Successful treatment of a patient with symptomatic long QT syndrome type 3 using ranolazine combined with a beta-blocker

Maarten P. van den Berg [a,*,1], Freek van den Heuvel [b,1], J. Peter van Tintelen [c,1], Paul G.A. Volders [d,1], Isabelle C. van Gelder [a,1]

[a] University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, The Netherlands
[b] University of Groningen, University Medical Center Groningen, Department of Pediatric Cardiology, Beatrix Children's Hospital, Groningen, The Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands
[d] Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Received 22 August 2013
Accepted 23 November 2013
Available online 4 December 2013

Keywords:
Long QT syndrome type 3
SCN5a
N1325S
Late inward sodium current
Ranolazine
Beta-blocker

Long QT syndrome type 3 (LQT3) is caused by gain-of-function mutations in *SCN5A*, the gene encoding for the α-subunit of the cardiac sodium channel which carries the sodium current (I_{Na}). In LQT3 persistent late inward I_{Na} thus causes prolongation of the action potential and hence the occurrence of early after-depolarizations, setting the stage for ventricular ectopy, including torsades de pointes (TdP). These events are usually triggered by bradycardia and, as a consequence, symptoms usually occur at rest or during sleep. Treatment of patients with LQT3 can be difficult since beta-blockers may be counterproductive and exacerbate bradycardia, and these patients often need a pacemaker or even an ICD (for an overview see ref. [1]). Here we report on a patient with LQT3 who was successfully treated with a combination of a beta-blocker and ranolazine, an agent that reduces late inward I_{Na} [2].

A 43-year-old female was referred because of palpitations (irregular heart beats, often repetitive), in particular during emotional arousal or physical exertion. Over time several drugs had been prescribed, including atenolol, propranolol, and even sotalol, all without much effect. At presentation, she was not taking any medication. Her ECG showed a prolonged corrected QT-interval (QTc) and peaked T-waves. DNA analysis revealed that she carried a mutation in *SCN5A* (c.3974A>G, p.Asn1325Ser (p.N1325S)). During 24-hour Holter monitoring QTc values were significantly increased, particularly during the night (Table 1). In addition, there were frequent premature ventricular complexes (PVC) with varying morphology. However, unlike the QTc-prolongation, the ventricular ectopy was particularly present during the day (Table 1). This was supported by exercise testing which showed frequent PVCs as well as a non-sustained ventricular tachycardia at peak exercise, resembling TdP (Fig. 1). The latter observations prompted us to try a beta-blocker again and she was started on 2.5 mg of bisoprolol once daily. In terms of symptoms, this treatment made no significant difference to her, but a Holter recording showed a remarkable change: the total number of PVCs had actually increased and were occurring particularly during the night. It was decided to hospitalize the patient and to add 500 mg of oral ranolazine twice daily, while continuing the bisoprolol. Within one day after beginning to take the ranolazine, the patient noticed a dramatic improvement, which was evident from Holter monitoring that showed an almost complete disappearance of the PVCs (Table 1). The remaining 34 PVCs occurred while the patient was exercising vigorously on a bicycle, but no complex ventricular arrhythmias (i.e. TdP) were seen. In addition, there was a striking effect on the premature atrial complexes (PACs) that were completely eradicated, including occasional short runs of atrial tachycardia which were present both at baseline and on bisoprolol, but not when ranolazine was added. Of note, there was no significant effect on the QTc values.

The *SCN5A* mutation p.N1325S was among the first to be reported in *SCN5A* in patients with LQTS [3]. In most *SCN5A* p.N1325S patients their symptoms occur in bradycardia conditions (rest, sleep), but the symptoms (arrhythmias) may also occur during non-bradycardia conditions, i.e. during physical or emotional stress [4]. In the *SCN5A* mutation p.N1325S, asparagine is substituted by serine at position 1325 in the cytoplasmic loop between segments 4 and 5 of domain III of the cardiac sodium channel. In vitro studies of p.N1325S expressed in either *Xenopus* oocytes [5] or transfected HEK-293 cells [6] have demonstrated that mutant I_{Na} is characterized by an initial peak inward current followed by dispersed reopenings of the channel during the inactivation phase, thus producing a late and persistent inward I_{Na}. In a transgenic overexpression mouse model, p.N1325S mice demonstrated myocyte action potentials with early after-depolarizations, prolongation of the QTc interval, and a high incidence of ventricular arrhythmias [7]. In a patch-clamp study the action-potential duration became prolonged and unstable at increasing activation rates, often with alternating repolarization phases [4], which could be corrected with verapamil. This implies that increased calcium influx and intracellular calcium-overload, secondary to the

Table 1
Twenty-four hour Holter recordings while off medication (baseline), while on bisoprolol and on combined bisoprolol and ranolazine.

	Baseline	Bisoprolol 2.5 mg o.d.	Bisoprolol 2.5 mg o.d. + ranolazine 500 mg. t.d.
Heart rate (beats/min)	71	62	66
Heart rate during the day (beats/min)	79	64	69
Heart rate during the night (beats/min)	57	56	56
QTc (s)	0.50	0.47	0.49
QTc during the day (s)	0.48	0.46	0.48
QTc during the night (s)	0.52	0.48	0.50
Total no. of PACs	66	89	0
Total no. of PVCs	747	2770	32
No. of PVCs/h during the day	48	55	2
No. of PVCs/h during the night	2	237	0

Note: "day" was defined as 6.00 to 24.00 h and "night" was defined as 0.00 to 6.00 h.

* Corresponding author at: University Medical Center Groningen, Department of Cardiology, PO Box 30001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 3612355; fax: +31 50 3611347.
E-mail address: m.p.van.den.berg@umcg.nl (M.P. van den Berg).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

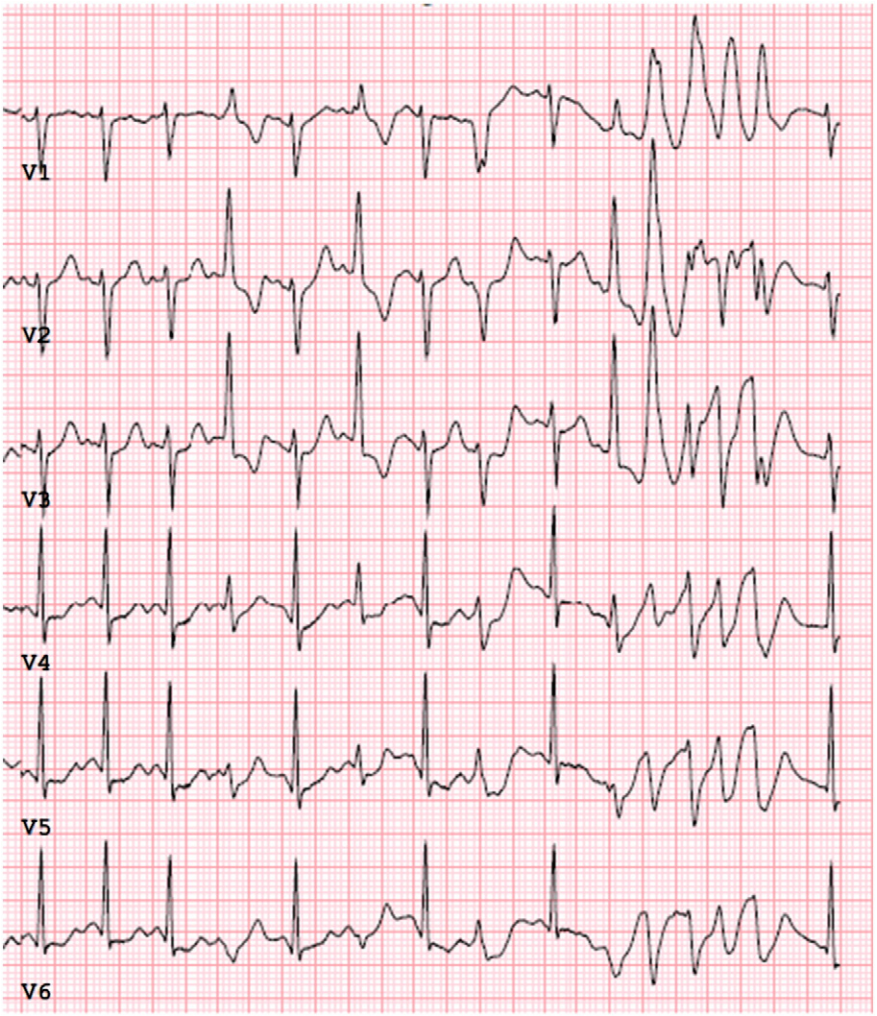

Fig. 1. Excerpt of ECG during exercise testing showing sinus tachycardia with a short ventricular tachycardia with torsades de pointes, preceded by a short-long-short cycle.

sodium influx, is probably involved in the arrhythmogenesis in *SCN5A* p.N1325S patients and would explain the occurrence of ventricular arrhythmias during non-bradycardia conditions or by heart rate acceleration during bradycardia. The clinical picture in our 43-year old patient with *SCN5A* mutation p.N1325S is in agreement with the above findings: her electrocardiogram shows features of LQT3 and QTc values are particularly increased during the night (i.e. bradycardia condition), but her symptoms/arrhythmias typically occur during physical or emotional stress, including TdP. Given the latter observation, we decided to treat her with a beta-blocker, but this did not alleviate the complaints from ventricular ectopy. If anything, it caused a sharp nocturnal increase. We then surmized that ranolazine might be beneficial, since this agent specifically blocks late inward I_{Na} [2]. Several experimental studies have reported on its beneficial effect in LQT3 models, including a study in p.N1325S mice, in which ranolazine was demonstrated to reverse the downstream effects of late inward I_{Na} [8]. One prior study [9] reported that, during an 8-hour intravenous infusion scheme, ranolazine reduced QT-interval prolongation in a group of patients with LQT3 without adverse effects. However, to our knowledge, there are no reports on its use to alleviate symptoms (arrhythmias) associated with LQT3. In our patient, oral maintenance treatment with ranolazine added to a beta-blocker was extremely effective with almost complete abolition of ventricular ectopy. In addition, there was a strikingly beneficial effect on her atrial ectopy, which reminded us that LQTS can also be associated with atrial ectopy. Indeed, in patients with LQTS, atrial repolarization is prolonged and, related to this, TdP-like atrial arrhythmias can be provoked in experimental dogs with cesium-induced prolongation of atrial repolarization [10]. The extra beneficial effect of ranolazine on the atrial ectopy in our patient can thus be readily explained: analogous to the effect on the ventricles, ranolazine probably led to shortening of the repolarization and/or restoration of the calcium stability in the atria.

References

[1] Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol 2012;5:868–77.
[2] Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004;110:904–10.
[3] Wang Q, Shen J, Li Z, et al. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. Hum Mol Genet 1995;4:1603–7.
[4] Yong SL, Ni Y, Zhang T, Tester DJ, Ackerman MJ, Wang QK. Characterization of the cardiac sodium channel *SCN5a* mutation, $N_{1325}S$, in single murine ventricular myocytes. Biochem Biophys Res Commun 2007;352:378–83.
[5] Dumaine R, Wang Q, Keating MT, et al. Multiple mechanisms of Na^+ channel linked long-QT syndrome. Circ Res 1996;78:916–24.
[6] Wang DW, Yazawa K, Makita N, George AL, Bennett PB. Pharmacological targeting of long QT mutant sodium channels. J Clin Invest 1997;99:1714–20.
[7] Tian XL, Yong SL, Wan X, et al. Mechanisms by which *SCN5a* mutation $N_{1325}S$ causes cardiac arrhythmias and sudden death in vivo. Cardiovasc Res 2004;61:256–67.
[8] Yao L, Fan P, Jiang Z, et al. $Na_v1.5$-dependent persistent Na^+ influx activates CaMKII in rat ventricular myocytes and $N_{1325}S$ mice. Am J Physiol Cell Physiol 2011;301: C577–86.

[9] Moss AJ, Zareba W, Schwarz KQ, Rosero S, McNitt S, Robinson JL. Ranolazine shortens repolarization in patients with sustained inward sodium current due to type-3 long-QT syndrome. J Cardiovasc Electrophysiol 2008;19:1289–93.

[10] Satoh T, Zipes DP. Cesium-induced atrial tachycardia degenerating to atrial fibrillation in dogs: atrial torsades de pointes? J Cardiovasc Electrophysiol 1998;9:970–5.

0167-5273/$ – see front matter
http://dx.doi.org/10.1016/j.ijcard.2013.11.066

Calibration of intravascular optical coherence tomography as presented in peer reviewed publications

Lasse Hebsgaard, Evald Høj Christiansen, Niels Ramsing Holm *

Department of Cardiology, Aarhus University Hospital, Skejby, Denmark

ARTICLE INFO

Article history:
Received 26 August 2013
Accepted 23 November 2013
Available online 4 December 2013

Keywords:
Optical coherence tomography
Calibration
Artifacts
Coronary

Intravascular optical coherence tomography (OCT) is a new imaging modality in interventional cardiology providing high-resolution intracoronary images. The modality is already established as an efficient and precise research tool and is increasingly used for guiding coronary intervention. The quantitative capabilities of marketed OCT systems have been validated and measurements are found accurate and precise in bench testing [1]. When using OCT it is important to carefully calibrate the system for accurate measurements [2,3]. Present standard in marketed systems is automated calibration. Still the calibration can be incorrect due to failed automated calibration, wrong manual adjustment, or changes to the length of the optic fiber due to altered bending of the imaging wire.

Correct calibration and the identification of incorrect calibration can be challenging due to mirror artifacts, blood in the imaging wire and proximity to the vessel wall.

Looking for guidance on calibration of intravascular OCT in published peer reviewed papers led to the identification of some inconsistencies similar to our own experience. Still we do not have a database of wrong calibrations owing to immediate corrections. Therefore we aimed at identifying patterns of failed calibration as presented in images in peer-reviewed papers. Using the PubMed internet database, we built a search containing following MESH-terms: "Tomography, Optical Coherence" AND ("Percutaneous Coronary Intervention" OR "Coronary Occlusion" OR "Coronary Stenosis" OR "Coronary Restenosis" OR "Coronary Vessels" OR "Coronary Disease" OR "Coronary Circulation" OR "Coronary Thrombosis" OR "Coronary Artery Disease" OR "Myocardial Reperfusion").

With this search more than 300 articles published since 1 January 2011 were identified. Of these, 222 were included in the analysis giving a total of 1164 OCT images with the information needed for evaluating the calibration. Articles which were excluded from the analysis are due to lack of images (N = 57), lack of fiduciaries (N = 38) or no full-text subscription by the local university library (N = 27). Calibration errors were divided into 8 groups, ranging from slightly incorrect through errors with potentially clinical relevant impact on quantitative measurements. Errors in classes that may likely affect stent sizing if applied in clinical practice were termed serious calibration errors (Classes 3, 4 and 6). Frames which we were unable to classify were not counted and if a frame appeared more than once or in more articles (e.g. editorials), it was only counted once.

Our findings (shown in Table 1) were 1) 640 images produced by time domain OCT systems. Of these 15% were in-assessable. Worse than slightly incorrect calibration, was found in 35% of assessable cases. Serious calibration incorrectness was seen in 16% of images. 2) A total of 524 images had been obtained by marketed frequency domain systems (482 by C7 system and 42 images by Illumien—both St. Jude Medical, USA). In images acquired by the C7 system serious calibration incorrectness was detected in 16% of cases. In images acquired by the Illumien system (42) only a single acquisition with 3 images was severely incorrect calibrated due to inverted calibration. Inverted calibration may cause the depicted catheter to resemble a correct calibrated OCT catheter. This is an occasional finding termed "inverted calibration" (Class 4 error). A related finding due to inverted calibration is the distortion of the image and appearance of vessel wall or wires inside the apparent imaging wire (Fig. 1 error Class 4). We propose the term "inverted calibration artifacts" for such findings.

The "slightly incorrect"-group was expanded to contain also the Class 1 categorized images, as the error in these groups only result in minimal error of the measurements.

For the C7 system 43% of images in articles presenting quantitative measurements showed any degree of incorrect calibration. For the M2 system, this was 40%.

We are aware, that images shown in articles are chosen for illustrative purpose. This is a process different from the systematic core lab evaluation, and we assume that all results derived were made from correctly calibrated images. Still, systematic errors in many or all images in a paper might induce a slight uncertainty about derived quantitative results. Incorrect calibration in images presented for tissue characterization or similar could be seen as unimportant. Still, when presented in high impact journals, in expert reviews or consensus reports some users might potentially adopt this as the gold standard of calibration.

In conclusion, a high incidence of incorrect calibrated images was found in systematic review of peer reviewed publications. Improved calibration facilities by newer generation OCT systems seems to reduce errors though not alleviating the risk associated with not identifying inverted calibration.

References

[1] Tahara S, Bezerra HG, Baibars M, et al. In vitro validation of new Fourier-domain optical coherence tomography. EuroIntervention 2011;6:875–82.

* Corresponding author at: Department of Cardiology, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark. Tel.: +45 78452254; fax: +45 78452260.
E-mail address: niels.holm@ki.au.dk (N.R. Holm).