Epidemiology of Cardiovascular Malformations: Prevalence and Risk Factors

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Epidemiological approaches to the study of cardiovascular malformations (CVMs) face challenges of disease definition, nomenclature, changing diagnostic methodologies, the rarity of the disease in the general population, and the incorporation of current knowledge on genetics and morphogenesis into designing studies to investigate risk factors and implement preventive strategies. Previous studies, especially the population-based Baltimore-Washington Infant Study, have documented variability in the prevalence of specific types of CVM by time, place, and personal characteristics and have highlighted the potential prevention of diabetes-associated heart malformations through timely medical management of pre-conception diabetes. Left-sided obstructive heart defects have been identified as targets for new studies of genetic risk factors. Potential environmental risk factors for CVMs also have been identified, such as organic solvents and pesticides, coincident with the emergence of new strategies to study genetic susceptibility and gene-environment interactions. Increased collaborative, multicenter research on these and other factors, such as nutritional factors in early pregnancy, offers new hope for potentially reducing the burden of CVM in the population.

Important historical studies of the epidemiology of CVMs were summarized by Ferencz and Correa-Villaseñor [1991]. This review highlights more recent epidemiological contributions and critical areas for future study.

The epidemiological approach to CVMs begins with consideration of the appropriate study design. Ideally, a knowledge of risk factors would be sufficiently advanced at this time for the implementation of randomized clinical trials to evaluate the efficacy and effectiveness of prevention strategies. Sadly, this is far from reality. Except for prenatal multivitamin supplements containing folic acid, which, it has been suggested, reduce the occurrence of cardiac outflow tract anomalies in some studies [Shaw et al., 1995; Botto et al., 1996], there are few preventive strategies on the horizon. An earlier step in the progression from identifying putative risk factors to reducing their impact is the prospective cohort study. In these studies, two groups of subjects are assembled with respect to the presence or absence of a risk factor and then are followed forward in time to see if the rate of development of the disease is different in the exposed than it is in the unexposed group. Evidence for causality therefore is founded on the temporal sequence from risk factor to disease development. However, the rarity of CVMs as a whole in the general population (see later discussion), and the even more extreme rarity of diagnostic subtypes, often precludes the prospective approach owing to its immense financial cost.

By necessity, the epidemiology of CVMs is best known from case-control studies. This study design is based on the identification of patients with a disease, the selection of an appropriate comparison group, and the retrospective evaluation of disease risk factors in the two groups. This method has the advantage of requiring far fewer study subjects than the prospective design, since affected persons can be ascertained readily from a few sources; it can therefore be more cost-effective than a large prospective cohort study. The major disadvantages are the potential for selection bias in...
assembling the case population, such that the cases are not representative of all patients with the disease [Feinstein, 1985]; nondifferential recall errors or biased recall in the retrospective assessment of exposures [MacKenzie and Lippman, 1989]; and limited ability to establish causality. A variation of this study design used by the Baltimore-Washington Infant Study (see later discussion) is the population-based case-control study, in which affected and nonaffected subjects are drawn from the same birth cohort, reducing potential selection bias.

Epidemiologists attempting to study CVMs face many challenges, even in case-control studies. The cardiovascular anomalies may show subtle symptoms. Many are strongly age-dependent in their manifestations, according to the natural history of the specific malformation. Some apparent heart defects, for example, small ventricular septal defects (VSDs), spontaneously resolve. There is no universal coding or nomenclature system, hampering communication among scientists. CVM is not a single disease, but rather encompasses many specific diagnoses, each of which may be distinct in origin and risk factors. Many fetuses with CVMs die in utero, resulting in a survival bias among the types of CVM present among live births. Technological advances in diagnosis, especially the recent widespread clinical use of two-dimensional echocardiography and color Doppler imaging, have increased the sensitivity of diagnosis [D’Orsogna et al., 1989], but this makes it difficult to compare modern and historical studies. Indeed, during the 1980s many clinicians noticed a large increase in the prevalence of muscular VSDs, but this turned out to be entirely due to better diagnostic methodologies [Martin et al., 1989; Wilson et al., 1993].

THE BALTIMORE-WASHINGTON INFANT STUDY

As the largest and most comprehensive case-control study of CVM to date, the Baltimore-Washington Infant Study (BWIS) has made major contributions.

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The BWIS (Charlotte Ferencz, Principal Investigator) was established in 1980 to generate hypotheses on possible genetic and environmental risk factors for CVM and describe the occurrence rates of the various diagnostic subtypes by characteristics of time, place, and person. Recruitment of subjects took place from 1981 through 1989 in Maryland, the District of Columbia, and adjacent counties of northern Virginia. Details about methods, the questionnaire, and major findings have been published [Ferencz et al., 1993, 1997]. Selected reports on specific subtypes of CVM include atrioventricular septal defects [Loffredo et al., 2001], tetralogy of Fallot [Karr et al., 1992], interrupted aortic arch [Loffredo et al., 2000], Ebstein anomaly [Correa-Villasenor et al., 1994], total anomalous pulmonary venous return [Correa-Villasenor et al., 1991a], and VSDs [Lewis et al., 1996].

Cases (N = 4,390) were made up of live-born infants with structural CVMs confirmed before 1 year of age by echocardiography, cardiac catheterization, surgery, or autopsy. Premature infants with patent arterial ducts were not included in the study. Nearly 100% complete regional ascertainment was achieved by enrolling the cases from multiple sources, including the six regional pediatric cardiology centers, infant death certificates, and pathology records in 53 hospitals with obstetrical services. Clinical follow-up reports from the pediatric cardiologists or autopsy findings updated the vital status and the diagnosis of cardiac and non-cardiac defects at 1 year of age. CVMs were coded by the International Society of Cardiology coding system [ISC, 1970]. A hierarchical order assigned a principal diagnosis to each case, giving priority to the structural malformation of earliest embryonic origin.

Control infants (N = 3,572) were free of CVMs and were selected from the 53 area birth hospitals by a computer-generated random sampling procedure that achieved a representative sample of the regional live birth cohort. Nonrespondents were replaced with alternates from the same birth hospital: 95% of the controls were first- or second-choice selections. Compared with the regional cohort of nearly one million live births, the BWIS controls were indistinguishable by gender, race, birth weight, plurality, season of birth, and maternal age distribution [Ferencz et al., 1993].

Home interviews were conducted with mothers of case infants and controls using a structured questionnaire, which recorded information on parental sociodemographic, medical, and environmental factors during the peri-conception exposure period ("critical period"), which encompassed the 3 months before the last menstrual period and the first trimester of pregnancy. Information on environmental factors included parental smoking, alcohol and caffeine intake, recreational and therapeutic drug use, diagnostic radiography, occupational history, and exposures to heavy metals, pesticides, paints, dyes, solvents and ionizing radiation. Of the 3,763 case families eligible for interview (including all infants with severe CVMs and a random sample of mild defects) 3,377 (90%) participated.

For CVMs as a whole, and separately for each of the selected cardiac diagnostic groups, we examined each variable in the database for evidence of association, using the unadjusted case-control odds ratio (OR) and 95% confidence interval (CI) to identify statistically significant candidate associations for further study. Multivariable logistic regression analysis [Kleinbaum et al., 1988] then was used to analyze for potential effect modifiers and statistical confounders, as described by Wilson et al. [1998].
PREVALENCE

Terminology pertaining to the “prevalence” of CVMs has problems stemming from the difficulties in defining and estimating the numerator and denominator populations. For congenital anomalies, the true incidence of the disease would need to include occurrences among spontaneous abortions. For this reason, many authors prefer to report prevalence at live birth as the number of cases of a particular disease divided by the total live births in the same time period and region (for convenience, this rate is often expressed in multiples of 1,000 live births).

Variations in the live birth prevalence of CVMs by time, place, and personal characteristics can yield, at best, tentative clues about risk factors and prevention. As an example, Miettinen et al. [1970] identified peak rates of coarctation of the aorta in winter months, plausibly suggesting an infectious source. In general, however, variability in study designs and methods makes it extremely difficult to compare meaningfully prevalence rates taken from different reports and time periods.

The overall prevalence of CVMs in the BWIS was four per 1,000 live births, consistent with the range of four to six per 1,000 live births reported in other studies using similar methodologies [Grabitz et al., 1988; Fixler et al., 1990]. Within the wide spectrum of specific types of CVM there is a considerable range of prevalence, as shown in Table I from BWIS data on the 20 most common diagnostic groups. Membranous VSD was by far the most frequently reported anomaly (9.87 per 10,000 live births), two to three times as common as the next most frequently reported anomalies, muscular VSD (4.73 per 10,000) and pulmonic valve stenosis (3.78 per 10,000).

The BWIS and other researchers in the United States have documented variability in the prevalence of CVM by gender and race. Increased prevalence of left-sided obstructive lesions among whites, especially coarctation of the aorta and aortic valve stenosis, has been reported consistently [Correa-Villaseñor et al., 1991b; Torfs et al., 1991; Storch and Mannick, 1992]. Pulmonic valve stenosis was more prevalent among African-Americans in the BWIS. Increased prevalence of transposition of the great arteries among male infants in the BWIS and of atrioventricular septal defects in females with Down syndrome [Ferencz et al., 1997 in Fig. 13.4], are well known to clinicians. There is yet no cogent explanation for these differences, but they may provide clues for future investigations.

FAMILIAL AGGREGATION

The characterization of familial patterns of CVMs has had an important impact on family counseling and has provided evidence of potential genetic factors in the origin of specific heart defects. For more than 50 years it has been recognized that children with CVMs are more likely than others to have affected siblings [e.g., Polani and Campbell, 1955; Lamy et al., 1957; Burn, 1983; Zavala et al., 1992]. More recently, the

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<table>
<thead>
<tr>
<th>Cardiac diagnostic group</th>
<th>Cases</th>
<th>Prevalence per 10,000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect, membranous</td>
<td>895</td>
<td>9.87</td>
</tr>
<tr>
<td>Ventricular septal defect, muscular</td>
<td>429</td>
<td>4.73</td>
</tr>
<tr>
<td>Pulmonic valve stenosis</td>
<td>341</td>
<td>3.78</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>320</td>
<td>3.53</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>296</td>
<td>3.26</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>291</td>
<td>3.21</td>
</tr>
<tr>
<td>Transposition of great arteries (TGA)</td>
<td>239</td>
<td>2.64</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>162</td>
<td>1.78</td>
</tr>
<tr>
<td>Laterality/looping defect</td>
<td>131</td>
<td>1.44</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>126</td>
<td>1.39</td>
</tr>
<tr>
<td>Patent arterial duct</td>
<td>80</td>
<td>0.88</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>74</td>
<td>0.81</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>67</td>
<td>0.74</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>60</td>
<td>0.66</td>
</tr>
<tr>
<td>Pulmonary atresia with intact ventricular septum</td>
<td>53</td>
<td>0.58</td>
</tr>
<tr>
<td>Interrupted aortic arch</td>
<td>53</td>
<td>0.58</td>
</tr>
<tr>
<td>Common arterial trunk</td>
<td>44</td>
<td>0.49</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>43</td>
<td>0.47</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>33</td>
<td>0.36</td>
</tr>
<tr>
<td>Double-outlet right ventricle, without TGA</td>
<td>30</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Denominator = 906,626 regional live births.

**a**Includes D-TGA with any of the following: intact ventricular septum (n = 115), ventricular septal defect (n = 68), double-outlet center ventricle (n = 31), or pulmonary/tricuspid atresia (n = 25).

**b**Includes L-transposition of the great arteries (n = 35), cardio-visceral discordance (n = 66), and pulmonary veins, and outflow tract anomalies.
heritability of CVM has become clearer in prospective studies of parents with CVM and the risks to their offspring [Rose et al., 1985; Whittemore et al., 1994; Burn et al., 1998]. In the BWIS, the sibling precurrence risks to probands were examined according to the specific cardiac diagnostic group. The sibling precurrence risk of CVM was 3.1% overall and highest among cases with so-called “left-sided obstructive heart defects,” notably, hypoplastic left heart, with an 8.0% precurrence rate, and coarctation of the aorta, with a precurrence rate of 6.3% [Ferencz et al., 1993]. Familial aggregation of left-sided obstructive heart defects, particularly coarctation and aortic valve stenosis, also has been reported by other investigators [Rose et al., 1985; Whittemore et al., 1994]. In addition, there are numerous reports of concordant left-sided obstructive heart defects (including bicuspid aortic valve) among siblings, parents, and other relatives of affected probands [Boughman et al., 1987]. In mathematical models testing for specific patterns of inheritance in this group of heart defects, Maestri et al. [1988, 1989] could not rule out a simple autosomal recessive model, suggesting that some of these defects could be the result of monogenic inheritance.

### MATERNAL RISK FACTORS

Maternal illnesses and medications used to treat these disorders have attracted attention as possible risk factors for CVMs. It is well accepted that maternal diabetes is a major risk factor for CVMs and other serious birth defects [Mills, 1982; McCarter et al., 1987; Becerra et al., 1990; Ferencz et al., 1990; Ramos-Arroyo et al., 1992] and that the greatest vulnerability is in early pregnancy [Mills et al., 1979; Reece et al., 1996]. These observations focus attention on the imperative for pre- and post-conception diabetes control to prevent these adverse pregnancy outcomes. The BWIS addressed the specificity of the diabetes–CVM association by evaluating the risks in defined anatomic subgroups (Table II). We found that the strongest associations with maternal diabetes were in infants with “early” cardiovascular abnormalities (i.e., defects of primary cardiogenesis), including laterality and cardiac looping defects, outflow tract anomalies with normally related great arteries, and complete (but not partial) atrioventricular septal defects [Ferencz et al., 1997; Loffredo et al., 2001]. Most defects arising later in cardiac development, that is, secondary defects of obstruction and shunting, were not significantly associated with diabetes.

Epilepsy and anticonvulsant medications also have been studied as possible risk factors for CVM. Several epidemiological studies identified associations between CVM and epilepsy [Dansky and Finnell, 1991; Pradat, 1992], but an unresolved question is whether the underlying risk factor is some aspect of the disease itself or of specific anticonvulsant medications, many of which are strongly implicated as teratogens [Hanson et al., 1976; Bossi, 1983; Zierler and Rothman, 1985; Bracken, 1986]. No specific pattern of heart defects seems to be closely related to these factors, with reported associations involving CVM as a whole as well as the common arterial trunk, transposed great

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TABLE II. Selected Associations of Maternal Exposures with Cardiovascular Malformations in the Baltimore-Washington Infant Study (1981–1989)*

<table>
<thead>
<tr>
<th>Maternal exposure</th>
<th>Diagnostic group</th>
<th>Exposed cases/total</th>
<th>Exposed controls/total</th>
<th>O.R.</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Laterality/looping*</td>
<td>5 / 104</td>
<td>23 / 3,572</td>
<td>8.3</td>
<td>3.0–23.0</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot*</td>
<td>4 / 204</td>
<td>23 / 3,572</td>
<td>3.1</td>
<td>1.1–9.0</td>
</tr>
<tr>
<td></td>
<td>Common arterial trunk*</td>
<td>3 / 38</td>
<td>23 / 3,572</td>
<td>13.2</td>
<td>3.8–46.1</td>
</tr>
<tr>
<td></td>
<td>Complete AVSDb</td>
<td>4 / 30</td>
<td>23 / 3,572</td>
<td>20.6</td>
<td>5.6–76.4</td>
</tr>
<tr>
<td>Fever</td>
<td>Pulmonic stenosis*</td>
<td>12 / 112</td>
<td>166 / 3,572</td>
<td>2.9</td>
<td>1.5–5.4</td>
</tr>
<tr>
<td>Influenza</td>
<td>TGA-IVSa</td>
<td>14 / 106</td>
<td>210 / 3,572</td>
<td>2.2</td>
<td>1.2–4.1</td>
</tr>
<tr>
<td>Herbicides</td>
<td>TGA groupc</td>
<td>8 / 66</td>
<td>28 / 771</td>
<td>2.8</td>
<td>1.2–6.9</td>
</tr>
<tr>
<td>Rodenticides</td>
<td>TGA groupc</td>
<td>5 / 66</td>
<td>13 / 771</td>
<td>4.7</td>
<td>1.5–14.2</td>
</tr>
<tr>
<td>Solvents (any)</td>
<td>Hypoplastic left heartc</td>
<td>9 / 138</td>
<td>80 / 3,572</td>
<td>3.4</td>
<td>1.6–6.9</td>
</tr>
<tr>
<td>Solvents (daily)</td>
<td>Coarctation of aorta c</td>
<td>5 / 120</td>
<td>68 / 3,572</td>
<td>3.2</td>
<td>1.3–7.9</td>
</tr>
</tbody>
</table>

*OR., adjusted odds ratio from multiple logistic regression; C.I., confidence interval; AVSD, atrioventricular septal defects; TGA-IVS, transposition of the great arteries with intact ventricular septum; TGA group, TGA-IVS plus TGA with other heart defects.

arteries, and septal defects. Maternal fever in the first trimester, possibly as the result of hyperthermia, and upper respiratory infections, including influenza, have been reported as possible risk factors for various types of CVM (Table II), specifically D-transposition of the great arteries, tricuspid atresia, and pulmonary valve stenosis [Ferencz et al., 1997] as well as atrial septal defect [Tikkanen and Heinonen, 1992b], and “conal” malformations [Tikkanen and Heinonen, 1992a]. No definitive studies have been published as yet. Isotretinoin and thalidomide are well-known examples of teratogenic medications with highly specific and time-dependent effects on cardiovascular development, for which comprehensive reviews are available [e.g., Lenz, 1988; Lynberg et al., 1990].

ENVIRONMENTAL RISK FACTORS

Maternal cigarette smoking and moderate consumption of alcohol have not been shown conclusively to be associated with the risk of CVM, but several studies reported weak associations with these lifestyle exposures. Tikkanen and Heinonen [1991b, 1992b] reported increased risks of atrial septal defects and VSDs in relation to any maternal alcohol consumption in the first trimester, but the dose-response trends in risk were inconsistent with a causal association. Similar results were reported by Ferencz et al. [1997] for muscular VSD, but no statistically significant associations were detected for atrial septal defect or membranous VSD. Wasserman et al. [1996] reported associations between parental smoking, particularly when both parents were smokers, and the risk for conotruncal heart defects. In the BWIS, cigarette smoking in early pregnancy was associated in a dose-dependent manner with the subset with transposition of the great arteries with VSD and with pulmonary valve stenosis [Ferencz et al., 1997]. The effects were seen only in certain, possibly susceptible subgroups, such as older mothers and those with a history of miscarriages. Parental exposures to lifestyle substances also were associated with certain malformations in the BWIS, particularly membranous VSD [Ewing et al., 1997].

Pesticide exposures in early pregnancy, specifically herbicides and rodenticides (Table II), were reported to be associated with an increased risk for D-transposition of the great arteries in the BWIS [Loffredo et al., 2001b]. In addition, Correa-Villasenor et al. [1991] reported an interaction between family history of congenital anomalies and pesticide exposures in their report on risk factors for total anomalous pulmonary venous return, suggesting a possible genetic susceptibility to these chemicals. These results are intriguing but have not been confirmed by other researchers [e.g., Shaw et al., 1999], and more research clearly is needed to characterize the exposures and determine the levels of risk.

Maternal exposures to organic solvents and paints in early pregnancy, at home and at work, are among the most commonly reported chemical exposures and are sources of concern to many pregnant women and clinicians [Scialli, 1989; Bentur and Koren, 1994]. Assessment of workplace exposures to this diverse group of chemicals yielded several reports of associations with CVM and other birth defects [McDonald et al., 1987; Tikkanen and Heinonen, 1988; Bao et al., 1991; Cordier et al., 1992; Shaw et al., 1992]. Tikkanen and Heinonen reported several associations of maternal occupation exposures to solvent-containing products with CVM: mineral oil products with coarctation of the aorta [1993]; dyes, lacquers, and paints with conal malformations [1992a]; and organic solvents with VSD [1991b]. Contamination of public drinking water supplies by chlorinated hydrocarbon solvents reportedly was associated with increased risks for CVM [Swan et al., 1989; Goldberg et al., 1990; Shaw et al., 1990; Dawson et al., 1993] and stimulated the development of animal models of cardiac teratogenesis of these chemicals [Loeber et al., 1988; Dawson et al., 1990].

In the BWIS, maternal reports of exposures to organic solvents at home and at work were associated with CVM as a whole and with specific subtypes (Table II). In particular, solvents were associated with elevated risks for left-sided obstructive heart defects, such as hypoplastic left heart and coarctation of the aorta [Loffredo et al., 1991, 1996; Ferencz et al., 1997]. Possible genetic susceptibility to the effects of solvents and paints was recently investigated [Loffredo et al., 1997a,b]: genetic polymorphisms in key solvent-metabolizing enzymes, glutathione-S-transferases, were found to mediate the risks of solvents and paints for pulmonic valve stenosis and atrial septal defect. Such studies of gene-environment interactions may be a promising avenue of future research on risk factors for CVM, as has been the case in other malformations, such as oral clefts [Hwang et al., 1995] and neural tube defects [Botto and Yang, 2000].

CONCLUSIONS

Advances in the understanding of the genetics and morphogenesis of CVM and new techniques in molecular epidemiology undoubtedly will stimulate new research into the causes and prevention of CVM. The rarity of these diseases will require multicenter collaborative approaches to best achieve these research goals. New studies must take into account the marked heterogeneity of congenital heart defects. The recent interest in folic acid supplementation is a case in point. Reductions in the risk of “conotruncal malformations,” a highly diverse category of CVM, have been reported among women who used multivitamins containing folic acid in the peri-conception period [Shaw et al., 1995; Botto et al., 1996]. Nevertheless, heterogeneity in this favorable response...
also has been reported, with a more apparent trend in risk reduction for transposition of the great arteries than for other malformations of the cardiac outflow tract [Scanolin et al., 1998]. Recent advances in preventing adverse birth outcomes through medical management of pre-gestational diabetes offers hope that similar success stories may be anticipated for the prevention of CVM.

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