

# Interventional creation of an atrial septal defect and its impact on right ventricular function: An animal study with the pressure-volume conductance system

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## Abstract

**Background:** *The aim of our study was to assess the suitability of different interventional techniques to create an atrial septal defect (ASD) and to evaluate the short-term effects of right ventricular (RV) volume overload on RV contractility in the growing swine.*

**Methods:** *Thirteen ASD and six control animals were studied. An ASD was created by balloon dilatation (BD) of the fossa ovalis ( $n = 4$ ) or by implantation of a multi-perforated Amplatzer Septal Occluder ( $n = 4$ ) or a patch-less nitinol device ( $n = 5$ ). After 4.8 (3.9–6.0) weeks, the amounts of left-to-right shunting ( $Qp/Qs$ ) and RV contractility (end systolic elastance —  $Ees$ ) were assessed.*

**Results:** *In the ASD group, a significant left-to-right shunt could be documented ( $Qp/Qs$   $1.5 \pm 0.4$ ). However, a shunt was absent in the BD subgroup ( $Qp/Qs$   $1.1 \pm 0.1$ ). In animals with devices implanted, a significant relationship between the post-mortem ASD area and  $Qp/Qs$  was found ( $r = 0.68$ ,  $p < 0.05$ ). Compared to controls, RV contractility was not significantly impaired at rest and during dobutamine in ASD animals ( $Ees$ :  $0.40 \pm 0.20$  vs  $0.54 \pm 0.12$  and  $0.75 \pm 0.29$  vs  $1.04 \pm 0.24$  mm Hg/mL,  $p = NS$  for both).*

**Conclusions:** *Device implantation is necessary to create a patent ASD resulting in significant left-to-right shunting. In an experimental ASD model, a five week period of chronic RV volume overload does not alter RV contractility significantly. (Cardiol J 2011; 18, 3: 289–296)*

**Key words:** atrial septal defect, right ventricular volume load, right ventricular function

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## Introduction

Many congenital heart lesions are associated with long-standing right ventricular (RV) volume overload, and it has become apparent that RV volume overload can lead to irreversible RV dysfunction later in life [1, 2]. RV volume overload can be caused by pulmonary regurgitation, which has been found to be the major determinant of long-term outcome in patients after repair of tetralogy of Fallot [3]. Clinical and experimental data suggest that, in the presence of pulmonary regurgitation, RV dysfunction ensues early in life [4, 5].

RV volume overload can also be caused by left-to-right shunting across an atrial septal defect (ASD). In these patients, RV reverse remodeling with normalization of RV volumes is well documented for pediatric and adult patients, and normal long term prognosis can be achieved so long as ASD closure is performed within the first two decades of life [6, 7]. However, no data exists about the presence of any early RV dysfunction in the presence of an ASD. To answer this question, we decided to develop an animal model of RV volume overload to investigate the early effects of atrial right-to-left shunting on load independent RV myocardial function (i.e. contractility) using the pressure-volume conductance system in the growing swine. Furthermore, we sought to compare the suitability of different interventional techniques to create a patent and significant atrial septal communication.

## Methods

### Study protocol

Nineteen pigs (German Landrace) were enrolled in the study. All animals underwent two experimental cardiac catheterization studies, including an initial experiment (cardiac catheterization study 1) with full hemodynamic assessment with or without creation of an ASD (ASD group and control group, respectively). A second cardiac catheterization study was performed a median of 4.8 (3.9–6.0) weeks later, again with hemodynamic assessment and RV function analysis using the pressure-volume conductance system (cardiac catheterization study 2). The protocol is summarized in Figure 1. The mean animal weight at the first study was  $25.2 \pm 1.0$  kg and had increased to  $40.0 \pm 6.2$  kg at the final experiment, with no difference between groups.

The treatment of the animals followed the guidelines in the Guide for the Care and Use of Laboratory Animals. The protocol was approved by

the animal research committee of the Christian-Albrechts-University of Kiel, Germany (reference number: V 742-72241.121-24).

### Cardiac catheterization study 1

This initial study was performed under sedation with the animal breathing spontaneously. Sedation was initiated with the use of azaperone (2 mg/kg IM) and maintained with ketamine (1–2 mg/kg IV) given on demand. Venous and arterial punctures were performed under local anesthesia.

**Creation of an atrial septal defect.** In 13 animals ('ASD group'), an ASD was created by balloon dilatation (BD) of the fossa ovalis using a 24 mm balloon catheter (AGA Medical Corporation, Plymouth, MN, USA). In four animals, no additional intervention was performed ('BD group'). In another four pigs, a custom-made modified Amplatzer Septal Occluder with a 10 mm waist containing four 5 mm holes (Prof. Kurt Amplatz, AGA Medical Corporation, Plymouth, MN, USA) was placed in the defect ('Amplatz group'). In an additional five animals, a self-made device cut from a single nitinol tube (Dr. Franz Freudenthal, La Paz, Bolivia) was implanted ('SM group'). This device contains five nitinol struts that after deployment form into two retention discs with a central 15 mm waist to self-centre in the defect.

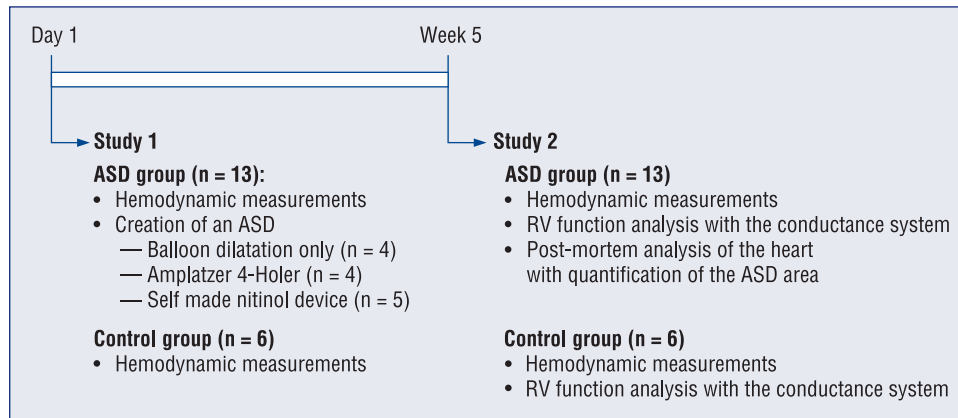
A group of six pigs served as controls ('control group'). These animals were age matched with the ASD group and underwent the first cardiac catheterization study solely to obtain hemodynamic data (Fig. 1).

**Hemodynamic measurements.** Cardiac pressures were measured with catheters connected to a fluid-filled pressure transducer. Pressures were measured in the right atrium, RV and main pulmonary artery. Blood samples were taken for oximetry from the superior (SVC) and inferior vena cava (IVC), the main pulmonary artery and the femoral artery. The ratio of pulmonary to systemic blood flow ( $Q_p/Q_s$ ) was calculated according to the formula:

$$Q_p / Q_s = \frac{SatArt - SatMV}{SatPV - SatPA}$$

where SatArt is the arterial oxygen saturation, SatMV is the mixed venous saturation, SatPA is the pulmonary artery oxygen saturation and SatPV is the pulmonary venous oxygen saturation. SatPV was assumed to be similar to SatArt or 98% in case SatArt was lower than this and normal pulmonary gas exchange could be documented. SatMV was calculated according the formula:

$$SatMV = (SatSVC + SatIVC) / 2$$



**Figure 1.** Study protocol; ASD — atrial septal defect; RV — right ventricular.

where SatSVC and SatIVC are the oxygen saturation in the SVC and the IVC, respectively.

### Cardiac catheterization study 2

This study was performed under general anesthesia. Anesthesia was initiated with azaperone (2 mg/kg IM) and propofol (4–6 mg/kg IV). After intubation, the animals were mechanically ventilated with room air using a volume-controlled ventilator (Siemens Servo 900C, Siemens AG, Erlangen, Germany). General anesthesia/analgesia was maintained with propofol (10–20 mg/kg/h IV) and fentanyl (6–8  $\mu\text{g}/\text{kg}/\text{min}$  IV).

**Conductance study.** Once hemodynamic data similar to that in study 1 was collected, including Qp/Qs calculation, a 4 F combined pressure-conductance catheter with 12 electrodes (CD Leycom, Zoetermeer, The Netherlands) was placed in the RV via the inferior caval vein in order to acquire RV pressure-volume loops. Pressure-volume signals were displayed online and digitized at a sample rate of 250 Hz (CFL 512, CD Leycom, Zoetermeer, The Netherlands). The pressure signal was calibrated with a standard calibration pulse from the amplifier (Sentron, Roden, The Netherlands). Conductance derived RV volume was calibrated for blood resistivity, gain factor  $\alpha$  and parallel conductance using thermodilution for cardiac output measurement and venous hypertonic saline injections [8, 9]. A 35 mm latex balloon catheter (AGA Numed, Hopkinton, NY, USA) was placed at the junction of the IVC and the right atrium and prepared to modify preload. Pressure volume data was recorded for 10–15 s with the respirator temporarily interrupted at end expiration. Pressure and volume signals were collected along with the ECG during steady state conditions and progressive vena caval occlusion to generate pressure-volume

loops over a wide range of filling pressures. Measurements were repeated at the end of a ten minute infusion of 10  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine. All data acquisition runs were repeated in triplicate and all runs containing premature ventricular contractions were excluded from analysis. Volume calibrations were performed at baseline and during dobutamine infusion.

**Post-mortem analysis of ASD size.** At the end of study 2, the animals were euthanized by an intravenous injection of 40 mL potassium chloride, and the heart was then excised. The patency of the atrial septum was evaluated and the size of the defect was quantified from digital images by digital planimetry using standard software (Adobe Photoshop 9.0, Adobe Systems Inc, San Jose, CA, USA).

### Calculations

Analysis of pressure volume loops was performed with custom-made software (Circlab 2008). Steady state hemodynamic data was calculated from pressure-volume loop recordings at baseline and after dobutamine infusion as means of all beats during a ten-second period.

Heart rate, cardiac output, stroke volume, end diastolic volume (EDV) and end systolic volume (ESV), RV ejection fraction (EF), end systolic and end diastolic pressure (ESP and EDP), maximal and minimal rate of RV pressure change ( $dP/dt_{\text{max}}$ ,  $dP/dt_{\text{min}}$ ) were analyzed. The time constant of relaxation ( $\tau$ ), reflecting the early active relaxation process, was calculated as the time constant of monoexponential pressure decay during isovolumic relaxation. The isovolumic period was defined as the period between the time point of  $dP/dt_{\text{min}}$  and the time point at which  $dP/dt$  reached 10% of the  $dP/dt_{\text{min}}$  value. Stroke work (SW) was calculated as the area enclosed by the pressure-volume loop.

Indices of systolic and diastolic function were derived from pressure-volume loops recorded during the preload reduction maneuver. For systolic function, we determined end systolic elastance ( $E_{es}$ ) as the slope of the end systolic pressure-volume relationship (ESPVR: ESP vs ESV) and the slope ( $Mw$ ) of the preload recruitable stroke work relation (PRSW; SW vs EDV). Diastolic stiffness ( $E_{ed}$ ) was determined as the slope of the end diastolic pressure-volume relationship (EDPVR: EDP vs EDV). These slopes are regarded as the optimal load-independent indices of intrinsic systolic ( $E_{es}$ ) and diastolic ( $E_{ed}$ ) ventricular function, reflecting contractility and lusitropy, respectively [10, 11].

All functional data was evaluated by an investigator blinded to the group affiliation of the respective animal.

### Statistical analysis

Differences in baseline and dobutamine hemodynamic and functional parameters between the control group and the ASD group were analyzed using an unpaired Student's  $t$ -test. The effects of dobutamine infusion on hemodynamic parameters were analyzed for each group using a paired Student's  $t$ -test. Comparison of Qp/Qs and ASD size between the three different subgroups of the ASD group were made by a Kruskal-Wallis test. If the Kruskal-Wallis test yielded a  $p < 0.05$ , *post-hoc* pairwise comparison of subgroups was performed using the Wilcoxon test. Univariate regression analyses were used to assess associations between continuous variables.

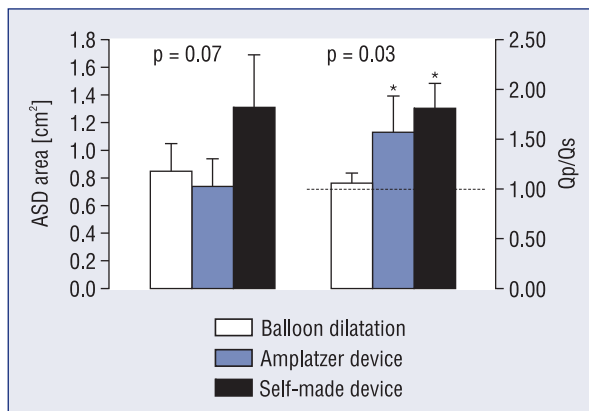
A  $p$  value  $< 0.05$  was considered statistically significant except for within- and between-group comparisons of baseline and dobutamine hemodynamic and functional data, where the significance level was adjusted to  $p < 0.003$  as the effects on 15 parameters were tested.

## Results

### ASD area and Qp/Qs

The data on ASD area and Qp/Qs for the three subgroups of the ASD group is set out in Figure 2.

Overall, in the ASD group, the initial experiment resulted in a significant left-to-right shunt with an increase in Qp/Qs from  $1.0 \pm 0.2$  to  $1.5 \pm 0.4$  at the second study ( $p < 0.001$ ). However, BD of the fossa ovalis alone (BD group) failed to induce a significant left-to-right shunt, even though a considerable defect was present in these animals on post-mortem examination (Fig. 3). The ASD area in the BD group was similar to that of the Amplatzer



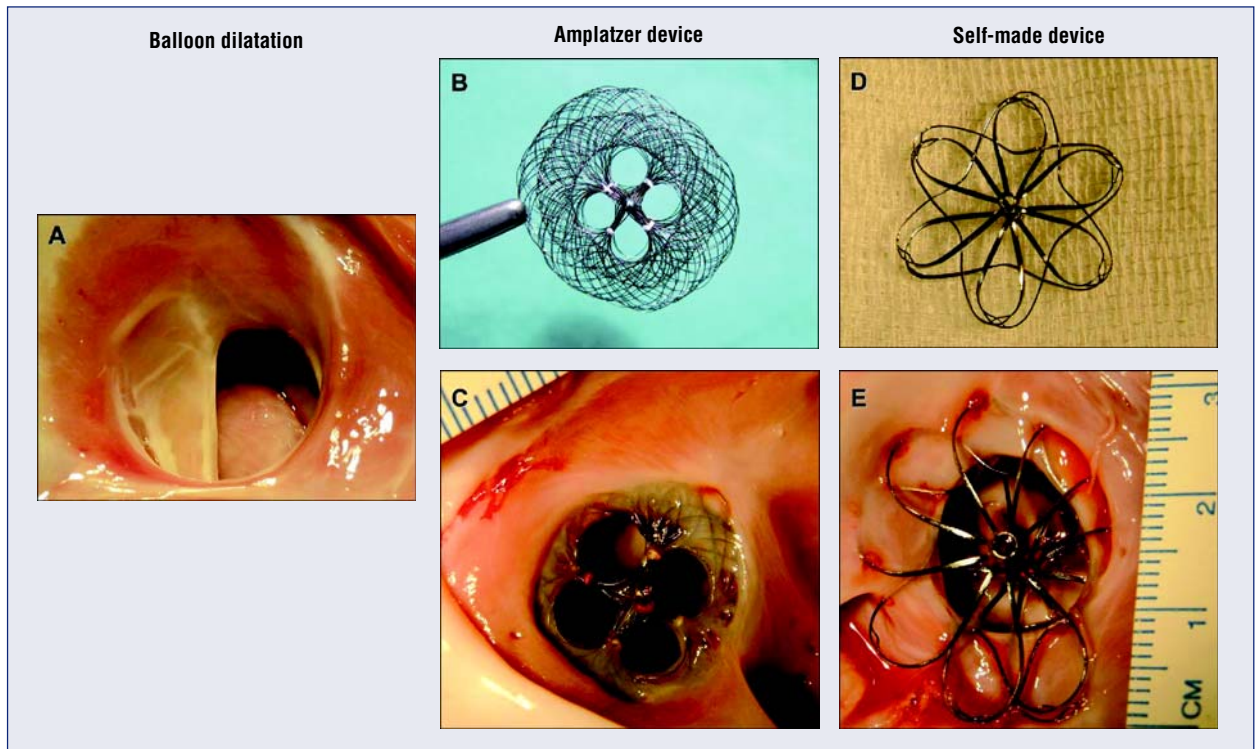
**Figure 2.** Atrial septal defect (ASD) area and Qp/Qs. Balloon dilatation only (white column) failed to produce a significant left-to-right shunt, although a considerable defect was visible on post-mortem inspection of the interatrial septum. The largest defect (and correspondingly the largest shunt) was achieved by implantation of the self-made, patch-less nitinol device (black column). The grey dotted lined represents a Qp/Qs of 1.0 indicating the absence of any intracardiac shunting; \* $p < 0.05$  Amplatzer and SM group vs BD group on *post-hoc* pairwise comparison of subgroups using the Wilcoxon test.

group, but only in the latter could a significant left-to-right shunt be documented by oximetry. The group of animals with a self-made device (the SM group) had the largest ASD area on post-mortem analysis and correspondingly the largest left-to-right shunt.

There was a significant linear relationship between the post-mortem ASD area and Qp/Qs at the final experiment when excluding the animals from the BD group from this analysis ( $r = 0.68$ ;  $p < 0.05$ ).

### ASD morphology

Gross examination of the implanted devices revealed unobstructed holes of the Amplatzer device and no obstruction of the meshwork of the self-made device, with only minimal intimal hyperplasia and without any superficial deposition of thrombus material. Full endothelialization of the Amplatzer device was obvious on macroscopic examination. The metal struts of the self-made nitinol device partly appeared uncovered by endothelium (Fig. 3). The defect area in the Amplatzer group was  $0.75 \pm 0.2$  cm<sup>2</sup>, exactly in the range of the expected area of four 5 mm holes, which is 0.78 cm<sup>2</sup>. This result indicates that no significant intimal hyperplasia obstructed the holes of the device. With an area of  $1.31 \pm 0.38$  cm<sup>2</sup>, the defects were largest in the SM group, but considerably smaller than the area



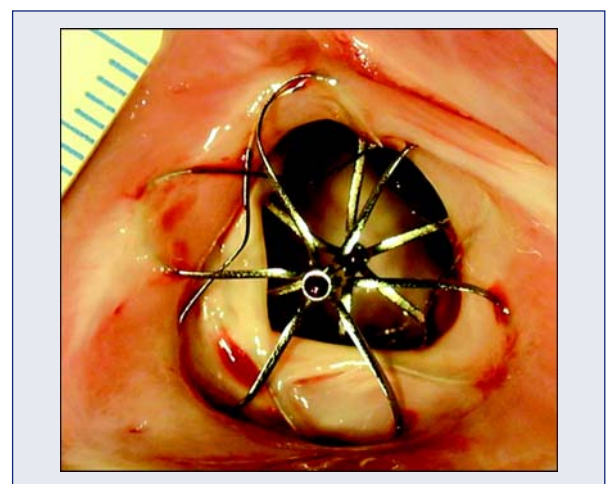
**Figure 3.** Atrial septal defect (ASD) devices and morphology. Creation of an ASD with balloon dilatation of the fossa ovalis only (A) and by implantation of custom-made Amplatzer device (B, C) or a patch-less self-made nitinol device (D, E). Both devices remained patent, creating a significant left-to-right shunt and no intimal hyperplasia was present on macroscopic inspection 4.8 weeks after implantation.

theoretically achievable by a device with a 15 mm waist, which is 1.77 cm<sup>2</sup>. This difference, and the wide scatter of defect area in the SM group (ranging from 0.91 to 1.64 cm<sup>2</sup>), indicate that this device does not allow an accurate prediction of the post-procedural ASD size. The variability in ASD size observed after implantation of the SM device results from the fact that in some cases the rim of the defect was not fully clamped by the waist of the device (Fig. 4).

### Hemodynamics and RV function

RV hemodynamic and functional parameters at baseline and during dobutamine infusion are given in Table 1.

Creation of an ASD with induction of significant left-to-right shunt did lead to a mild increase in EF in the ASD group, both at baseline and during dobutamine infusion. However, this increase only mirrors a non-significant increase in SV corresponding with a non-significant decrease in ESV in the ASD group. As heart rate tended to be lower in the ASD group under both conditions, cardiac output was similar between control animals and those with an ASD.



**Figure 4.** Right atrial aspect of a self-made device implanted to create a persisting atrial septal defect. The rim of the defect was not fully clamped by the waist of the device, resulting in the smallest defect area in the SM group of 0.91 cm<sup>2</sup>.

The ESP was mildly lower in the control group at baseline but not during dobutamine infusion. The EDP tended to be lower in the ASD group under dobutamine infusion only.

**Table 1.** Hemodynamics and indices of right ventricular function.

	Control			ASD			ASD effect — p		
	Baseline	Dobutamine	Dobutamine effect (%)	Baseline	Dobutamine	Dobutamine effect (%)	Baseline	Dobutamine	Dobutamine effect
HR [1/min]	98 ± 14	145 ± 11**	47.4 (49)	86 ± 15	134 ± 24**	48.2 (56)	0.14	0.32	0.93
EDV [mL]	106.4 ± 27.1	86.7 ± 25.1	-19.7 (19)	101.0 ± 29.2	77.3 ± 24.9*	-23.7 (23)	0.71	0.47	0.77
ESV [mL]	58.4 ± 16.0	37.7 ± 14.5**	-20.7 (35)	47.3 ± 19.5	24.3 ± 16.4**	-23.0 (49)	0.29	0.11	0.81
SV [mL]	49.2 ± 14.7	51.4 ± 13.6	2.2 (4)	55.4 ± 13.0	58.2 ± 18.3	2.8 (5)	0.38	0.43	0.93
EF [%]	46 ± 8	60 ± 8*	14.5 (32)	56 ± 8	75 ± 13**	19.2 (34)	0.02	0.02	0.43
Cardiac output [L/min]	4.8 ± 1.6	7.4 ± 1.9*	2.6 (54)	4.8 ± 1.4	7.8 ± 2.6**	3.0 (63)	0.96	0.79	0.70
ESP [mm Hg]	23 ± 3	32 ± 5**	9.0 (39)	17 ± 5	26 ± 8**	9.0 (53)	0.03	0.08	0.64
EDP [mm Hg]	11 ± 2	9 ± 3	-2.0 (18)	8 ± 5	3 ± 5**	-5.0 (63)	0.07	0.01	0.07
SW [mm Hg × mL]	958 ± 388	1512 ± 398*	554.0 (58)	989 ± 265	1808 ± 786**	819.0 (83)	0.84	0.40	0.35
dP/dt <sub>max</sub> [mm Hg/s]	381 ± 66	959 ± 105**	578.0 (152)	413 ± 12	1025 ± 309**	612.0 (148)	0.53	0.62	0.75
dP/dt <sub>min</sub> [mm Hg/s]	302 ± 65	595 ± 115**	293.0 (97)	297 ± 83	553 ± 271**	256.0 (86)	0.90	0.72	0.71
τ [ms]	41 ± 5	31 ± 11	-10.5 (25)	44 ± 10	32 ± 8**	-12.2 (28)	0.47	0.82	0.69
Ees [mm Hg/mL]	0.54 ± 0.12	1.04 ± 0.24*	0.5 (93)	0.40 ± 0.20	0.75 ± 0.29*	0.4 (88)	0.19	0.11	0.58
Mw [mm Hg]	16.6 ± 8.1	27.3 ± 5.9*	10.7 (64)	14.8 ± 5.0	34.7 ± 11.7**	19.9 (134)	0.57	0.17	0.10
Eed [mm Hg/mL]	0.26 ± 0.22	0.26 ± 0.21	0.0 (0)	0.21 ± 0.15	0.16 ± 0.10	-0.05 (24)	0.57	0.23	0.69

ASD — atrial septal defect; HR — heart rate; EDV — end diastolic volume; ESV — end systolic volume; SV — stroke volume; EF — ejection fraction; ESP — end systolic pressure; EDP — end diastolic pressure; SW — systolic stroke work; Ees — end systolic elastance; Mw — preload recruitable stroke work; Eed — diastolic stiffness. Dobutamine changes vs baseline: \* p < 0.05; \*\* p < 0.003. The significance level of within- and between-group comparisons of baseline and dobutamine hemodynamic and functional data had to be adjusted to p < 0.003 in order to account for multiple testing of 15 parameters

Load-dependent indices of RV function such as  $dP/dt_{max}$  and SW increased similarly with dobutamine in both groups.

The time constant of isovolumic relation was also similar between groups during baseline and dobutamine recordings.

The load independent indices of RV myocardial contractility,  $Ees$  and  $Mw$ , increased similarly in both groups with dobutamine infusion. Comparison of these indices at both conditions did not reveal any significant difference between control and ASD animals.

There was no correlation between the amount of left-to-right shunting ( $Qp/Qs$ ) and the indices of load independent RV function in the group of animals with an ASD ( $Qp/Qs$  vs  $Ees$ :  $r = 0.27$ ,  $p = 0.25$ ;  $Qp/Qs$  vs  $Mw$ :  $r = 0.29$ ,  $p = 0.37$ ). Such a relationship was also absent when calculated for animals with a  $Qp/Qs$  greater than 1.5, even though a trend towards an impaired RV end systolic elastance ( $Ees$ ) with increasing  $Qp/Qs$  was found in this subgroup ( $Qp/Qs$  vs  $Ees$ :  $r = -0.50$ ,  $p = 0.08$ ).

Diastolic stiffness,  $Eed$ , was similar between groups at both conditions and did not change with dobutamine infusion.

## Discussion

In this experimental animal study, we demonstrated that device implantation is necessary to attain significant shunting across an interatrial communication produced by BD of the fossa ovalis. We also found that RV volume overload from atrial left-to-right shunting does not alter right heart hemodynamics or RV contractility within a period of about five weeks.

### Technique of ASD creation

The magnitude and direction of flow through any ASD depend on the size of the defect and the relative diastolic filling properties of the left and right ventricles. Looking at the ASD size in the three subgroups of animals in whom an ASD was created, one would therefore expect a significant left-to-right shunt also in the group of animals who received a BD solely of the fossa ovalis. The post-mortem ASD area in this group was comparable to those animals in which a perforated Amplatzer device was implanted (Fig. 2). The fact that even so no shunt across the septum could be demonstrated by oximetry about five weeks after the intervention may indicate a discrepancy between the defect size on post-mortem analysis, and the effective defect size in the beating heart of animals with a defect

resulting from BD alone. ASD size does vary throughout the cardiac cycle with a maximum at end systole and a minimum at end diastole [12, 13]. A more slit-like and unsplinted defect may well be small or nearly closed during diastole, when flow across the defect would be maximal [14].

Certain congenital heart defects require the creation of an unrestrictive ASD to relieve atrial hypertension, to maintain systemic cardiac output, or to achieve adequate atrial mixing to improve systemic oxygen saturation. We describe an interventional method to create such defects and show that device implantation is mandatory in case a defect is desired that allows significant left-to-right shunting.

After a period of five weeks, we found the perforated Amplatzer device fully endothelialized and without significant intimal hyperplasia. As opposed to the SM device, the area of the defect created by the Amplatzer device was nearly exactly that theoretically expected from its design. This finding suggests that this device is particularly suitable in producing a permanent ASD of a predictable size. The Amplatzer device is a modified Amplatzer Septal Occluder with a similar, well-established implantation procedure [15]. The design of this device would also allow alternative modifications with holes of varied number and size.

Our self-made nitinol device did not seem to be entirely covered by endothelium on gross inspection. However, a thin but complete endothelial layer on the surface of the implant might well have been detectable histologically [16].

### RV function in the presence of atrial left-to-right shunting

Our study was initiated primarily to establish a practical experimental model of RV volume overload; in this respect, a significant left-to-right shunt on atrial level should be created. This goal was achieved in the ASD group with a mean  $Qp/Qs$  of  $1.5 \pm 0.4$  after a five week follow-up period.

The amount of this volume overload equals that of severe pulmonary insufficiency with a regurgitant fraction of 50%. However, no impact on RV contractility either at baseline or during dobutamine infusion could be found. This result is at odds with the effect of pulmonary insufficiency on the RV in a comparable animal model of the growing swine reported by Kuehne et al. [5]. Differences in study protocol are probably responsible for this. Firstly, the animals in our study were older and therefore heavier, with a weight of 25 kg at the beginning of the study as opposed to 13.9 kg. Secondly, the time period between the initial experiment with initial

tion of RV volume overload and the RV function study was considerably shorter (4.8 vs 12 weeks on average). This difference might well explain the absence of any impact of RV volume overload on RV contractility in our investigation. However, whether an extension of the follow-up period and a creation of an ASD earlier in life would result in a comparable impairment in RV contractility, or whether an RV responds fundamentally differently to volume overload resulting from pulmonary back-flow as opposed to an increased trans-tricuspid inflow remains to be elucidated by additional experiments.

### Limitations of the study

As the breed of swine used in our study is growing fastly, we chose a follow-up interval of only five weeks when planning the study. As discussed above, this interval might have been too short to detect any late impact of atrial left-to-right shunting on intrinsic RV function.

Nowadays, cardiac magnetic resonance imaging is the method of choice to determine RV volumetric data. We did not use this method in the present study and therefore cannot compare the volumes obtained by the conductance system to this gold standard. However, the conductance technique is regarded as the best available method to analyse load-independent ventricular function, which was the main intention of this study.

The conductance technique was developed to obtain pressure-volume loops in the more elliptically shaped left ventricle, and may be less accurate in the RV. Nevertheless, serial validation studies have shown that it can also be applied with accuracy in the RV [17, 18].

### Conclusions

The present study shows that BD of the fossa ovalis alone is not sufficient to create a persisting atrial communication leading to significant transseptal blood flow, and that device implantation is necessary as an additional procedure to achieve this goal. Furthermore, it shows that RV volume overload from atrial left-to-right shunting does not alter right heart hemodynamics or intrinsic RV function within a period of five weeks in an experimental model of the growing swine.

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The authors do not report any conflict of interest regarding this work.

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