Cardiology in the Young

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Heterotaxy: fluctuat nec mergitur

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Abstract

The International Pediatric and Congenital Cardiac Code (IPCCC) states that *visceral heterotaxy* is defined as "a congenital malformation in which the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body. By convention, in congenital cardiology, heterotaxy syndrome does not include patients with complete mirror-imaged arrangement of the internal organs along the left-right axis also known as "total mirror imagery" or "situs inversus totalis"." [www.ipccc.net]

In patients with heterotaxy, it is important to describe both the cardiac relations and the junctional connections of the cardiac segments, with documentation of the arrangement of the atrial appendages, the ventricular topology, the nature of the unions of the segments across the atrioventricular and the ventriculoarterial junctions, the infundibular morphologies, and the relationships of the arterial trunks in space. Particular attention is required for the venoatrial connections, since these are so often abnormal. The relationship and arrangement of the remaining thoraco-abdominal organs, including the lungs, the spleen, the liver, and the intestines, also must be described separately, because, although common patterns of association have been identified, there are frequent exceptions to these common patterns. Therefore, in patients with heterotaxy, it is important to describe each thoracic and abdominal organ independently.

Letter to the Editor

Cite this article: Houyel L, Moreau de Bellaing A, and Bonnet D (2021) Heterotaxy: fluctuat nec mergitur. *Cardiology in the Young* **31**: 1200–1201. doi: 10.1017/S1047951121002961

Received: 30 June 2021
Accepted: 1 July 2021

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As we indicated in our article,[1] and as Anderson et al demonstrate in their commentary,[2] the exact definition of heterotaxy is still actively debated and needs urgent clarification. In this regard, we have to recognise that we erroneously shortened the definition of heterotaxy as published by The International Society of Nomenclature for Paediatric and Congenital Heart Disease in 2017 and that we omitted a fundamental part of it that is the word "***complete***". The exact quote of the definition of *visceral heterotaxy* is "A congenital malformation in which the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body. By convention, in congenital cardiology, heterotaxy syndrome does not include patients with complete mirror-imaged arrangement of the internal organs along the left-right axis also known as "total mirror imagery" or "situs inversus totalis"." [3,4,5,6] (In fact, this definition of heterotaxy was originally published by The International Society for Nomenclature of Paediatric and Congenital Heart Disease in 2007, in a manuscript where Professor Anderson was the second author.[3]) It is thus incorrect to interpret the definition adopted by The International Society of Nomenclature for Paediatric and Congenital Heart Disease as excluding anything other than complete or 'totalis' situs inversus or solitus, which means that, as already demonstrated in various studies, heterotaxy can be found with a normal heart and normal atrial appendages.[7,8]

The second incorrect statement from the authors of the commentary is that they describe our patient as having a "usual arrangement of the atrial appendages", while we stated that "atrial appendages on CT-scan had a similar external shape, triangular with multiple indentations" (as showed in Fig 2B). As "the resolution of the CT-scan did not allow us to assess the morphology of the pectinate muscles inside the atria", we could not show with certainty that the atrial appendages were isomeric. However, had truly our patient had situs solitus arrangement of the pectinate muscles, he also had left bronchial isomerism, a midline liver, and asplenia. These features would unequivocally classify this patient as having "visceral heterotaxy", not only according to Lin's criteria that we quoted in our article[9] but also according to the definition of The International Society of Nomenclature for Paediatric and Congenital Heart Disease.

One of the major problems in our daily practice of paediatric cardiology is that it remains very difficult with the current imaging techniques to clearly assess the anatomy of the pectinate muscles within the atria. The image provided by Anderson et al in their commentary is far from being demonstrative in this regard, as no pectinate muscles are visible within the right atrial appendage, where there are located in all normal and abnormal hearts! We agree with Anderson et al that defining atrial situs solitus by the connection of the inferior caval vein to the right-sided atrium, like the vast majority of paediatric cardiologists and prenatal echocardiographists still do in clinical practice, is in contradiction with the principles of the morphological method developed by the Van Praaghs,[10] even if connection of the inferior caval vein to the morphologically left atrium is absolutely exceptional.[11] This will

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hopefully change in the future with the constant improvements in CT-scan and MRI techniques.

Anderson et al quote the translation and analysis of the work of Isidore Geoffroy Saint Hilaire about "anomalies of organization in human and animals", in which he defines heterotaxy as "congenital changes in the situation of organs, in which the *relative* position and connections of the parts are not altered", which can be interpreted according to the following paragraph as situs inversus totalis, also called "transposition of the viscera".[12] The argument of anteriority that the authors are putting forward, concerning this definition of heterotaxy dating from the first half of the nineteenth century, does not withstand rigorous analysis. Numerous examples of this could be given, particularly in the domain of CHD but in all other domains of science. Science is made of building blocks, added by the ongoing discussions and controversies between scientists, based on the results of observations and experiments, and is therefore a work in constant progress. If it was not the case, should not we for example come back to the term "partial transposition", coined by Herman Vierordt in 1898,[13] to design the anomaly now known as "double outlet right ventricle", on the sole argument of anteriority?

Indeed, situs inversus totalis (total mirror-imagery) and heterotaxy are two different entities, albeit being both laterality defects and therefore "other arrangements", implicitly "other than normal". In situs inversus totalis, defined by The International Society of Nomenclature for Paediatric and Congenital Heart Disease in 2017 as "complete mirror-imaged arrangement of the internal organs along the left–right axis of the body", the organs are arranged, like in situs solitus, in a harmonious fashion, while in heterotaxy, the arrangement of the various organs of the thorax and the abdomen is by essence disharmonious. In addition, it has been demonstrated in a large epidemiologic study that these two "syndromes" have a very different cardiac phenotype, with 96.6% of associated CHD in heterotaxy versus 43.2% in situs inversus totalis, and a significantly different distribution of complex CHD in the two syndromes.[9] Therefore, we do not approve the proposal of Anderson et al to include situs inversus totalis in the category of "heterotaxy". We also disagree with the statement that the term "heterotaxy" is redundant and should be abandoned, to be replaced by its two subsets of right and left isomerism. The reason for this is that, as Anderson et al themselves recognise it, the atrial appendages can be lateralised (normal or mirror-imaged) in the setting of visceral heterotaxy.[14] In that case, if as they propose, "analysis starts with description of atrial arrangement", how would they categorise these patients? The essence of heterotaxy is indeed potential disharmony between the situs of bronchi, abdominal organs, and the atrial appendages.

Consequently, we are in total agreement with Anderson et al that the best and only way to resolve these controversies is "to describe each thoracic and abdominal organ independently, including the segments of the heart and the venous and arterial connections", and especially, as they suggest in their commentary, "the crucial venoatrial connections". However, there is no reason to discard the term heterotaxy, and this accurate description should be performed within the framework of the definition provided by The International Society of Nomenclature for Paediatric and Congenital Heart Disease.

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https://doi.org/10.1017/S1047951121002961 Published online by Cambridge University Press