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CASE REPORTS

Cardiac arrhythmias associated with volume-assured pressure support mode in a patient with autonomic dysfunction and mitochondrial disease

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A 15-year-old boy with autonomic dysfunction and mitochondrial disease was diagnosed with sleep-related hypoventilation at 6 years of age and treated with bilevel positive airway pressure therapy. At 12 years of age, treatment was transitioned to volume-assured pressure support (VAPS) due to clinical evidence of respiratory muscle weakness. Subsequent titration polysomnogram revealed the emergence of cardiac arrhythmia (isolated premature ventricular contractions, bigeminy, and trigeminy) while on VAPS mode that improved after transition to bilevel positive airway pressure therapy. During the titration study, higher tidal volumes correlated with increased pressures and the presence of arrhythmia. Prior to initiation of VAPS therapy, the patient had normal electrocardiogram evaluations. This case highlights the potential relationship between VAPS therapy and cardiac arrhythmias, especially in patients with underlying conditions with associated cardiac abnormalities, such as autonomic dysfunction and mitochondrial disease. While using VAPS mode, patients should be closely monitored for cardiac rhythm abnormalities.

Keywords: sleep hypoventilation, volume-assured pressure support, cardiac arrhythmia, mitochondrial disease and autonomic dysfunction

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INTRODUCTION

Volume-assured pressure support (VAPS) is a volume-targeted mode of noninvasive ventilation that incorporates bilevel positive airway pressure (BPAP) with a set range of inspiratory positive airway pressure (IPAP) or pressure support that is adjusted by the device to provide a consistent set tidal volume (Vt) or minute ventilation, respectively. Typically, VAPS is effective in treating disorders of hypoventilation and well tolerated without significant published adverse events. We present a patient who developed premature ventricular contractions (PVCs), including bigeminy and trigeminy, while he was using VAPS, which improved with transition to BPAP mode during the titration polysomnogram (PSG).

REPORT OF CASE

A 15-year-old White boy presented at 6 years of age with restless sleep, mouth breathing, neck hyperextension, leg movements, sweating, sleep-talking, and excessive daytime sleepiness. Diagnostic PSG at 6 years of age revealed an apnea-hypopnea index of 0.4 events/h and an elevated end-tidal carbon dioxide of more than 50 mm Hg for 84% of total sleep time, which was consistent with a diagnosis of sleep-related hypoventilation (SRH) in children. A positive airway pressure (PAP) titration PSG performed later that year showed resolution of SRH on BPAP therapy. In light of anthropometric changes throughout the subsequent years, he underwent multiple repeat PAP titration PSGs to determine optimal settings, typically with BPAP settings of IPAP of 8–10 cm H_2O and expiratory positive airway pressure (EPAP) of 4–5 cm. Due to significant growth in height, we repeated a diagnostic PSG at 8 years of age, which revealed persistence of hypoventilation with an end-tidal carbon dioxide more than 50 mm Hg for 57.9% of total sleep time.

In light of his persistent fatigue and sleep hypoventilation, whole-exome sequencing was ordered. which revealed mitochondrial DNA POLG (polymerase gamma) mutations at 2 loci (p.P587L, p.T251I). Our patient did not have epilepsy, encephalopathy, ataxia, or exam findings of neuromuscular weakness. He subsequently underwent pulmonary function testing for dyspnea with exertion and persistence of SRH on a subsequent diagnostic PSG. Pulmonary function testing revealed grossly normal lung function but lower than expected maximal inspiratory pressure (MIP) of −37 cm H_2O and maximal expiratory pressure (MEP) of +42 cm H_2O, suggesting decreased respiratory muscular strength. Due to heart palpitations, dizziness, and fatigue, he underwent tilt-table testing at 12 years of age which demonstrated heart rate variability and changes in sympathetic activity consistent with mild–moderate autonomic dysfunction (dysautonomia).

Given the history of mitochondrial disease, autonomic dysfunction, and evidence of respiratory muscular weakness, VAPS mode was initiated at 12 years of age to treat the SRH. Initial VAPS settings were based on recommendations from the Philips Respironics (Murrysville, PA) titration protocol reference guide with settings of respiratory rate 10 bpm;

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IPAPmax, 25 cm H_2O; IPAPmin, 8 cm H_2O; and EPAP, 4 cm H_2O. In light of his young age and the disparity between his height (167.6 cm and 95th percentile for age) to weight (42.7 kg and 43rd percentile for age) proportion, the Vt was started at a lower setting of 340 mL and titrated up to 370 mL with effective treatment of SRH. The patient subsequently underwent repeat VAPS titration PSGs at 13 and 14 years of age due to interim growth in height (180.3 cm and 185.4 cm, respectively) with the same VAPS settings, except for higher Vt, which ranged from 370 mL to 400 mL to achieve resolution of SRH.

The VAPS titration PSG performed at 14 years of age was initiated with settings of respiratory rate 10 bpm; Vt, 400 mL; IPAPmax, 25 cm H_2O; IPAPmin, 8 cm H_2O; EPAP, 4 cm H_2O; inspiratory time, 1.5 seconds with titration of Vt to 380 and 370 mL. Unlike the previous BPAP and VAPS titration PSGs, the electrocardiogram (EKG) on this study showed new PVCs with isolated beats, bigeminy, and trigeminy (**Figure 1**). Worsening arrhythmias occurred with higher Vt and corresponding IPAP, which were recorded within the sleep software (**Table 1**). After 1 hour and 45 minutes, the mode was changed to BPAP with IPAP of 9 cm H_2O and EPAP of 4 cm H_2O with fewer PVCs per time at that setting, shorter events, and resumption of predominant normal sinus rhythm (**Figure 2**). The leak rate while on VAPS ranged from 30 to 35 liters per minute (LPM), up to 42 LPM with corresponding IPAP of 20 cm H_2O. While on BPAP mode, the leak rate averaged 28 LPM. The manufacturer's specifications for the intentional mask leak rate for the Philips Respironics (Murrysville, PA) Amara View oronasal mask used during the study was 18.7 LPM at PAP of 5 cm H_2O, 26.2 LPM at PAP of 10 cm H_2O, and 37 LPM at PAP of 20 cm H_2O. The transcutaneous carbon dioxide was mostly 46–51 mm Hg with readings typically in the 40s, especially while patient was on VAPS with Vt of 400 mL and BPAP mode.

Device data download information from his home VAPS machine via the Amara View oronasal mask revealed that his exhaled Vt averaged 390 mL, leak rate averaged 18–25 LPM, attained IPAP was 10–11 cm H_2O, and attained EPAP was 3.9 cm H_2O. BPAP download data revealed similar findings, with average exhaled Vt of 399 mL, leak rate of 15–23 LPM, attained IPAP of 9 cm H_2O, and attained EPAP of 4 cm H_2O.

Given the new cardiac arrhythmias in the setting of autonomic dysfunction and mitochondrial disease, pediatric cardiology evaluated the patient with EKG, 24-hour Holter monitoring, and echocardiogram. All EKGs performed in clinic before and after VAPS titration PSGs showed normal sinus rhythm according to the cardiologist's documentation. Echocardiogram performed at 14 years of age showed normal cardiac anatomy and function with an ejection fraction of 73%. Prior to starting VAPS mode, the Holter study at age 11 showed sinus rhythm with an average heart rate of 81 bpm and no ventricular or supraventricular arrhythmias. While on home VAPS therapy, a Holter study at age 14 showed predominant sinus rhythm with 164 ventricular events (153 isolated, 3 pairs, 1 bigeminy event, 5 bigeminy beats) and 2644 supraventricular events, mostly premature atrial beats. The patient started propranolol 1 week after the VAPS titration PSG at 14 years of age. A repeat Holter study at age 15, while on BPAP therapy and propranolol, showed sinus rhythm with an average heart rate of 71 bpm and only 1 isolated ventricular event.

DISCUSSION

In children, SRH is diagnosed when the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) or surrogate parameter is above 50 mm Hg for more than 25% of total sleep time.[1] Hypoventilation in the context of mitochondrial disease and autonomic dysfunction has been described in the literature. Patients with mitochondrial disease are at increased risk for respiratory muscle weakness due to possible diaphragmatic weakness and/or decreased central respiratory drive.[2] On the other hand, hypoventilation in autonomic dysfunction disorders is linked to disproportionate change in respiratory rate and Vt in response to hypoxia and hypercapnia.[3]

Respiratory muscular strength can be assessed by MIP and MEP. Recently, prediction equations were published to provide reference ranges in children for MIP and MEP tests based on age, height, and weight.[4] Some children may not fully cooperate or understand the breathing techniques, which can lead to underestimation of the patient's respiratory muscular strength. The technician on the pulmonary function testing report documented that our patient demonstrated good effort and cooperation with breathing maneuvers. Regardless, he was only able to produce an MIP of −37 cm H_2O and MEP of +42 cm H_2O, which is well below the reference value determined by the predictive equations for MIP of −80 cm H_2O and MEP of +95 cm H_2O. The low measurements are most likely reflective of his clinical history of a neuromuscular (mitochondrial) disease.

Arrhythmias associated with sleep apnea may lead to increased cardiovascular mortality and morbidity. Sleep apnea predisposes the patient to a higher risk for arrhythmias due to repetitive hypoxia caused by recurrent apnea/hypopnea events, autonomic dysregulation, increased oxidative stress, and/or inflammation. PVCs are early ventricular depolarizations that may occur in the context of myocardial stretch, high-catecholamine state, cardiomyopathy, valvular heart disease, electrolyte disturbances, certain medications, or infections. Although typically benign, PVCs may increase the risk for other tachyarrhythmias and cardiomyopathy. In young patients without structural or ischemic heart disease, PVCs are unlikely to cause significant morbidity.[5]

It is unclear if the development of arrhythmias may be reflective of cardiac dysfunction associated with progression of underlying disease (mitochondrial disease and autonomic dysfunction) vs the effect of VAPS on cardiac function. Cardiac abnormalities have been described in mitochondrial disease. Debray et al[6] assessed the clinical presentation of 73 pediatric patients with mitochondrial disease. Cardiac involvement was noted in 13 (18%) patients, all with hypertrophic nonobstructive cardiomyopathy. Cardiac hypertrophy was frequently asymptomatic and not associated with increased mortality. Scaglia et al[7] noted that 45 patients out of 113 pediatric patients with mitochondrial disease had cardiomyopathy, including hypertrophic cardiomyopathy (58%), dilated cardiomyopathy (29%), and left ventricular noncompaction (13%). There were only 11% of patients who had arrhythmias, mostly ventricular tachycardia. The mean age at presentation was 33 months. Limongelli et al[8] evaluated 32 adults (37.8 ± 12.6 years) and found cardiovascular abnormalities in 26 patients (81%). Of

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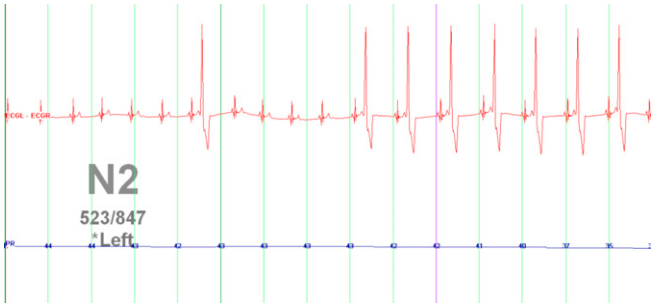
those, 22 patients (68%) had EKG abnormalities, including left ventricular pre-excitation, atrioventricular block, intraventricular conduction abnormalities, left ventricular hypertrophy, etc. In summary, cardiac abnormalities associated with mitochondrial disease in children typically presented as cardiomyopathy while the prevalence of cardiac conduction system disease increased with age.[9] In mitochondrial disease, ventricular arrhythmias may occur as a result of dissipation of the potential along the myocardial mitochondrial membrane and inhibition of ATP synthesis.[10] Our patient had mutations in the POLG gene which cause progressive depletion or errors in mitochondrial DNA and result in a wide spectrum of clinical manifestations, including, but not limited to, epilepsy, chronic progressive external ophthalmoplegia, axonal neuropathy, myopathy, ataxia, hearing loss, cardiomyopathy headaches, and gastrointestinal dysmotility. The heterogeneity of presenting symptoms is further complicated by the lack of specific genotype–phenotype correlation.[11] Our patient was 14 years of age when we first noted cardiac arrhythmias. However, an echocardiogram did not reveal changes consistent with cardiomyopathy. Although the EKG abnormalities may be due to mitochondrial disease progression, his age of presentation does not fit the typical course of cardiac manifestations in mitochondrial disease. At the time of this writing, the patient has not experienced clinical manifestations beyond isolated respiratory neuromuscular dysfunction. However, given the unclear prognostic implications of his genetic mutation, he should be monitored for disease progression as he ages.

As for autonomic dysfunction or dysautonomia, sinus tachycardia is the most common rhythm disorder noted, which may be

Figure 1—Isolated PVC and bigeminy while patient was on VAPS mode during PAP titration polysomnogram at 14 years of age.



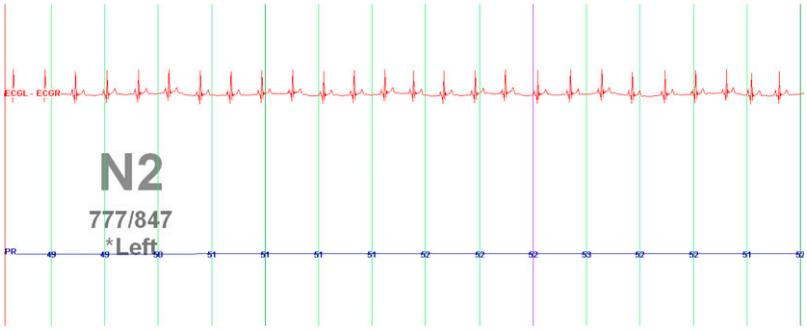
PAP = positive airway pressure; PVC = premature ventricular contraction; VAPS = volume-assured pressure support.

Table 1—VAPS/BPAP titration polysomnogram at 14 years of age with corresponding recorded IPAP and arrhythmia description.

	Mode			
	VAPS	**VAPS**	**VAPS**	**BPAP**
Settings	Vt 400 mL*	Vt 380 mL*	Vt 370 mL*	IPAP 9; EPAP 4
Time, minutes	46	44	15	312
Recorded IPAP, cm H_2O	Variable (mostly 19–21)	10–20 (mostly 17–18)	10–16 (mostly 13–14)	9
Minute ventilation, LPM	4.8	3.8	3.7	—
Average leak rate, LPM	30–42	30–35	30–35	28
Isolated PVC episodes (PVCs/hour)	85 (110.9)	34 (46.4)	40 (160)	135 (26)
Bigeminy episodes (number/hour)	5 (6.5)	0	0	0
Trigeminy episodes (number/hour)	4 (5.2)	5 (6.8)	1 (4)	10 (1.9)
Average transcutaneous carbon dioxide, mm Hg	46–47	49–50	49–51	48–49

Patient's actual weight = 56.5 kg. Ideal body weight = 67.4 kg, height = 185.4 cm. BPAP = bilevel positive airway pressure; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; LPM = liters per minute; PVC = premature ventricular contraction; TST = total sleep time; VAPS = volume-assured pressure support; Vt = tidal volume. *VAPS settings also include respiratory rate, 10 bpm; IPAPmax, 25 cm H_2O; IPAPmin, 8 cm H_2O; EPAP 4 cm H_2O.

Figure 2—Predominant sinus rhythm while patient was using BPAP mode during PAP titration polysomnogram at 14 years of age.



BPAP = bilevel positive airway pressure; PAP = positive airway pressure.

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due to increased sympathetic overdrive and impaired parasympathetic responsiveness.[12] The prevalence of inappropriate sinus tachycardia (a form of autonomic dysfunction) is higher than other reported arrhythmias. Specifically, inappropriate sinus tachycardia (1.16%) exceeds the reported prevalence for the Wolff–Parkinson–White syndrome (0.15–0.31%), paroxysmal supraventricular tachycardia (0.23%), and ectopic atrial tachycardia (0.46%) in a middle-aged population.[13] We spoke with our dysautonomia center cardiologist who noted that progression of autonomic dysfunction and development of other types of arrhythmias is a rare finding in the pediatric patient population although, there is a paucity of published data in this population.

VAPS provides greater improvement in $PaCO_2$ levels and an equal improvement in nocturnal oxygenation, sleep quality, and health-related quality of life in comparison to BPAP therapy, particularly in patients with amyotrophic lateral sclerosis.[14] Due to our patient's underlying neuromuscular disease and low MIP of less than 60 cm H_2O, VAPS mode was initiated to treat SRH. VAPS is not typically utilized in children; therefore, there is little guidance on initiation and titration of the settings. Due to the disparity in our patient's height relative to weight, we chose to start at a lower than recommended Vt, which was ultimately effective in treating his SRH. Our patient underwent significant growth in height of 17.8 cm (7 inches) over a 2-year period, which led to repeated VAPS titration PSGs. However, we only adjusted Vt between 370 mL and 400 mL in 10- to 20-mL increments during the BPAP/VAPS titration study performed at 14 years of age. Although the arrhythmias worsened at higher volumes, the Vt was still significantly lower than the recommended Vt based on a height of 185.4 cm or 73 inches (630 mL) and ideal body weight of 67.4 kg multiplied by 8 mL/kg (540 mL) per the Philips Respironics (Murrysville, PA) titration protocol reference guide. Regardless, as Vt increased, there was corresponding higher recorded IPAP, which may have affected cardiac function. Even though the leak rate measured during the VAPS/BPAP titration study and on the device download information was close to the manufacturer's specifications for mask intentional leak rate for the corresponding PAP setting, there was overall more leak on VAPS relative to BPAP mode, which may have resulted in higher IPAP. The range for transcutaneous carbon dioxide was relatively similar between all of the settings and mostly within the normal range of less than 50 mm Hg. We think the variability is within the error range for transcutaneous carbon dioxide readings.

We postulate that higher recorded inspiratory peak pressures to achieve the set Vt in the VAPS mode may have led to increased sympathetic drive, decreased vagal response, and decreased cardiac output and thus potentially increase the risk for arrhythmogenesis. Although data in regard to higher inspiratory peak pressure and autonomic dysfunction leading to arrhythmia are lacking, there are data that higher positive end-expiratory pressure may lead to reduced baroreflex sensitivity with exaggerated sympathetic response and/or dysrhythmias.[15] During tidal ventilation, sinus arrhythmia may occur in response to autonomic changes with increased heart rate due to withdrawal of vagal stimulation during inspiration and decrease in heart rate from enhanced vagal tone during expiration. Higher peak airway pressure exacerbates these autonomic responses. Furthermore, the fluctuation in intrathoracic pressure can result in variability in venous return to the heart. This instability of cardiac function due to a relative decrease in oxygen delivery to cardiac muscle increases the susceptibility to cardiac arrhythmias. In addition, cardiovascular autonomic neuropathy associated with dysautonomia is also an independent risk factor for silent ischemia and myocardial dysfunction, which may increase the propensity for cardiac arrhythmias. Last, intrathoracic pressure changes may lead to myocardial stretch and stimulation of mechano-gated nonselective ion channels with membrane potential changes that trigger ectopic excitation and, thus, arrhythmogenesis.[16]

Since our patient did not have cardiomyopathy, which is the typical manifestation of mitochondrial disease at his age, we surmise that adjustment in mode of ventilation was the primary reason for improvement in arrhythmias. During the titration PSG at 14 years of age, transition of VAPS to BPAP mode resulted in a lower recorded IPAP, which led to the improvement in PVCs, as noted by fewer and shorter events per time at the specific setting (**Table 1**). After transitioning to BPAP mode at home and treatment with propranolol, the subsequent Holter study showed near resolution of the atrial and ventricular arrhythmias. We suspect that lowered IPAP improved the arrhythmias and the addition of propranolol led to the complete resolution of the remaining abnormal rhythms. Because of the potential arrhythmias associated with VAPS use, it is important to use the lowest volume and pressure settings to effectively treat the underlying sleep disorder.

In conclusion, our findings suggest that VAPS mode of ventilation may be associated with arrhythmias. Close cardiac monitoring should be considered while using VAPS in patients, especially those with underlying conditions that may be associated with cardiac dysfunction.

ABBREVIATIONS

BPAP, bilevel positive airway pressure
EKG, electrocardiogram
EPAP, expiratory positive airway pressure
IPAP, inspiratory positive airway pressure
LPM, liters per minute
MEP, maximal expiratory pressure
MIP, maximal inspiratory pressure
$PaCO_2$, partial pressure of carbon dioxide in the arterial blood
PAP, positive airway pressure
PSG, polysomnogram
PVC, premature ventricular contraction
SRH, sleep-related hypoventilation
VAPS, volume-assured pressure support
Vt, tidal volume

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DISCLOSURE STATEMENT

All authors have seen and approved the submitted manuscript. Polysomnography was performed at Memorial Hermann Memorial City Hospital, Pediatric Sleep Center, Houston, Texas. The authors report no conflicts of interest.

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