

Surgical outcomes for patients with pulmonary atresia/major aortopulmonary collaterals and Alagille syndrome[†]

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Abstract

OBJECTIVES: Pulmonary atresia with major aortopulmonary collateral arteries (PA/MAPCAs) is a complex congenital heart defect that has undergone significant advances in treatment over the past 15 years. A small subset of patients with PA/MAPCAs have associated Alagille syndrome, which can have an adverse impact on many other organ systems. The purpose of this study was to review our institutional outcomes for the surgical patients with PA/MAPCAs and Alagille syndrome.

METHODS: This was a retrospective review of patients with PA/MAPCA's and Alagille who underwent surgical reconstruction from November 2001 to August 2011. Fifteen patients were identified in our data base. Thirteen had pulmonary atresia with ventricular septal defect (PA/VSD) and two had pulmonary atresia with intact ventricular septum (PA-IVS).

RESULTS: There has been no early or late mortality in this cohort of 15 patients with PA/MAPCA' and Alagille syndrome. The patients have undergone a total of 38 cardiac surgical procedures. Ten of the 13 patients with PA/VSD have achieved complete repair, including unifocalization, a right ventricle to pulmonary artery conduit and closure of all intra-cardiac shunts. The three unrepaired patients with PA/VSD remain potential candidates for eventual complete repair, while the two patients with PA-IVS remain viable candidates for a single ventricle pathway. The patients in this series have also undergone 12 major non-cardiac procedures.

CONCLUSIONS: The data demonstrate that surgical reconstruction of PA/MAPCAs can be successfully achieved in patients with Alagille syndrome. The longer-term prognosis remains guarded on the basis of the multi-organ system involvement of Alagille syndrome.

Keywords: Congenital heart disease • Liver • Pulmonary arteries/veins • Pulmonary vascular resistance/hypertension

INTRODUCTION

Pulmonary atresia with major aortopulmonary collateral arteries (PA/MAPCA's) is a relatively rare form of congenital heart defect. Advances in the surgical treatment of PA/MAPCA's over the past 15 years have led to improved outcomes for these patients [1–4]. However, a significant number of patients with PA/MAPCA's have associated chromosomal syndromes. The most frequently cited genetic defects identified with PA/MAPCA's include chromosome 22q11 deletion and Alagille syndrome. The presence of genetic syndromes has been shown to adversely affect outcomes for a wide range of congenital heart defects [5]. This principle is particularly applicable in more complex defects, and poorer outcomes have been documented separately for correction of tetralogy of Fallot [6] and pulmonary atresia [7]. Given the complexity of treatment required for PA/MAPCA's, it is anticipated that outcomes would be significantly influenced by these chromosomal syndromes.

Alagille syndrome is a dominantly inherited disorder linked to mutations of the *JAG1* gene [8]. This disorder affects multiple

organ systems, including the heart, liver, kidneys, vasculature, skeleton, eyes and face. More than 90% of patients with Alagille syndrome have congenital heart defects, with the majority of these involving the right-sided cardiac structures [9]. The sine qua non of Alagille syndrome from a cardiac standpoint is branch pulmonary artery stenosis. However, a small subset of patients with Alagille syndrome will have tetralogy of Fallot (10–15%) or tetralogy of Fallot with pulmonary atresia (5%) [10]. The incidence of PA/MAPCA's in association with Alagille syndrome has not been well documented to date.

The purpose of this study was to review our institutional experience in the surgical management of PA/MAPCA's and Alagille syndrome. It is our goal that this may reveal important principles regarding the combination of a complex congenital heart defect and genetic disorder.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB) at Stanford University. Medical records were reviewed and a

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written questionnaire was sent to the families to ascertain the health status of the children. Current follow-up was obtained in all of the patients through these mechanisms.

This study summarizes our surgical experience with 15 patients (from November 2001 to August 2011) who had the combination of PA/MAPCA's and Alagille syndrome. During this time frame, we applied the same criteria for surgical reconstruction of PA/MAPCA's with Alagille syndrome that we would have applied to patients without Alagille syndrome, and there were no patients who were turned down due to the presence of extra-cardiac malformations. The diagnosis of PA/MAPCA's was confirmed through a combination of findings on echocardiography, cardiac catheterization and CT angiogram. The clinical diagnosis of Alagille syndrome was made on the basis of patients demonstrating three of the following five features: chronic cholestasis, cardiovascular anomalies, vertebral anomalies, ocular anomalies and characteristic facies [9]. This is a modification of the original criteria proposed by Alagille [8], which required confirmation through liver biopsy.

Our algorithm for management of patients with major aortopulmonary collaterals has been reviewed in several recent publications [11, 12]. The goal of this therapy is to achieve a single compartment with unobstructed flow into a low-pressure pulmonary circulation. Because of the diversity of the aortopulmonary collateral system in patients with PA/MAPCA's, it is

imperative to investigate nearly all neonates with a cardiac catheterization. This catheterization study provides the data to initiate the management algorithm (Fig. 1). The vast majority (80%) of patients with MAPCA's have abnormally arborizing or absent native branch pulmonary arteries, have no ductus and no significant areas of dual blood supply and clinically have mild to moderate cyanosis. In this predominant circumstance, we defer surgical intervention and plan to perform an elective unifocalization between 3 and 6 months of age. We would typically re-study these patients prior to surgery due to the unpredictable natural history of the aortopulmonary collaterals. In those patients who have MAPCA's without significant segmental level stenoses, a complete unifocalization is performed through a midline approach (Fig. 2). The majority (73%) of these patients can undergo a simultaneous intra-cardiac repair (representing 56% of all patients in our experience), whereas a minority (27%) of patients (i.e. those with higher pulmonary artery pressures) will undergo a staged intra-cardiac repair (accounting for 20% of all patients in our experience). This differentiation is defined by an intra-operative pulmonary artery flow study, with pressures less than 25 mmHg (at a flow rate of 3 litres per minute per metre square performed at a temperature of 25°C) deemed as conclusive indication that the ventricular septal defect can be closed and a right ventricle to pulmonary artery placed (Fig. 3). Patients who are deemed not suitable for complete repair based

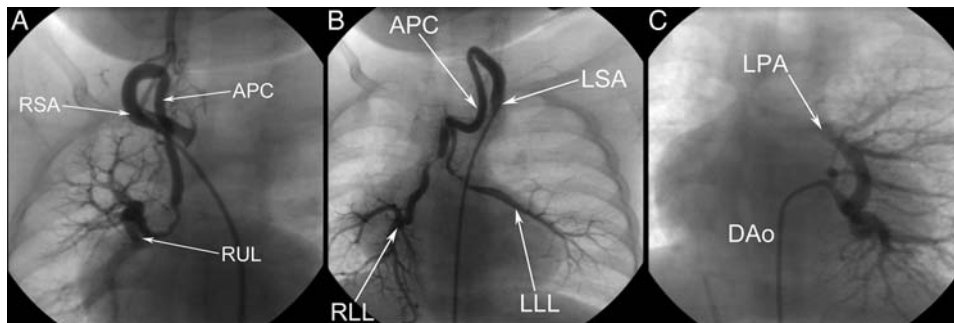


Figure 1: Pre-operative angiogram in a patient with Alagille syndrome. (A) Selective angiogram of an aortopulmonary collateral (APC) originating from the right subclavian artery (RSA). There is filling of the right pulmonary artery (RPA) and right upper lobe branches. (B) Selective angiogram of an APC originating from the left subclavian artery (LSA) with severe stenoses bilaterally before giving rise to the left (LLL) and right lower lobe (RLL) segments. (C) Selective angiogram of an APC originating from the thoracic descending aorta (DAo) with distribution to the remaining left pulmonary (LPA) segments.

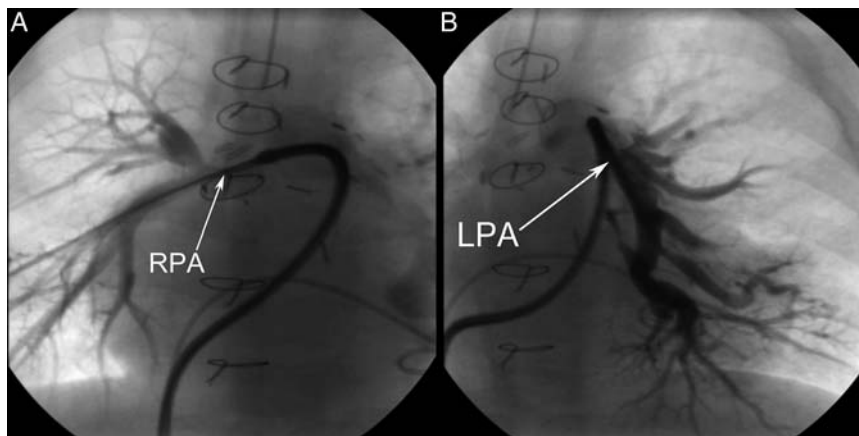


Figure 2: Post-operative angiogram of the same patient as shown in Fig. 1. The patient underwent a complete single stage unifocalization, and has subsequently outgrown the previously placed right ventricle to pulmonary artery conduit. He is being evaluated prior to elective conduit replacement. (A) Selective angiogram of the reconstructed right pulmonary artery system. (B) Selective angiogram of the reconstructed left pulmonary artery system.

on the intra-operative flow study have a central shunt placed as the source of pulmonary blood flow (Fig. 4).

There are a number of specific circumstances based on anatomy and/or physiology which mandate an alternative approach to that outlined above. Newborns who present with either severe pulmonary overcirculation or profound cyanosis may require neonatal unifocalization with or without intra-cardiac repair (as dictated by the underlying physiology). Newborns with MAPCA's to one lung and a ductus to the other may require early intervention to control the pressure and flow to the ductal-dependent lung. Collectively, these indications for early intervention account for only 5–10% of all patients with PA/MAPCA's.

A separate group of patients that can be identified during the neonatal cardiac catheterization study are those patients with MAPCA's and hypoplastic but confluent native pulmonary arteries with dual blood supply to the majority of lung segments (normal arborization). These patients are candidates for creation

of an aortopulmonary window, with or without ligation of some or all of the MAPCA's. This group comprises ~10% of patients presenting with PA/MAPCA's.

Finally, there are a few specific indications for a staged thoracotomy approach to unifocalization of patients with PA/MAPCA's. This includes patients with numerous segmental level arterial stenoses which would not be amenable to repair through a midline approach. There is also the rare circumstance of patients with pulmonary atresia and intact ventricular septal defect, MAPCA's and right ventricular-dependent coronary circulation in whom it may be advisable to avoid the use of cardiopulmonary bypass if at all feasible. We do have some patients who are referred from outside institutions who have undergone a unilateral unifocalization, in which case we would begin our management algorithm from that point.

The management of patients with PA/MAPCA's and Alagille syndrome is identical to that outlined above from a cardiac standpoint. However, the patients with Alagille's do require

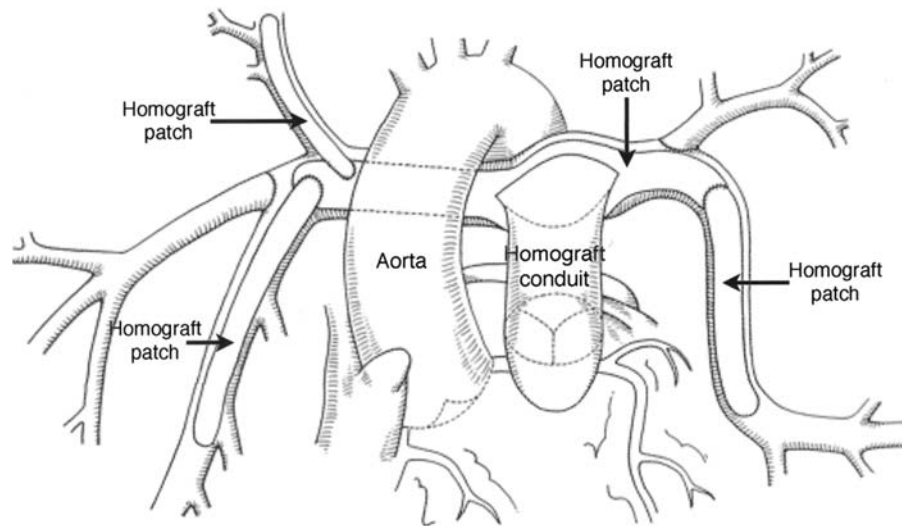


Figure 3: Artist's illustration of the anatomy following complete repair of PA/MAPCAs. The collaterals have been unifocalized into a central confluence, and a homograft conduit placed from the right ventricle to the unifocalized pulmonary artery confluence. Illustrations for Figs 3 and 4 created by Erin Anne Mainwaring.

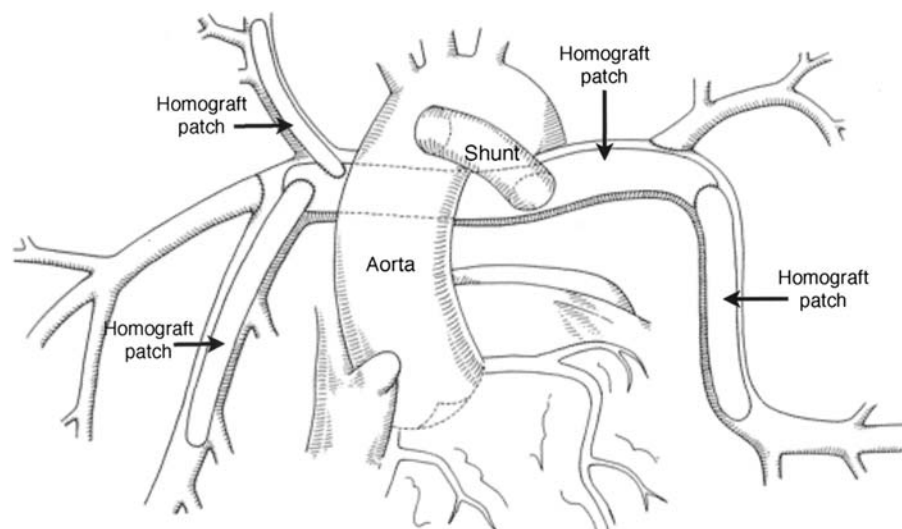


Figure 4: Artist's illustration of the anatomy following complete unifocalization with a central shunt from the ascending aorta to pulmonary artery confluence. Illustrations for Figs 3 and 4 created by Erin Anne Mainwaring.

additional evaluation and focus on the multi-organ systems involved with this syndrome.

RESULTS

There were 15 patients who were identified with both PA/MAPCA's and Alagille syndrome who have undergone surgical treatment at our institution. This included 10 males and 5 females. Thirteen patients had pulmonary atresia with ventricular septal defect (PA/VSD, with two ventricles), and 2 patients had pulmonary atresia with intact ventricular septum (PA-IVS, with functionally single ventricle).

The 15 patients in this series have undergone a total of 38 cardiac surgical procedures. There has been no early or late

mortality in this cohort of patients with PA/MAPCA's and Alagille syndrome. The median duration of follow-up from the date of the first surgical intervention to the most recent point of contact has been 3.9 years (range 11 months to 9.9 years).

The median age at the time of the first cardiac procedure was 6 months (range 1 month to 3 years) and the median weight was 5.8 kg (range 3.3–12.5 kg). A summary of these initial procedures is shown in Table 1. The median length of stay for the 15 patients was 27 days (range 13–88 days). A summary of the subsequent 23 cardiac procedures is shown in Table 2.

Ten of the 13 patients (77%) with PA/VSD have achieved complete repair, including unifocalization of the MAPCA's, a right ventricle to pulmonary artery conduit and closure of all intra-cardiac shunts (Fig. 5). Three of these 10 had a single-stage complete repair. The median cross-clamp and cardiopulmonary bypass times for the three patients who had a single stage complete repair was 32 and 242 min, respectively. Among the other seven patients, the average number of operations between the initial procedure and complete repair were 1.5 (range 1–4).

Three patients with PA/VSD have currently not achieved a complete repair, but all three remain potential candidates for repair. In addition, there are two patients with PA-IVS in the series. Both of these patients are potential candidates for a single ventricle pathway, although neither one has undergone a bidirectional Glenn as of yet. The one patient with PA-IVS is now 11 months old and clinically doing well. The second patient had PA-IVS and mixed anomalous pulmonary venous drainage of the left lung. This patient is clinically doing well and has unobstructed pulmonary venous drainage after one primary procedure and two subsequent revisions of the left pulmonary veins. These five patients are all confined to the more recent portion (birth dates 2008–2010) in our series.

The patients in this series have also undergone a total of 12 major non-cardiac procedures. These procedures are summarized in Table 3. Four patients have undergone a biliary drainage procedure, and two have had successful liver transplantation.

The follow-up family written questionnaires indicated that five children were reported to be doing well, five were doing satisfactorily, while the remaining five families reported significant concerns about their child's progress. These latter five children

Table 1: Summary of the initial procedures performed in the 15 patients with PA/MAPCAs and Alagille syndrome

Single stage complete repair	n = 3
Complete bilateral unifocalization + shunt	n = 6
Unilateral unifocalization + shunt	n = 3
Creation of aortopulmonary window	n = 2
Right ventricle to pulmonary artery shunt	n = 1

Table 2: Summary of the 23 cardiac procedures performed subsequent to the initial operation performed in patients with PA/MAPCAs and Alagille syndrome

Complete repair	n = 7
Bilateral unifocalization	n = 4
Unilateral unifocalization	n = 2
Revision of previous unifocalization	n = 4
Conduit change	n = 4
Pulmonary vein procedure	n = 2

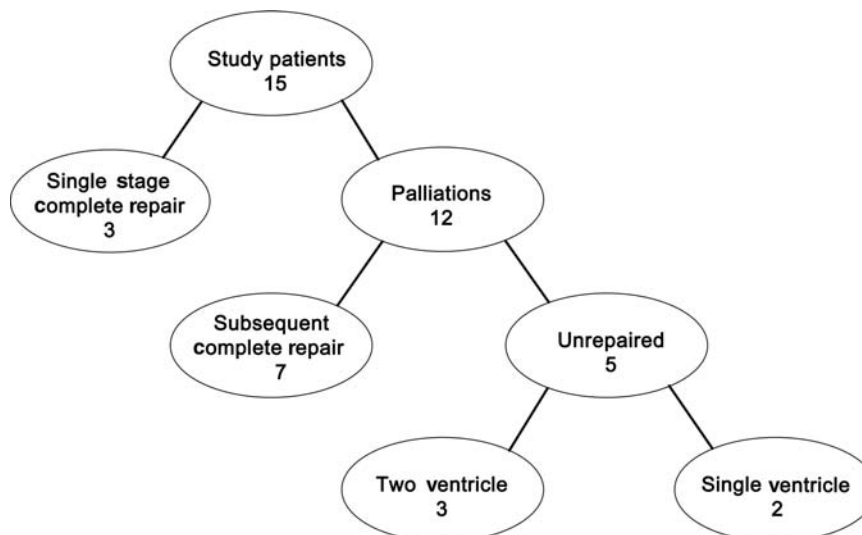


Figure 5: Flow diagram of the 15 patients in this series with pulmonary atresia/major aortopulmonary collaterals and Alagille syndrome.

Table 3: Summary of the 12 major non-cardiac procedures performed for the 15 patients with PA/MAPCA's and Alagille syndrome

Biliary diversion procedure	<i>n</i> = 4
Liver transplantation	<i>n</i> = 2
Abdominal exploration for malrotation	<i>n</i> = 1
Gastrostomy	<i>n</i> = 3
Anti-reflux procedure	<i>n</i> = 1
Tracheal reconstruction	<i>n</i> = 1

were uniformly identified as those with liver and/or other organ system illnesses. Specifically, the families that provided the lowest assessments for their children were those patients that manifested signs and symptoms of jaundice beginning in infancy. This observation underscores the variable nature of hepatic dysfunction associated with Alagille syndrome.

DISCUSSION

This study summarizes our institutional experience with 15 patients who had both PA/MAPCA's and Alagille syndrome. Although this group of patients has required a total of 38 cardiac and 12 major non-cardiac operations, there has to date been no early or late mortality. These results suggest that the short-term prognosis for patients with PA/MAPCA's and Alagille syndrome may be more favourable than that for other chromosomal syndromes, such as DiGeorge syndrome, and certainly may exceed our pre-conceived expectations for this group.

Thirteen of the 15 patients in this series had the anatomic diagnosis of PA/VSD and MAPCA's. Ten of these 13 patients have been able to achieve a complete repair, either primarily (*n* = 3) or secondarily (*n* = 7). The rate of single-stage complete repair for patients with Alagille syndrome was lower than that which we have previously reported for all patients (23 versus 56%) [11]. Conversely, the number of patients with Alagille syndrome who underwent a complete unifocalization plus a shunt (6 of 13) was twice the rate (46 versus 20%) than what we have previously reported for all patients. This disparity may be related to a higher incidence of peripheral (segmental) stenoses in the pulmonary architecture associated with Alagille's. However, the eventual complete repair rate for patients with Alagille syndrome in our series (10 of 13, or 77%) approaches the rate seen for all patients (90%). There are currently three remaining patients with Alagille syndrome who are in various stages of surgical reconstruction, and all three are viewed as good candidates for ultimate repair.

There have been three major series on PA/MAPCA's published in the past 5 years, and all three have demonstrated that achieving complete repair is the single most important factor that confers a survival advantage [2-4]. This survival advantage was independent of whether complete repair was achieved in a single stage or in multiple stages. The cohort of 13 patients with pulmonary atresia, ventricular septal defect and MAPCA's in combination with Alagille syndrome has achieved a high rate of complete repair, and thus should be in a relatively low-risk group from a cardiovascular standpoint.

Two of the 15 patients in this series had PA-IVS with functionally single ventricle, MAPCA's and Alagille syndrome. Both of these patients have been encountered in the relatively recent portion of this experience, and have not progressed to a bidirectional Glenn procedure as of yet. It was unclear whether patients with MAPCA's and functional single ventricle could achieve separation of their systemic and pulmonary circulations. In a report from our group, Reinhartz *et al.* [13] reported successful bidirectional Glenn procedures in 6 patients and successful Fontan procedures in 3 patients out of a series of 14 with MAPCA's and single ventricle. The long-term prognosis of patients with single ventricle and MAPCA's will likely be enhanced when separation of the circulations can be achieved due to the reduction in ventricular volume load. Several other small series have subsequently confirmed the feasibility of successful Fontan procedures in patients with single ventricle and MAPCA's [14-16].

There is currently a paucity of information regarding the implications of Alagille syndrome on management of complex congenital heart disease. Blue *et al.* [7] found in their data base 505 patients with pulmonary atresia, 26 patients with Alagille syndrome and 5 patients with both pulmonary atresia and Alagille. Four of these patients had PA/VSD, and one had PA-IVS. Their review indicated that patients with pulmonary atresia and Alagille syndrome had a poor prognosis, and speculated that this was due to lack of pulmonary arterial growth. Our experience summarized in this manuscript with the 15 patients who had PA/MAPCA's and Alagille syndrome would suggest that this combination comprises ~3% of our overall unifocalization population. In contrast to the report of Blue, our data would indicate that patients with PA/MAPCA's and Alagille syndrome had relatively favourable early outcomes from a cardiovascular standpoint. We had anticipated that this would not be the case, given the generic implications of syndromic conditions on outcomes in congenital heart surgery, and specifically due to the burden of the multiple organ systems affected by Alagille syndrome. We would hypothesize that the significant difference in prognosis between chromosome 22q11 deletion and Alagille syndrome could potentially be explained by the fact that Alagille syndrome does not have compromise of the immune system that is so frequently and profoundly associated with 22q11 deletion and DiGeorge syndrome.

The extra-cardiac manifestations of Alagille syndrome will undoubtedly have an impact on long-term survival. The original description of this syndrome was centred on the unique hepatic findings of cholestasis and underdevelopment of the interlobular bile ducts [8]. Hepatic function is frequently the most life-threatening issue for patients with Alagille syndrome [17], and there were four patients in our series who have had a biliary diversion procedure for treatment of hyperbilirubinemia [18]. Two of these patients have subsequently undergone liver transplant [19]. The management of these patients is complicated by the presence of complex congenital heart disease, as there is frequently a reluctance to perform complicated non-cardiac procedures in patients with uncorrected or palliated cardiac defects. It is part of our institutional protocol that these procedures are deferred until the patients with PA/MAPCA's have achieved complete repair. Vascular anomalies in Alagille syndrome are another significant cause of morbidity and mortality [20]. Vascular abnormalities include intracranial aneurysms and coarctations and aneurysms of the aorta. These abnormalities accounted for 34% of the mortality in this population, and were linked to the mutations of *JAG1* and the Notch signalling pathway. To date, we have

not encountered any morbidity or mortality on the basis of vascular anomalies, but this may be more fortuitous than anything related to specific management strategies.

One question that remains unanswered by this study is whether all patients with PA/MAPCA's and Alagille syndrome should undergo surgical correction. This single question can be parsed into three separate components; medical, ethical and financial. From a medical standpoint, the results of this study would indicate that the combination of PA/MAPCA's and Alagille syndrome can be successfully managed with mid-term results comparable to patients who do not have Alagille syndrome. Ethically, one might question whether this approach can be justified given that this cohort of 15 patients has undergone 38 cardiac and 12 non-cardiac procedures. However, public policy in the USA currently mandates care to patients for whom there is viable medical option, and this study would support the premise that this treatment provided better outcomes than would have been observed if the patients were not offered treatment. Finally, while the cost of treatment for these patients has been quite expensive and the resources required have been extraordinary, medical providers in our current system are not asked to decide whether these costs are justified but rather are required to provide that care when it is feasible and possible. These mandates in public policy may change over time given the constraints of medical resources and financial limitations.

In summary, patients with PA/MAPCA's and Alagille syndrome have a combination of two life-threatening conditions. Our data would indicate that this cohort can undergo unifocalization procedures successfully and without additional risk. The rate of single-stage complete repair for patients with Alagille syndrome appears to be somewhat lower compared with our historical controls, and may reflect a difference in arborization associated with this syndrome. However, the rate of ultimately achieving a staged complete repair is comparable with patients without Alagille's. The extra-cardiac manifestations of Alagille syndrome may play a dominant role in the longer-term prognosis for these patients.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr A. Carotti (Rome, Italy): Nowadays, surgical treatment of congenital heart disease associated with extracardiac anomalies and genetic syndromes represents a real challenge of modern paediatric cardiac surgery.

The demonstrated correlation between genotype and phenotype, and the possible identification of specific cardiac and extracardiac surgical risk factors may lead to the definition of protocols for specific treatment of these patients based on genetic diagnosis and/or syndromic association. Alagille syndrome may constitute a clear example of this.

With specific reference to the reported 15 cases of pulmonary atresia and collaterals in association with Alagille syndrome, the treatment algorithm strongly focused on unifocalization is the key to success of this particular series. The collaterals, being systemic vessels, are likely to be affected by the disease in a very marginal way compared to the true pulmonary arteries, in view of the fact that Alagille syndrome is typically associated with right-sided cardiovascular abnormalities and much more rarely with left-sided ones, the latter often associated with right-sided malformations, but not vice versa.

My first question: Have you noticed any particular anatomical or functional difference of collaterals in patients with Alagille syndrome compared to those of patients with non-syndromic association?

Dr Mainwaring: Looking at the collaterals in the operating room, I do not know that we would have the impression that these would be different. The comments that I made in my presentation were when we do the repairs, do

an intraoperative flow study, there were very few patients who were able to go on to the single-stage complete repair. So physiologically it seems as if there is some difference.

Dr Carotti: Moving from the association with Alagille syndrome and focusing on the intraoperative pulmonary artery flow study, the authors report different parameters compared to those that they have historically and at least initially used. This is a flow rate of 3 l/min/m² and a mean pulmonary arterial pressure cut-off value of 25 mmHg.

Our own experience based strictly on Dr. Hanley's initial protocol, using a flow rate of 2.5 l/min/m² with a mean pulmonary arterial pressure cut-off value of 30 mmHg showed a 94% accuracy of the test in predicting the possibility of simultaneous VSD closure, and a 91% accuracy in predicting the post-repair mean pulmonary arterial pressure.

My second question: Why did you abandon the original parameters and how did you develop the new ones?

Dr Mainwaring: It is a good question. The change occurred about a decade ago, and we increased the threshold. We did not abandon what we were doing. We increased the threshold because we had a few patients in whom we closed the VSD, got into the ICU, and then found that they were having trouble. So we have increased our parameters, as you said, to 3 l/min/m² and accepting under 25 mmHg of pressure in the pulmonary arteries.

Dr Carotti: And my last question: I noticed that, within the noncardiac procedures, a tracheal reconstruction is reported. Was it due to a primary lesion of the trachea, or to a secondary lesion occurring during the unifocalization procedure?

Dr Mainwaring: Most of the noncardiac procedures were liver-related, but there was one patient who, about a year after unifocalization, presented with tracheal stenosis and underwent tracheal reconstruction.

Dr R.A. Neirotti (Brookline, MA, USA): How many of those patients who underwent complete two ventricle repair, end up having normal pulmonary artery pressure in their follow-up?

Dr Mainwaring: We only would have cath data in a small number of those patients, so I did not pull that data for this study.

Dr Neirotti: I think that is a very important piece of information, both in this group of patients as well as in those patients without the syndrome in order to justify such a major operation.

Dr Mainwaring: Your point is well taken. The patients in whom we would have data would be those patients who are coming back for conduit change where we would do a cardiac catheterization, so that would have been four patients.

Dr V. Hraska (Sankt Augustin, Germany): I have a very brief question. What is your policy on genetic counselling of the parents in this specific disease? The combination of Alagille syndrome with MAPCAs sounds pretty peculiar.

Dr Mainwaring: Yes. That is an excellent question. I thought you were going to ask me how much we had invested in each patient, which would probably exceed a million dollars per patient. But right now our public policy in the United States is to take care of virtually every patient unless there is something that is so clearly lethal that that would provide a mandate. But until our public policy changes, we move forward and treat what we can treat.