Accepted Manuscript

Is Non-sustained ventricular tachycardia a predictor of sudden death in adults with congenital heart disease?

Eric Lim, Tom Wong

PII: S0167-5273(16)30160-7
DOI: doi: [10.1016/j.ijcard.2016.01.161](https://doi.org/10.1016/j.ijcard.2016.01.161)
Reference: IJCA 21916

To appear in: *International Journal of Cardiology*

Received date: 6 January 2016
Accepted date: 7 January 2016

Please cite this article as: Lim Eric, Wong Tom, Is Non-sustained ventricular tachycardia a predictor of sudden death in adults with congenital heart disease?, *International Journal of Cardiology* (2016), doi: [10.1016/j.ijcard.2016.01.161](https://doi.org/10.1016/j.ijcard.2016.01.161)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

IS NON-SUSTAINED VENTRICULAR TACHYCARDIA A PREDICTOR OF SUDDEN DEATH IN ADULTS WITH CONGENITAL HEART DISEASE?

Eric Lim (1,2, 3), Tom Wong (1)

(1) Royal Brompton & Harefield Hospitals and
National Heart and Lung Institute, Imperial College, London
United Kingdom

(2) National Heart Center Singapore, Singapore

(3) National Medical Research Council, Singapore

Address for Correspondence

Dr Tom Wong

Phone: +44 20 7351 8619

Heart Rhythm Centre

Fax: +44 20 7351 8629

The Royal Brompton & Harefield Hospitals Email: tom.wong@imperial.ac.uk

Sydney Street,

London, SW3 6NP

United Kingdom

ACCEPTED MANUSCRIPT

Sudden death is a prominent cause of death in patients surviving to adulthood with congenital heart disease. In the Dutch CONCOR registry (1), sudden death accounted for 19% of all deaths in this cohort of patients. In the majority of cases, the the cause of sudden cardiac death is believed to be arrhythmic, specifically ventricular arrhythmias, although evidence for this is indirect, largely coming from the high frequency of appropriate shocks in adults with congenital heart disease (ACHD) with implantable cardioverter defibrillators (ICD) (2). In contrast to the wealth of data that associates ventricular arrhythmia with sudden death in patients with acquired heart disease, there is a paucity of high quality data in ACHD. In this issue of the Journal, Teuwen and colleagues examine the common clinical problem of ACHD patients in whom non-sustained ventricular tachycardia (NSVT) has been detected and to attempt to address the question is NSVT an adverse prognostic sign in such patients and does it pre-sage sudden death?

The study enrolled 145 ACHD patients with a range of lesions, from simple (e.g. atrial septal defect) to complex (e.g. tetralogy of Fallot, congenitally corrected transposition of the great arteries), but notably, does not include a control arm, only patients who had NSVT documented on surface ECG, Holter or implantable cardioverter defibrillator, or alternatively, had suffered an out-of-hospital cardiac arrest were studied. They were then followed up for subsequent events over a median duration of 5 years. Due to the lack of a control arm, the relative risk associated with NSVT cannot be derived, but the absolute risk would appear to be low. Of the 103 subjects with NSVT, only 5 developed VT/VF over the period of follow-up, corresponding to a per annum risk of just 1%. The interesting conclusion drawn by the authors was therefore that NSVT is only rarely a harbinger of subsequent sustained ventricular tachycardia, ventricular fibrillation or sudden death. This stands in contrast to patients with sustained VT (n=25) or VF (n=17), where recurrence was common as estimated by ICD shock discharges or death.

It is helpful to review the lessons learned from patients with acquired heart disease and ventricular arrhythmia in interpreting the result of this study by Teuwen and colleagues. The most reliable data in the non-ACHD setting comes from patients with coronary artery disease, where it has long been observed that NSVT is frequent during the first week after acute myocardial infarction (6% to 13% of patients) (3,4) and linked to sudden death. In the

1980s, the Cardiac Arrhythmia Pilot Study (CAPS) showed that several anti-arrhythmic drugs (flecainide, encainide and moricizine) were able to suppress ventricular ectopy (5). The reasonable supposition was that these anti-arrhythmic drug should therefore reduce sudden death. The Cardiac Arrhythmia Suppression Trial (CAST) (6,7) was initiated in 1987 to test just this hypothesis. Unexpectedly (at the time), exactly the opposite result was reached – in 1989, the trial was discontinued prematurely because there was an excess of arrhythmic and total deaths in patients receiving flecainide and encainide, in spite of demonstrable suppression of ventricular ectopy.

In fact, subsequent epidemiological studies have shown that once covariates are taken into account (specifically left ventricular systolic function), NSVT in the post-myocardial infarction setting is not a particularly powerful predictor of sudden death. In DANAMI-2 (Danish Trial in Acute Myocardial Infarction-2; 501 patients with fibrinolysis and 516 patients with primary angioplasty) (8) and the CARISMA (Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction) (9) studies, NSVT did not predict either arrhythmic death or total mortality, whereas in a study of 2,130 infarct survivors, Makikallio and colleagues reported that NSVT predicted sudden death only in patients with left ventricular ejection fraction less than 35% (10). Of contemporary studies, only the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) (11) study that enrolled 1,071 post-MI patients found NSVT to be an independent predictor of adverse prognosis.

This is reminiscent of the situation in patients with NSVT and structurally normal hearts – this includes patients with outflow tract premature ventricular contractions, in whom episodes of monomorphic NSVT are commonly found, as well as patients with idiopathic left VT (4,12). In both groups, sudden death is exceptional and prognosis is good.

The fact that NSVT can be dissociated from the risk of sudden death leads to the inescapable conclusion that either NSVT is simply a surrogate marker of something more fundamental, or that NSVT must be combined with other factors to substantially elevate the risk of sudden death. The accumulated insight over the past two decades support this idea. More than a decade ago, Gatzoulis and colleagues used repaired tetralogy of Fallot (rTOF) as a paradigm for arrhythmic death in congenital heart disease. In a landmark study that

included 793 patients, they clearly showed that the dominant structural lesion for ventricular arrhythmias and sudden death in rTOF is pulmonary regurgitation. In fact, in this large cohort, sudden death only occurred in patients who had at least moderate pulmonary regurgitation. The mechanistic link with sudden death is presumably through the haemodynamic consequence of longstanding pulmonary regurgitation, leading to volume overload of the right ventricle. Similarly, in unoperated ventricular septal defect, NSVT or VT is common and found in approximately 6%. This includes high grade ventricular ectopy which seems associated with higher mean pulmonary arterial pressures. Nevertheless, sudden death is uncommon unless Eisenmenger syndrome supervenes.

The idea that these various studies seem to be converging upon is that sudden death is the product of the anatomy, haemodynamic physiology and electrophysiology associated with each specific form of congenital cardiac lesion (14, 15). Accurate risk stratification will depend on assessment of all three of these areas; NSVT should be treated as a possible indicator of sudden death risk but it cannot be interpreted in isolation.

With this conceptual framework in place, the findings of Teuwen and colleagues are not so surprising. The study cohort included a mixed bag of ACHD with vastly different anatomies, haemodynamics and electrophysiological substrates. It would be unrealistic to expect NSVT to carry the same weight in these disparate populations. By including many subjects where sudden death risk is expected to be low, the subgroups where NSVT might confer significant incremental risk would be diluted out. This contrasts with studies in specific ACHD populations where NSVT has been associated with sudden death risk – for example, in patients with tetralogy of Fallot and an implantable cardioverter defibrillator, it has been shown that NSVT independently predicts appropriate ICD discharges with a hazard ratio of 3.7 ($p=0.004$) (14).

In summary, perhaps the answer to the question, “does NSVT predict sudden death for my ACHD patient” is, “it depends”. Although NSVT may not, in a general ACHD population, be a particularly powerful predictor of sudden death, this is not necessarily the case for a specific cohort of the ACHD population. An astute clinician will need to weigh up factors derived from the anatomy of the ACHD lesion together with the haemodynamics and

electrophysiology associated with it in order to best determine individual risk (15). In the ACHD lesion perhaps more strongly associated with sudden death such as rTOF (as apposed to patients with atrial septal defect), integrated risk scores exist (14), and NSVT should be considered alongside such scores rather than in isolation. However, given the endless variation of ACHD pathologies that exist, in our opinion, the judgment of an experienced ACHD physician will always remain invaluable.

Selected References

1. Verheugt CL, Uiterwaal C, van der Velde E et al. Mortality in adult congenital heart disease. *Eur Heart J* (2010) 31, 1229-1229.
2. Koyak Z, de Groot JR, Van Gelder IC et al. Implantable cardioverter defibrillator therapy in adults with congenital heart disease: who is at risk of shocks? *Circ Arrhythm Electrophysiol* (2012); 5:101-110.
3. Høfsten DE, Wachtell K, Lund B, Mølgaard H, Egstrup K. Prevalence and prognostic implications of non-sustained ventricular tachycardia in ST-segment elevation myocardial infarction after revascularization with either fibrinolysis or primary angioplasty. *Eur Heart J*. 2007;28:407-414.
4. Katritsis DG, Zareba W, Camm J. Nonsustained ventricular tachycardia. *J Am Coll Cardiol*. 2012;60(20):1993-2004.
5. CAPS Investigators. The Cardiac Arrhythmia Pilot Study. *Am J Cardiol* 1986; 57(1):91-5.
6. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321:406-412.
7. The Cardiac Arrhythmia Suppression Trial-II Investigators. Effect of antiarrhythmic agent moricizine on survival after myocardial infarction: the Cardiac Arrhythmia Suppression Trial-II. *N Engl J Med*. 1992;327:227-233.
8. Busk M, Maeng M, Rasmussen K, Kelbaek H, Thayssen P et al. The Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction (the DANAMI-2 trial): outcome after 3 years follow-up. *Eur Heart J*. 2008; 29(10):1259-66. Epub 2007 Oct 23.

9. Bloch Thomsen PE, Jons C, Raatikainen MJ, Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. *Circulation* 2010;122:1258-1264.
10. Makikallio TH, Barthel P, Schneider R., Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J*. 2005;26:762-769.
11. La Rovere MT, Pinna GD, Hohnloser SH. Autonomic tone and reflexes after myocardial infarction. *Circulation* 2001;103:2072-2077.
12. Prystowsky EN, Padanilam BJ, Joshi S, Fogel, R. Ventricular Arrhythmias in the Absence of Structural Heart Disease. *J Am Coll Cardiol*. 2012;59(20):1733-1744. doi:10.1016/j.jacc.2012.01.036.
13. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile CP et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000; 356(9234):975-981.
14. Khairy P, Louise H, Landzberg M, Viswanathan S, Barlow A et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation* 2008; 117: 363-370.
15. Valente AM, Gauthreau K, Egidy Assenza G, Babu-Narayan SV, Schreier J, Gatzoulis MA, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart* 2014 Feb;100(3):247-53. doi: 10.1136/heartjnl-2013-304958. Epub 2013 Oct 31.