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Pulmonary Artery Occlusion for Palliation of Unilateral Total Pulmonary Vein Obstruction: Procedure Results and Mid-term Follow-up

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Key Words: occlusion, transcatheter, outcomes, hemoptysis, flow reversal

Abbreviations

1V	single ventricle anatomy
2V	double ventricle anatomy
AP	aorto-pulmonary
bPA	branch pulmonary artery
PVO	pulmonary vein occlusion
RV	right ventricle

Abstract

Objectives: Report efficacy and mid-term outcomes for transcatheter occlusion of ipsilateral branch pulmonary artery (bPA) to palliate unilateral total pulmonary vein obstruction (PVO).

Background: Patients with PVO who are acutely symptomatic and not eligible for surgery have limited transcatheter treatment options. Few palliative catheter-based treatments exist for patients with unilateral PVO who are acutely symptomatic and are not eligible for surgery.

Methods: Procedure results and follow-up were reviewed for patients who underwent transcatheter ipsilateral bPA occlusion to treat pulmonary artery flow reversal or hemoptysis caused by unilateral total PVO at Rady Children's Hospital San Diego between 2003 and 2020.

Results: Seven patients were identified who underwent bPA occlusion with implantation of occluder devices and/or coils. All patients presented with total unilateral PVO, (six left and one right). Three patients had single ventricle anatomy (1V) and four patients had biventricular circulation (2V). Indications for intervention included bPA blood flow reversal ipsilateral to PVO and pulmonary hemorrhage. Procedures were successful in all patients; flow reversal and hemoptysis resolved, and hemodynamic stability was maintained after device placement. There was no difference in pulmonary artery pressure (2V), Fontan pressure (1V), and systemic oxygenation. Systemic blood pressure was not different in 2V

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patients, whereas it increased in 1V patients. Most recent follow-up ranged from 4 months to 16 years (median = 2.8 yrs). All 1V patients were being evaluated for transplant at most recent visit. Two patients were lost to follow-up.

Conclusion: In patients with unilateral total PVO, device occlusion of the ipsilateral bPA may offer palliative benefits.

Introduction

Despite advances in endovascular and surgical techniques for pulmonary vein repair, few interventional techniques exist to treat acutely symptomatic patients with pulmonary vein obstruction (PVO) who are not candidates for surgery.

PVO can arise either as a primary congenital cardiac lesion, which occurs in conjunction with other cardiac abnormalities in 50% of patients, or as a complication secondary to surgical manipulation of the pulmonary veins, as seen in TAPVR repair.[1,2] Although the mechanism behind PVO is poorly understood, its sequelae have been previously documented in the literature.[1,2] PVO causes congestion of the ipsilateral pulmonary and bronchial vasculature, resulting in damage to the lung parenchyma and the pulmonary vasculature. Parenchymal and vascular damage manifests as: alveolar hemorrhage, pulmonary hypertension, friable endobronchial mucosa, recurrent respiratory tract infections, and cyanosis.[1,2,3] In the presence of aortopulmonary (AP) collaterals, as seen in single ventricle patients, PVO can also manifest itself with flow reversal into the contralateral lung, which can be visualized on angiography.[4] As a result of the damage to the lung parenchyma and vasculature or significant alterations in pulmonary artery hemodynamics, patients typically present with acute exertional dyspnea, cough, chest pain, and/or hemoptysis.[1,2]

Current first-line interventions for PVO consist primarily of pulmonary vein surgical reconstruction or recanalization and endovascular balloon angioplasty or stenting.[5] Despite the development of multiple treatment approaches, limited success has been noted in maintaining patency of the pulmonary veins.[6,7] Nevertheless, pulmonary vein rehabilitation can be pursued whenever feasible, particularly prior to progression from stenosis to occlusion.[8] The progressive stenosis leads to occlusion in a sub population of patients who will become symptomatic from lung parenchyma damage caused by chronically high pressures in the ipsilateral lung from diminished prograde blood flow. In cases where primary pulmonary vein repair has failed or may not be feasible, a definitive approach to addressing the symptoms associated with PVO is ipsilateral lobectomy or pneumonectomy.[9] However, a pneumonectomy is a highly invasive procedure associated with significant morbidity and may not be suitable for all patients.[9] Palliating the sequelae of PVO is a critical step to bridging the patient to transplant, which offers a definitive treatment for PVO. Therefore, a minimally invasive treatment is needed for palliating patients suffering from the clinical consequences of unilateral total PVO, who have failed primary transcatheter vein repair and/or are not surgical candidates.

At our institution, a novel procedure has been employed for treating PVO involving the isolation of the branch pulmonary artery (bPA), which corresponds to the obstructed pulmonary veins (e.g. left bPA occluded in case of left PVO), by implanting occluding devices into that pulmonary artery. Despite complexity of the physiological variables controlling both pulmonary and arterial pressures, as well as differences between pulmonary and arterial resistance reserves, we propose that hemodynamic isolation of the ipsilateral bPA prevents both prograde flow into a lung with damaged lung parenchyma and retrograde flow through AP collaterals. This approach may be helpful in cases where patients are acutely symptomatic from PVO and not eligible to undergo transcatheter or surgical repair. As a palliative treatment for PVO, bPA occlusion has rarely been reported. We were able to identify only two case reports in which selective occlusion of a pulmonary artery branch was used to treat PVO in three patients.[11,12]

The aims of this report are to describe the efficacy and outcomes of bPA occlusion as a palliative treatment for PVO. We reviewed the procedures and devices used for bPA occlusion and evaluated the efficacy of this novel treatment by analyzing hemodynamic data, clinical impact of interventions, and mid-term sequelae. We report patients with both single and two ventricle anatomy and physiology who had ipsilateral bPA occlusion.

Methods

This study was approved by the Institutional Review Board of the University of California, San Diego. The study was conducted by reviewing the clinical databases of Rady Children's Hospital San Diego. The study included all patients who had transcatheter occlusion of an ipsilateral bPA to treat unilateral total PVO between January 2003 and June 2020.

The procedures involved right heart catheterization, confirmation of total unilateral PVO via pulmonary angiography **(Figure 1A)**, and implantation of occlusion device(s) **(Figure 1B)**. Patients' clinical presentation, cardiac anatomy and physiology, occlusion devices implanted, hemodynamic measurements, clinical sequelae, and follow-up were reviewed. Systemic blood pressure, pulmonary artery pressure (for two ventricle patients), Fontan pressure (for single ventricle patients), and oxygen saturation before and after the placement of the occlusion device were analyzed for single and two ventricle patients to identify hemodynamic differences. Hemodynamic data of single ventricle and two ventricle patients were analyzed separately. Descriptive statistics were used to analyze hemodynamic data (mean ± standard deviation), and statistical analysis using a paired t-test in MS-Excel (Microsoft 2010, Redmond, WA) was conducted. A p-value ≤ 0.05 was considered the threshold for statistical significance. The effects of bPA branch occlusion were analyzed either intra-operatively, where flow reversal was observed to be eliminated after bPA occlusion via angiography, or clinically by the resolution of hemoptysis.

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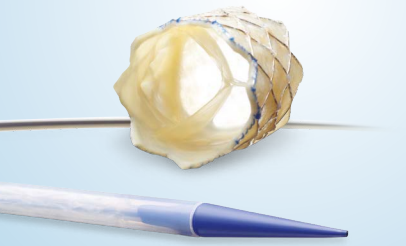

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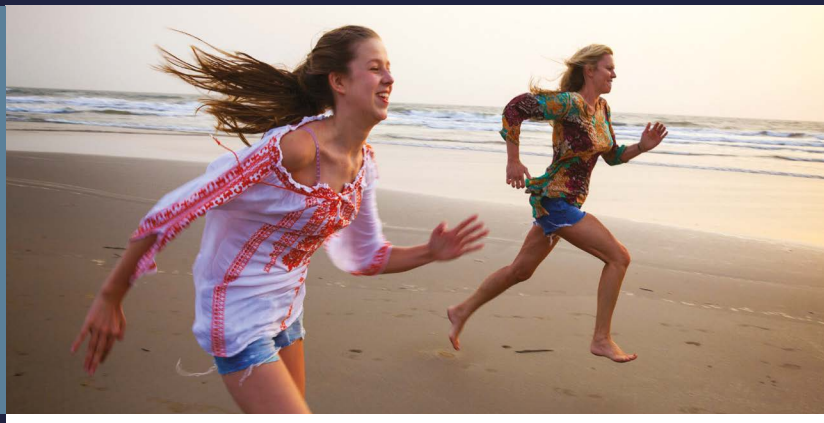

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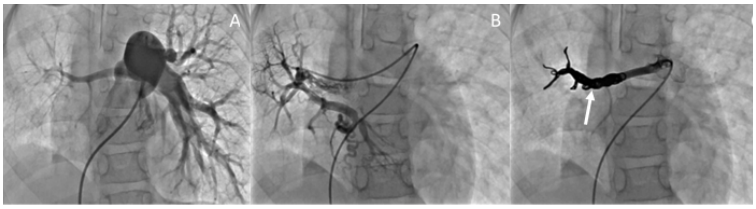

FIGURE 1 *AP view of cardiac fluoroscopy during bPA (branch pulmonary artery) Occlusion Procedure: **(A)** fluoroscopy demonstrating left lung without pulmonary venous occlusion, **(B)** fluoroscopy demonstrating right lung with pulmonary venous occlusion and **(C)** fluoroscopy in the same patient post-occlusion of the right pulmonary artery with the white arrow indicating the occlusion device.*

Results

Patient Characteristics and Patient Selection

During the study period, seven patients underwent transcatheter ipsilateral bPA occlusion. Patient ages ranged from 1.3 to 12.5 years, with the average age at intervention of 5.2 years **(Table 1)**. Congenital cardiac diagnoses varied among patients, but all patients had undergone prior surgical intervention with palliation to either single (n = 3) or two ventricle (n= 4) physiology **(Table 1)**. Prior interventions involving pulmonary veins had been performed among three patients: two had angioplasty of the left and right pulmonary veins and the third had stenting of the left upper pulmonary vein. None had prior pulmonary vein surgery. All patients ultimately developed total obstruction of left pulmonary veins (n = 6) or right pulmonary veins (n = 1). The indications for performing ipsilateral bPA occlusion were either the presence of blood flow reversal in the bPA ipsilateral to the PVO, noted during prior catheterization (n=3) or pulmonary hemorrhage presenting with hemoptysis (n=4) **(Table 1)**. Additionally, all patients were evaluated for surgical intervention at the time of presentation to Rady Children's Hospital but were not good surgical candidates. Patients 1, 4, 6, and 7 presented with hemoptysis, while patients 2, 3, and 5 were asymptomatic other than the flow reversal present on catheterization. Patient 1 experienced three episodes of hemoptysis prior to bPA occlusion. Patient 4 experienced two episodes of hemoptysis and bPA occlusion was conducted as treatment for the second hemoptysis episode. Patient 6 had at least two episodes of hemoptysis with the second involving cardiac arrest and urgent catheterization. Patient 7 underwent bPA occlusion after the first episode of hemoptysis due to persistent pulmonary hemorrhage.

TABLE 1 *Patient Cardiac Anatomy, Presenting Symptoms, and Age at Time of Intervention*

Patient	Age at Procedure (yrs)	Anatomy	Number of Ventricles	PVO Laterality	Presentation
1	3.4	PA/IVS s/p Fontan	1 ventricle	Left	Pulmonary Hemorrhage
2	12.5	HLHS s/p Fontan	1 ventricle	Left	Flow Reversal
3	4.0	Heterotaxy, unbalanced AV canal s/p Glenn	1 ventricle	Left	Flow Reversal
4	3.1	PA, VSD MAPCAs s/p unifocalization and VSD closure	2 ventricles	Left	Pulmonary Hemorrhage
5	3.3	Scimitar, occluded right pulmonary veins	2 ventricles	Left	Flow Reversal
6	8.7	Goldenhar Syndrome, Hypoplastic right lung	2 ventricles	Right	Pulmonary Hemorrhage
7	1.3	DORV, DMGA s/p ASO, VSD closure	2 ventricles	Left	Pulmonary Hemorrhage

TABLE 2 *bPA Occlusion Procedural Details and Follow-Up*

Patient	Device Used	Additional AP Collateral Coiling	Symptom Resolution	Transplant Evaluation	Lost to Follow-Up	Follow-up (months)
1	10/8 ADO (Abbott, Santa Clara, CA)	No	Yes	Yes	No	192
2	12 mm AVP II (Abbott, Santa Clara, CA)	No	Yes	Yes	No	83
3	10 mm AVP I (AGA Med Corp, Plymouth, MN)	Yes	Yes	Yes	Yes	4
4	15 mm ASO (Abbott, Santa Clara, CA)	Yes	Yes	No	No	147
5	Two 8 mm AVP IVs (Abbott, Santa Clara, CA)	No	Yes	No	No	26
6	Six 0.035 Azur coils (Terumo Interv Sys, Somerset, NJ)	No	Yes	No	No	34
7	12 mm AVP II (Abbott, Santa Clara, CA)	No	Yes	No	No	1

Devices and Hemodynamic Data

bPA occlusion was accomplished with a variety of transcatheter occluder devices and/or coils **(Table 2)**. In a subset of patients (n= 2), coil occlusion of AP collaterals was also performed **(Table 2)**. Patients underwent concurrent AP coiling if coiling was indicated and considered feasible during catheterization. In all patients, prograde and retrograde pulmonary artery flow in the lung corresponding to the obstructed pulmonary veins was successfully terminated with bPA occlusion.

To assess changes in the pulmonary circulation, the Fontan pressure or the pulmonary artery pressure (for two ventricle patients) were analyzed. Among single ventricle patients, comparison of pre-bPA to post-bPA occlusion Fontan pressures showed no difference (pre: 20±6 mmHg, post: 19±2 mmHg, p = 0.30; **Figure 2A**). In two ventricle patients, there was no difference in systolic (pre: 34±10 mmHg, post: 33±8 mmHg, p = 0.42; **Figure 2C**), mean (pre: 21±2 mmHg, post: 22±3 mmHg, p = 0.37; **Figure 2B**), or diastolic (pre: 11±6 mmHg, post: 12±3 mmHg, p = 0.40; **Figure 2D**) pulmonary artery pressures. Of note, pulmonary artery pressures were available for three of four patients with two ventricle cardiac anatomy.

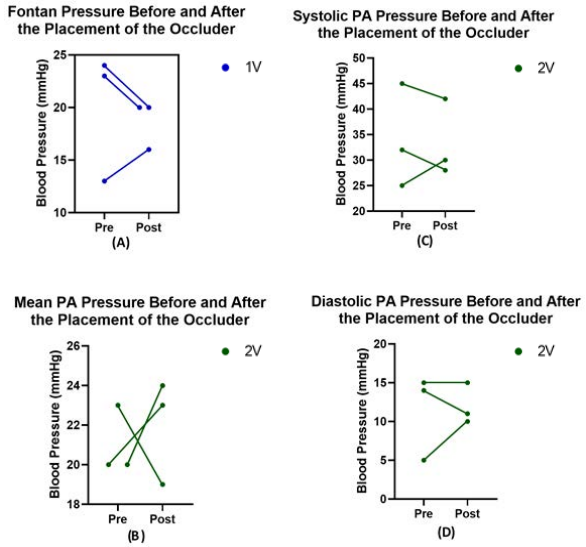

FIGURE 2 *Plots of **(A)** Fontan Pressure in one ventricle heart anatomy, and **(B)** Mean Pulmonary Pressure, **(C)** Systolic Pulmonary Pressure, and **(D)** Diastolic Pulmonary Pressure in two ventricle heart anatomy before and after the placement of the occluding device in the pulmonary artery. Filled circles denote individual patient measurements and lines indicate trends. **(1V)** Single ventricle heart anatomy and **(2V)** Biventricular heart anatomy.*

To assess changes in the arterial circulation, systemic blood pressure and oxygen saturation were analyzed. In single ventricle patients, comparison of pre-bPA occlusion to post-bPA occlusion blood pressures showed a significant increase in mean BP (pre: 46±6 mmHg, post: 58±6 mmHg, p = 0.04); **Figure 3A**, systolic BP (pre: 67±15 mmHg, post: 85±12 mmHg, p = 0.05); **Figure 3C**, and diastolic BP (pre: 34±2 mmHg, post: 42±2 mmHg, p = 0.01). For two ventricle patients, comparison of pre-bPA occlusion to post bPA occlusion blood pressures showed no difference, mean BP (pre: 62±4 mmHg, post: 65±4 mmHg, p = 0.31); **Figure 3A**, systolic BP (pre: 83±9 mmHg, post: 92±7 mmHg, p = 0.21) and **Figure 3D,** diastolic BP (pre: 46±4 mmHg, post: 48±6 mmHg, p = 0.57). No significant change was noted in systemic oxygen saturation before and after bPA occlusion in single (pre: 68 ± 17%, post: 81±14 %, p = 0.33); **Figure 3B** and two (pre: 99±1%, post: 98±2%, p = 0.55); **Figure 3B** ventricle patients. Right ventricle assessment by pre- and post-procedural echocardiography did not show a difference in RV size or function.

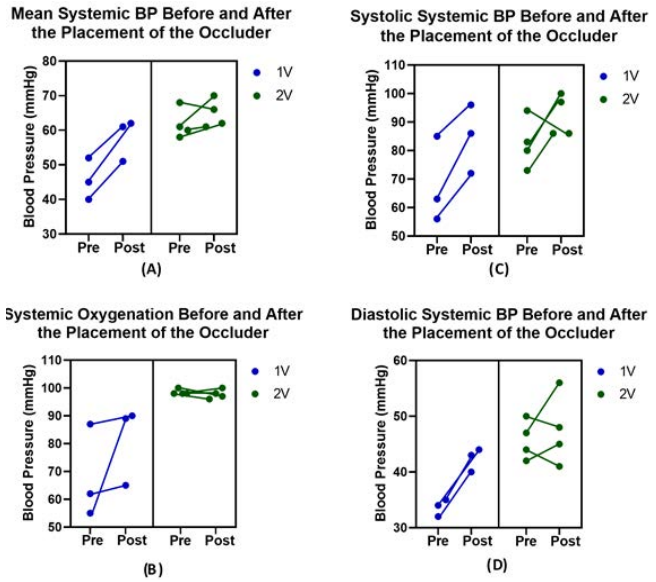

FIGURE 3 *Plots of **(A)** Mean Blood Pressure, **(B)** O2 Saturation, **(C)** Systolic Blood Pressure, and **(D)** Diastolic Blood Pressure before and after the placement of the occlusion device in the pulmonary artery. Filled circles denote individual patient measurements and lines indicate trends. **(1V)** Single ventricle heart anatomy and **(2V)** Biventricular heart anatomy.*

Immediate Post-Procedural Period and Follow-Up

All patients tolerated the procedure well and experienced resolution of pulmonary artery flow reversal or hemoptysis **(Table 2)**. Post procedure follow-up ranged from one month to sixteen years, median follow-up 2.8 years **(Table 2)**. Two patients were lost to follow-up. At the time of last follow-up, all single ventricle patients had been referred for a heart-lung transplant evaluation, but none had completed transplantation **(Table 2).** Of the patients who presented with hemoptysis, all patients, except for patient 4, had complete resolution of their hemoptysis. Patient 4 continued to have intractable hemoptysis to the point where he underwent pneumonectomy with complete resolution of hemoptysis. No procedural complications, major adverse events or mortality related to bPA occlusion had been noted at time of the most recent follow-up evaluations.

Discussion

In this study, we demonstrated that occlusion of the ipsilateral bPA in patients with unilateral total PVO can serve as a minimally invasive, effective treatment in palliating symptoms associated with PVO without any major complications. The study showed that hemodynamic stability and systemic oxygenation saturation was maintained both acutely and in mid-term follow up and that a variety of devices and/ or coils may be implanted to achieve complete bPA occlusion. The study also suggests that occlusion of the ipsilateral bPA serves as an alternative to pneumonectomy or other major surgical interventions in cases where the patient is acutely symptomatic and not a candidate for surgery.

All patients in this study experienced immediate clinical resolution of bPA flow reversal or hemoptysis. No patients had experienced any serious adverse events related to the procedure or occlusion devices at the time of last follow-up. Acutely, there was no recurrence of hemoptysis or flow reversal. However, in the follow-up period, one patient who presented with hemoptysis underwent pneumonectomy for intractable hemoptysis recurrence. None of the patients who presented with flow reversal underwent subsequent pneumonectomy.

Overall hemodynamic stability was maintained following bPA occlusion. No significant changes were observed in systemic oxygen saturation, whereas systemic blood pressure increased (1V) or remained the same (2V). Systemic oxygen saturation, Fontan pressure and pulmonary artery pressure were unchanged by the procedure in all patients. The maintenance of systemic oxygenation and lack of significant change in pulmonary artery pressure is most likely due to the limited contribution provided by the affected lung to oxygenation prior to the procedure. If most of the RV output were being directed to the unaffected lung as a result of lower pressure, bPA occlusion may not significantly impact pulmonary artery pressure or oxygenation. In single ventricle patients, post-procedure systemic blood pressure increased by elimination of run off through the lung via AP collaterals thereby increasing systemic blood flow.

Although one of seven patients experienced recurrence of hemoptysis, in general, bPA occlusion successfully treated hemoptysis and flow reversal by hemodynamically isolating the lung ipsilateral to the PVO. We propose that bPA occlusion treats flow reversal from AP collaterals by preventing reverse flow into the contralateral lung. Occlusion of the bPA may increase pressure within the AP collaterals as the pulmonary artery circulation becomes isolated with occlusion of both the branch pulmonary artery and pulmonary vein. The increased pressure within the AP collaterals may prevent flow from the aorta into the collateral vessels. Limiting flow through the ipsilateral lung is responsible for hemoptysis resolution. Since the pulmonary artery delivers over 90% of the blood volume to the lungs, bPA occlusion significantly limits blood delivery to friable lung parenchyma and thereby decreases further parenchymal damage as well as available blood which can leak into the alveolar space.[12] However, even with bPA occlusion, we have observed one case of hemoptysis recurrence in patient 4. One can postulate two conditions in which hemoptysis

could recur after bPA occlusion: 1) formation of new AP collaterals or 2) extensive pre-existing damage to the lung parenchyma such that tissue is prone to significant bleeding for an extended time post-intervention even if only supplied by the bronchial vasculature.

Application of ipsilateral bPA occlusion is intended for patients who are acutely symptomatic from PVO and not candidates for surgery or other catheter interventions. Currently, first line treatment for PVO involves primary pulmonary vein repair by either surgical (e.g. pericardial patch venoplasty, intrapulmonary artery separation) or catheter based approaches (e.g. balloon angioplasty or stenting).[1,2,6,13] While primary repair eliminates the initial occlusion/stenosis, re-stenosis is consistently observed regardless of approach.[6] High rates of re-stenosis highlight the progressive nature of pulmonary vein stenosis to occlusion, which can lead to a need for lung transplant or pneumonectomy in patients who become acutely symptomatic or develop pulmonary hypertension.[6] However, at the time of presentation, not all patients are eligible for a surgical intervention or catheter-based intervention. Some patients, as seen in this study, may have failed multiple primary interventions and continue to experience symptoms from PVO. Therefore, ipsilateral bPA occlusion constitutes a means of palliating the symptoms associated with unilateral PVO without major manipulation of pulmonary vasculature or lung parenchyma.

Compared to pneumonectomy, ipsilateral bPA occlusion has a low, side-effect profile, while functionally achieving a similar end result. Pneumonectomy and lobectomy have been used in the treatment of hemoptysis associated with PVO and the resulting functionality is similar to bPA occlusion.[14,15,16] Pneumonectomy and lobectomy are highly invasive procedures and subject patients to peri-operative morbidities such as bronchopleural fistula, ARDS, pneumothorax, and post-pneumonectomy syndrome and are limited to patients who are able to tolerate surgery.[17] When ipsilateral bPA occlusion is employed, further damage or inflammation of the lung parenchyma is unlikely as the bPA is coiled proximally and perfusion for lung tissue viability is maintained via the bronchial circulation. Additionally, the relatively high incidence of post-operative arrhythmias (approximately 20%) associated with pneumonectomy was not observed in the patients who underwent bPA occlusion, included in this study.[18] bPA occlusion acts as a type of "functional pneumonectomy", since blood volume is no longer oxygenated by the occluded lung. It provides the functionality of pneumonectomy without the associated invasiveness and post-operative morbidity. However, "functionally" removing the affected lung compared to physically removing the affected lung may interfere with compensatory lung growth seen after pneumonectomy. The mechanical strain on lung tissue caused by mediastinal shift and increased alveolar inflation due to lung removal are key factors in stimulating lung tissue proliferation.[18,19] Increase of perfusion of the remaining functional lung, as would be in the case of bPA occlusion, may not exercise the same magnitude effect of promoting compensatory lung growth.[20] While bPA occlusion does not correct PVO, it can be employed as a palliative measure in patients who are not eligible for surgery and are experiencing the clinical consequences of PVO to help bridge them to transplant.

Limitations of this report include the small number of patients and the retrospective nature of the study from a single institution. The small number of patients is attributed to the fact that these are rare and challenging patients. The constraint to a single center study is due to the fact that this a novel treatment that has been largely unique to our institution. Future applications of this technique will need to be mindful of emerging treatments for primary and secondary pulmonary vein stenosis and obstruction, such as hybrid pulmonary venous repair and refined endovascular interventions. Due to the retrospective nature of the study, there were limitations in the available quantitative and imaging data for meaningful comparison across cases, as the diagnostic and treatment needs of each patient were evaluated on a case specific basis.

Conclusion

In this study, we report that adverse clinical consequences of total unilateral PVO may be palliated with ipsilateral bPA occlusion. This procedure can effectively resolve pulmonary artery flow reversal or hemoptysis without major complications. Compared to pneumonectomy, ipsilateral bPA occlusion serves as a less-invasive treatment option that can be employed as long-term palliation and a bridge to transplantation for patients who are not eligible for surgery.

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The PICS Society Advocacy Program: Power in Numbers! Part 4

Hideshi Tomita, MD, PhD, FPICS; Natalie Poli, Ed.S.; Kamel Shibbani, MD; Norm Linsky, MPA, MA

As a global community dedicated to minimally-invasive treatment of Congenital Heart Disease (CHD), do we have shared policy goals regardless of where we live and where we work? If so, how can we achieve those goals? As Dr. Shibbani says, ***"Do we have Power in Numbers?"***

This month we continue our interviews with PICS Society advocacy leaders through a discussion with Professor Hideshi Tomita, Director of Pediatric and Adult CHD, Showa University, Tokyo Japan. Dr. Tomita is Co-Chair of the PICS Advocacy Committee along with Dr. John Cheatham (Chair) and Dr. Cliff Kavinsky (Co-Chair).

Dr. Tomita is recognized by his peers for working closely with the PMDA in Japan (Pharmaceuticals and Medical Devices Agency, similar to the US FDA). Thanks to the leadership of Dr. Tomita and his distinguished colleagues, progress has been made in shortening the device approval process in Japan—while maintaining the highest standards of safety and efficacy.

Dr. Shibbani: Dr. Tomita, what is the single most important policy issue that faces you and your colleagues in Japan? Are there ways the PICS Society can help you address that issue?

Dr. Tomita: Our biggest issue historically has been a significant time lag in having CHD interventional devices reviewed and approved by our country's regulatory system. To address this, in 2003 authorities in Japan and the USA formalized the "US-Japan Medical Device Harmonization by Doing" (HBD) agreement. Since that time, researchers, industry and others in both countries have worked diligently to plan clinical trials and data reporting standards that could be submitted both to the PMDA in Japan and to the FDA in the US.

My colleagues and I used this as an opportunity to expand our dialogue with the PMDA, urging that harmonization of device review processes internationally would benefit patients in Japan and elsewhere. We encouraged more data sharing, maintenance of the highest standards and alignment with the HBD framework wherever possible. We recognized that progress would not happen overnight, but our pediatric community believed this would be an important opportunity.

Initially we focused on adult heart disease, an example being drug-eluting stents (DES) for adults. It was critical to start "breaking the device approval lag" in our country, in this case by focusing on a condition with a relatively large patient population. We reduced the research-to-approval time difference between Japan and the US. Then we expanded to interventional devices for the pediatric and adult congenital population. We encouraged and participated in more international clinical trials, working with innovators in industry and academic medical centers, again, starting with the "Harmonization by Doing" framework.

In 2016 we took another important step: We established the "Harmonization By Doing-for-Children (HBD-for-Children) Working Group" as a global collaboration amongst academia, industry and regulatory agencies in Japan and the United States. This newer group focuses on promoting development of pediatric medical devices. One recent example is the area of transcatheter pulmonary valve replacement, focused on the Harmony™ valve. This has been very successful both clinically and in terms of application of the HBD "harmonization" framework *[Editor's Note: the term "harmony" for both this valve and the 'Harmonization by Doing' framework is coincidental].*

Building on HBD's experience regarding approval of DES for adult heart disease, we next applied that experience to reduce the time difference between our two nations in approval of this vitally-needed pulmonary valve technology. Harmony™ received FDA approval in the US in March 2021 and PMDA approval in Japan very shortly thereafter (August 2021). This is very encouraging. Real-world clinical use will start in spring 2022 when we anticipate approval by the Statutory Health Insurance System in Japan.

Clearly this shows that using international clinical trial data for approvals in Japan will be important moving forward. We must broaden international data harmonization for trials of new devices in our field. Our next goal should be to expand this to include more data from regions beyond Japan and the US.

"Years ago the PMDA [Japanese equivalent of the US FDA] paid little attention to pediatric device approval. That has changed: progress has been made in recent years. Our next goal is for critically-needed devices to be approved in Japan and other nations simultaneously. Harmonization of review processes globally would dramatically benefit patients everywhere." *—Hideshi Tomita, MD, PhD, FPICS*

Dr. Shibbani: Are you suggesting the PICS Society could play a role by providing an international platform for sharing data related to new devices, to speed up the approval process in Japan and probably elsewhere?

Dr. Tomita: Yes, very much so. Regulatory body roles have important differences from country-to-country. We have to discuss uniform requirements for approval everywhere. We need to discuss the need for some uniformity in data necessary for regulatory review and approval country-to-country. BUT, we also need to adjust and accommodate for significant differences amongst nations in terms of data needed, regulatory review processes and resources available.

Dr. Shibbani: Can the PICS Society help investigators understand the different processes, data requirements, reporting requirements from country-to-country?

Dr. Tomita: Yes, again, very important. This would be quite helpful, through education, publications, an online clearinghouse or other means.

Mrs. Poli: Very honored to meet you Dr. Tomita! I am a stroke survivor and a recipient of two of the Amplatzer™ Atrial Septal Defect devices. I was 29 when I had my stroke. Little did I know I was born with two PFO's and an atrial septal defect. One minute I was fine, the next minute I was not. If it weren't for physicians like you, Dr. Hijazi and Dr. Kavinsky, I never would have had a minimally invasive procedure, a full recovery and an extraordinarily rewarding family and professional life ever since.

Dr. Tomita: I am very happy for you and so pleased to meet someone who was successfully treated through minimally-invasive means. Your story and those of so many others are precisely why our community of doctors and industry innovators works so hard to bring better devices and techniques into daily practice.

Dr. Shibbani: Beyond the regulatory environment, what else do you think the PICS Society can do to assist your profession?

Dr. Tomita: Industry innovation is so important, as is partnership with those who treat patients, educate the next generation of physicians, set guidelines and the like. We must partner with industry in the US, in Japan and worldwide. We must advocate for streamlined device approval processes that maintain the highest possible standards AND reduce delays in approval unrelated to the science. Such delays discourage industry from investing in product development and reduce the tools available to us to effectively treat our patients. We must work together on this.

Dr. Shibbani: Should the PICS Society act as an informational clearinghouse for regulatory information around the world, and what approaches have worked in individual countries?

Dr. Tomita: Yes. When innovators can better navigate the regulatory process by becoming better informed about processes, everyone will benefit—especially patients.

Remember, the field of pediatric cardiovascular devices is a relatively small market, especially within a single country. But when we work together globally, we are much larger. We need to think of ourselves as a global marketplace, which is not a small one. That would incentivize companies to expand the innovation pipeline.

Mrs. Poli: Dr. Tomita, are there examples of high priority areas where more international cooperation would be important?

Dr. Tomita: In Japan, continued development of transcatheter pulmonary valve devices is a very high priority. Stent design for small children is also a very high priority. Only a small number are officially approved in Japan and US, so more options are urgently needed. Industry must continue to be incentivized to develop these, and international collaboration in our field is an urgent need.

Dr. Shibbani: Dr. Tomita, if I could summarize:

- There are urgent needs—and opportunities—to collaborate with regulatory agencies to streamline device review and approval. Progress is slowly being made, much effort lies ahead.
- Working on clinical trial standards, data sharing and consistent regulatory agency policies would be major contributions to the field.
- The PICS Society can play a role by fostering communication, centralizing information and educating all stakeholders regarding device approval processes globally.

Dr. Tomita: I concur and thank you. Encouraging progress has been made, we have made a good start. We look forward to working with the PICS Society and our colleagues throughout the world.

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ATTENTION FELLOWS & RESIDENTS: Congenital Cardiology Today Provides a Great Opportunity!

John W. Moore, MD, MPH

Share your clinical experiences or your research projects in a well-established and widely circulated pediatric and congenital cardiology-oriented publication. The staff of Congenital Cardiology Today (CCT) is well aware that trainees have significant research and educational requirements as part of the curriculum. Congenital Cardiology Today offers the unique opportunity to fast-track clinical and research projects into publications which a large part of the pediatric and congenital cardiology community will encounter. Publication in CCT can provide excellent exposure for your work and will assist you in meeting training requirements and in securing additional training opportunities and jobs!

CCT accepts interesting case reports and case series as well as reviews of clinical topics relevant to the practice of pediatric and congenital cardiologists. Such manuscripts are generally not eligible for review and publication in standard cardiology journals. Moreover, in the few journals which consider case-centered-manuscripts, there is often a prolonged delay after submission for review and publication. In addition, there is no fee for publication, including color images, in CCT. Our editorial policies encourage these submissions, and we provide timely review and publication. On average, approximately 50% of submissions are accepted, and accepted articles are generally published within four to six months of receipt of the manuscript. Congenital Cardiology Today has found that such articles are often of considerable interest to our readership of busy practitioners.

CCT encourages you to write up the very interesting cases you encounter in training. Make sure to include some good figures, tables, etc. Send them to us for review. Also, if you have prepared a Grand Rounds or an interesting lecture for presentation in your hospital, consider writing it up and sending it for review and likely publication.

Instructions for authors are easily accessed on the website: https://www.congenitalcardiologytoday.com/editorial

Submit your article to Kate.f.Baldwin@gmail.com

I look forward to reviewing your submissions.

Photon-Counting CT – A Quantum Leap in Computed Tomography

After more than 15 years of development, the world's first photon-counting system is here to redefine what's possible in cardiac imaging. For cardiologists, this means the ability to scan and diagnose previously excluded patients.

After the introduction of spiral CT in 1990, wide detector CT in 2004, Dual Source CT in 2005 and Dual Layer CT detectors in 2013, computed tomography is a mature modality that has reached a saturation phase. Despite technological progress, limitations remain for current CT technology.

With photon-counting CT, we are developing a radically new technology for clinical routine. At its core is a new kind of detector that is substantially different from a standard energy-integrating detector.

These photon-counting detectors have the potential to overcome the limitations of current CT detectors, by providing CT data at high spatial resolution, without electronic noise, with improved contrast-to-noise ratio, at lower radiation dose and with intrinsic spectral information.

What Makes Photon-Counting Detectors Different?

All medical CT systems today are equipped with solid-state scintillation detectors. In a two-step conversion process, the absorbed X-rays are first converted into visible light in the scintillation crystal. The light is then converted into an electrical signal by a photodiode attached to the backside of each detector cell.

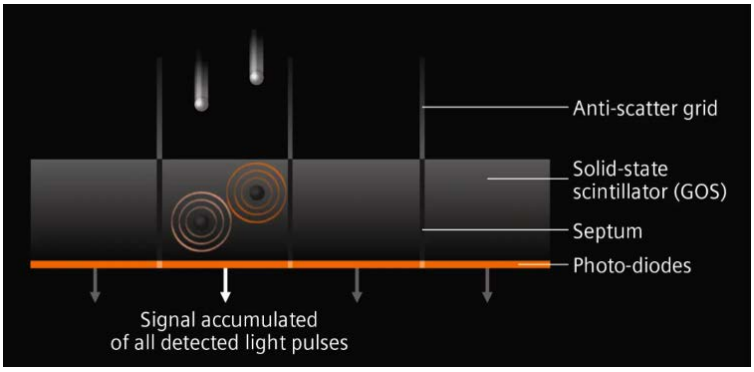


FIGURE 1 *Energy-integrating detector*

The low-level analog electric signal of the photodiodes is susceptible to electronic noise, which sets an ultimate limit to potential further radiation dose reduction.

At the same time, it is problematic to significantly increase the spatial resolution of solid-state scintillation detectors beyond today's performance levels.

As part of this two-step conversion process, the light created by thousands of x-ray photons is accumulated over the integration time and measured as a whole, thereby losing the spectral information of the incoming signal.

Photon-counting detectors, by contrast, can directly transform X-ray photons into electrical signals.

In a direct conversion process, the absorbed X-rays create electron-hole pairs in the semiconductor. The charges are separated in a strong electric field between cathode on top and pixelated anode electrodes at the bottom of the detector.

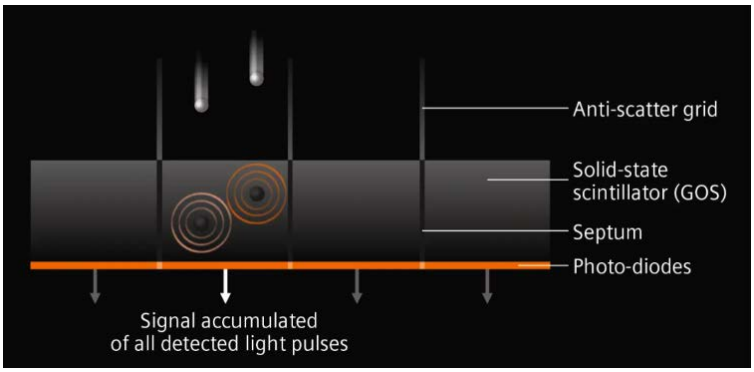


FIGURE 1 *Photon-counting detector*

Compared to solid-state scintillation detectors, photon-counting detectors have several advantages. The individual detector cells are defined by the strong electric field between common cathode and pixelated anodes **(Figure 2)**, and there is no need for additional septa between the detector pixels to avoid optical cross-talk inherent to scintillation detectors. The geometrical dose efficiency is, therefore, better than that of scintillation detectors and only reduced by the anti-scatter collimator blades or grids that are also present in scintillation detectors. Furthermore, each "macro" detector pixel confined by collimator blades may be divided into smaller detector sub-pixels which are read-out separately to significantly increase spatial resolution.

With a photon-counting detector being able to count the charges created by individual x-ray photons as well as measuring their energy level, we now have a detector that has intrinsic spectral sensitivity in every scan.

What Does This Mean For Computed Tomography – And For You?

The direct signal conversion of photon-counting detectors can have great impact: They are much more dose-efficient than current detectors. Also, their pixels are much smaller, which can significantly increase the spatial resolution. Based on this new technology, patients can expect even further reduction of radiation dose and less use of contrast agent. In addition, physicians can work with images that visualize even very fine tissue structures, such as the smaller bronchi of the lungs or metastases in bones.

- No downweighting of lower energy quanta: Improved image contrast
- Smaller detector pixels: High spatial resolution without losing dose efficiency
- Eliminate electronic noise: Lower radiation dose
- Intrinsic spectral sensitivity: Multi-energy information

TAVR with SAPIEN 3 Demonstrated as Economically-Dominant Treatment Strategy Compared to Surgery in Partner 3 Analysis

PRNewswire – Edwards Lifesciences has announced that a cost-effectiveness analysis comparing transcatheter aortic valve replacement (TAVR) to surgery demonstrated that TAVR with SAPIEN 3 is an economically-dominant treatment strategy, offering improved outcomes and reduced cost. This analysis from the PARTNER 3 trial was presented during the late-breaking clinical trials at the 33rd Transcatheter Cardiovascular Therapeutics (TCT), the annual scientific symposium of the Cardiovascular Research Foundation.

The study compared healthcare costs, life expectancy and quality-adjusted life expectancy for patients with severe aortic stenosis at low risk for surgery, who were treated with TAVR or surgery in the PARTNER 3 trial.

A formal cost-effectiveness analysis conducted for the study found:

- TAVR using the SAPIEN 3 valve resulted in cost savings of greater than $2,000 per patient through the 2-year study period. This was achieved through marked reductions in hospital length of stay and substantially lower follow-up costs, which overcame higher index hospitalization and procedural costs for TAVR.
- Over the 2-year follow-up period, TAVR also led to a small but significant improvement in quality-adjusted life expectancy, driven by improved early quality of life and also survival.
- The probability that TAVR is highly cost-effective versus SAVR is approximately 95%.

"In addition to the outstanding clinical results compared with surgery, the finding that TAVR with SAPIEN 3 is also a lower cost strategy for low-risk patients empowers both cardiologists and patients with real choice in determining the right treatment option for severe aortic stenosis," said David J. Cohen, MD, MSc, Director of Clinical and Outcomes Research at the Cardiovascular Research Foundation and Director of Academic Affairs at St. Francis Hospital in New York. "TAVR is a unique technology with advantages over surgery from the perspective of both the patient and the healthcare system."

The PARTNER 3 trial randomized 1,000 patients at 71 centers between March 2016 and October 2017. Patients were assigned to undergo either TAVR with the SAPIEN 3 valve or surgery with any commercially available surgical valve. Clinical results from the PARTNER 3 trial were presented in 2019 and published in The New England Journal of Medicine.

"As we celebrate the 10-year anniversary of the SAPIEN valves' FDA approval in the United States, it is inspiring to reflect on the impact this technology has had on the treatment of patients with severe aortic stenosis," said Larry Wood, Edwards' Corporate Vice President, Transcatheter Aortic Valve Replacement. "These data add to the substantial body of evidence showing the advantages of TAVR over surgery in terms of effectiveness and cost efficiency at all surgery risk levels. We are proud that SAPIEN TAVR continues to stand out as a unique technology that extends patients' lives, improves quality of life and saves money for the healthcare system."

About Edwards Lifesciences

Edwards Lifesciences is the global leader of patient-focused innovations for structural heart disease and critical care monitoring. We are driven by a passion for patients, dedicated to improving and enhancing lives through partnerships with clinicians and stakeholders across the global healthcare landscape. For more information, visit Edwards.com and follow us on Facebook, Instagram, LinkedIn, Twitter and YouTube.

This news release includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These forward-looking statements include, but are not limited to, statements made by Mr. Wood and statements regarding expected product benefits, patient outcomes, product impacts to the healthcare system, future plans related to the product lines, objectives and expectations and other statements that are not historical facts. Forward-looking statements are based on estimates and assumptions made by management of the company and are believed to be reasonable, though they are inherently uncertain and difficult to predict. Our forward-looking statements speak only as of the date on which they are made, and we do not undertake any obligation to update any forward-looking statement to reflect events or circumstances after the date of the statement. Investors are cautioned not to unduly rely on such forward-looking statements.

Forward-looking statements involve risks and uncertainties that could cause results to differ materially from those expressed or implied by the forward-looking statements based on a number of factors as detailed in the company's filings with the Securities and Exchange Commission, including its Annual Report on Form 10-K for the year ended December 31, 2020, and its Quarterly Report on Form 10-Q for the quarters ended March 31, 2021, and June 30, 2021. These filings, along with important safety information about our products, may be found at Edwards.com.

Expert Consensus Update to SCAI SHOCK Stage Classification Incorporates New Data to Enhance Applicability in Clinical & Research Settings

TCT 2021: Two-year update includes modifications and clarifications to account for the dynamic process of cardiogenic shock

A newly-developed expert consensus statement will provide updated guidance on the use of the SCAI SHOCK Stage Classification, a five-stage system intended to facilitate communication about the diagnosis, presentation and evolving nature of cardiogenic shock (CS). The updated classification will be presented live at 9AM EST on Friday, November 5 by Srihari S. Naidu, MD, Director of the Cardiac Catheterization Laboratory at Westchester Medical Center and Trustee of SCAI, during a featured session titled New Directions in Cardiogenic Shock at the 33rd annual Transcatheter Cardiovascular Therapeutics (TCT) conference. The document was developed in collaboration with the American College of Cardiology, American College of Emergency Physicians, American Heart Association, European Society of Cardiology Association for Acute Cardiovascular Care, Cardiac Safety Research Consortium, Society of Critical Care Medicine, and the Society of Thoracic Surgeons, each of which had representation on the writing group.

Cardiogenic shock (CS) is a serious and life-threatening condition that occurs when the heart is unable to pump enough blood to the body's vital organs and is most commonly triggered by heart attack or heart failure. Mortality from cardiogenic shock complicating MI remains high, approaching or exceeding 50%, despite the development of percutaneous mechanical circulatory support technologies and the national standard of emergent angioplasty and stenting.

SCAI developed and released the SHOCK Stages classification in 2019 to provide a unified and standardized vocabulary that would translate across settings and providers from emergency room physicians and emergency medical services, to critical care physicians, heart failure physicians, interventional cardiologists and surgeons. While the system has been widely adopted for its simple and intuitive framework, and ability to discern gradations of severity of CS for the first time, recent validation studies conducted since 2019 have uncovered areas in need of refinement.

"Studies continue to validate the SCAI SHOCK Stage classification as a tool to help clinicians and researchers better understand cardiogenic shock and offer guidance on treatment pathways to improve survival," said Timothy Henry, MD, MSCAI, president of SCAI and Vice Chair of the Writing Group. "The updated expert consensus will underscore the benefit of the classification system across a broad patient spectrum and provides meaningful changes that we believe will enhance both clinical care and future research."

Key points and highlights of the updated classification include:

- SCAI SHOCK Stage is an indication of shock severity and comprises one component of mortality risk prediction in CS patients, along with etiology/phenotype and other risk modifiers; a 3-axis model of risk stratification in CS has been proposed to position SCAI SHOCK Stage in context.
- Validation studies have underscored the correlation of SCAI SHOCK Stage with mortality across all clinical subgroups, including CS with and without acute coronary syndrome, cardiac intensive 20 care unit (CICU) patients, and those presenting with out-of-hospital cardiac arrest (OHCA).
- Progression across the SCAI SHOCK stages continuum is a dynamic process, incorporating new information as available, and patient trajectories are important both for communication among clinicians and for decision-making regarding the next level of care and therapeutics.
- A hub and spoke model for transfer of higher risk patients including those with deteriorating SCAI SHOCK Stage has been proposed.
- Cardiac arrest (CA) as described herein relates to that accompanied by coma, defined as the inability to respond to verbal stimuli, most commonly associated with Glasgow Coma Scale < 9, where there is concern for significant anoxic brain injury.
- The SCAI SHOCK pyramid and associated figure now reflect gradations of severity within each stage and pathways by which patients progress or recover.
- A streamlined table incorporating variables that are most typically seen, and the revised CA modifier definition, is also provided and incorporates lessons learned from validation studies and clinician experience.
- Lactate level and thresholds have been highlighted to detect hypoperfusion but may be dissociated from hemodynamics in cases such as chronic heart failure. In addition, patients may demonstrate other manifestations of end-organ hypoperfusion with a normal lactate level and there are also important causes of an elevated lactate level other than shock.

"The new Figures and updated Table should leave less room for interpretation and enhance the standardization significantly, including placing the SCAI SHOCK Stages in context with other variables that must be evaluated when managing a patient with CS", states Dr. Naidu, who Chaired the Writing Group as well as the original one in 2019. "We also highlight new lactate thresholds and provide needed clarification for the pivotal SCAI SHOCK Stage C and the cardiac arrest modifier."

The writing group was organized to ensure a diversity of perspectives and stakeholder representation and achieve multi-specialty consensus around the updated classification scheme.

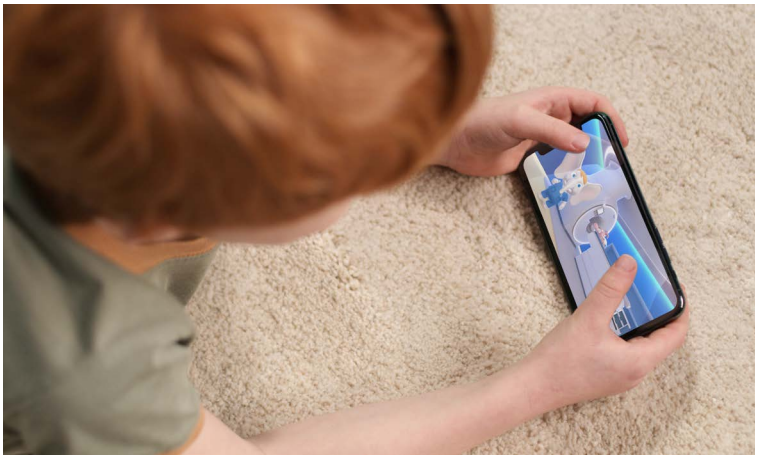
SCAI anticipates publication of the manuscript in the coming months.

Philips Launches Pediatric Coaching to Enhance MR Imaging Patient Experience for Young Children at RSNA 2021

Holistic, play-based coaching can help reduce use of general anesthesia1 and lower the risk of healthcare-induced trauma in many pediatric patients who feel anxious during MRI scans

Philips Ambient Experience solution uses augmented reality, gamification, and 'buddy system' techniques to engage and guide children through their entire MRI scan journey, from the home to the hospital

Royal Philips, a global leader in health technology, today announced the launch of Philips Pediatric Coaching, a holistic solution designed to be a less stressful experience for parents and their children undergoing MRI scans. Using gamification and 'buddy system' techniques to prepare children and their parents beforehand, the solution helps guide young children through the MRI procedure to significantly enhance the patient experience. Pediatric Coaching is the latest initiative launched within the Philips Ambient Experience portfolio, featuring a wide range of dedicated solutions to help enhance the experience of patient and staff.



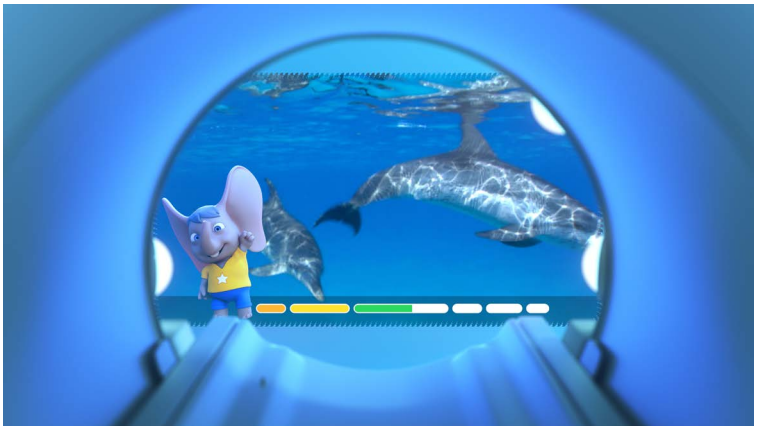
Acquiring high quality images in pediatric MRI can be challenging for both radiologists and the child undergoing the scan. Fear of the unfamiliar environment of an MRI system can be stressful for a younger child, making them agitated and unable to lie still, which is required for good image quality. As a result, scans are often performed under sedation or general anesthesia, which according to parents, carries disadvantages such as post-scan irritability for the child and concerns of repeated anesthesia exposure.[2] Having to resort to such measures or deal with a conscious but distressed child is challenging for hospital staff, increasing procedure time and costs. By helping to empower children during an MRI scan, the Philips Pediatric Coaching solution overcomes many of these issues.

"As adults, many of us can experience anxiety and stress during an MRI exam, and this is especially true for our youngest patients. By removing factors that can trigger stress, we are enhancing the patient engagement experience for pediatric patients to help improve outcomes," said Werner Satter, General Manager Philips Healthcare Environment and Experience Design. "With Philips Pediatric Coaching, we deploy gamification to help children better prepare for their MRI scan in a non-threatening environment at home, interacting with the same character and voice like Ollie the Elephant and friends, who also coaches them at the hospital, and can even coach them during the MRI procedure itself."

To prepare for their MRI scan, children are provided with a gamified mobile app that familiarizes the child and their parents with an MRI procedure in a playful way. The app also introduces the child to a virtual 'buddy' they can role-play with to perform an MRI scan - for example,

pretending to be the system operator and helping their buddy to lie still in order to get the best picture. The app also uses augmented reality to allow the child to explore the MRI system at home before entering the hospital. Many parents express a willingness to help prepare their child ahead of time, and by playing alongside their child, they can also learn more about the procedure.

When the family visits the radiology department, the same familiar virtual buddy interacts with the child as they play with Philips' newly enhanced 'Kitten Scanner' - a small scale educational scanner that allows children to scan various toy animals and view what's inside each animal for a better understanding of the upcoming procedure. When the child has their scan, their buddy's familiar voice and image are projected onto Philips' Ambient Experience in-bore Connect solution, to guide the child through the scan procedure by coaching them, for example, on when and how to hold their breath. With the new Pediatric Coaching Solution, parents are reassured, and the child is empowered and well-prepared, helping ensure the high-quality images needed for an accurate diagnosis of the child's condition are captured.



Today's announcement follows a similar child patient-centric initiative between Philips and the Walt Disney Company EMEA earlier this year to test the effects of custom-made animations, including specially made Disney stories, within Philips' Ambient Experiencehospital environments. An overview of breakthrough innovations in pediatric imaging to help improve care for younger patients, including how to reduce pediatric patients' fear and anxiety, is also discussed in a recent blog article by Dr. Julia Dmitrieva, KOL Engagement Leader for Precision Diagnosis at Philips.

The Philips Pediatric Coaching Solution is being launched at the 2021 International Pediatric Radiology Congress (IPR 2021), October 11 - 15, 2021, in Rome, Italy. Next to the MRI journey, Philips also plans to make its Pediatric Coaching available in other diagnostic imaging modalities such as CT. The solution was also demonstrated in the Philips booth at the 2021 Radiological Society of North America Annual Meeting (RSNA 2021), Nov. 28 - Dec 2, 2021, in Chicago, USA.

To see the video, please visit **https://www.philips.com/a-w/about/news/archive/standard/news/press/2021/20211011-philips-launches-pediatric-coaching-to-enhance-mr-imaging-patient-experience-for-young-children.html**

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FEBRUARY

17-19

CATCH: Caring for Adults and Teens with Congenital Heart Disease
Oahu, Hawaii, USA
https://www.hawaiipacifichealth.org/CATCH

26-01

CRT22
Washington, D.C., USA
https://crtmeeting.org/Default.aspx?mkt_tok=MjcxLVJPVS0xMjQAAAGARtmr7GGCAKCWH-KPGINB9OBz_gWE70ZTgkzti5b8yjBY_CBNiT3RArF_35KpicybtR-8YhHFysgwOThFq5ffpeaYr01wsngBVdWx

MARCH

15-17

ALICE 2022 – Advanced Live Interventional Course of Essen
Essen, Germany
https://alice-the-course.info/

26-27

CSI Focus LAA & PFO
Tokyo, Japan
https://www.csi-congress.org/laa-pfo

APRIL

02-04

ACC22
Washington, D.C., USA
https://accscientificsession.acc.org/

03-05

EHRA 2022
Copenhagen, Denmark
https://www.escardio.org/Congresses-&-Events/EHRA-Congress

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