

Diazoxide-associated pulmonary hypertension in a patient with noncompaction cardiomyopathy

Rachel T. Sullivan , Kathryn A. Tillman, Steven J. Kindel and Stephanie S. Handler

Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, WI, USA

Abstract

Development of pulmonary hypertension after initiation of diazoxide for the treatment of neonatal hyperinsulinemic hypoglycemia is a rare, but previously described association. Risk factors for development of diazoxide-associated pulmonary hypertension include lower gestational age and congenital heart disease. This novel case report describes an infant with noncompaction cardiomyopathy who developed pulmonary hypertension shortly after initiation of diazoxide for hyperinsulinemic hypoglycemia which resolved upon cessation of the drug. This case highlights the benefit of having pre-treatment knowledge of underlying cardiac anatomy and makes a case for routine echocardiographic screening for neonates initiating diazoxide treatment.

Keywords

cardiomyopathy, pediatric cardiovascular disease, pulmonary hypertension

Date received: 22 October 2020; accepted: 18 December 2020

Pulmonary Circulation 2021; 11(1) 1–3

DOI: 10.1177/2045894020987117

Case description

A term male infant, followed prenatally for a single umbilical artery and cerebral ventriculomegaly, presented with hypoglycemia at 8 h of age. Initially controlled on intravenous dextrose containing fluids, he ultimately maintained appropriate blood glucose levels on fortified ad lib feeds at one week of age. Postnatal workup for multiple congenital anomalies revealed mild cerebral ventriculomegaly and mild bilateral hydronephrosis. Initial echocardiogram demonstrated mild aortic isthmus hypoplasia without discrete coarctation, biventricular hypertrophy with prominent biventricular myocardial trabeculations, and an ostium secundum atrial septal defect (ASD) without signs of pulmonary hypertension.

On day of life 11, repeat echocardiogram more clearly demonstrated noncompaction cardiomyopathy with moderately diminished left ventricular function (ejection fraction 40%), mildly diminished right ventricular function, and no evidence of pulmonary hypertension. N-terminal-pro B-type natriuretic peptide (NT-pro-BNP) was elevated at 1760 pg/mL (lab normal <350 pg/mL), and enalapril was started for afterload reduction. He was hospitalized at three weeks of age for continued hypoglycemia and started on diazoxide when workup confirmed hyperinsulinism. He transiently required furosemide for pulmonary edema;

however, prior to hospital discharge had clinically improved with NT-pro-BNP of 494 pg/mL and was discharged without diuretics.

At one month of age, he returned to cardiology clinic with lethargy and hypoxia with a systemic saturation of 62%. Echocardiogram demonstrated severe pulmonary hypertension with severe right atrial and ventricular dilation, interventricular septal flattening, mild right ventricular hypertrophy, mildly diminished right ventricular function, dilated main and branch pulmonary arteries, and bidirectional shunting at the ASD (Fig. 1). NT-pro-BNP was markedly elevated at 26,600 pg/mL. Saturations improved to 95% on supplemental oxygen via nasal cannula, and he was admitted. Due to concern for diazoxide-induced pulmonary hypertension given the temporal relation to drug initiation, diazoxide was discontinued. Three days after diazoxide discontinuation, echocardiogram demonstrated improvement in secondary findings of pulmonary hypertension, with improved right heart dilation and function,

Corresponding author:

Stephanie S. Handler, MD 9000 W Wisconsin Ave, MS 217 Milwaukee, WI 53226, USA.

Email: shandler@chw.org



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
journals.sagepub.com/home/pul



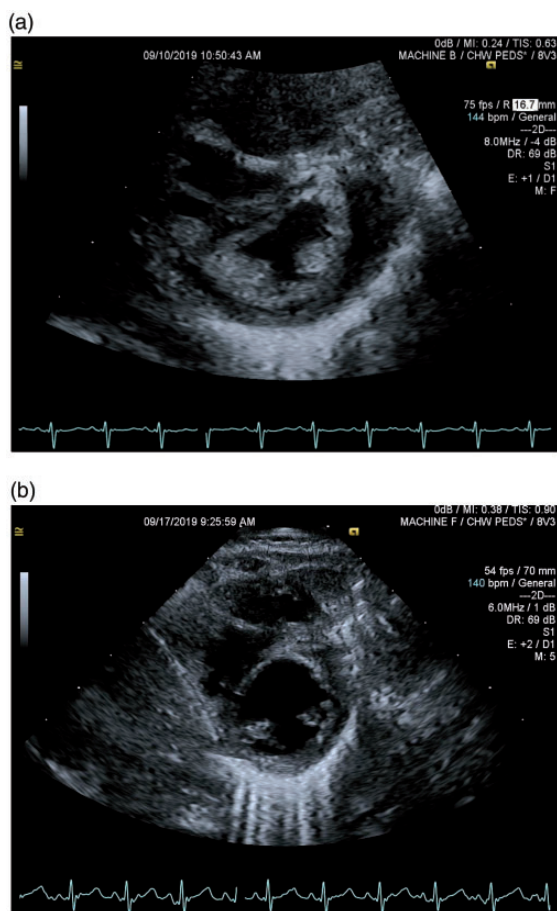


Fig. 1. Panel (a) demonstrates Echocardiographic evidence of severe pulmonary hypertension after diazoxide initiation with severe interventricular septal flattening (a). Panel (b) shows Complete resolution of pulmonary hypertension within nine months of diazoxide discontinuation with normal interventricular septal configuration.

improved interventricular septal position, and left to right shunting across the ASD (Fig. 1). NT-pro-BNP had decreased to 1340 pg/mL. He weaned off supplemental oxygen and discharged after four days on no pulmonary vasodilator therapy with stable blood glucose off diazoxide.

Within nine months following hospital discharge, he had no further evidence of pulmonary hypertension, and his left ventricular function normalized on ACE inhibitor monotherapy. Additionally, he was diagnosed with idiopathic interstitial lung disease based on chest CT demonstrating diffuse bilateral ground glass opacities with interlobular septal thickening and a new oxygen requirement well after resolution of his pulmonary hypertension. To date, no additional pulmonary laboratory or invasive testing has been pursued given mild nature of symptoms and no further evidence of pulmonary hypertension. He continues with routine pulmonary follow-up. Genetic testing revealed an unbalanced chromosomal translocation, with chromosome 1p36 deletion and 4q32 duplication. Regions involved in this translocation do not overlap with genes on

commercially available gene panels for pulmonary hypertension, congenital hyperinsulinism, or left ventricular noncompaction.

Discussion

This case report describes a patient with noncompaction cardiomyopathy and chromosomal translocation who developed diazoxide-associated pulmonary hypertension. Immediate recognition and discontinuation of the diazoxide led to clinical improvement and resolution of pulmonary hypertension within several days.

Diazoxide, a K_{ATP} channel opener, is the first-line therapy for the treatment of hyperinsulinemic hypoglycemia by inhibiting release of insulin from the pancreas. It also leads to smooth muscle cell relaxation with both systemic and pulmonary vasodilation.¹ While diazoxide is well tolerated in the majority of infants receiving this therapy, there is a known association with the development of pulmonary hypertension. In 2015, the Federal Drug Agency (FDA) issued a drug safety communication citing 11 cases of diazoxide associated pulmonary hypertension.²

The first case report describing pulmonary hypertension in a patient treated with diazoxide was noted in 2004.³ Since that time, even in light of the FDA drug safety communication, less than 50 cases of diazoxide-associated pulmonary hypertension are reported in the literature. In series published from single centers or regional cohorts, the incidence of diazoxide-associated pulmonary hypertension is estimated to be 2.4–7%.^{4–6} Potential risk factors for development of diazoxide-associated pulmonary hypertension include lower gestational age, fluid overload, and congenital heart disease.^{4–6} Reported concomitant congenital heart disease diagnoses are variable in terms of hemodynamic significance and likelihood of potential contribution to pulmonary hypertension in the neonatal period, ranging from small ASD to patent ductus arteriosus to more complex lesions such as double outlet right ventricle and atrioventricular septal defect.^{3–8} There is one reported case associated with a restrictive cardiomyopathy.⁵

Diazoxide's initial clinical use was as an antihypertensive via its action as a systemic vasodilator. This prompted evaluation of diazoxide as a pulmonary vasodilator, with some report of efficacy in idiopathic pulmonary hypertension.⁹ The relationship between K_{ATP} channels and the development of pulmonary hypertension is complex, with differential expression of different channel subtypes depending on tissue type and physiologic state. Loss of function in one subtype can lead to heritable pulmonary hypertension.¹⁰ Gain of function in a different subtype causes a genetic disorder called Cantu syndrome, which manifests similarly to the side effects of diazoxide with edema, hypertrichosis, and pulmonary hypertension.¹⁰ One can speculate that some predisposition (e.g. a K_{ATP} channel gene mutation or overexpression) may lead to the diazoxide-associated pulmonary hypertension when stimulated by initiation of

diazoxide therapy, similar to a “two-hit hypothesis” in other fields.

To the best of our knowledge, this report is the first case described in a patient with noncompaction cardiomyopathy in addition to an ASD. Noncompaction cardiomyopathy with left ventricular diastolic dysfunction may predispose to pulmonary arterial hypertension secondary to elevated post-capillary pressure; however, this is usually not a primary feature in young infants with cardiomyopathy. Importantly, our patient’s pulmonary hypertension was detected on what was intended as routine follow-up for his known cardiomyopathy, and he had not had prior echocardiographic or clinical evidence of significant diastolic dysfunction or restrictive physiology. Our center does not have routine echocardiogram protocols for initiating diazoxide treatment for neonatal hyperinsulinemic hypoglycemia. This case highlights the benefit of pre-treatment knowledge of underlying cardiac concerns and makes a case for routine post-treatment echocardiographic screening, particularly in patients with identifiable risk factors for development of pulmonary hypertension. Further, this adds to the body of literature of potential associations in this rare clinical entity.

Contributorship

Sullivan was a fellow at the time of data collection and patient involvement and was responsible for the primary composition of the written manuscript draft. Tillman and Kindel contributed with review of patient-specific details with regard to pulmonary hypertension and underlying cardiomyopathy, respectively. Handler contributed as senior author, with primary role in case selection and case report oversight. All authors were involved in review and final approval of this article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Written informed consent was obtained from the patient’s parent for patient information to be published.


Guarantor

SH.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Rachel T. Sullivan  <https://orcid.org/0000-0003-4580-9965>

References

1. Coetzee WA. Multiplicity of effectors of the cardioprotective agent, diazoxide. *Pharmacol Ther* 2013; 140: 167–175.
2. FDA Drug Safety Communication: FDA warns about a serious lung condition in infants and newborns treated with Proglycem (diazoxide), www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safetycommunication-fda-warns-about-serious-lung-condition-infants-and-newborns-treated (2015, accessed 15 June 2020).
3. Silvani P, Camporesi A, Mandelli A, et al. A case of severe diazoxide toxicity. *Pediatr Anesth* 2004; 14: 607–609.
4. Chen SC, Dastamani A, Pintus D, et al. Diazoxide-induced pulmonary hypertension in hyperinsulinaemic hypoglycaemia: recommendations from a multicentre study in the United Kingdom. *Clin Endocrinol (Oxf)* 2019; 91: 770–775.
5. Herrera A, Vajravelu ME, Givler S, et al. Prevalence of adverse events in children with congenital hyperinsulinism treated with diazoxide. *J Clin Endocrinol Metab* 2018; 103: 4365–4372.
6. Thornton P, Truong L, Reynolds C, et al. Rate of serious adverse events associated with diazoxide treatment of patients with hyperinsulinism. *Horm Res Paediatr* 2019; 91: 25–32.
7. Ziad A, Antonín L, Kateřina M, et al. Development of pulmonary hypertension in an infant treated with diazoxide for hyperinsulinism, a case report and literature review. *Am J Pediatr* 2015; 1: 1–3.
8. Nebesio TD, Hoover WC, Caldwell RL, et al. Development of pulmonary hypertension in an infant treated with diazoxide. *J Pediatr Endocrinol Metab* 2007; 20: 939–944.
9. Wang SW, Pohl JE, Rowlands DJ, et al. Diazoxide in treatment of primary pulmonary hypertension. *Heart* 1978; 40: 572–574.
10. McClenaghan C, Woo KV and Nichols CG. Pulmonary hypertension and ATP-sensitive potassium channels: paradigms and paradoxes. *Hypertension* 2019; 74: 14–22.