EDITORIAL

Idiopathic ventricular outflow tract tachycardia

A Farzaneh-Far, B B Lerman

Heart 2005;**91**:136–138. doi: 10.1136/hrt.2004.033795

Although the pathogenesis of ventricular outflow tract tachycardia has not been fully elucidated, recent findings suggest that defects in cAMP signalling may be involved

The paradigm for understanding the genesis of ventricular tachyarrhythmias (VT) rests on the notion that structural heart disease provides an electroanatomic substrate for re-entrant arrhythmias. Although this is sufficient for explaining most forms of clinical VT, approximately 10% occur in the absence of structural heart disease. Pioneering studies within the last few years have shown that some of these arrhythmias are caused by inherited channelopathies—for example, long QT syndrome, Brugada syndrome, and catecholaminergic VT.[1 2] The mechanisms underlying some other forms of idiopathic VT, such as verapamil sensitive fascicular tachycardia[3] and idiopathic ventricular fibrillation,[4] remain unclear, although it is known that they originate from Purkinje fibres.

The most common form of idiopathic VT originates from the ventricular outflow tract. Approximately 90% arise from the right ventricular outflow tract (RVOT), whereas the remainder are from the left.[3] Two clinical manifestations of this tachycardia have been described: exercise (stress) induced VT and repetitive monomorphic VT (which occurs at rest). The latter, as first described by Gallavardin in 1922, is characterised by ventricular extrasystoles, couplets, and recurrent salvos of non-sustained VT. This editorial will highlight some of the insights gained into the mechanisms of outflow tract tachycardia over the past decade.

DIAGNOSIS AND MECHANISM

Outflow tract tachycardia is often induced with programmed stimulation and has a characteristic electropharmacologic response. Unlike any other form of VT, this tachycardia terminates in response to adenosine, β blockers, calcium channel blockers, and Valsalva manoeuvres.[5 6] Mechanistically, these findings are consistent with triggered activity secondary to cyclic adenosine monophosphate (cAMP) mediated delayed afterdepolarisations (DADs). DADs are oscillations of membrane potential that occur after the action potential repolarises and depend on the preceding action potential for their initiation. When a DAD achieves sufficient amplitude to reach threshold potential, another action potential is triggered. This action potential may in turn be followed by another DAD and the sequence of events is repeated, resulting in a sustained ''triggered arrhythmia''.

DAD induced triggered action potentials have been shown to occur under a variety of conditions that cause increased intracellular calcium (Ca^{2+}) concentrations, including catecholamine stimulation and digitalis exposure. In the case of catecholamines, stimulation of the β adrenergic receptor results in increased intracellular concentrations of cAMP and activation of protein kinase A (fig 1). This results in an increase of the slow inward Ca^{2+} current ($I_{Ca(L)}$) as well as increased calcium release from the sarcoplasmic reticulum through phosphorylation of the ryanodine receptor. Increased intracellular Ca^{2+} in turn leads to further release of Ca^{2+} from the sarcoplasmic reticulum and activation of the transient inward sodium current I_{Ti}, giving rise to a DAD. I_{Ti} is generated by the Na^{+}-Ca^{2+} exchanger.

Adenosine terminates cAMP mediated triggered activity through its antiadrenergic effects. The inhibitory G protein G_i couples the A_1 receptor to adenylyl cyclase, decreasing stimulated concentrations of intracellular cAMP (fig 1). Increased release of acetylcholine during the Valsalva manoeuvre acts via muscarinic–cholinergic receptors and G_i to also decrease cAMP concentrations. Calcium channel blockers terminate VT due to triggered activity by directly inhibiting $I_{Ca(L)}$, whereas β blockers exert their antiarrhythmic effects through inhibition of β receptor activation.

Although β blockers and calcium antagonists (unlike adenosine) can be effective in certain forms of VT because of re-entry and abnormal automaticity, termination of outflow tract tachycardia by adenosine is thought to be pathognomonic for VT caused by cAMP triggered DADs. This is based on several lines of evidence. Firstly, adenosine's electrophysiologic effects in ventricular myocardium and Purkinje fibres are singularly antiadrenergic, having no known direct effect on these tissues.[7 8] Therefore in the presence of catecholamine stimulation, adenosine reverses the electrophysiologic effects mediated by stimulation of cAMP—that is, increases in $I_{Ca(L)}$ and I_{Ti}—but has no effect on these currents in the absence of cAMP stimulation. Secondly, adenosine abolishes DADs caused by cAMP stimulation, but it has no effect on digitalis induced DADs, which are mediated by a different mechanism (inhibition of Na^{+}, K^{+}-ATPase).[7] Thirdly, adenosine has no effect on

See end of article for authors' affiliations

Correspondence to: Bruce B Lerman, Department of Medicine, Division of Cardiology, Cornell University Medical Center, 525 East 68th Street, Starr 409, New York, NY 10021, USA; blerman@med.cornell.edu

Abbreviations: ARVD, arrhythmogenic right ventricular dysplasia; cAMP, cyclic adenosine monophosphate; DAD, delayed afterdepolarisation; GTP, guanosine triphosphate; MRI, magnetic resonance imaging; RVOT, right ventricular outflow tract; VT, ventricular tachyarrhythmia

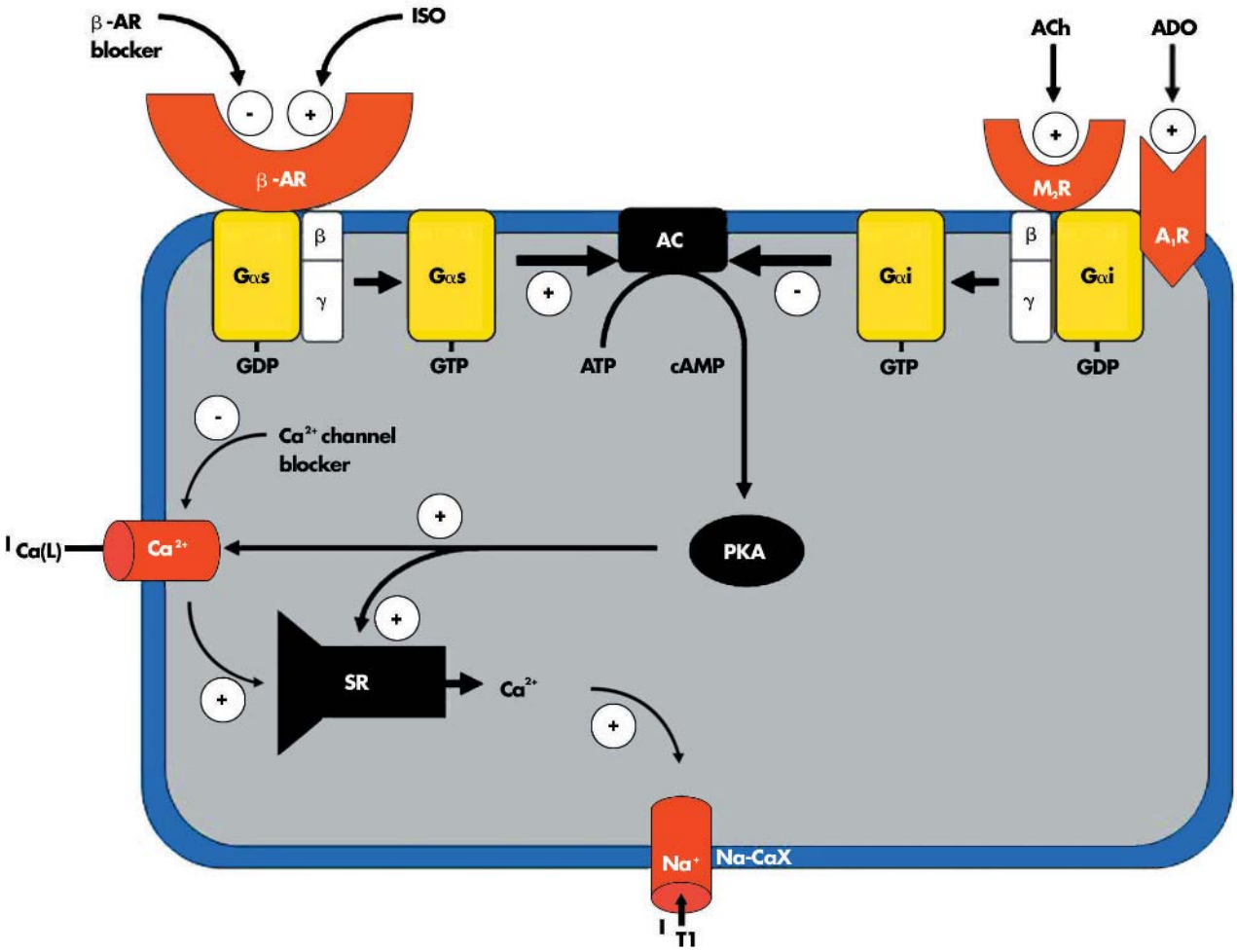


Figure 1 Receptor schema for activation and inactivation of cAMP mediated triggered activity caused by delayed afterdepolarisations. β adrenergic receptor stimulation (β-AR) results in the stimulatory G-protein (G_s) releasing its bound GDP and binding GTP. The active $G_{\alpha s}$-GTP complex then dissociates from $G_{\beta\gamma}$ and stimulates adenylyl cyclase (AC), leading to an increase in cAMP and activation of protein kinase A (PKA). This results in an increase of the slow inward calcium current ($I_{Ca(L)}$) as well as an increase in calcium release from the sarcoplasmic reticulum (SR), with consequent activation of a transient inward current (I_{Tl}) through the Na^+-Ca^{2+} exchanger (Na-CaX). Adenosine (ADO), by binding to the adenosine A_1 receptor (A_1R), acts via an inhibitory G-protein G_i. In response to adenosine binding, G_i releases its bound GDP and binds GTP. The active $G_{\alpha i}$-GTP complex then dissociates from $G_{\beta\gamma}$ and inhibits adenylyl cyclase. This leads to a decrease in $I_{Ca(L)}$ and SR calcium release with consequent attenuation of (I_{Tl}). ACh, acetylcholine; ISO, isoproterenol; M_2R, muscarinic cholinergic receptor.

triggered activity caused by early afterdepolarisations.[7] Fourthly, adenosine's effect on VT caused by automaticity is readily differentiated from its effect on VT caused by triggered activity. Adenosine *transiently suppresses* (<20 s) catecholamine induced automaticity,[8] whereas it *terminates* VT caused by triggered activity. Finally, adenosine appears to have no effect on re-entrant VT caused by structural heart disease, including that which is catecholamine facilitated.[9]

STRUCTURAL INVESTIGATION

The possibility that subtle structural defects in the right ventricle might contribute to the pathogenesis of RVOT tachycardia is based on provocative data derived from magnetic resonance imaging (MRI). These studies show that as many as two thirds of patients may have right ventricular thinning, fatty infiltration of the myocardium, or wall motion abnormalities.[10–13] This raises two important issues: (1) Are these MRI abnormalities causative or simply epiphenomena? (2) Is there a relationship between ventricular outflow tract tachycardia and arrhythmogenic right ventricular dysplasia (ARVD)?

Curiously, the right ventricular MRI abnormalities are identified at sites disparate from the outflow tract and remote from the sites of successful catheter ablation,[11] so a causative relationship is difficult to invoke. Furthermore, the technology and the criteria for identifying MRI abnormalities have changed during the last 10 years when most of these studies were performed. False positive identification of intramyocardial fat has been reduced by the use of black blood imaging techniques with double inversion recovery fast spin echo imaging. In addition, improved edge detection and volumetric data can now be obtained by ECG gated, steady state free precession imaging pulse sequence.[14] Therefore, reassessment of outflow tract tachycardia patients with newer MRI technologies will be required before we can define the significance of the original findings.

Difficulties in differentiating between outflow tract tachycardia and ARVD will, however, likely remain despite improvements in MRI technologies. This is because VT in patients with ARVD may occur when anatomic involvement is relatively modest, eluding detection by MRI. Although other clinical criteria have been proposed for establishing the

diagnosis of ARVD, their sensitivity and specificity have not been rigorously established. We believe that the response of VT to adenosine may prove to be an important criterion for distinguishing between ARVD and RVOT tachycardia since preliminary data suggest that adenosine has no effect on VT related to ARVD.[9]

BIOCHEMICAL AND MOLECULAR SUBSTRATE

In the absence of a clear anatomic substrate to account for arrhythmogenesis in outflow tract tachycardia and because of the lack of a familial inheritance pattern, we hypothesised that somatic mutations in the cAMP signalling pathway could contribute to the arrhythmogenic substrate. To that end, we identified a somatic point mutation in the inhibitory G protein $G\alpha_{i2}$, from the myocardial site of origin of the arrhythmia in a patient with an atypical or adenosine insensitive form of RVOT tachycardia.[15] The mutation (F200L) localises to the guanosine triphosphate (GTP) binding domain and functionally increases intracellular cAMP concentration in response to catecholaminergic stimulation. This mutation was not identified at myocardial sites disparate from the site of origin or from peripheral lymphocytes, consistent with a somatic origin of the tachycardia. Preliminary data have identified additional mutations in the cAMP signalling cascade in other patients that may be responsible for the typical adenosine sensitive form of outflow tract tachycardia.

CONCLUSION

Outflow tract tachycardia remains an intriguing clinical entity. Although its clinical presentation and amenability to therapeutic cure through catheter ablation have been well delineated, its pathogenesis remains more obscure. We have outlined some of the recent findings in this regard. Despite the obstacles ahead, it is likely that within the next decade, the cellular and molecular pathogenesis of this entity will be more fully elucidated.

ACKNOWLEDGEMENTS

The work was supported in part by grants from National Institutes of Health (ROI HL-56139), The Rosenfeld Heart Foundation, The Michael Wolk Foundation, The Raymond and Beverly Sackler Foundation, and New York Cardiology Associates.

Authors' affiliations

A Farzaneh-Far, B B Lerman, Department of Medicine, The Maurice & Corinne Greenberg Division of Cardiology, Cornell University Medical Center, New York, USA

REFERENCES

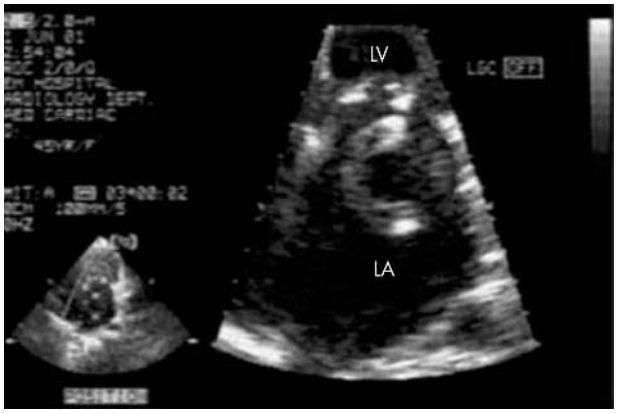
1 **Glassner IW**, Kass RS, Clancy CE. Mechanism of genetic arrhythmias: from DNA to ECG. *Prog Cardiovasc Dis* 2003;**40**:259–70.
2 **Priori SG**, Napolitano C, Memmi M, *et al*. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;**106**:69–74.
3 **Lerman BB**, Stein KM, Markowitz SM, *et al*. Ventricular tachycardia in patients with structurally normal hearts. In: Zipes DP, Jaife J, eds. *Cardiac electrophysiology: from cell to bedside*, 4th ed. Philadelphia: WB Saunders, 2004:668.
4 **Haissaguerre M**, Shah DC, Jais P, *et al*. Role of Purkinje conduction system in triggering of idiopathic ventricular fibrillation. *Lancet* 2002;**359**:677–8.
5 **Lerman BB**, Belardinelli L, West GA, *et al*. Adenosine-sensitive ventricular tachycardia: evidence suggesting cyclic AMP-mediated triggered activity. *Circulation* 1986;**74**:270–80.
6 **Lerman BB**, Stein K, Engelstein ED, *et al*. Mechanism of repetitive monomorphic ventricular tachycardia. *Circulation* 1995;**92**:421–9.
7 **Song Y**, Thedford S, Lerman BB, *et al*. Adenosine-sensitive afterdepolarizations and triggered activity in guinea pig ventricular myocytes. *Circ Res* 1992;**70**:743–53.
8 **Lerman BB**, Wesley RC, DiMarco JP, *et al*. Antiadrenergic effects of adenosine on His-Purkinje automaticity: evidence for accentuated antagonism. *J Clin Invest* 1988;**82**:2127–35.
9 **Lerman BB**, Stein KM, Markowitz SM, *et al*. Catecholamine facilitated reentrant ventricular tachycardia: uncoupling of adenosine's antiadrenergic effects. *J Cardiovasc Electrophysiol* 1999;**10**:17–26.
10 **Carlson MD**, White RD, Trohman RG, *et al*. Right ventricular outflow tract ventricular tachycardia: detection of previously unrecognized anatomic abnormalities using cine magnetic resonance imaging. *J Am Coll Cardiol* 1994;**24**:720–7.
11 **Markowitz SM**, Litvak BL, Ramirez de Arellano EA, *et al*. Adenosine-sensitive ventricular tachycardia: right ventricular abnormalities delineated by magnetic resonance imaging. *Circulation* 1997;**96**:1992–200.
12 **Globits S**, Kreiner G, Frank H, *et al*. Significance of morphological abnormalities detected by MRI in patients undergoing successful ablation of right ventricular outflow tract tachycardia. *Circulation* 1997;**96**:2633–40.
13 **White RD**, Trohman RG, Flam SD, *et al*. Right ventricular arrhythmia in the absence of arrhythmogenic dysplasia: MR imaging of myocardial abnormalities. *Radiology* 1998;**207**:743–51.
14 **Tandri H**, Bomma C, Calkins H, *et al*. Magnetic resonance and computed tomography imaging of arrhythmogenic right ventricular dysplasia. *J Mag Reson Imagining* 2004;**19**:848–58.
15 **Lerman BB**, Dong B, Stein KM, *et al*. Right ventricular outflow tract tachycardia due to a somatic cell mutation in G protein subunit$_{\alpha i2}$. *J Clin Invest* 1998;**101**:2862–8.

IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2004.040584

Ring in the heart

A 45 year old woman was admitted with New York Heart Association functional class III dyspnoea, with occasional orthopnoea and paroxysmal nocturnal dyspnoea. She was diagnosed as having rheumatic heart disease with severe mitral stenosis and atrial fibrillation. Echocardiography showed severe mitral stenosis, with a mitral valve area of 0.8 cm, mild mitral regurgitation, mild pulmonary hypertension, and good ventricular function. There were two echogenic structures with central translucency resembling the visual impression of rings in the left atrium. One was 3.2 cm × 2.9 cm lying close to the interatrial septum and was mobile, while the other was small and adhered to the posterior atrial wall. The mobile ring intermittently obstructed the mitral valve inflow, coinciding with the patient developing an episode of coughing. Our provisional diagnosis of organised clots was confirmed during surgery, following which the patient made a good recovery.



C Lanjewar
P Nyadhish
P Kerkar
charanlanjewar@hotmail.com