The impact of an atrial septal defect on the progression of atrial tachypacing-induced atrial fibrillation in a Danish Landrace pig: A case report

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Due to comparable cardiac anatomy and electrophysiology to humans pigs are increasingly used as an experimental model for cardiovascular research [1,2]. The prevalence of congenital heart diseases in pigs is ~ 5%, with atrial septal defects (ASD) accounting for ~ 40% of all cases [3]. In humans, ASD is one of the most common congenital heart defects [4], which strongly increases the risk of atrial fibrillation (AF) [5] (Table 1). Although surgical closure of ASD reduces the prevalence of atrial arrhythmias, studies indicate that these patients still carry an increased long-term risk of developing AF (Table 1). Since pigs are increasingly used as AF models, the potential impact of congenital heart diseases should be taken into consideration. Here, we present a case of a Danish Landrace pig with ASD, identified in a study aiming to investigate the mechanisms of AF progression in pigs subjected to atrial tachypacing (license number 2020–15-0201–00616).

The 9-week old Danish Landrace pig (25 kg) pig did not show any signs of distress upon arrival and during the following week of acclimatization. No arrhythmias were detected in the baseline electrocardiogram (P-wave: 75 ms, QRS: 58 ms, QT-interval: 220 ms, PR: 129 ms, RR: 438 ms). As a part of the study protocol, the pig was sedated with an i.m. mixture of tiletamin (125 mg) / zolazepam (125 mg) / xylazine (125 mg) / ketamine (125 mg) / butorphanol (20 mg) / methadone (20 mg) and underwent a pacemaker surgery under general anesthesia (propofol[10 mg/kg/h]/fentanyl[5 µg/kg/h]), where two leads (TENDRIL STS, St. Jude Medical) were placed in the lateral wall of the right atrium (Fig. 1A) and connected to a neurostimulator (Itrel4, Medtronic). During placement of the atrial leads AF was induced, persisted for two hours post-surgery, and cardioverted to sinus rhythm spontaneously. AF recurrence was monitored by an implanted loop

recorder (Reveal LINQ, Medtronic). Post-operative recovery proceeded without any complications. The pig was randomized to receive 0.5 mg colchicine twice daily and 250 µg digoxin once daily for the rest of the experimental period.

One week following the surgery, atrial tachypacing at 420 bpm (~7Hz) was initiated. Within 6 h of tachypacing, the pig displayed reduced appetite and activity, which required a pause of tachypacing and a resting period of ~ 12 h. Re-initiation of tachypacing induced the same symptoms, which improved over time. Therefore tachypacing was continued as per study protocol. During the study period, the loop recorder detected 21 ventricular pauses with a duration of $\geq$ 3 sec, with a maximum of 4 sec and with the underlying rhythm being AF. One episode (pause of 3 sec) was observed by one of the researchers and was followed by syncopy. The pig did not have a lower ventricular rate compared to the rest of the study group, which was continuously monitored by the loop recorder. The pig developed flecainide-resistant self-sustained AF 11 days after the initiation of tachypacing, which is a much shorter time period compared to what has been reported before in similar AF pig models (~18 days) [6,7] and what we see in the current model (~20 days), thereby pointing to the evolution of an early AF-maintaining substrate.

After 41 days of tachypacing, the pig was included in a terminal follow-up study. During the time period of atrial tachypacing the pig did not show any clinical signs of discomfort. For the terminal follow-up study, the pig was sedated and kept under general anesthesia as described above. For the echocardiographic examination, an iE33 Echocardiography System scanner (Philips Medical Systems Netherlands) with a S5-1-xMATRIX array transducer (1–5 MHz) was

Table 1
Prevalence of supraventricular arrhythmias in patients with atrial septal defect.

	Study	Population	Intervention	Age at inclusion/ intervention (years)	Atrial arrhythmia prevalence	Follow-up time (years)
Early surgical repair	Oliver et al. (2002)[1]	192	Surgical repair	9.0 ± 7.2	15.6%	35
	Roos-Hesselink et al. (2003)[2]	135	Surgical repair	7.5 ± 3.5	6%	At age 35.8 ± 18
	Cuypers et al. (2013)[3]	135	Surgical closure	7.5 ± 3.5	16%	35
					mean: 12.5%	
Late surgical repair	Murphy et al. (1990)[4]	123	Surgical repair	26 ± 17	30.1 %	27–32
	Konstantinides et al. (1995)[5]	84	Surgical repair	56 ± 7	15.5%	8.9 ± 5.2
	Gatzoulis et al. (1999)[6]	213	Surgical repair	41 ± 14	13.6 %	3.8 ± 2.5
	Berger et al. (1999)[7]	211	Surgical repair	42.2 (range: 18.5–74.9)	14.7%	> 0.5
	Mantovan et al. (2003)[8]	136	Surgical closure	36.8 ± 17.8	11.7%	5.7 ± 3.0
	Nyboe et al. (2015)[9]	863	Surgical and transcathether closure	45.4 ± 0.5	41%	9.6
					mean: 21.1%	
No surgical repair	Konstantinides et al. (1995)[5]	95	Medical (digitalis, diuretics, nitrates)	52	16.8%	8.9 ± 5.2
	Oliver et al. (2002)[1]	94	None	47 ± 17	13.8%	Age matched with the surgical group
	Nyboe et al. (2015)[9]	305	None	69.4 ± 1.2	37%	Age matched with the surgical group
					mean: 22.5%	

[1]Oliver JM et al., Am J Cardiol. 2002; [2]Ross-Hesselink JW et al., Eur Heart J. 2003; [3]Cuypers JA et al., Heart. 2013; [4]Murphy JG et al., N Engl J Med. 1995; Konstantinides S et al., N Engl J Med. 1995; [6]Gatzoulis MA et al., N Engl J Med. 1999; [7]Berger F et al., Abb Thorac Surg. 1999; [8]Mantovan R. et al., Europace. 2003; [9]Nyboe C et al., Heart. 2015.
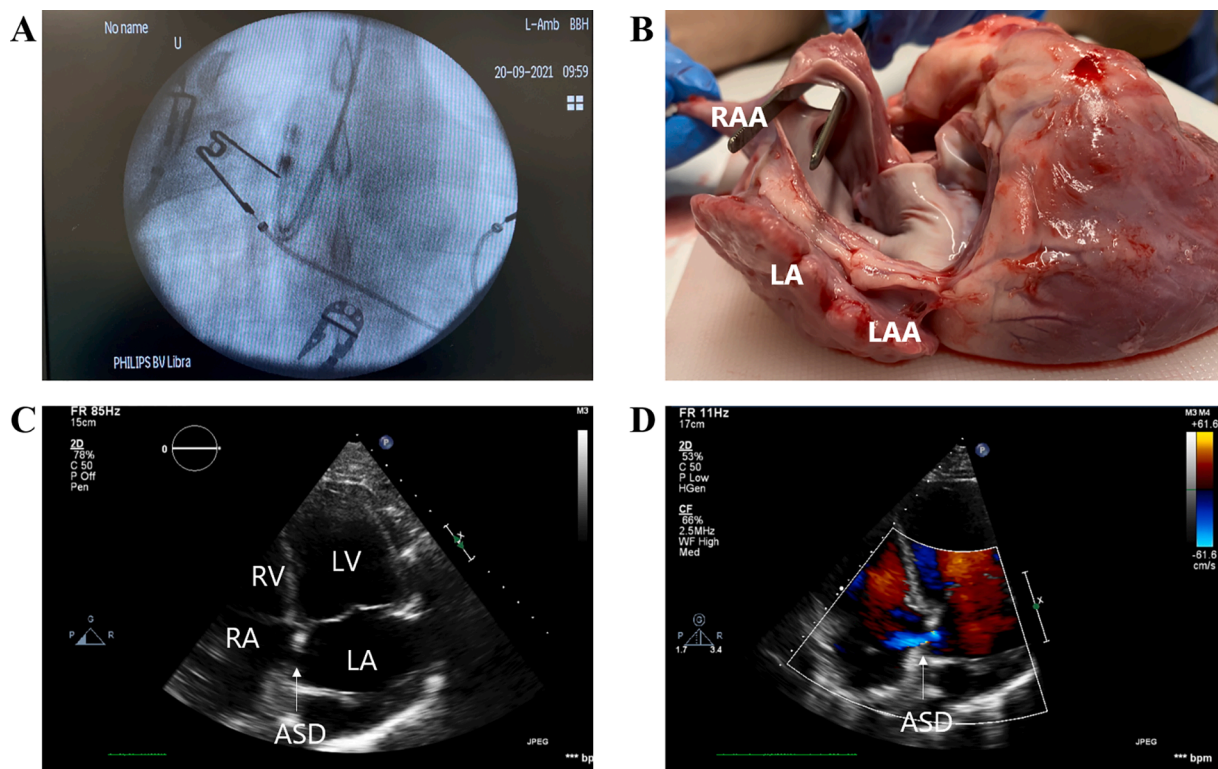

Fig. 1. A. Chest X-ray seen in the anterior-posterior view showing placement of the two leads in the lateral wall of the right atrium (RA). B. ASD confirmed by the post-mortem examination. C. Echocardiography (4 chamber view; B-mode) with elear defect of the atrial septum. D. Echocardiography with color-flow Doppler revealed left–right shunt. ASD: atrial septal defect: LA: left atrium, LAA: left atrial appendage, RAA: right atrial appendage, RV: right ventricle.

used. A surgical insertion sub-sternum was made in order to obtain a better image quality due to the size of the pig (48 kg). The echocardiographic examination revealed a 10 mm ASD (Fig. 1C and D) with left-to-right shunt. The pig had both a dilated left atrium (86 mL) and a dilated left ventricle (65 mm), along with reduced left ventricular ejection fraction (37%; calculated with biplane Simpson's method of discs), and a dilated right ventricle (48 mm) with compromised function (tricuspidal annular plane systolic excursion 12 mm). A moderate mitral valve regurgitation and a discreet aortic valve regurgitation were also identified. The presence of ASD was clearly validated during the post-mortem examination (Fig. 1B).

Previous work in humans with ASD showed that ASD is associated with chronic right atrial volume overload with subsequent right atrial stretch and remodeling [8]. Besides the right side of the heart being affected, studies in humans also demonstrated that the left atrium is also subjected to chronic stretch due to volume overload resulting in left atrial enlargement, which is associated with a greater susceptibility for AF in these patients [9]. These data suggest that ASD causes remodeling of both the right and left atrium, thereby creating a substrate for AF induction, maintenance, and progression. Of note, it appears that timing of ASD closure has a significant impact on the prevalence of AF, as closure in early childhood results in a lower prevalence of AF (~12%), while closure later in life is associated with a higher prevalence of AF (~21%) (Table 1). Thus closure of ASD should be performed as early as possible to prevent the induction and progression of AF and its clinical complications.

Our findings in this pig are consistent with clinical observations in humans with ASD. Compared to the rest of our study population (unpublished observations) and previous reports [6,7], the aggressive progression of AF in the presented pig is very likely promoted by ASD. This case demonstrates that undiagnosed congenital heart defects in pigs could be an important bias when performing cardiac research, particularly studying arrhythmias. Since congenital heart diseases are also reported in other large animals commonly used in cardiovascular research (dogs [10–12], goats [13], and horses [14]), diagnostic tools to detect congenital heart defects should be considered [15]. In humans echocardiography is the most common diagnostic tool for congenital heart diseases. However, for research purposes, echocardiography is not used routinely in such settings, as the technique requires appropriate equipment and trained staff. Thus, there is a clear unmet need to develop appropriate tests and detection methods of congenital heart defects in animal models of cardiac diseases.

In conclusion, the presented animal case indicates that ASD may contribute to development of an arrhythmogenic substrate for AF development, consistent with clinical observations in humans. Although congenital heart defects in animals likely increase the variability of study outcome, they could also provide a unique opportunity to study the complex interplay between congenital heart diseases and cardiac arrhythmias.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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