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Cardiology in the Young (2015), **25**, 237–244
doi:10.1017/S1047951113002072

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Original Article

Cerebral microemboli detection and differentiation during transcatheter closure of atrial septal defect in a paediatric population

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Abstract *Introduction:* The aim of this prospective study was to determine the frequency and composition of cerebral microemboli in a paediatric population during transcatheter atrial septal defect closure. *Methods:* Multi-frequency transcranial Doppler was used to detect microembolic signals in the middle cerebral artery of 24 patients. Embolic signals were automatically identified and differentiated according to their composition, gaseous or solid. The procedure was divided into five periods: right cardiac catheterisation; left cardiac catheterisation; pulmonary angiography; balloon sizing; and device placement. *Results:* Microemboli were detected in all patients. The median number of signals was 63 and over 95% gaseous. The total number of microembolic signals detected during two periods – balloon sizing and sheath placement and device placement – was not significantly different (median: 18 and 25, respectively) but was significantly higher than each of the other three periods ($p < 0.001$). In eight patients, the device was opened more than once and the number of embolic signals decreased with each successive device deployment. There was no correlation between the number of microembolic signals and fluoroscopic time, duration of procedure, age, or device size. *Conclusion:* This is the first study to investigate the timing and composition of cerebral microemboli in a paediatric population during cardiac catheterisation. Microembolic signals were related to specific catheter manipulations but were not associated with fluoroscopic time or duration of procedure.

Keywords: Atrial septal defect; transcranial Doppler; systemic emboli

Received: 27 January 2013; Accepted: 29 September 2013; First published online: 13 February 2014

During the past two decades there has been a marked increase in interest regarding the effects of cardiac surgery on the brains of both adults and children. Despite its extensive use, the cerebral aspects of paediatric cardiac catheterisation have not received similar attention. Interventional cardiac catheterisation in both adult and paediatric populations is, however, known to be associated with the formation of cerebral microemboli.[1–4]

Transcatheter closure of atrial septal defects, one of the most common paediatric catheter-based interventions, was first approved by the US Food and Drug Administration in 2001. Since then, the use of the Amplatzer septal occluder device (AGA Medical, Golden Valley, Minnesota, United States of America) has become an accepted first-line treatment option.[5–9] The procedure compares favourably with surgical closure as it is less invasive, requires a shorter hospital stay, and is considered safe. Furthermore, it has been postulated that surgical repair, utilising cardiopulmonary bypass, may have a detrimental effect on subsequent neurodevelopmental outcome.[10] The results of this retrospective study have, however, been disputed by subsequent findings.[11,12]

Transcatheter closure involves the placement of catheters, a balloon, and a septal occluder device

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https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

within the left atrium. There is therefore a risk of microembolus formation, with direct communication to the systemic and subsequently cerebral arterial circulation. Furthermore, paediatric cardiac catheterisation has previously been shown to impose transient fluctuations in cerebral blood flow.[13,14] Major adverse events are reported in 1–4% of paediatric cardiac catheter procedures.[15–20] Acute neurological events are less common but do occur.[16,21–25]

A recent study investigated the timing and factors associated with cerebral microembolic signals in a mixed adult and paediatric population during transcatheter closure of atrial septal defects.[1] The authors found a correlation between the time taken for device placement and the number of embolic signals detected; two similar studies in adults have also been published. However, to date there have been no published studies investigating either the composition of the microemboli detected – gaseous or solid – during atrial septal defect occlusion or the timing of cerebral microembolic signals in a purely paediatric population.

Aims

The aim of this prospective study was to use multi-frequency transcranial Doppler to determine the quantity, timing, composition, and factors associated with the formation of cerebral microembolic signals during transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder.

Materials and methods

The population in this prospective cohort study consisted of consecutive children who underwent transcatheter closure of secundum atrial septal defects at the Oslo University Hospital, Rikshospitalet. The study protocol was approved by the regional ethics committee. Written, informed consent to participate in the study was obtained from all families the day before catheterisation. Patient demographics are presented in Table 1. The median age was 3 years (range 17 months to 17 years). There were eight male and 16 female patients. Of the 32 consecutive patients included in the study from whom recordings were made, eight were excluded: three because of poor signal quality and five because of technical problems with real-time data storage, which made it impossible to control the findings off-line after the procedure. The indication for transcatheter closure of the defect was in accordance with AHA guidelines for interventional treatment, with haemodynamic significance defined as evidence of right-sided heart volume overload.[26] In practice, a complete evaluation also including ECG and X-ray was performed in all patients. There were three patients who were under 2 years of age. The interventional paediatric cardiologists at Rikhospitalet have previously published their results following catheterisation of younger patients but have recently moved to a more conservative approach in keeping with other European centres.[27]

Transcranial Doppler measurements

Patients were placed in a supine position in the catheterisation laboratory under general anesthesia. Continuous, unilateral monitoring of either the left or right middle cerebral artery for both cerebral microemboli and cerebral blood flow velocities was performed beginning 3–5 minutes before femoral venous access was obtained and until all catheters and femoral venous access lines were removed. The middle cerebral artery is responsible for 70% of blood flow to the ipsilateral cerebral hemisphere. The right or left middle cerebral artery was non-invasively monitored through the temporal bone, which had the best acoustic window. The bifurcation of the middle cerebral artery (M1 segment, antegrade flow) and anterior cerebral artery (A1 segment, retrograde flow) was then identified, ensuring a reproducible window and the sample volume was then set. Range-gated, multi-frequency transcranial Doppler instrumentation (EmboDop, DWL, Singen, Germany) was used. Cerebral microembolic signals were automatically identified and differentiated. The timing and occurrence of signals relative to catheter and device manipulations was simultaneously registered.

The multi-frequency Doppler instrumentation insonates simultaneously with 2.0 and 2.5 MHz frequencies. Embolus differentiation is based on the principle that solid microemboli reflect more ultrasound at 2.5 than 2 MHz. The opposite is true for gaseous microemboli. The criteria for the automatic detection and differentiation of cerebral microembolic signals were based on those previously detailed[28–30] but were refined for the paediatric population as follows: the detection level for microembolic signals was a 9.5-dB power increase above the background level (dEBR; embolus blood ratio), which lasted 4 ms simultaneously in both 2.0- and 2.5-MHz frequency channels and the lower dEBR detection limit for solid emboli was $y = -0.1x - 0.12$ dB where $y = \text{dEBR}$ and $x = 2.0$ MHz EBR.[30] All real-time recordings were saved and all automatically detected emboli and decibel levels were manually controlled off-line.

Measurements of maximum cerebral blood flow velocities were continuously monitored and recorded. The patients mean arterial pressure, temperature, and oxygen saturation were also monitored and noted every 5 minutes.

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

Table 1. Patient demographics.

Patient	Age (years)	Weight percentile	Device size (mm)	No. of device deployments	Fluorscopic time (minutes)	Procedure time (minutes)	No. of microembolic signals	No. of solid microembolic signals	Microembolic signals per time period				
									Right catheterisation	Left catheterisation	Pulmonary angiography	Balloon sizing	Device placement
1	3.2	10	18	5	16.5	55	61	1	1	1	0	28	30
2	7.2	90	16	2	11.8	49	21	0	0	1	0	7	13
3	10.25	50	20	1	18.8	65	74	1	2	3	0	12	57
4	5.4	50	14	1	8	65	69	10	0	14	0	35	20
5	3.1	90	8	2	14.6	58	73	10	0	8	3	29	33
6	2.6	<2.5	18	9	16.6	58	46	2	2	0	1	16	25
7	1.5	25	14	1	17.1	55	47	2	0	6	0	16	25
8	5.6	<2.5	13	1	16.5	33	38	4	0	1	0	13	24
9	1.5	50	13	1	15.7	65	44	2	0	21	1	4	18
10	2.8	2.5	17	1	6.2	45	63	1	0	3	0	28	32
11	17	50	12	2	8.2	34	27	2	0	0	0	2	21
12	2.25	2.5	14	1	7.6	40	67	0	0	2	0	19	46
13	9.75	75	12	4	13	42	76	11	0	1	0	9	66
14	1.6	10	7	1	11	67	91	0	0	0	1	71	19
15	3	2.5	15	5	13.6	45	112	1	7	1	1	46	57
16	9	50	10	1	12.7	55	36	0	0	1	3	14	18
17	15	50	9	1	6.4	39	9	0	0	0	0	1	7
18	3.75	90	12	1	6.4	44	104	0	0	34	0	47	23
19	12.75	25	22	1	10.3	51	69	0	0	14	16	17	22
20	2.6	10	11	1	5.5	42	58	1	0	0	0	37	21
21	9.2	90	9	1	10.3	50	86	0	11	14	0	33	28
22	2.75	2.5	20	3	7.8	25	91	4	19	1	0	26	45
23	2	2.5	16	5	6.2	47	84	3	11	0	0	28	45
24	2.5	25	8	1	26.5	90	242	6	28	19	0	91	96

Catheterisation

The National Hospital, Rikshospitalet, Oslo, is the sole tertiary referral centre for interventional paediatric cardiac procedures in Norway. All catheterisations were elective and were performed by either one of the three experienced interventional paediatric cardiologists practising in Norway. All procedures were carried out under general anesthetic with trans-oesophageal echocardiography monitoring. Following the introduction of femoral access sheaths, intravenous Heparin (either 75 or 100 Unit/kg) was administered. Oxygen saturation measurements were obtained from the vena cava, right atrium and right ventricle, and the pulmonary arteries. Similar measurements were obtained from the left atrium and/or pulmonary veins in all patients by passing the catheter through theatrical septal defect. Pressures were measured in both atria and the pulmonary arteries. In all but one patient, pulmonary artery angiography was also performed before sizing of the septal defect.

Following these diagnostic procedures, a stiff guide wire was placed in a pulmonary vein. A long sheath and sizing balloon and was then advanced over the guide wire and inflated within the septal defect. The balloon size was measured both radiographically and with trans-oesophageal echocardiography. The balloon was then deflated and withdrawn. A long sheath/device introducer was then advanced into the pulmonary vein and the selected septal occluder device introduced via this long sheath. The Amplatzer TorqVue Delivery system, Terumo Introducer Sheath, Amplatzer Sizing Balloon, and Super Stiff guide wire was used in all cases.

Monitoring periods

The entire procedure was divided into five periods: right cardiac catheterisation; left cardiac catheterisation; pulmonary angiography; balloon sizing; and device placement, including long sheath placement). The number and type of cerebral microembolic signals in each of these periods was calculated and compared.

Statistical analysis

The numbers of microembolic signals detected during the monitoring periods are shown as median and range (non-normal distribution). The Mann–Whitney test was used for comparison of independent samples, and Freidman's test was used for assessment of variance within patients. Pearson's correlation coefficient was used to determine the correlation between cerebral microembolic signals – gaseous, solid, and combined – and the total procedure time, total fluoroscopic time, device placement time – both with and without long sheath placement – and time for combined balloon sizing and device placement. All calculations were carried out using the statistical software SPSS for Windows (Version 16; SPSS Inc, Chicago, Illinois, United States of America).

Results

Cerebral microembolic signals were detected in all patients. A total of 1688 signals were detected during the 24 procedures. Of the total emboli, 1628 (95.3%) were gaseous and 60 (4.7%) were solid. The median number of all microembolic signals – both gaseous and solid – was 67, range 9–242. The median number of gaseous signals was 62, range 9–236. The median number of solid signals was 1, range 0–11. Solid emboli were detected in 16 of the 24 patients. All microembolic signals were detected after vascular access was obtained. Over 99% of the signals were temporally associated with specific catheter or device manipulations.

Detection of microembolic signals in two periods, balloon sizing and device placement and release, was significantly higher than in the three remaining periods: right cardiac catheterisation, left cardiac catheterisation, and pulmonary angiography (Table 2). Of all the microembolic signals, 84.4% were detected during these two time periods. A further 8.5% of all signals were detected during left cardiac catheterisation. Similar results were obtained for the detection of solid emboli (Table 1). For the purposes of statistical analysis, the two time periods above were further subdivided. First, balloon sizing was subdivided into guide wire and catheter advancement and balloon sizing. Second, device placement was divided into long sheath placement and device placement. There was no significant difference in the detection of embolic signals between these four periods and detection in these four periods remained significantly higher than in the three remaining periods (Table 3).

There was no correlation with either the number of either total or gaseous cerebral microembolic signals and total procedure time, fluoroscopic time, device placement time – both including and not including long sheath placement – or combined balloon sizing and device placement time. No correlation between device size, introducer size, or sheath size with either the total number of all microembolic signals or gaseous microembolic signals was detected during the entire procedure or during device manipulation.

In eight of the patients, the occlusion device was deployed several times in order to ensure optimal and secure placement. In all but one of these patients (patient 1), the number of microembolic signals detected decreased with each successive deployment. In patient 1, the device was deployed three times before it became attached to fixed structures within the atrium as an attempt to close it again was made.

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

Table 2. This table shows the five periods of the transcatheter procedure and the median and total number of MES detected during each period in all patients.

Procedure periods	Median number of MES detected (range)	Total MES detected in all patients (%)	% patients in who MES were detected	Freidman's test rank (significance < 0.01)
Right cardiac catheterisation	0 (0–28)	78 (4.6)	5 (21)	1.88
Left cardiac catheterisation	1 (0–34)	144 (8.5)	17 (71)	2.55
Pulmonary angiography	0 (0–16)	25 (1.5)	5 (21)	1.71
Balloon sizing	22.5 (1–91)	629 (37.4)	23 (96)	4.17
Long sheath and device placement	25 (7–96)	794 (47)	24 (100)	4.71

MES = microembolic signals

The percentage of patients in whom MES were detected in each period is given in column 4. The Friedman's test ranking illustrates that the number of emboli detected during balloon sizing and device placement was significantly higher than during the other three periods

Table 3. Number of microembolic signals with each successive deployment of the occluder device in the eight patients in whom the device was opened more than once.

		Number of microembolic signals						
Patient	Total number of device deployments	Deployment	1	2	3	4	5	6
1	4		12	2	1	10		
1	1 (new device)		5					
2	2		10	3				
5	2		15	0				
6	9		12	4	1	1	0	0
11	2		14	0				
13	4		34	16	0	0		
15	5		22	10	9	0	0	
23	3		26	9	2			

In one patient (patient 1) the device was deployed three times before becoming attached to fixed structures within the atrium when an attempt to draw it into the delivery catheter was made. It was fully deployed again before being closed and withdrawn from the patient.

With each of these three consecutive deployments, the number of embolic signals decreased. Following further manipulation, however, the number of embolic signals increased with a fourth deployment. This device was then completely withdrawn and a new device introduced and successfully placed. For patient 6, the atrial septal defect was measured to 18 mm and the device was deployed a total of nine times. The child was 2.6 years old and weighed 10.5 kg and it was therefore technically challenging to securely attach an 18 mm device.

In 20 patients, solid microembolic signals were detected during the device placement phase of the procedure. In five of these patients, the device was deployed more than once, but solid embolic signals were only detected during the first deployment of the left atrial disk.

All catheterisation procedures were successful with regard to device placement. In one patient, the oxygen saturation fell because of lung atelectasis during the procedure: this was quickly corrected by the attending anesthetist. No other adverse events – moderate or severe – were noted during any of the other procedures. No episodes of systemic hypotension or decreases cerebral blood flow velocity were observed in any of the patients included in this study. All patients were discharged the following day. No patients developed signs or symptoms consistent with neurological dysfunction either immediately following the procedure or within the 24 hours leading up to discharge.

Discussion

This is the first study to use multi-frequency transcranial Doppler instrumentation for the detection and differentiation of cerebral microembolic signals during transcatheter closure of atrial septal defects. It is in addition the first study to investigate the timing and number of cerebral microembolic signals in a purely paediatric population undergoing any form of interventional cardiac catheterisation. No correlation between either the number of embolic signals detected, the duration of the procedure, fluoroscopic time, or time used for placement of the Amplatzer septal occlusion device was found.

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

Over 96% of the detected embolic signals were gaseous. The majority were detected during the periods of balloon sizing or septal device deployment. It has been demonstrated, however, that in those patients in whom the occlusion device was deployed more than once, the number of microembolic signals detected decreased with each successive deployment. Furthermore, in a subgroup of patients in whom solid microemboli were detected during device placement and in whom the device was deployed more than once, solid microemboli were only detected with the first deployment of the septal occluder. The findings do not indicate increasing risk of embolus formation in relation to the length of the procedure, thereby supporting the common practice of giving a single dose of heparin. However, most procedures lasted <60 minutes, and the study population size does not allow for a statistical evaluation of the effect of antithrombotic prophylaxis in longer procedure times. In a recent paediatric study, however, the measured level of heparinisation correlated negatively with procedure time.[31]

A total of only 15 emboli, <0.1% of the total number detected, were not directly temporally related to a specific catheter or device manipulation. These signals, which we have determined to label as random, were instead detected during a period of occluder device preparation or, more commonly, following balloon inflation. It is important to note that no signals were detected before the start of the procedures – venous line access – or after the catheter devices were removed.

There are three studies investigating the timing and detection of microemboli during transcatheter closure of either a patent foramen ovale or secundum atrial septal defect that have previously been published.[1–3] Ferrari et al monitored 35 adult patients (age range 24–59 years): 29 during patent foramen ovale closure and a further six during atrial septal defect closure. Cerebral microembolic signals were detected in 33 patients. The highest rates of signals were observed when the septum was crossed with a guide wire, when the left atrial disc was deployed and with balloon sizing. Patients underwent neuropsychological testing both before and after the procedure. There was no evidence of a general neuropsychological impairment following the procedure and no association between the number of cerebral microemboli and changes in neuropsychological scores.[2] Morandi et al examined 29 adult patients (mean age 45 ± 15 years) undergoing transcatheter closure of patent foramen ovale. All had previously suffered a stroke or transient ischaemic attack. They reported the highest rates of microembolic signals during left disc opening (96% of patients) and with septal catheterisation (48% of patients), with an average count of 31 (range 1–135) and 3 (range 1–18), respectively.[3]

Itoh et al used transcranial Doppler to investigate the frequency and factors associated with cerebral microemboli during transcatheter closure of secundum atrial septal defects in 16 patients from a mixed adult and paediatric population (age range 7.8–42.3 years). The median number of embolic signals was 31.5 (range 3–113), with the majority of signals being detected during balloon sizing and long sheath placement and device placement, with median numbers of 9.6 and 6.5, respectively.[1] This contrasts with the larger number of emboli detected in our study (63). Itoh et al used single frequency transcranial Doppler and automated embolic signal detection software (FS1) for embolus detection. However, they did not describe their detection criteria, provide a reference, or state whether if they had modified their embolus detection software for paediatric use. We used multi-frequency Doppler with pre-defined Doppler energy criteria, and all of the automatically detected emboli were also manually controlled off-line. The difference in embolus detection criteria may therefore explain the difference with regard to the number of emboli detected in the two studies.

In adult populations undergoing diagnostic left cardiac catheterisation[4,32] or transluminal coronary angioplasty,[33] emboli formation occurs mainly with angiography and has been shown to be significantly related to the volume of contrast used[4] or the duration of the procedure.[34] No such relationship was demonstrated in this study. This is due to the fact that patients in this study underwent only one angiographic study with contrast injected into the pulmonary arteries. Itoh et al demonstrated a positive correlation between time for device manipulation and total number of microembolic signals ($r = 0.77$).[1] Again, this result was not reproduced in this study, even when the period for device placement time was further subdivided into long sheath placement and device placement time. This is consistent with our finding that when an occluder device is opened several times the number of cerebral microembolic signals decreases with each successive deployment. In this study, neither the number of total emboli or gaseous emboli correlated with total procedure time, fluoroscopic time, or contrast volume.

The microembolic signals – except those labelled random – were detected in clusters, as opposed to single embolic signals. Therefore, groups of microemboli enter the cerebral circulation with the advancement of stiff guide wires, balloon inflation, or device deployment. There remains some debate regarding the pathological significance of such microemboli. Diffusion-weighted magnetic resonance imaging has identified silent, acute brain

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

injury following percutaneous cardiac catheterisation in adult populations.[4,34] In one of these studies, patients with new lesions following catheterisation had significantly higher numbers of solid microemboli. In addition, cognitive impairment following catheterisation was shown to be related to the degree of brain injury demonstrated by magnetic resonance imaging before the procedure, suggesting differing degrees of intra-patient tolerance to microembolic injury.[4] Studies in patients with a mechanical heart valve suggest that gaseous microemboli do not cause cerebral injury,[35,36] whereas the detection of solid microemboli was significantly higher in patients who had suffered a cerebrovascular event.[37] There are conflicting results from studies investigating the effects of cerebral microembolic signals during carotid endarterectomy and carotid angioplasty and stenting. Whereas several authors have not found a link between embolic signals and new onset symptoms of cerebrovascular disease,[38–40] other studies have demonstrated an association.[41–43] The findings of one of these studies suggest that both solid and gaseous emboli may be harmful to the brain,[41] a finding that is supported by other authors.[44,45]

Of all the cerebral microembolic signals detected, 84.4% were detected during either balloon sizing or device placement. A further 8.5% were detected with blood tests or saturation measurements from the left atrium or pulmonary veins. The formation of cerebral microemboli in this paediatric population was therefore related to specific manipulations but not their duration. Although the use of a balloon for sizing of the septal defect is the accepted standard, two recent articles have advocated sizing of the septal defect without the use of a balloon.[46,47] In addition, by refining techniques further, for example the preparation and attachment of the occluder device to its introducer or by deploying the device at least once in the vena cava, the burden of cerebral microemboli could be greatly reduced.

Study limitations

All patients were discharged the day following cardiac catheterisation. All procedures were described as uncomplicated and none of the patients developed new, clinical neurological symptoms at the time of discharge. Acute, "silent" neurological injury could not be excluded, however, as diffusion-weighted magnetic resonance imaging was not performed either pre or post catheterisation as in this paediatric population such an investigation would, in the vast majority of these patients, have required an additional general anesthetic.

Monitoring as the middle cerebral artery on one side only, as opposed to monitoring both middle cerebral arteries simultaneously. In addition, given that the microemboli tend to come in clusters, it is almost impossible to be certain that each individual signal is included.

Conclusion

Cerebral microemboli are frequent during paediatric cardiac catheterisation and are associated with specific catheter manipulations. No correlation between the number of embolic signals and fluoroscopic time or duration of procedure was demonstrated in this purely paediatric population. Although the majority of these emboli are gaseous, it cannot be excluded that both solid and gaseous emboli may be harmful to the brain. Transcranial Doppler is a beat-to-beat online monitoring system that can inform the interventionalist that microemboli are beginning to enter the brain's circulation. This may allow immediate procedure adjustments that may prevent further microembolisation.

Acknowledgement

Dr Wallace received a research grant from the Norwegian Foundation for Health and Rehabilitation.

References

1. Itoh S, Suda K, Kishimoto S, et al. Microembolic signals measured by transcranial Doppler during transcatheter closure of atrial septal defect using the Amplatzer septal occluder. Cardiol Young 2011; 21: 182–186.
2. Ferrari J, Baumgartner H, Tentschert S, et al. Cerebral microembolism during transcatheter closure of patent foramen ovale. J Neurol 2004; 251: 825–829.
3. Morandi E, Anzola GP, Casilli F, Onorato E. Silent brain embolism during transcatheter closure of patent foramen ovale: a transcranial Doppler study. Neurol Sci 2006; 27: 328–331.
4. Lund C, Nes RB, Ugelstad TP, et al. Cerebral emboli during left heart catheterization may cause acute brain injury. Eur Heart J 2005; 26: 1269–1275.
5. Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. J Am Coll Cardiol 2002; 39: 1836–1844.
6. Rigatelli G, Cardaioli P, Hijazi ZM. Contemporary clinical management of atrial septal defects in the adult. Expert Rev Cardiovasc Ther 2007; 5: 1135–1146.
7. Thomas VC, Vincent R, Raviele A, Diehl H, Qian H, Kim D. Transcatheter closure of secundum atrial septal defect in infants less than 12 months of age improves symptoms of chronic lung disease. Congenit Heart Dis 2012; 7: 204–211.
8. Cardenas L, Panzer J, Boshoff D, Malekzadeh-Milani S, Ovaert C. Transcatheter closure of secundum atrial defect in small children. Catheter Cardiovasc Interv 2007; 69: 447–452.
9. Diab KA, Cao QL, Bacha EA, Hijazi ZM. Device closure of atrial septal defects with the Amplatzer septal occluder: safety and outcome in infants. J Thorac Cardiovasc Surg 2007; 134: 960–966.

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press

10. Visconti KJ, Bichell DP, Jonas RA, Newburger JW, Bellinger DC. Developmental outcome after surgical versus interventional closure of secundum atrial septal defect in children. Circulation 1999; 100: II145–II150.
11. Stavinoha PL, Fixler DE, Mahony L. Cardiopulmonary bypass to repair an atrial septal defect does not affect cognitive function in children. Circulation 2003; 107: 2722–2725.
12. Quartermain MD, Ittenbach RF, Flynn TB, et al. Neuropsychological status in children after repair of acyanotic congenital heart disease. Pediatrics 2010; 126: e351–e359.
13. Rodriguez RA, Hosking MC, Duncan WJ, Sinclair B, Teixeira OH, Cornel G. Cerebral blood flow velocities monitored by transcranial Doppler during cardiac catheterizations in children. Cathet Cardiovasc Diagn 1998; 43: 282–290.
14. de Vries JW, Hoorntje TM, Sreeram N. Neurophysiological effects of pediatric balloon dilatation procedures. Pediatr Cardiol 2000; 21: 461–464.
15. Bergersen L, Gauvreau K, Jenkins KJ, Lock JE. Adverse event rates in congenital cardiac catheterization: a new understanding of risks. Congenit Heart Dis 2008; 3: 90–105.
16. Bergersen L, Marshall A, Gauvreau K, et al. Adverse event rates in congenital cardiac catheterization – a multi-center experience. Catheter Cardiovasc Interv 2010; 75: 389–400.
17. Momenah TS, McElhinney DB, Brook MM, Moore P, Silverman NH. Transesophageal echocardiographic predictors for successful transcatheter closure of defects within the oval fossa using the CardioSEAL septal occlusion device. Cardiol Young 2000; 10: 510–518.
18. Rigby ML. The era of transcatheter closure of atrial septal defects. Heart 1999; 81: 227–228.
19. Thanopoulos BD, Laskari CV, Tsaousis GS, Zarayelyan A, Vekiou A, Papadopoulos GS. Closure of atrial septal defects with the Amplatzer occlusion device: preliminary results. J Am Coll Cardiol 1998; 31: 1110–1116.
20. Kannan BR, Francis E, Sivakumar K, Anil SR, Kumar RK. Transcatheter closure of very large (> or = 25 mm) atrial septal defects using the Amplatzer septal occluder. Catheter Cardiovasc Interv 2003; 59: 522–527.
21. Cassidy SC, Schmidt KG, Van Hare GF, Stanger P, Teitel DF. Complications of pediatric cardiac catheterization: a 3-year study. J Am Coll Cardiol 1992; 19: 1285–1293.
22. Vitiello R, McCrindle BW, Nykanen D, Freedom RM, Benson LN. Complications associated with pediatric cardiac catheterization. J Am Coll Cardiol 1998; 32: 1433–1440.
23. Zeevi B, Berant M, Fogelman R, Galit BM, Blieden LC. Acute complications in the current era of therapeutic cardiac catheterization for congenital heart disease. Cardiol Young 1999; 9: 266–272.
24. Agnoletti G, Bonnet C, Boudjemline Y, et al. Complications of paediatric interventional catheterisation: an analysis of risk factors. Cardiol Young 2005; 15: 402–408.
25. Rhodes JF, Asnes JD, Blaufox AD, Sommer RJ. Impact of low body weight on frequency of pediatric cardiac catheterization complications. Am J Cardiol 2000; 86: 1275–1278, A9.
26. Feltes TF, Bacha E, Beekman RH, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation 2011; 123: 2607–2652.
27. Bjørnstad PG, Holmstrøm H, Smevik B, et al. Transcatheter closure of atrial septal defects in the oval fossa: is the method applicable in small children? Cardiol Young 2002; 12: 352–356.
28. Brucher R, Russell D. Automatic online embolus detection and artifact rejection with the first multifrequency transcranial Doppler. Stroke 2002; 33: 1969–1974.
29. Russell D, Brucher R. Online automatic discrimination between solid and gaseous cerebral microemboli with the first multifrequency transcranial Doppler. Stroke 2002; 33: 1975–1980.
30. Russell D, Brucher R. Embolus detection and differentiation using multifrequency transcranial Doppler. Stroke 2006; 37: 340–341.
31. Chen D, Långstrom S, Petaja S, et al. Thrombin formation and effect of unfractionated heparin during pediatric cardiac catheterization. Catheter Cardiovasc Interv 2013; 81: 1174–1179.
32. Leclercq F, Kassnasrallah S, Cesari JB, et al. Transcranial Doppler detection of cerebral microemboli during left heart catheterization. Cerebrovasc Dis 2001; 12: 59–65.
33. Bladin CF, Bingham L, Grigg L, Yapanis AG, Gerraty R, Davis SM. Transcranial Doppler detection of microemboli during percutaneous transluminal coronary angioplasty. Stroke 1998; 29: 2367–2370.
34. KA Busing, Schulte-Sasse C, Fluchter S, et al. Cerebral infarction: incidence and risk factors after diagnostic and interventional cardiac catheterization – prospective evaluation at diffusion-weighted MR imaging. Radiology 2005; 235: 177–183.
35. Kofidis T, Fischer S, Leyh R, et al. Clinical relevance of intracranial high intensity transient signals in patients following prosthetic aortic valve replacement. Eur J Cardiothorac Surg 2002; 21: 22–26.
36. ZG Nadareishvili, Beletsky V, SE Black, et al. Is cerebral microembolism in mechanical prosthetic heart valves clinically relevant? J Neuroimaging 2002; 12: 310–315.
37. Skjelland M, Michelsen A, Brosstad F, Svennevig JL, Brucher R, Russell D. Solid cerebral microemboli and cerebrovascular symptoms in patients with prosthetic heart valves. Stroke 2008; 39: 1159–1164.
38. Poppert H, Wolf O, Resch M, et al. Differences in number, size and location of intracranial microembolic lesions after surgical versus endovascular treatment without protection device of carotid artery stenosis. J Neurol 2004; 251: 1198–1203.
39. ER Bossema, Brand N, Moll FL, Ackerstaff RG, van Doornen LJ. Perioperative microembolism is not associated with cognitive outcome three months after carotid endarterectomy. Eur J Vasc Endovasc Surg 2005; 29: 262–268.
40. van Heesewijk HP, Vos JA, Louwerse ES, et al. New brain lesions at MR imaging after carotid angioplasty and stent placement. Radiology 2002; 224: 361–365.
41. Skjelland M, Krohg-Sorensen K, Tennoe B, Bakke SJ, Brucher R, Russell D. Cerebral microemboli and brain injury during carotid artery endarterectomy and stenting. Stroke 2009; 40: 230–234.
42. Muller M, Reiche W, Langenscheidt P, Hassfeld J, Hagen T. Ischemia after carotid endarterectomy: comparison between transcranial Doppler sonography and diffusion-weighted MR imaging. Am J Neuroradiol 2000; 21: 47–54.
43. Muller M, Behnke S, Walter P, Omlor G, Schimrigk K. Microembolic signals and intraoperative stroke in carotid endarterectomy. Acta Neurol Scand 1998; 97: 110–117.
44. Stump DA. Embolic factors associated with cardiac surgery. Semin Cardiothorac Vasc Anesth 2005; 9: 151–152.
45. CM Muth, Shank ES. Gas embolism. N Engl J Med 2000; 342: 476–482.
46. Wang JK, Tsai SK, Lin SM, Chiu SN, Lin MT, Wu MH. Transcatheter closure of atrial septal defect without balloon sizing. Catheter Cardiovasc Interv 2008; 71: 214–221.
47. Quek SC, Wu WX, Chan KY, Ho TF, Yip WC. Transcatheter closure of atrial septal defects–is balloon sizing still necessary? Ann Acad Med Singapore 2010; 39: 390–393.

https://doi.org/10.1017/S1047951113002072 Published online by Cambridge University Press