Cardiology in the Young 2011; Page 1 of 8
doi:10.1017/S1047951111000990

Original Article

Chronic hypobaric hypoxia, patent arterial duct and a new interventional technique to close it

Franz P. Freudenthal,[1] Alexandra Heath,[1] Jorge Villanueva,[1] Janne Mendes,[1] Ximena Vicente,[1] Inge von Alvensleben,[1] Gabriel Echazú,[2] Joaquin Navarro,[2] Nora Lang,[3] Rainer Kozlik-Feldmann[3]

[1]*Department of Pediatric Cardiology, Kardiozentrum, University of San Andrés, La Paz;* [2]*Department of Pediatric Cardiology, Centro Médico Quirúrgico Boliviano Belga, University of San Simon, Cochabamba, Bolivia;* [3]*Klinikum Grosshadern, Ludwig Maximilian University, Munich, Germany*

Abstract *Background:* Interventional closure of patent arterial duct has become an accepted alternative to surgical closure. Clinical trial with "Nit-Occlud® PDA-R". *Methods and results:* To assess the safety and efficacy of the device, we performed a prospective clinical study between June, 2009 and December, 2010 in La Paz, Bolivia. In all, 29 – 22 female patients and 7 male patients – out of 59 patients were selected on the basis of inclusion criteria. The procedures were performed under sedation at an age and weight of 5.7 years and 22.7 kilograms, respectively, with 4–6 French arterial sheaths and 5–7 French venous sheaths. The minimal diameter of the duct was 3.5 millimetres. The procedure, fluoroscopy, and hospitalisation times were 96.4 minutes (55 to 145), 13.1 minutes (3 to 25.2), and 24 hours, respectively. The "Nit-Occlud® PDA-R" was successfully deployed in all patients. Immediate, 24-hour, 1-, 3-, and 6-month closure rates were 65.5%, 79.3%, 96.5%, and 100%, respectively. The systolic pulmonary pressure diminished from 37 millimetres of mercury (21 to 57) before the intervention to 31 millimetres of mercury (21 to 45) after the intervention. No early or late embolisation, haemolysis, left pulmonary artery, or descending aorta obstruction occurred. *Conclusions:* We conclude that the "Nit-Occlud® PDA-R" device is safe and effective in closing patent arterial duct up to a diameter of 8 millimetres.

Keywords: "Nit-Occlud® PDA-R"; percutaneous closure; high altitude

Received: 12 April 2011; Accepted: 7 June 2011

"(…) THAT I MAY BE ALLOWED TO BRING THIS suggestion for a new operation before your Society, I ask on the basis that it has not been hastily conceived. On the contrary, long ago I demonstrated its technical possibility on the cadaver of newborn children, and I felt that it was justifiable on the living. At various times I have tried to inspire the paediatric specialist with my views, but in vain. Now, in view of the recent advances in cardiac surgery, for much of which we are indebted to the surgeons of this city, I will venture to place my ideas before you, asking that you do not dismiss them hastily".[1]

Correspondence to: Dr A. Heath, MD, PhD, Pediatric Cardiologist, Interventional cardiologist, Department of Pediatric Cardiology, Kardiozentrum, Obrajes, Calle 14, 669, La Paz, Bolivia. Tel: 005912 2785037; E-mail: draheath@gmail.com

Thus began John Munro's[1] description of the possibility of treating a patent arterial duct more than 100 years ago. Indeed, the patent arterial duct is one of the first congenital cardiac diseases in which it was possible to think about possible solutions. Since Munro published his article in the *Annals of Surgery* in 1907, years passed before the first successful operation occurred. This condition began to be treatable in 1938 when Robert Edward Gross[2] successfully operated on a patent arterial duct.

Congenital cardiac disease has a worldwide incidence of 0.8–1.2% of living newborns.[3–6] It has been demonstrated that this incidence varies depending on the altitude above sea level. The studies by Chen Qiu-Hong[7] and Miao[8] on populations in China revealed an increase in the prevalence of congenital cardiac disease in higher altitude cities.

Chen also found an increased incidence of patent arterial duct in altitudes between 2535 and 4200 metres above the sea level in relation to low level.[7] The Asian observations are corroborated by authors in the Andes from Peru and Bolivia.[9–11]

This clinical trial was conducted in a patient cohort living at high altitude – 3600–4200 metres above the sea level – mostly Aymara people from La Paz, Bolivia. In our institution, on the basis of 1658 echocardiograms from children with congenital cardiac disease, patent arterial duct was as frequent as ventricular septal defect – both being the most commonly diagnosed types of congenital cardiac disease – with 15% and 15.3% (248 and 253 out of 1658), respectively; atrial septal defect was the third most frequent congenital cardiac disease, with a prevalence of 7.8% (A Heath, unpublished data).[12] The patent arterial duct is also bigger in its minimal diameter and longer,[12,13] and thus these big channels lead to more clinical compromise and early elevated pulmonary pressure.[12] The gender distribution is the same as in lowland patients; girls are twice more affected than boys.[4,5,14]

The oxygen saturation in blood at sea level is normal at 95%; however, it is only 79% at 4540 metres above the sea level.[15,16] Chronic hypobaric hypoxia leads to persistent patent ductus arteriosus. Nevertheless, not only the altitude may play a role in the patency of the duct, but also the fact that the temperature diminishes 6.5°C every 1000 metres, the sun radiation augments by 4%, and the ambient humidity is lower.[17,18] Together with hypobaric hypoxia and malnutrition of the Aymara people at high altitude, the elevation of the sun radiation might also play a role. The patency of duct was found to have a relationship with cosmic activity, as published by Stoupel et al.[19]

Materials and methods

Patients

Between June, 2009 and December, 2010, 59 patients living at high altitude with residence between 2800 (Cochabamba) and 4200 metres above the sea level (El Alto) underwent an attempt of percutaneous closure of patent arterial duct – 47 female patients and 12 male patients – in Kardiozentrum, La Paz, Bolivia – 3600 metres above the sea level). All patients had patent ductus arteriosus confirmed by echocardiography.

The inclusion criteria were echocardiographic diagnosis of patent arterial duct in the absence of concomitant congenital cardiac disease requiring surgery: Patent arterial duct between 2 and 8 millimetres minimal diameters; pulmonary pressure equal to or below 67% of the systemic pressure; absence of concomitant chronic disease; body weight higher than 10 kilograms; no pregnancy; absence of acute or chronic infections; and absence of allergy to contrast medium.

In all, 29 of the 59 patients met the inclusion criteria and were included in the clinical trial. The final decision to close the patent arterial duct was made in the catheterisation laboratory after assessment of haemodynamics and angiography.

In the initial group of 59 patients, the mean minimal diameter of the duct was 4.3 millimetres, with a range from 1 to 15.6 millimetres, and the mean systolic pulmonary pressure was 46.5 millimetres of mercury, with a range from 21 to 115 millimetres of mercury. There were 47 female patients and 12 male patients, with mean age of 7.2 years, with a range from 1 to 47 years.

A total of 30 patients were excluded because of the minimal diameter of the patent arterial duct was bigger than 8 millimetres (four patients); patent arterial duct was smaller than 2 millimetres (eight patients), elevated pulmonary pressure (eleven patients), a weight lower than 10 kilograms (nine patients), and because of the presence of an additional congenital heart disease requiring surgery (ten patients). In all, 29 patients – 22 female patients and 7 male patients – met the inclusion criteria with a mean age of 5.7 years, ranging from 1.2 to 18 years, and a standard deviation of 4.7 years. The youngest patient was 1 year and 2 months and the oldest patient was 18 years old. The mean weight was 22.7 kilograms, ranging from 10 to 67 kilograms, with a standard deviation of 15.1 kilograms. One patient had mild aortic stenosis with a gradient measurement of 19 millimetres of mercury and another a restrictive perimembranous ventricular septal defect as concomitant cardiac disease.

Study design

A prospective non-randomised clinical trial was performed. The ethics committee has approved the protocol (Identifier: 08082009, University Mayor San Andres, La Paz, Bolivia).

All patients or their parents signed the informed consent.

The device

The "Nit-Occlud® PDA-R" (pfm S.R.L, La Paz, Bolivia) is an implant developed for the closure of the patent arterial duct ranging in size between 2 and 8 millimetres (Fig 1).

It is made of Nitinol, an alloy with super elastic properties and shape memory; in this case, it assumes the form of a hat. Polyester fabric is added to ensure thrombosis. The retention disc has a unique reconfiguration that fixes the implant to the aortic ampoule so as to avoid embolisation. The tubular part

of the prosthesis is a cylindrical structure that expands towards the ductal wall without protrusion into the aorta or the pulmonary artery. There are two platinum markers in the device to enhance fluoroscopic visibility. The device is attached to a controlled release system. Once the duct measures are known, the device is chosen primarily according to the minimal diameter. The device is available in seven sizes 2–8 (Table 1).

The delivery system consists of the following parts:

- PUSHER: A 0.3-millimetre stainless steel wire that is used to slide the implant through an introduction catheter.
- LOCKING WIRE: A 0.1-millimetre stainless steel wire; these wires along with the guide wire fix the implant to the delivery system.
- GUIDE WIRE: A 0.4-millimetre Nitinol wire; it is an essential piece inside the pusher. Removing this wire releases the implant.
- Y CONNECTION: 10 French; it is used as a fixing point.
- SILICON HOSE: It is used to fasten the locking wires to the Y connector.
- TORQUE: It serves to control the guide wire; it is used to pull the guide wire, and hence to liberate the implant.
- SEAL: It avoids a non-desired release of the implant and must be detached from the pusher in order to start the release process.
- CHARGE CATHETER: It is a 5-centimetre catheter used to load the implant in it before loading it to the short introducer sheath.
- INTRODUCER SHEATH: It allows loading the device to the long introduction sheath. It can be used also to purge the whole system due to the attached three-way valve.

The delivery system and the device are shown in Fig 2.

Protocol

The procedures were performed under sedation. Right and left heart catheterisation was performed percutaneously via the right femoral vein and artery. In all, 50 units per kilogram Heparin was given immediately after the arterial cannulation. Cefazoline at a dose of 30 milligrams per kilogram endovenous was given at the beginning of the session and after 8 and 16 hours. An angiogram of the descending aorta was performed in the straight lateral projection and three measurements were documented: minimal diameter, diameter of the

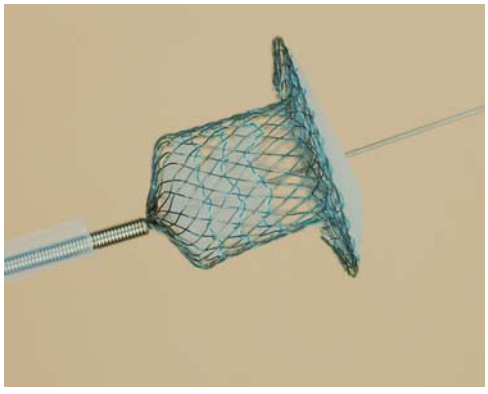


Figure 1.
Nit-Occlud® PDA-R.

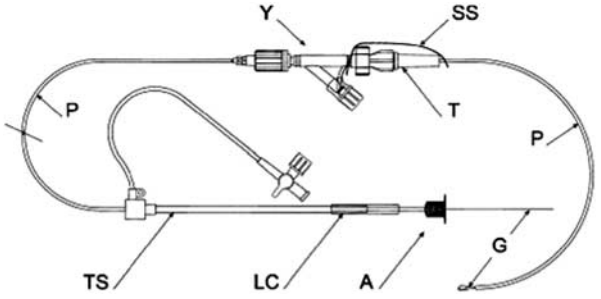
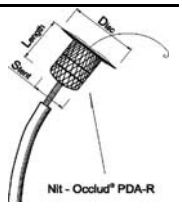


Figure 2.
Device and delivery system: A, device; SS, security band; T, Torque, fixing a security wire; TS, short sheath; G, security wire, Y, Y-connection; P, pusher; LC, additional sheath for premounting.

Table 1. Device availability with measures of the parts and recommended introducer.

Device number/indicated for PDA-(MD)	Stent (mm)	Retention disc (mm)	Length (mm)	Wire (INCH)	Number of membranes	Introducer (Fr)
2	4	8	6.5	0.004	2	5
3	5.5	10	7	0.004	2	5
4	7	12	9	0.004	3	5–6
5	8.5	14	10	0.005	3	6
6	10	16	11	0.005	4	7
7	11.5	18	12	0.005	4	7
8	13	20	13,5	0.006	4	9



Fr, French; INCH, inches; MD, minimum diameter; PDA, patent ductus arteriosus

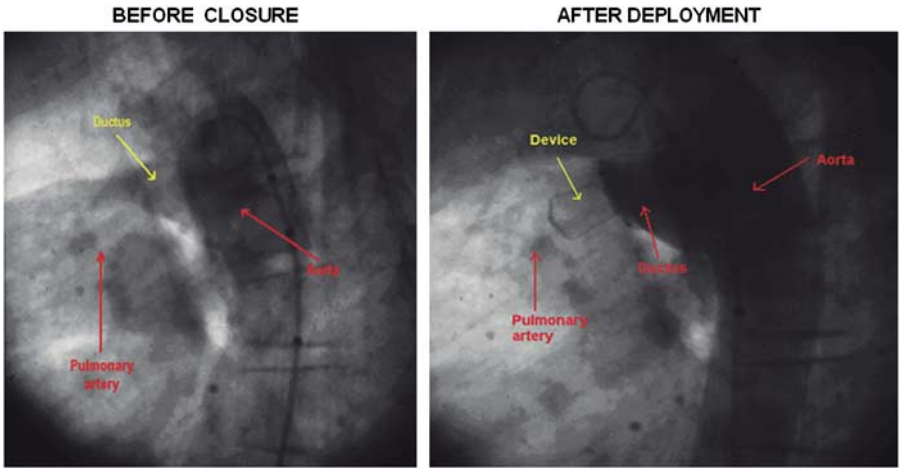


Figure 3.
Angiographic images pre- and post-interventional closure with device "Nit-Occlud® PDA-R" number 5 – minimal diameter: 5.0 millimetres; aortic ampoule: 13.3 millimetres; length: 10.0 millimetres; pulmonary pressure: 47 millimetres of mercury before and 22 after the closure.

aortic end, and length of the duct. On occasions, another angiogram was performed in different projections to obtain such measurement. The device was chosen on the basis of the measured minimal diameter. The tubular part of the device must be 1.5–2 times the minimal diameter. The retention disc had to be 2 millimetres larger than the aortic ampoule, and the length of the device must fit the length of the duct itself. The device was fixed to the delivery system by a wire, and thus we also made sure that the wire moved gently. The system was then flushed using heparin solution.

The duct was crossed anterogradely using a multi-purpose catheter. Afterwards, the multi-purpose catheter was exchanged and the proper-sized delivery system was advanced over the wire to the descending thoracic aorta. The proper device was then inserted in the large introducer and pushed up to its distal orifice. The delivery introducer was then gently retracted so that the distal disc was placed in front of the aortic end of the duct. The retention disc was then pushed and delivered; its reverse configuration assured that the surrounding tissue was not damaged. The introducer was then slowly pulled so far that the retention disc accommodated itself in the aortic ampoule and the resistance was felt. The rest of the device was pushed under tension into the duct itself to close the defect. After that, with the device still fixed on the delivery system, a repeat angiogram was performed to assess the position of the device inside the duct. If the device was in the proper position, it was released by pulling the wire from the delivery system and device. After 15 minutes, haemodynamic assessment and angiogram were repeated (Fig 3).

Follow-up

All patients were admitted for 24 hours in the hospital. Clinical and echocardiographic assessments were done at 24 hours, 1, 3, and 6 months. Particular attention was given to assess any residual shunt, size of the left atrium and ventricle, flow in the left pulmonary artery and descending aorta. Urine analysis was performed in all cases the day after the intervention to rule out haemolysis.

All patients were asked to avoid contact sports for 1 month. Endocarditis prophylaxis was also recommended for 6 months.

Results

The device was successfully deployed in all 29 patients. The clinical data of the patients are listed in Table 2. The mean minimal diameter of the duct as by echocardiography was 4.4 millimetres, ranging from 2 to 7.3 millimetres, with a standard deviation of 1.4 millimetres. By angiography the mean minimal diameter of the duct was 3.5 millimetres, ranging from 2 to 7.2 millimetres, with a standard deviation of 1.6 millimetres. The mean size of the aortic ampoule as measured by angiography was 8.1 millimetres, ranging from 3.5 to 17.2 millimetres, with a mean length of 8.1 millimetres, ranging from 3.3 to 17.9 millimetres (Table 3). In all, 52% of the patent arterial ducts were larger than 5 millimetres, 38% were between 3 and 5 millimetres, and only 10% were smaller than 3 millimetres.

Krichenko classification

A total of 22 patients showed conical patent arterial duct (type A), one patient showed a short duct

Table 2. The clinical data of the patients.

Patients	Sex	Age (years)	Weight (kg)	Size (cm)	DM (eco; mm)
1	F	2.3	11	81	4.3
2	M	15	56	163	4.9
3	F	6	17	107	5.7
4	F	4.5	26	102	3.4
5	F	18	55	154	5.6
6	F	4	13.5	99	3.1
7	M	2.4	18	95	4.2
8	F	4	14	92	3.9
9	F	10	40	130	4.1
10	F	2.7	13.5	92	3.1
11	F	2.4	11	82	7.3
12	M	8	21	110	6.0
13	F	9.1	29	136	3.5
14	F	11	30.3	134	5.0
15	M	1.2	10.5	82	2.8
16	M	2.1	13.5	87	6.0
17	F	3	18.5	101	3.0
18	F	8	23.5	125	5.0
19	F	4	31.8	114	6.0
20	M	1.6	10.2	89	3.6
21	F	4.2	14.4	99	2.4
22	F	5.1	21.4	115	4.0
23	F	11	33	147	6.3
24	F	16	67	161	6.8
25	F	2.1	11.2	90	4.5
26	M	4.1	19	110	6.6
27	F	1.5	10	79	3.3
28	F	1.1	10.1	78	3.7
29	F	2	10.1	84	2.0

DM, diametre minimum; eco, echocardiography; F, female; M, male

(type B), four patients showed tubular ones (type C), no patient showed complex duct (type D), and two patients showed elongated ones (type E).

Procedural results

For the closure, we used 4–6 French arterial introducers and 5–7 French venous introducers. We used devices ranging from 2 to 8, with a mean of 3.7. The mean procedure time was 96.4 minutes, with a standard deviation of 26.1, ranging from 55 to 145 minutes, and mean fluoroscopy time was 13.1 minutes, ranging from 3 to 25.2 minutes, with a standard deviation of 5.1.

The device was pushed into the delivery catheter without problems, and configured as planned inside the duct. No problems occurred with the delivery system.

Effectiveness criteria

Immediate complete closure was achieved in 65.5% of the patients, that is, in 19 out of 29 patients. A total of 10 patients showed foaming or trivial shunt through the device. After 24 hours, 79.3% – that is, 23 patients – showed complete closure and only six patients showed trivial residual shunt. Of the 29 patients, 28 showed complete closure of the defect (96.5%) and only one patient had residual shunting when examined 1 month after the intervention. In this patient, the shunt was closed at the 3 months control. In the 3 and 6 months' follow-up, 24 out of 24 and 28 out of 28 had complete closure (100%; see Fig 4). One patient did not come to her 6 months control because of residency change.

Pulmonary pressure. According to the inclusion criteria, no patient showed a systolic pulmonary pressure exceeding 67% of the systemic pressure. The relation of systolic pulmonary pressure to systolic aortic pressure was 43.6% before closure and fell to 31.8% immediately after. The mean systolic pulmonary pressure before the intervention was 37 millimetres of mercury, with a range from 21 to 57 millimetres of mercury; it fell to a mean of 31 millimetres of mercury, with a range from 21 to 45 millimetres of mercury, immediately afterwards.

Safety criteria

In all, five patients developed ecchymosis at the puncture site, and one child developed transient fever without signs of infection. No cases of haemolysis occurred. No other complications were encountered during or after the closure. No early or late embolisation occurred in this series. No significant Doppler gradient was measured in the left pulmonary artery or in the aortic arch immediately after or during follow-up as assessed by Doppler echocardiography.

Discussion

Persons at high altitude are at an increased risk of maintaining patency of the arterial duct.[12,13] We hypothesise that chronic hypobaric hypoxia is an important factor in this issue, as the values for oxygen saturation and arterial oxygen pressure are lower at high altitude.[15,16,20] Out of the 59 patients who were brought into the catheter laboratory in 1 year (June, 2009 to June, 2010), only 29 could be selected for the clinical study. The remaining 30 patients were excluded mostly because of the elevated pulmonary pressure and big minimal diameter of the ducts.

Both publications by scientists researching at sea level and at high altitude have shown that even big ducts can be closed with percutaneous techniques.[21–25] Nevertheless, complications happen, being the scariest the embolisation of the device.[21–25]

This system has been already tested in animals with good results.[26] We also made an initial clinical experience with the device showing the feasibility of

Table 3. Ductus measures and devices used.

P	Device (D)	DM (angio; mm)	Stent (device; mm)	Aortic amp (duct; mm)	Ret disc (device; mm)	Length (duct; mm)	Length (device; mm)	Venous introducer used
1	3	3.11	5.5	8.37	10	4.7	7	5
2	3	2.62	5.5	6.97	10	3.31	7	5
3	7	6.9	11.5	13.8	18	17.9	12	7
4	2	2	4	3.85	8	3.71	6.5	5
5	6	6.5	10	13	16	11	11	7
6	4	3.5	7	9.2	12	6.9	9	6
7	4	3.9	7	12.3	12	12.7	9	5
8	2	2	4	7.86	8	4.43	6.5	5
9	3	2.45	5.5	5.7	10	4.29	7	5
10	2	2.35	4	7.4	8	3.86	6.5	5
11	5	5	8.5	6.87	14	3.7	10	6
12	4	2.5	7	7.31	12	5.35	9	6
13	3	2.5	5.5	3.5	10	12	7	5
14	3	2.7	5.5	6.4	10	…	7	5
15	3	2.79	5.5	7.41	10	5.45	7	5
16	4	2.2	7	…	12	6.8	9	6
17	2	2	4	9.8	8	14.2	6.5	5
18	3	3.05	5.5	10.3	10	14.2	7	5
19	5	3.5	8.5	…	14	9	10	6
20	2	2	4	4.8	8	…	6	5
21	4	3.9	7	6.1	12	16.2	9	6
22	4	3.4	7	3.8	12	…	8	6
23	6	5.09	10	13.3	16	10.02	11	7
24	5	4.3	8.5	7.5	14	3.5	10	6
25	6	7.2	10	17.2	16	…	11	7
26	7	6.37	11.5	9.78	18	6.96	12	7
27	5	5.2	8.5	7.4	14	9.9	10	6
28	2	2.16	4	4.86	8	6.52	6.5	5
29	2	2	4	4.5	8	…	6.5	5

angio, angiogram; DM, diametre minimum; P, pusher

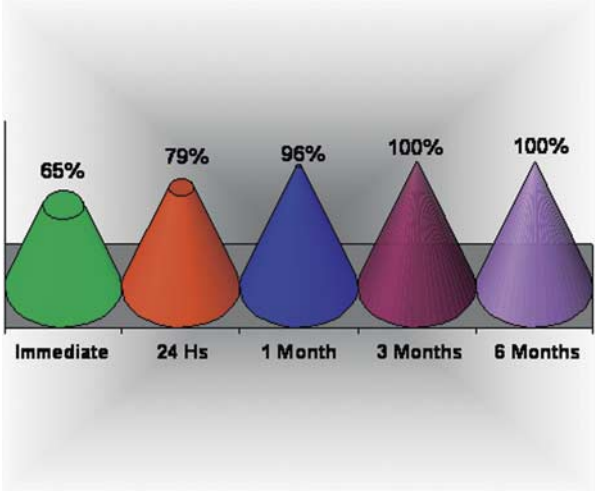


Figure 4.
Closure rate during the control period.

using this device (A Heath et al[27]). Patients coming from this initial clinical experience are already up to 3 years under observation, without showing late complications. In all, five early embolisations occurred in this initial experience in patients with pulmonary hypertension. Nevertheless, we think that it is important to treat patients with ductus and pulmonary hypertension. Zabal et al[28]recently published, in Mexico, a very interesting article about hypertensive ducts. We can corroborate this observation: patients with hypertensive ducts at high altitude tend to show an improvement of the elevated pulmonary pressure after closing the defects and maintain it low with the time. Habitants of high altitude maintain a thick muscular media.[15,20,29] This anatomical feature may provide some protection against irreversible changes in the small pulmonary vessels.[30]

In our trial, the pulmonary pressure was over 35% of the systemic pressure in 20 patients (68.9%), but diminished immediately after closure. We treated 100% of the 29 patients selected for the clinical trial.

Our study describes the results of percutaneous closure in this special group of patients with a novel closure device: "Nit-Occlud® PDA-R". Despite some similarities with the Amplatzer Duct Occluder (Aga Medical Corporation, Golden Valley, MN, USA),

we think that the absence of welding sites in the "Nit-Occlud® PDA-R" may minimise the risk of corrosion.[31]

The delivery system has an original and sure conception: the "wire pull-out system". One security wire crosses the device through wire loops in the device. When the final position of the "Nit-Occlud® PDA-R" is reached and the final angiography is performed, pulling this wire gently releases the device. As long as the wire crosses the stent loops, one can recover the device into the long sheath if desired. This aspect enhances the security of the closure system.

In other device systems, the device must be connected to the delivery cable by a micro screw fixed to the device before loading it into the long sheath. The device is released by unscrewing it. To our opinion, the fact that the whole "Nit-Occlud® PDA-R" system is preassembled by the manufacturer, and that there is no screw, may minimise the risk of premature release of the device.

We had no problems assembling and pushing the device into and through the introducer. During the manoeuvre of push and pull in order to verify the stability of the device inside the duct, no device embolised.

The long venous introducer sheath was 5–7 French; the arterial introducer was only 4–6 French. The small delivery system makes this device suitable for use in small children. The relatively short procedure (55–145 minutes) and fluoroscopy (3–25 minutes) times are appealing. In some patients, these times were increased due to the necessity of exchanging the device for a bigger one or due to the difficulty in crossing the duct. The hospital stay was only 1 day in all 29 patients.

The foaming seen in 11 patients 15 minutes after release of the device was not haemodynamically significant. This residual shunt further disappeared at the 3-month follow-up. Complications encountered were minor and mainly vascular in nature. With proper techniques of vascular access and closure, such complications can be completely avoided. Only one patient had transient fever, with negative blood culture. No other complications were encountered.

Conclusions

The device "Nit-Occlud® PDA-R" is safe and effective in patients with a weight of more than 10 kilograms, patent arterial duct between 2 and 8 millimetres minimal diameter, and pulmonary pressure less than 67% of the systemic pressure. More clinical trials are necessary to confirm these initial observations.

Acknowledgements

The authors thank Professor Ziyad M. Hijazi, MD, MPH, FSCAI, FACC, FAAP; James A. Hunter, University Chair; Professor of Pediatrics and Internal Medicine; Director, Rush Center for Congenital and Structural Heart Disease; Section Chief, Pediatric Cardiology, Rush University Medical Center for the critical review of the manuscript. This study was supported by the Private–Public Partnership Project: 04.1003.5-203.4 (German Federal Ministry for Economic Cooperation and Development/German Technical Cooperation/PFM medical), Fundación Cardioinfantil, La Paz, Bolivia. Clinical Trial Registration: URL: http://Register.ClinicalTrials.gov Identifier: NCT01063712.

References

1. Munro J. Ligation of the ductus arteriosus. Ann Surg 1907; 46: 335–338.
2. Gross RE, Hubbard JP. Surgical ligation of a patent ductus arteriosus: report of the first successful case. JAMA 1939; 112: 7729–7749.
3. Carlgreen L-E. The incidence of congenital heart disease in Gotheburg. Proc Ass Eur Paed Cardiol 1969; 5: 2–8.
4. Feldt RH, Avasthey P, Yoshimasu F, Kurland LT, Titus JL. Incidence of congenital heart disease in children born to residents of Olmsted county, Minnesota 1950–1969. Mayo Clin Proc 1971; 46: 794–799.
5. Ferencz C, Neill CA. Cardiovascular malformation prevalence at live birth. In: Freedom RM, Benson LN, Smallhorn JF (eds). Neonatal Heart Disease. Springer, Heidelberg, 1992, p 274.
6. Fyler DC. Report of the New England regional Infant cardiac program. Pediatrics 1980; 65(Suppl): 375–461.
7. Chen QH, Wang XQ, Qi SG. Cross-sectional Study of congenital heart disease among Tibetan children aged from 4 to 18 years at different altitudes in Qinghai province. Chin Med J 2008; 121: 2469–2472.
8. Miao CY, Zuberbuhler JS, Zuberbuhler JR. Prevalence of congenital cardiac anomalies at high altitude. J Am Coll Cardiol 1988; 12: 224–227.
9. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes. Circulation 2007; 115: 1132–1146.
10. Gamarra A. Una historia de malformaciones cardiacas en la altura. Arch Bol Hist Med 2005; 11: 46–49.
11. Gamarra A. Cardiopatías congénitas en la altura. Arch Inst Cardiología Mex 1973; 43: 230.
12. Heath A, Freudenthal F, Taboada C, Mendes J. Pulmonary hypertension and congenital heart defects at high altitude. In: Yuan JX-J, Garcia JGN, Hales CA, Rich S, Archer SL, West JB (eds). Textbook of Pulmonary Vascular Disease. Springer Science Business Media, Springer New York Dordrecht Heidelberg London, 2011, pp. 1223–1230.
13. Penaloza D, Arias-Stella J, Sime F, Recavarren S, Marticorena E. The heart and pulmonary circulation in children at high altitudes: physiological, anatomical and clinical observations. Pediatrics 1964; 34: 568–582.
14. Apitz J, Stoermer J. Über die Lebensaussichten von Säuglingen mit kongenitalen Angiokardiopathien. Mschr Kinderheilkd 1967; 115: 365–371.
15. Hurtado GL, Calderón A. Hipoxia de altura en la insuficiencia cardiaca del lactante. Bol Soc Boliv Pediatr 1965; 9: 11–23.

16. Hurtado A. Animals in high altitude: resident man. In: Handbook of Physiology: Adaptation to the Environment. Dill DB (ed.). American Physiological Society, Washington, DC, 1964, pp. 843–860.
17. Reeves J, Weil J. Presión Barométrica, Reducción, Aclimatación Ventilatoria a Grandes Alturas. www.insht.es/InshtWeb/Contenidos/Documentacion/.../37.pdf
18. Berger K, Rom WN. Efectos Fisiológicos de la Reducción de la Presión Barométrica.www.insht.es/InshtWeb/Contenidos/Documentacion/.../37.pdf
19. Stoupel E, Birk E, Kogan A. Congenital heart disease: correlation with fluctuations in cosmophysical activity, 1995–2005. Int J Cardiol 2009; 135: 207–210.
20. Arias-Stella J, Saldaña M. The terminal portion of the pulmonary arterial tree in people native to high altitude. Circulation 1963; 28: 915–925.
21. Lin MC, Fu YC, Jan SL, Ho CL, Chi CS, Hwang B. Transcatheter closure of large patent ductus arteriosus using the Amplatzer ductal occluder. Acta cardio Sin 2007; 23: 103–108.
22. Zapata HH, Gómez M, Tenorio C, Dager A. Percutaneous closure of persistent large patent ductus arteriosus with the Amplatzer device: inmediate result and middle term follow up. Rev Colomb Cardiol 2004; 11: 261–265.
23. Pass RH, Hijazi Z, Hsu DT, Lewis V, Hellenbrand W. Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial. J Am Coll Cardiol 2004; 44: 513–521.
24. Hijazi ZM, Feldmann T, Abdullah Al-Qbandi MH, Sievert H. Transcather Closure of ASDs and PFOs. Cardio text Publishing, Minneapolis, MN, 2010.
25. Szkutnik M, Menacho-Delgadillo R, Palmero-Zilveti E, Bialkowski J. Transcatheter closure of patent ductus arteriosus among native high-altitude habitants. Pediatr Cardiol 2008; 29: 624–627.
26. Lang N, Schmitz C, Lehne A, et al. Preclinical evaluation of a new self-expanding device for closure of muscular ventricular septal defects in a pig model. Catheter Cardiovasc Interv 2010; 75: 408–415.
27. Heath A, Lang N, Levi DS, et al. Transcatheter closure of large patent ductus arteriosus at high altitude with a novel nitinol device. Catheter Cardiovasc Interv (in press).
28. Zabal C, García-Montes JA, Buendia-Hernandez A, et al. Percutaneus closure of hypertensive ductus arteriosus. Heart 2010; 96: 625–629.
29. Arias-Stella J, Castillo Y. The muscular pulmonary arterial branches in stillborn natives of high altitudes. Lab Invest 1966; 15: 1951–1959.
30. Heath A, Stewart K, Mendes J, Ramirez M, Freudenthal F. Does High altitude protect against irreversible pulmonary hypertension? PVRI Review 2010; 2: 131–133.
31. Paine JS, Rogers CA. Shape-memory alloys for damage-resistant composite structures. In Soc Optical Eng 1995; 2427: 358–371.