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EDITORIAL COMMENT

Changes in heart rate variability after ventricular septal defect closure in children. Where do we stand? Adaptation mechanism, sequela or complications?

Alterações na variabilidade da frequência cardíaca após encerramento da comunicação interventricular em crianças. Qual é a nossa posição? Mecanismo de adaptação, sequela ou complicação?

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Ventricular septal defects (VSDs) are one of the most frequent congenital heart defects and occur as an isolated lesion or associated with other more complex heart defects. According to van der Linde et al., VSDs have a birth prevalence of 2.62 per 1000 live births,[1] with the majority of defects being small, spontaneously closing in about 30% of cases still in childhood or otherwise they remain open, but without symptoms. Rare complications can emerge, such as bacterial endocarditis or aortic regurgitation in defects located at the membranous septum below right coronary and noncoronary cusps of aorta.

Defects presenting with a significant left-to-right shunt may cause left ventricular (LV) overload, pulmonary arterial hypertension (PAH), ventricular dysfunction, arrhythmias, and aortic regurgitation.[2] Surgical closure at a young age is indicated in large and medium size defects with symptoms of heart failure and other complicated defects and remains the treatment of choice. It presents good mid- to long-term results for survival, morbidity, and quality of life.[3]

Recently, in properly selected cases, the percutaneous approach has been the technique of choice, for which several devices are available. Most frequent treatment complications are arrhythmias, right bundle brunch block or rarely complete atrio-ventricular block (CAVB).[4] While surgeons have improved their technique diminishing complications, the percutaneous approach still presents a complication rate that cannot be overlooked, with CAVB being the most feared.

Percutaneous VSD closure has not yet become the treatment of choice, mainly because it is aimed at small and medium size defects and because of trauma to the conducting tissue during procedural maneuvers or the compressing device. Iatrogenic CAVB has been an issue occurring with early or late onset and has an estimated pooled incidence rate between 1.1% and 2.4%.[5,6] Other concerning

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complications of this technique is injury of the tricuspid or aortic valve with associated regurgitation; in general, this has been reported with an incidence of 1.3%.[5,6]

Whatever the procedure, patients who undergo VSD closure or those with small open defects have been considered to have a benign long-term course,[3,4,7] except for those cases with long-term left heart failure, left ventricle dilation, mild elevation of pulmonary vascular resistance or other significant complications, occurring pre and post VSD closure. Nevertheless, several investigators have demonstrated emerging evidence of late morbidity in adults who had surgical or percutaneous closure,[4,8,9] and even in those with small untreated defects.[9,10] This emerging evidence has reported changes that were not so obvious, such as increased pulmonary pressure and resistance during exercise testing. Abnormal strain pattern and abnormal force-frequency relationship of the right ventricle (RV), which correlates with exercise capacity and may reflect adaptative measures to abnormal pulmonary pressure during exercise.[9,11,12]

There is also evidence that even minor changes in RV function and in pulmonary vascular resistance in adults, might alter pulmonary and systemic homeostasis due to RV pressure or volume overload.[13] Homeostasis regulation depends on autonomic nervous system (ANS) balance and flexibility or regulatory capacity that enables the cardiovascular system to adapt and deal with changing demands, due to intrinsic and extrinsic factors.[14]

This emerging evidence may raise questions about the suitability of standard practice for patients with even simple or asymptomatic congenital heart defects.

The ANS is a component of the peripheral nervous system that controls various organ systems inside the body, it innervates cardiac muscle, smooth muscle, and various endocrine and exocrine glands, which in turn regulate blood pressure, urination, bowel movements, and thermoregulation as well as other visceral activities that maintain homeostasis. The ANS functions continuously without conscious effort. However, it is controlled by centers located in the spinal cord, brain stem, and hypothalamus,[15] in a complex and still not well understood mechanism.

When the balance between the sympathetic nervous systems and parasympathetic nervous systems is disturbed by some events, such as serious stress, inflammation or heart failure, it might shift the ANS homeostasis toward sympathetic dominance, leading to various changes associated with sympathomodulation, involving the whole system.

Since fetal life, congenital heart defects (CHD) present with altered hemodynamics, and adaptation mechanisms to maintain an adequate cardiac output. The ANS has an important role in maintaining cardiac and vascular homeostasis in these patients, from fetus to postnatal life.[16,17] Of course, during fetal development and after birth, the ANS undergoes developmental changes, attaining maturation similar to adults after 5-6 years of age. Both arms of the ANS evolve differently according to sex and this evolution is asymmetrical; it occurs more quickly in males and for the parasympathetic system.[16–18]

Studying heart rate variability (HRV) as a parameter to evaluate cardiovascular ANS function, it has been demonstrated that ANS adaptation mechanisms occur in different CHD, including VSD in adolescents and adults. Although investigators have demonstrated that HRV bears several pitfalls,[19] and that its relevance is still unclear in pediatric ages, the interest in the study of HRV has increased significantly since the first reports of its association with an increased risk of mortality after acute myocardial infarction in adults.

It has been demonstrated, in patients without CHD, that sympathetic dominance occurs during heart failure or after myocardial infarction and is a poor prognostic factor for mortality and lethal arrhythmias. Despite controversies, these results have encouraged researchers to study HRV both as a diagnostic as a prognostic factor for assessing cardiovascular autonomic dysfunction.[20] Still, we need to stress that ANS and HRV are subject to diverse extrinsic influences, such as cardiac surgery, anesthesia, cardiovascular drugs, level of physical activity, obesity, among others, that may lead to a biased interpretation. Each evaluation of HRV is a snapshot of a particular moment in time, and requires replicated results and consistency, so we need to take particular care with this methodology when performing clinical studies to avoid confounding variables and rushed conclusions.

Several investigators have described an overall altered ANS function in children with CHD, with reduced HRV both before and after surgery or percutaneous interventions. However, large scale studies to measure ANS function for prolonged periods of time in well-defined cohorts and along pediatric ages are still lacking. This makes it difficult, in our opinion, to understand the extent and prognostic value of ANS dysfunction in children with CHD.[21–23]

Heart rate variability is a non-invasive measure of variation of inter-beat intervals that reflects the balance of ANS to the heart.[24] HRV presents atypical patterns in patients with CHD, that may result from incomplete cardiac development, hemodynamic changes associated with abnormal pressure or volume loading conditions, medications or interventions needed to manage CHD.[25] However, recent studies have demonstrated that HRV abnormalities in children with CHD correlate well with those described in adult patients who have undergone ASD and VSD closure as children. These HRV abnormalities favored sympathetic predominance, and Nederend et al. suggested a possible iatrogenic etiology for patients who underwent surgery, since we have to consider the possible contribution of partial surgical vagotomy at the time of correction as a cause of lifelong abnormalities in HRV. Current data are unable to determine whether CHD in itself or the surgical procedure causes HRV abnormalities in these patient cohorts that have been associated with increased morbidity. Large scale longitudinal studies are required definitively understand definitively HRV changes after surgery or other interventions in CHD.[25]

In the present study, Sunkak et al.[26] present the results of the effect of percutaneous closure of VSD on HRV in a group of 19 children. They concluded that HRV was lower in the patient group before procedure and normalized after VDS transcatheter closure, compared to the control group. The study would be more robust if the authors had described more thoroughly the clinical presentation of the patients, including hemodynamic data and other clinical relevant data, such as medication, level of exercise or others. Nevertheless, we should emphasize some limitations that the authors did not point out in their study but are important

to manage the discussion and draw conclusions. First, although, this is a prospective short-term study, the authors did not prolong the study enough to demonstrate replication and consistency of the results. Second, conditions during Holter monitoring between comparison groups were not identical, the authors compared patient group before and after procedure and three months post-procedure patient group with the initial control group. This could raise significant bias, since the Holter performed after procedure, during hospitalization, with limited mobilization and after an anesthetic procedure, cannot be compared with those preformed under different conditions. It would have been more accurate if the control group had also repeated the 24 hours Holter evaluation after three months, under the same conditions.

Additionally, the authors should explain better how this procedure was planned, the selection of the device, according to the anatomical type of VSD or applied technique and the chosen device itself. Although, they pointed out that the risks of CAVB have to be taken into account and can be minimized with technical maneuvers or other devices, however they are one of the main reasons why CAVB has not become a first-choice technique. Since the majority of VSD cases were membranous (18 over 19), it would have been interesting to read the authors considerations of other techniques and devices, since there are varying incidence rates of postprocedural complications according to device type.[27] The likelihood of complications may increase with younger patients[28] and therefore it has been demonstrated that to minimize complications, a low-profile device with a small delivery system and adequate size for the measured defect would be recommended, to avoid undersized residual shunts or oversized injury to valves or the myocardium.[29]

The authors demonstrated results in line with others, either concerning pediatric or adult patients, although those studies have used different methodologies. They still advanced with hypothetical reasons to understand the results. Pulmonary vascular resistance with RV dysfunction, and left heart dysfunction could always play a role, but it seems there must be a still hidden mechanism behind the evolution and adaptation of the ANS from fetal development to adulthood in patients with CHD that we still do not fully understand. Improvement in long-term knowledge of autonomic regulation and abnormalities in patients with CHD could let us consider changes in current practice for CHD treatment, to avoid unnecessary dysfunction and morbidity burdens.

Despite numerous published papers addressing HRV in healthy subjects and in patients with various clinical conditions, our understanding of the development of ANS is still limited. ANS dysfunction seems to play a meaningful role in long-term complications in patients with CHDs. Compensatory changes may deteriorate heart function, cause arrhythmias and other morbidities in these patients, but are we facing adaptative mechanisms, sequelae or complication issues? A better understanding of ANS adaptative changes and regulation and the link to long-term clinical outcomes are crucial to perceive the possible etiological role of ANS in CHD and the possible benefits of further and earlier intervention to treat CHD.

Conflicts of interest

None declared.

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