

Statement on Cardiac Pauses in CCHS and Recommendations on Cardiac Pacing in CCHS

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We know that CCHS is a genetic disorder of the autonomic nervous system, not just a disorder of control of breathing. As we have mastered ways to adequately ventilate CCHS patients, we now begin to worry about other complications, including life-threatening cardiac arrhythmias, which are not so easily treated or predicted. We were the first group to suggest autonomic nervous system dysfunction based on abnormal cardiac responses to environmental stimuli (appended , Woo, M.S., M.A. Woo, D. Gozal, M.T. Jansen, T.G. Keens, and R.M. Harper. Heart rate variability in congenital central hypoventilation syndrome. *Pediatric Research*, 31: 291-296, 1992). Debbie Weese-Mayer's group described a small sample of CCHS patients, which included two deaths out of three children with asystolic pauses ≥ 3 -seconds on a 72-hour Holter monitor study (Debbie Weese-Mayer' group published a paper (appended: Gronli, J.O., B.A. Santucci, S.E. Leurgans, E.M. Berry-Kravis, and D.E. Weese-Mayer. Congenital central hypoventilation syndrome: PHOX2B genotype determines risk of sudden death. *Pediatr. Pulmonol.*, 43: 77-86, 2008). These abnormalities were most commonly seen in the PHOX2B 20/27 PARM mutation group. Fewer 20/26 PARM mutation patients had problems, but no 20/25 PARM mutation patients had these problems. In our experience in Los Angeles, we have had maybe 10% of our patients receiving cardiac pacemakers. Some were in the 20/25 PARM mutation group. Some patients had fainting spells without an obvious cause, which was assumed to be due to cardiac arrhythmias, and we recommended cardiac pacemaker implantation.

So, we support the Gronli paper's recommendation that anyone with an asystolic pause ≥ 3 -seconds on Holter monitoring should have cardiac pacemaker implantation prophylactically (that is, before any symptoms). In addition, we have recommended cardiac pacemakers in patients with fainting spells which are otherwise unexplained. Thus, we have implanted some 20/25 PARM mutation patients, who are not at risk according to the Gronli study.

I have been asked if life-threatening cardiac arrhythmias are an inevitable consequence of CCHS, and thus whether or not all patients, or all patients with certain genotypes, should have cardiac pacemakers implanted prophylactically to prevent these sudden deaths, assumed to be cardiac. We do not have that information based on science. In our experience, our oldest CCHS patients, now ~37-years of age, do not have cardiac pacemakers, and they have no clinical signs suggesting the need for one. On the other hand, as mentioned, we have some 20/25 PARM mutation patients, who should not be at risk according to Gronli, who have had fainting spells and/or abnormal Holter monitor studies, in whom we have implanted cardiac pacemakers. So, I am afraid it is uncertain. My opinion (not based on scientific studies, as none exist) is that requiring a cardiac pacemaker is not an inevitable consequence of CCHS. Therefore we recommend Holter monitoring (annually in the highest risk group 20/27 PARM). Gronli et al described the highest risk in the 20/27 PARM group, but he did not study patients with higher PARM or NPARM mutations. Therefore, we do not know if these patients are also at risk for life-threatening cardiac arrhythmias.

We just do not have all of the information. **My recommendation for CCHS patients is:**

- Perform annual Holter monitor studies if you are in the 20/26 or 20/27 PARM group. It is unclear if patients with higher PARM or with NPARM mutations should be studied at the same frequently. **The answer is probably.**

- If any Holter study shows ≥ 3 -second asystolic pauses, a cardiac pacemaker should be placed prophylactically.
- If a patient has unexplained fainting spells, a cardiac pacemaker should be placed, based on the assumption that this may progress to a life-threatening cardiac arrhythmia.
- At this time, prophylactic placement of cardiac pacemakers, in the absence of symptoms or Holter abnormalities, is not advised. However, I freely acknowledge that we do not have complete scientific information. Therefore, if a family and physician decided to place a cardiac pacemaker prophylactically, I would not say they were wrong.
- More study is required.