

Muscle Sympathetic Nerve Traffic During Spontaneous-Versus Adenosine-Mediated Termination of Idiopathic Right Ventricular Outflow Tract Tachycardia

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Idiopathic right ventricular outflow tract (RVOT) tachycardia is a well-described example of an adrenergically mediated form of ventricular tachycardia (VT).¹ The mechanism responsible for RVOT VT is cyclic adenosine monophosphate-mediated triggered activity. A characteristic and identifying feature of this form of VT is termination in response to a bolus dose of adenosine, which is believed to be related to its antiadrenergic effects. This effect of adenosine on RVOT tachycardia may be mediated on at least 2 sites: (1) the cardiac myocyte,² and (2) the presynaptic postganglionic sympathetic nerve fibers.³

Although continuous intravenous infusion of adenosine increases sympathetic nerve traffic,⁴ we have previously demonstrated that a bolus of adenosine results in a biphasic response of muscle sympathetic nerve activity (MSNA).³ An initial increase in MSNA is immediately followed by profound sympathetic withdrawal. We therefore sought to determine if adenosine's antiarrhythmic effects mediated on RVOT VT were solely related to its direct antiadrenergic effects at the cardiac myocyte, or were also temporally related to its potentially synergistic suppressive effects on MSNA, consistent with a presynaptic postganglionic mechanism of action.

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We studied 3 patients with RVOT tachycardia who were referred for diagnostic cardiac electrophysiologic study and ablation. All subjects gave informed written consent for a protocol approved by the institutional review board. These patients had the repetitive monomorphic form of RVOT tachycardia.⁵ This phenotype is characterized by frequent ventricular ectopy as well as multiple episodes of spontaneous sustained VT that increase in frequency and duration during infusion of isoproterenol. This permitted collection of multiple data points within each patient. Patient characteristics are listed in Table 1. All pa-

tients had sustained VT with left bundle branch block and inferior axis morphology that terminated with an intravenous bolus of adenosine. VT cycle length in these patients was between 360 and 400 ms. Two patients had structurally normal hearts, and the 1 patient with nearly incessant VT had decreased left ventricular function (ejection fraction 35%). Cardiac catheterization and echocardiography in this patient demonstrated no significant coronary artery or valvular disease and the etiology of the cardiomyopathy was believed to be related to the tachycardia.

Subjects underwent continuous recording of 12-lead electrocardiography, continuous noninvasive blood pressure monitoring (Finapres, Ohmeda, Louisville, Colorado), and monitoring of respiratory cycles and peroneal MSNA. Peripheral sympathetic nerve traffic was measured by direct microneurographic recordings of efferent MSNA as previously described.⁶

Bursts of MSNA throughout the entire recording were manually marked. The onset (t_i) and offset (t_f) points of each burst were identified. The area (A) of each burst was calculated as the sum of the voltage (relative to baseline) $V_i - V_f$ at all times t within the burst ($t_i \leq t \leq t_f$). A baseline recording of ≥ 2 minutes was obtained at the beginning of each study. Bursts during the entire recording period were manually annotated and the area A of each burst was calculated as previously described. From this baseline 2-minute recording, the average of all burst areas was calculated, A_{avg} . For each subsequent portion of the study, the total area of all bursts A_T (where A_T is the sum of A for each individual burst during time period T) was calculated. The number of normalized bursts occurring during time T is $N = A_T/A_{avg}$. The frequency of normalized bursts is N/T in units of bursts per second. Continuous noninvasive blood pressure was analyzed as systolic, diastolic, and mean pressures (mm Hg) throughout the recordings.

Analysis of variance for repeated measures within subjects was used to determine the statistical significance of changes observed before, during, and after episodes of VT. All data were expressed as mean \pm SD. A p value < 0.05 was considered statistically significant.

Consistent with the adrenergic-mediated mechanism of RVOT tachycardia, all patients demonstrated an increase in ventricular ectopy as well as sustained VT frequency during infusion of isoproterenol (mean dose 1.5 $\mu\text{g}/\text{min}$). Sustained VT was also initiated or terminated with programmed stimulation. Antiadrenergic perturbations that terminated VT included aden-

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Patient	Age (yrs)/Gender	Cardiac Diagnosis	EF (%)	Adenosine Response (no. bolus doses administered/successful VT termination)	MSNA Response to Adenosine-mediated Termination of VT
1	43/F	NL	55	1/1	Increase
2	62/F	NL	57	10/10	Increase
3	75/M	CM-TIC	35	2/2	Increase

CAD = coronary artery disease; EF = ejection fraction; NL = normal; TIC = cardiomyopathy-tachycardia induced; VT = ventricular tachycardia.

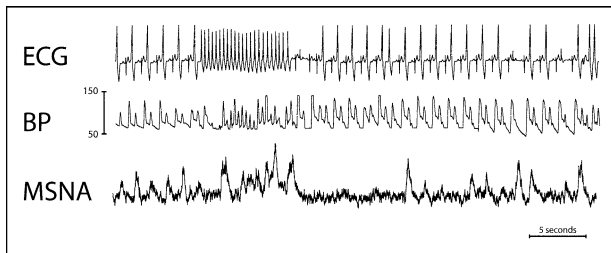


FIGURE 1. Ventricular bigeminy was abruptly interrupted by a run of spontaneous VT, which was followed by resumption of ventricular bigeminy. BP = blood pressure; ECG = electrocardiogram.

osine bolus in all 3 patients (Table 1) and carotid sinus massage, which was performed in 2 patients. Data from the entire recording period were analyzed.

Spontaneous initiation of VT was consistently marked by a decrease in blood pressure and a corresponding increase in MSNA (Figure 1). Mean arterial blood pressure during sinus rhythm was 88 ± 7 mm Hg, which decreased to 81 ± 21 mm Hg during VT ($p < 0.001$) and returned to baseline (88 ± 9 mm Hg) upon spontaneous termination of VT ($p = 0.002$). MSNA bursts increased by $370 \pm 106\%$ immediately after spontaneous initiation of VT ($p < 0.01$), which is consistent with previous studies that showed arterial and cardiopulmonary baroreceptor unloading during VT increases MSNA.⁷ During episodes of sustained VT, loss of MSNA pulse synchronicity as well as a progressive decline in MSNA burst amplitude and frequency were observed.

Upon spontaneous termination of VT, MSNA decreased by $450 \pm 220\%$, and then gradually increased (within 10 to 15 seconds) to pre-VT levels ($p < 0.01$ compared with MSNA during VT) (Figure 1). Blood pressure immediately after VT termination was consistently elevated above pre-VT levels. As blood pressure and carotid baroreceptor loading conditions returned to baseline, pulse-synchronous MSNA bursts returned (Figure 1).

Adenosine-mediated termination of VT yielded strikingly different results compared with spontaneous termination. There was no immediate response of MSNA during VT to the adenosine bolus; however, at the moment of VT termination, MSNA increased by $244 \pm 110\%$ ($p < 0.001$) above that observed during VT, despite an increase in mean blood pressure (Figure 2). MSNA remained elevated for 15 to 20 seconds and was followed by complete withdrawal of MSNA (Figure 2).

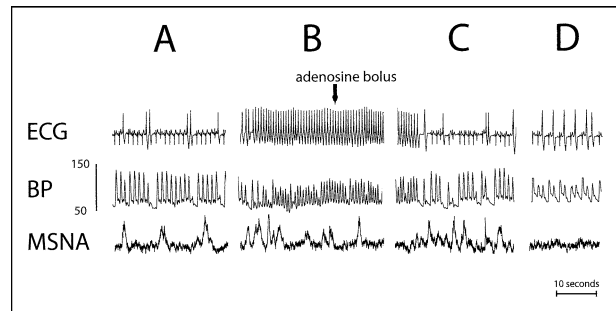


FIGURE 2. A, baseline sinus rhythm. B, spontaneous initiation of VT was marked by a decrease in BP and an increase in MSNA. A bolus dose of adenosine (12 mg) was administered at the time indicated by the arrow and initially no increase in nerve traffic was observed. C, VT terminated 12 seconds after administration of adenosine and was associated with an increase in MSNA that lasted 10 to 15 seconds. D, 15 seconds after VT termination, MSNA was completely suppressed. Abbreviations as in Figure 1.

We report the results of the first direct sympathetic nerve traffic recordings in patients during adrenergically mediated RVOT tachycardia. Our findings demonstrate a clear dissociation between adenosine's cellular antiadrenergic effects (termination of VT) and its sympathoexcitatory effects as reflected by MSNA. Therefore, adenosine's antiarrhythmic effects on RVOT tachycardia appear to be mediated solely at the level of the cardiomyocyte.

During sustained VT, a bolus dose of adenosine had no effect on MSNA until the moment of VT termination. Despite an increase in blood pressure at the termination of VT, MSNA increased dramatically. Although adenosine's sympathoexcitatory effects were shortly followed by sympathetic withdrawal, termination of VT occurred during the period of increased MSNA, indicating that adenosine's antiadrenergic effect on RVOT tachycardia are mediated primarily at the cardiac myocyte level (however, inhibition of norpeinephrine release from efferent sympathetic nerves cannot be entirely excluded as a contributing factor).⁸

We have previously demonstrated a biphasic response of MSNA to bolus doses of adenosine. Initially, there is a marked increase in MSNA following an intravenous bolus which is followed by complete suppression of MSNA lasting 90 seconds.³ Based on the time course of adenosine's effects on VT (termination within 10 seconds of the bolus dose), the antiadrenergic effects of adenosine at the level of the cardiomyocyte appear to predominate because termi-

nation corresponds to a period of discordance between adenosine's sympathoexcitatory effect on MSNA and its clinical effect (VT termination).

The initial sympathoexcitatory effects of adenosine are due to several factors, including vasodilation and baroreceptor unloading, direct stimulation of adenosine A₂ carotid chemoreceptors,⁹⁻¹¹ and stimulation of angiotensin II type I receptors.¹² Once these effects recede and no longer overwhelm the opposing effects of increased blood pressure and carotid baroreceptor engagement, as expected, there is withdrawal of MSNA.

In summary, termination of RVOT tachycardia with adenosine occurs despite a coincident increase in peripheral sympathetic nerve traffic. The dissociation between adenosine's cellular antiadrenergic effects (termination of VT) and its sympathoexcitatory effects as reflected by MSNA, suggest that adenosine's antiarrhythmic effects on RVOT tachycardia are mediated primarily at the level of the cardiomyocyte.

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Prevalence and Significance of Lead-Related Thrombi in Patients With Implantable Cardioverter Defibrillators

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The objectives of this study are to prospectively investigate the prevalence of transvenous implantable cardioverter defibrillator (ICD) lead-related thrombi and to examine the clinical and echocardiographic predictors for the development of ICD lead-related thrombi.

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We evaluated consecutive patients who received ICDs at the University of Ottawa Heart Institute, Canada, between 1991 and 1999. All patients who received ICDs were eligible for this study. Patients were excluded if they had atrial fibrillation, refused or had a contraindication to transesophageal echocardiography (TEE), were <18 years of age, could not give informed consent, or could not be prospectively followed. The left ventricular (LV) ejection fraction was assessed with radionuclide study, echocardiogram, or left ventriculogram. Each patient had a minimum of 1

transvenous defibrillation lead placed in the right ventricle. Additional transvenous defibrillation and pacing leads were positioned in the superior vena cava (SVC), right atrium, and/or coronary sinus at the implanting physician's discretion. The ICD leads used were from Medtronic (models 6881, 6884, 6894, 6932, 6933, 6936, 6937, 6940, 6942, 6943, 6945, 6963, and 6966; Minneapolis, Minnesota), CPI/Guidant/Intermedics (models 0125, 0145, 4038, 4068, 4244, 4269, 4294, and 497-20; Indianapolis, Indiana), and Vetritex (model SPO2, Sunnyvale, California).

Patients underwent both transthoracic echocardiography and TEE at 120 ± 213 days after ICD implantation. Two-dimensional transthoracic echocardiography was performed with Hewlett-Packard Sonos 2000, 2500, 4500 or 5500 ultrasound systems (Hewlett-Packard, Andover, Massachusetts). All patients were studied in the left lateral decubitus position and a comprehensive 2-dimensional examination was performed according to the guidelines of the American Society of Echocardiography.¹ All measurements were performed directly from the video screen using the track ball system and algorithm supplied by the manufacturer. Multiple determinations were done in each patient to ensure reproducibility of measure-

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