Adenosine-insensitive right ventricular tachycardia: Novel variant of idiopathic outflow tract tachycardia

Jim W. Cheung, MD, FHRS, James E. Ip, MD, FHRS, Ravi K. Yarlagadda, MD, Christopher F. Liu, MD, FHRS, George Thomas, MD, Linna Xu, BS, David Wilkes, PhD, Steven M. Markowitz, MD, FHRS, Bruce B. Lerman, MD, FHRS

From the Department of Medicine, Division of Cardiology, Weill Cornell Medical College, New York, New York.

BACKGROUND A hallmark of idiopathic right ventricular outflow tract (RVOT) tachycardia is its sensitivity to adenosine (ADO), which is consistent with a triggered mechanism. We have identified a novel group of patients with ADO-insensitive, non-reentrant RVOT tachycardia.

OBJECTIVE This study aimed to identify the clinical and electrophysiologic characteristics of ADO-insensitive RVOT tachycardia.

METHODS The response of ventricular tachycardia (VT) to ADO was evaluated in 46 consecutive patients with inducible sustained idiopathic RVOT tachycardia. The clinical and electrophysiologic characteristics of patients with ADO-insensitive RVOT tachycardia were compared with patients with ADO-sensitive VT and arrhythmogenic right ventricular cardiomyopathy (ARVC) VT.

RESULTS Sustained RVOT tachycardia terminated with ADO in 41 patients (89%), while 5 patients (11%) had ADO-insensitive VT. The electrophysiology study findings of patients with ADO-sensitive and ADO-insensitive RVOT tachycardia were similar. Compared with a group of 10 patients with ARVC, patients with ADO-insensitive RVOT tachycardia had no ARVC-associated electrocardiographic or right ventricular morphologic findings, as well as fewer inducible VT morphologies. Analysis of myocardial biopsies at VT origin sites from 3 of 5 patients with ADO-insensitive RVOT tachycardia demonstrated somatic mutations in the A_1 ADO receptor (R296C) in 1 patient and in the inhibitory G protein (F200L) in another patient, as described previously. These mutations were not identified at remote myocardial sites. Over a median follow-up period of 4.8 years, no patients insensitive to ADO developed an ARVC phenotype.

CONCLUSION Although most forms of idiopathic RVOT tachycardia are characterized by ADO sensitivity, we described a variant of ADO-insensitive VT that, in some cases, can be linked to somatic myocardial mutations involving the A_1 ADO receptor–associated cyclic adenosine monophosphate–mediated pathway.

KEYWORDS Adenosine; Ventricular tachycardia; Arrhythmogenic right ventricular cardiomyopathy; Catheter ablation

ABBREVIATIONS **A_1AR** = A_1 adenosine receptor; **ADO** = adenosine; **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **cAMP** = cyclic adenosine monophosphate; **ECG** = electrocardiography/electrocardiogram; **$G_{\alpha i2}$** = inhibitory G; **ICD** = implantable cardioveter-defibrillator; **IQR** = interquartile range; **RVOT** = right ventricular outflow tract; **VT** = ventricular tachycardia

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Introduction

Idiopathic right ventricular outflow tract (RVOT) tachycardia is the most common form of ventricular tachycardia (VT) that presents in patients without structural heart disease.[1] A hallmark finding of RVOT tachycardia is its termination with adenosine (ADO), a response that is mechanistically consistent with triggered activity owing to cyclic adenosine monophosphate (cAMP)–mediated delayed afterdepolarizations.[2–4] Although this group of patients is well characterized with respect to its clinical characteristics, tachycardia properties, and cellular mechanism, we have identified a subgroup of patients with RVOT tachycardia whose arrhythmia is ADO-insensitive. Insensitivity of RVOT tachycardia to ADO may reflect a reentrant mechanism,[2] possibly due to a preclinical phase of arrhythmogenic right ventricular cardiomyopathy (ARVC),[3] myocarditis,[4] or cardiac sarcoidosis.[5] However, on the basis of its electrophysiologic properties as well as previous observations from our laboratory,[6] we hypothesized that ADO-insensitive RVOT tachycardia represents a unique form of idiopathic RVOT tachycardia.

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In this study, we sought to identify and characterize a novel subset of patients with ADO-insensitive RVOT tachycardia by comparing their clinical and electrophysiologic characteristics with those of patients with ADO-sensitive RVOT tachycardia and those with ARVC VT.

Methods

Study population

We evaluated 68 consecutive patients who were referred for evaluation of idiopathic VT and had *sustained* RVOT tachycardia *reproducibly induced* during the electrophysiology study. Of these, 46 (68%) patients received ADO during VT and therefore comprised the RVOT tachycardia patient group. For the ARVC patient group, we studied 10 consecutive patients with ARVC who had inducible sustained VT during the electrophysiology study and received ADO during VT. All patients received a diagnosis of ARVC, which was made on the basis of the International Task Force Criteria.[7,8] This study was approved by the Cornell University Medical College Institutional Review Board.

Clinical and electrophysiologic evaluation

All patients had a standard 12-lead electrocardiogram (ECG) recorded during sinus rhythm at the time of electrophysiologic testing. The precordial leads V_1-V_3 were specifically examined for the presence of T-wave inversions, epsilon waves, localized prolongation of the QRS complex (>110 ms), and delayed S-wave upstroke (≥ 55 ms) in leads V_1-V_3.[8] All patients underwent transthoracic echocardiography. Thirty-three patients (59%) underwent cardiac magnetic resonance imaging.

After written informed consent was obtained, electrophysiologic testing was performed. Patients were locally anesthetized with 0.25% bupivacaine and sedated with midazolam and fentanyl. The ventricular stimulation protocol included up to triple ventricular extrastimuli at 2 paced cycle lengths from the right ventricular apex and RVOT at baseline and during infusion of isoproterenol (2–20 μg/min) to assess for catecholamine facilitation of VT. If catecholamine infusion was required for VT induction, VT was defined as *catecholamine-dependent*.

When sustained VT was induced, ADO was administered as a rapid bolus (starting dose ~ 150 μg/kg) followed by saline flush. If VT failed to terminate and there was no clear evidence of ADO effect (eg, transient sinus slowing/arrest or ventriculoatrial block), the ADO dose was increased. VT was classified as *ADO-sensitive* if VT terminated within 15 seconds of ADO administration and *ADO-insensitive* if a negative chronotropic and/or dromotropic ADO effect was seen and yet VT failed to terminate. In select cases, the effects of verapamil (10–15 mg intravenous push) were also assessed.

Electroanatomic mapping was performed in 33 patients with RVOT tachycardia (72%) and 6 patients with ARVC (60%). Activation mapping of VT and voltage mapping of the right ventricle was performed by using either a contact mapping system (n = 36; CARTO, CARTO XP, or CARTO 3, Biosense Webster, Diamond Bar, CA) or a noncontact mapping system (n = 3; Ensite, Endocardial Solutions, St Paul, MN). *Activation* was defined as focal if a centrifugal pattern emerged from the earliest site of activation and $<50\%$ of the VT cycle length could be mapped. Attempts to entrain tachycardia were performed with bipolar pacing by the mapping catheter at a cycle length 10–40 ms shorter than the tachycardia cycle length. Voltage mapping was performed during sinus rhythm and/or VT.

Right ventricular biopsy and mutation analysis

As part of a protocol approved by the Cornell University Medical College Institutional Review Board, informed consent was obtained for right ventricular biopsy to be performed specifically for mutational analysis in 3 of 5 patients with ADO-insensitive RVOT tachycardia. Biopsy specimens were obtained via the femoral vein using a disposable bioptome by applying a long sheath technique. At least 3 biopsy samples were obtained from the RVOT at the site of earliest activation of VT as defined by fluoroscopic and/or 3-dimensional mapping. In addition, at least 2 biopsy specimens were obtained from the right ventricular apical septum. DNA was extracted from biopsy samples, amplified with polymerase chain reaction, and sequenced with an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Complete sequencing of all exons of the A_1 ADO receptor (A_1AR) and inhibitory G ($G_{\alpha i2}$) protein was performed. Blood samples were also drawn for DNA analysis of peripheral lymphocytes. A control group consisting of 9 patients with idiopathic outflow tract tachycardia and 1 patient with ARVC underwent mutational analysis of RVOT biopsy samples, and an additional control group of 25 patients underwent mutational analysis of peripheral lymphocytes (9 patients with ARVC, 8 with idiopathic outflow tract tachycardia, and 8 patients with syncope).

Radiofrequency ablation

Ablation was performed with a 4-mm tip ablation catheter (NaviStar or EPT Blazer II, Biosense Webster) using a maximal power of 50 W and a maximal temperature of 60°C or with a 3.5-mm-tip external irrigated ablation catheter (ThermoCool NaviStar or ThermoCool RMT, Biosense Webster) using a maximal power of 50 W and a maximal temperature of 42°C. In patients with focal VT, activation mapping and pace mapping were performed to confirm appropriate sites for ablation. In patients with reentrant VT, ablation was performed at the critical isthmus defined by substrate and entrainment mapping. If VT was no longer inducible >30 minutes after ablation, the procedure was considered an acute success.

Follow-up of patients with ADO-insensitive RVOT tachycardia and patients with ARVC

Follow-up using medical record review and telephone contact was performed in patients with ADO-insensitive RVOT tachycardia and those with ARVC. In all patients who underwent implantable cardioveter-defibrillator (ICD) implantation, records for all ICD follow-up visits were assessed for appropriate ICD therapy for VT.