Velo-cardio-facial syndrome: Cardiac anomalies and treatment

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Abstract

Velo-cardio-facial syndrome (VCFS) is the second most frequent genetic syndrome in humans. Specific types and subtypes of cardiac defects have been described in children with this syndrome as well as in other genetic syndromes. The congenital heart defects occurring in patients with VCFS include tetralogy of Fallot, pulmonary atresia with ventricular septal defect, truncus arteriosus, interrupted aortic arch, isolated anomalies of the aortic arch, and ventricular septal defect. Moreover in the setting of VCFS these types of cardiac defects are frequently associated with specific additional cardiovascular patterns.

During the last 30 years, the results of surgery for congenital heart defects have been continuously improving. Also in children with VCFS and cardiac defects specific diagnostic and surgical protocols have resulted in significant decrease of morbidity and mortality.

Introduction

Velo-cardio-facial syndrome (VCFS) is associated with congenital heart defects in about 75% of cases and these malformations represent the major cause of mortality and morbidity in infancy. Most studies suggest that this condition is highly associated with conotruncal heart defects occurring early in development, involving the outflow tract of the

heart and faulty septation/connection of the great. Similar to other genetic syndromes, specific types and subtypes of heart defects have been described in patients with VCFS. The conotruncal heart defects occurring in this syndrome include:

1. tetralogy of Fallot (TF)
2. pulmonary atresia with ventricular septal defects (PA-VSD)
3. truncus arteriosus (TA)
4. interrupted aortic arch (IAA)
5. isolated anomalies of the aortic arch (AAA)
6. ventricular septal defect (VSD).

In people with VCFS these heart defects are frequently associated with specific additional cardiovascular anomalies (Figure 1) particularly at the level of:

- aortic arch (right sided or double);
- pulmonary arteries (diffuse hypoplasia, discontinuity);
- subclavian arteries (aberrant, isolated);
- infundibular septum (hypoplasia, absence);
- pulmonary valve (dysplasia, stenosis)
- aorto-pulmonary collaterals (as blood supply to the lungs).

During the last 30 years results of surgery for congenital heart defects have been continuously improving as a synthesis of progresses accomplished in diagnosis, technology, and perioperative approach to the patient. Fetal echocardiography and new diagnostic technologies have modified timing, risk, and accuracy of diagnostic definition of congenital heart defects. The result of such acquisitions has been a shift in surgical management of patients toward primary repair in infancy with a significant decrease of morbidity and mortality even in the treatment of most challenging malformative conditions.

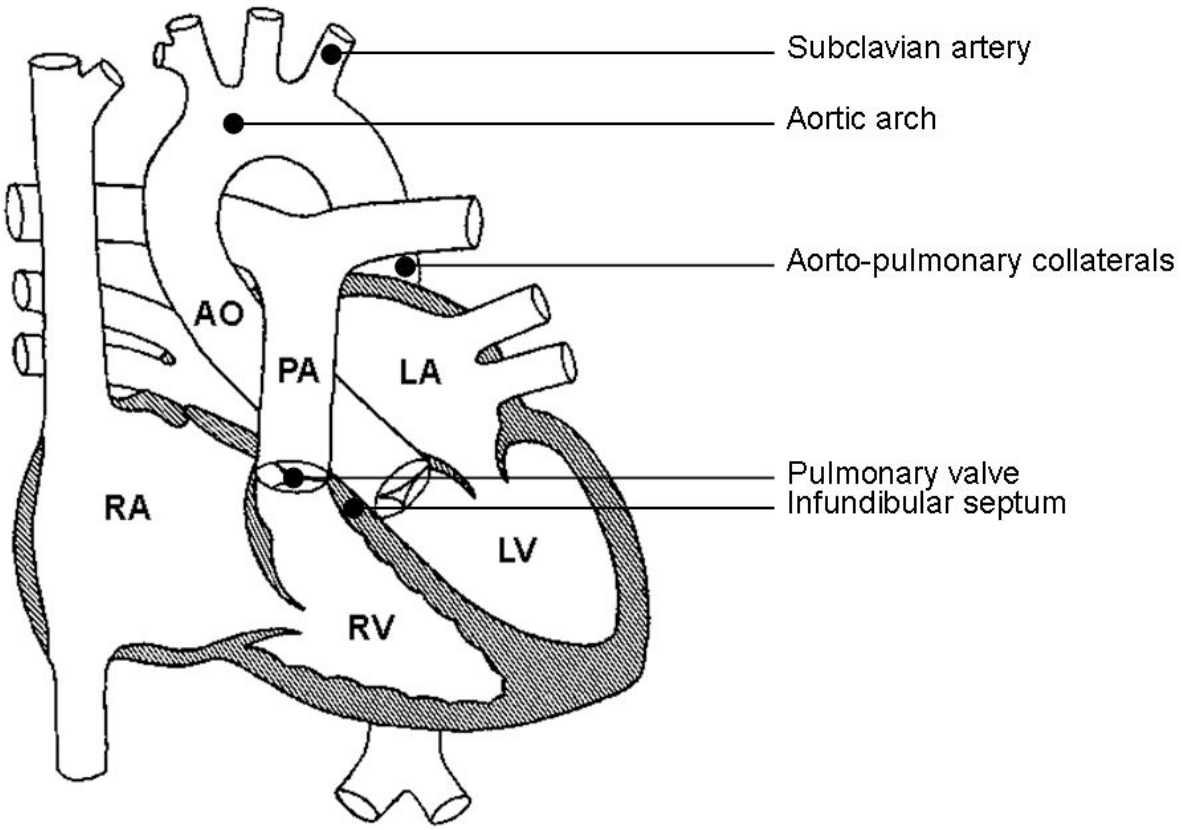

Figure 1. Additional cardiovascular anomalies sometimes present in people with VCFS (AO, Aorta; PA, Pulmonary artery; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle)

Conotruncal heart defects

1. Tetralogy of Fallot

Tetralogy of Fallot (TF) is defined as the abnormal superior, anterior, and leftward displacement of the infundibular septum resulting in narrowing of the right ventricular outflow tract, nonrestrictive malalignment type ventricular septal defect, overriding of the aorta, and secondary hypertrophy of the right ventricle. Approximately 10% of patients with ‘‘classic form’’ of TF have VCFS, which appears to be the most frequent genetic defect associated with TF. Fifty percent of children with TF and VCFS present with associated cardiac anomalies, e.g., absent or hypoplastic infundibular septum, absent pulmonary valve, hypoplastic pulmonary arteries, and aortic arch anomalies.

Surgical treatment; Primary repair, especially beyond the neonatal period, appears to be the best surgical strategy for patients with VCFS, with no additional risk for mortality and higher freedom from reintervention. Adaptation of routine surgical techniques based on specific cardiac phenotype has significantly improved surgical results in patients with VCFS and TF. Recent data show that, if appropriate treatment is provided, these additional cardiac defects do not worsen surgical prognosis, and VCFS is not a surgical risk factor in children with TF.

2. *Pulmonary Atresia with Ventricular Septal Defect (otherwise defined Tetralogy of Fallot with Pulmonary Atresia)*

Pulmonary atresia with ventricular septal defect (PA-VSD) constitutes the extreme spectrum of tetralogy of Fallot where pulmonary arterial perfusion is not provided by antegrade blood flow, but by alternative sources, namely the arterial duct in the Type A (the true TF with PA) or the major aorto-pulmonary collateral arteries (MAPCAs) in Type B and C. In general VCFS may occur in 16 to 40% of cases of PA-VSD, with variable proportion in the different anatomic varieties of the disease. Type C PA-VSD is the most severe anatomic expression of the disease where pulmonary blood perfusion is provided exclusively by MAPCAs and in this anatomic form the prevalence of VCFS is significantly higher.

Surgical treatment: Concerning surgical treatment, patients with VCFS and Type A PA-VSD are treated similarly to those with “classic form” of TF and pulmonary stenosis, and the presence of the syndrome does not seem to represent a surgical risk factor.

The situation is completely different for patients with Type B or C PA-VSD. Their surgical treatment is usually carried out according with various strategies where the final goal is to reach a complete repair of the disease, by connecting a unifocal, normal sized, as functionally normal as possible pulmonary arterial tree to the right ventricle using a valved conduit, and closing the VSD. An association between reduced survival and presence of VCFS has been reported, probably related to increased susceptibility to infectious events associated with a depressed immunological status and tendency toward airway bleeding.

3. Truncus Arteriosus

Truncus arteriosus (TA) is a cardiac defect consisting of a single outlet from the heart supplying the systemic, the coronary, and the pulmonary circulation. Since the first successful repair, surgical management of TA has markedly evolved to include earlier surgical timing. Most centers now successfully perform TA repair in the neonatal age. Standard repair includes patch closure of the VSD connecting the left ventricle with the aorta and right ventricle-to-pulmonary artery valved conduit interposition.
Approximately 30–35% of patients with TA have VCFS, whereas among patients with VCFS syndrome TA occurs in as much as 5–10% of cases. Patients with TA and VCFS have a higher incidence (10–15%) of associated cardiac anomalies (e.g. discontinuity of the pulmonary arteries, dysplastic truncal valve leading to incompetence and/or stenosis, interrupted aortic arch, and coronary artery abnormalities.

Surgical timing and technique need to be modified depending on the cardiac phenotype of the patient.

Although associated IAA, truncal valve incompetence, coronary abnormalities, and age above 100 days have been reported as risk factors of increased mortality at repair of TA, recent data suggest excellent survival of patients undergoing truncus repair in neonatal age even in cases with major associated abnormalities.
The association between TA and IAA, typical of VCFS, has been reported as a risk factor for increased mortality in a recent Congenital Heart Surgeons Society (CHSS) study on IAA. In spite of that, there is no evidence in the literature of increased risk at surgery of patients with TA and VCFS, even at long-term follow-up.

4. Interrupted Aortic Arch

Interrupted aortic arch (IAA) is a rare congenital heart defect, associated with VSD in virtually all cases and, sometimes with other complex cardiovascular anomalies (i.e. subaortic obstruction).

VCFS occurs in 40–50% of patients with IAA and is usually associated with more proximal location of the arch interruption, i.e., Type C (between innominate and left carotid artery) or Type B (between left carotid and left subclavian artery). Patients with type B IAA have VCFS in as many as 60–80% of cases, reflecting one of the conotruncal phenotypes more strongly related to genetic syndromes.

Current treatment of IAA consists of a one-stage primary neonatal repair by means of aortic arch repair and VSD closure, with concomitant management of subaortic obstruction, if needed.

Although VCFS has not been yet been definitely recognized as an incremental risk factor, particularly for mortality, many anatomic features typically associated with this syndrome can influence the surgical technique and can represent a risk factors for increased mortality.

5. Isolated Aortic Arch Anomalies

Isolated aortic arch anomalies (AAA) are significantly more common in patients with VCFS than in individuals without this syndrome. The variability of isolated aortic arch anomalies, demands a full preoperative anatomical definition followed by an individualized surgical approach.

6. Ventricular Septal Defect

A VSD, usually perimembranous or subarterial, occurs in 10–50% of patients with VCFS and is associated with anomalies of the position and branching of the aortic arch more commonly compared to individuals without this condition.

Surgical closure of a perimembranous VSD is usually feasible through the tricuspid valve, while subarterial VSD is best approached through the pulmonary valve.

There are no data supporting any difference in prognosis after VSD repair between patients with VCFS compared to other individuals.

Extracardiac anomalies

Cardiologists and surgeons should be alerted by the presence of this syndrome as indicator of complex cardiac anatomy but also to evaluate the presence of extracardiac anomalies that can be associated with VCFS.

The extracardiac anomalies occurring in this syndrome include:

- Hypocalcemia;
- Airway obstruction (vascular ring, laryngeal web, bronchospasm);
- Vasomotor instability (hypertension, hypotension);
- Infections (bacterial, fungal);
- Esophageal and other gastrointestinal anomalies;
- Renal defects.
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Specific diagnostic protocols and specific management mast be utilized in these patients with the contribution of other specialist pediatricians.

Conclusions

The cardiac phenotypes and the extra cardiac defects of children with VCFS may require a modified perioperative diagnostic and surgical techniques and an individualized approach to the patient.

Surgical prognosis may be influenced by the syndrome itself and/or by the anatomy of cardiac defects typically associated with VCFS.

Recognition of specific associated cardiac and extracardiac anomalies and recognition of specific risk factors induce to prepare adequate diagnostic and surgical protocols in order to provide appropriate treatment for these patients reducing the operative mortality and improving prognosis.

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