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Title:
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Date:
2019-12-01

Citation:
Wertaschnigg, D., Rolnik, D. L., Ramkrishna, J., da Silva Costa, F. & Meagher, S. (2019). The gap between the aorta and the superior vena cava: A sonographic sign of persistent left superior vena cava and associated abnormalities. Prenatal Diagnosis, 39 (13), pp.1213-1219. https://doi.org/10.1002/pd.5569.

Persistent Link:
https://hdl.handle.net/11343/286522

The gap between the aorta and the superior vena cava: a sonographic sign of persistent left superior vena cava and associated abnormalities

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Running head: a novel sonographic sign of persistent left superior vena cava

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Main text word count: 2,681
Figures: 4
Tables: 3

Fundings, Conflict of interest

DW is supported by a grant from the Paracelsus Medical University Salzburg, Austria (PMU Research Fund – PMU-FFF Number I-18/02/006-WET) and by Drs. Haarkert Foundation, Germany.

The other authors report no conflicts of interest.

What is already known about this topic? A persistent left superior vena cava is associated with other structural anomalies and chromosomal abnormalities.

What does this study add? An increased distance between the aorta and right superior vena cava is a new sonographic sign for a persistent left superior vena cava.

This could facilitate the diagnosis of persistent left superior vena cava and should lead to a further detailed examination.

Data Availability: Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT

Objectives: To assess the distance between the right superior vena cava (SVC) and the aorta in fetuses with bilateral superior vena cava as a possible sonographic marker for this.

Methods: This was a nested case-control study including 20 cases of bilateral SVC and 40 gestational age-matched controls. The distance between the right SVC and the aorta was measured at the level of the three-vessel trachea view in stored images, as well as the diameters of the aorta and the right SVC.

***Results*:** The distance between the aorta and the right SVC was significantly larger in the cases of a left SVC compared to controls, $p < 0.001$. A distance of 2.0 mm or more was found in 70% of the cases and 5% of the controls, with a gestational-age adjusted area under the receiver-operating characteristics (ROC) curve for the diagnosis of left SVC of 0.93 (95% CI 0.87-0.99). The aorta and the right SVC were significantly smaller in cases compared to controls, and there was a significant association with other cardiac and extra-cardiac abnormalities amongst cases of persistent left SVC.

***Conclusion*:** An increased distance between the aorta and the right SVC is associated with the diagnosis of bilateral SVC.

INTRODUCTION

Persistent left superior vena cava (SVC) or bilateral SVC is the most common anatomical variant in the thoracic venous system.[1-4] In the general population, the estimated prevalence ranges between 0.3 and 0.5%,[2,5-7] whereas the association in patients with congenital heart disease is higher and between 4 and 8%.[1,3,5,8] More than one in five newborns (21.3%) diagnosed with coarctation of the aorta present with bilateral SVC.[1,5,9,10] Cardiac anomalies, chromosomal disorders and extra-cardiac malformations are more common in the setting of a persistent left SVC.[2,5,11] However, it can be assumed that the real prevalence of an isolated persistent left SVC in healthy population is higher, as the detection in a routine transthoracic echocardiographic examination can be challenging and an isolated finding of this venous variant usually lacks clinical relevance.[1,5]

The addition of the three-vessel trachea view in the examination of the fetal heart at the mid-trimester morphology scan has contributed to improved detection of outflow tract anomalies and also of persistent left SVC.[3,12,13] In spite of the improved detection of outflow anomalies the small diameter of the left SVC can make the diagnosis of bilateral SVC challenging and often overlooked.[14] In a prenatal ultrasound examination, the typical finding of a persistent left SVC is an abnormal three-vessel trachea view as an additional fourth vessel is seen juxtaposed to the pulmonary artery.[14] In the four-chamber view, it appears as a “bleb” inside the left atrium, because it usually drains into the coronary sinus leading to its dilatation.[6,14,15] A failure of involution of the left

anterior cardinal vein results in a persistent left SVC, in which case the venous drainage of the upper body occurs through both left and right SVC.[7,16] The left brachiocephalic vein that usually crosses horizontally in the upper mediastinum anteriorly to the three branches of the aortic arch and finally empties into the right brachiocephalic vein is often missing.[17,18] Therefore, it is plausible that the traction of the left brachiocephalic vein on the right SVC towards the midline of the mediastinum is absent. Consequently, the right SVC is displaced in the mediastinum towards the right side (Figures 1 and 2). Furthermore, the smaller diameter of the aorta and the right SVC in these cases, particularly when associated with heart abnormalities such as coarctation of the aorta, could further increase the distance between the aorta and the right SVC. This increased distance between the aorta and the right SVC could serve as a marker for the detection of persistent left SVC, prompting a more detailed targeted examination of the fetal heart given its frequent association with other structural defects.

The aim of this study is to examine the distance between the right superior vena cava and the aorta in cases of persistent left SVC and the association of this condition with cardiac and extra-cardiac malformations.

METHODS

Study design and population

This is a nested case-control study. The cases and controls were obtained from the ultrasound database at Monash Ultrasound for Women, Melbourne, Australia, which is a dedicated tertiary obstetric and gynecological ultrasound practice and center for fetal diagnosis, offering first and second trimester screening for chromosomal and structural anomalies during pregnancy.

The ultrasound database was searched for all cases of persistent left SVC (including also the term bilateral superior vena cava) who had ultrasound examinations at Monash Ultrasound for Women, between January 2012 and February 2019. All the cases had a targeted examination with an obstetric sonologist and pediatric cardiologist. The images and the report of the targeted fetal echocardiographic examination were reviewed, as well as prenatal and postnatal findings and pregnancy outcomes recorded in the database.

Two gestational-age matched controls (case-control 1:2 ratio) were then randomly selected from the same database for each case. All controls had normal second trimester morphology scan including a detailed assessment of the fetal heart according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines,[12,19] and resulted in a phenotypically normal neonate of appropriate birth weight for gestation.

Ultrasound examinations were performed using Voluson E10 and Voluson E8 (General Electric Healthcare Ultrasound, Zipf, Austria) machines, equipped with a 3D 4–8-MHz probe for transabdominal ultrasound.

Ethics

As a retrospective anonymized audit project that did not seek pregnancy outcome data apart from those routinely collected in the service, this study met the criteria for quality assurance activities outlined by the National Health and Medical Research Council.[20] Therefore, ethical approval was not required.

Procedures and measurements

The distance between the right SVC and the aorta was measured at the level of the three-vessel trachea view in stored images from fetuses with bilateral SVC. The calipers were placed at the outer right sided wall of the aorta to the outer left sided wall of the right SVC to measure the distance between these two blood vessels (Figure 2). In addition, diameters (outer wall to outer wall) of right SVC and the aorta were measured at the same level. If the stored image at the diagnosis showed poor quality, a better image from a follow-up study at a later gestational age was chosen for the measurement.

Statistical analysis

Associated cardiac and extra-cardiac abnormalities, as well as the use of invasive testing for fetal karyotyping and chromosomal microarray and their

results, are described as absolute numbers and proportions of the cases. Continuous variables are expressed as median and ranges. The distance between the aorta and the right SVC, as well as the aorta and the right SVC diameters, in millimeters, are reported as median and ranges for each subgroup and represented in box-and-whiskers and scatter plots with curves of locally estimated scatterplot smoothing (LOESS). Differences between controls and cases of bilateral SVC, with and without associated major heart defects, were investigated with the use of generalized estimating equations (GEE), using as strata each case and its two gestational age-matched controls. A gestational age-adjusted receiver-operating characteristic (ROC) curve was produced to assess the predictive accuracy of the gap measurement in the diagnosis of bilateral SVC. Statistical analysis was performed with the R statistical package,[21] and significance level was set at 5%.

RESULTS

Between January 2012 and February 2019, there were 20 cases of bilateral superior vena cava in our database. The median gestational age at diagnosis was 21.05 (13.1-32.1) weeks and the median gestational age of the included images was 24.8 (15.7-36.1) weeks, and these did not differ between cases and controls. There were additional ultrasound findings in thirteen (65%), and major heart defects were identified in eight cases (40%), including two cases of hypoplastic left heart syndrome (10%), one case of double-outlet right ventricle (5%) and five cases of coarctation of the aorta (25%, with one associated with ventricular septal defect).

Regarding extra-cardiac anomalies, abnormal fingers were noted in one of the cases of hypoplastic left heart syndrome and fetal growth restriction in one case of coarctation of the aorta. One case of coarctation was diagnosed with tracheoesophageal fistula after delivery. In another six cases (30%) without major cardiac abnormalities, other findings were reported: one case with a single umbilical artery, one case of polyhydramnios, one case of oligohydramnios, one case of persistent right umbilical vein, one case of fetal growth restriction, and one case with large for gestational age and low-set ears.

Invasive testing (chorionic villous sampling or amniocentesis) for fetal karyotyping and chromosomal microarray was offered in all cases and performed in eight (40%), of which all had other abnormal findings. Genetic testing revealed abnormal results in two of the eight cases (25%, one case of mosaic trisomy of the chromosome 16 associated with fetal growth restriction

and one case of microdeletion/microduplication syndrome in the long arm of the chromosome 15 (15q11q13), associated with polyhydramnios. Details of each case and the association with other ultrasound findings or chromosomal abnormalities are given in Table 1.

The distance between the aorta and the right superior vena cava in the three-vessel trachea view was significantly increased among cases (median 2.4 mm, range 1.3 mm to 7.8 mm) than in the control group (median 1.1 mm, range 0.1 mm to 4.6 mm), $p < 0.001$ – Table 2 and Figure 3. This difference was significant in cases of isolated bilateral SVC and even more so in those with associated heart abnormalities.

The right SVC was significantly smaller among the cases (median 2.5 mm, range 1.1 mm to 4.4 mm in the cases group *versus* median 3.3 mm, range 1.7 mm to 6.1 mm in the control group, $p < 0.001$). However, no significant difference in the right SVC diameter was observed between cases of isolated bilateral SVC and those with associated heart defects ($p=0.588$).

Similarly, the diameter of the aorta was smaller in the group of cases of persistent left SVC (median 3.7 mm, range 1.3 mm to 6.1 mm in the cases *versus* median 4.6 mm, range 2.1 mm to 7.5 mm in the control group, $p < 0.001$). The aorta was significantly smaller in cases of bilateral SVC with other congenital heart anomalies, than in controls ($p < 0.001$), but not in those with an isolated bilateral SVC ($p = 0.351$).

All but two fetuses in the control group had the aorta-right SVC distance above 2.0 mm, and both of these measurements were taken in the third trimester (one at 32 weeks and the other one at 36 weeks of gestation). A distance between

the aorta and the right SVC of 2.0 mm or more was found in 70% of the cases and 5% of the controls, with an area under the gestational age-adjusted ROC curve for the diagnosis of persistent left superior vena cava of 0.93 (95% CI 0.87-0.99, Figure 4). As seen in Figure 3b, the distance between the aorta and the right SVC is particularly discriminant between cases and controls before 24 weeks of gestational age.

The multivariate analysis by GEE revealed that the distance between the aorta and the right SVC was positively influenced by the presence of bilateral SVC and by gestational age but was not significantly influenced by the aorta and the SVC diameters (Table 3).

DISCUSSION

Main findings

This case-control study showed that the distance between the right SVC and aorta measured at the level of the three-vessel trachea view is substantially larger in fetuses with bilateral SVC, with and without associated heart abnormalities, than in normal controls. Discrimination between cases and controls was good, particularly before 24 weeks of gestation. The right SVC and the aorta are considerably smaller in cases of bilateral SVC, the latter being mainly due to associated heart defects.

Study strengths and limitations

To our knowledge, this is the first study to report the association of an increased distance between the aorta and the right SVC with the diagnosis of bilateral SVC. The main limitation of this study is its case-control design with a limited number of included cases of this relatively uncommon venous variation. The gestational age range of included cases and controls was wide, and this limitation was minimized by including gestational age-matched controls and by adjusting the ROC curve analyses for this covariate. The distance between the aorta and the right SVC is significantly increased in cases when compared to controls at the same gestational age. Lastly, we did not adjust the gap measurement thresholds for the gestational age and, despite a strong correlation of its measurement with the presence of bilateral SVC, the use of

specific measurement cut-offs requires caution as the distance increases in size with gestation. The two normal controls that had a gap measurement of more than 2.0 mm were above 30 weeks of gestational age, suggesting that the finding may be less specific in the third trimester.

Clinical implications

While the presence and the course of the left brachiocephalic vein could not be retrospectively assessed in all cases and controls, we hypothesize that the findings can be explained by the fact that in the case of a bilateral SVC, the left brachiocephalic vein is missing in up to 65% of the cases[18] and that the two vessels share the venous drainage of the upper part of the body to the right atrium.[17] Moreover, if the venous drainage from the left to right brachiocephalic vein is missing, the traction on the right SVC towards the left side might be less pronounced. That could consequently lead to a displacement of the right SVC towards the right side of the thorax, and therefore more tissue of the mediastinum is present between the right SVC and the aorta. In fact, Karl *et al.*, evaluating the course of the left brachiocephalic vein in over one thousand fetuses, reported that the absence of the left brachiocephalic vein in association with a persistent left SVC was found in one in 350 pregnancies.[22] Furthermore, venous return from the upper left head and neck through the persistent left SVC drains into the coronary sinus and eventually into the right atrium. Dilatation of the coronary sinus in case of persistent left SVC due to the increased blood flow in the sinus has been previously described in the literature.[6] However, in this different hemodynamic situation, the venous drainage through the right

SVC is decreased, which could explain the smaller diameter of the right SVC.[23] The smaller size of the aorta could be explained by the high association with left ventricular outflow tract obstructions such as anomalies of the aortic arch and aortic valve.

This sonographic sign which may be readily visualized in the routine three-vessel tracheal view and should draw the operator's attention to thoroughly look for the presence of a left SVC, facilitating the often-challenging diagnosis of bilateral SVC. As this diagnosis is commonly associated with cardiac and extra-cardiac abnormalities, a meticulous examination of the fetus should also be prompted. Despite an increase in the prenatal identification of fetal heart defects in the last decades, some diagnoses are still challenging even in more experienced hands.[12] The most commonly overlooked conditions are coarctation of the aorta, interruption of the aortic arch, total anomalous pulmonary venous connection and aortic valve stenosis.[24-26]

In our study, the incidence of additional cardiac abnormalities in cases of bilateral SVC was 40% and left ventricular outflow tract abnormalities were diagnosed in 35%, with coarctation of the aorta being the most common (20%). A systematic review and meta-analysis of persistent left SVC from 2016 showed similar findings: additional cardiac defects were present in 60.7% (95% CI, 44.2-75.9%) and coarctation of the aorta in 21.3% (95% CI, 13,6-30.3%) of the cases of persistent left SVC.[5] Hence, the authors recommended close follow up studies in the setting of a persistent left SVC until the end of pregnancy to rule out evolving coarctation of the aorta.[5] We found extra-cardiac abnormalities in 45% and genetic abnormalities in 10%. These results are comparable with the

reported numbers in the systematic review with 37.8% (95% CI, 31,0-44.8%) for extra-cardiac abnormalities and 12.5% (95% CI, 9.0-16.4%) for chromosomal anomalies[5]. The association with other cardiac and extra-cardiac anomalies as well as chromosomal abnormalities shows the importance of the detection of this anatomical venous variation and should lead to further detailed examination of the fetus. The high association of bilateral SVC with coarctation of the aorta should also trigger follow up ultrasound examinations later in gestation by an experienced sonologist or pediatric cardiologist, as subtle and even moderate abnormalities of the aortic arch can be missed at mid-trimester scan and some of these anomalies can evolve with time.[5]

Future prospective series with a larger number of cases at different gestational ages are necessary to confirm our findings. While the detection of heart abnormalities should not rely on indirect signs and we do not advocate for systematic measurement of the distance between the aorta and the right SVC, the findings of this study suggest that a large distance should draw one's attention to evaluate the cardiac anatomy even more carefully.

In conclusion, the association of bilateral SVC with other fetal abnormalities is high. A more evident gap between the right SVC and the aorta can be a sign of persistent left SVC and should lead to a detailed examination of the fetus to exclude other associated cardiac and extra-cardiac anomalies as well as chromosomal abnormalities.

Data Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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FIGURE LEGENDS

Figure 1. a) Schematic representation of the three-vessel view showing the pulmonary artery, the aorta and the right superior vena cava (SVC); b) Schematic representation of the three-vessel trachea view in case of bilateral SVC showing a more pronounced gap between the aorta and the SVC.

Figure 2. Sonographic image of a persistent left SVC, in which an increased distance between the aorta and the smaller right SVC can be identified. LSVC: Left superior vena cava; PA: Pulmonary artery; Ao: Aorta, RSVC: Right superior vena cava.

Figure 3. a) Boxplot demonstrating the median values of the distance between the between the aorta and the right superior vena cava (SVC) in cases and controls; b) Measurement of the distance between the aorta and the right SVC with curves of locally estimated scatterplot smoothing (LOESS) in controls (open circles and solid line) and in cases of persistent left SVC (closed squares and dashed line) with 95% confidence intervals (shaded areas).

Figure 4. Gestational age-adjusted receiver-operating characteristics (ROC) curve for the detection of bilateral superior vena cava using the distance between the aorta and the right superior vena cava at the three-vessel trachea level. Area under the ROC curve 0.93 (95% CI 0.87-0.99, $p < 0.001$)

TABLE 1

Case	Gestation at diagnosis (weeks)	Cardiac findings	Extra-cardiac findings	1st trimester Combined screening	cffDNA test	Genetic testing	Result of invasive genetic testing
1	13+1	HLHS	Abnormal fingers	–	Low risk	CVS	normal
2	20+1	–	–	Low risk	–	–	–
3	21+0	–	Single umbilical artery	Low risk	–	–	–
4	19+5	–	–	Low risk	–	–	–
5	26+5	–	LGA, low-set ears	Low risk	–	AC	Normal
6	30+2	–	FGR	High risk T18	–	CVS & AC	Placental mosaicism Trisomy 16
7	22+2	–	–	Low risk	–	–	–
8	20+2	HLHS	–	Low risk	–	–	–
9	20+5	–	–	Low risk	–	–	–
10	22+5	–	Right umbilical vein	–	–	AC	Normal
11	22+0	–	Polyhydramnios	Low risk	–	AC	Copy number triplication of 15q11.1q13.2 Copy number duplication 15q13.2q13.3
12	19+6	DORV	–	Low risk	–	CVS	Normal
13	20+1	–	–	Low risk	–	–	–
14	25+6	Coarctation	–	Low risk	Low risk	–	–

15	21+1	–	–	Low risk	Low risk	–	–
16	20+4	Coarctation	Tracheoesophageal fistula †	Low risk	–	AC	Normal
17	28+5	Coarctation, VSD	–	Low risk	–	AC	Normal
18	20+2	–	Oligohydramnios	Low risk	–	–	–
19	32+1	Coarctation	–	Low risk	–	–	–
20	25+0	Coarctation	–	Low risk	–	–	–

Table 1: characteristics of all cases with bilateral superior vena cava. cffDNA – cell-free DNA test; HLHS-hypoplastic left heart syndrome; CVS – chorionic villous sampling; AC-amniocentesis; LGA – large for gestational age; FGR – fetal growth restriction; T18 – Trisomy 18; DORV- double outlet right ventricle; VSD-ventricle septal defect; † diagnosed only postpartum.

TABLE 2

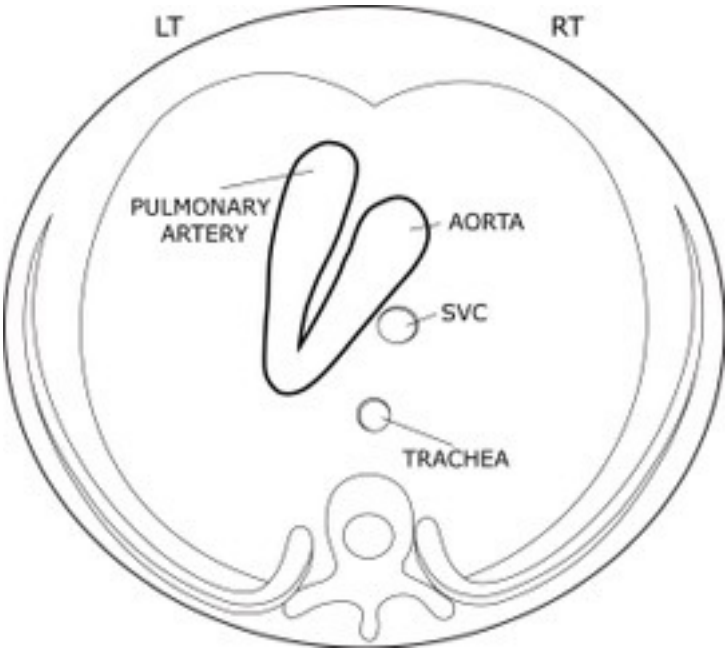
	Cases bilateral SVC n=20	Controls n=40	p-value*
Gap right SVC-aorta in mm, median (range)	2.4 (1.3-7.8)	1.1 (0.1-4.6)	< 0.001
Diameter right SVC in mm, median (range)	2.5 (1.1-4.4)	3.3 (1.7-6.1)	< 0.001
Diameter aorta in mm, median (range)	3.7 (1.3-6.1)	4.6 (2.1-7.5)	< 0.001

Table 2. Measurements of the gap between right superior vena cava (SVC) and the aorta, diameter of right superior vena cava and aorta in the three-vessel trachea view in fetuses with bilateral superior vena cava and gestational age matched controls

TABLE 3

	Regression Coefficient	Standard Error	p-value
Intercept	-2.561	0.661	< 0.001
Gestational age (weeks)	0.135	0.034	< 0.001
Bilateral SVC without heart anomalies	1.516	0.309	< 0.001
Bilateral SVC with heart anomalies	2.543	0.412	< 0.001
Aorta diameter	-0.124	0.169	0.462
Right SVC diameter	0.193	0.162	0.233

Table 3. Coefficients from generalized estimating equation showing a significant positive association of gestational age and the presence of bilateral superior vena cava (SVC) with the distance between the aorta and the right SVC; Corrected Quasi Likelihood under Independence Model Criterion (QICC): 61.4.



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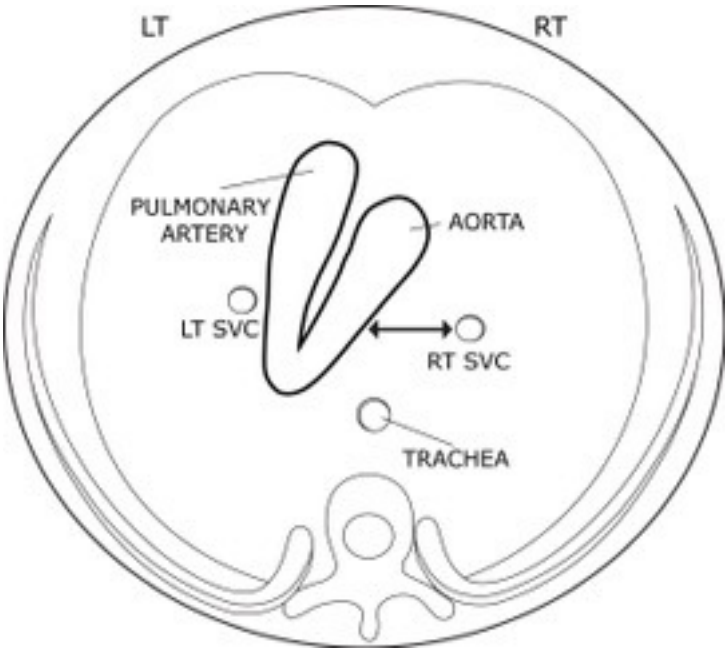

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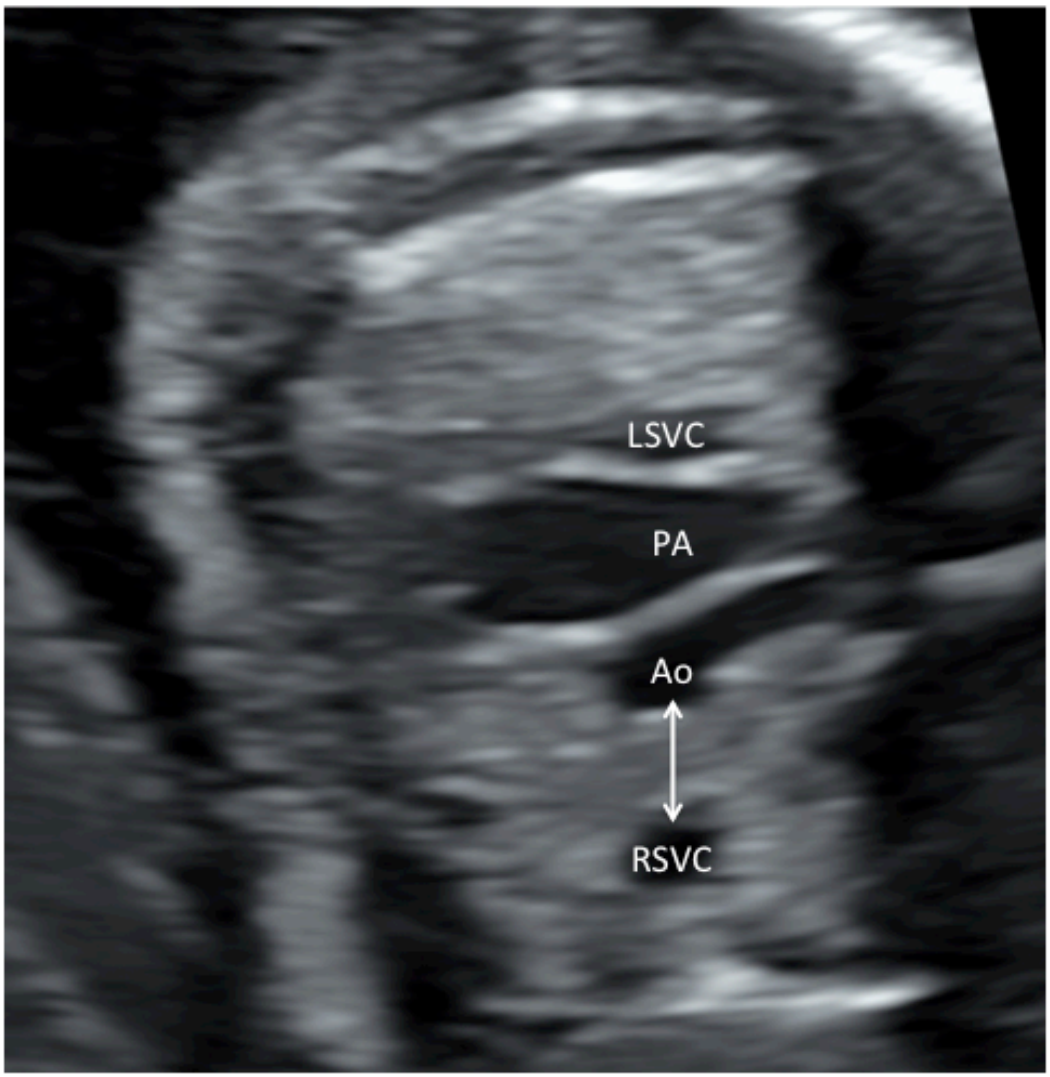

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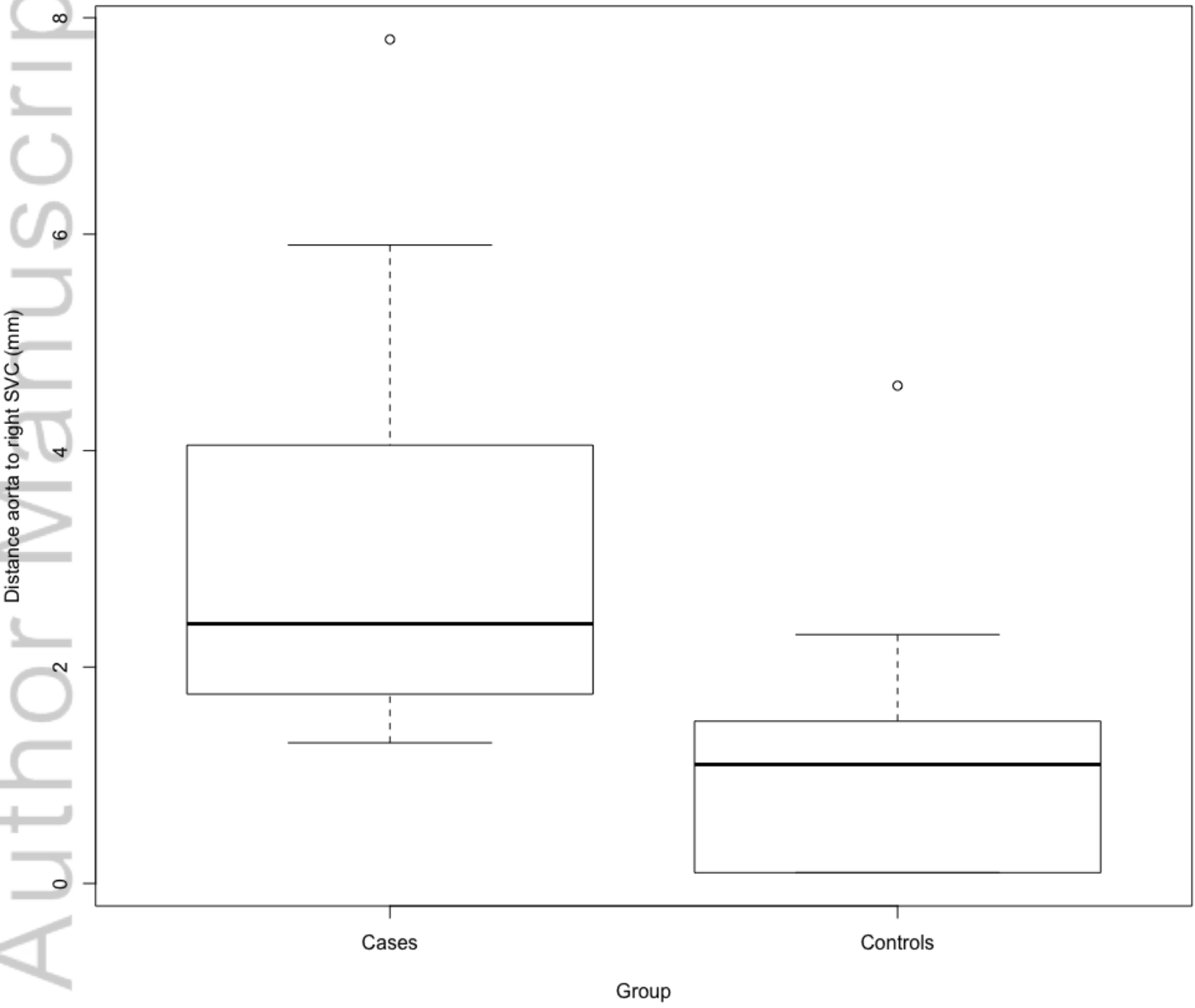

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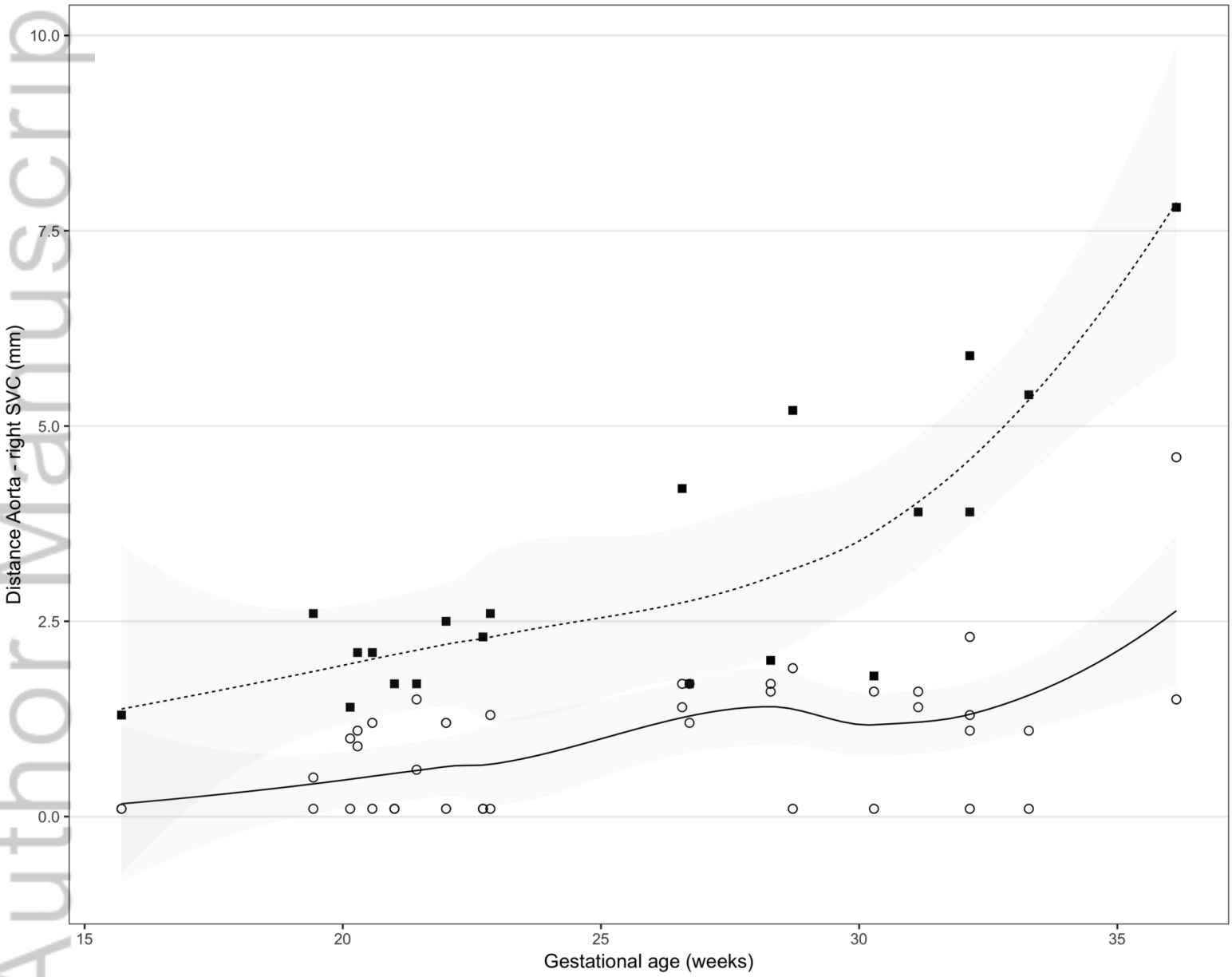
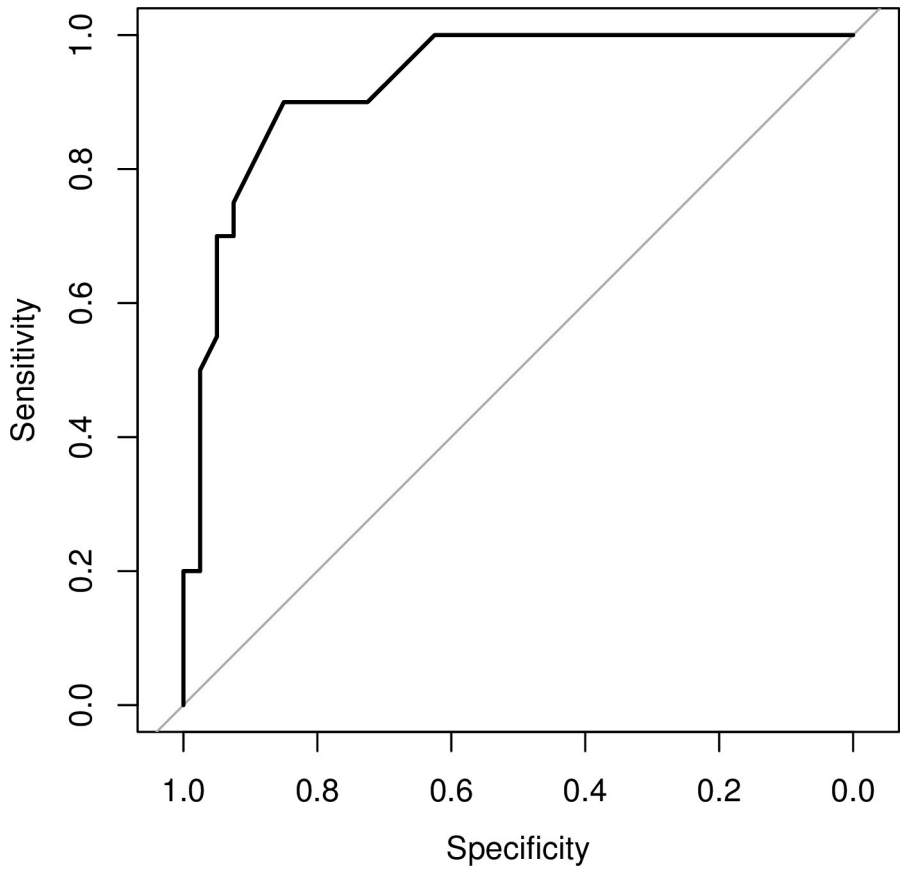


PD_5569_Figure3B.tiff



pd_5569_figure4.eps