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Determining situs by abdominal aorta and inferior vena caval findings: It is neither complicated nor ambiguus

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A B S T R A C T

We reviewed our center's experience with isomeric situs for those identified prenatally or born between 2003 and 2018. We defined left isomerism as an absent hepatic portion of the inferior vena cava with azygos/hemiazygos venous return to the superior vena cava. We defined right isomerism as an ipsilateral abdominal inferior vena cava and aorta. For the period 2003 to 2018, we identified 101 patients that met criteria. Of the 101, 70 (69%) had left isomerism, and 31 (31%) had right isomerism. Of the 101 patients, 89 were live born. For those with left isomerism, 24/70 (34%) had functionally univentricular hearts versus 30/31 (97%) with right isomerism ($p = 0.00001$). Overall mortality for live-born patients was higher for right isomerism 42% versus 13% for left isomerism ($p = 0.029$). For the period 2014–2018, 27/27 (100%) of patients with isomerism were diagnosed prenatally compared to 29/57 (51%) for the period 2003–2013 ($p = 0.0003$). In conclusion, left or right isomerism can be determined by ultrasound imaging of the abdominal aorta and inferior vena caval relationships. To date, all patients have had a discernable situs without any deemed uncertain. Further, our current prenatal diagnosis of isomerism stands at 100%.

1. Introduction

Discernable situses include solitus, inversus, left isomerism, and right isomerism; although, isomerism lacks exact bilateral symmetry. Some advocate that situs identification begins with assessing atrial appendage morphology [1]. Nevertheless, as atrial appendage morphology is not readily evident by transthoracic echocardiography at all ages, transesophageal echocardiography, computed tomography, or magnetic resonance imaging may be required [2–4]. In contrast, the abdominal aorta and inferior vena caval anatomy may also be used as signs for situs determination, and these structures can usually be imaged by routine clinic-based ultrasound [5].

This study describes our center's statewide experience with isomeric situs in patients born since 2003. We emphasize the practicality of determining left or right isomerism by abdominal ultrasound scanning. Additionally, as a follow up to our previous publication [6], we report our center's current prenatal detection results for those born in Southern Nevada over the previous five years.

2. Methods

This investigation received approval from the local Institutional Review Board, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. We received from the local IRB a waiver for informed consent. We accessed data for this study by inquiring our research database (Epi-InfoTM) and electronic medical records (EMR). For the searchable parts of our EMR, we used Perspective Software by Lexmark International, Inc. Lexington, KY, USA. For statistical analysis, we used SPSS version 13.0 (SPSS Inc., Chicago, Illinois, United States of America). We used nonparametric testing, and we set a p-value of < 0.05 as significant.

For this retrospective, observational, nonrandomized report we identified patients evaluated at our center with right and left isomerism that were prenatally identified or born between 2003 and 2018. We do not define situs, either prenatally or postnatally, by the position of the stomach, liver, or gallbladder. Further, we do not define isomerism by the presence of contralateral cardiac and stomach positions, by the cardiac axis, by the atrioventricular or ventricular arterial connections, or by the presence of specific cardiac malformations. We define situs by the position of the abdominal aorta and inferior vena cava alone. We define the presence of left isomerism by the absence of the hepatic portion of the inferior vena cava, which results in lower body venous return via the azygos and hemiazygos venous systems to the superior vena cava. We define the presence of right isomerism when the abdominal aorta and inferior vena cava have an ipsilateral course. We consider polysplenia, left atrial isomerism, left atrial appendage isomerism, and bilateral left-sidedness all synonyms for left isomerism, and we consider asplenia, right atrial isomerism, right atrial appendage isomerism, and bilateral right-sidedness all synonyms for right isomerism. All patients had confirmation of their abdominal aorta and

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Table 1
Data on all 101 isomerism patients.

	Patients with isomerism	Functional univentricle	2-Ventricle	Fetal demise	Live born	Live-born male
Left isomerism n (%)	70 (69)	24 (34)	46 (66)	7 (10)	63 (90)	31 (49)
Right isomerism n (%)	31 (31)	30 (97)	1(3)	5 (16)	26 (84)	15 (58)
Total	101	54	47	12	89	46
p	N/A	0.0001	0.0001	0.75	0.62	0.37

Table 2
Data on live-born patients' functional univentricular versus two-ventricular hearts.

Type of isomerism	Functional univentricle			2-Ventricle		
	Live born	Postnatal deaths	Surgical deaths Deaths/total surgeries (%)	Live born	Postnatal deaths	Surgical deaths Deaths/total surgeries
Left isomerism	17	8	7/16 (44)*	46	0	0/13
Right isomerism	25	11	6/20 (30)*	1	0	N/A
Total	42	19	13/36 (36)	47	0	0

* *p* 0.51.

Table 3
Cardiac anatomical sub-types in functional univentricular versus two-ventricular hearts.

Type of isomerism	Functional univentricle	2-Ventricle	Total
Left isomerism	11 unbal AVSD + PS/PA 6 HLH	33 normal 6 AVSD/ASD 4 CoAo/VSD 1 SubAS 1 ToF 1 PAPVR	63
Right isomerism	23 unbal AVSD + PS/PA 2 unbal AVSD no PS/PA	1 Normal	26
Total	42	47	89

ASD atrial septal defect, *AVSD* atrioventricular septal defect, *CoAo* coarctation of the aorta, *HLH* hypoplastic left heart, *PA* pulmonary atresia, *PAPVR* partial anomalous pulmonary venous return, *PS* pulmonary stenosis, *SubAS* subaortic stenosis, *ToF* tetralogy of Fallot, *unbal* unbalanced, *VSD* ventricular septal defect.

Table 4
Malrotation and arrhythmia information.

Type of isomerism	Ladd for malrotation per GI work up* n Ladd/n GI WU (%)	EKG* with EAR n EAR/n EKG (%)	Pacemaker per LB n PM/n LB (%)
Left isomerism	13/33 (49)	14/52 (24)	7/63 (11)* PO 4/7 (57) NPO 3/7 (33)
Right isomerism	2/16 (13)	5/19 (23)	2/26 (8)* PO 2/2 (100)
p	0.13	0.85	0.57*

Cong congenital, *EAR* ectopic atrial rhythm, *GI* gastrointestinal, *LB* live birth, *PM* pacemaker, *PO* post-operative, *WU* workup.
* Not all patients had GI work ups or EKGs.

inferior vena caval findings by ultrasound scanning, either prenatally or postnatally, using standard echocardiographic equipment. The Children's Heart Center is the sole provider of congenital heart care in Nevada; thus, our databases and EMR contain information on all patients with isomeric situs seen in Nevada. To identify patients' records in our EMR, we utilized the following search terms: left and right isomerism, left and right atrial and atrial appendage isomerism, heterotaxy, situs ambiguous and ambiguus, asplenia, polysplenia, interrupted inferior vena cava, absence of the hepatic portion of the inferior vena cava, azygos continuation, and bilateral left and right sidedness. Following the inquiry of our research database and EMR, we reviewed patient records and collated data for analysis. We calculated our recent prenatal detection rate for those born since 2014 by comparing the number of prenatally detected patients to the total of all Southern Nevada, live-born patients with isomeric situs during the same period. We compared our current prenatal detection rate with that for the period 2003–2013. For prenatal detection rates, we elected to use data from Southern Nevada, as it was more complete than data from Northern Nevada during the period analyzed. We previously reported the mechanics of our center's prenatal program [7]. For Nevada birth numbers, we inquired United States census information [8].

3. Results

We identified 101 patients that met criteria. Of the 101, 70 (69%) had left isomerism, and 31 (31%) had right isomerism. Of the 101 patients, 89 were live born. Of the 89 live-born patients, 63 had left isomerism, and 26 had right isomerism. Overall mortality for live-born patients with right isomerism was 11/26 (42%) versus 8/63 (13%) for left isomerism ($p = 0.029$). All patients with situs ambiguus or ambiguous, as part to their diagnosis in the medical record, had their situs re-identified as either left or right isomerism by ultrasound determination of their abdominal aorta and inferior vena caval findings. No patient had an uncertain or ambiguus situs.

Table 1 lists the total patients identified with either left or right isomerism, a breakdown of those with functionally univentricular versus two-ventricular hearts, numbers experiencing fetal demise, live-born numbers, and sex differences. Right isomerism patients were statistically significantly more likely to have a functionally univentricular heart than those with left isomerism. Table 2 reports mortality data for the live-born with patients those with functionally univentricular hearts versus those with two-ventricular hearts. No postnatal or surgical deaths occurred in two-ventricular patients, and surgical death rates were similar between those with right or left isomerism. Table 3 breaks down anatomical subtype data by type of isomerism for functional univentricular versus two-ventricular hearts. Table 4 records the data for Ladd procedures for positive malrotation gastrointestinal workups per the total number of gastrointestinal workups. We found no statistical differences in the Ladd surgical rates for the two groups. Table 4 also analyzes differences between those with ectopic atrial rhythm and separately those that required pacing, and, again, we found no

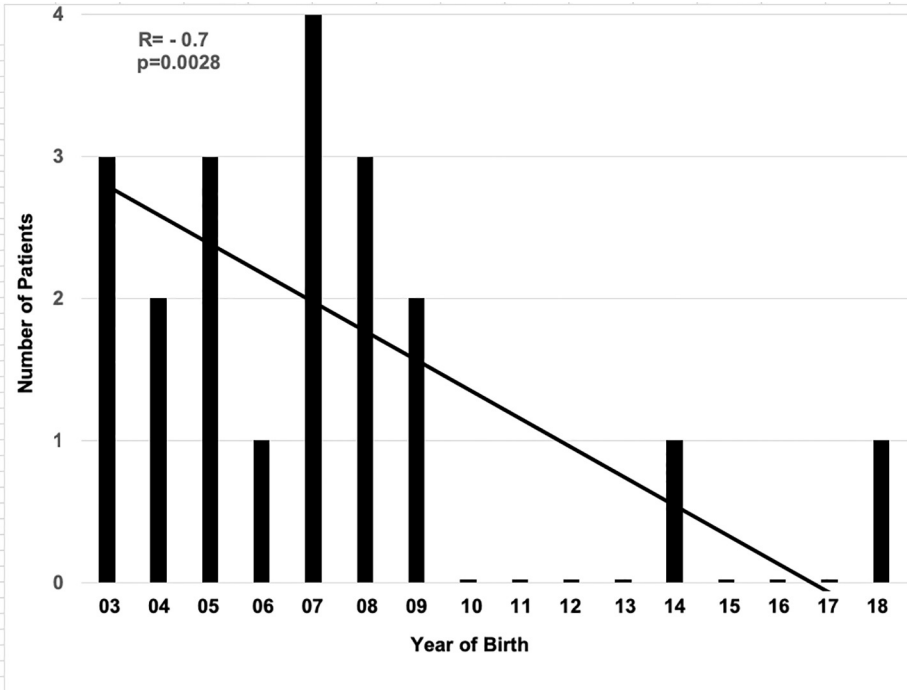

Fig. 1. Declining use of the terms ambiguus or ambiguous for situs.

Table 5
Prenatal detection of isomerism.

Type of isomerism	So NV LB PN detection 2003–2013 by type n D/n total (%)	So NV LB PN detection 2014–2018 by type n D/n total (%)	*p*
Left isomerism	24/39 (62)	19/19 (100)	0.018
Right isomerism	5/18 (28)	8/8 (100)	0.0065
Total	29/57 (51)	27/27 (100)	0.0003

D detected, *LB* live birth, *PN* prenatal, *So NV* southern Nevada.

differences between groups. Of the 9 pacemakers, 6 (67%) were post-operative; nevertheless, post-operative requirement for pacing was not always clearly surgical related or an underlying conduction abnormality. Fig. 1 shows the statistically significant declining use of the term ambiguus or ambiguous in our center's patient records over time by patients' year of birth.

Table 5 records the prenatal detection rates. Between 2014 and 2018, we identified 27 patients with isomerism born in Southern Nevada, and 27/27 (100%) were diagnosed prenatally, resulting in a highly statistically significant improvement over the period 2003–2013. The 27 prenatally diagnosed patients between 2014 and 2018 were identified from 7967 pregnant women undergoing fetal echocardiography for fetal congenital heart disease risk factors. Using the estimated number of live births between 2014 and 2018 at 140,000, we calculated a left isomerism prevalence of 1.3/10,000 live births and a right isomerism prevalence of 0.6/10,000 live births. The combined right-left isomerism prevalence of 1.9/10,000 live births is higher than our previously reported combined rate of 1.3/10,000 live births [6], likely reflecting our improved prenatal detection rate.

4. Discussion

We did not quantitate the occurrence of all situs descriptors used in patients' records; however, we noted, from local patient notes and medical records accompanying patients relocating to Nevada from other centers, the following terminology examples: abdominal situs solitus with asplenia, situs ambiguous with polysplenia, abdominal situs inversus with azygos continuation. Further, a simple literature search revealed publications, too numerous to reference, with similar confused situs descriptions. Thus, the use of situs terminology is far from uniform. In our opinion, discrepant approaches to terminology between centers and even differences between individual clinicians and researchers within centers have led to confusion, which is reflected in congenital heart patients' medical records and the literature. Although there have been ongoing clarifications, previously published statements such as, “all patients with heterotaxy should also be considered to have ‘situs ambiguus’ and all patients with ‘situs ambiguus’ also have heterotaxy syndrome” [9], have, in our opinion, further contributed to situs nomenclature confusion among clinicians.

In 1966, at the University of Minnesota, Elliot, Cramer, and Amplatz (creator of the Amplatzer septal occluder) were the first to report the angiographic finding that an ipsilateral abdominal aorta and inferior vena cava relationship is a specific sign for asplenia [10]. Similarly, again Elliot et al. described interrupted inferior vena cava and azygos continuation as an angiographic sign in polysplenia in 1971 [11]. In 1982, Huta et al. first reported the echocardiography findings of situs determination by the relationship of the abdominal aorta and inferior vena cava [5]. However, the likely first recorded depiction of polysplenia, interrupted inferior vena cava with azygos continuation, and transverse liver, accompanied by dextrocardia, presumably without a significant intracardiac abnormality (as none noted), was in John Abernethy's 1793 report, made famous for an incidental observation of a portosystemic shunt (an Abernethy malformation) (Figs. 2 and 3) [12]. Abernethy also described a spleen composed of 7 separate portions, each with a splenic artery. Although we are unaware of the embryologic mechanism contributing to the ipsilateral abdominal aorta and inferior vena caval findings in right isomerism, the embryology of agenesis of the hepatic portion of the inferior vena cava has been described. The failure of the union of the subcardinal venous system with the hepatocardiac channel, leading to agenesis of the hepatic portion of the inferior vena cava and successive connection of the subcardinal venous system to the supracardinal venous system, which subsequently develops into the azygos and hemiazygos systems [13].

Recognition of situs abnormalities and the history of situs

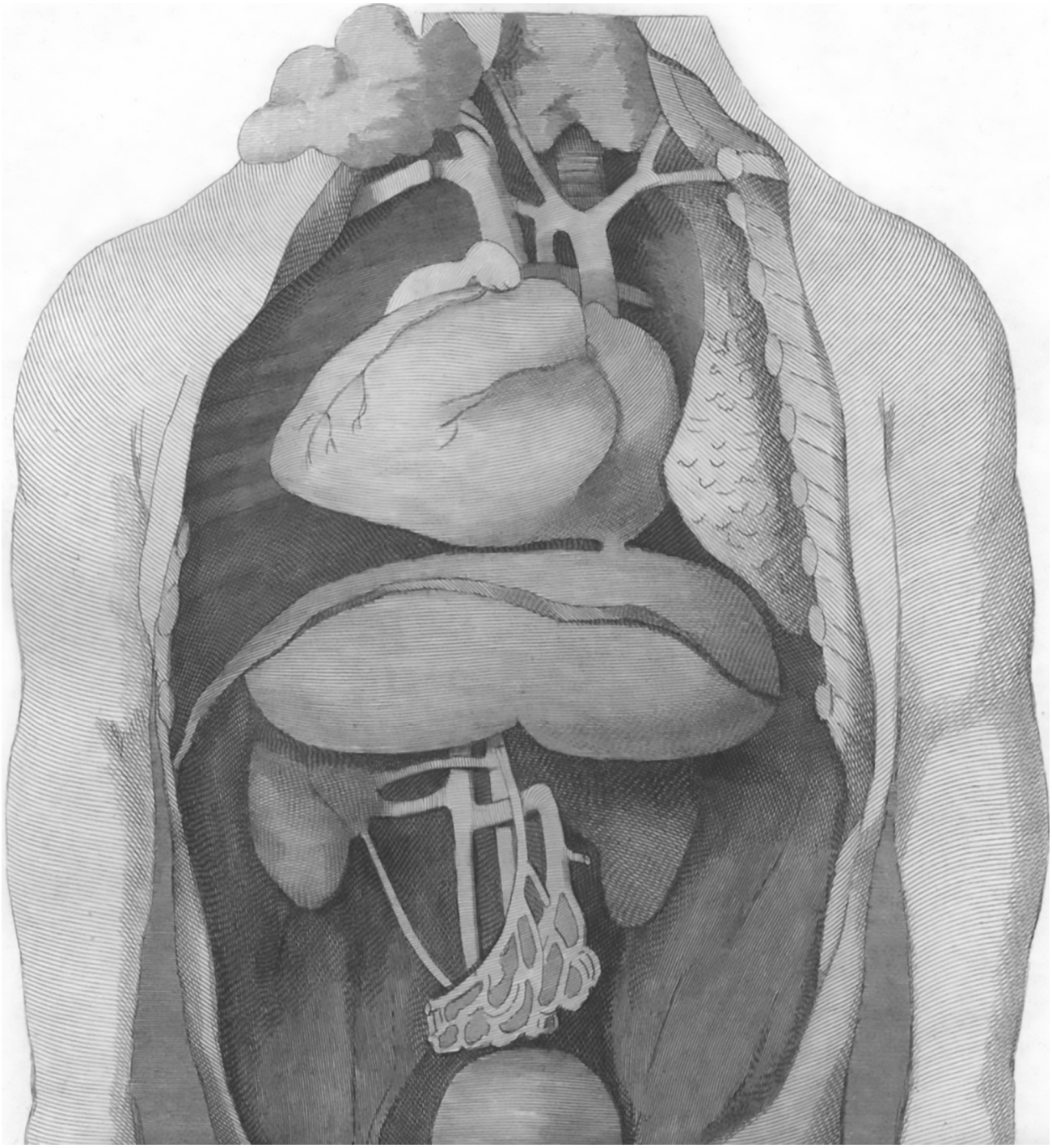

Fig. 2. Plate 1 from Abernethy's 1793 article.
Transverse liver, dextrocardia, left atrial appendage isomerism.

nomenclature extend back to the 17th century [14]. In the 1950s, Biörn Ivemark, detailed the association between abnormal splenic numbers and situs [15]. In the 1970s, Lodewyk Van Mierop et al. coined the term situs ambiguus for seemingly uncertain situs [16]. Although patients with uncertain situs may exist, in each of our 101 patients, we categorized them by their abdominal aorta and inferior vena caval findings as right or left isomerism. Additionally, others have also reported their doubt concerning the existence of uncertain or ambiguus situs [1].

Determining situs by the angiographic or ultrasound relationships of the abdominal aorta and inferior vena cava is not new, as both techniques were first recognized decades ago. Nevertheless, an argument could be made regarding the best method of determining situs. Some maintain that specifying situs should begin with determining atrial appendage morphology [1]. However, such a determination is often not practical, as to do so may require complicated imaging methods beyond clinic-based echocardiography. The consistency between ultrasound determined abdominal aorta and inferior vena caval relationships and isomerism may not be 100% concordant, but the evidence for consistency is high [17]. Of note, even left atrial appendage isomerism may not be present in every patient with left isomerism [18]. Additionally, studies report inconsistencies between the presence of polysplenia and asplenia for determining left or right isomerism [19].

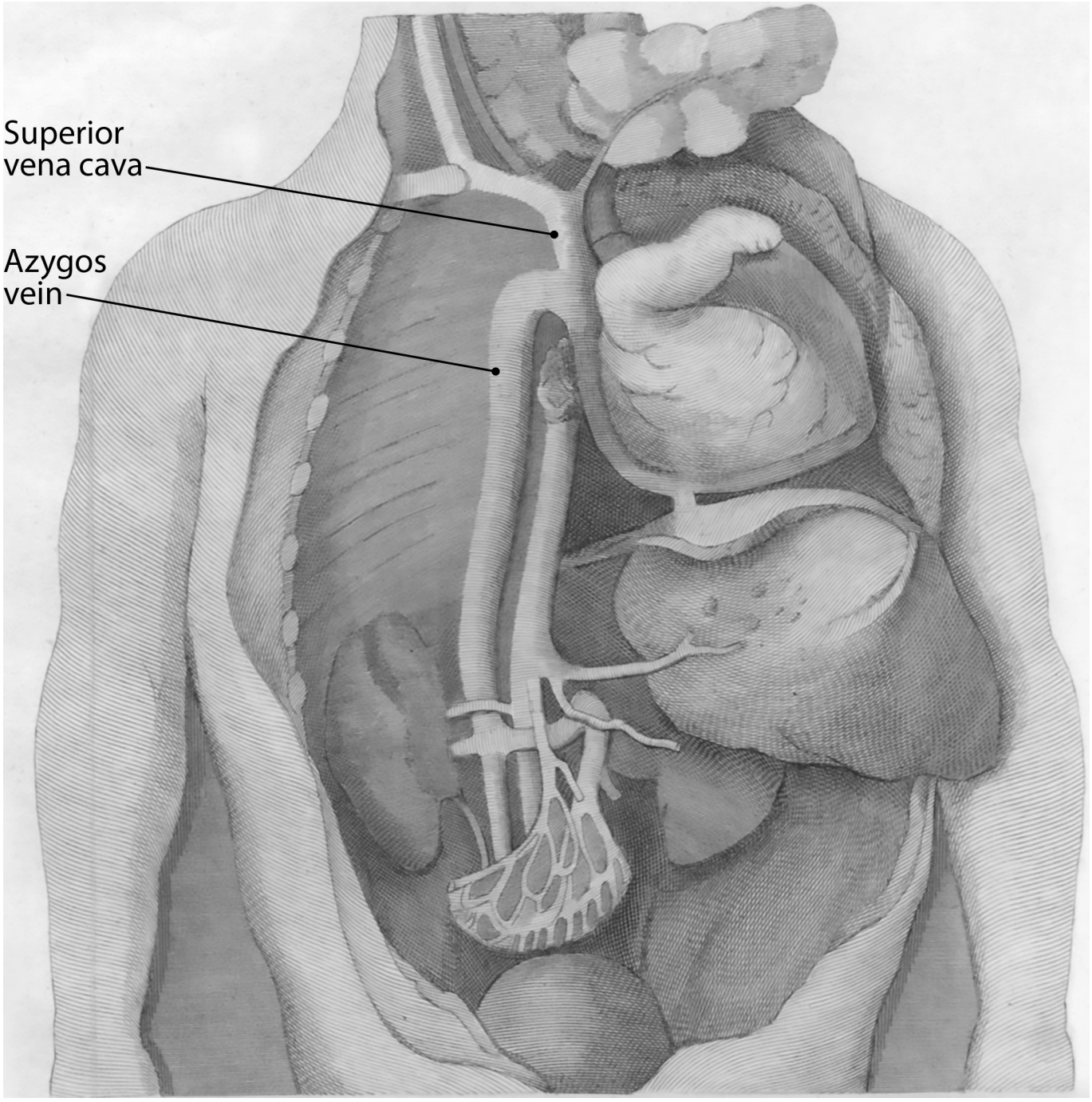

Fig. 3. Plate 2 from Abernethy's 1793 article.
Heart and liver pulled to left showing azygos continuation to superior vena cava.

Diagnosing isomerism is important not only for the association of congenital heart disease and cardiac arrhythmias but also for an array of related problems including those with the gastrointestinal tract, immune system, genitourinary abnormalities, pulmonary pathology, central nervous system issues, thromboembolism, venous anomalies like Abernethy malformations, and ciliary motility dysfunction [19]. Prenatal detection is optimal, as it also allows for early diagnosis of these various associated problems. Prenatal diagnosis via abdominal aorta and inferior vena caval findings was reported as early as 1984 [20]. Currently, our program is achieving a 100% prenatal detection rate for left and right isomerism. We principally attribute improved prenatal detection, especially since 2014, to continuing sonographer education and experience and enhanced screening recommendations by national organizations. Additionally, our center has documented this progressive improvement in our regional prenatal detection of congenital heart disease in a previous publication [7]. We recommend that all infants with isomeric situs have consultations with pediatric surgery, immunology, and other services if manifestations of associated problems arise following birth.

This report's limitations include its retrospective nature and the limited number of patients for analysis; however, such limitations are intrinsic to retrospectively studying rare conditions. Further, we cannot account for asymptomatic or symptomatic undiagnosed individuals. Strengths include our high prenatal detection rates, robust database management, electronic health records on all diagnosed patients from the state of Nevada, and avoidance of relying on third-party sources.

In conclusion, left or right isomerism can be determined by ultrasound imaging of the abdominal aorta and inferior vena caval relationships. To date, all patients have had a discernable situs without any deemed uncertain. Further, our current prenatal diagnosis of isomerism stands at 100%.

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Declaration of competing interest

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References

[1] Anderson RH, Spicer DE, Loomba R. Is an appreciation of isomerism the key to unlocking the mysteries of the cardiac findings in heterotaxy? J Cardiovasc Dev Dis 2018;5(1). https://doi.org/10.3390/jcdd5010011. pii: E11.
[2] Tuccillo B, Stümper O, Hess J, et al. Transoesophageal echocardiographic evaluation of atrial morphology in children with congenital heart disease. Eur Heart J 1992;13:223–31.
[3] Mori S, Anderson RH, Nishii T, et al. Isomerism in the setting of the so-called "heterotaxy": the usefulness of computed tomographic analysis. Ann Pediatr Cardiol 2017;10:175–86.
[4] Yim D, Nagata H, Lam CZ, et al. Disharmonious patterns of heterotaxy and isomerism: how often are the classic patterns breached? Circ Cardiovasc Imaging 2018 Feb;11(2):e006917https://doi.org/10.1161/CIRCIMAGING.117.006917.
[5] Huhta JC, Smallhorn JF, Macartney FJ. Two dimensional echocardiographic diagnosis of situs. Br Heart J 1982;48:97–108.
[6] Evans WN, Acherman RJ, Restrepo H. Heterotaxy in southern Nevada: prenatal detection and epidemiology. Pediatr Cardiol 2015;36:930–4.
[7] Evans W, Castillo W, Rollins R, et al. Moving towards universal prenatal detection of critical congenital heart disease in southern Nevada: a community-wide program. Pediatr Cardiol 2015;36:281–8.
[8] National Vital Statistics Reports. Available at http://www.cdc.gov/nchs/products/nvsr.htm, Accessed date: 1 November 2018.
[9] Jacobs JP, Anderson RH, Weinberg PM, et al. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. Cardiol Young 2007;17(Suppl. 2):1–28.
[10] Elliott LP, Cramer GG, Amplatz K. The anomalous relationship of the interior vena cava and abdominal aorta as a specific angiocardiographic sign in asplenia. Radiology 1966;87:859–63.
[11] Vaughan TJ, Hawkins Jr. IF, Elliott LP. Diagnosis of polysplenia syndrome. Radiology 1971;101:511–8.
[12] Abernethy J, Banks J. Account of two instances of uncommon formation, in the viscera of the human body. Philosophical Transactions of the Royal Society of London 1793;83:59–66.
[13] Slosman F, Schmid MR, Pfammatter T. Agenesis of the hepatic segment of the inferior vena cava with portal continuation. AJR Am J Roentgenol 2001;177:120–2.
[14] Evans WN. Thoracoabdominal situs: a practical approach accompanied by a short history of descriptive terms. Pediatr Cardiol 2010;31:1049–51.
[15] Ivemark B. Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood: analysis of the heart malformations in splenic agenesis syndrome, with fourteen new cases. Acta Paediatr 1955;44(Suppl. 104):7–110.
[16] Van Mierop LH, Eisen S, Schiebler GL. The radiographic appearance of the tracheobronchial tree as an indicator of visceral situs. Am J Cardiol 1970;26:432–5.
[17] Lee SH, Kwon BS, Kim GB, et al. Clinical characteristics and independent factors related to long-term outcomes in patients with left isomerism. Korean Circ J 2017;47:501–8.
[18] Mori S, Anderson RH, Nishii T, et al. Isomerism in the setting of the so-called "heterotaxy": the usefulness of computed tomographic analysis. Ann Pediatr Cardiol 2017;10:175–86.
[19] Kothari SS. Non-cardiac issues in patients with heterotaxy syndrome. Ann Pediatr Cardiol 2014;7:187–92.
[20] Stewart PA, Becker AE, Wladimiroff JW, Essed CE. Left atrial isomerism associated with asplenia: prenatal echocardiographic detection of complex congenital cardiac malformations. J Am Coll Cardiol 1984;4:1015–20.