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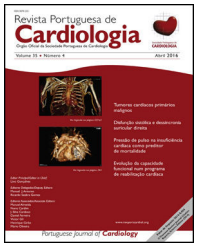

EDITORIAL COMMENT

Congenitally corrected transposition of the great arteries. Does situs arrangement influence the outcome?

Transposição congenitamente corrigida das grandes artérias. Será o *situs* relevante para o resultado?

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Congenitally corrected transposition of the great arteries (ccTGA) is a rare congenital heart defect that accounts for <1% of all forms of congenital heart disease and is characterized by atrioventricular (AV) and ventriculoarterial discordance.[1] This anatomic hallmark corrects the physiology of blood flow, ensuring that it flows in the correct direction, despite the complex anatomic derangement. It derives from an embryonic malrotation of the atria, ventricles, and great arteries that results in double discordance and presents with a wide variety of associated intracardiac defects.[2–4] This complex cardiac defect presents a wide variety of anatomic, hemodynamic and electrophysiologic abnormalities, leading to a range of clinical presentations and outcomes.

In its most frequent form, ccTGA presents with situs solitus, but it can also occur with situs anomalies, including situs inversus. These anomalous organ arrangements are usually associated with defects in thoracic and abdominal organs and in venous connections, increasing its complexity. Its pathogenesis is multifactorial and familial recurrence is rare.[5] Situs inversus has been described in association with primary ciliary dyskinesia (PCD), found in approximately 20%-25% of patients with this genetic anomaly,[6] and research has indicated a relationship between PCD and ccTGA, suggesting a genetic influence in its pathogenesis, adding to concerns over long-term outcomes.[7]

Genetic anomalies and the mirror arrangement of the atria typical of situs inversus may reflect an even more complex disease due to the presence of dextrocardia, anomalous systemic and pulmonary venous connections, and even abnormalities of abdominal organs. Anomalous connections of the coronary arteries may also occur, posing more challenges for management and outcome.[8] In such cases, the presentation and the surgical options may be determined by these associated anomalies, with increased morbidity and worse outcome.

The natural history of ccTGA is highly variable, depending on the associated defects, reflecting its anatomic variability. Most published studies report results in adult populations, and although favorable outcomes without surgery have been described, most patients will suffer progressive congestive heart failure (CHF) and rhythm disturbances at some point in their lives.[9–12] Decisions on the best management remain difficult, and must be tailored to each case. It is, however, clear that long-term outcome depends on three inter-related

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complications: systemic right ventricular (RV) dysfunction, tricuspid valve regurgitation, and complete atrioventricular block (CAVB) or arrhythmias.

Graham et al. demonstrated in a multicenter study that systemic RV dysfunction and CHF are common in adult life and increase in frequency with advancing age, in patients both with and without associated abnormalities.[10] The pathogenesis of RV dysfunction is multifactorial, but remains a matter of debate. In addition to previous surgical insult, ventricular structure, geometry and function and myocardial perfusion, together with chronic low-grade coronary insufficiency, may all contribute to progression of systemic RV dysfunction in this population.[13,14] This adverse outcome can be challenged by earlier and more aggressive surgical management, either correcting tricuspid valve regurgitation or 're-correcting' the left ventricle as the systemic ventricle through anatomic surgical repair.[15–17]

Progressive tricuspid regurgitation has been shown to develop in patients with ccTGA whether or not they have undergone intracardiac repair, and represents a major risk factor for poor outcome. The etiology of its development is not clear, as it may depend on an intrinsic anatomic malformation of the tricuspid valve (identified as 'Ebstein-like') due to elongated chordae, or related to systemic RV dilatation, further burdened with RV dysfunction, deficient myocardial perfusion and CAVB. This interdependence highlights the importance of early surgical correction of tricuspid regurgitation, and the influence of this anomaly in decision planning, as described by several authors.[11,17–19]

Rhythm disturbances are another frequent complication in long-term follow-up of ccTGA patients. CAVB and arrhythmias represent a major risk factor impacting on the natural history of ccTGA. They are more common in patients with situs solitus, with risk increasing by 2% per year after diagnosis, both before and after corrective or palliative interventions.[9,11,20–22] Their etiology has been related to the malalignment of the atrial and ventricular septum that is found in atrioventricular discordance with situs solitus, causing elongation of the His bundle.[20] Anomalous histology and anterior positioning of the AV node, with connections to the ventricular myocardium, have also been reported.[20] In situs inversus, some patients exhibit important differences in conducting tissue, with predominantly posterior connections and decreased elongation, as demonstrated by Wilkinson et al.[21] Nevertheless, the precise location of the conducting tissue in the various forms of ccTGA cannot be predicted in advance, which is a major issue for surgical correction in these patients and for long-term outcome.[20–22] In order to overcome this problem, some authors have even proposed the routine prophylactic placement of biventricular epicardial leads or early biventricular pacing during surgical intervention.[23]

Situs inversus is a rare anomaly of organ arrangement, found in about 2% of the general population. It can occur in association with ccTGA, although less frequently than situs solitus. In a study by Bilicier-Denktas et al.,[24] situs abnormalities were present in 34% of pediatric patients with ccTGA and situs inversus was found in 11%. The novelty of this study was to identify the presence of more severe preoperative CHF, need for previous operation and preoperative cardiac rhythm other than sinus rhythm as risk factors for late mortality, although they found no relation between situs anomalies and outcomes.

When dealing with a complex cardiac defect with heterogeneous presentation, diverse surgical interventions and poor outcome, the identification of factors impacting favorably on results since infancy would be of paramount importance. Oliver et al.[25] were the first to report situs inversus as a possible protective factor for the outcome of ccTGA patients. They concluded that long-term outcomes of adult patients with ccTGA and situs inversus, defined as decreased incidence of CHF, tricuspid regurgitation and CAVB, were significantly better than with situs solitus. These results could be explained by a better alignment of the atrial and ventricular septum and fewer conducting tissue anomalies. Although not statistically significant, there were also decreases in mortality and hospital admissions for CHF in situs inversus patients.

In their study published in this issue of the *Journal*, Kasar et al.[26] retrospectively assessed the clinical profile of a cohort of 21 pediatric patients with ccTGA and situs inversus, comparing their data with published studies. The authors emphasize that situs inversus ccTGA cannot be regarded as a mirror image of the situs solitus variant, because of differences in atrial and ventricular septal alignment, and anatomic and physiologic variations. Accordingly, they reported a lower incidence of CAVB and of tricuspid regurgitation, in line with Oliver et al.[25] These differences affected clinical management and could lead to a better long-term outcome. Interestingly, the authors did not report any cases of PCD or respiratory anomalies in their series, which could also have had a negative impact on the results. Their findings lack statistical significance, due to various study limitations such as the short follow-up period, the small sample size and the retrospective nature of the study, and their conclusions should be regarded with caution.

According to Graham et al., ventricular pacing is needed in about 38% of adult patients with ccTGA by the age of 40 years, and it is associated with worsening of systemic RV function in multiple reports.[10,27] Bautista-Hernandez et al. reported that CAVB presented preoperatively in 14%, with a post-surgery incidence of CAVB of 27%. In this study, 38% of patients required pacing in a mean follow-up of 5.2 years.[28] CAVB can be present from birth, but studies with larger number of patients and longer follow-up periods have revealed that the peak incidence of CAVB occurs later in life, the risk increasing with advanced age.[22] In the present study, Kasar et al. reported only one patient with CAVB, related to surgery, and no cases of spontaneous etiology in a mean follow-up of 48 months.[26] Kasar et al.'s data are relevant, but taking into account other research, it would be advisable to assess these patients for a longer follow-up period, in order to draw more robust conclusions.

The question can thus be raised, does situs arrangement in ccTGA influence the outcome? There is insufficient evidence to answer this question. Although some authors report better outcomes, with fewer classical complications, these studies were performed in small and heterogeneous populations and lack data on other important issues, such as PCD, repeated respiratory infections, and associated anomalous venous drainage, and even more importantly, accurate assessments of the long-term impact of the various treat-

ment options. Although the present study is important, assessing a reasonable number of pediatric patients, its conclusions are not sufficiently strong to propose new guidance on management.

The morphologic diversity of ccTGA and associated defects do not allow a straightforward surgical approach, with different possibilities determined by the physiologic and anatomic substrate. The pursuit of better results has led to alternate surgical approaches performed earlier in life and focusing on anatomic correction (double switch operation, a combination of the Senning and arterial switch operations), as opposed to physiologic repair.[14,18,28,29] Nevertheless, this operation is not suitable for all, and its complications are still significant. Although the early results seem to be better, it has been demonstrated that the quality of life of patients who undergo anatomic as opposed to physiologic correction are similar, with poorer school performance in those treated by anatomic correction.[30]

The best clinical approach remains uncertain, as decision-making is still based on small studies and single-center reports. Regardless of the clinical variant, situs arrangement and selected approach, late complications are relatively common, so ongoing outpatient assessment should be a priority in congenital heart defect reference centers, and accurate assessment of results requires further and extended collaborative long-term follow-up studies.

Conflicts of interest

The author has no conflicts of interest to declare.

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