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**Case Report**

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# Factors influencing pulmonary arterial pressure in three related patients with Cantú syndrome: glyburide may provide precision care

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## Abstract

A range of pulmonary arterial pressures was observed in three related patients with Cantú syndrome. The incident patient developed a moderately high pulmonary vascular resistance. Several factors influenced the severity of his pulmonary vascular disease and the events, which ultimately resulted in his death. However, he had an acute improvement in blood pressure and respiratory support after a single dose of glyburide when he was critically ill. The father and sister of the incident patient have evidence of mildly increased pulmonary arterial pressure with normal pulmonary vascular resistance. They are being treated with glyburide to potentially decrease the high cardiac output associated with a gain in $K_{ATP}$ channel function. Additional experience with glyburide or other $K_{ATP}$ channel inhibitors is needed to determine the most appropriate agent, dose, time, and duration of treatment for patients with Cantú syndrome.

**Keywords:** Adenosine triphosphate-sensitive potassium channel, Cantú syndrome, glyburide, high cardiac output, pulmonary hypertension

## INTRODUCTION

A syndrome of congenital hypertrichosis, cardiomegaly, and musculoskeletal malformations was initially

reported by Cantú and associates[1]. Cantú syndrome is caused by variants in the *ABCC9* gene that result in a gain of function in adenosine triphosphate-sensitive potassium ($K_{ATP}$) channels[2,3]. The phenotypic features are well described in the International Cantú Syndrome Registry[4]. A high cardiac output state is one feature of the syndrome, which may be the result of structural cardiovascular defects and low vascular tone[4-7]. A patent ductus arteriosus is present in many patients[4]. This defect may increase the volume load on the left ventricle unless the left-to-right shunt is limited by a very small vessel diameter or a relatively high pulmonary vascular resistance. Gain of function in the $K_{ATP}$ channels and vasodilation may induce a high cardiac output state even when a patent ductus arteriosus is not present[5,7,8]. Cardiomegaly, an increase in myocardial mass, enlarged major vessels, and enlarged neurovascular vessels are hallmarks of this process. Some patients develop an increase in pulmonary arterial pressure[4,9]. Here, the affected members of a family are described to improve our understanding of factors that may increase pulmonary arterial pressure and the potential importance of providing precision care with a $K_{ATP}$ channel inhibitor before starting treatment with pulmonary vasodilators.

## CASE REPORTS

### Case 1 (incident patient)

*Hospitalization 1*

A male infant experienced a respiratory and cardiac arrest at 3 months of age that was attributed to a respiratory syncytial virus infection. He was resuscitated and admitted to the Pediatric Intensive Care Unit of Primary Children's Hospital. He was born at full term and his past medical history was unremarkable. However, he shared facial features and findings of hypertrichosis with his father and older sister, and mild scoliosis with his older sister. During this hospitalization, rapid whole genome sequencing identified a pathogenic heterozygous variant in the *ABCC9* gene c.3461G > A (p. Arg 1154 Gln) that has been reported in several patients with Cantú syndrome. His father and older sister also tested positive for this variant. A genetic counselor and geneticist discussed the results of genetic testing with the parents and provided information for the family to understand how Cantú syndrome may affect the cardiovascular system and other organs. Care providers were cautioned to avoid medications that may stimulate $K_{ATP}$ channels or cause systemic vasodilation. The genetics team remained available for additional questions during the hospitalization and planned a follow-up outpatient evaluation with the family several months after genetic testing.

He had a large patent ductus arteriosus and very small patent foramen ovale. He needed inotropic support to maintain normal systemic arterial pressures during hospital days 1 to 10. He was treated with inhaled nitric oxide during hospital days 3 to 14 due to an intermittent right-to-left ductal shunt. His highest measured arterial oxygen tension was 153 mmHg on hospital day 3 during conventional ventilation with inspired oxygen of 50% and a positive end-expiratory pressure of 10 cm $H_2O$. A CT angiogram and dynamic evaluation of his airways were performed on hospital day 23. Figure 1 shows images from the airway evaluation with more narrowing of the lower trachea when the positive end-expiratory pressure was 4 cm $H_2O$ than when the positive end-expiratory pressure was 12 cm $H_2O$. The bronchi also appeared narrow between the right pulmonary artery and thoracic spine.

The ductus arteriosus was successfully closed with a 5/4 Amplatzer Duct Occluder on hospital day 25. He was separated from support with assisted ventilation on hospital day 28. A prolonged transition period of support from noninvasive positive pressure support to low-flow nasal cannula oxygen was subsequently needed. He was sent home on hospital day 47 and maintained on supplemental oxygen as an outpatient. An echocardiogram was performed at 6 months of age. His left ventricular end-systolic eccentricity index was 1.12-1.18 (normal to mildly flattened septal configuration) with a systolic systemic blood pressure of 90

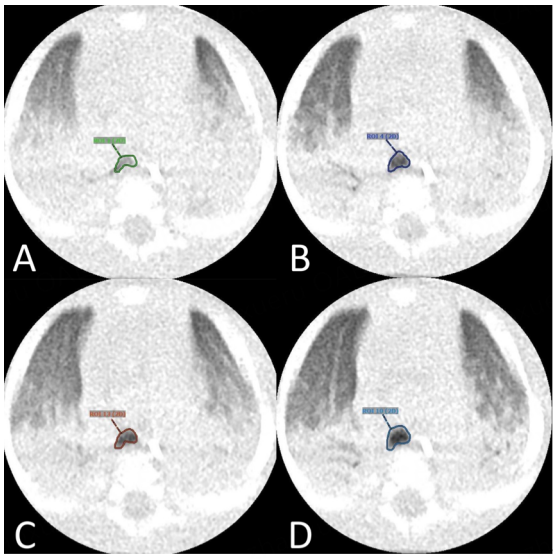


**Figure 1.** Images from a CT scan of the chest of the incident patient with dynamic evaluation of the airways at 3 months of age before closure of the ductus arteriosus. There was a minimum transverse area of 25.2 $mm^2$ (A) and a maximum transverse area of 33.2 $mm^2$; (B) of the lower trachea with a positive end-expiratory pressure of 4 cm $H_2O$. There was a minimum transverse area of 30.3 $mm^2$; (C) and a maximum transverse area of 47.3 $mm^2$; (D) of the lower trachea with a positive end-expiratory pressure of 12 cm $H_2O$.

mmHg. His oxygen saturation measurements were intermittently monitored and remained normal while he was transitioned to room air over several days. He was living at an altitude of approximately 1,735 m.

*Hospitalization 2*

He developed a rhinovirus infection at 7 months of age and was again admitted to the Pediatric Intensive Care Unit of Primary Children's Hospital. He had echocardiographic evidence of pulmonary hypertension, normal left ventricular systolic function, and a subjective appearance of hypertrophy of the right and left ventricles. Tricuspid valve regurgitation gradients were consistent with near systemic to suprasystemic systolic pulmonary arterial pressures. A left ventricular mass Z-score of 4.5 was measured during one of the echocardiograms. He was experiencing intermittent episodes of systemic hypotension and lactic acidosis that were attributed to pulmonary hypertensive crises. He was being treated with inhaled nitric oxide, milrinone, and intermittently with intravenous epinephrine to manage these episodes. A 1 mg/kg trial dose of sildenafil was associated with a decrease in systemic blood pressure and an increased need for epinephrine. He subsequently tolerated treatment with bosentan, up to 1.5 mg/kg/dose twice a day.

Figure 2 shows images from a CT angiogram on hospital day 4 with evidence of lung disease and severe left bronchial narrowing with apparent crowding by an enlarged right pulmonary artery, the occluded ductus arteriosus, the descending aorta, and a mildly curved thoracic spine despite a positive end-expiratory pressure of 8 cm $H_2O$. Tests for rhinovirus cleared by hospital day 13. His highest measured arterial oxygen tension during this hospitalization was 100 mmHg on hospital day 9 during high-frequency percussive ventilation with an inspired oxygen of 60% and a positive end-expiratory pressure of 10 cm $H_2O$, raising concern for a potential intrapulmonary shunt. Serial echocardiograms with color Doppler imaging typically showed evidence of a very small left-to-right atrial level shunt.

Due to persistent echocardiographic evidence of pulmonary hypertension and apparent resolution of his viral illness, heart catheterization was performed on hospital day 21. His hemodynamic measurements are listed in Table 1. He had evidence of a moderately high cardiac index, moderately high pulmonary vascular

**Table 1. Results of heart catheterization. Incident patient**

| | Baseline | AVT |
|---|---|---|
| Age: 8 months | | |
| Baseline oxygen and medications | | |
| 60% Oxygen | | |
| Inhaled nitric oxide 20 ppm | | |
| Milrinone 0.5 mcg/kg/min | | |
| Bosentan 3 mg/kg/day | | |
| Acute vasodilator testing | | |
| 100% Oxygen | | |
| Epoprostenol 14 ng/kg/min | | |
| Systemic arterial blood gas measurements | | |
| pH | 7.41 | 7.43 |
| Carbon Dioxide Tension, mmHg | 37 | 41 |
| Oxygen Tension, mmHg | 66 | 74 |
| Oxygen Saturation, % | 92 | 95 |
| Hemodynamic measurements | | |
| Mean PAP, mmHg | 43 | 39 |
| Mean PAWP/LAP, mmHg | 11 | 11 |
| Mean SAP, mmHg | 50 | 57 |
| Mean RAP, mmHg | 9 | 9 |
| Hemodynamic calculations | | |
| Cardiac index, L/min•$m^2$ | | |
| Fick principle | 5.0 | 5.9 |
| Pulmonary vascular resistance, WU•$m^2$ | 6.4 | 4.7 |
| Systemic vascular resistance, WU•$m^2$ | 8.2 | 8.2 |

AVT: acute vasodilator testing; L/min•$m^2$: Liter/minute•meters squared; mcg: microgram; mg: milligram; ng: nanogram; PAP: pulmonary arterial pressure; PAWP/LAP: pulmonary arterial wedge pressure/left atrial pressure; ppm: parts per million; RAP: right atrial pressure; SAP: systemic arterial pressure; WU•$m^2$: wood units•$m^2$ (mmHg•minute•meters squared/Liter).

resistance, and low systemic vascular resistance. His pulmonary arterial pressure decreased, and his systemic blood pressure increased during an acute infusion of epoprostenol. Evidence of a potential intrapulmonary shunt was confirmed with a systemic arterial oxygen tension of 74 mmHg during conventional ventilation with 100% oxygen and color Doppler evidence of a very small left-to-right atrial level shunt. His patent foramen ovale was enlarged by dilation with a 15 mm by 3 cm Tyshak II balloon catheter following his hemodynamic evaluation to decrease the risk of potential pulmonary hypertensive crises. The subsequent atrial septal defect appeared small to moderate in size by color Doppler imaging immediately following the procedure.

On hospital day 22, he was started again on sildenafil using a lower dose of 0.5 mg/kg/dose three times a day. He experienced intermittent mild to moderate hypoxemia when his sedation was transiently decreased. His hemoglobin was 9.4 g/dL and he was transfused up to a hemoglobin value of 11.3 g/dL. On hospital day 23, he was given a 0.5 mcg dose of inhaled iloprost. At that time, he did not have adequate vascular access to start intravenous epoprostenol. He subsequently developed severe hypoxemia and hypotension that required bag ventilation, intravenous epinephrine, and intravenous phenylephrine. Oxygen saturation measurements were then frequently less than 70%. He had echocardiographic evidence of poor right ventricular function and an increase in right-to-left atrial level shunting. He was transfused up to a hemoglobin value of 15.9 g/dL. He had a mildly increased troponin I of 0.22 ng/mL (normal range <

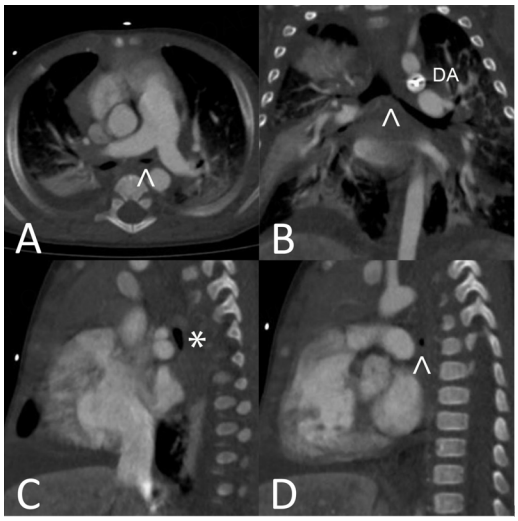


**Figure 2.** Images from a CT angiogram of the chest of the incident patient at 7 months of age (3 months after device closure of the ductus arteriosus). (A) An axial image showing a large MPA, mild to moderate flattening of the right bronchus, and severe flattening of the left bronchus (arrow) between the right pulmonary artery, descending aorta, and mildly curved spine; (B) A coronal image showing a device in the DA and a very small proximal left bronchus (arrow); (C)* A sagittal image showing mild to moderate flattening of the right bronchus; (D) A sagittal image showing severe narrowing of the left bronchus (arrow). DA: ductus arteriosus.

0.03 ng/mL). Despite the severity of his hypoxemia, his lactic acid levels did not exceed 0.5 mmol/L and his base deficit did not exceed 2 mmol/L, which suggests he was maintaining adequate systemic oxygen delivery. After a period of approximately five hours of bag ventilation and escalation in vasopressor support, he was treated with an enteral dose of 0.5 mg (0.06 mg/kg) glyburide, a $K_{ATP}$ channel inhibitor. A similar starting dose was tolerated in a previously reported infant[10]. His oxygenation improved and stabilized to the point that bag ventilation was no longer needed to maintain oxygen saturation measurements greater than 85% using no additional vasoactive agents within 30 minutes of treatment. However, his intensive care providers decided to redirect care and he passed away soon after the family agreed to withdraw support.

### Case 2 (Incident patient's father)

The father was 37 years of age when the incident patient was born. He underwent surgical ligation of a patent ductus arteriosus at 9 months of age. He developed lower extremity edema around 18 years of age. This finding is frequently seen in adults with Cantú syndrome[4]. An echocardiogram at 33 years of age showed evidence of a pericardial effusion, mild to moderate left ventricular enlargement, and increased pulmonary arterial pressure. Heart catheterization was performed at 34 years of age. His hemodynamic measurements are listed in Table 2. He had a mildly increased mean pulmonary arterial pressure, a high cardiac output, a normal pulmonary vascular resistance, and a low systemic vascular resistance. His mean systemic arterial pressure was estimated using a blood pressure cuff on an arm during heart catheterization. At 35 years of age, he developed pulmonary edema while traveling at an altitude greater than 3,000 m. He has experienced exertional dyspnea at his home altitude of 1,735 m during the past few years.

After discussing the potential benefits of precision care and the risk of hypoglycemia, he was started on treatment with glyburide 1.25 mg once a day, 3-4 months following the death of his son, to potentially decrease the workload on his heart and decrease his lower extremity edema. He is being treated with a low dose of glyburide and his blood glucose levels are monitored infrequently. No major or symptomatic episodes of hypoglycemia have been observed. There was a slight improvement in the swelling of his feet. However, he developed bilateral lower extremity venous thrombosis 2-3 months after the onset of therapy

**Table 2. Results of heart catheterization. Father of the incident patient**

| | Baseline | AVT |
|---|---|---|
| Age: 34 years | | |
| Baseline oxygen and medications | | |
| 21% Oxygen | | |
| Acute vasodilator testing | | |
| Inhaled Nitric Oxide 20 ppm | | |
| Hemodynamic measurements | | |
| Mean PAP, mmHg | 26 | 23 |
| Mean PAWP, mmHg | 13 | 13 |
| Mean SAP, mmHg | 78 | - |
| Mean RAP, mmHg | 6 | 6 |
| Hemodynamic calculations | | |
| Cardiac output, L/min | | |
| Fick principle | 8.6 | 13.7 |
| Thermodilution | 6.7 | 8.1 |
| Pulmonary vascular resistance, WU | | |
| Fick principle | 1.5 | 0.7 |
| Thermodilution | 1.9 | 1.2 |
| Systemic vascular resistance, WU | | |
| Fick principle | 8.4 | - |
| Thermodilution | 10.7 | - |
| Age: 38 years, after 6 months of treatment with glyburide | | |
| Baseline oxygen and medications | | |
| 21% Oxygen | | |
| Acute vasodilator testing | | |
| Not performed | | |
| Hemodynamic measurements | | |
| Mean PAP, mmHg | 41 | - |
| Mean PAWP, mmHg | 19 | - |
| Mean SAP, mmHg* | 91 | - |
| Mean RAP, mmHg | 10 | - |
| Hemodynamic calculations | | |
| Cardiac output, L/min | | |
| Fick principle | 8.1 | - |
| Thermodilution | 9.8 | - |
| Pulmonary vascular resistance, WU | | |
| Fick principle | 2.7 | - |
| Thermodilution | 2.2 | - |
| Systemic vascular resistance, WU | | |
| Fick principle | 10.0 | - |
| Thermodilution | 8.3 | - |

AVT: acute vasodilator testing; L/min: Liter/minute; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; ppm: parts per million; RAP: right atrial pressure; SAP: systemic arterial pressure; WU: Wood units (mmHg•minute/Liter); *1/3(systolic systemic arterial pressure- diastolic arterial pressure) + diastolic arterial pressure.

and was started on a factor Xa inhibitor. A lupus anticoagulant was detected through an evaluation for thrombophilia. No evidence of pulmonary thromboembolic disease was identified with lung ventilation and

perfusion scans. After a temporary pause in treatment, his glyburide was resumed. No noticeable changes in facial features or the severity of hypertrichosis have been observed during treatment with glyburide thus far.

Table 2 shows the results of repeat heart catheterization 6 months after the onset of therapy with glyburide. He has persistently high values of cardiac output and pulmonary arterial pressure with normal pulmonary vascular resistance and low systemic vascular resistance. His pulmonary arterial wedge pressure, or left ventricular filling pressure, has increased.

### Case 3 (Incident patient's sister)

The sister was 5 years of age when the incident patient was born. The sister was noted to have a small patent ductus arteriosus during early infancy. The family was told that the vessel spontaneously closed. However, a follow-up echocardiogram at 6 years of age showed a very small persistent patent ductus arteriosus. There was a systolic left-to-right ductal gradient of 55-68 mmHg and a left ventricular eccentricity index of 1.15-1.20 with a systemic blood pressure of 103/63 mmHg suggesting that she potentially has a mildly increased systolic pulmonary arterial pressure. She also had mild left ventricular enlargement, normal left ventricular systolic function, and an increased left ventricular mass (Z-score of 2.90). Images of the CT angiogram of her chest are shown in Figure 3. She has mild cardiomegaly, a subjective increase in left ventricular mass, a large aorta, a large main pulmonary artery, a very small patent ductus arteriosus, and several small systemic to pulmonary arterial collateral vessels (not shown). The ductus arteriosus and systemic to pulmonary arterial collaterals do not appear large enough to cause a significantly increased volume load on the left ventricle. A CT angiogram of her head and neck revealed no enlarged cerebral or neck arteries.

After discussing the potential benefits of precision care and the risk of hypoglycemia, she was started on treatment with glyburide 0.625 mg once a day with blood glucose monitoring, 2-3 months after the death of her brother, to potentially decrease the workload on her heart. Her starting dose was based upon the report by Ma and associates and adjusted as needed while monitoring blood glucose levels four to six times a day for a few days as an inpatient[10]. This relatively low maintenance dose was continued as an outpatient to avoid problems with hypoglycemia. Her blood glucose levels are monitored two to three times a day, and she receives care from a pediatric endocrinologist. No major or symptomatic episodes of hypoglycemia have been observed. To date, no noticeable changes in the severity of hypertrichosis have been observed during treatment with glyburide. A follow-up echocardiogram 4-5 months after the onset of treatment with glyburide showed no apparent difference in her ductus arteriosus or estimates of pulmonary arterial pressure. However, her left ventricular mass Z-score decreased to 1.49. Echocardiographic measurements of left ventricular mass may vary between observers. Thus, her left ventricular mass Z-scores were repeated by an independent reviewer to determine with additional scrutiny whether a decrease in mass truly occurred. Repeat Z-score measurements of left ventricular mass were 1.77 before and 0.71 after treatment with glyburide.

## DISCUSSION

This report describes three related individuals with Cantú syndrome who have a range of pulmonary arterial pressures and pulmonary vascular resistances. The incident patient ultimately developed a moderately high pulmonary vascular resistance. The father and sister of the incident patient likely have normal pulmonary vascular resistances with mildly increased pulmonary arterial pressures due to the increased cardiac output state associated with Cantú syndrome.

### Factors associated with pulmonary hypertension in the incident patient

Several factors may explain why the incident case had varying degrees of pulmonary hypertension over the

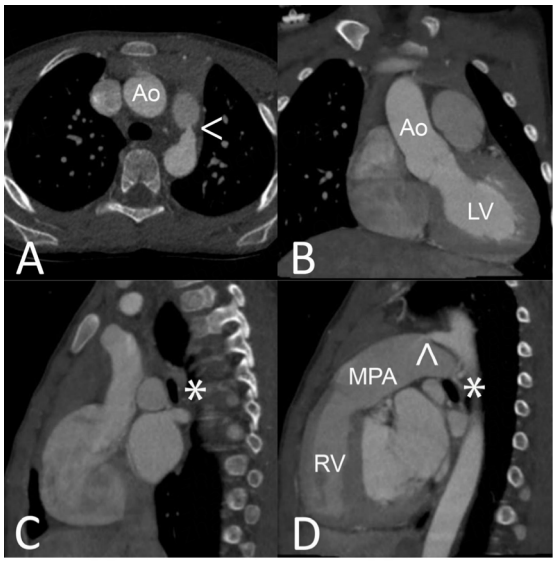


**Figure 3.** Images from a CT angiogram of the chest of the sister of the incident patient at 6 years of age. (A) An axial image showing a very small patent ductus arteriosus (arrow) as the vessel joins with the main pulmonary artery, and an enlarged ascending aorta; (B) A coronal image showing a subjectively increased mass of the LV and an enlarged Ao; (C) A sagittal image showing mild flattening of the proximal right bronchus (asterisk); (D)* A sagittal image showing a very small patent ductus arteriosus (arrow), a large MPA, subjectively increased mass of the left ventricle, subjectively normal mass of the RV, and mild flattening of the proximal left bronchus. LV: left ventricle; Ao: ascending aorta; MPA: main pulmonary artery; RV: right ventricle.

course of his life.

• His pulmonary arterial pressure was initially elevated in the setting of a large patent ductus arteriosus. Pulmonary arterial pressure normalizes in most patients following closure of the ductus arteriosus at a young age. There was evidence that his pulmonary arterial pressure improved following ductal closure while he was being treated with supplemental oxygen between his viral infections and hospitalizations.

• Infancy might be a vulnerable time for patients with a gain of function in $K_{ATP}$ channels to develop pulmonary hypertension or fail to transition from a high fetal pulmonary vascular resistance. Diazoxide stimulates $K_{ATP}$ channels and is used to treat infants with hyperinsulinemia and hypoglycemia. Some infants develop pulmonary hypertension while being treated[11]. Diazoxide is not a known cause of pulmonary hypertension later in life. Long-term treatment with diazoxide may even be beneficial for a small subset of adult patients with pulmonary hypertension who do not have Cantú syndrome[12-14].

• He experienced two serious respiratory viral infections at a young age. Respiratory viruses, including rhinovirus, may be associated with the onset of pulmonary hypertension[15]. A history of pulmonary hypertension may also increase the severity of a viral illness[16].

• He lived at a moderately high altitude and could have experienced a mild or subclinical amount of alveolar hypoxia. His father and sister lived at elevations 1,400 m and 825 m during early infancy, respectively. Based upon the presence of right ventricular hypertrophy at the onset of his rhinovirus infection, some degree of pulmonary hypertension potentially developed after stopping supplemental oxygen before his second hospitalization.

• There was evidence of a mismatch in ventilation and perfusion or an intrapulmonary shunt before atrial septostomy when he had a very small left-to-right atrial level shunt. He appeared to have significant left airway compression. It is unclear whether airway narrowing with regional alveolar hypoxia was a cause or a result of his increase in pulmonary arterial pressure. The method of ductal closure was also a potential factor in airway narrowing as devices must slightly enlarge the vessel to be securely deployed. Ductal devices may also further approximate the position of the aorta and pulmonary arteries over time. Ductal ligation and division might have been a more appropriate method of ductal closure in this patient, who already had some evidence of airway crowding or compression before the intervention. Bronchomalacia has been observed infrequently in patients with Cantú syndrome[4]. The sister of the incident patient has only mild flattening of her bronchi with a potential mild increase in systolic pulmonary arterial pressure. More observation is needed to determine whether enough airway narrowing occurs in some patients to influence oxygenation.

### Factors associated with the death of the incident patient

Episodes of potential pulmonary hypertensive crises before enlargement of the foramen ovale and severe hypoxemia after enlargement of the foramen ovale were potentially not a result of acute increases in pulmonary arterial pressure alone. His pulmonary vascular resistance seemed relatively high, in part because his systemic vascular resistance was quite low. Several factors potentially had an adverse impact on the outcome of the incident patient.

• A better outcome might have occurred if he received precision care using a $K_{ATP}$ inhibitor, such as glyburide, before treating his pulmonary hypertension. Glibenclamide, or glyburide, inhibits $K_{ATP}$ channel overactivity and reverses the cardiovascular abnormalities of Cantú syndrome in animal models[17,18]. Glibenclamide has been used in a limited number of patients with Cantú syndrome. One premature newborn experienced a decreased need for support with bilevel positive airway pressure and a decrease in edema after being treated with glibenclamide[10]. The report did not indicate whether bronchomalacia or airway compression was a factor in the need for bilevel positive airway pressure support. The incident patient in this report experienced improvement and stabilization in his systemic blood pressure and oxygenation with a single enteral dose of glyburide. There was a distinct temporal relation between the time needed for glyburide to be absorbed and his improvement. His condition might have improved more gradually if the systemic vasodilatory effects of iloprost or other medications were simply wearing off. Unfortunately, we do not know whether additional treatment would have resulted in sustained improvement and long-term survival.

• A less pronounced systemic vasodilatory effect might have occurred by using a more calibrated approach with pulmonary vasodilator therapy. Milrinone, bosentan, and sildenafil were targeting multiple vasodilatory pathways of signal transduction. His acute decrease in pulmonary arterial pressure and increase in systemic arterial pressure when treated with epoprostenol during heart catheterization suggested that he might benefit from treatment with a prostacyclin analog, as well. In hindsight, however, adequate vascular access should have been established to provide a short-acting, titratable agent. Alternatively, a smaller starting dose of iloprost should have been used.

• The atrial level shunt was potentially larger than initially estimated following balloon dilation of the foramen ovale. The atrial shunt and level of hypoxemia did not appear concerning until his level of sedation was decreased following heart catheterization and after a dose of iloprost despite deep sedation. Calibrating the size of an atrial level shunt in patients with pulmonary hypertension is difficult, even with graded balloon dilations of the atrial septum[19,20]. His hemoglobin value was relatively low when the patent foramen

ovale was enlarged. Transfusion averse strategies are not appropriate when an atrial septostomy is being used in the management of pulmonary hypertension. Kerstein and associates recommend attaining a hematocrit greater than 40% before performing the atrial septostomy[19]. An increase in oxygen carrying capacity maintains oxygen delivery, increases the oxygen saturation of systemic venous return, and limits the severity of hypoxemia that occurs with right-to-left cardiovascular shunts, even if an increase in cardiac output does not occur.

• In the setting of a supine patient with intermittent right-to-left shunting after atrial septostomy, he could have experienced ischemia of the right ventricular myocardium if small air bubbles were inadvertently introduced with intravenous fluids and entered the anterior right coronary artery. Accordingly, an acute decrease in right ventricular function or compliance could explain the observed change in his right-to-left atrial level shunt, not an excessive systemic vasodilatory effect of medications for pulmonary hypertension alone.

• Regional alveolar hypoxia might explain why his pulmonary vascular resistance was elevated. Many patients with Cantú syndrome, including his father and sister, may only have elevated pulmonary arterial pressures due to a high cardiac output state with normal pulmonary vascular resistance. A trial of assisted ventilation in a prone position might have helped to delineate whether airway compression contributed to his difference in alveolar and systemic arterial oxygen. Selective measurements of oxygen content in each pulmonary vein during heart catheterization might have also better clarified whether he had an intrapulmonary shunt or severe mismatch in ventilation and perfusion due to airway compression. If airway compression was contributing to the incident patient's increase in pulmonary vascular resistance, pulmonary vasodilators might not have been needed if the airway compression had been initially addressed. Less crowding of the airway might have occurred by removing the occlusion device and dividing the ductus arteriosus.

• S-nitrosohemoglobin levels are not typically monitored in a clinical setting. However, S-nitrosohemoglobin levels may increase during inhaled nitric oxide therapy and augment systemic vasodilation in the setting of hypoxemia through the nitric oxide pathway of signal transduction[21].

• There was no uniform agreement among care providers that a sustained trial of treatment with glyburide was worthwhile when he was critically ill. His outcome might have been improved by using a program for rare and undiagnosed diseases with consistent coordination between genetic specialists and appropriate subspecialists, as proposed by Pinto e Vairo and associates[22]. In this case, the continuity of care could have been improved while he was an inpatient and an outpatient. At the time of his initial diagnosis, a subspecialty physician champion with some expertise in vascular biology could have been designated to oversee his cardiovascular care, consider the benefits and risks of all options for closure of the ductus arteriosus, regularly consult with the local program for rare and undiagnosed diseases, seek advice from individuals with expertise in Cantú syndrome at other institutions, and implement precision care before he was critically ill. Institutions need to support care providers in this role for the framework of a precision care program for rare and undiagnosed diseases to succeed.

### Treatment of the father and sister of the incident patient with glyburide

The father and sister of the incident patient are being treated cautiously with glyburide. Treatment might decrease the high cardiac output state and decrease the risk of associated cardiovascular complications long-term. The sister's left ventricular mass has potentially decreased with treatment based on serial echocardiograms. The impact of glyburide on the father's ventricular mass has not been evaluated. $K_{ATP}$

inhibition might directly limit lymphatic dysfunction and alleviate or prevent lower extremity edema[23]. A persistently high cardiac output state was observed during the father's second heart catheterization after a period of low-dose therapy with glyburide. A lack of improvement might have occurred if glyburide was simply not effective, the dose of drug was not adequate, the drug was not consistently used, or the drug was withheld and not present in the circulation due to fasting before the procedure. We and others may be able to monitor the magnitude and duration of the hemodynamic effect of a test dose of glyburide during future catheterization procedures. An increase in left ventricular filling pressure is concerning and may indicate a progressive decrease in left ventricular function from a chronic high output state.

The ductus arteriosus of the incident patient's sister did not close after treatment with glyburide. However, her ductus arteriosus has been patent for several years and is potentially no longer able to dilate or constrict. Diazoxide stimulates $K_{ATP}$ channels and has been associated with the reopening of the ductus arteriosus in an infant[24]. Additional observation is needed to determine whether the size of the ductus arteriosus might decrease by inhibiting $K_{ATP}$ channels in newborns with Cantú syndrome. Her patent ductus is very small and could easily be closed with an intervention; however, it is unlikely to increase the workload on her heart or significantly increase her pulmonary arterial pressure. Further, a small patent ductus arteriosus could be used to create a reverse Potts shunt if she develops severe pulmonary hypertension over the course of her life.

The Cantú syndrome registry may provide a framework to collectively monitor the impact of inhibiting $K_{ATP}$ in a sufficiently large number of patients to refine precision care for affected individuals[4].

In summary, a range of measured and estimated pulmonary arterial pressures was observed in three related patients with Cantú syndrome. The incident patient developed moderately high pulmonary vascular resistance. Several factors potentially influenced the severity of his pulmonary vascular disease and his ultimate outcome. He had a favorable acute improvement in the need for systemic blood pressure and respiratory support after a dose of glyburide when he was critically ill. Additional experience with glyburide or other $K_{ATP}$ channel inhibitors is needed to determine the most appropriate agent, dose, time, and duration of treatment that might help patients with Cantú syndrome. This report underscores the need to increase awareness of the mechanism of cardiovascular complications in Cantú syndrome. We believe patients should be treated with glyburide before using most targeted therapies for pulmonary hypertension in this setting. We will better understand the risks and benefits of therapy if more clinicians are willing to use precision care to inhibit $K_{ATP}$ channels and collectively monitor its effect on outcomes.

## DECLARATIONS

### Authors' contributions

Made substantial contributions to the conception or design of the work, the acquisition of data and images, and the interpretation of data, and drafted the work and all revisions: Day RW

Made substantial contributions to the acquisition of data, reviewed the manuscript, and recommended appropriate revisions: Call BF

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

The University of Utah Institutional Review Board did not require approval or consent for this report. The information for this report was gathered retrospectively from medical records. No identifying information is included in the report.

### Consent for publication

Not applicable.

### Copyright



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