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Atrio-Ventricular Block in Children With Multisystem Inflammatory Syndrome

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Table of Contents Summary:

In this study we describe the incidence of atrioventricular block in children with multisystem inflammatory syndrome.

What's Known on This Subject:

Children with multisystem inflammatory syndrome are at risk of cardiovascular complication, including ventricular dysfunction and coronary artery dilation.

What this Study Adds:

Patients with multisystem inflammatory syndrome are also at risk of atrioventricular conduction disease, especially those who present with hypotension/shock and ventricular dysfunction. PR prolongation on electrocardiogram may identify patients at risk of progression to high-grade atrioventricular block.

Contributors' Statement

Audrey Dionne conceptualized and designed the study, collected the data, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript.

Douglas Mah, MaryBeth Son, Pui Lee, Lauren Henderson, Annette Baker, Sarah de Ferranti, David Fulton and Jane Newburger were responsible for acquisition and interpretation the data and critically reviewed the manuscript for important intellectual content.

Kevin Friedman conceptualized and designed the study, interpreted the data and critically reviewed the manuscript for important intellectual content.

ABSTRACT

Background: Children are at risk for multisystem inflammatory syndrome (MIS-C) following infection with SARS-CoV-2. Cardiovascular complications, including ventricular dysfunction and coronary dilation, are frequent, but there are limited data on arrhythmic complications.

Methods: Retrospective cohort study including children ≤21 years admitted with MIS-C. Demographic characteristics, electrocardiogram (ECG), echocardiogram and hospital course were described.

Results: Among 25 patients admitted with MIS-C (60% male, median age 9.7 [interquartile range (IQR) 2.7, 15.0] years), ECG anomalies were found in 14 (56%). First-degree AVB was seen in 5 (20%) patients a median of 6 [IQR 5, 8] days after onset of fever, and progressed to 2nd or 3rd degree atrioventricular block (AVB) in 4 patients. No patient required intervention for AVB. All patients with AVB were admitted to the ICU (prior to onset of AVB) and had ventricular dysfunction on echocardiogram. All patients with 2nd or 3rd degree AVB had elevated BNP level, while the patient with 1st degree AVB had normal BNP. No patient with AVB had elevated troponin level. QTc prolongation was seen in 7 patients (28%) and non-specific ST segment changes in 14 patients (56%). Ectopic atrial tachycardia was observed in one patient, and none developed ventricular arrhythmias.

Conclusion: Children with MIS-C are at risk of atrioventricular conduction disease, especially those who require ICU admission and have ventricular dysfunction. ECGs should be monitored for evidence of PR prolongation. Continuous telemetry may be required in patients with evidence of 1st degree AVB due to risk of progression to high-grade AVB.

Key words: SARS-CoV-2, atrioventricular block, multisystem inflammatory syndrome

INTRODUCTION

The SARS-CoV-2 virus is the cause of the current worldwide coronavirus-19 (COVID-19) pandemic, with over 5 million confirmed cases. Children were initially thought to be largely spared from severe disease.[1,2] In April 2020, initial reports emerged from the United Kingdom of patients presenting with Kawasaki disease-like features and a severe inflammatory syndrome. Most cases occurred in children testing positive for current or recent infection with SARS-CoV-2. Children presented with fever, hypotension, multiorgan involvement and markedly elevated inflammatory markers. Gastrointestinal and myocardial involvement were frequently observed, while respiratory symptoms were rarely seen.[3] Additional cases were reported throughout Europe[4] and America, leading to a health advisory from the US Centers for Disease Control and Prevention (CDC) in May 2020 for multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19.[5]

Cardiovascular complications, including shock, decreased left ventricular systolic function, coronary artery dilation and aneurysms were reported in a high proportion of patients in the initial European reports.[3,6] In our institutional experience, we also observed arrhythmias and electrocardiogram (ECG) changes in children with MIS-C. In this single-center series, we characterize the incidence of arrhythmias and ECG changes in patients with MIS-C.

METHODOLOGY

Population

We completed a retrospective cohort study including children aged 0-21 years who were admitted with a diagnosis of MIS-C between March 1st 2020 and May 30th 2020. Patients with previously diagnosed atrioventricular conduction disease were excluded from analysis. This

included one patient with cardiac surgery complicated by complete heart block the week prior to MIS-C diagnosis. As most of the cardiac and electrocardiogram findings described in this series are not applicable to this patient in the immediate post-operative period, he was excluded from analysis. This study was approved under exemption from informed consent by the Institutional Review Board at Boston Children's Hospital.

Data collection and definitions

Data elements including demographic characteristics, electrocardiogram, echocardiogram and hospital course were collected from the electronic medical record. MIS-C was defined using the CDC case definition as an individual aged < 21 years presenting with fever (≥38.0°C for ≥24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); and no alternative plausible diagnosis; and positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.[5]

Hypotension or shock was defined as requirement for fluid resuscitation (> 20 mL/kg) or inotropic support. Elevated troponin T was defined as a troponin value > 0.09 ng/mL. Elevated BNP was defined as > 100 pg/mL. Echocardiograms were reviewed during hospital admission and follow-up after discharge for ventricular function, valvar function, pericardial effusion and coronary artery dimensions. Ventricular dysfunction was defined as a left ventricular ejection

fraction < 55%. Coronary artery Z-scores were calculated for the left main coronary artery, proximal right coronary artery and proximal left anterior descending artery using the Boston formula.[7] Coronary artery dilation was defined as a coronary artery Z-score ≥2 but < 2.5. Coronary artery aneurysms were defined as having a coronary artery Z-score ≥2.5, and classified as small if Z-score ≥2.5 to <5, medium if Z-score ≥5 to < 10, and large or giant if Z-scores were ≥10 or ≥8 mm in diameter, based on the American Heart Association guidelines.[8] First degree AVB was defined as delayed conduction (prolonged PR interval) from the atrium to the ventricle without interruption in atrial to ventricular conduction, based on normal values for age.[9] Second degree AVB was defined as intermittent atrial conduction to the ventricle, and further classified as Mobitz type I (with progressive PR prolongation before the dropped beat) or Mobitz II (without progressive PR prolongation before the dropped beat). Third degree AVB was defined as no atrial conduction to the ventricle. Prolonged QTc interval was defined as a QTc interval > 98th percentile for age and gender.[9] All ECGs were reviewed by the investigator (AD) blinded to the patients' clinical course.

Statistical analysis

Descriptive statistics were obtained for all study variables. Quantitative variables were summarized as median [interquartile range, IQR], and categorical variables as frequencies and percentages. Due to the small sample size, no statistical tests were used to compare differences between groups.

RESULTS

Patient characteristics

During the study period, 25 patients were admitted for management of MIS-C of whom 15 (60%) were male and median age was 9.7 [IQR 2.7, 15.0] years. (Table 1). Forty percent of patients (n =10) had significant prior morbidities, including asthma (n=3, 15%), obesity (n=3, 15%), prior episode of Kawasaki disease (n=2, 8%), sickle cell anemia (n=1), mitochondrial disease (n=1) and triploidy with prematurity and chronic respiratory failure status post tracheostomy (n=1).

Fever was present in all patients followed in frequency by gastrointestinal symptoms (n=18, 72%), dermatologic manifestations (n=14, 56%), respiratory symptoms (n=11, 44%), hypotension or shock (n=11, 44%), hematologic anomalies (n=7, 28%), acute renal failure (n=2, 8%) and neurologic symptoms (n=1, 4%). All patients had documented SARS-CoV-2 infection (RT-PCR in 15 patients (60%), serologies in 13 patients (52%)). Four patients had positive RT-PCR 2-8 days prior to MIS-C diagnosis, while the remainder were positive at the time of hospital admission and MIS-C diagnosis.

Intensive care unit admission for monitoring and treatment was required in 14 patients (56%) for a median of 7 [IQR 4, 11] days. Inotropic support was administered in 7 patients (28%), non-invasive positive pressure ventilation in 6 patients (24%) and mechanical ventilation in 1 patient (4%). The only patient requiring mechanical ventilation had a past medical history of chronic lung disease and had prior tracheostomy.

Treatment received included intravenous immunoglobulin in 16 patients (64%), steroids in 13 patients (50%), anakinra in 4 patients (15%) and remdesivir in 9 patients (35%). A majority of patients were treated with aspirin (14 patients, 56%) and/or enoxaparin (14 patients, 56%).

At the time of publication, patients had a median follow-up of 51 [IQR 38, 64] days after onset of illness; and all patients were discharged from hospital.

Echocardiographic anomalies

All patients with a diagnosis of MIS-C had an echocardiogram performed during hospital admission, and 23 patients (92%) had at least one follow-up echocardiogram.

Left ventricular systolic dysfunction (left ventricular ejection fraction < 55%) was found in 15 patients (60%), at a median of 5 [IQR 3, 8] days after onset of fever (Table 2). The majority of patients had mild ventricular dysfunction, while 2 patients (8%) had ≥ moderate ventricular dysfunction (left ventricular ejection fraction <40%). Of those with ventricular systolic dysfunction during the acute phase of illness, function normalized in 13/15 patients (87%) at a median of 5 [3, 8] days after onset of dysfunction, with persistent mild ventricular dysfunction in 2/15 (13%).

New coronary artery enlargement was diagnosed in 5 patients (20%) at a median of 5 [IQR 2, 5] days after onset of fever (excluding patient with prior history of Kawasaki disease and coronary aneurysm). Of those, 3 patients had coronary artery dilation (Z-score ≥2 but < 2.5) and 2 patients had small coronary artery aneurysms (Z-score ≥ 2.5 but < 5). One of the patients with coronary artery aneurysms had a prior diagnosis of Kawasaki disease, and no significant change in coronary artery dimension following MIS-C diagnosis.

Troponin level was elevated in 2 patients (13%), both of whom had ventricular dysfunction. BNP level was elevated in 10/15 patients (67%) with ventricular dysfunction (median 395 [IQR 105, 1008] pg/mL), and in only 1/10 patients (10%) with normal biventricular systolic function (median 35 [IQR 16, 79] pg/mL).

Electrocardiogram anomalies

ECGs were performed in all patients, and 20 (80%) patients had multiple ECGs to review. First degree AVB was found in 5 (20%) patients admitted with MIS-C, at a median of 6 [IQR 5, 8] days after onset of fever (Figure 1, Supplemental Table). Of the 5 patients with 1st degree AVB, 4/5 had a normal admission ECG and subsequently developed AVB and 1/5 had 1st degree AVB on admission ECG**.** AVB progressed to 2nd or 3rd degree in 4/5 patients during hospital admission (Mobitz type I in 2 patients, Mobitz type II in 1 patient (without QRS widening) and third degree AVB in 1 patient) within 0-3 days after onset of 1st degree AVB. No patient required acute resuscitation, medication to improve atrioventricular conduction or increase escape rate, nor pacing. Second and third degree AVB resolved in all patients within 1-6 days. First degree AVB resolved in 4/5 patients between 10-14 days after onset of fever; 1 patient had persistent 1st degree AVB on latest outpatient follow-up (75 days after onset of fever).

All patients with AVB had ventricular dysfunction on echocardiogram (mild in 4 patients, moderate in 1 patient). All were admitted to the intensive care unit (unrelated to AVB) and 4/5 patients required inotropic support for hypotension/shock at time of initial. One patient was intubated due to cardiogenic shock, and another required positive pressure ventilation for COVID pneumonia. While 2nd and 3rd degree AVB occurred during initial intensive care unit

admission in 2/4 patients, it occurred later in the course of the disease in the other 2 patients, requiring transfer back to the ICU or to a cardiology floor for closer monitoring. All patients who developed 2nd or 3rd degree AVB presented with hypotension/shock, gastrointestinal symptoms and dermatologic manifestations. The other patient with 1st degree AVB presented with COVID pneumonia and hypotension responsive to fluid resuscitation, but no gastrointestinal or dermatologic manifestations as opposed to those who progressed to higher grade AVB. None of the patients with AVB had elevated troponin levels. All patients with 2nd or 3rd degree AVB had elevated BNP levels (median 1407 [IQR 1127, 1776] pg/mL), while the patient with first degree AVB had normal BNP level. .

QTc prolongation was seen in 7 patients (28%) at a median 6 [IQR 2, 8] days after onset of fever (median QTc 484 [IQR 474, 493] msec). QTc prolongation was more often seen in patients with ventricular dysfunction (n=6) patients compared to those with normal ventricular function (n=1) and those with AVB (4/5 (80%) patients with AVB vs. 3/20 (15%) patients without AVB). Nonspecific ST segment changes were seen in 14 patients (56%), without a difference between those with and without ventricular dysfunction (9/15 versus 5/10 patients respectively). All patients with AVB had non-specific ST segment changes on ECG, compared to only 9 (45%) of patients without AVB.

Two patients had atrial ectopy, and another patient had sustained ectopic atrial tachycardia. No ventricular arrhythmias were seen. No patient required antiarrhythmic medication.

DISCUSSION

In this series, ECG anomalies were found in 14 (56%) children with MIS-C, and included PR prolongation, ST segment changes and QTc prolongation. First degree AVB was found in 5 children (20%) during hospital admission, with 4/5 patients progressing to 2nd or 3rd degree. The incidence of AVB was highest among patients requiring ICU admission (4/14 patients, 29%). All patients with 2nd and 3rd degree AVB presented with hypotension/shock, gastrointestinal symptoms and dermatologic manifestation and had evidence of ventricular dysfunction on echocardiogram. ECGs should be monitored for evidence of PR prolongation throughout admission in patients with MIS-C. Patients who develop 1st degree AVB may benefit from continuous telemetry due to the risk of progression to high-grade AVB.

Evidence of myocardial injury is common among adults hospitalized with COVID-19. Possible causes of myocardial injury in patients with COVID-19 include myocarditis, hypoxic injury, stress (Takotsubo) cardiomyopathy, ischemic injury caused by cardiac microvascular damage or coronary artery disease, right heart strain (acute cor pulmonale) and systemic inflammatory response syndrome.[10-14] Clinical presentation ranges from asymptomatic troponin elevation to fulminant myocarditis requiring extracorporeal membrane oxygenation support. Atrial and ventricular arrhythmias have been reported in 3-17% of adults hospitalized with COVID-19.[15-17] Bradyarrhythmias have not been typically seen, but there was one reported case of transient complete heart block in a critically ill 54-year-old woman with COVID-19 pneumonia, who required cardiopulmonary resuscitation for ~ 10 minutes until resumption of normal sinus rhythm.[18]

Initial reports suggested that children with COVID-19 have much milder form of COVID-19 than adults.[1,2] However, there have now been multiple reports of cases of MIS-C in children with

recent SARS-CoV-2 infection. Published case series have shown cardiovascular involvement in a significant proportion of patients, with reports of elevated troponin, elevated BNP, ventricular dysfunction and coronary artery dilation and aneurysm.[5,6] No significant tachyarrhythmias have been reported in children, compared with adult patients, in whom a much higher prevalence has been seen.

There has been one recent report of transient complete heart block in a child following SARS-CoV-2 infection.[19] The etiology of the AVB remains unclear, but may result from inflammation and edema of the conduction tissue as part of a more diffuse process of myocardial injury.

An earlier single center series of children with non-COVID-related acute myocarditis reported a high incidence of arrhythmias, occurring in 38 patients (45%) and including supraventricular tachycardia in 9 patients, ventricular arrhythmia in 30 patients, and complete heart block in 11 patients.[20] The clinical course of AVB in patients with MIS-C differs from the prior experience with myocarditis. In non-COVID related myocarditis, complete heart block was generally present at the time of initial presentation and frequently required interventions including pacing and extracorporeal membrane oxygenation. In comparison, AVB developed later in the hospital course in MIS-C patients, and no patients required pacing or extracorporeal membrane oxygenation due to AVB. However, this initial experience with MIS-C is based upon a small number of patients and our understanding will likely evolve as we learn more about the disease.

In contrast, AVB seen in MIS-C patients appears more similar to the prior experience with Lyme carditis. In a surveillance study in the United States, cardiac manifestations were present in 84/875 patients (10%) with Lyme disease, including conduction abnormalities in 16 patients (1.8%).[21] Similarly, patients with Lyme carditis presented with 1st degree AVB that progressed to high-grade AVB, with the highest risk of progression in patients with a PR interval greater than

300 ms.[22-24] This is similar to findings in our cohort, where most patients had initially normal ECG and developed 1st degree AVB prior to higher grade AVB (although the progression occurred the same day in some cases). In MIS-C, patients with a prolonged PR interval for age were at high risk of progression of AVB, even with only mild PR prolongation (i.e. < 300 ms, Figure 1).

The course of AVB remains unclear in patients with MIS-C. While higher grade AVB resolved within ~ 1 week in this series, some patient still had persistent 1st degree AVB at the time of discharge. Antibiotic treatment has been shown to decrease the duration of cardiac manifestations in Lyme carditis.[25] Anti-inflammatory treatment of patients with MIS-C patients with intravenous immunoglobulin, steroids or anakinra may help decrease the incidence of AVB in MIS-C, however we were unable to assess the impact of therapy due to the empiric treatment of the most severe cases. Ongoing outpatient follow-up of patients with MIS-C will help us better understand the trajectory of AVB in patients with MIS-C. Until we know more about AVB in MIS-C, children should have frequent ECGs during admission to monitor for PR prolongation and long-term follow-up following discharge. Twenty-four hours Holter monitor should be considered in patients with persistent 1st degree AVB during outpatient follow-up.

This study should be interpreted in light of its limitations. This is a retrospective series including only a small number of patients from a single institution. Moreover, there was no systematic protocol for ECG testing, and some patients without follow-up ECG study or telemetry may have been missed. The limited follow-up on patients at the time of publication limits our ability to comment on long-term outcome.

CONCLUSION

In this series, MIS-C was associated with a high incidence of atrioventricular conduction disease in children, particularly in patients presenting with hypotension/shock and with ventricular dysfunction. This experience highlights the importance of ECG monitoring throughout admission to identify patients with PR prolongation at risk of progression to high-grade AVB. Large, multi-center studies are required to better understand the pathophysiology, clinical presentation, and impact of treatment on atrioventricular conduction disease in MIS-C.

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Table 1: Baseline characteristics of patients with MIS-C based on presence or absence of 2nd or 3rd degree atrioventricular block

	All patients (n=25)	AVB (n=5)	No AVB (n=20)
Age (years)	9.7 [2.7, 15.0]	12.1 [10.3, 16.2]	7.2 [2.2, 13.7]
Male	15 (60)	2 (40)	13 (65)
Past medical history	10 (40)	1 (20)	9 (45)
Hospital course			
Duration of fever (days)	6 [4, 8]	7 [6, 9]	5 [4, 6]
Hospital length of stay (days)	7 [3, 11]	11 [9, 12]	6 [3, 9]
ICU admission	14 (56)	5 (100)	9 (45)
ICU length of stay (days)	7 [4, 11]	6 [3, 14]	7 [4, 10]
Inotropic support	7 (28)	4 (80)	3 (15)
Non-invasive positive pressure ventilation	6 (24)	1 (20)	4 (20)
Intubation	1 (4)	1 (20)	1 (5)
Treatments received			
IVIG	16 (64)	5 (100)	11 (55))
Steroids	13 (52)	5 (100)	9 (45)
Anakinra	4 (16)	2 (40)	2 (10)
Aspirin	14 (56)	4 (80)	10 (50)
Enoxaparin	14 (56)	4 (80)	10 (50)
Remdesivir	9 (36)	3 (60)	6 (30)
SARS-CoV-2 testing			
PCR	15 (60)	3 (60)	12 (60)
Antibodies	13 (52)	2 (40)	11 (55)

AVB: atrioventricular block; ICU: intensive care unit; IVIG: intravenous immunoglobulin

Table 2: Cardiac complications in patients with MIS-C based on presence or absence of 2nd or 3rd degree atrioventricular block

	All patients (n=25)	AVB (n=5)	No AVB (n=20)
Ventricular dysfunction			
EF < 55%	15 (60)	5 (100)	10 (50)
EF < 40%	2 (8)	1 (20)	1 (5)
Coronary artery dilation			
Dilation (Z-score ≧2, but <2.5)	3 (12)	1 (25)	2 (10)
Aneurysm (Z-score ≧ 2.5)	3 (12)	0 (0)	3 (15)
ECG changes			
1st degree AVB	5 (20)	5 (100)	0
2nd degree AVB, Mobitz 1	2 (8)	2 (40)	0
2nd degree AVB, Mobitz 2	1 (4)	1 (20)	0
3rd degree AVB	1 (4)	1 (20)	0
QTc prolongation	7 (28)	4 (80)	3 (15)
QTc prolongation > 500 ms	1 (4)	1 (25)	0
Non-specific ST segment changes	14 (56)	5 (100)	9 (45)
Laboratory testing			
Elevated troponin	2 (8)	0 (0)	2 (10)
Elevated BNP	11 (44)	4 (80)	8 (40)

AVB: atrioventricular block; EF: ejection fraction; BNP: brain natriuretic peptide

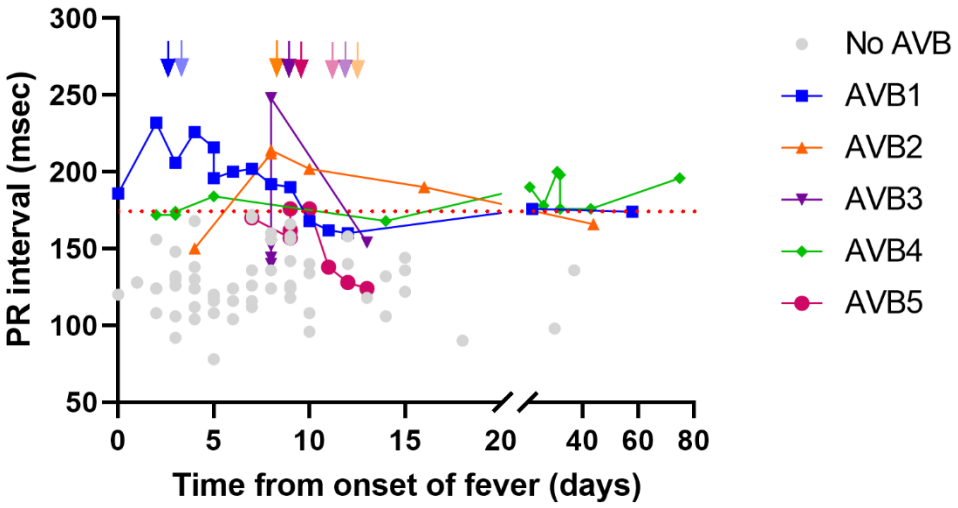

Figure 1: PR interval in patients with and without atrio-ventricular block by days from onset of fever. Arrows show onset and resolution of higher grade atrio-ventricular block (2nd and/or 3rd degree).

Supplemental Table: Characteristics of patients with atrio-ventricular block

Patient	Gender	Age (years)	PMH	ICU admission	Inotropic support	PPV or intubation	Maximum PR interval	2nd or 3rd degree AVB	Day of illness at time of 2nd or 3rd degree AVB	Maximum QTc interval	ST segment changes	Tachyarrhythmias	Worst EF	Coronary dilation	Highest BNP	Highest troponin (normal < 0.09)
1	F	9	Asthma, obesity	Yes	Yes	No	232	Yes	3	527	Yes	No	51%	Yes	1407	0.03
2	M	10	None	Yes	Yes	No	214	Yes	7	477	Yes	No	53%	No	5290 (NT-proBNP)	0.01
3	M	11	None	Yes	Yes	Yes	248	Yes	9	434	Yes	No	32%	No	2145	0.07
4	F	17	None	Yes	No	Yes	200	No		489	Yes	Atrial ectopy	55%	No	10	0.01
5	F	16	None	Yes	Yes	No	176	Yes	9	497	Yes	No	47%	No	1046	0.01

PMH: past medical history; ICU: intensive care unit; PPV: positive pressure ventilation; AVB: atrioventricular block

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