Cardiology in the Young

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Post-operative course of pulmonary artery pressure after complete atrioventricular canal defect repair

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Original Article

Cite this article: Pierre Louis ME, Bhutta A, Holloway A, and Gaskin P (2022) Post-operative course of pulmonary artery pressure after complete atrioventricular canal defect repair. *Cardiology in the Young* **32**: 398–404.
doi: 10.1017/S1047951121002201

Received: 19 June 2020
Revised: 11 March 2021
Accepted: 17 May 2021
First published online: 11 June 2021

Keywords:
Pulmonary vascular resistance; atrioventricular canal defect; pulmonary artery hypertension

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Abstract

Complete atrioventricular canal defect is a CHD associated with intra-cardiac shunting of blood, which can lead to irreversible changes in pulmonary vascular resistance and pulmonary artery hypertension if unrepaired. Patients with Trisomy 21 are at risk for early development of pulmonary artery hypertension if left uncorrected.[1,2]

Objectives: The purpose of this study is to describe the evolution of pulmonary artery hypertension after repair of complete atrioventricular canal defect and to determine the time to normalisation of pulmonary artery pressure in both patients with and without Trisomy 21. *Methods:* This is a single centre, retrospective analysis of patients with complete atrioventricular canal defect admitted for surgical repair at the University of Maryland Medical Center from 2005 to 2015. T-test or Mann–Whitney test and Chi-Square or Fisher's exact tests were used to compare the two groups (patients with Trisomy 21 and those without). Repeated measures of analysis of variance and serial measurement analysis were performed. *Results:* Twenty-nine patients meeting the inclusion criteria underwent repair of complete atrioventricular defects during the study period. The right ventricular pressure estimate remained elevated over time and did not show a significant difference between the two groups. Right ventricular to systolic blood pressure ratios for all patients remained > 0.5 over the time periods assessed. *Conclusions:* Our study suggests that in patients with complete atrioventricular canal defects, the right ventricular pressure remains elevated and does not normalise on echocardiograms performed up to one year after surgery, suggesting a sustained elevation in pulmonary vascular resistance.

Complete atrioventricular canal defects account for approximately 4–5% of people with CHD and are seen in 33–48% of children with Trisomy 21.[3–6] They are among the most common cardiac abnormalities found in children with Trisomy 21.[4,7,8] Complete atrioventricular canal defect, if untreated, may lead to progressive increases in pulmonary artery pressure and pulmonary vascular resistance leading to remodelling of pulmonary arteries.[9] This remodelling is more prominent and occurs at an earlier age in children with Trisomy 21.[7,10,11] Without surgical repair, 80% of patients with complete atrioventricular canal defect will die by 2 years of age.[5,6] Those who survive are likely to develop irreversible pulmonary vascular disease at a young age leading to the development of Eisenmenger Syndrome.[12–15]

In children with complete atrioventricular canal defect, it has been demonstrated that pulmonary vascular changes commence as early as 6 months of age.16 The histologic changes in the pulmonary arterioles may prevent the pulmonary vascular resistance from returning to normal after surgical repair.[6] After surgical repair these patients remain at risk for morbidity associated with elevated pulmonary vascular resistance.[17,18] Pulmonary artery hypertension remains a significant risk factor for morbidity and mortality, and the long-term results after surgery depend on the pre-operative pulmonary vascular resistance.[6,9,14,19] Early diagnosis and surgery are recommended to prevent irreversible progression of pulmonary vascular disease.[10,11,15,18,20,21] Over time pulmonary artery pressures are thought to normalise; however, the timing of this event has not been clearly determined.[19] Many gaps remain in our knowledge regarding the timing to resolution of the pulmonary artery hypertension and whether Trisomy 21 is associated with suboptimal outcomes. The purpose of this study is to describe the evolution of pulmonary artery hypertension after complete atrioventricular canal defect and to assess whether patients with Trisomy 21 are at higher risk of prolonged elevation of pulmonary artery pressure after surgical repair.

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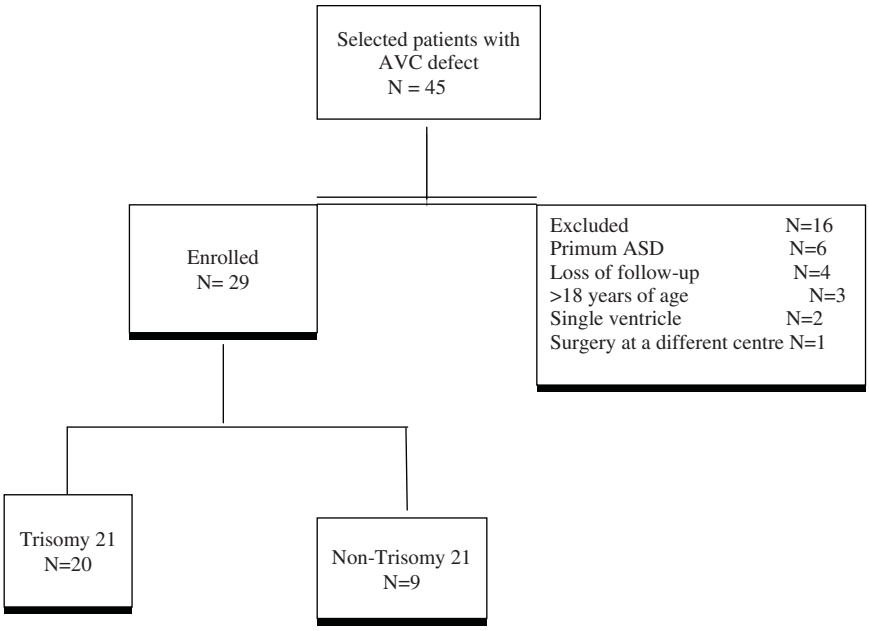

Figure 1. Study population.

Methods

Patient selection

The study was approved by the institutional review board at University of Maryland, Baltimore. We performed a single centre, retrospective analysis, involving all patients from birth to 18 years old diagnosed with complete atrioventricular canal defects and admitted for surgical repair at the University of Maryland from 2005 to 2015. We excluded patients from our study if the complete atrioventricular canal defect was associated with single ventricle physiology, congenital lung malformation, chronic lung disease, and those with missing data.

Data collection

We collected data from the electronic medical record and the echocardiographic database. The demographic information included the child's age at the time of surgery, race, sex, weight, and height. We collected operative data including bypass time and cross clamp time. The post-operative data included the duration of mechanical ventilation, oxygen therapy, the use and duration of nitric oxide, the use of sildenafil, the ICU length of stay, the post-operative complications, and medications on discharge.

Echocardiography

Post-operative echocardiographic data were collected to look for signs of pulmonary artery hypertension, including tricuspid regurgitation jet velocity, presence or absence of septal flattening, atrioventricular valve regurgitation, and right ventricular dilation. Data from the echocardiographic report were compared with the reviewed images for consistency. The right ventricular pressure estimate was calculated with the Bernoulli equation (4(tricuspid regurgitation jet velocity)^2 + right atrial pressure) using a right atrial pressure of 8 mmHg for all the patients. The right ventricular pressure estimate is a reflection of pulmonary artery pressure when right ventricular outflow tract obstruction and pulmonary valve stenosis are absent.[22–24] We calculated the estimated right ventricular pressure over three time periods post-operatively (0–7 days; 8–30days; >30 days to 1 year), making sure to have at least one measurement for each time period.

The right ventricular pressure estimate/systolic blood pressure ratio was calculated for the three time periods. This ratio was used as an estimate of the severity of pulmonary artery pressure independent of age. For missing blood pressure, we used systolic blood pressure of 80 mmHg for less than 1 year old, and a systolic blood pressure of 90 mmHg for more than 1-year-old children. All data from the archive were reviewed by a single paediatric cardiologist. Each individual had several measurements for each time period, and these measurements were averaged to report the mean value. Thirteen estimated blood pressures were used for more than 140 data points.

Statistical analysis

The demographic, pre-operative, and post-operative data were summarised by using frequencies, medians, and means with the standard deviation as appropriate. Data were analysed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). We performed t-test or Mann–Whitney test on parametric and non-parametric data as well as Chi Square or Fisher's exact to compare the two groups (patients with Trisomy and patients without). Non-parametric data that were able to be logarithmically transformed to parametric data were evaluated using t-tests, and data are reported as geometric means. The repeated measures of analysis of variance and serial measurement analysis were performed to follow the variation of right ventricular pressure estimate over three time periods post-operatively (0–7 days; 8–30 days; > days to 1 year).

Results

Forty-five patients were identified in our surgical database as having complete atrioventricular canal defects over the study period. Sixteen patients were excluded as the inclusion criteria were not met. The data from the remaining 29 patients were analysed. (Fig 1) 20 (69%) patients had a diagnosis of Trisomy 21 (Table 1) and 9 patients (31%) did not. The Trisomy 21 patients

https://doi.org/10.1017/S1047951121002201 Published online by Cambridge University Press

Table 1. Patient demographic data & operative times for patients who had AV canal repair.

	Trisomy 21 n = 20	Non-Trisomy 21 n = 9	p Value
Demographic and Operative Data			
Age in months (Geometric mean, [95% CI])	3.79 [2.75–5.24]	7.32 [4.18–12.83]	p = 0.02
Race, n (%)			
Caucasian	13 (65)	2(22.2)	p = 0.02
African American	5 (25)		
Hispanic	2 (10)	7(77.7)	
Sex, n (%)			
Male	14 (70)	3 (33.3)	p = 0.06
Female	6 (30)	6 (66.6)	
Weight, in kg Mean ± SD	5.4 ± 2.2	7.3 ± 3.2	p = 0.08
Height in cm (Mean + SD)	57.9 ± 9.33	66.6 ± 10.9	p = 0.05
Bypass time in minutes. (Geometric mean, [95% CI])	111.53 [93.37–133.22]	100.48 [76.57–131.87]	p = 0.49
Cross cramp time in minutes (Geometric mean, [95% CI])	61.70 [52.02–73.17]	55.50 [39.20–78.57]	p = 0.50

Age presented a geometric means and [95th percentile confidence interval]
Sex- n and (percentage of the group); Weight and height –mean ± standard deviation SD; Bypass and cross clamp time – geometric mean and [95th percentile confidence interval]

Table 2. Postoperative data after repair of AV canal defect.

	Trisomy 21	Non-Trisomy 21	p Value
Post Operative Data			
Mechanical Ventilation in days Median with IQR	3.0(1–13.5)	0(0–2.3)	p = 0.03
Duration of O2 in days Geometric mean [95% CI]	8.86 [4.63–16.99]	2.1[1.02–4.39]	p = 0.009
Nitric oxide use, n (%)			
Yes	11(55)	2 (22.2)	p = 0.10
No	9 (45)	7 (77.7)	
Duration of INO Median with IQR	1 (0–9)	0 (0–0.25)	p = 0.07
Sildenafil use, n (%)			
Yes	4 (20)	1 (11.1)	p = 0.55
No	16 (80)	8 (88.8)	
PICU LOS in days Geometric mean [95% CI]	13.38 [7.40–24.18]	6.7 [2.95–15.56]	p = 0.17

INO = inhaled nitric oxide; IQR = interquartile range; LOS = length of stay; O2 = oxygen; PICU = Pediatric ICU; 95% CI = 95th percentile confidence intervals

were statistically different from patients without that diagnosis based on race (p = 0.02) and age at surgery (p = 0.02). There were no differences between these two groups of patients regarding weight at the time of surgery, cardiopulmonary bypass time, or other intraoperative variables.

In the immediate post-operative period, patients with Trisomy 21 had a longer mean length of mechanical ventilation (3 days (1 to 13.5, interquartile range) vs.0 days (0 to 2.25, interquartile range); (p = 0.03). The duration of oxygen therapy for the Trisomy 21 group was almost 9 days versus 2 days for the non-Trisomy 21 group, p = 0.009 (Table 2). There were no differences between these two groups regarding the use of inhaled nitric oxide and sildenafil, inhaled nitric oxide, or overall ICU length of stay.

The were no echocardiographic differences between the two groups. Pulmonary artery hypertension was reported in 6 patients (30%) in the Trisomy 21 group versus to 1 patient (11.1%) in the non-Trisomy 21 group with a (p = 0.27) (Table 3). There were no differences between in right ventricular dilation, degree of mitral and tricuspid regurgitation, or septal flattening.

The Trisomy 21 group was more likely to have a clinical diagnosis of pulmonary artery hypertension during the post-operative period compared to the non-Trisomy 21 group with a (p = 0.04). There were no differences in other complications or discharge medications (Tables 4 and 5).

The right ventricular pressure estimate/systolic blood pressure ratios for all patients did not vary significantly over the three time

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Table 3. Postoperative echocardiographic data after AV canal repair.

	Trisomy 21	Non-Trisomy 21	p Value
Echocardiographic data			
Pulmonary hypertension			
Yes, n (%)	6 (30)	1 (11.1)	p = 0.27
No, n (%)	14 (70)	8 (88.8)	
RV Dilatation			
Yes, n (%)	10 (50)	4 (44.4)	p = 0.78
No, n (%)	10 (50)	5 (55.5)	
Mitral regurgitation			
Mild, n (%)	10 (50)	5 (55.5)	p = 0.78
Moderate/severe, n (%)	10 (50)	4 (44.4)	
Tricuspid regurgitation			
Mild, n (%)	15 (75)	8 (88.8)	p = 0.39
Moderate/severe, n (%)	5 (25)	1 (11.1)	
Septal flattening			
Yes, n (%)	7 (35)	5 (55.5)	p = 0.29
No, n (%)	13 (65)	4 (44.4)	

Number = n, (percentage of the group)

Table 4. Postoperative complications after AV canal repair.

	Trisomy	Non-Trisomy	p Value
Complications			
Pulmonary hypertension			
Yes, n (%)	10 (50)	1 (11.1)	p = 0.04
No, n (%)	10 (50)	8 (88.8)	
Arrhythmia			
Yes, n (%)	10 (50)	3 (33.3)	p = 0.40
No, n (%)	10 (50)	6 (66.6)	
Pericardial effusion			
Yes, n (%)	3 (15)	2 (22.2)	p = 0.77
No, n (%)	17 (85)	7 (77.7)	

Number = n, (Percent of the group)

Table 5. Sildenafil and oxygen use at discharge after AV canal repair.

	Trisomy	Non-Trisomy	p Value
Discharge medications			
Sildenafil			
Yes, n (%)	3 (15)	1 (11.1)	p = 0.77
No, n (%)	17 (85)	8 (88.8)	
Oxygen			
Yes, n (%)	3 (15)	1 (11.1)	p = 0.15
No, n (%)	17 (85)	8 (88.8)	

n = number in the group, (percentage of the group)

periods and remained above 0.5 (i.e., greater than half systemic) for all thrr time points (Fig 2).

Repeated measures of analysis of variance analysis factoring age in months and right ventricular pressures estimates showed a significant difference between the two groups (Trisomy 21 vs. non-Trisomy 21) for age at repair only ($p = 0.001$) but not for the RVP ($p = 0.051$). The time weighted right ventricular (RV) pressure from the Trisomy 21 group was 43 mmHg versus 48 mmHg for non-Trisomy 21 group. ($p > 0.05$) (Table 6).

Discussion

The timing of normalisation of right ventricular and pulmonary pressures after surgical repair of complete atrioventricular canal defects is unclear. Sharma in 2012 reported that 14 of 19 patients with complete atrioventricular canal in his cohort developed pulmonary artery hypertension.[25] Children with complete atrioventricular canal defect are assumed to have near systemic or systemic RV pressures preoperatively depending on the size of the ventricular defect.[4,6,15] None of our patients had cardiac catheterisations prior to surgery, and therefore, data on pre-operative shunt calculations and pulmonary vascular resistance were not available. It is expected that the pulmonary artery pressure should drop at some point after surgical repair. However, the timing and extent of this drop is not known. Our study suggests that in patients with complete atrioventricular canal defect, the right ventricular pressure estimate remains elevated up to one year after surgery. We used the non-invasive estimate of the ratio of right ventricular to systemic pressure as an indicator of severity of pulmonary artery hypertension.[26] The ratio of right ventricular pressure estimate to systolic blood pressure remained greater than 0.5.

Patients with complete atrioventricular canal defect are at risk for developing pulmonary artery hypertension due to both volume and pressure overload.[9,15] If left uncorrected, patients may progress to development of pulmonary arterial hypertension associated with CHD.[9,14,15,25,27] It is widely believed that if surgical repair is carried out before 9 months of age the pulmonary artery hypertension will normalise within the next year.[19] In our study, we were not able to determine the exact timing of the drop in pulmonary artery pressure. However, it is evident that the pulmonary artery pressure remains elevated beyond the first month after surgery to 1 year post-operatively. Careful examination of a larger cohort needs to be performed to understand the timing of decrease of pulmonary artery pressure to normal levels.

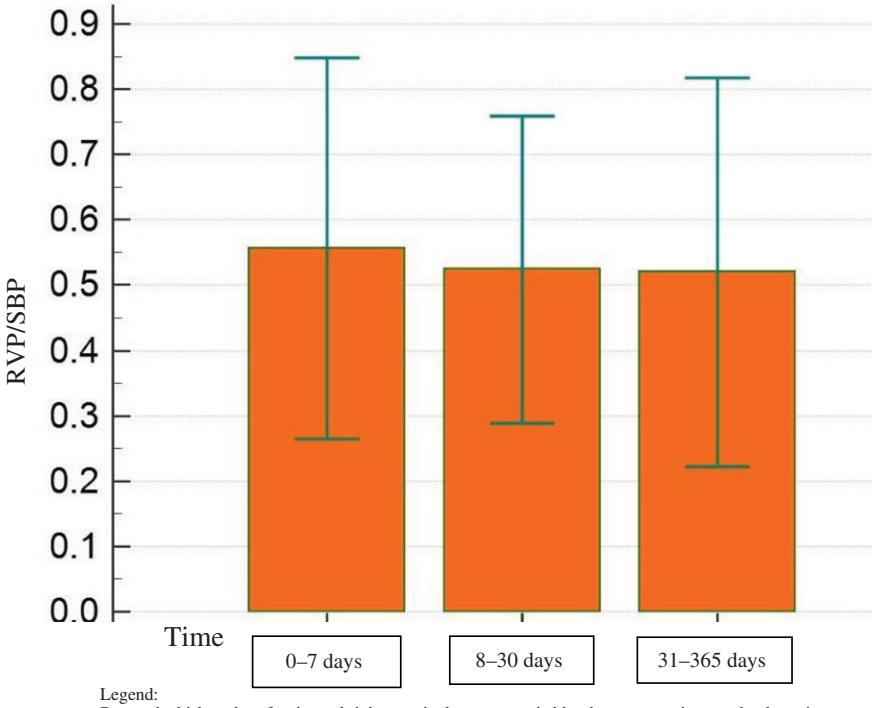
Children with Trisomy 21 are at a higher risk of developing pulmonary artery hypertension due to the independent association of Trisomy 21 with pulmonary artery hypertension secondary to abnormal pulmonary vascular remodelling.[6,10,14] At our centre, patients with complete atrioventricular canal defect associated with Trisomy 21 are operated on earlier in life[1] and have longer periods of mechanical ventilation in the immediate post-operative period. However, their total ICU length of stay did not differ from the non-Trisomy 21 group. There was no significant difference in right ventricular pressure estimate/systolic blood pressure ratios on follow-up over time between the two groups (with Trisomy 21 vs. without Trisomy 21). Our results are consistent with findings by Toth et al[6,28] who showed no differences in surgical outcomes in children with Trisomy 21 when compared to those without. St. Louis[29] found that children with Trisomy 21 who underwent repair of CHD were more likely to survive to discharge than those without

https://doi.org/10.1017/S1047951121002201 Published online by Cambridge University Press

Table 6. Time Weighted average of right ventricular pressure estimate after AV canal repair by group.

Group	n	Mean	95% CI	SD	Median	95% CI
Non-Trisomy 21	20	42.667	34.857–50.478	16.688	40.250	32.628–45.497
Trisomy 21	9	48.146	30.383–65.910	23.109	46.900	28.914–66.509

n = number in the group; mean and 95th percentile confidence interval (95% CI); SD = Standard deviation; median and 95th percentile confidence interval (95% CI)



Legend:
Box and whisker plot of estimated right ventricular to systemic blood pressure ratio over the three time periods. Time period 0–7 days after surgery, ratio 0.556 with standard deviation 0.29. Time period 8–30 days after surgery, ratio 0.523 with standard deviation 0.23. Time period 31–365 days, ratio 0.52 with standard deviation 0.3.

Figure 2. Right ventricular pressure estimate/systolic blood pressure ratio over 3 time periods.

Trisomy 21. Consistent with other studies, our patients with Trisomy 21 were more likely to carry a clinical diagnosis of pulmonary artery hypertension in the immediate post-operative period. However, the echocardiographic data did not show a statistically significant difference between the two groups. None of the study patients received post-operative cardiac catheterisations to directly measure pulmonary artery pressure.

Children with history of significant CHD are at increased risk of readmissions within the first year after their surgery.[30] Additionally, children with significant pulmonary artery hypertension are also at increased risk for readmission.[31] Many of these readmissions are secondary to respiratory infections.[32,33] This puts them at risk for significant morbidity and mortality from viral respiratory infections and requires ongoing vigilance to reduce risk of infections including the use of palvizumab.[29,31,34] There were no readmissions and no mortality during the study period.

In our study, children with complete atrioventricular canal defect associated with Trisomy 21 were significantly younger, had longer duration of mechanical ventilation and clinical diagnosis of pulmonary artery hypertension in the immediate post-operative period compared to those without Trisomy 21. There were, however, no significant differences over time between the two groups in regard to the right ventricular pressure estimate to systolic blood pressure ratio. In this cohort, we were not able to answer the question regarding the exact timing to resolution of pulmonary artery hypertension. A detailed prospective study may be able to answer this question in the future.

The data suggest that patients with repaired complete atrioventricular canal defect have pulmonary artery hypertension well beyond the immediate post-operative period.

Limitations

This was a retrospective, single centre study with a small sample size. In addition, there was a lack of uniformity in post-operative care over time during the study period including the timing of echocardiograms. There were two primary surgical operators, and surgical differences were not accounted for in this study. Sildenafil, the most widely used pulmonary vasodilator in pulmonary artery hypertension in children, was not used in the earlier enrolled patients. Chart review provided limited data on the dose and duration of therapy.

We used right ventricular pressure estimate/systolic blood pressure as a surrogate for pulmonary vascular resistance/systemic vascular resistance as no patients received cardiac catheterisation to allow for direct calculation. Though cardiac catheterisation

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assessment of pulmonary artery pressure is the gold standard, it is not always practical. Sohail reported correlation of 0.917 between cardiac catheterisation and echocardiography for the assessment of systolic pulmonary artery pressure.[35] Echocardiography, therefore, provides very useful information about the estimation of right heart pressure given that the World Health Organization's definition of pulmonary hypertension by cardiac catheterisation is an adult definition and cannot be easily or routinely applied to infants. We made assumptions about the right atrial and systolic blood pressures, which may be of limited accuracy. Left atrioventricular valve regurgitation may lead to pulmonary artery hypertension, and its effect may be difficult to quantify and may change with time. Although there were no reoperations for atrioventricular valve regurgitation in any of our patients, atrioventricular valve regurgitation needs to be accounted for in the evolution of pulmonary artery hypertension. Lastly, a prospective study with a larger sample size, with more uniform follow-up utilising a core echo lab, would be required to better assess the change in pulmonary artery pressure with time after repair of complete atrioventricular canal defects.

Conclusion

In summary, patients with complete atrioventricular canal defect were noted to have elevated ratio of the right ventricular pressure estimate to systolic blood pressure, up to 1 year after surgery.

Our study suggests that in patients who have had repaired complete atrioventricular canal defects, the right ventricular pressure does not normalise on echocardiograms performed up to 1 year after surgery and may suggest a sustained elevation in pulmonary vascular resistance.

Acknowledgements. We thank Alicia Chaves for her assistance in the completion of this project.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflict of interest. None.

Ethical standards. This research was reviewed and approved by the Human Research Protections Office of the University of Maryland.

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