mean peak = 0.56 ± 0.63 ng/ml), with almost all (33) of these 34 patients showed an early peak value at 8 hours postprocedural. There was, on the average, a small but distinct higher relative increase (5.6 times) in cTnT concentration from the upper limit of reference range compared with those of CK (1.5 times) and CK-MB peak activity (0.9 time).

In conclusion, cTnT exhibited a minor but distinst elevation in its concentration and demonstrated a higher rate and magnitude of increase following radiofrequency current application than the conventional CK and CK-MB isoenzyme. Measurements of cTnT serum concentration may thus provide a useful test method for assessing the effect of the new transcatheter ablation procedures on myocardial tissue.

Key word : Cardiac Troponin T Measurement, Minor Myocardial Injury, Radiofrequency Current-Induction, Improved Detection

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Catheter ablation by radiofrequency current is being increasingly used in the management of various forms of cardiac arrhythmias and was proposed to be the method of choice for the treatment of arrhythmias complicating Wolff-Parkinson-White (WPW) syndrome and atrioventricular nodal reentrant tachycardia (AVNRT)[1,2]. Compared with the conventional method using catheter ablation with direct current (DC) shock which was associated with a high rate of procedure-related complications[1,3], this novel approach was reported to have high success and low complication rates and was also being offered in many pediatric centers as first line therapy instead of long-term antiarrhythmic medication[4-6].

In the past, non-invasive assessment of the degree of myocardial cell necrosis induced by radiofrequency energy using biochemical markers of myocardial injury was almost exclusively the measurement of the activity of enzyme creatine kinase (CK) and CK-MB isoenzyme[7-10]. Creatine kinase usually showed, however, a low cardiospecificity due to its presence in a significant amount in skeletal muscle and previous studies[7,9,10] have reported a low rate of an increase in the activity of both enzymes after radiofrequency ablative procedure. The novel heart specific protein troponin T (cTnT), on the other hand, was recently found to be a sensitive marker of minor myocardial injury in a significant number of patients with unstable angina as well as in those undergoing percutaneous transluminal coronary angioplasty[11-15]. Since the degree of myocardial damage induced by radiofrequency current is usually minimal, the purpose of this study was to investigate the diagnostic efficiency of cTnT compared with CK and CK-MB to detect small damage to myocardial tissue performed on patients undergoing radiofrequency catheter ablation of supraventricular tachycardia.

MATERIAL AND METHOD

The study population consisted of 34 patients undergoing radiofrequency (RF) catheter ablation of cardiac arrhythmias. There were 14 male and 20 female patients with a mean age of 38.3 ± 15.6 years (Table 1).

Electrophysiologic study and ablation procedure

Procedures of the electrophysiologic study and radiofrequency catheter ablation have been previously described[16]. Briefly, the study was performed in a fasting state and under sedation. Quadripolar electrode catheters (6 French) were inserted percutaneously into the femoral vein and advanced to the right ventricular apex, right atrium and across the tricuspid valve for recording the local electrocardiogram of the right ventricle, right atrium and His bundle. A 7 French octapolar electrode catheter was inserted into the right internal jugular vein advancing to the coronary sinus under fluoroscopic guidance to record the coronary sinus electrocardiogram.

For the application of radiofrequency current a 7 French quadripolar deflectable-tip catheter with a 4 mm distal electrode and 2 or 5 mm interelectrode spacing was used. Radiofrequency energy was typically applied with 20-40 watts of power for 20-60 seconds. We used the noninducibility, loss of preexcitation pattern and disappearance of eccentric activation as the criteria of success.

Laboratory analysis

Blood samples were drawn just before and every 8 hours for 24 hours after the ablative procedure. Serum total CK activity was determined within 1 hour by CK-NAC activated reagent at 37°C (the upper limit of normal is 195 IU/L) and CK-MB activity (25 IU/L) was measured with the same method after immunoinhibition of CK-M subunit activity using fully-automated chemical analyzer Hitachi 717.

Serum concentration of cardiac troponin T (cTnT) was determined by a newly available second-generation cTnT assay which is based on a single step sandwich principle with streptavidin coated tubes as the solid phase and two monoclonal antibodies directed against two different epitopes on cTnT molecule and was performed on an automated immunoassay analyzer ES 300 (Boehringer Mannheim). The cross-reactivity of cTnT with

Table 1. Patient characteristics.

Male : female ratio (n)	14 : 20
Mean age (year)	38.3 ± 15.6
Age range (year)	12 - 68
Types of arrhythmias (n) :	
Accessory pathways :	17
- WPW syndrome	9
- Concealed accessory pathway	8
Atrioventricular node reentry	17

skeletal muscle TnT was reported to be < 0.3 per cent[17]. The upper limit of reference range for cTnT, as stated by the manufacturer, was 0.10 ng/ml.

The results are expressed as mean ± standard deviation. Statistical analysis was performed using analysis of variance and $p < 0.05$ was considered significant.

RESULTS

Radiofrequency (RF) catheter ablation was successful in all patients with atrioventricular nodal reentrant tachycardia and in all but one with accessory pathways, resulting in an overall success rate of 97 per cent. A median of 7 (range 1-39) RF current pulses were applied per session at a mean power of 27.3 ± 7.3 watts delivered for a mean duration of 38.9 ± 9.2 seconds. Direct current shocks eventually succeeded in interrupting 3 accessory pathways.

Of the 34 patients who underwent RF ablation 12 (35.3%) and 10 (29.4%) demonstrated an increase in the activity of creatine kinase (CK) and CK-MB fraction above the upper limit of normal of 195 IU/L and 25 IU/L, respectively. The peak activity of CK (mean peak activity = 285.8 ± 517.7 IU/L, Table 2) occurred at a different time during 24 hours after the ablative procedure and the time to peak of CK infrequently coincided with that of CK-MB peak activity (mean peak activity = 23.1 ± 8.0 IU/L). An increase in the concentration of cardiac troponin T (cTnT) above the upper limit of the reference range of 0.10 ng/ml, on the other hand, was observed in 30 of 34 patients (88.2%), with all except one of these patients showing a peak value (mean peak concentration = 0.56 ± 0.63 ng/ml) early at 8 hours following the ablative procedure. In 19 of 22 patients and 20 of 24 patients with no increase in CK and CK-MB activity, respectively, a significant elevation of cTnT concentration was observed. Of the 4 patients with no increase in cTnT value above the upper limit of normal, none showed an increase in CK and CK-MB activity and 3 of these 4 patients demonstrated a distinct elevation of cTnT concentration from preprocedural baseline value with a rising and falling pattern of myocardial release (Fig. 1).

Table 2. Activity of CK and CK-MB and cTnT concentration (SD) before and during 24 hours after RF ablation.

	Baseline value	Peak value	Value at 24 hours
CK (IU/L)	89.7 (67.2)	285.8 (517.7)	275.6 (520.3)
CK-MB (IU/L)	13.4 (5.0)	23.1*# (8.0)	18.4+ (8.8)
cTnT (ng/ml)	0.009 (0.013)	0.563*# (0.633)	0.275÷ (0.468)

* $p < 0.0001$,
\+ $p = 0.01$,
÷ $p = 0.02$ compared with baseline value
\# $p = 0.01$ compared with value at 24 hours.

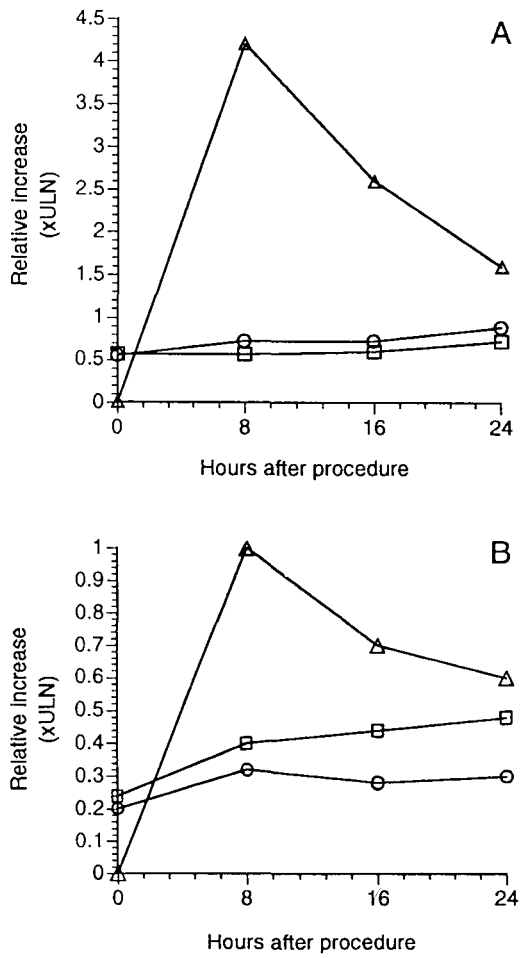

Fig. 1. Typical pattern of cTnT (△) release in one patient with no increase in CK (○) and CK-MB (□) activity (A), compared with one showing no increase above the upper limit of normal (ULN) in all myocardial marker proteins (B).

There was, on the average, a small but distinct relative increase (5.6 times) in cTnT concentration from the upper limit of the reference range (Table 2) compared with those of CK (1.5 times) and CK-MB peak activity (0.9 time). In 25 of 30 patients (83.3%) with an increase in postprocedural cTnT concentration the peak value was less than 1.0 ng/ml which is indicative of minor myocardial injury.

DISCUSSION

The test method used for assessing the degree of myocardial damage and monitoring of complications developed after radiofrequency (RF) ablation procedure using serum biochemical markers of myocardial injury was, in the past, almost exclusively the measurement of the enzymes creatine kinase (CK) and CK-MB activity[7-10]. Creatine kinase usually showed, however, a low specificity to the heart muscle as a result of its presence in a significant amount in tissues other than myocardium. An increase in the activity of CK to > 5 times the upper limit of normal was reported after skeletal muscle injury induced by intramuscular injections of certain drugs[18,19], as well as following direct current (DC) cardioversion[20,21], which in some cases also resulted in a significant elevation of CK-MB activity[22,23]. As in our study an increase in CK activity (with or without increased CK-MB activity) was observed in 3 of 5 patients receiving intramuscular injections during sedation and in all 3 patients, in whom DC cardioversion for interruption of arrhythmias after ablative procedure was performed, the overall frequency of an postprocedural increase in CK and CK-MB activity of about one third of 34 patients may be overestimated and may not truly reflect the effect of RF energy alone. We have also observed increased CK-MB activity in 5 of 6 blood specimens with *in vitro* hemolysis, which, as reported by others[24], seems to be a frequent problem in general laboratory practice. Cardiac troponin T (cTnT), on the other hand, was shown not to be associated with an increase in its concentration after skeletal muscle injury from various etiologies[25,26], and slight to moderate degree of hemolysis did not cause interference with the measurement of this marker protein[27]. As has been recently reported[17], the newly developed second generation cTnT immunoassay used in our study showed a substantial improvement in terms of cardiospecificity compared with the first generation assay.

Previous studies on patients undergoing catheter ablation of cardiac arrhythmias have used direct current (DC) shocks as energy source. This approach requires, however, general anesthesia and usually generates large amounts of heat and energy as well as considerable local barotrauma, which may result in a variety of potentially serious complications including cardiac perforation and tamponade[1,3]. A high magnitude of an increase in the activity of CK and CK-MB after DC catheter ablation was, therefore, a constant finding in these trials[28,29]. Catheter ablation with RF energy, on the other hand, is being increasingly used in the management of various forms of cardiac arrhythmias, particularly in those of accessory pathways and atrioventricular nodal reentrant tachycardia as a result of its high success and low complication rates. This novel approach performed on patients with these types of supraventricular tachycardia was reported, however, to be associated either with no increase in CK activity[7] or with a low rate (10-15%) and low magnitude of increase in CK and CK-MB activity[9,10]. The rate of an increase in these enzymes found in our study of around 30 per cent is somewhat higher, but may be overestimated because of concomitant skeletal muscle injury (in the case of CK) and methodological interference (in the case of CK-MB) described above. Nevertheless, this low sensitivity of CK and CK-MB in detecting myocardial damage is surprising by the fact that multiple RF lesions per session are usually administrated and because experimental studies have shown that RF energy typically produced small but well-circumscribed areas of coagulation necrosis in the myocardium[1]. One possible explanation of this finding came from the study of Haines et al[3,30] on the effect of RF ablation on myocardial CK activity in a porcine model. They found CK activity within a RF lesion to be only 29 per cent of control and concluded that measurement of serum CK activity after RF ablation is not an accurate marker of myocardial injury because of thermal-mediated inactivation of the enzyme by RF energy.

To the best of our knowledge, there have been thus far 2 trials investigating the frequency and magnitude of an increase in cTnT concentration compared with CK and CK-MB activity following RF ablation procedure. Muller-Bardorff et al[31] reported an elevation of cTnT levels in all 25 patients undergoing RF ablation compared with

60 per cent of patients with increased CK activity. The relative increase was 6.5 fold the discriminative value for cTnT and only 1.5 fold the upper limit of normal for CK. In a more recent study by Shyu et al[32] performed on 16 patients with supraventricular tachycardia, however, the frequency of elevated cTnT of 31 per cent was not different from those of CK (37%) and CK-MB activity (25%). Our results of 35 per cent and 29 per cent of increased CK and CK-MB activity, respectively, obtained from 34 patients with accessory pathways and atrioventricular nodal reentrant tachycardia are in accordance with those from Shyu et al, but the frequency of increased cTnT concentration found in our 30 patients (88%) was closer to those reported by Muller-Bardorff et al[31]. We have at present no explanation for these differences but the mean peak cTnT level reported by Shyu et al[32] of 0.44 ± 0.47 ng/ml was comparable to that found in our study (0.56 ± 0.63 ng/ml). Furthermore, the magnitude of an increase of cTnT found in our and in 2 studies mentioned above[31,32] indicated that, successful application of RF current is associated with a small but distinct elevation of cTnT concentration indicative of minor myocardial injury. Even in the 4 patients in the present study with no increase in cTnT concentration above the reference range, 3 demonstrated a rise and fall in its concentration which pointed to a small release of this myocardial marker protein (Fig 1B). The results from our study also showed that determination of cTnT concentration is a more sensitive method in detecting minor myocardial damage induced by RF energy than the activity measurement of CK and CK-MB. This increased sensitivity of cTnT may be explained by the fact that its concentration in the myocardial tissue is higher than that of CK-MB[33] and that RF energy may partially inactivate the activity of enzymes[3,30]. Whether the mass measurement of CK-MB (CK-MB mass) will provide a more useful test in detecting myocardial damage than the activity measurement of CK-MB remains to be determined in further studies.

SUMMARY

The present study evaluated the effectiveness of cardiac troponin T (cTnT) compared with the enzyme creatine kinase (CK) and CK-MB isoenzyme in detecting myocardial damage performed on 34 patients undergoing radiofrequency catheter ablation of accessory pathways and atrioventricular nodal reentrant tachycardia. Our results showed that cTnT has a higher rate of increase following application of radiofrequency energy than the conventional CK and CK-MB. In addition, postprocedural cTnT levels demonstrated a higher magnitude of increase compared with the activity of enzymes. Determinations of cTnT serum concentration may thus provide a useful test for assessing the frequency and degree of myocardial damage induced by the novel transcatheter ablation technology.

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การเพิ่มประสิทธิภาพในการบอกถึงภาวะ minor myocardial injury จากการทำ radiofrequency catheter ablation ในผู้ป่วยหัวใจเต้นผิดปกติ โดยการตรวจหาระดับซีรั่ม cardiac troponin T

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ได้มีการรายงานถึงการเพิ่มขึ้นของ activity ของเอ็นไซม์ creatine kinase (CK) และ CK-MB isoenzyme ในอัตราที่ต่ำหลังจากการทำ radiofrequency (RF) catheter ablation ในผู้ป่วยหัวใจเต้นผิดปกติ ขณะเดียวกันได้มีการแสดงถึงประสิทธิภาพของ cardiac troponin T (cTnT) ที่ดีกว่า CK และ CK-MB ในการบอกถึงภาวะ minor myocardial injury ในผู้ป่วย unstable angina จึงได้ทำการศึกษาเปรียบเทียบประสิทธิภาพของซีรั่มโปรทีนดังกล่าวในการวินิจฉัยภาวะ myocardial damage ในผู้ป่วยหัวใจเต้นผิดปกติ 34 ราย ที่ได้รับการรักษาโดยวิธี RF ablation โดยได้มีการตรวจหาระดับซีรั่ม CK และ CK-MB activity ก่อน และหลังการรักษาโดยวิธี enzymatic และ immunoinhibition ตามลำดับ โดยเครื่องมือ Hitachi 717 One-step sandwich ELISA (ES 300, Boehringer Mannheim) เป็นวิธีที่ใช้ในการตรวจหาระดับ cTnT ในซีรั่ม

หลังจากการทำ RF ablation พบว่ามีการเพิ่มขึ้นของ activity ของ CK และ CK-MB จากค่าสูงสุดของค่าปกติเพียง 12 (35%) และ 10 (29%) ราย จากผู้ป่วยทั้งหมด 34 รายตามลำดับ โดยที่ในผู้ป่วยหลายรายพบว่าค่าสูงสุดของ CK ไม่ได้อยู่ในช่วงเวลาเดียวกันกับ CK-MB activity ในขณะเดียวกันตรวจพบระดับซีรั่ม cTnT สูงขึ้นอย่างมีนัยสำคัญในผู้ป่วย 30 ราย (88%) โดยที่ใน 33 ราย พบค่าสูงสุดในช่วง 8 ชั่วโมงหลังการทำ RF ablation. นอกจากนี้พบว่ามีการเพิ่มขึ้นของระดับ cTnT โดยเฉลี่ยมากกว่า 5 เท่าของค่าสูงสุดของค่าปกติ ซึ่งมากกว่าอัตราการเพิ่มขึ้นของ CK (1.5 เท่า) และ CK-MB activity (0.9 เท่า) ในซีรั่ม

ผลของการศึกษาแสดงให้เห็นว่า หลังจากการทำ RF catheter ablation ได้มีการเพิ่มขึ้นของระดับ cTnT ในซีรั่ม ในอัตราและปริมาณที่สูงกว่า activity ของเอ็นไซม์ CK and CK-MB isoenzyme อย่างชัดเจน การตรวจหาระดับซีรั่ม cTnT จึงน่าจะมีประโยชน์ในการทดสอบผลของการทำ transcatheter ablation วิธีใหม่ ต่อกล้ามเนื้อหัวใจ

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