Invasive electrophysiological study in the Jervell and Lange-Nielsen syndrome

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SUMMARY Repeated invasive electrophysiological studies in a 7-year-old boy with the classic Jervell and Lange-Nielsen syndrome disclosed increased ventricular refractoriness, unusual late diastolic endocardial waveforms, and the inability to induce ventricular fibrillation. Despite apparently beneficial electrophysiological responses to left stellate block, surgical left cervical sympathectomy was followed by spontaneous ventricular fibrillation, an unchanged QT interval and ventricular refractoriness, and persistence of late diastolic endocardial waveforms. These electrophysiological observations, which are unique, may reflect temporal and spatial inhomogeneity of repolarisation resulting from cardiac autonomic imbalance. The absence of electrophysiological change despite left stellate block is disconcerting and re-emphasises our incomplete understanding of the pathogenesis of syndromes involving long QT intervals. Invasive electrophysiological study should be considered in the assessment of future patients with this disorder.

Prolongation of the QT interval in combination with recurrent ventricular flutter-fibrillation, causing recurrent syncope and ultimately sudden death, is a recognised but poorly understood syndrome. When the additional clinical feature of congenital deafness is present, the condition may be referred to as the Jervell and Lange-Nielsen syndrome, which has a pattern of autosomal recessive inheritance.¹ When deafness is absent and a pattern of autosomal dominant inheritance is present, the term Romano-Ward syndrome has been applied.^{2,3} In addition to these eponymic forms of the long QT interval syndrome, various sporadic forms appear to exist.⁴

Since the original report by Moss and McDonald,⁵ on the basis of animal and limited human investigation⁵⁻⁷ left cervical sympathectomy has been recommended and performed with apparent success in at least 15 patients. However, because the long QT interval syndrome appears to result from various idiopathic and secondary causes, the precise pathophysiological mechanisms, natural history, clinical course, and response to treatments such as cervical sympathectomy remain obscure.

No thorough reports of invasive electrophysiological studies performed in this condition have appeared. We describe unique electrophysiological findings in a 7-year-old boy with the classic Jervell

and Lange-Nielsen syndrome who underwent repeated invasive electrophysiological study both before and after left stellate block and cervical sympathectomy.

Case report

A 7-year-old congenitally deaf boy suffered recurrent "seizures" characterised by syncope, apnoea, cyanosis, and prolonged somnolence. Repeated neurological examination was normal. The diagnosis of Jervell and Lange-Nielsen syndrome was considered when the boy was 4 years old, after an electrocardiogram showed an uncorrected QT interval exceeding 600 ms, with broad, biphasic, and deeply inverted T waves in multiple leads (Fig. 1). Phenobarbitone, phenytoin, and propranolol all failed to control the syncopal attacks, which increased in frequency and duration. Consequently, in April 1978, the patient underwent invasive electrophysiological investigation.

Before the induction of halothane anaesthesia, the surface QT interval was 650 ms at a heart rate of 75/min. After induction, the QT interval and T wave morphology fluctuated greatly, with a decrease in QT interval to 420 ms during the deeper stages of anaesthesia.

Fig. 1 Resting 12 lead electrocardiogram illustrating pronounced repolarisation abnormalities.

Standard invasive electrophysiological techniques were used. Sinus node function and atrioventricular conduction were normal. Electrode catheter recordings from the right ventricular apex disclosed that the intracardiac QT interval exceeded that seen on the surface electrocardiogram. This local intracardiac QT interval increased further during ventricular pacing, with unusual, late slow waveforms present on the right ventricular apex electrogram. The ventricular effective refractory period determined in sinus rhythm (725 ms cycle length) was greatly prolonged at 440 ms, decreasing to 305 ms at a paced cycle length of 400 ms. Ventricular pacing at 200/min resulted in 2:1 ventricular capture despite a stimulator output of 20 mA. Programmed ventricular stimulation from the right ventricular apex and pulmonary outflow tract using one, two, and three stimuli failed to induce a single repetitive ventricular beat. Though spon-

taneous ventricular ectopics did not occur during the electrophysiological study, after catheter removal and while the patient was awakening from anaesthesia, spontaneous late coupled ventricular extrasystoles occurred with R on T phenomena and there were six episodes of ventricular fibrillation which required direct-current countershock (Fig. 2). Intravenously administered propranolol prevented ventricular fibrillation by suppression of ventricular ectopics without change in the surface QT interval.

Ventricular fibrillation occurred again 48 hours later upon induction of halothane anaesthesia for a further electrophysiological study with extensive endocardial catheter mapping. Bipolar electrode catheters were positioned at multiple sites within the right ventricle for recording intracardiac electrograms and QT intervals. Unusual and bizarre low frequency waveforms, occurring long

Fig. 2 Spontaneous self-induction of ventricular fibrillation after emergence from anaesthesia. All electrocardiographic leads show a distinctly prolonged QT interval with deeply inverted T wave. Arrows point to spontaneous ventricular ectopics occurring on terminal portions of T wave. Paper speed 50 mm/s, 1000 ms between time lines.

after the surface QT interval had ended, were recorded in multiple sites, thus suggesting the presence of both temporal and spatial differences in repolarisation (Fig. 3). These late "repolarisation waveforms" were consistently present and recorded despite the withdrawal and repositioning of the catheter. After left stellate block, the intracardiac QT intervals decreased by approximately 90 ms and the unusual, late repolarisation waveforms diminished or disappeared, producing an apparent equalisation of intracardiac with surface QT intervals. The ventricular effective refractory period was determined at multiple cycle lengths and had decreased relative to the previous study. Anaesthesia was discontinued, and there was no recurrence of ventricular ectopics or fibrillation.

Excision of the left stellate ganglion plus the left sympathetic chain ganglion down to and including the level of T6 was performed four days later. On

emergence from halothane anaesthesia, the patient had ventricular ectopics, and developed repeated ventricular fibrillation requiring direct-current countershock. Propranolol administered intravenously suppressed the ectopics and prevented further episodes of ventricular fibrillation. Despite a "complete" sympathectomy (suggested by the presence of a pronounced Horner syndrome and a temperature differential between the arms), the QT interval remained long, with bizarre T wave morphology.

The invasive electrophysiological study was repeated on the sixth postoperative day. The right ventricular effective refractory period was 400 ms (cycle length 730 ms), decreasing to 310 ms at a paced cycle length of 400 ms. Endocardial electrode catheter recordings from areas previously assessed showed persistence of the unusual, late repolarisation waveforms. Anaesthetic injection into the

Fig. 3 Bipolar electrode catheter recording from right ventricular apex (panel A) and right ventricular anterior wall (panel B). The surface QT interval has decreased to 430 ms; unusual late diastolic waveforms greater than 590 ms were recorded after QRS complex

previous region of the left stellate ganglion produced no change in QT interval. Right stellate block lengthened the surface QT interval by 40 ms without change in the intracardiac waveforms. Again, extensive programmed ventricular stimulation failed to induce repetitive beating or fibrillation.

The patient was discharged on propranolol, 20 mg four times daily. No syncopal episodes have occurred during an 18-month follow-up period, though the 12-lead electrocardiogram shows no change.

Discussion

The electrophysiological observations made in this case have not been previously described. A striking finding was the greatly prolonged ventricular refractoriness shown by the extrastimulus technique and manifested by 2:1 ventricular capture during ventricular pacing at 200 beats/min. The ventricular effective refractory period (440 ms) greatly exceeded reported normal values⁸ and those determined in more than 300 patients studied in our laboratory. In our experience, 1:1 ventricular capture normally occurs at ventricular paced rates exceeding 280/min, contrasting with observations in this patient.

We performed programmed ventricular stimulation in only two right ventricular sites. If, in this syndrome, reliable induction of ventricular fibrillation could be achieved through ventricular stimulation it would serve as a controlled model for electrophysiological and pharmacological testing in a manner similar to that reported by us⁹ and others in the management of recurrent ventricular tachycardia. Our inability to induce repetitive ventricular beating or ventricular fibrillation despite extensive programmed stimulation was unexpected, particularly in view of the patient's demonstrated ability for self-induction of ventricular fibrillation with appropriately timed spontaneous ventricular extrasystoles. Possibly if programmed ventricular stimulation had been performed in additional sites, including several in the left ventricle, ventricular fibrillation would have resulted. This hypothesis needs to be tested in future patients.

The unusual, prominent, late repolarisation waveforms recorded in multiple right ventricular endocardial sites are of unknown genesis and significance. The magnitude and timing of this activity varied from place to place within the right ventricle, thus suggesting spatial as well as temporal inhomogeneity of repolarisation. Though the possibility of artefact must be considered, similar diastolic "slow waves" of this magnitude, constancy, and reproducibility have not been identified in nearly 1000 electrophysiological studies per-

formed in our laboratory. Whether or not these diastolic waveforms truly represent local repolarisation and should be considered part of the "T wave", or possibly the intracardiac counterpart of the "U wave", is unknown. Their initial disappearance after left stellate block suggests an abnormality of autonomic innervation, but their persistence after left cervical and thoracic chain sympathectomy suggests that the autonomic nervous system abnormality is not anatomically localised to that region.

This case is particularly important because of the failure of left cervical sympathectomy to prevent recurrent ventricular fibrillation despite the benefit predicted by the response to left stellate block. The fact that syncope has not recurred during an 18-month period since operation is encouraging but does not necessarily indicate that the procedure has been "successful". This symptom-free interlude on propranolol in high dosage may be consistent with the natural history of the illness. Though a transient period of "denervation hypersensitivity" immediately after sympathectomy may have contributed to the postoperative occurrence of ventricular fibrillation, persistence of the basic predisposition to ventricular fibrillation is suggested by this event, by the abnormal postoperative electrophysiological study, and by the late 12 lead electrocardiogram. The failure of the QT interval to shorten with cervical sympathectomy in this and other patients reported may reflect the variable and possibly multiple pathogeneses of the long QT interval syndromes.

The failure of the QT interval to shorten despite suppression of ectopics by propranolol suggests that the symptomatic long QT interval syndromes have two coexistent yet separate abnormalities. The first is prolonged and inhomogeneous ventricular repolarisation resulting from cardiac sympathetic imbalance and the second the occurrence of ventricular ectopics, which may result from or be facilitated by the autonomic abnormality or may be present for unrelated reasons.

In our patient general anaesthesia was necessary. Though not a direct myocardial irritant, halothane sensitises the myocardium to circulating catecholamines¹⁰ and this may have contributed to the development of ventricular ectopics and fibrillation during the induction and emergence from anaesthesia.

The Jervell and Lange-Nielsen syndrome and other long QT interval syndromes are uncommon, incompletely understood, and lethal, and thus aggressive investigation of individual patients, including invasive electrophysiological study, is indicated in an attempt further to determine the pathophysiology and the effective treatment.

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