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Can the physical exam predict impending heart failure in infants with ventricular septal defect?

1. Study Purpose and Rationale:

A. Background

Ventricular septal defect (VSD), a hole between the left and right ventricles of the heart, is the most common congenital heart defect comprising 25-40% of all cardiac malformations. The prevalence of VSDs is estimated from 1.35-2.94 per 1000 births[1].

The ventricular septum has four components: an ***inlet*** septum between the atrioventricular vales, an ***outlet*** septum separating the outlets of the ventricles, a ***trabecular*** septum that separates the main body and apices of the two ventricles, and a small ***membranous*** portion where the inlet, outlet and trabecular components meet. A VSD, which may occur in any of these portions, allows for mixing of blood between both ventricles. The direction of blood flow through the defect depends on the relative resistance of the systemic and pulmonary vasculature and in the absence of pulmonary hypertension or right-ventricular outflow tract obstruction is pre-dominantly left-to-right. Based on the size and location of the VSD, it may either close spontaneously or remain open predisposing the infant to a range of complications including but not limited to: congestive heart failure, bacterial endocarditis, recurrent pulmonary infections, and Eisenmenger's syndrome. Small defects (< 3 mm diameter) occur in 75% of patients, and have a spontaneous closure rate of 75-80%[2,3]. Trabecular and membranous defects close often, while it virtually does not occur with the inlet or outlet types[2]. It is not clear whether size[1,2] or location[4] is more important in determining the physiologic course of the patient.

Congestive heart failure (CHF) may occur with moderate to large defects from chronic left-to-right shunting, pulmonary overcirculation and an increased volume load on the left atrium and ventricle. This potentially fatal complication occurs in 10-15% of affected infants and may occur anytime in the first six months of life[1]. The development of CHF depends largely in part on the degree of left-to-right shunting, which in turn is dependent on pulmonary vascular resistance. The expected decrease in pulmonary vascular resistance after birth occurs more slowly in VSD patients and so the maximal hemodynamic effects of a large defect may not be reached for several weeks[2]. For this reason, follow-up of infants is scheduled at three to four weeks of life to coincide with the expected onset of symptoms. Due to an inability to predict the onset of heart failure after this initial visit, there is currently no consensus for timing and frequency of subsequent follow-up exams and echocardiographic evaluation of patients. Improved identification of VSD infants more likely to develop CHF will lead to earlier detection and initiation of an appropriate treatment strategy.

B. Review of Literature

The growth of patients with VSD has been well studied and has demonstrated the following: 1. The degree of growth retardation for both height and weight correlates positively with the degree of hemodynamic disturbance, and even those with a small defect have subnormal growth[5]. 2. In cases where the VSD spontaneously closed, height and weight were normal at all ages[6]. 3. Elevation of mean pulmonary artery pressure, commonly observed with large defects, is associated with low weight percentiles in infants[7]. Interestingly a study from the Netherlands showed that in patients with moderate to large defects, the presence of weight retardation was associated with increased odds of requiring surgical closure in the future. In the absence of significant weight retardation, however some of these defects reduced in size and a few even closed on their own[4]. This particular finding demonstrates the potential prognostic value of weight. A limitation of all of the above studies is their measurement of weight, a static parameter, instead of weight velocity, a dynamic parameter.

Given the time period of the above studies, all hemodynamic data was obtained directly from cardiac catheterization, a method that is now obsolete given the advances made in echocardiography. Taggart et al recently used echocardiography to show that left atrial volume increases secondary to chronic increases in left ventricular preload in VSD patients[8]. However data correlating the echo measurements with physical exam parameters was lacking making it difficult to ascertain whether symptoms preceded abnormal echocardiographic changes or vice versa.

C. Hypothesis

Infants with a ventricular septal defect who are more likely to develop congestive heart failure (CHF) will exhibit specific pre-failure physical exam signs at age three to six weeks defined as: an increase in basal respiratory rate (RR) and heart rate (HR), and a decreased weight velocity (WV) prior to the appearance of CHF symptoms or abnormal changes on echocardiography.

2. Study Design and Statistical Procedures

A. Design

This will be a single-center retrospective nested case-control study of children born at or referred to CUMC with the diagnosis of isolated ventricular septal defect, who were evaluated and treated medically or surgically. We will conduct a chart review of infants diagnosed with solitary or multiple ventricular septal defects in the perinatal period (i.e. from prenatal ultrasonography/echocardiography or perinatal echocardiography) to identify those with documented congestive heart failure by age six months (cases). For each case identified, we will then attempt to select VSD patients without evidence of any treatment for CHF, as closely matched for age, sex, and ethnicity as possible to serve as nested controls. To improve our statistical power, we will strive to select at least two nested controls for each case. It is assumed that a patient with a hemodynamically insignificant VSD not requiring medical therapy will behave like a healthy control with respect to the variables we are studying. To test this assumption, we will compare measurements of our nested control to the established normal parameters for RR, HR and

WV. Inclusion and exclusion criteria for subjects are further delineated under the "Study subjects" heading.

Primary outcome measures will be initiation of cardiac medication for treatment of congestive heart failure as an inpatient or outpatient (e.g. Digoxin, Furosemide, Spironolactone, Hydrochlorothiazide, Aldactazide, ACE-inhibitor) or need for surgical procedure defined as: palliative operation such as pulmonary arterial banding, surgical closure performed in the OR, device-based closure performed via cardiac catheterization. Secondary outcome measures will include number of pulmonary infections and number of hospitalizations. We will compare these outcome measures with predictive clinical characteristics such as: birth weight, basal respiratory rate (breaths/min), basal heart rate (beats/min), and weight (kg) recorded specifically at age 3-6 weeks and at subsequent follow-up visits, as well as echocardiographic measures of left-ventricular end diastolic volume, ejection fraction, left-atrial volume, trans-defect pressure gradient, and Qp:Qs ratio obtained at all visits.

B. Statistical Procedures

An unpaired t-test will be used to compare three specific variables among VSD patients with and without congestive heart failure: respiratory rate, heart rate and weight velocity measured at age 3-6 weeks. Based on normal values obtained from healthy infants[9,10,11], a clinically meaningful difference in these variables would be: 10 breath/min increase in respiratory rate, 10 beat/min increase in heart rate, 5 grams/day decrease in weight velocity. In order to achieve a power of 80% with an alpha-error rate of 0.05, a minimum n = 60 patients in each group is needed to detect such differences. There have been at least 200 patients evaluated for VSD at CUMC per year for the past 3 years so we do not anticipate difficulties in achieving this sample size.

3. Study Procedures:

Using a keyword search of the MS-CHONY Pediatric cardiology echocardiogram database, we will identify a preliminary list of infants and children diagnosed with or treated for any type of ventricular septal defect(s). We will then filter this list to only include patients with isolated ventricular septal defect(s) and to exclude those with other cardiac anomalies. Other inclusion and exclusion criteria are further outlined under "Subjects."

As described under study design, we will identify those patients with isolated VSD who received medical and/or surgical therapy for congestive heart failure and then find VSD patients who never received therapy as closely matched as possible for age, sex, and ethnicity to serve as controls. Electronic and paper medical records of all patients selected for inclusion will be reviewed and relevant data outlined above will be entered into a spreadsheet. Identifying information will be removed and each patient will be assigned a unique study ID number. A separate password-protected file matching patients to their study ID number will be maintained. Once information regarding demographics and status as a case or control has been removed from the medical record, a research assistant will be asked to review each chart, identifiable only by the study ID number,

and extract the information outlined under "Study design" to minimize bias. Continuous and dichotomous variables will be analyzed using student's t-test and chi-square analysis respectively.

4. Study Drugs or Devices*:* None.

5. Study Questionnaires: Not applicable.

6. Study Subjects:

A. Inclusion criteria: Any patient living or deceased that was evaluated and or treated at the MS-CHONY pediatric heart center for ventricular septal defect(s) diagnosed perinatally (from prenatal ultrasonography/echocardiography or perinatal echocardiography performed in first week of life) within the past three years will be included.

B. Exclusion criteria:

- *Did not have documented respiratory rate, heart rate, weight or ECHO at age 3-6 weeks*
- *Age < 1 year at the time of patient search*
- *Gestational age of less than 37 weeks*
- *Presence of additional anatomic heart defects*
- *Born to a mother with SLE, or history of congenital heart block*
- *APGARS at birth less than 8*
- *Patient received treatment with diuretics and/or surgery prior to 6 weeks of age*
- *History of congenital diaphragmatic hernia*
- *History of any significant pulmonary abnormality including but not limited to:* cystic fibrosis, chronic lung disease.
- *History of any significant gastrointestinal abnormality including but not limited to:* necrotizing enterocolitis, short-gut syndrome, biliary atresia, and tracheoesophageal fistula.

7. Recruitment: Not applicable.

8. Confidentiality of Study Data:

Access to all patient data will be restricted to the study investigators. Research assistants who will perform data collection will be blinded to patient identifying information and their status as a case or control as explained above. This blinding will also apply to statisticians performing analysis, peer reviewers, etc.

9. Potential Risks:

As this study requires only retrospective chart reviews there is no potential risk to the patient. The only conceivable risk is to the confidentiality of patient data. This risk is minimized as described above.

10. Potential Benefits:

This retrospective chart review will not provide any immediate benefit to the patient. However the information gained from this review will help identify patients with isolated ventricular septal defect(s) who are more likely to develop congestive heart failure. Patients who are identified earlier may have more frequent follow-up leading to earlier initiation of medical and/or surgical therapy.

11. Alternatives: N/A
12. Compensation and/or Costs to Subjects: None
13. Radiation or Radioactive Substances: N/A

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