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Occlusion of the Perimembranous Ventricular Septal Defect Using CERA® Devices

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Background: **High incidence of atrioventricular (AV) block has been the major limitation of percutaneous closure of perimembranous ventricular septal defect (PMVSD).** ***Methods***: **Prospective, multicenter, nonrandomized study including 55 patients who were submitted to 56 procedures from March 2010 to November 2010. Inclusion criteria were PMVSD with diameter $\geq$ 5 mm or if $\leq$5 mm with hemodynamic significance and age $\geq$ 1 year. Exclusion criteria were fixed pulmonary arterial hypertension and associated congenital heart disease needing surgical repair. Procedures were performed under general anesthesia and monitored by transthoracic echocardiography (TTE). The device choice was based on left ventricle (LV) angiography and on TTE images. PMVSDs were crossed by retrograde approach.** ***Results***: **Mean age was 9.3 ± 7.5 years, and mean weight was 29.1 ± 15.9 kg. Thirty-five (63.6%) patients were females. Mean pulmonary arterial mean pressure, mean LV diastolic diameter, and mean Q_p/Q_s were 24.0 ± 6.5 mm Hg, 43.0 ± 5.9 mm, and 2.2 ± 0.8, respectively. Associated nonsurgical malformations were present in 9 (16.3%) patients, and PMVSDs were multifenestrated in 16 (46.2%) cases. Mean PMVSDs diameter was 5.8 ± 1.8 mm by angiography and 6.8 ± 2.3 mm by TTE. New rhythm disturbance without clinical significance was observed in 29% of the patients and was reversible in 87.5%. After procedure, trivial residual shunt was present in 5 (8.9%) patients and moderate residual shunt in other 5 (8.9%). At late FU (mean of 298.7 ± 88.9 days), 91% of the patients had no residual shunts. Third-degree AV block and severe aortic regurgitation occurred in one patient each.** ***Conclusions***: **In this experience, PMVSD closure with CERA® devices showed to be safe and effective with low incidence of complications at immediate and mid-term FU.** © 2012 Wiley Periodicals, Inc.

Key words: congenital heart disease; percutaneous intervention; congenital septal defect

INTRODUCTION

Perimembranous ventricular septal defect (PMVSD) has always been a challenge to interventional cardiologists when there is no associated aneurysm formation. In the recent past, the Amplatzer® device for PMVSD was developed with an asymmetric design, and pediatric interventional cardiologists were optimistic about its value, especially with regard to the concerns about the aortic valve and its proximity to the device edges [1–4]. However, the reported experience has shown that incidence of atrioventricular (AV) block during mid and long-term follow-up was significant compared to surgery [5,6].

In this study, we present our experience in PMVSD closure of 55 patients using three different types of CERA® devices, which were all designed specifically to treat this defect.

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Conflict of interest: Nothing to report.

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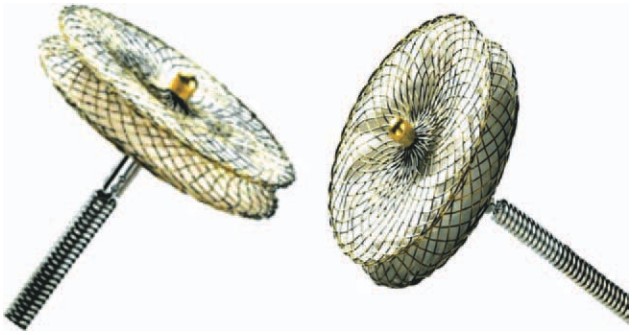

Fig. 1. Symmetric device—type 1. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

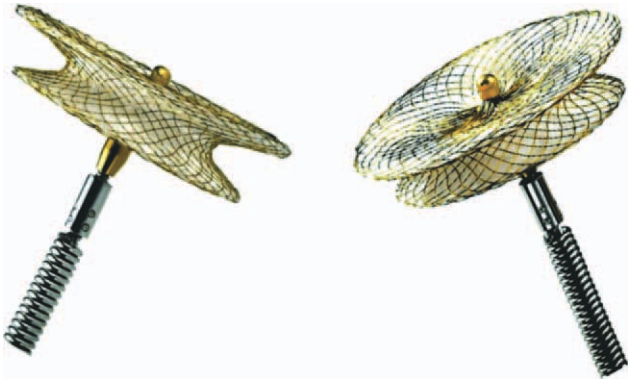

Fig. 2. Symmetric device with larger left disc—type 2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

METHODS

Study Design

Prospective, multicenter, nonrandomized study conducted between March and November, 2010, in two Brazilian Institutions (Hospital IMIP–Recife and Hospital Pequeno Príncipe–Curitiba) including patients with PMVSD deemed suitable for device closure. All patients were assessed clinically and with EKG and transthoracic echocardiography (TTE) during the hospital admission and at 1, 6, 12, 24, 36, 48, and 60 months after the procedure. All patients were given aspirin (5 mg/kg daily, whilst the adult patients $\geq$ 40 kg received 200 mg per day) and endocarditis prophylaxis for 6 months. Informed consent was obtained from the patients or their parents.

Inclusion Criteria

1. Patients who had PMVSD with or without aneurysm of the membranous septum, confirmed by TTE and/or transesophageal echocardiography (TEE), with left-to-right shunt, and without fixed pulmonary arterial hypertension.
2. PMVSD with diameter $\geq$ 5 mm or if <5 mm, with hemodynamic significance defined by $Q_p/Q_s > 1.5:1$ and/or left ventricle (LV) enlargement and/or elevation of right ventricular and pulmonary artery (PA) pressure.
3. Age $\geq$ 1 year.

Definitions

1. Successful procedure was defined as implantation of the device without major complications.
2. Major complications during or after the procedure were defined as presence of large residual shunt with the device in place, development of third degree AV block, severe aortic regurgitation, and/or death.
3. Residual shunt was defined as trivial (<1-mm color jet width), small (1–2-mm color jet width), moderate (2–4-mm color jet width), or large (>4-mm color jet width).
4. Minor complications during or after the procedure were defined as rhythm disturbance including incomplete right bundle branch block (IRBBB), left anterior fascicular block (LAFB), first or second-degree AV block or any other rhythm disturbance, groin hematoma from the puncture site, femoral arterial thrombosis, that could be resolved without surgery, device embolization that could be retrieved percutaneously, and/or presence of trivial, small, or moderate residual shunt with the device in place.

Characteristics of the CERA® (Lifetech) Prosthesis for PMVSD Closure

- Symmetric device—type 1—consists of self-expandable device with two symmetric discs containing a nitinol frame covered by ceramic coating (Fig. 1).
- Symmetric device with larger left disc—type 2—similar to the previous device, but with the right ventricular disc 5 mm larger than the central waist and the left ventricular disc 7.6 mm larger than the central waist (Fig. 2).
- Asymmetric device—type 3—self-expandable device with two asymmetric discs containing a nitinol frame covered with a ceramic coating. Each disc is 6 mm larger than the central waist. The left ventricular disc has a 1-mm gold marker, identifying its lower part (Fig. 3).

In all three devices, the distance between the discs is 3 mm, and the right ventricular discs carry the attachment mechanism, where the delivery cable is screwed on

Fig. 3. Asymmetric device—type 3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to the device. The inner parts of the nitinol frame, which includes the two discs and the central waist, are covered by ePTFE. Left and right disc diameters, waist diameter, waist length, and recommended sheath size of each one of the devices can be found in Tables I–III.

Implantation Technique

All the procedures were performed using intravenous and inhalation general anesthesia and were given antibiotic prophylactic doses. Femoral venous access was obtained with insertion of 5 or 6 Fr sheath, and 4 Fr sheath was inserted to the femoral artery. All patients received 100 U/kg of heparin and an additional dose, in case the procedure lasted more than 1 hr, according to the routine of each institution. Patients were maintained intubated during the procedure, and postprocedure recovery was performed according to the routine procedures.

The device choice was based on LV angiography in a cranial LAO projection and on TTE images.

The VSD was crossed by retrograde approach from the aorta to LV to RV using a 4 Fr JR or an internal mammary catheter, with a radiofocus (0.032″ × 260 cm) Terumo® guidewire. As far as possible, the VSD must be crossed with the guidewire, followed by the catheter. The guidewire was positioned in the PA, superior vena cava, or even in inferior vena cava. The operator must ensure that the guidewire has not crossing through tricuspid valve chordate tendinea by echocardiographic guidance. The guidewire was snared and withdrawn through venous sheath. A long delivery sheath, appropriate for the selected device, was passed over the guidewire from the femoral vein into the ascending aorta, and the dilator was withdrawn ~3–4 cm inside the sheath. Over the guidewire circuit, the delivery sheath, with the dilator still inside it, was positioned as near as possible to the LV apex. The dilator was then removed from the sheath, and the guidewire circuit was then broken. The delivery cable with the device screwed on its tip was passed through the delivery sheath. The distal disc was opened in the LV, and the whole system was withdrawn up to and against the LV orifice of the VSD. Once in correct position, the right ventricular disc was opened on the right ventricular side of the VSD, whilst checking the position of the device, the tricuspid and aortic valves by echocardiography and then the device was released.

TABLE I. Characteristics of the Symmetric Devices (Type 1)

Waist diameter	Right disc diameter	Left disc diameter	Waist lenght	Recommended sheath size
4	8	8	3	5F–6F
5	9	9	3	5F–6F
6	10	10	3	6F–7F
7	11	11	3	6F–7F
8	12	12	3	7F–8F
10	14	14	3	7F–8F
12	16	16	3	9F–10F
14	19	19	3	9F–10F
16	21	21	3	9F–10F
18	23	23	3	10F–12F
20	25	25	3	10F–12F
22	27	27	3	12F
24	29	29	3	12F

TABLE II. Characteristics of the Symmetric Devices with Larger Left Disc (Type 2)

Waist diameter	Right disc diameter	Left disc diameter	Waist lenght	Recommended sheath size
4	9	11.6	3	5F–6F
5	10	12.6	3	5F–6F
6	11	13.6	3	6F–7F
7	12	14.6	3	6F–7F
8	13	15.6	3	7F–8F
10	15	17.6	3	7F–8F
12	17	19.6	3	9F–10F
14	19	21.6	3	9F–10F
16	21	23.6	3	9F–10F
18	23	25.6	3	10F–12F
20	25	27.6	3	10F–12F
22	27	29.6	3	12F
24	29	31.6	3	12F

RESULTS

Demographic Characteristics

In both centers, a total of 56 procedures were performed in 55 patients. The mean age was 9.3 ± 7.5 (range from 1.1 to 51.2) years, and the mean weight was 29.1 ± 15.9 (range from 10 to 78) kg. Thirty-five (63.6%) patients were female.

Associate malformations were present in 9 (16.3%) of the patients; three (5.4%) patients had Down syndrome, one (1.8%) aortic coarctation (treated previously with a stent), and a bicuspid aortic valve and a

TABLE III. Characteristics of the Asymmetric Devices (Type 3)

Waist diameter	Right disc diameter	Left disc diameter	Waist lenght	Recommended sheath size
4	10	10	3	5F–6F
5	11	11	3	5F–6F
6	12	12	3	6F–7F
7	13	13	3	6F–7F
8	14	14	3	7F–8F
10	16	16	3	7F–8F
12	18	18	3	9F–10F
14	20	20	3	9F–10F
16	22	22	3	9F–10F
18	24	24	3	10F–12F
20	26	26	3	10F–12F
22	28	28	3	12F
24	30	30	3	12F

history of a previous episode of endocarditis, one (1.8%) with a 1.8-mm type A PDA (closed in the same procedure with a Flipper 3 × 3 coil); in one (1.8%) the VSD was residual after previous cardiac surgery, one (1.8%) had previous endocarditis, one (1.8%) had a subaortic membranous stenosis with systolic gradient of 22 mm Hg, and one (1.8%) had situs inversus totalis with apex dextroposition.

VSD Characteristics

The mean VSD diameter was 5.8 ± 1.8 (range from 3.2 to 11.7) mm by angiography and 6.8 ± 2.3 (range from 3.4 to 13.3) mm by TTE, both measured from the RV side. The VSD was single in 29 (52.7%) patients, multifenestrated with two holes in 12 (21.8%) and with three holes in 14 (24.4) patients. The mean Q_p/Q_s was 2.2 ± 0.8.

The mean pulmonary arterial mean pressure was 24 ± 6.5 (range from 13 to 40) mm Hg, and the mean LV diastolic diameter was 43 ± 5.9 (range from 30 to 56) mm measured by hemodynamic study and TTE, respectively.

Procedural Outcomes

Procedure success was achieved in 51 (91.0%) of 56 procedures. In one (1.8%) patient, a 51-year-old female, a 12-mm type 3 device was implanted, but because of a large residual shunt, was retrieved, and a 14-mm type 3 device was implanted. The device embolized to the right PA 12 hr later and was retrieved percutaneously, and a third device (type 2, 14 mm) was then implanted. This also had to be retrieved due to malposition and a large residual shunt, and the patient was sent to surgery. In other two (3.6%) patients, the devices were retrieved after implantation but before release, due to large residual shunts. Two (3.6%) patients had their procedures abandoned due to the development of third degree AV block during manipulation of the catheter and/or when the VSD was crossed.

Patients were discharged from hospital in a mean period of 24 ± 6 hr after the procedure.

Rhythm disturbances were the most common minor complication observed during and immediately after the procedure. IRBBB was already present in 17 (30.9%) patients before the procedure. Of these, two (3.6%) developed LAFB, one (1.8%) reverted to normal during procedure, and 14 (25.4%) patients continued to have IRBBB during longer-term follow-up. Five (9.0%) patients had LAFB before the procedure. One (1.8%) developed a transient second-degree AV block and IRBBB while in the catheter lab. EKG 30 days later continued to show IRBBB but reverted to normal and sinus rhythm at 90 days of follow-up. The remaining four (7.3%) patients maintained LAFB at long-term follow up. One (1.8%) patient, who had IRBBB + LAFB previously, developed an ectopic atrial rhythm during the procedure. He was discharged from the hospital 24 hr later with IRBBB + LAFB. His EKG 30 days later was normal. EKG before the procedure had shown an ectopic atrial rhythm in one (1.8%) patient, who developed IRBBB during PMVSD closure. He was discharged from the hospital 24 hr later, still with IRBBB. EKG at 30 days follow-up was normal.

From the patients who presented a normal EKG before procedure, three (5.4%) developed LAFB immediately after the procedure, which persisted at 90 days of follow-up. One (1.8%) patient developed first-degree AV block and four (7.3%) cases of RBBB after the procedure. All reverted to normal within the first 24 hr after the procedure.

Four days after discharge from the hospital, one (1.8%) patient developed third-degree AV block. The patient was treated with dexamethasone for 48 hr but intermittent third-degree AV block persisted. She received an epicardical pacemaker, and 1 month later, the EKG showed sinus rhythm.

Residual shunt was evaluated by angiography and/or by TTE immediately after the procedure. Forty-six (82.1%) patients had no residual shunt, five (8.9%) had a trivial residual shunt, and five (8.9%) a moderate residual shunt. These persisted at the discharge TTE 24 hr after the procedure.

One (1.8%) patient developed severe aortic regurgitation immediately after the procedure and was referred for surgery.

During the late follow-up of a mean of 298.0 ± 88.9 (range from 127 to 383) days, there were no deaths. There was no onset of new third-degree AV block. Of the five (8.9%) patients, who had trivial residual shunt immediately after the procedure, only one (1.8%) continued with the shunt. From the five (8.9%) patients

TABLE IV. Procedural Complications

	In hospital patients (%)	Late patients (%)
Minor complications		
Rhythm disturbance (except third degree AVB)	13 (23.5%)	3 (5.4%)
Groin hematoma	0	0
Femoral arterial thrombosis	0	0
Device embolization	1 (1.8%)	0
Trivial RS	5 (8.9%)	1 (1.8%)
Moderate RS	5 (8.9%)	4 (7.1%)
Major complications		
Third degree AVB	1 (1.8%)	1 (1.8%)
Severe AI	1 (1.8%)	0
Large RS	4 (7.2%) proc.	Unsuccessful proc.
Death	0	0

AVB, AV block; AI, aortic insufficiency; RS, residual shunt; Proc, procedures.

with moderate residual shunts, in one, there was no residual shunt and four (7.1%) continued with the same degree of shunting. In summary, 91% of the enrolled patients had no residual shunt in the late-clinical follow-up, which was confirmed by TTE. Additionally, the mean LV diastolic diameter decreased from 43 ± 5.9 mm to 38 ± 5.6mm (range from 25 to 53).

Table IV summarizes the minor and major complications observed among these patients.

DISCUSSION

The present analysis demonstrates the feasibility and safety of the percutaneous approach of PMVSD with the novel dedicated CERA® device, with high-acute success rate and low incidence of third-degree AV block up to the midterm follow-up.

The traditional treatment for VSD with hemodynamic significance is surgical repair, which was performed for the first time by Lillehei et al. [7] in 1954. In 1988, Lock et al. [8] published the first VSD closure using a transcatheter approach.

The first device specifically designed for PMVSD closure was the asymmetric Amplatzer® device, whose initial experience was reported in 2002 [1].

The largest experience with the Amplatzer® asymmetric device was published by Carminati et al. [9] in the European Register, where, for PMVSD closure, the main complication was third-degree AV block with an incidence of 5%.

Since then, isolated publications have reported on PMVSD closure using either the Nit Occlud® device or other devices not specifically designed for this purpose [9].

The CERA® asymmetric device presents at least three significant modifications compared to the

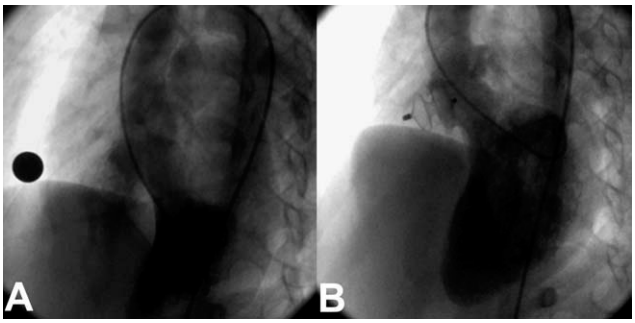

Fig. 4. A: Multifenestrated PMVSD associated with an aneurysm. B: PMVSD closed with a type 2 device.

Amplatzer® asymmetric prosthesis: first of all, the nitinol wire mesh from CERA® is covered by titanium nitride deposition, which seems to result in an earlier and more homogeneous endothelialization when compared with nitinol [10]. Furthermore, the distance from the waist to the inferior edge of the LV disc is 2.5 mm (1 mm less than in the asymmetric Amplatzer® device), and finally, the distance between the discs is 3 mm and not 1.5 mm (this modification is presented in all three types of PMVSD CERA® devices).

With the first and the second aforementioned modifications, the friction and the erosion of the devices edge against the His bundle are reduced, leading to a lower incidence of arrhythmia and probably less rhythm disturbances. Regarding to the third modification, the discs of the devices certainly apply a lower compression at the His bundle, and this may result in lower incidence of AV block.

In this study, we observed only one case (1.8%) of third-degree AV block, and, in this patient, the asymmetric device was not used. These device modifications may also explain the low incidence of third-degree AV block in the immediate and mid-term follow-up; however, it is important to have in mind that third-degree AV block may still occur during the long-term follow-up. The onset of a new rhythm disturbance was 29%, relatively low, without clinical significance, and reversible in the great majority of them (87.5%).

As in most new procedures, we should acknowledge the existence of a learning curve. For PMVSD closure using CERA® devices, even in experienced hands, the most difficult issue for the authors was to choose the ideal device for the appropriate type of the ventricular septal defect. As a result, 11 devices were initially not properly selected and needed to be replaced by the correct type and size.

An incidence of 5% of trivial and moderate residual shunts was observed in this study. At mid-term follow up, only one out of five patients had persistent trivial residual shunt by either TTE or TEE, and four of five patients had persistent moderate residual shunt. Of the

five patients who maintained residual shunt at 6-month TEE, four had multifenestrated PMVSD associated with an aneurysm (Figs. 4A and B). In these patients, it was impossible to close all the holes in trying to cover the inner part of the aneurysm with only one device, even when a device with a big left ventricular disc (type 2, CERA® device) was chosen. As multifenestrated PMVSDs have variable distances between the holes inside the aneurysmatic sac and these holes are located in different plans, implantation of two smaller devices inside the aneurysmatic sac may be a better strategy to close the left to right shunt completely.

In this study, situs inversus was not a technical problem for the procedure, as it was not the presence of an interinfundibular VSD. In this last one, with the impossibility to profile correctly the defect even during multiple angiographies, the TTE was a perfect guide to positioning both devices correctly in these cases.

One patient presented severe aortic regurgitation and was referred for surgery. During open-heart surgery, 7 days after the procedure, it was noticed that the device was in good position, but a 3-mm perforation was observed in the noncoronary leaflet caused probably by trauma. The perforation was repaired with a direct suture, and the device was left in place, because, in the surgeon opinion, it was away from the aortic valve leaflets. The patient was discharged from hospital after 7 days without aortic regurgitation and with the device in place.

Prolapse of aortic leaflets in the VSD is another problem. The authors did not encounter any problem when only one aortic leaflet prolapsed into the VSD. Therefore, when TTE showed prolapse of two leaflets into the VSD, it was very difficult to measure the exact size of the defect. This may lead to an incorrect decision in selecting the size of the device. Thus, in this study, prolapse of two leaflets was considered a contraindication for percutaneous closure of the PMVSD.

REFERENCES

1. Hijazi Z, Hakim F, Haweleh AA, Madani A, Tarawna H, Hiari A, Cao QL. Catheter closure of perimembranous ventricular septal defects using the new Amplatzer membranous VSD occluder: Initial clinical experience. Catheter Cardiovasc Interv 2002;56:508–515.
2. Bass JL, Kalra GS, Arora R, Masura J, Gavora P, Thanopoulos BD, Torres W, Sievert H, Carminati M, Fisher G, et al. Initial human experience with the Amplatzer perimembranous ventricular septal occluder device. Catheter Cardiovasc Interv 2003;58:238–245.
3. Pedra CA, Pedra SRF, Esteves CA, Pontes SC, Braga SL, Arrieta SR, Santana MV, Fontes VF, Masura J. Percutaneous closure of perimembranous ventricular septal defects with the Amplatzer device: Technical and morphological considerations. Catheter Cardiovasc Interv 2004;61:403–410.
4. Yun-Ching Fu, Bass J, Amin Z, et al. Transcatheter Closure of Perimembranous Ventricular Septal Defects Using the New Amplatzer Membranous VSD Occluder. Results of the U.S. Phase I Trial. J Am Coll Cardiol 2006;47:319–325.
5. Butera G, Chessa M, Carminati M. Late complete atriovenous block after percutaneous closure of a perimembranous ventricular septal defect. Catheter Cardiovasc Interv 2006;67:938–941.
6. Chessa M, Butera G, Negura D, Bussadori C, Giamberti A, Fesslova V, Carminati M. Transcatheter closure of congenital ventricular septal defects in adult: Mid-term results and complications. Int J Cardiol 2009;133:70–73.
7. Lillehei CW, Cohen M, Warden HE, Varco RL. The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Urg Gynecol Obstet 1955;101:447.
8. Lock JE, Block PC, McKay RG, Baim DS, Keane JF. Transcatheter closure of ventricular septal defects. Circulation 1988;78:361–368.
9. Carminati M, Butera G, Chessa M, De Giovanni J, Fisher G, Gewillig M, Peuster M, Piechaud JF, Santoro G, Sievert H, Spadoni I, Walsh K. Transcatheter closure of congenital ventricular septal defects: Results of the European Registry. Eur Heart J 2007;28:2361–2368.
10. Lifeng Z, Yan H, Dayun Y, Xiaoying L, Tingfei X, Deyuan Z, Ying H, Jinfeng Y. The underlying biological mechanisms of biocompatibility differences between bare and TiN-coated NiTi alloys. Biomed Mater 2011;6:1–12.