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ORIGINAL RESEARCH

Right and left ventricular function in hospitalized children with respiratory syncytial virus infection

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Background: Extrapulmonary manifestations including cardiac dysfunction have been demonstrated in children with respiratory syncytial virus (RSV) infection requiring intensive care. The aim of this study was to examine cardiac function in hospitalized children with moderate RSV infection admitted to a regular pediatric ward.

Methods: We used echocardiography to determine cardiac output, and right and left ventricular function in 26 patients (aged 2 weeks to 24 months) with RSV infection. The echocardiographic results were compared with s-troponin, the need for supplementary oxygen or noninvasive respiratory support, and capillary refill time.

Results: The number of measured s-troponins (ten [38%] of the included children) was too low to assess differences between children with elevated levels and those with normal levels. There were no differences in cardiac function between patients receiving oxygen treatment or respiratory support and those who did not. Capillary refill time did not correlate with any of the echocardiographic parameters. Both left and right ventricular output (mL/kg/min) was higher than published reference values. All other echocardiographic parameters were within the reference range.

Conclusion: Children with moderate RSV infection had an increased left and right ventricular output, and cardiac function was well maintained. We conclude that routine cardiac ultrasound is not warranted in children with moderate RSV infection. The role of an elevated s-troponin in these patients remains to be determined.

Keywords: bronchiolitis, capillary refill time, child, echocardiography, respiratory syncytial virus

Plain language summary

Because children with critical respiratory syncytial virus (RSV) infection have been found to have a reduced heart function, we wanted to investigate if this was also the case in children with less severe RSV infection. In this situation, drug treatment that increases the heart's performance and function may be warranted. We performed cardiac ultrasound (echocardiography) in children admitted with RSV infection to our pediatric department. In ten (38%) of the 26 included children, we performed the blood test s-troponin that may indicate strain on the heart. We found that children with RSV infection did not have signs of reduced heart function on echocardiography. We conclude that routine cardiac ultrasound is not warranted in children with less severe RSV infection. The number of s-troponin samples was too low to conclude on the usefulness of this marker.

Background

RSV is one of the most frequent causes of viral lower respiratory tract infection in children and is associated with approximately 600,000 annual deaths worldwide.[1]

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In children with RSV infection requiring intensive care, extrapulmonary consequences including cardiac arrhythmias and primary mechanical myocardial dysfunction have been described.[2–5] Elevated levels of s-troponin have been found in children with RSV infection,[6] and the proposed mechanism has been pulmonary hypertension leading to right ventricular dysfunction.[7]

There is a lack of knowledge about extrapulmonary manifestations including cardiac dysfunction in children with less severe RSV infection, who are admitted to a regular pediatric ward. However, many children with moderate RSV infection admitted to regular pediatric wards have clinical signs of hypoperfusion. Symptoms of cardiac failure, for example, tachypnea, tachycardia, prolonged capillary refill time, and mottling of the skin, may be difficult to distinguish from the symptoms of RSV bronchiolitis itself.[8] Thus, Caplow et al[8] suggested that CO as a measure of cardiac function should be assessed in hospitalized infants with RSV infection. The aim of this study was to investigate a predefined set of echocardiographic functional parameters, including right and left ventricular output, in relation to s-troponin, the need for supplementary oxygen or noninvasive respiratory support, and capillary refill time in children with RSV infection admitted to a regular pediatric ward. We hypothesized that children with moderate RSV infection have some degree of myocardial dysfunction.

Methods

Ethics statement

The Regional Committee for Medical and Health Research Ethics approved the project. Participation in the study was voluntary, and written informed consent was obtained from the parents or guardians of participating children. Blood samples for the project were only drawn if the child was scheduled to have blood samples taken for assessment and treatment in general.

Setting

This was an observational cohort study performed at the level II Department of Pediatric and Adolescent Medicine, Akershus University Hospital in Norway.

Patients

Inclusion criteria were hospitalization with confirmed RSV infection diagnosed by real-time PCR of genes for the RSV nucleocapside in nasopharynx secretions, and availability of the echocardiographer. At the time of data collection, children with mild RSV disease, defined as having a modified respiratory distress assessment instrument[9] score ≤8 were not admitted, but treated as outpatients and were thus excluded from the study. Other protocolled exclusion criteria included severe chronic disease, congenital heart disease, including cardiac shunts, or structural abnormalities found during examination. According to the admission criteria, all hospitalized children with RSV infection had moderate disease with the majority requiring supplemental oxygen and/or noninvasive respiratory support (CPAP or HFNC).

Clinical information and blood sample analysis

Capillary refill time is routinely recorded on admission and once per nursing shift for all children admitted to our department. This information, together with information about the need for supplementary oxygen and/or noninvasive respiratory support, was retrospectively collected from the patient electronic records. S-troponin was measured by Troponin T hs electrochemiluminescence immunoassay (Cobas e 602 analyzer; Roche Diagnostics, Basel, Switzerland). According to Eisenhut et al,[10] we considered troponin to be elevated if values were >10 pg/mL.

Echocardiography

We used a Vivid 9E ultrasound scanner (GE Vingmed, Horten, Norway) with a 5S standard phase array multi-frequency transducer probe (2.0–5 MHz) and a predefined protocol for all patients. Aortic and pulmonary annulus diameter was measured in the parasternal long axis view, whereas left ventricular FS was measured in the parasternal short axis projection. Flow measurements over the mitral and tricuspid valve were made in the apical four-chamber projection. In the apical four-chamber projection, we also measured TAPSE by placing an M-mode cursor through the tricuspid lateral annulus and measuring the amount of longitudinal (base to apex) motion in millimeters of the tricuspid annulus at peak systole. MAPSE was also measured using the standard M-mode technique with the cursor placed at the lateral side of the annulus from the apical four-chamber view. Left ventricular end diastolic and systolic dimension from the four- and two-chamber view was measured to calculate LVEF using the biplane Simpson's formula.[11]

Cardiac output

2D ultrasound and Doppler measurements are used together to calculate CO. 2D measurement of the diameter of the aortic or pulmonary valve annulus allows calculation of the flow cross-sectional area, which is then multiplied by the VTI of the Doppler flow profile across the valve to determine

the flow volume per beat. The result is then multiplied by the HR to obtain CO.[12] In this study, we measured the VTI derived from at least three consecutive pulsed wave Doppler signals over the aortic valve in the five-chamber projection to calculate left ventricular CO. Pulsed wave Doppler flow over the pulmonary valve in the parasternal short axis projection was used for calculating right ventricular CO.

Data processing and statistical analyses

The echocardiographic recordings were analyzed offline using the EchoPac software version 113 (GE Vingmed, Horten, Norway). The investigator performing all the analyses (TH) was blinded to the clinical information about the patients. Linear regression analyses were performed to calculate Spearman's rho (r_s) for correlation between different parameters. Differences between groups were assessed with independent samples *t*-test and Mann–Whitney *U* test for normally and non-normally distributed parameters, respectively. A p-value <0.05 was considered significant. Statistical analyses were performed with IBM SPSS for Mac Version 22 (IBM Corporation, Armonk, NY, USA).

Results

We enrolled a prospective convenience sample of 26 patients, aged 2 weeks to 24 months, from February 2012 to March 2014. One cardiologist (TH) examined all but two patients. Characteristics of the included children are summarized in Table 1. Seven patients received CPAP or HFNC treatment. One of these patients was subsequently treated with mechanical ventilation in the neonatal intensive care unit. The patients who required noninvasive respiratory support had a longer hospital stay compared to patients who did not need such treatment (p<0.001). No other differences were found between patients receiving respiratory support and those who did not. Children receiving oxygen treatment had a trend toward a longer capillary refill time and hospital stay than those who did not require supplementary oxygen (Table 2). No other differences were found between patients receiving oxygen treatment and those who did not.

S-troponin was measured in ten of the 26 patients. Six (60%) of these patients had elevated levels of s-troponin, and four had levels below the detection level. The patients with elevated s-troponin had a median (interquartile range) level of 28.0 (24.5–33.3) pg/mL. Characteristics of patients with elevated s-troponin vs. patients with undetectable levels of s-troponin are presented in Table 3.

Table 1 Characteristics of the study population (n=26)

Male/female	15/11
Age (months)‡	2 (1–24)
Weight (kg)‡	5.4 (4.5–7.6)
Length of stay (days)‡	5 (2–13)
Day examined#	2 (2–3)
Oxygen requirement*	18 (69)
CPAP/HFNC*	7 (27)
S-troponin T (pg/mL)#	28 (25–33)
Left ventricular output (mL/kg/min)#	240 (190–270)
Right ventricular output (mL/kg/min)#	362 (324–408)
Ejection fraction (biplane) (%)#	60 (55–64)
Fractional shortening (%)#	38 (34–41)
TAPSE (mm)#	11.9 (10.8–13.9)
MAPSE (mm)#	8.0 (6.9–8.6)
Heart rate (bpm)#	146 (128–164)

Notes: ‡Median (range). #Median (interquartile range). *Number (%).
Abbreviations: CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion; bpm, beats per minute.

Left ventricular function and CO

MAPSE, a measure of left ventricular contractility, was within published reference values.[13] Left ventricular CO (mL/kg/min) was slightly higher than the upper reference level.[14,15] As there was a significant positive correlation between HR and CO (r_s=0.43, p=0.023), the higher CO could largely be explained by a high HR in the patients (Table 1). FS was within the reference range[10] and LVEF in the lower reference range[16] (Table 1), with no difference between patients with an elevated and those with a normal s-troponin (Table 3). There was a weak negative correlation between s-troponin and CO (p=0.11).

Right ventricular function and CO

In patients in different age categories, TAPSE, a measure of right ventricular contractility, was comparable to published reference values[17] (Table 1). Right ventricular output was higher than the upper reference level (Table 1).[14]

Capillary refill time

Capillary refill time did not correlate with any of the echocardiographic parameters. However, there was a trend toward a longer capillary refill time in children who needed supplementary oxygen (p=0.08).

Discussion

In this study, we examined whether children with RSV infection admitted to a regular pediatric ward had signs of myocardial dysfunction as measured by, for example, decreased right and left ventricular CO and/or elevated s-troponin. This is one of very few published studies on myocardial function in children with RSV infection not admitted to an intensive care unit. Even though a high proportion of measured s-troponins

Table 2 Comparison of patients with and without a need for oxygen treatment

	Oxygen treatment (n=18)	No oxygen treatment (n=8)	*p*-value
Length of stay (days)	6 (5–9)	4 (3–7)	0.080
Capillary refill time (s)	2.2 (0.4)	1.9 (0.4)	0.080
Left ventricular output (mL/kg/min)	230 (178–273)	250 (200–250)	1.000
Right ventricular output (mL/kg/min)	362 (346–446)	336 (307–408)	0.432
Ejection fraction (biplane) (%)	57 (55–62)	63 (55–64)	0.315
Fractional shortening (%)	39 (35–41)	37 (33–40)	0.400
TAPSE (mm)	11 (11–13)	14 (10–16)	0.595
MAPSE (mm)	8 (4–9)	7 (6–8)	0.161
Heart rate (bpm)	145 (126–163)	146 (133–166)	0.630

Note: Results are presented as median with interquartile range in parentheses, except capillary refill time which is presented as mean with standard deviation in parentheses.
Abbreviations: TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion; bpm, beats per minute.

Table 3 Comparison of patients with elevated and non-elevated s-troponin

	Elevated troponin (n=6)	Undetectable troponin (n=4)	*p*-value
Length of stay (days)	8 (6–11)	5 (3–11)	0.257
Capillary refill time (s)	2 (2–2)	2 (2–2)	0.762
Left ventricular output (mL/kg/min)	275 (215–333)	270	1.00
Right ventricular output (mL/kg/min)	400 (376–488)	362	0.286
Fractional shortening (%)	38 (34–43)	40 (39–ND)	0.643
Ejection fraction (biplane)	61 (53–64)	ND	0.667
TAPSE (mm)	11 (11–14)	12 (11–ND)	1.000
MAPSE (mm)	8 (7–8)	9 (9–)	0.071
Heart rate (bpm)	147 (122–157)	140 (116–ND)	1.000

Note: Results are presented as median with interquartile range in parentheses.
Abbreviations: TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion; bpm, beats per minute; ND, not determined.

were slightly elevated, the number of samples was too low to draw any conclusions about the usefulness of this parameter. Both right and left ventricular outputs were higher than the reference range, and all other echocardiographic parameters were within the reference range. No echocardiographic parameters were associated with the need for supplementary oxygen or respiratory support, or a prolonged capillary refill time.

S-troponin

As pulmonary hypertension with an elevated right ventricular afterload might lead to cardiac dysfunction, physiological plausibility points to the right ventricle as the origin of the elevated s-troponin measured in children with RSV infection. Thus, the s-troponin level may be an indicator of the severity of the pulmonary disease. As opposed to the findings of Moynihan et al[6] that s-troponin is a predictor of need for respiratory support, we found no difference in troponin levels between children with and without a need for respiratory support, likely due to a lack of power for this parameter.

Cardiac output

Although commonly used in clinical medicine, echocardiographic CO measurements have wide test–retest variability. Sources of variability include the 2D measurement of the aortic valve diameter[12,18] and beat-to-beat variation in stroke volume, and even slight differences in probe position affect the measured VTI.[18] An alternative to measuring left ventricular output is measuring right ventricular CO, as in the absence of significant intracardiac shunting they should be similar. Tsai-Goodman et al[14] compared measurements of left and right ventricular output. They measured a mean left ventricular output of 241 mL/kg/min and a mean right ventricular output of 255 mL/kg/min, a difference of 6%, which is less than the substantial difference between left and right CO we found in our study. Tsai-Goodman et al[14] argue that since the right ventricular outflow tract is a more elastic structure than the aortic root, and thus tends to expand more during systole, repeatability and reliability of right ventricular output may be poor compared to left ventricular output.[14] This may explain the relatively large difference between the right and left ventricular output in our study. However, as the same person performed almost all the data collection and analyses, and since our intention was to compare subgroups of patients, not to assess their absolute values, we argue that our conclusions are still valid.

The elevated right and left CO can largely be explained by the higher HR in the patients. An elevated-to-normal CO has also been demonstrated in animal models of severe

respiratory distress syndrome.[19] de Vroomen et al[20] demonstrated in a lamb model that in the newborn heart, the right ventricle is able to maintain its output by improving contractile performance, through the so-called homeometric autoregulation and not by increasing end-diastolic volume (Frank–Starling mechanism). A possible mechanism of homeometric autoregulation could be release of endogenous catecholamines in response to an increased right ventricular afterload,[21] which might explain that also left ventricular output was modestly increased in our patients, that is, through an increase in HR.

Capillary refill time

Our concern was that children hospitalized with RSV infection with clinical signs of poor peripheral circulation, as assessed by prolonged capillary refill time, had a reduced myocardial function. In this situation, drug treatment that increases myocardial contractility may be warranted, while excessive fluid therapy may be contraindicated. Adrenergic stimulation that leads to peripheral vasoconstriction may also be a potential mechanism for a prolonged capillary refill time. None of the patients in our study had a capillary refill time exceeding 3 s at the time of examination, possibly making the interpretation of the correlation between capillary refill time and cardiac mechanical parameters less reliable.

Limitations

Limitations of this study include the low number of included patients. Especially, the number of patients where s-troponin was measured was low.

Conclusion

Results from the present study indicate that children with moderate RSV bronchiolitis do not have cardiac dysfunction. In these patients, CO is likely maintained through the so-called homeometric autoregulation. Although our study is too small to conclude on the value of s-troponin alone, it might be useful to identify patients where echocardiographic examination may be warranted.

Abbreviations

2D – two-dimensional
CO – cardiac output
CPAP – continuous positive airway pressure
FS – fractional shortening
HFNC – high flow nasal cannula
HR – heart rate
LVEF – left ventricular ejection fraction
MAPSE – mitral annular plane systolic excursion
RSV – respiratory syncytial virus
TAPSE – tricuspid annular plane systolic excursion
VTI – velocity time integral

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Author contributions

TH, OA, and ALS contributed to concept and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version as submitted. BN contributed to concept and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version as submitted.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Howard TS, Hoffman LH, Stang PE, Simoes EA. Respiratory syncytial virus pneumonia in the hospital setting: length of stay, charges, and mortality. *J Pediatr*. 2000;137(2):227–232.
2. Giles TD, Gohd RS. Respiratory syncytial virus and heart disease. A report of two cases. *JAMA*. 1976;236(10):1128–1130.
3. Huang M, Bigos D, Levine M. Ventricular arrhythmia associated with respiratory syncytial viral infection. *Pediatr Cardiol*. 1998;19(6):498–500.
4. Menahem S, Uren EC. Respiratory syncytial virus and heart block--cause and effect? *Aust N Z J Med*. 1985;15(1):55–57.
5. Thomas JA, Raroque S, Scott WA, Toro-Figueroa LO, Levin DL. Successful treatment of severe dysrhythmias in infants with respiratory syncytial virus infections: two cases and a literature review. *Crit Care Med*. 1997;25(5):880–886.
6. Moynihan JA, Brown L, Sehra R, Checchia PA. Cardiac troponin I as a predictor of respiratory failure in children hospitalized with respiratory syncytial virus (RSV) infections: a pilot study. *Am J Emerg Med*. 2003;21(6):479–482.
7. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation*. 2002;106(10):1263–1268.
8. Caplow J, McBride SC, Steil GM, Wong J. Changes in cardiac output and stroke volume as measured by non-invasive CO monitoring in infants with RSV bronchiolitis. *J Clin Monit Comput*. 2012;26(3):197–205.
9. Inchley CS, Sonerud T, Fjærli HO, Nakstad B. Nasal mucosal microRNA expression in children with respiratory syncytial virus infection. *BMC Infect Dis*. 2015;15:150.

10. Eisenhut M, Sidaras D, Johnson R, Newland P, Thorburn K. Cardiac Troponin T levels and myocardial involvement in children with severe respiratory syncytial virus lung disease. *Acta Paediatr*. 2004;93(7):887–890.
11. Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440–1463.
12. Pees C, Glagau E, Hauser J, Michel-Behnke I. Reference values of aortic flow velocity integral in 1193 healthy infants, children, and adolescents to quickly estimate cardiac stroke volume. *Pediatr Cardiol*. 2013;34(5):1194–1200.
13. Koestenberger M, Nagel B, Ravekes W, et al. Left ventricular long-axis function: reference values of the mitral annular plane systolic excursion in 558 healthy children and calculation of z-score values. *Am Heart J*. 2012;164(1):125–131.
14. Tsai-Goodman B, Martin RP, Marlow N, Skinner JR. The repeatability of echocardiographic determination of right ventricular output in the newborn. *Cardiol Young*. 2001;11(2):188–194.
15. Alverson DC, Aldrich M, Angelus P, Backstrom C, Werner S. Longitudinal trends in left ventricular cardiac output in healthy infants in the first year of life. *J Ultrasound Med*. 1987;6(9):519–524.
16. Koestenberger M, Nagel B, Ravekes W, et al. Reference values of the mitral annular peak systolic velocity (Sm) in 690 healthy pediatric patients, calculation of Z-score values, and comparison to the mitral annular plane systolic excursion (MAPSE). *Echocardiography*. 2014;31(9):1122–1130.
17. Koestenberger M, Ravekes W, Everett AD, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. *J Am Soc Echocardiogr*. 2009;22(6):715–719.
18. Chew MS, Poelaert J. Accuracy and repeatability of pediatric cardiac output measurement using Doppler: 20-year review of the literature. *Intensive Care Med*. 2003;29(11):1889–1894.
19. Lopes Cardozo RH, Steendijk P, Baan J, Brouwers HA, De Vroomen M, Van Bel F. Right ventricular function in respiratory distress syndrome and subsequent partial liquid ventilation. Homeometric autoregulation in the right ventricle of the newborn animal. *Am J Respir Crit Care Med*. 2000;162(2 Pt 1):374–379.
20. de Vroomen M, Cardozo RH, Steendijk P, van Bel F, Baan J. Improved contractile performance of right ventricle in response to increased RV afterload in newborn lamb. *Am J Physiol Heart Circ Physiol*. 2000;278(1):H100–H105.
21. von Anrep G. On the part played by the suprarenals in the normal vascular reactions of the body. *J Physiol*. 1912;45(5):307–317.