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HEMODYNAMICS CHANGES IN CHILDREN WITH HYPERCAPNIC RESPIRATORY FAILURE DURING RESPIRATORY SYNCYTIAL VIRUS INFECTION

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Acute bronchiolitis associated with Respiratory Syncytial Virus (RSV) infection is an example of progressive hypercapnic hypoventilation. Acute bronchiolitis is the most difficult course of the disease, and lower airways' obstruction is difficult to control (1, 2). Typical symptoms are progressive tachypnoea, grunting, chest retraction, increased difficulty in breathing, hypoventilation, and mixed dyspnoea, all of which are resistant to bronchodilatory or anti-inflammatory therapy (3). Increased airway resistance causes parallel hyperinflation and alveoli consolidation. These pulmonary pathophysiological changes are a source of such complications as pneumonia, fluidothorax, and others (4, 5). Severe pulmonary pathology causes cardiopulmonary interaction that has an adverse impact on blood circulation. The consequences of such interaction are right ventricle pressure overload, a reduction in pulmonary flow, and a decrease in cardiac output. This situation has caused complications and limits the possibilities of conventional ventilation (6).

Effective protection against this serious infection is not reliable. Active immunization is not possible for multiple RSV genome polymorphisms. Continuous immunoprophylaxis with monoclonal antibodies or antiviral therapy also has not produced the expected results (7, 8).

A reliable, effective treatment can be addressed only by the consequences of RSV infection. Our research was motivated by clinical experience.

PATIENTS AND METHODS

Inclusion criteria of this study confirmed RSV infection, acute hypercapnic respiratory failure, a predicted Pediatric Risk Index Scoring of Mortality (PRISM) of more than 10 points, and a Lung Injury Score (LIS) above 1.0 point (9, 10). Exclusion criteria included an end of mechanical ventilation within 48 hours of initiation.

The study population was divided into two groups according to severity of the pulmonary affection. Group A included at-risk patients with PRISM values of more than 20 points and LIS above 1.5 points. Children without risk and with PRISM values from 10 to 19 points and LIS from 1.0 to 1.4 points were placed in Group B.

For rapid diagnosis of the active RSV infection, the Rapid-VIDI test was used (www.vidia.cz). PCR RNA of RSV isolation of real-time and KFR RSV antibodies were used for a definitive laboratory diagnosis.

After the patients' admission to the Pediatric Intensive Care Unit (PICU), basic input information was obtained. Standard examinations, such as a chest X-ray, an ECG, transthoracic echocardiography, microbiological analysis of tracheal aspirate, and biochemical analysis of blood and urine, complemented anamnesis and clinical examinations. The ECG waveform, respiratory/breath rate (RR/BR; breath/min), heart rate (HR; beat/min), mean central venous pressure (CVP; mmHg), systolic (SBP; mmHg), mean (MAP; mmHg) and diastolic arterial blood pressure (DBP; mmHg), pulse oximetry (SpO_2; %), core temperature (°C) by bedside monitoring system (Diascope G2; USA), and urine output (UO; ml/kg/h) were monitored continuously.

Study protocol and data collection

Data in the study were recorded after recovery, i.e., one hour after the introduction (time-1), and, subsequently, after 24 hours and 48 hours of comprehensive treatment (time-2 and time-3), for statistical evaluation.

Conventional mechanical ventilation was conducted, based on the protective principle, by positive pressure mode (Evita-4, Dräger Medical; Germany or Avea, Bird Viasys Healthcare, Care Fusion; USA). Unconventional forms of ventilation used were high-frequency oscillatory ventilation (SensorMedics 3100A, Viasys Healthcare; the Netherlands); exogenous surfactant replacement therapy (Curosurf, Chiesi Farmaceutici, S.p.A.; Parma, Italy); inhalation of nitric oxide (Pulmonox-Mini NO, Messer Griesheim; Austria); prone position ventilation, and tracheal gas insufflation (11).

The study collected the data with the following parameters: alveolar-arterial oxygen difference ($AaDO_2$; kPa), arterial-alveolar oxygen difference (a/ADO_2; kPa), hypoxic ratio (PaO_2/FiO_2; mmHg), oxygenation index (OI; –), ventilation index (VI; –), dead space-to-tidal volume ratio (V_D/V_T; %), dynamic lung compliance (C_{dyn}; ml/cmH_2O/kg), and dynamic airway resistance (R_{aw}; cmH_2O/l/s). These parameters were calculated to assess the quality of ventilation.

Hemodynamics was monitored by noninvasive techniques. The ultrasound cardiac output monitor (USCOM; Spacelabs Healthcare; Australia) is a device that converts a real-time continuous Doppler signal from the transthoracic probe (2.2 MHz) to a pulse waveform. From the left, the parasternal approach displays on the screen USMOM a pulse waveform from pulmonary annulus; the suprasternal approach shows an aortic pulse waveform. The pulse waves are analyzed beat-to-beat to obtain hemodynamic parameters. In the study, we collected data with the following parameters: stroke volume (SV; ml), stroke volume index (SVI; ml/m^2), stroke volume variation (SVV; %), stroke work (SW; mJ), peak velocity of flow (Vpk; m/s), velocity time integral (Vti; cm), flow time (FT; ms), flow time corrected (FTc; ms), ejection time percent (ET%; %), pulmonary vascular resistance (PVR; dyn.sec/cm^5), pulmonary vascular resistance index (PVRI; dyn.sec/cm^5/m^2), systemic vascular resistance (SVR; dyn.sec/cm^5), systemic vascular resistance index (SVRI; dyn.sec/cm^5/m^2), mean pressure gradient (Pmn; mmHg), minute distance (MD; m/min.), cardiac output (CO; l/min.), cardiac index (CI; l/min/m^2), and cardiac power output (CPO; W) (12).

On the basis of current and real-time information on hemodynamics, a strategy was chosen of pharmacological support of circulation by the following means: vasoactive (noradrenalin 0.01–0.25 mikrog/kg/min. intravenously), inotropes support (dobutamine 3.0–8.0 mikrog/kg/min.

intravenously), ino-vasodilatation (milrinone 0.35–0.75 microg/kg/min. intravenously), selective vasodilatation (inhaled nitric oxide; INO 30–40 ppm; Pulmonox-Mini NO, Messer Griesheim; Austria), and nonselective vasodilatation (sildenafil 1.0–2.0 mg/kg/day enterally). Treatment was accompanied by fluid management, nutrition, analgosedation (sufentanil 0.8–1.3 microg/kg/hr with midazolam 0.2–0.3 mg/kg/hr) intravenously, and inhalations of 3% sodium chloride solution. Antibiotics were used causally according to the results of a microbiological analysis of tracheal aspirate. Pleural and pericardial fluid collections were drained under general anesthesia and ultrasonographic navigation (Vygon, SA; France and Arrow ECS; Czech Republic). Permanent suction was used in a closed system (Atrium Ocean, Mediform; Czech Republic) for complete evacuation.

Statistical analysis

All data were presented as a mean with a standard deviation (mean ± SD). For analysis, a student's t-test, a distribution-free Wilcoxon's test, and a two-way ANOVA test were applied. Levels of statistical significance of $P < 0.05$ were accepted. The data were analyzed using Statistica® software (StatSoft; Tulsa, Oklahoma, U.S.A.).

Ethical consideration

This study was preformed according principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Faculty of Medicine in Pilsen, Czech Republic.

RESULTS

In total, from 2008 to 2012, 324 children were admitted to our PICU for respiratory insufficiency heterogeneous etiology. Only 58 children (18%) met the inclusion criteria of the study. The clinical and complementary characteristics of the study cohorts, on admission, in both groups are listed in (Tab. 1).

Tab. 1 The input characteristics of the study population on admission to the PICU

Characteristics	**Group A** *N = 28*	**Group B** *N = 30*	**Values** *P<*
Age *Years; mean ± SD*	0.76 ± 0.42	1.30 ± 0.34	0.05
Male/female *N*	13 / 15	12 / 17	NS
Body weight *Kg; mean ± SD*	8.92 ± 5.04	9.05 ± 6.01	NS
Risk factors *N (%)*	18 (64)	8 (27)	0.05
Immunoprophylaxis *N (%)*	6 (21)	1 (3)	0.01

Characteristics	**Group A** *N = 28*	**Group B** *N = 30*	**Values** *P<*
Treatment before admission *Days; mean ± SD*	6.23 ± 1.16	3.07 ± 1.07	0.05
Complications *N (%)*	10 (36)	1 (3)	0.01
PRISM *Points; mean ± SD*	20.73 ± 2.25	12.06 ± 1.14	0.01
LIS *Points; mean ± SD*	2.57 ± 0.38	1.35 ± 0.17	0.01
PaO_2/FiO_2 *Torr; mean ± SD*	196.60 ± 53.43	285.78 ± 50.33	0.01
MAP *mmHg; mean ± SD*	58.81 ± 7.22	64.17 ± 7.64	NS

Risk factors in group A represented the seven times low age, six times congenital heart defect with left-to-right shunt, seven times bronchopulmonary dysplasia premature and twice children with a genetic abnormality defect and hypoxic encephalopathy. Group B had only a potential risks, such as the five families of smokers and three families with low socio-economic standard.

Life-threatening complications in Group A consisted of seven times more acute respiratory distress syndrome with the multiple organ dysfunction syndromes, six times more unilateral fluidothorax, and one exudative pericarditis. Group B had only one parainfectious fluidothorax.

Transthoracic echocardiography at 6-month girl with exudative pericarditis cased by RSV infection is shown in (Fig. 1).

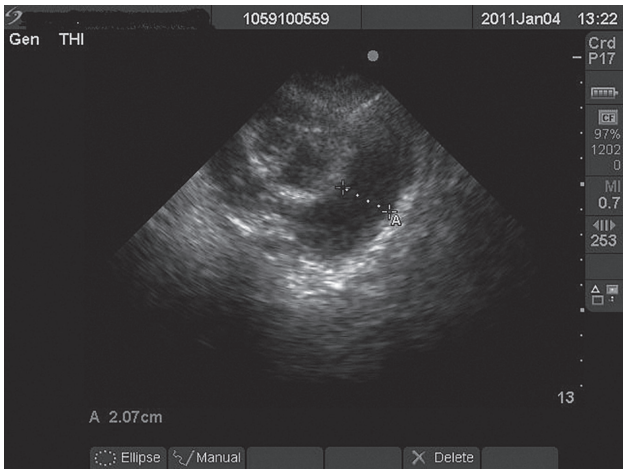

Fig. 1 Cardiac tamponade with exudative pericarditis

On the left, echocardiography view in the left parasternal short axis. At admission the patient‘s heart sections were compressed an extensive pericardial fluid collection. Re: significant cardiac tamponade.

The study had data on 1392 ventilation parameters. Comparison of input data of ventilation parameters in both groups are shown in (Tab. 2).

Tab. 2 Differences input data of ventilation parameters between groups

Parameters	**Group A**	**Group B**	**Values P<**
$AaDO_2$	16.74 ± 5.11	12.21 ± 4.70	0.05
a/ADO_2	0.64 (0.41 to 0.99)	0.52 (0.23 to 0.54)	0.05
OI	15.14 ± 1.44	11.24 ± 1.14	0.05
PaO_2/FiO_2	203.42 ± 75.73	297.17 ± 52.22	0.01
VI	49.64 ± 19.30	30.189 ± 11.32	0.01
V_D/V_T	51.16 ± 9.04	33.52 ± 7.78	0.01
C_{dyn}	27.92 ± 3.13	36.35 ± 2.07	0.001
R_{awe}	1.86 ± 0.91	1.04 ± 0.34	0.05

Changes in ventilation parameters at time-2 were not significant for either group, but the difference in dates of the groups remained the same. The insignificant, but expected, increasing hypoxic ratio and decrease in oxygenation index were at time-3 in both groups. However, some differences in the groups persisted, as higher VI (26.64 ± 13.06 vs. 20.75 ± 8.47; $P < 0.05$), V_D/V_T (29.14 ± 8.55 vs. 23.81 ± 5.80; $P < 0.05$), R_{awe} (1.22 ± 0.81 vs. 0.77 ± 0.16; $P < 0.05$) in group A compared with group B. Differences in other parameters were not statistically significant.

The study obtained data on 3132 the right ventricle and the same number of data from the left ventricle. No significant difference in load of the left ventricle existed in the groups. At time-1, higher mean values of PVR (2802 ± 193 vs. 1065 ± 155 dyn.sec/cm^5; $P < 0.01$) were found in both groups compared with reference values. Tab. 3 and Tab. 4 document the development of the preload stroke volume, myocardial contractility, stroke work, afterload, and cardiac output of the right ventricle during the study period for each group.

Tab. 3 Overview of right ventricular hemodynamic data obtained in Group A

Parameters	**TIME-1**	**TIME-2**	**TIME-3**	**Values P<**
CVP	7.06 ± 1.58	6.72 ± 1.94	7.32 ± 3.44	NS
SV_{RV}	5.42 ± 1.59	7.78 ± 1.25	9.07 ± 0.96	0.05
Vpk_{RV}	0.56 ± 0.19	0.73 ± 0.20	1.12 ± 0.25	0.05
PVR	2667.52 ± 456.57	2030.15 ± 417.30	1715.38 ± 507.03	0.01
SW_{RV}	67.85 ± 4.51	57.72 ± 2.20	51.33 ± 3.74	0.05
CO_{RV}	1.04 ± 0.03	1.67 ± 0.06	2.23 ± 0.12	0.05
CI_{RV}	2.11 ± 0.17	3.20 ± 0.12	3.87 ± 0.20	0.05

Tab. 4 Overview of right ventricular hemodynamic data obtained in Group B

Parameters	**TIME-1**	**TIME-2**	**TIME-3**	*Values P<*
CVP	6.87 ± 1.06	7.27 ± 2.11	7.35 ± 3.08	NS
SV_{RV}	5.68 ± 2.60	7.16 ± 1.32	9.43 ± 1.06	0.05
Vpk_{RV}	0.74 ± 0.28	0.82 ± 0.31	1.09 ± 0.14	0.05
PVR	2052.07 ± 506.15	1974.05 ± 431.19	1484.72 ± 338.67	0.05
SW_{RV}	52.04 ± 2.01	50.77 ± 4.03	49.23 ± 3.97	NS
CO_{RV}	1.93 ± 0.09	2.04 ± 0.11	2.34 ± 0.10	0.05
CI_{RV}	2.87 ± 0.22	3.85 ± 0.17	4.07 ± 0.19	0.05

Legend to Tab. 3 and Tab. 4: SW, stroke work (mJ); Vpk, peak velocity of flow (ml/s); Vti, velocity time integral (cm); PVR, pulmonary vascular resistance (dyn.sec/cm^5); PVRI, pulmonary vascular resistance index (dyn.sec/cm^5/m^2); CO, cardiac output (l/min.); CI, cardiac index (l/min/m^2); CPO, cardiac power output (W); CVP, central venous pressure (mmHg). All data are presented as mean ± standard deviation.

Tab. 5 presents a comparison of right ventricular hemodynamics data between groups at time intervals of the study.

Tab. 5 Comparison of data between groups A and B

Parameters	**TIME-1** *Values P<*	**TIME-2** *Values P<*	**TIME-3** *Values P<*
CVP	NS	NS	NS
SV_{RV}	NS	NS	NS
Vpk_{RV}	0.05	NS	NS
PVR	0.05	NS	0.05
SW_{RV}	0.05	NS	NS
CO_{RV}	0.05	0.01	NS
CI_{RV}	0.05	0.05	NS

Tab. 6 presents the characteristics of the study population during hospitalization.

The mean duration of ventilation time was 7.8 ± 1.18 days with a 1.7% real mortality rate of the file study.

Tab. 6 Characteristics of the study population during hospitalization

Characteristics	**Group A** *N = 28*	**Group B** *N = 30*	*Values P<*
Non-conventional ventilation *N (%)*	23 (82)	7 (23)	0.01
Associated bacterial infection *N (%)*	7 (25)	6 (20)	NS
Associated viral infection *N (%)*	5 (18)	7 (23)	NS

Characteristics	**Group A** *N = 28*	**Group B** *N = 30*	*Values* *P<*
Ventilation time *Days; mean ± SD*	8.45 ± 2.06	5.75 ± 1.82	0.05
Deaths during hospitalization *N (%)*	1 (3.6)	0 (0)	0.05
Total duration of hospitalization *Days; mean ± SD*	14.0 ± 2.66	8.5 ± 1.74	0.05

DISCUSSION

The microbiological characteristics of RSV infection, pathogenesis, and diagnosis options are well known. Human RSV is classified in the family *Paramyxoviridae*, subfamily *Pneumovirinae*. It occurs in two subtypes with multiple polymorphisms. The genome of a single coil of viral RNA is composed of 11 structural proteins and two nonstructural proteins. Structural proteins penetrate the syncytia and paralyze intercellular communication. Nonstructural proteins inhibit interferon IFN-1 synthesis. High invasiveness and immunosuppressive activity are typical features of human RSV. Droplet transmission of an RSV infection usually occurs seasonally. During the 2- to 7-day asymptomatic incubation period, the RSV replicates and floods all the respiratory tract mucosa. The infected mucosa with cytolysis, necrosis, and loss of cilia are potent stimulators of the body's immune system. The local inflammatory response leads to the activation of macrophages, the release of the pro-inflammatory mediators, and the formation of specific IgE antibodies. The result of these processes is a progressive obliteration lower airway, increasing dynamic resistance (13–15).

In the present study, acute bronchiolitis was diagnosed based on the typical clinical presentation and confirmation of an active RSV infection. Microbiological analysis of tracheal aspirate confirmed an active RSV infection in all enrolled patients. In accordance with recent literature data, we observed, in the study, that children with acute RSV bronchiolitis responded or did not respond well to acute bronchodilators or anti-inflammatory treatment (16–18)]. Many studies recommended ribavirin, RSV immunoglobulin, and palivizumab for emergency therapy of RSV infection (19–21). At the conclusion of this study, we cannot fully agree. In the high-risk group was greater number of children with immunoprophylaxis, paradoxically, the more numerous complications and significantly severe respiratory failure and especially right ventricular overload. We believe that hypercapnic respiratory failure or complications of the RSV infection come many days after RSV virus incubation, when immunoprophylaxis or antiviral treatment was not effective. For these reasons, antiviral therapy and immunological prophylaxis were not included in the treatment of acute conditions in this study. The main problem of the acute phase of the disease is that immunoprophylaxis or antiviral treatment could not handle progressive obstruction of lower airways. The severity of pulmonary lesion in the high-risk group shows that it was necessary to use unconventional ventilation to stabilize lung function in 82% of the subjects. Early conversion of conventional to nonconventional ventilation contributed to optimizing

lung function and reducing overload in the right ventricle. Many high-quality studies addressed in detail the need for urgent treatment of an RSV infection, but did not emphasize the issue of blood circulation (22–24). Our study demonstrates a direct correlation between the severity of pulmonary lesion and right ventricular overload. The pulmonary vascular bed of premature, chronic lung diseases or congenital heart defects with a left-to-right shunt or hypoxemic children rapidly react by increasing pulmonary vascular resistance. The higher pulmonary vascular resistance is related to the development of pulmonary and extra-pulmonary complications, including adverse effects on blood circulation. The blood circulation of children with hypercapnic respiratory failure is not preload dependent, as is true for most critically ill patients. It depends exclusively on right ventricle afterload. The contribution of this study is that we find that effective treatment of hypercapnic respiratory failure requires parallel modifications of ventilation and blood circulation. Myocardial performance was monitored and evaluated using the recommendations of professional societies only noninvasive, i.e., by ultrasound with the continuous Doppler wave (24–29). In this study, when they were admitted to the PICU, both groups of patients had signs of severe respiratory failure because of high dynamic airway resistance and right-ventricular overload. The results confirm that comprehensive therapy with individual modification of ventilation and pulmonary hemodynamics resulted in a decrease in airway resistance to improve ventilation in 48 hours. The authors are aware that echocardiography during mechanical ventilation has limitations related to methodology, parameter selection, and investigator experience. Choosing the optimal axis of the Doppler probe may be a limitation of the investigator, depending on his experience. These limitations do not detract from the importance of cardiac output and other hemodynamic parameters as noninvasive, easily obtainable, and reproducible tools for the assessment of cardiac load in clinical intensive care. Based on our experience and the experience of others, serial measurements of these indices are likely to be a valuable tool in the close monitoring of hemodynamics in critically ill patients (30). The study demonstrated that the data from the separate monitoring of hemodynamics were easily interpretable. A high pulmonary vascular resistance increased right ventricle afterload. Increased end-diastolic volume of the right ventricle activates neurohumoral regulation. Higher concentrations of the endogenous catecholamine in the myocardium of the right ventricle supported the inotropes activity of the myocardium (Vpk), contributed to an increase in stroke work (SW), and stabilized the decline of right ventricular cardiac output (CO_{RV}, CI_{RV}). By adequate saturation of endogenous catecholamine, the myocardium did not require a further increase in inotropes. By reducing the right-ventricular overload, selective and non-selective vasodilatation stabilized cardiac output (32–35). The aim of the study was met. Easily available information and its correct interpretation have contributed to the successful treatment of patients in critical care.

CONCLUSIONS

The course of hypercapnic respiratory failure was complicated by the adverse change in pulmonary haemodynamics. Right ventricular afterload increased, depending on the

duration of the hypoventilation. To handle blood circulation safely, up to date and easily evaluable hemodynamic information are required. Reliable control of pulmonary haemodynamics and management of complications in therapy provide the noninvasive hemodynamic monitoring.

SUMMARY

The aim of the study was to evaluate the cotribution of monitoring hemodynamics for therapy optimization. Included in the study were 58 children (age of 1.57 ± 1.13 years). The children were divided into two groups according to the severity of respiratory failure. Group A (n = 28) included patients with risks and with LIS ≥ 1.5 points; PRISM ≥ 20 points. Group B (n = 30) included children without risks and with LIS values from 1.0 to 1.4 points; PRISM values from 10 to 19 points. Hemodynamics was measured using an ultrasound cardiac output monitor. Data were collected one hour after initiation (time-1), and after 24 hours and 48 hours (time-2, 3) of treatment. At time-1, there was higher right ventricular afterload in Group A ($p < 0.05$) compared to that of group B. At intervals of time-2, 3, there was decreased right ventricular overload in both groups. Mean ventilation time in the study was 7.8 ± 1.18 days with a 1.7% real mortality rate.

Conclusion: Hemodynamic monitoring provides real-time relevant information for individualizing and optimizing the treatment of critically ill patients.

Hemodynamické změny u dětí s hyperkapnickým respiračním selháním v průběhu RSV infekce

SOUHRN

Cílem studie bylo vyhodnotit přínos monitorace hemodynamiky pro optimalizaci léčby. Do studie bylo zařazeno celkem 58 dětí (průměrný věk 1,57 ± 1,13 roku). Děti byly rozděleny do dvou skupin podle závažnosti respiračního selhání a rizika komplikací. Ve skupině A (n = 28) byly děti s vysokým rizikem komplikací, LIS skóre ≥1,5 bodů a PRISM ≥20 bodů. Do skupiny B (n = 30) byly zařazeny děti bez rizika s LIS skóre mezi 1,0–1,4 body a PRISM od 10 do 19 bodů. Hemodynamika byla monitorována a měřena metodikou USCOM (ultrasound cardiac output monitor). Data byla získávána hodinu po zahájení ventilace (čas-1) a po 24 a 48 hodinách (čas-3, 3) léčby. V čase-1 bylo vyšší dotížení pravé komory ve skupině A ($p < 0,05$) v porovnání se skupinou B. V dalším průběhu (čase-2, 3) pozvolna klesala tlaková zátěž pravé komory v obou skupinách. Průměrná doba ventilace dětí ve studii byla 7,8 ± 1,18 dne, reálná mortalita 1,7 %.

Závěry: Hemodynamická monitorace v reálném čase přinesla relevantní informace pro individualizaci a optimalizaci léčby kriticky nemocných pacientů.

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ABBREVIATIONS

PICU – Pediatric Intensive Care Unit
RSV – Respiratory Syncytial Virus
PRISM – pediatric Predicted Risk Index Scoring of Mortality
LIS – Lung Injury Score
CVP – mean central venous pressure (mmHg)
SV_{RV} – right ventricle stroke volume (ml)
Vpk_{RV} – right ventricle peak velocity of flow (m/s)
PVR – pulmonary vascular resistance (dyn.sec/cm^5)
SW_{RV} – right ventricle stroke work (mJ)
CO_{RV} – right ventricle cardiac output (l/min.)
CI_{RV} – right ventricle cardiac index (l/min/m^2)

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