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Transcatheter device closure of atrial septal defects: More to think about than just closing the hole

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Abstract

Purpose of the review—To review current controversies in the transcatheter device closure of ostium secundum atrial septal defects (ASD).

Recent findings—Trans-catheter device closure of ASD (TC-ASD) has well-established efficacy and safety. For most individual patients with suitable anatomy, TC-ASD is the preferred method for treating ASD. The availability of large multicenter datasets has made it possible to study practice patterns at a range of hospitals across the United States. These studies have revealed differences in practice that were not previously appreciated. 1) Interpretation of the indications for TC-ASD, specifically the definition of right ventricular volume overload varies between hospitals. 2) In response to concern about device erosion, an increasing proportion of patients are being referred for operative ASD closure. 3) Over the last decade, the average age at which ASD closure occurs has decreased. These trends demonstrate previously under-appreciated differences in opinion between cardiologists across the country, and suggest that further research is necessary to address knowledge gaps limiting consistency of practice.

Summary—As TC-ASD and congenital interventional cardiology mature as a field, studies of real-world practice provide increasingly valuable information about aspects of care where there are disagreements about best practices and where further research is necessary.

Keywords

erosion; pediatric cardiology; transcatheter intervention; outcomes

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Introduction

Ostium secundum atrial septal defects (ASD) are one of the most common forms of congenital heart disease with an incidence of 6 to 10 per 10,000 live births[1]. Transcatheter device closure of ASD (TC-ASD) was first reported by King and Mills in 1976[2]. TC-ASD with the current generation of devices has favorable rates of technical success and risk of adverse events when compared to operative closure of ASD (O-ASD)[3–8]. TC-ASD is the dominant technique for closing ASD; >80% of isolated ASD treated at primary pediatric hospitals in the United States are closed in the catheterization laboratory[9]. Though new devices continue to be developed, the technique for TC-ASD has remained essentially unchanged since the introduction of the Amplatzer Septal Occluder (ASO) in the early 2000's. Recent studies have taken advantage of large multicenter datasets, providing an opportunity to study real-world practice in an innovative fashion. These studies have revealed significant variability in hospital practice in closure of ASD and thus an opportunity to improve the quality of care for patients with ASD.

Current options for device closure of ASD

The history of device development has been summarized elsewhere[10]. Two devices are currently widely available in the United States (Figure 1): the ASO (St. Jude Medical, St. Paul MN) (Figure 1A) and the Gore Cardioform device (W.L. Gore and Associates, Flagstaff, AZ) (Figure 1B). In multicenter series of US centers, the ASO is used in between 70-86% of cases, with the HSO being used in 5-21% of cases[11,12]. The ASO was the first device approved by the FDA for TC-ASD demonstrating safety and efficacy in a non-randomized IDE trial[3], which was reinforced in a subsequent multicenter registry study[13]. It has been in use long enough for several large single-center case series to report excellent medium and long-term outcomes[14–16]. The Gore Helex Septal Occluder (W.L. Gore and Associates, Flagstaff, AZ) also demonstrated excellent safety and efficacy in both short[17–19] and middle term outcomes[20], but is no longer sold in the US. It has been replaced by the Gore Cardioform device, which has a Nitinol wire frame covered with an expanded tetrafluoroethylene membrane. Like the Helex before it, this device was not self-centering and limited to relatively small defects. The initial device trial and continuing access series are complete with manuscripts pending at this time. Gore has produced a second Cardioform device – the Cardioform Atrial Septal Defect Occluder (C-ASDO)-with a larger diameter central waist and an expanded range of diameters, both designed to facilitate closure of larger diameter ASD's (Figure 1C). The newer C-ASDO device is currently undergoing an FDA Pivotal trial(Gore ASSURED Trial; Clinical Trials.gov Identifier NCT02985684) in the United States. In a multicenter series from Canada, both Gore Cardioform devices have demonstrated similar safety and efficacy to previous devices[21]. The Amplatzer multi-fenestrated septal occluder ("Cribriform" device) (St. Jude Medical, St. Paul, MN) resembles the ASO device but has symmetric discs and a narrow waist, designed to allow it to cover the septum when there are multiple ASD.

TC-ASD has demonstrated equal efficacy at closure with excellent safety in comparisons to O-ASD[3,6,8]. In addition, as a relatively non-invasive technology TC-ASD results in less discomfort, superior cosmesis, and shorter hospital length of stay. All of these are potentially

preferable to patients, and when accompanied by improved economic cost represent superior value from the perspective of the entire health system. Comparing current outcomes following TC-ASD and O-ASD is challenging. There are relatively few contemporary series comparing the results of TC-ASD and O-ASD. Large multicenter series are necessary for comparisons because of systematic differences between patients undergoing O-ASD and TC-ASD and the need for statistical adjustment to account for confounding by indication. Representative multi-center series have demonstrated that in-hospital mortality after TC-ASD is between 0-0.015%[11,12,22]. Using data from the Society for Thoracic Surgeons Congenital Heart Surgeons database, the estimated risk of in-hospital mortality for O-ASD is between 0.3-0.9% even after adjusting for pre-operative risk factors[23]. In terms of peri-procedural morbidity, analysis of data from the Pediatric Health Information Systems Database (PHIS) by Ooi and colleagues demonstrated that the adjusted risk of complications and infection were higher following O-ASD than TC-ASD[24]. Morbidity is also reflected in a longer length of stay following O-ASD[5]. Measuring economic cost provides a way to compare the impact of O-ASD and TC-ASD on patients, integrating resource utilization and risk of adverse events in a single measure. Early attempts to compare cost of TC-ASD and O-ASD had equivocal results[25–28], but more recent studies with sufficient sample sizes for case-mix adjustment have demonstrated that the total hospital costs of TC-ASD (including cost of device) are less than those associated with O-ASD[5,24]. Cost savings arise not only from a shorter length of stay but also from reduced pharmacy, radiology, and laboratory costs[5].

The introduction of minimally invasive cardiac surgery (MICS), through "mini-sternotomy" or video assisted thoracoscopic surgery (VATS) (with or without robotic assistance) has the potential to provide a method of closing ASD with reduced morbidity, shorter length of stay, and improved cosmesis compared to O-ASD[29]. In the past year, three case series of MICS for O-ASD have been published[30–32]. The largest series demonstrates that MICS patients were exposed to increased cardiopulmonary bypass times but spent less time on the ventilator [30]. In each of the three series, the median lengths of stay remain between 5-7 days[30–32], which remains significantly longer than LOS for TC-ASD (usually less than a day). Cost comparison of MICS to traditional O-ASD, or TC-ASD for that matter, were not attempted. Given longer length of stay, one would expect that MICS will be more expensive than either O-ASD or TC-ASD. At this time, enthusiasm for MICS is limited to a few centers, and its future as an alternative to conventional O-ASD and TC-ASD remains uncertain.

Practice variation in ASD closure

Traditional studies of ASD closure, either as part of a device trial or through retrospective review of cases, have been effective at demonstrating the safety and efficacy of various ASD closure strategies. Recent access to multicenter databases has allowed research about variability in real-world practice between different hospitals. The presence of inter-center variability points toward a lack of consensus in the delivery of care and an opportunity to improve quality of care. Reducing practice variation through standardization in practice has demonstrably improved resource utilization and traditional patient outcomes for adult cardiac patients in both inpatient[33,34] and outpatient[35–42] settings, as well as adult[43]

and pediatric[44–47] patients with congenital heart disease. In the case of closure of ASD, studies have demonstrated significant practice variation in 1) the distribution and interpretation of indications for TC-ASD, 2) choice between TC-ASD and O-ASD to close ASD, and 3) the age at which ASD closure is pursued (regardless of method). These findings are the results of the first studies of their kind. They highlight the importance of this type of research and suggest avenues for further research with the potential to continue to improve care of patients with ASD.

Indications for ASD closure

Indications for TC-ASD were published by the American Heart Association in 2011 (Table 1)[48]. The IMproving Pediatric and Adult Congenital Treatment (IMPACT®) Registry provides the first opportunity to study how the practices in transcatheter procedures vary between hospitals. IMPACT® is an American College of Cardiology Foundation and National Cardiovascular Data Registry funded clinical registry of hospitals performing transcatheter procedures in children and adults with congenital and acquired cardiac disease and contains demographic, clinical, and procedural information about patients and their procedures[22,49,50]. Special attention is given to six procedures including TC-ASD[50], about which more detailed procedural information is collected. TC-ASD account for 6% of all cases recorded in IMPACT®[11,22,51]. Indications for TC-ASD in IMPACT® are right ventricular volume overload (RVVO), failure to thrive, recurrent respiratory infections/ chronic lung disease, cyanosis and stroke prevention, with the majority (83%) of cases having RVVO as an indication.

Analysis of this dataset demonstrated significant differences in the distribution of these indications by both census region and hospital setting (urban vs. suburban or rural), which could not be explained by measurable confounders[51]. Further analysis studied the subset of cases with RVVO as an indication, measuring the proportion of these cases at each hospital where there was a small shunt (as defined by either the ratio of pulmonary to systemic blood flow (Qp:Qs) or the size of the defect). In this study, 33% of patients whose ASD were closed with RVVO as the listed indication had a Qp:Qs <1.5:1. Importantly, the proportion of these cases at individual hospitals varied systematically with hospital characteristics. Specifically, hospitals with a smaller TC-ASD volume and those with a larger adult catheterization volume had a higher proportion of TC-ASD for the stated indication of RVVO with a small magnitude shunt[51]. It is not possible in this analysis to differentiate between variation in referral patterns and variation in interventional cardiologist practice. However, variation of this kind potentially exposes patients to greater risk of adverse outcome and increases resource utilization unnecessarily. At a minimum, it asserts that current practice guidelines have not resulted in consensus regarding the indications for TC-ASD.

Practice variation in TC-ASD vs. O-ASD

In analysis of data from the PHIS database, TC-ASD accounted for >80% of ASD closure procedures at US pediatric hospitals[9]. However, there was significant variation in how individual centers chose to pursue ASD closure with the range of ASD closure performed in

the catheterization laboratory between 30 and nearly 100%[9]. Even after adjusting for differences in case-mix, there remained significant inter-hospital variability in the choice between O-ASD and TC-ASD[9]. To our knowledge, no other studies have assessed practice variation in ASD closure, but their presence reflects lack of consensus in deciding the strategy to close ASD.

Device erosion and its potential impact on practice patterns

Clinical decision-making is multi-factorial, and it is not possible to assert a causal relationship in an observational study. However, device erosion remains a singular concern for physicians caring for patients with ASD. Erosions of ASO were first reported in a series of case reports in 2003 and 2004[52–54], and a board of physicians was convened to review known cases[55]. Deficient anterior-superior or retro-aortic rim (along with device over-sizing) was identified as a risk factor present in all of their cases. Concern regarding erosions precipitated a United States Food and Drug Administration Panel Review in May of 2012 followed by revision of the manufacturers Indication for Use, labeling a retro-aortic rim <5mm in diameter as a relative contraindication to TC-ASD with an ASO device[56–58]. Subsequent research has demonstrated that the prevalence of deficient retro-aortic rim is between 40-60% of children referred for TC-ASD[11,16,59,60] and slightly lower in adult patients[61].

Concern for device erosion has persisted [62–66], but limitations in longitudinal follow-up of implanted devices has made it impossible to accurately measure the number of devices implanted, the total number of erosions, and the risk of erosion. Best estimates of risk are between 0.04 and 0.3% of device implants[55,57,62,63,67]. The majority of cases present early after device implantation, but remote erosions as late as 8 years after device implantation have been reported[68,69]. The low overall rates of erosion and limited experience at individual centers has complicated identification of patient- and procedure-level risk factors for device erosion. Neither the first version of the IMPACT® [11] nor C3PO [12] contained data about post-discharge adverse events. Since that time, a prospective post-market surveillance study of the ASO was initiated. However, enrollment was stopped in 12/2016, and the results have not been published. The second version of the IMPACT® registry includes the capacity to include follow-up data for pre-specified interventions including TC-ASD. Access to other large observational data-sets (e.g. insurance claims data) may improve our estimates of post-procedural risk.

Moreover, our understanding of the mechanism underlying erosions and identification of the patients at highest risk of erosion has not progressed. Specifically, it is unclear whether 1) anatomic variations (bare vs. small retro-aortic rim or concomitant deficient superior tissue rim) or 2) a combination of anatomy and choice of device (a patient with deficient retro-aortic or superior rim and a large or over-sized device) can provide predict superior risk stratification[55,67,70]. A recent case-control study by McElhinney and colleagues using data from the Erosion Board's collection of cases and controls derived from the ASO Post-Approval Study reiterated that deficient retro-aortic and superior vena cava rims were present in a much higher proportion of cases than controls. In cases with erosion, ASD were larger in diameter and in proportion to patient weight than in controls. Finally, several

factors consistent with device over-sizing (balloon size much larger than static defect size or device much larger than static defect size) were more common in cases and controls[67]. Although this study confirms risk factors for erosion, it was unable to identify a subgroup of patients in which the risk of erosion exceeds the risk of O-ASD.

Moreover, the effect of the erosion debate on actual practice has until recently been challenging to study. Single center studies are subject to small sample sizes and limited generalizability to the general population[71]. Analysis of clinical registry data demonstrated that patients with deficient retro-aortic rim were no less likely to receive ASO devices than those with larger retro-aortic rims[11]. More recently, analysis of administrative data allowed, for the first time, measurement of temporal trends in practice, specifically the propensity to pursue O-ASD and TC-ASD[9]. It demonstrated that prior to 2013, the proportion of TC-ASD was increasing, but that between 2013 and 2015 this trend reversed and the proportion of O-ASD increased slightly relative to TC-ASD (Figure 2).

Though referring patients for O-ASD will inevitably reduce the risk for erosion, this practice only results in a net reduction in harm to patients if the benefit exceeds the inherently higher risks of O-ASD. This can only be accomplished by identifying subgroup(s) of patients with a significantly higher risk of erosion than the overall population risk. The heterogeneity of practice and anatomy combined with the low event rate are real challenges to solving this problem. Post-market surveillance studies have the potential to address these concerns but have not to date made progress. Alternative research strategies to address these concerns may be necessary.

Timing of ASD closure

Another important decision in the care of patients with ASD is the age at which to intervene. From the outset of TC-ASD, there has been interest in treating young (and small) patients with ASD. The original trial for the ASO device did not restrict age or size for the TC-ASD arm. The median age was 9.8 years but with a range from 0.6 to 82 years[3]. The first multicenter study reporting real-world use of the ASO device was a case series from the Mid-Atlantic Group of Interventional Cardiology (MAGIC), which reported the results of 478 cases from 13 centers performed between 2004 and 2007[13]. The median age of patients in this series was 6 years, but again with a broad range (spanning from infancy until 80's). At that time, 33% of reported cases were performed in small patients (defined as <16 kg). Multiple case series demonstrate that TC-ASD can be performed even in patients <10 kg[59,72–76]. At the same time, the majority of cases continue to be performed in school-age patients. Multicenter series from IMPACT® report that the median age of closure remains between 5-7 years)[11,22], and in a study from C3PO, 85% of subjects were older than 3 years[12].

Natural history studies of large ASD demonstrated a decrease in life expectancy, but in almost all patients childhood symptoms due to congestive heart failure are rare, as is the development of pulmonary vascular disease [77–79]. The majority of small defects found in infants close spontaneously[80–82], but the natural history of larger defects has not been well defined. In cross-sectional analyses, an association has been demonstrated between

older patient age at diagnosis and larger defect size[81,82]. This may be due to spontaneous closure of smaller defects, but some have hypothesized that some ASD increase in size over time [83]. This has been used as a justification for early intervention. No studies have followed ASD longitudinally to confirm if some ASD do grow over time. Even if some ASD did grow, it is unclear whether how often that growth would complicate TC-ASD.

In the face of this uncertainty, a recent study of trends in ASD closure using PHIS data demonstrated that patients undergoing ASD closure at primary pediatric hospitals in the US were progressively younger between 2007 and 2015[9]. This was independent of measurable patient-level confounders. It is impossible to determine in this study design the reasons behind this trend. Sensitivity analyses demonstrated that this was not driven by the aforementioned trend to increasing use of O-ASD and was present regardless of closure method. There is also no evidence that the trend is the result of increasing prevalence of pulmonary disease or prematurity that might aggravate the physiological effects of an atrial level shunt.

This trend has the potential to have real ramifications on patient safety. The effect of small size on the risk of adverse events or technical failure has been equivocal in multiple studies [11,12,16]. However, McElhinney and colleagues demonstrated that larger defect size to patient size was a risk factor for device erosion[67]. Therefore, for TC-ASD, the optimal age for closure is not clear. We recommend discussing ASD cases with an interventional cardiologist to determine the right timing for each individual patient.

CONCLUSION

Transcatheter device closure of ostium secundum atrial septal defects has been performed for over forty years. Over that time it has become the gold-standard therapy for closure of most ASD, comparing favorably to operative ASD closure in efficacy, safety, and cost. Large multicenter data-sets have allowed researchers to study practice patterns in the community and identify areas where uncertainty persists. It is our hope that identification of these knowledge gaps will motivate future research that will improve outcomes of patients with ASD.

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KEY POINTS

1. Transcatheter device closure of ostium secundum atrial defects (ASD) has a lower risk of mortality, lower risk of morbidity, shorter length of stay, and lower cost than operative closure of the same defect.
2. Minimally invasive surgical approaches to operative closure of ASD are being used. In skilled hands and appropriately selected patients, they have similar risk of adverse events and length of stay (but improved cosmesis) to conventional surgical approaches, but remain inferior to transcatheter device closure.
3. Studying practice patterns in ASD closure has identified that smaller hospitals and hospitals with predominantly adult patients are more likely to close a small defect with the indication of right ventricular volume overload. The effect of this on clinical outcomes is not clear but it highlights that there are persistent differences in the interpretation of the indications for transcatheter intervention.
4. Erosion of devices after transcatheter closure of ASD remains a concern. The overall risk is between 0.04-0.3% of device implants. The most recent data found that cases were more likely than controls to have smaller superior rims, larger defects relative to the septum and patient size, and were more likely to have an oversized device. Further research is necessary to determine whether a specific subset of patients can be identified whose risk of device erosion exceeds the risks of operative ASD closure.
5. Studying trends in practice have found that transcatheter ASD closure is the predominant method of ASD closure in children and young adults, but that in recent years there is a trend towards increasing use of operative ASD closure. This is coincident with concern for the risk of device erosions. The effect of this trend on outcomes is not clear at this time, but deserves additional attention.

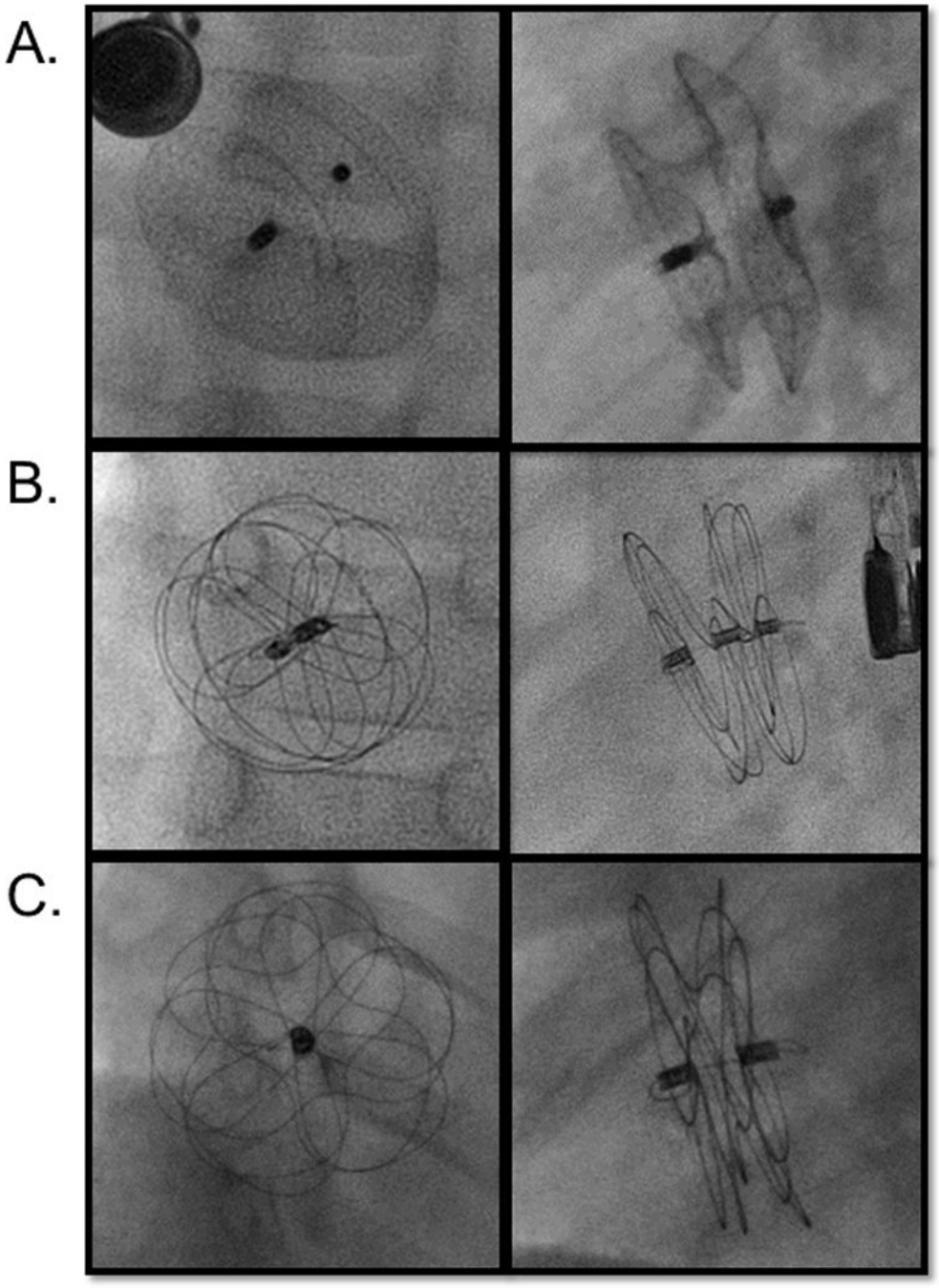

Figure 1. Current TC-ASD Devices Available in the United States

Digital acquisition images of A) Amplatzer septal occlude (anterior posterior and lateral projections), B) Gore Cardioform device (en face and orthogonal views), C) Cardioform Atrial Septal Defect Occluder (en face and orthogonal views).

Figure 2. Estimated probability of TC-ASD vs. O-ASD 2007-2015

Probability of operative ASD closure versus transcatheter ASD closure

Conditional standardization was used to calculate an adjusted probability of operative ASD closure vs. transcatheter device closure, for a hypothetical white male six year old boy with no co-morbid conditions (maroon line with 95% CI represented by the dashed grey lines). This was based on the mixed effects multivariate generalized linear model summarized in Table 2. The probability of operative ASD closure decreased significantly from 2007 until 2012 (OR: 0.95 per year, p=0.02). In 2013, there was a significant shift in probability favoring ASD (OR: 1.21 per year, p=0.006).

Taken from *O'Byrne et al 2017 Increasing Propensity to Pursue Operative Closure of Atrial Septal Defects Following Changes in the Instructions for Use of the Amplatzer Septal Occluder Device An Observational Study Using Data from the Pediatric Health Information Systems Database. Am Heart J (in press)*

Table 1

Indications for transcatheter closure of atrial septal defects

Indication	Class	LOE
Closure is indicated		
Hemodynamically significant ASD with suitable anatomic features	I	B
Transient right to left shunt with history of sequelae of paradoxical emboli	IIA	B
Right to left shunt with symptomatic cyanosis who do not require the communication to maintain cardiac output	IIA	B
Small ASD who are believed to be at high risk of thromboembolic events	IIB	C
Closure is not indicated		
Small secundum ASD without hemodynamically significant shunt with other risk factors	III	B
ASD other than secundum ASD	III	C
Patients with advanced pulmonary vascular obstructive disease	III	C

Abbreviations: ASD atrial septal defect, LOE level of evidence

Feltes TF, Bacha E, Beekman RH, Cheatham JP, Feinstein JA, Gomes AS, Hijazi ZM, Ing FF, de Moor M, Morrow WR, 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.