Biventricular stimulation improves right and left ventricular function after tetralogy of Fallot repair: Acute animal and clinical studies

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BACKGROUND Optimal treatment of right ventricular (RV) dysfunction observed in patients after tetralogy of Fallot (TOF) repair is unclear. Studies of biventricular (BiV) stimulation in patients with congenital heart disease have been retrospective or have included patients with heterogeneous disorders.

OBJECTIVE The purpose of this study was to determine the effects on cardiac function of stimulating at various cardiac sites in an animal model of RV dysfunction and dyssynchrony and in eight symptomatic adults with repaired TOF.

METHODS Pulmonary stenosis and regurgitation as well as RV scars were induced in 15 piglets to mimic repaired TOF. The hemodynamic effects of various configurations of RV and BiV stimulation were compared with sinus rhythm (SR) 4 months after surgery. In eight adults with repaired TOF, RV and left ventricular (LV) dP/dt_{max} were measured invasively during SR, apical RV stimulation, and BiV stimulation.

RESULTS At 4 months, RV dilation, dysfunction, and dyssynchrony were present in all piglets. RV stimulation caused a decrease in LV function but no change in RV function. In contrast, BiV stimulation significantly improved LV and RV function ($P < .05$). Echocardiography and epicardial electrical mapping showed activation consistent with right bundle branch block during SR and marked resynchronization during BiV stimulation. In patients with repaired TOF, BiV stimulation increased significantly RV and LV dP/dt_{max} ($P < .05$).

CONCLUSION In this swine model of RV dysfunction and in adults with repaired TOF, BiV stimulation significantly improved RV and LV function by alleviating electromechanical dyssynchrony.

KEYWORDS Cardiac resynchronization; Congenital heart disease; Right ventricular dysfunction; Tetralogy of Fallot; Ventricular dyssynchrony

ABBREVIATIONS **BBB** = bundle branch block; **BiV** = biventricular; **LV** = left ventricular; **RV** = right ventricular; **SR** = sinus rhythm; **TOF** = tetralogy of Fallot

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Introduction

The population of adults with repaired tetralogy of Fallot (TOF) and other congenital heart diseases is growing rapidly.[1,2] In particular, surgical repair of TOF is highly successful but later may be complicated by right ventricular (RV) or biventricular (BiV) dysfunction due to volume and pressure overload.[3,4] The incompletely understood mechanisms of these delayed adverse developments may be partially due to surgically induced permanent right bundle branch block (BBB) and ventricular dyssynchrony.[5–7] Unlike left ventricular (LV) failure, RV failure is poorly understood and its management remains largely empirical. In contrast to the vast experience with BiV stimulation gathered in adults with acquired LV dysfunction,[8–10] studies of the safety and efficacy of cardiac resynchronization in patients with congenital heart disease and RV dysfunction are limited to case reports, retrospective analyses of heterogeneous populations, and small, crossover trials conducted in the immediate postoperative period.[11–16] Although preliminary results are encouraging, the applications of resynchronization in patients with repaired TOF and the mechanisms by which it might be therapeutic remain unclear.

The aims of the present study were to (1) develop a reliable and reproducible long-term swine model of RV dysfunction and RV dyssynchrony, (2) study the electrophysiologic and hemodynamic effects of stimulation at different ventricular sites and configurations in this model

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compared to control animals, and, based on these observations, (3) compare the immediate hemodynamic effects of RV versus BiV stimulation in adults with repaired TOF and RV dysfunction.

Methods

Studies in an animal model of repaired TOF

The experimental protocols were in compliance with the *Guiding Principles in the Use and Care of Animals* published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996).

Creation of the swine model

The experimental study included 15 newborn piglets weighing less than 8 kg. The animals were sedated with intramuscular injection of 20 mg/kg ketamine hydrochloride and anesthetized with 10 mg/kg sodium pentobarbital before endotracheal intubation. Anesthesia was maintained with ketamine 500 mg/hour, and prophylactic intravenous antimicrobials were administered. Peripheral oxygen saturation, heart rate, and blood pressure were monitored continuously. Via left thoracotomy, the RV outflow tract was occluded partially with a clamp and incised longitudinally across the pulmonic valve annulus. The operation was designed to cause (1) RV volume overload from valvular regurgitation by excision of two pulmonic valve leaflets, (2) RV pressure overload by a loose tape partially occluding the pulmonary artery, and (3) RV outflow tract scar around the patch placed to close the RV incision. After the procedure was completed, the animals were extubated and received supplemental oxygen and analgesia as needed, before their transfer to a long-term postoperative care facility.

Study of the animal model

The index operation was performed in 15 animals, of which 1 died in the immediate postoperative period and 2 in the late postoperative period. After 4 months of postoperative recovery, we studied the electrophysiology and hemodynamic characteristics of our model of repaired TOF in the first 7 of the 12 long-term survivors. The animals were sedated, intubated, and anesthetized in the catheterization laboratory, as described earlier. A 7Fr catheter was introduced into the internal jugular vein for infusion of pharmaceuticals and fluids. A 7Fr Millar catheter tip micromanometer was placed inside the LV cavity via the left carotid artery, and inside the RV cavity via the right jugular vein, to measure intraventricular pressures and LV and RV dP/dt_{max}. The heart was exposed via median sternotomy and lateral thoracotomy and suspended in a pericardial cradle. After stabilization for 20 minutes, baseline LV pressure, aortic flow, and surface ECG were recorded. Signals were digitized at 200 Hz and stored on disk for offline analysis.

Echocardiographic cine loops of three cardiac cycles were analyzed offline to confirm the presence of pulmonic valve stenosis. Pulmonic and tricuspid valve insufficiency were assessed using conventional criteria by two-dimensional imaging and color Doppler flow from a Vivid Seven digital ultrasound system (GE Healthcare, London, UK). Aortic ejection and velocity–time integrals were measured using pulsed-wave Doppler imaging. Tissue Doppler imaging of segmental wall motion was used to quantify intra-LV and intra-RV dyssynchrony as previously described.[6] Briefly, *intra-LV dyssynchrony* was defined as the difference between the shortest and longest of four basal LV electromechanical delays (lateral, septal, anterior, inferior). *Intra-RV dyssynchrony* was defined as the difference between electromechanical delay of septum and RV free wall.

The same experimental protocol was performed and the same measurements were made for comparison in a control group of seven age-matched, previously nonoperated animals.

Study of the hemodynamic effects of BiV stimulation in the animal model

The hemodynamic effects of stimulating at different sites were studied in the seven animals used to characterize the model. Temporary myocardial pacing leads were attached to (1) the roof of the right atrium; (2) the epicardial surface of the RV apical, lateral, and anterior walls; and (3) the epicardial surface of the lateral LV wall. The leads were connected to a four-channel external pulse generator (Medtronic, Inc., Minneapolis, MN, USA) for measurements of capture threshold at each site and stimulation from each electrode, separately or in combination.

Baseline hemodynamic measurements were made during (1) sinus rhythm (SR); (2) stimulation from each of the three RV sites; and (3) BiV stimulation between the LV site and each of the three RV sites, in random order. The pacing mode was VDD (atrial sensing triggering ventricular stimulation), and the atrioventricular delay was programmed between 20 and 40 ms to ensure ventricular capture in all pacing configurations. Measurements were averages of 10 cardiac cycles made after 30 seconds of stimulation. At the end of the experiments, the animals were sacrificed with an intravenous overdose of pentobarbital.

Electroanatomic mapping during SR and BiV stimulation in the animal model

The five remaining animals were similarly operated 4 months after the index procedure. In this subgroup, temporary myocardial pacing leads were attached to the roof of the right atrium and to apical RV and lateral LV epicardial walls. Dyssynchrony was echocardiographically ascertained during SR and during BiV stimulation. BiV epicardial electroanatomic mapping was performed with CARTO navigation system (Biosense Webster, Diamond Bar, CA, USA), as previously described.[17] The torso of the animal was covered by three magnetic fields of different frequencies. A location reference was fixed on the back of the pig while a mapping catheter navigated on the epicardium of the animal. The magnetic sensor in the tip of the catheter and the location reference compared the intensities of the three magnetic fields, ensuring that the location of the catheter could be accurately determined. Color-coded, three-dimensional maps of epicardial activation were constructed during

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