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Patent ductus arteriosus at low and high altitudes: anatomical and haemodynamic features and their implications for transcatheter closure

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Abstract

Background: Living at high altitude increases the prevalence of patent ductus arteriosus (PDA) and may affect its morphology.

Aim: To compare the anatomical and haemodynamic features of isolated PDA in patients living at low and high altitudes (1,500–4,200 metres above sea level — m.a.s.l.).

Methods: We studied retrospectively data from 1,404 consecutive patients — 708 living in lowland areas (group L) and 696 in highland areas (group H), in whom transcatheter closure of PDA was attempted. The mean age of the patients in group L was 9.9 ± 13.5 years and in group H it was 8.2 ± 19.7 years.

Results: The diameter of PDA in group L was 2.3 ± 1.3 mm and 4.1 ± 1.2 mm in group H ($p < 0.001$), while the mean pulmonary artery pressure was 17.9 ± 5.9 mm Hg and 25.5 ± 12.3 mm Hg, respectively ($p < 0.001$). Angiographic PDA type A was more frequently observed in highland patients. In groups L and H, self expanding nitinol occluders (mostly Amplatzer devices) were used in 25.7% *vs* 92.2% of patients ($p < 0.001$), whereas coils were used in 69.2% *vs* 7.5% ($p < 0.001$), respectively. Double umbrella systems were used in 4.8% of patients in group L.

Conclusions: In catheterised patients with PDA living at high altitude, larger ductal diameter, anatomic type A and higher pulmonary artery pressure were more frequently observed. This finding has important implications for future strategy regarding transcatheter closure in populations living at different altitudes.

Key words: ductus arteriosus, catheterisation

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INTRODUCTION

The atmospheric pressure at 700 m is 94 kPa, with 92% of the sea-level oxygen being available. At 1,500 m, the values are 85 kPa and 84%, whilst at 4,000 m they are 63 kPa and 63%. The postnatal persistence of pulmonary hypertension in a hypoxic environment and delayed closure of ductus arteriosus are contributing factors to the high prevalence of patent ductus arteriosus (PDA) at high altitude [1]. The morphology of PDA among patients living at low (group L) and high (group H) altitudes have not been investigated extensively [2].

In 1989, Kirchenko et al. [3] proposed an angiographic classification of isolated PDA, which was regarded as important in choosing the method of transcatheter closure. Since then, numerous devices have been introduced, expanding the applicability of the technique to various ductal characteristics and shapes. The PDA in subjects living at high altitudes is considered more challenging for catheter closure [2, 4].

The purpose of this study was to explore the anatomical and haemodynamic features of PDA in the two prespecified groups of patients. In addition, we examined the implications of these features on transcatheter occlusion. To the best of our knowledge, this is the largest study reported to date on catheterisation findings in patients undergoing transcatheter closure of PDA.

METHODS

Patients

This is a retrospective analysis of 1,404 consecutive patients undergoing catheterisation procedures for ductal closure in isolated PDA. The procedures were performed between 1990 and 2009. An Excel table was created for data collection and submitted to multiple investigators, who retrospectively reviewed angiographic and haemodynamic features of PDA closure performed at their institutions within the study period. The table included non-confidential data only. The completed table was then submitted to the principal investigator (JB) for review and data analysis. Each investigator obtained internal permission for review of patient data in accordance with their own institutional regulations. Only patients with a complete set of data were included in the study.

Group L was composed of patients treated in two centres: Silesian Centre for Heart Diseases, Zabrze, Poland (altitude 340 metres above sea level — m.a.s.l.) and Hospital Ramon y Cajal, Madrid, Spain (altitude 650 m.a.s.l.). In this group, only patients living below 700 m were included in the study.

Group H included patients living permanently at high altitude — above 1,500 m.a.s.l. They were treated in the following centres: Instituto Nacional de Cardiologia and Hospital CNM 20 de Noviembre ISSSTE, both located in Mexico City, Mexico (altitude 2,240 m.a.s.l.), Hospital UNICAR, Guatemala City, Guatemala (altitude 1,500 m) and Hospital Obrero, La Paz, Bolivia (3,800 m). In this group, patients living permanently at an altitude below 1,500 m were excluded from the study.

Procedures

The procedures were performed under conscious sedation and local anaesthesia in adults, and deeper sedation or general anaesthesia in children. Following complete right and left heart catheterisation, angiography in lateral and/or right anterior oblique view was performed to demonstrate PDA morphology in all patients. The PDA anatomy was classified as type A, B, C, D or E according to Kirchenko et al. [3]. Additionally, PDA type R was noted for patients with recanalisation or with residual shunt after previous interventional catheterisation/surgical ligation.

In cases with pulmonary hypertension and pulmonary to systemic pressure ratio over 0.5, as well as when pulmonary pressure did not decrease by at least 20% on 100% O_2, balloon test occlusion was performed for 10–15 min and repeated haemodynamic measurements were obtained. Test occlusion was achieved using an 18 or 24 mm Amplatzer sizing balloon (AGA Medical Corp, USA) or a wedge catheter inflated with a diluted contrast solution. The PDA occlusion was confirmed by aortography [5, 6]. If the response to test occlusion and oxygen concentration = 100% (FiO_2 1.0) was non-conclusive, additional vasodilators, such as nitric oxide inhalation or pharmacological agents such as adenosine infusions, were used to estimate the reversibility of pulmonary hypertension. Patients with fixed pulmonary hypertension not responsive to vasodilator therapy were excluded from the study and percutaneous closure.

The PDA diameter at the narrowest end was estimated using magnification correction. In cases with large PDA and enlarged aorta, particularly in adults in whom image definition was limited and measurements of PDA difficult, balloon sizing was performed over a guidewire [6, 7]. The appropriate device was chosen on the basis of diameter size and angiographic PDA type. In cases where PDA catheterisation from the venous side was difficult but necessary in order to place the device (PDA closure with Amplatzer Duct Occluder or Rashkind umbrella implantation), an arterio-venous loop was created with guidewire in compliance with the previously described technique [8].

Depending on anatomical features and device availability, the following devices were used for closure in the two groups: coils — Gianturco or detachable — (Cook Inc, USA or Cook Europe, Denmark), Nit-Occlude (PFM AG, Germany), Gianturco-Grifka bag (Cook Inc, USA) and self-expanding nitinol wire mesh occluders — Amplatzer Duct Occluder types I and II, Amplatzer Muscular Ventricular Septal Defect Occluder, Amplatzer Atrial Septal Occluder (AGA Medical Corp, USA), and Cardio-O-Fix PDA Occluder (Starway Medical Technology Inc, China). Generally, when the narrowest PDA diameter exceeded 2 mm, self-expanding nitinol wire-mesh occluders were used. In cases of smaller PDAs, coils were implanted. Nowadays, only these devices (coils and nitinol wire-mesh occluders) are used in daily practice for transcatheter PDA closure. Additionally, in group L, double umbrella systems — Rashkind Occluder (Bard USCI, USA) or Starflex device (NMT Inc, USA) were also used.

Statistical analysis

Statistical software Statistica 8.0 for Windows was used. Quantitative data were expressed as mean ± SD. The U Mann-Whitney test was performed to compare the mean values of analysed parameters between the two groups. The χ^2 analyses of proportions and linear regression were used to explore the association of PDA diameter with the altitude of habitation. A p value < 0.05 was considered significant.

RESULTS

Demographic data

In group L, the mean age of the 708 patients was 9.9 ± 13.5 years (range 0.1–84.5) and weight — 27.7 ± 20.6 kg (range 3.1 to 100 kg). There were 621 (87.7%) children, of whom 386 (54.5%) were under five years, and 87 (12.3%) adults, of whom 464 (65.5%) were female. In group H, there were 696 patients with a mean age of 8.2 ± 19.7 years (range 0.2–63) and weight was 23.2 ± 18.3 kg (range 3 to 95 kg). There were 613 (88%) children, of whom 411 (59%) were under five years, and 83 (12%) adults, of whom 518 (74.4%) were female.

Table 1. Catheterisation data obtained from patients with patent ductus arteriosus living at low (Group L) and high (Group H) altitudes

	Group L	Group H	P
MPAP [mm Hg]	17.9 ± 5.9	25.5 ± 12.3	< 0.001
PDA diameter [mm]	2.3 ± 1.3	4.1 ± 1.2	< 0.001
Type of PDA:			
A	353 (50%)	560 (80.5%)	< 0.001
B	33 (4.7%)	13 (1.9%)	< 0.01
C	37 (5.2%)	18 (2.6%)	< 0.05
D	56 (7.9%)	22 (3.2%)	< 0.001
E	173 (24.4%)	79 (11.4%)	< 0.001
R	55 (7.7%)	4 (0.6%)	< 0.001
Technique details:			
Balloon test occlusion	9 (1.3%)	48 (6.9%)	< 0.001
Balloon sizing	12 (1.7%)	53 (7.6%)	< 0.001
A-V loop	26 (3.7%)	14 (2.0%)	NS
Device:			
Rashkind/StarFLEX	34 (4.8%)	0	
Coil	490 (69.2%)	52 (7.5%)	< 0.001
Nitinol wire mesh*	182 (25.7%)	642 (92.2%)	< 0.001
None	2 (0.3%)	2 (0.3%)	NS

A-V loop — requiring the creation of an arterio-venous loop; MPAP — mean pulmonary artery pressure; p — probability of statistical significance; PDA diameter — minimal patent ductus arteriosus diameter; type of PDA — types of PDA according to Kirchenko; Rashkind/StarFLEX — double umbrella systems; *self-expanding nitinol wire-mesh occluders (mostly Amplatzer devices)

Procedural data

Catheterisation data from groups L and H are summarised in Table 1. The PDA diameter and the mean pulmonary artery pressure in group L were lower than in group H (Table 1). In children (age < 18 years), mean pulmonary artery pressure in group H was 24.9 ± 6.4 mm Hg *vs* 18.2 ± 12.0 mm Hg in group L (p < 0.001), and in adults it was 29.4 ± 10.4 mm Hg *vs* 20.3 ± 15.6 mm Hg (p < 0.001), respectively. Mean diameter of PDA in children in group H was 3.97 ± 2.0 mm *vs* 2.3 ± 4.2 mm (p < 0.001) in group L, and in adults it was 5.35 ± 2.2 mm *vs* 1.7 ± 3.6 mm (p < 0.001), respectively. Angiographic PDA type A was more frequently observed in group H, while in group L types B, C, D, E and R were more prevalent.

Balloon occlusion test which excluded irreversible pulmonary hypertension, and calibration with balloon to estimate precise PDA diameter, were used more frequently in patients from group H than in patients from group L. Arteriovenous loop creation to allow long sheath positioning was necessary in similar proportions in both groups (Table 1).

Device implantation was successful in 704 out of 708 (99.4%) patients from group L and in 690 out of 696 (99.1%) patients from group H (NS). In 31 patients from group L and 26 from group H, the device had to be removed and replaced due to embolisation, slippage or residual shunt. In four patients (two in group L and two in group H) with tiny PDA (0.5–0.8 mm of diameter) the procedure was abandoned after ineffective crossing of the PDA with multiple guidewires. Remarkably, in all four cases, colour Doppler examination demonstrated PDA closure on the following day.

With regard to the PDA morphology, in group L, the majority of patients (69.2%) received coils, whereas in group H — Amplatzer occluders (92.2%; Table 1).

DISCUSSION

This study demonstrates differences in the anatomy and physiology of PDA in patients living at high and low altitudes. It seems that permanent living at high altitude is an independent predictor of increased pulmonary pressure and wider PDA diameter. Taking into consideration the original classification of PDA proposed by Kirchenko et al. [3] we found important differences in the distribution of ductal size and type depending on the patients' place of origin. In the original study by Kirchenko et al. [3], 79 patients probably lived at low altitude and the most frequent anatomic type of PDA observed was type A (64.6%). Although Kirchenko did not mention ductal size exclusion criteria, all the reported PDA were more than 2 mm in diameter. The only transcatheter technique of PDA closure available at that time was the double Rashkind umbrella system.

Various anatomical features have been reported, with PDA size discrepancy in different institutions. In a study by Magee et al. [9] presenting the results of the European registry of transcatheter coil occlusion of PDA, there were 1,258 patients with a mean minimum PDA diameter of 2 mm and an incidence of type A PDA of 43.8%. In our study, patients in group L had a similar mean PDA diameter (2.1 mm), type A was present in 50%, and the incidence of coil application was 69.2%.

Other studies have reported much larger mean ductal diameters. In the study by Wang et al. [10], analysing the closure of selected moderate and large PDAs (68 patients) with Amplatzer Duct Occluder, the mean diameter was 4.1 mm and type A PDA was present in 83.3% of patients. Interestingly, these features were similar to those we observed in group H: a PDA diameter of 4.1 mm, an incidence of type A PDA of 80.5% and a prevalence of Amplatzer devices (92.5%) for closure. In selected patients with pulmonary pressure over 60% of the systemic pressure, Amplatzer Muscular Ventricular Septal Defect Occluders or Atrial Septal Occluders were used [4, 7] to minimise the risk of device embolisation from a single retention disc.

The higher pulmonary pressure, as well as larger minimal PDA diameter, in group H has implications for the selection of closure technique. Balloon test occlusion was used more frequently in this group with a view to excluding the possibility of irreversible pulmonary hypertension. Similarly, this group had greater use of balloon sizing technique to estimate PDA diameter. In group H, type A was significantly more frequent, while types B, C, D, E and R were common in group L. Given the higher incidence of type B PDAs in group L, there was a higher use of double umbrella device systems, especially useful in this anatomy of the duct [3, 11].

The lower oxygen concentration at high altitude may play a role in the observed differences in shape, with wider ducts and higher pulmonary artery pressure. However, the actual mechanism of this phenomenon remains unclear. Such observations were described in a small recent study conducted in La Paz (Bolivia) at an altitude of 3,800 m.a.s.l. [2]. Similar observations were reported by Wang [12] who presented his experience in transcatheter closure of PDA with self-expanding nitinol wire-mesh occluders — Cardio-O-Fix in 1,000 patients living in China, in the province of Qinghai (altitude 2,260–3,270 m). This device is very similar to the Amplatzer Duct Occluder but its use in Europe is limited [13].

Our study illustrates two decades of development of devices for the percutaneous closure of PDA. Despite controversies over the closure of small PDAs, it is common practice to occlude all patent ducts, regardless of ductal size, to avoid bacterial endarteritis in patients undergoing catheterisation. Historically, the incidence of endarteritis of the duct has been reported to be 1% per year, and continues to be a risk, especially in less developed countries [14]. Today, the incidence of endarteritis is probably much lower, with the routine use of antibiotics and a higher detection rate due to high quality echo-Doppler equipment. In addition, the possibility of occluding PDA safely and effectively via transcatheter techniques has led many to routinely close any persistent ducts, even silent ones. However, this practice remains highly controversial. There are occasions where tiny ducts cannot be crossed and therefore cannot be closed. Indeed, in four of our patients, the ducts could not be crossed but, presumably due to mechanical endothelial disruption related to multiple attempts at crossing the duct with catheter and wire combinations, they closed spontaneously. Closure persisted and was confirmed by echocardiography on the day after catheterisation [15]. The use of coils proved to be effective for closure of small to moderate ducts at any age, as demonstrated in group L [16, 17]. Initially, the Gianturco and other free release coils were used, and were later replaced by coils with a controlled release mechanism, such as Flipper or Nit Occlud. With the introduction of the Amplatzer Duct Occluder, which is now widely used for ducts with a minimal diameter over 2–3 mm [18], the use of coils has decreased significantly, and is now limited to small ducts only [19]. Given the larger size of ducts at high altitude (group H), self expanding nitinol wire mesh occluders are especially useful in this group.

It is important to emphasise that more than 140 million people worldwide live at > 2,500 m.a.s.l. [20]. Therefore, the results of this study can be applied to a large population, including mountainous areas such as the Andes in South America, the Himalayas in Asia [12] or the high plains of Ethiopia and Lesotho in Africa. Although our study was not epidemiological, it should be stressed that the prevalence of PDA is 30 times greater at high altitudes than at sea level [20]. Nevertheless, we did not confirm a direct association between PDA diameter and the altitude of habitation.

Limitations of the study

Our study has the limitations inherent in a retrospective review, and thus only a limited set of data, focusing on the procedural aspects and immediate results, could be obtained. Follow-up data could not be included, given the varying amounts of information available at participating institutions. Varying physician practices may have influenced the use of different devices for closure. In addition, there could be significant biases in relation to improved regional access to care at low altitude sites compared to high altitude institutions, and thus a larger proportion of haemodynamically significant ducts being diagnosed and treated in group H than in group L.

CONCLUSIONS

In patients living at high altitude, especially larger ductal diameter, anatomic type A and increased pulmonary artery pressure are present, leading to differences in the technique used for closure. Despite these differences, the immediate success of the procedure was high and equal for both groups.

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Conflict of interest: *none declared*

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Przetrwały przewód tętniczy w warunkach wysokogórskich i nizinnych: różnice w morfologii i hemodynamice oraz ich znaczenie dla przezcewnikowego zamykania

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Streszczenie

Wstęp: Częstość występowania przetrwałego przewodu tętniczego (PDA) u osób zamieszkujących od urodzenia tereny wysokogórskie jest większa; również morfologia przewodu w tych warunkach może być zmieniona.

Cel: Celem pracy było porównanie cech morfologicznych i hemodynamicznych izolowanych PDA występujących u pacjentów żyjących na terenach nizinnych oraz wysokogórskich (na wysokości 1500–4200 m.n.p.m.).

Metody: Badaniom retrospektywnym poddano grupę kolejnych 1404 pacjentów — 708 żyjących na terenach nizinnych (grupa L) oraz 689 żyjących na terenach wysokogórskich (grupa H). U wszystkich podjęto próbę przezskórnego zamykania PDA. Średni wiek w grupie L wynosił 9,9 ± 13,5 roku, a w grupie H — 8,2 ± 19,7 roku.

Wyniki: Średnica PDA w grupie L wynosiła 2,3 ± 1,3 mm, a w grupie H — 4,1 ± 1,1 mm (p < 0,001), podczas gdy średnie ciśnienie w tętnicy płucnej odpowiednio 17,9 ± 5,9 *v*. 25,5 ± 12,3 mm Hg (p < 0,001). W grupie H częściej obserwowano angiograficzny typ A. W grupach L i H stosowano implanty z samorozprężalnej nitynolowej siatki (głównie Amplatzery) u 25,7 *v*. 92,2% pacjentów (p < 0,001), podczas gdy sprężynki wewnątrznaczyniowe (*coile*) odpowiednio u 69,2 *v*. 7,5% (p < 0,001) osób. W celu zamknięcia PDA w grupie L stosowano zestawy podwójnych parasolek u 4,8% pacjentów.

Wnioski: U osób poddanych cewnikowaniu serca żyjących na terenach wysokogórskich częściej obserwuje się większą średnicę przewodu, wyższe ciśnienie w tętnicy płucnej oraz częstsze występowanie angiograficznego typu A PDA, co ma istotne znaczenie dla strategii przezskórnego zamykania PDA w różnych miejscach w zależności od lokalizacji geograficznej.

Słowa kluczowe: przetrwały przewód tętniczy, cewnikowanie serca

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