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Original article

Circulating heart-type fatty acid-binding protein levels predict ventricular fibrillation in Brugada syndrome

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ABSTRACT

Background: The association between ongoing myocardial damage and outcomes in patients with Brugada syndrome who had received an implantable cardioverter-defibrillator (ICD) is unclear.
Methods: Consecutive patients with Brugada syndrome (n = 31, 50 ± 13 years) who had received an ICD were prospectively enrolled. Minor myocardial membrane injury [heart-type fatty acid-binding protein (H-FABP) >2.4 ng/mL] and myofibrillar injury (troponin T >0.005 ng/mL) were defined using receiver operating characteristic curves. Patients were followed for a median period of 5 years to an endpoint of appropriate ICD shock.
Results: Myocardial membrane injury (29%) and myofibrillar injury (26%) were similarly prevalent among patients with Brugada syndrome who had received ICDs. Appropriate ICD shocks occurred in 19% of patients during the follow-up period. Multivariate Cox regression analysis showed that serum H-FABP level >2.4 ng/mL, but not troponin T level, was an independent prognostic factor for appropriate ICD shock due to ventricular fibrillation [hazard ratio (HR) 25.2, 95% confidence interval (CI) 1.33–1686, p = 0.03].
Conclusions: Evaluating myocardial damage using H-FABP may be a promising tool for predicting ventricular arrhythmia in patients with Brugada syndrome who have received ICDs.

Introduction

Although implantable cardioverter-defibrillator (ICD) therapy is recommended for patients with Brugada syndrome with cardiac arrest or syncope, the risk stratification of these patients remains challenging. In addition, the reported incidence of ICD-related complications is high in patients with Brugada syndrome [1–4]. Therefore, novel risk stratification methods are required to select candidates who should receive ICDs and to identify those patients with ICDs who are at risk of experiencing cardiac events [5].

Brugada syndrome was originally considered to occur in individuals with structurally normal hearts. However, pathological data suggest that structural alterations, such as myocarditis, may occur in this syndrome [6]. Some patients with Brugada syndrome may exhibit myocardial damage [7,8], but the incidence of this characteristic and the associated outcomes remain poorly defined.

Two cardiac-specific biomarkers, heart-type fatty acid-binding protein (H-FABP) and troponin, are indicators of myocardial damage. The release of H-FABP peaks 4–6 h after myocardial injury, and due to rapid renal clearance, H-FABP levels return to baseline within 20 h. Conversely, cardiac troponin T levels do not peak until approximately 12 h after myocardial injury onset [9]. Large cohort studies have clearly shown that the cytosolic marker H-FABP has superior sensitivity to the myofibrillar component troponin T for detecting ongoing myocardial damage [10,11].

The aim of this study was to determine whether, (1) patients with Brugada syndrome exhibit myocardial damage, and (2) whether the cardiac-specific cytosolic marker H-FABP can be used to predict ICD shocks in patients with Brugada syndrome undergoing ICD implantation.

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Methods

Study population

Between January 2000 and April 2010, 173 consecutive patients underwent implantation of pectoral ICDs at Yamagata University Hospital. From this population, 34 consecutive patients with Brugada syndrome (33 men, 1 woman, mean age 51 ± 12 years, range 27–71 years) were prospectively enrolled in the study. The baseline clinical characteristics of 120 consecutive patients with structural heart disease (86 men, 34 women, mean age 64 ± 11 years, range 34–87 years) were also investigated (Fig. 1).

Among patients with Brugada syndrome, serum H-FABP levels were not measured in two patients, and one patient was lost to follow-up. The remaining 31 patients with Brugada syndrome were prospectively included in the study. Informed consent was obtained from all patients prior to participation, and the study protocol was approved by the institutional Human Investigations Committee. We ruled out structural heart disease by performing echocardiograms (ECGs), stress tests, and coronary angiography. All examinations were performed by an experienced cardiologist who had no knowledge of the biochemical data on the day the device was implanted. β-Blockers were administered in three (9.6%), calcium channel blockers in eight (26%), and amiodarone in two (6.4%), respectively. Amiodarone was stopped after ICD implantation.

Definitions and diagnosis

Brugada syndrome is diagnosed when a type 1 Brugada ECG is observed in the presence or absence of a sodium channel-blocking agent. In addition, patients with Brugada syndrome in this study had at least 1 of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years, inducibility of VT with programmed electrical stimulation, and syncope. Type 1 Brugada ECG was defined as a coved-type ST-segment elevation ≥2 mm (0.2 mV) followed by a negative T wave in more than 1 of the right pericardial leads (V1–V3). Patients with type 2 (saddle-back type) or 3 (ST-segment elevation <1 mm) Brugada ECG underwent a drug challenge test (pilsicainide, 1 mg/kg) to unmask the diagnostic ECG pattern. The test was considered positive if a type 1 Brugada ECG was obtained [12,13].

Electrophysiological study

Electrophysiological studies (EPS) and VF induction were performed before ICD implantation for at least 1 week. EPS were performed in 27 patients (87%). The protocol in this study included two basic cycle lengths (600 and 400 ms) with up to three extra stimuli from two right ventricular sites (apex and outflow tract). The extra stimuli were anticipated in 10-ms decrements up to the shortest coupling interval that resulted in the ventricular threshold. The endpoint of EPS was sustained ventricular arrhythmia (lasting >30 s or requiring early termination because of hemodynamic instability) or the last extra stimulus reaching a coupling interval of 200 ms or refractoriness, whichever was reached first [13,14].

Defibrillator implantation and device programming

All patients received a transvenous lead system via the subclavian vein, and a pulse generator was placed in the left pectoral region (Medtronic Inc., Minneapolis, MN, USA, $n = 19$; St. Jude Medical Inc., Sunnyvale, CA, USA, $n = 10$; Boston Scientific Inc., Natick, MA, USA, $n = 2$). All devices were programmed using single VF zones (>188 bpm) and implanted according to the Heart Rhythm Society/European Heart Rhythm Society guidelines [12].

Measurement of H-FABP, troponin T, and brain natriuretic peptide

Serum levels of H-FABP, troponin T, and brain natriuretic peptide (BNP) were measured before ICD implantation (1st measurement), which was performed when the patient had been stable and free from clinical ventricular arrhythmia for at least 2 weeks. EPS and VF induction were performed before blood sampling for at least 1 week. Blood samples for measuring serum H-FABP levels and troponin T were centrifuged at 2500 × g for 15 min at 4 °C, within 30 min of collection, and the serum was stored at −70 °C until analyzed. H-FABP levels were measured using a two-step sandwich enzyme-linked immunosorbent assay (MARKIT-M H-FABP, Dainippon Pharmaceutical Co. Ltd., Tokyo, Japan) [8,15,16].

To assess the stability of serum H-FABP levels, blood sampling (2nd measurement) was performed in 20 patients on the day of device clinic (6–12 months after device implantation).

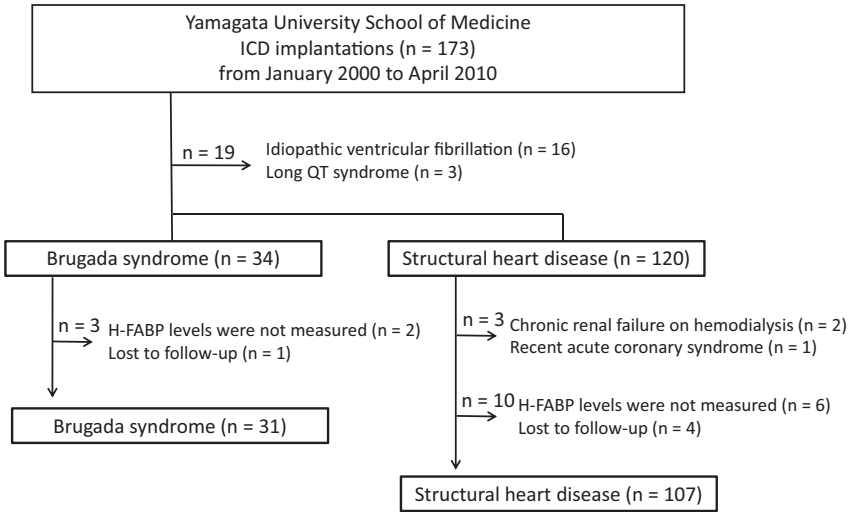

Fig. 1. Enrollment of patients with implantable cardioverter-defibrillator (ICD) at the Yamagata University School of Medicine. H-FABP, heart-type fatty acid-binding protein.