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■ Original Article ■

Effectiveness of Bradycardia as a Single Parameter in the Pediatric Acute Response System

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Background: Various tools for the acute response system (ARS) predict and prevent acute deterioration in pediatric patients. However, detailed criteria have not been clarified. Thus we evaluated the effectiveness of bradycardia as a single parameter in pediatric ARS.
Methods: This retrospective study included patients who had visited a tertiary care children's hospital from January 2012 to June 2013, in whom ARS was activated because of bradycardia. Patient's medical records were reviewed for clinical characteristics, cardiologic evaluations, and reversible causes that affect heart rate.
Results: Of 271 cases, 261 (96%) had ARS activation by bradycardia alone with favorable outcomes. Evaluations and interventions were performed in 165 (64.5%) and 13 cases (6.6%) respectively. All patients in whom ARS was activated owing to bradycardia and another criteria underwent evaluation, unlike those with bradycardia alone (100.0% vs. 63.2%, $p = 0.016$). Electrocardiograms were evaluated in 233 (86%) cases: arrhythmias were due to borderline QT prolongation and atrioventricular block (1^{st} and 2^{nd}-degree) in 25 cases (9.2%). Bradycardia-related causes were reversible in 202 patients (74.5%). Specific causes were different in departments at admission. Patients admitted to the hemato-oncology department required ARS activation during the night (69.3%, $p = 0.03$), those to the endocrinology department required ARS activation because of medication (72.4%, $p < 0.001$), and those to the gastroenterology department had low body mass indexes (32%, $p = 0.01$).
Conclusions: Using bradycardia alone in pediatric ARS is not useful, because of its low specificity and poor predictive ability for deterioration. However, bradycardia can be applied to ARS concurrently with other parameters.

Key Words: bradycardia; heart arrest; hospital rapid response team; pediatrics; retrospective studies; tertiary healthcare.

Introduction

In children, cardiopulmonary arrest resulting from respiratory arrest or circulatory shock (i.e., asphyxia arrest) is more common than that resulting from primary cardiac causes.[1] These patients often present with signs of physiologic deterioration within a few hours before cardiopulmonary arrest occurs.[2] Therefore, many hospitals have implemented an acute response system (ARS) with the aim of reducing adverse events such as unexpected arrest and unplanned admission to pediatric intensive care unit (PICU) through early detection of warning signs and preemptive management.

Since the introduction of a pediatric ARS, several tools have been developed, based on different criteria such as age-related parameters, subjectivity or objectivity, and whether the number of system triggers. Of these tools, the ARS in our hospital, based on Tibballs's tool,[3] was launched in January 2010. It was not difficult to implement because it uses simple criteria. Conversely, the ARS has been frequently initiated in unnecessary situations likely because of its low positive predictive value, as has been indicated in previous studies.[4,5] It is presumed that these findings may mainly be related to bradycardia using this tool. However, the

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usefulness of each criterion, especially bradycardia, has not yet been fully clarified in terms of a pediatric ARS.

The present study attempted to analyze the characteristics of patients in the ARS was activated because of bradycardia through outcomes, the results of cardiologic evaluations, and reversible causes of bradycardia. The aim of our study was to evaluate the effectiveness of bradycardia as a single parameter in the ARS.

Materials and Methods

1) Participants

This study retrospectively reviewed patients in whom ARS was activated because of bradycardia at a 311-bed tertiary care children's hospital from January 2012 to June 2013. We excluded patients with cardiopulmonary arrest or a heart rate < 60 beats/min accompanied by poor perfusion despite oxygenation or ventilation, when ARS team was notified. The cause of exclusion was need for cardiopulmonary resuscitation instead of ARS intervention as part of the Pediatric Advanced Life Support (PALS) algorithm.[6]

2) Acute response system operation

At our hospital, the ARS was piloted in one ward from October 2010 to February 2011 after modification of Tibball's tool (Table 1). Thereafter, the ARS was used in all wards, except the PICU, neonatal intensive care unit, and emergency room. The ARS team was comprised of PICU attending physicians, PICU fellow and senior pediatric residents. One of these individuals was responsible for the ARS 24 hours per day and 7 days per week.

When patient met any of the calling criteria, the ARS was activated, and a warning message was automatically sent to a dedicated cellular phone for the ARS team. Once the ARS was activated, the team was expected to examine the patient, discuss management, including therapeutic interventions, with the primary physician, and determine the optimal location for patient care.

3) Data collection

We reviewed patients' medical records and collected their clinical variables including age, sex, diagnosis, department of admission, the ARS criteria activated, underlying cardiologic diseases, the lowest heart rate, height, and body weight. Department of admission was classified depending on the patients' current problem, regardless of the underlying diseases. We evaluated the presence of congenital heart disease, arrhythmia, and heart dysfunction. The lowest heart rate ever seen during admission was expressed as an age-dependent percentile according to the chart that Christopher and colleagues reported for hospitalized children.[7] In addition, interventions after the ARS activation were reviewed. Each evaluation included the physician's examination, blood test, 12-lead electrocardiogram (ECG), echocardiography, and 24 h ECG. Interventions included actions that were conducted exclusively on the doctor's orders. The clinical outcomes were recorded as a planned admission to the PICU or as adverse events such as an unplanned admission to the PICU, cardiopulmonary arrest, or death within 24 hours after ARS activation. We also analyzed the results of the ECG, echocardiography, and 24 h ECG within 1 month before the ARS activation to identify any hidden cardiologic diseases. The reports of the ECGs were double checked by a physician. Additionally, the extrinsic causes of bradycardia, ARS activation time, body temperature, electrolytes in the blood, body mass index (BMI), and medications were evaluated.[8] BMI was expressed as a percentile by using the reference of weight for the height of a child < 2 years old and the Korean national pediatric BMI chart of a child > 2 years old.[9] Medications that may have caused bradycardia were also examined (e.g., beta blocker, calcium channel blocker, digoxin, and clonidine).

Bradycardia was defined as a heart rate under the age-dependent ARS criterion. Each newly hospitalized patient was counted. According to Bazett's formula, the normal corrected QT interval was defined as ≤ 0.47s in the first month of life, ≤0.45s in the first 6 months of life, and ≤0.44s in children 6 months and older.[10] Night ARS activation was defined from 10:00 PM to

Table 1. Criteria for activation of the acute response system

Age	Heart rate (beats/min)	Respiratory rate (/min)	Systolic BP (mmHg)	SpO_2 (%)	Decreased perfusion	Mental change	Urine output (mL/kg/hr)
< 3 mon	< 100 or > 180	< 25 or > 60	< 50				< 1
4-24 mon	< 100 or > 180	< 20 or > 50	< 60				< 1
2-4 yr	< 90 or > 150	< 15 or > 40	< 70	< 90	Yes	changed	< 0.5
5-10 yr	< 80 or > 140	< 15 or > 35	< 80				< 0.5
> 10 yr	< 60 or > 130	< 12 or > 30	< 90				< 400 mL/d

BP: blood pressure; SpO_2: pulse oxygen saturation.

9:00 AM, considering that in this time period, patients mainly slept. Hypothermia and low body temperature were defined as < 35℃ and 36℃ as the axillary temperature, respectively. Hypokalemia and hyperkalemia were defined as the serum potassium level < 2.5 mEq/L and > 6.0 mEq/L, respectively; hypocalcemia was the serum total calcium < 8.4 mg/dl or ionized calcium < 4.75 mg/dl; and hypercalcemia was the serum total calcium > 10.2 mg/dl. Normal ventricular systolic function meant that the ejection fraction was 56-78%, and heart dysfunction was defined when the ejection fraction was < 55%.[11,12]

This study was approved by the Institutional Review Board and informed consent was waived (IRB number: 1407-009-591).

4) Statistical analysis

Categorical and continuous variables are expressed as numbers and percentages, and medians and ranges, respectively. The differences in the ARS activation criteria and department of admission were analyzed using the Pearson χ^2 test and Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) analysis was performed to study the maximum sensitivity and specificity of bradycardia, as a single parameter. ROC curve was investigated through the relation between the number of evaluation and treatments, when ARS was activated by bradycardia alone. The area under the curve (AUC) was used as a measure of the overall performance of the ROC curve, as reflected. All statistical analyses were performed using SPSS, version 21.0 (IBM SPSS Statistics, Armonk, NY, USA). A p value < 0.05 was considered statistically significant.

Results

1) General characteristics of the patients

There were 976 cases with any criteria managed by the ARS activation. Among these, the ARS because of bradycardia was activated in 271 cases. The mean age was 6.7 years old (range, 0-24 years old), and 165 cases (60.9%) were male. Cases from hemato-oncology, endocrinology, and gastroenterology departments were the most common (55.4%, 10.7%, and 9.2%, respectively). Thirty cases (11.1%) had cardiologic diseases regardless of their current problem. Patients in whom the ARS was activated because of bradycardia alone accounted for 96.3% of cases, while those in whom ARS was activated owing to bradycardia and more than one other criterion accounted for 3.7%. Criteria that accompanied bradycardia were low blood pressure, decreased saturation, and mental change (Table 2). The lowest heart rate in 86% of cases (233/271 patients) was under the fifth percentile for the age reference.

Table 2. The clinical characteristics of the patients

Characteristic	Values n (%)
Bradycardia for ARS activation, n	271
Age, yr	6.8 (0.1-24.1)
Male sex, n (%)	165 (60.9)
Department of admission, n (%)	
Hemato-oncology	150 (55.4)
Endocrinology	29 (10.7)
Gastroenterology	25 (9.2)
Nephrology	14 (5.2)
Cardiology	12 (4.4)
Infection	12 (4.4)
Pulmonology	11 (4.1)
Neurology	8 (3.0)
Others	9 (3.3)
Underlying cardiologic disease, n (%)	30 (11.1)
Congenital heart disease	23 (8.5)
Arrhythmia*	5 (1.8)
Secondary heart disease	2 (0.7)
Activated ARS criteria, n (%)	
Bradycardia	261 (96.3)
Bradycardia, Low BP	6 (2.2)
Bradycardia, Low SpO2	3 (1.1)
Bradycardia, Mental change	1 (0.4)
The lowest heart rate Percentiles as age	
10-≤50th	10 (3.7)
5-≤10th	28 (10.3)
≤5th	233 (86)

*Arrythmia with pacemaker (1). ARS: acute response system; BP: blood pressure; SpO_2: pulse oxygen saturation.

Table 3. Intervention after the activation of the acute response system according to the activated criteria

Intervention	Bradycardia alone, n (%)	Bradycardia with other criteria, n (%)	p value
None	86 (32.9)	0	0.028
Evaluation	165 (63.2)	10 (100)	0.016
Treatment	23 (8.8)	5 (50)	0.001
Electrolyte correction	5	0	
Medication adjustment	2	0	
Warming	2	1	
Fluid supply	13	3	
Flumazenil infusion	1	0	
Bag-mask ventilation	0	1	

Of 271 cases, one case had a planned PICU admission within 24 hours after the ARS activation for continuous renal replacement therapy, which resulted from volume overload. However, there was no adverse event in any other cases.

2) Intervention after the acute response system activation

The ARS team conducted evaluations and various interventions in 175 (64.5%) and 28 cases (10.3%), respectively neither evaluation nor intervention was performed in 86 cases (31.7%). Compared to patients who fulfilled the bradycardia parameter alone, patients in whom ARS was activated owing to bradycardia and one additional criterion were all evaluated (63.2% vs. 100.0%, p = 0.016). Interventions were performed in half of the patients of the latter group (5 cases, 50%), and in 4 of those cases, interventions were performed to improve hypotension and desaturation (i.e., fluid supply and bag-mask ventilation), not bradycardia (Table 3).

For patients with bradycardia alone, ROC analysis demonstrated unacceptable system performance (AUC 0.51, 95% CI 0.363-0.639). The maximum values of sensitivity and specificity, derived from the ROC analysis, were 56.5% and 36%, respectively.

Table 4. The results of cardiologic evaluations 1 month before the acute response system activation

Cardiologic evaluation	Values (%)
Electrocardiogram	233 (86.0)
Sinus rhythm*	208 (76.7)
Borderline prolonged QT	22 (8.1)
1ST and 2nd-degree AV block	3 (1.1)
Echocardiography	128 (54.9)
Normal heart function	115 (42.4)
Decreased heart function	1 (0.4)
24 h electrocardiogram	34 (12.5)
Sinus bradycardia	32 (11.8)
PVC couplet, bigeminy	2 (0.7)
RR interval	1.46 (0.98-2.46)

*Includes sinus tachycardia, normal sinus rhythm, and sinus bradycardia. AV: atrio-ventricular; PVC: premature ventricular contraction.

3) Results of the cardiologic evaluations

We analyzed the findings of ECG, echocardiography, and 24 hours ECG in 233 (86%), 128 (54.9%), and 34 cases (12.5%), respectively. The arrhythmias identified by the ECGs were borderline prolonged QT in 22 (8.1%) and atrioventricular (AV) block in 3 cases (1.1%). Of 3 cases, one was a Morbitz type I second-degree AV block, pre-determined because of underlying heart disease; the remaining cases were first-degree AV blocks. Only 1 patient of the 128 cases evaluated by echocardiography showed a new heart dysfunction. The 24 hours ECG reported abnormal findings in 2 cases (0.7%); there was couplet or bigeminy premature ventricular contraction (PVC) in 26% and 8% of total heart beats (Table 4), while others reported sinus rhythm or PVC in 1%.

4) Reversible causes of bradycardia

Two hundred and two patients (74.5%) had more than one reversible cause of bradycardia. In 169 patients (62.4%), the ARS was activated at night. Bradycardia in 36 patients (13.3%) was related to the administration of certain medications such as beta blockers, calcium channel blockers, digoxin or clonidine. Although hypothermia was not observed in anyone, 10% had a low body temperature. There were 42 patients (15.5%) with a low BMI under the fifth percentile, and 5 (1.8%) had an electrolyte imbalance, such as hypokalemia, hyperkalemia, hypocalcemia, or hypercalcemia (Table 5).

Patients in the departments of hemato-oncology, endocrinology, and gastroenterology, which were the most common departments at admission, had more reversible causes than those from other departments, but there was no statistical significance (74% vs. 86.2% vs. 84% vs. 67.2%, respectively; p = 0.158). Nevertheless, the detailed causes of bradycardia differed in each department. In the patients from the hemato-oncology department, ARS was more commonly activated at night (69.3% vs. 34.5% vs. 76% vs. 58.5%, respectively; p = 0.003). Bradycardia was more commonly related to medications in endocrinology department patients (4.7% vs. 72.4% vs. 8% vs. 9%, respectively;

Table 5. Possible reversible causes of bradycardia according to the department of admission

	All (n = 271)	HO (n = 150)	Endocrinology (n = 29)	GI (n = 25)	Others (n = 67)	p value
All causes	202 (74.5)	111 (74.0)	25 (86.2)	21 (84.0)	45 (67.2)	0.158
ARS Activation at night	169 (62.4)	104 (69.3)	10 (34.5)	19 (76)	24 (58.5)	0.003
Low BMI (< 5 percentile)	42 (15.5)	15 (10)	2 (6.9)	8 (32)	17 (25.4)	0.001
Medication	36 (13.3)	7 (4.7)	21 (72.4)	2 (8.0)	6 (9)	< 0.001
Low body temperature*	27 (10.0)	14 (9.3)	2 (6.9)	5 (20)	6 (9)	0.038
Electrolyte imbalance	5 (1.8)	3 (2)	0	0	1 (2.4)	0.622

*< 36℃. HO: hemato-oncology; GI: gastroenterology; ARS: acute response system; BMI: body mass index.

$p < 0.001$). In gastroenterology department patients, bradycardia was more commonly related with a low BMI under the fifth percentile (10% vs. 6.9% vs. 32% vs. 25.4%, respectively; $p = 0.001$).

Discussion

In this study designed to evaluate the effectiveness of bradycardia as a single parameter in pediatric ARS, 27.8% of the ARS activations were accompanied owing to bradycardia, and in most, the activations were due to bradycardia alone. The analysis of the 271 cases of ARS activation with bradycardia indicated that bradycardia was more related with reversible than intrinsic, cardiac causes. In addition, although there were some interventions in a few cases, all of them showed favorable outcomes for bradycardia. It is assumed that bradycardia alone is a temporary finding or that it does not require any intervention. Therefore, we can speculate that bradycardia alone is not an appropriate single parameter for the activation of ARS because of its low positive predictive value.

According to one systematic review, 10 tools have been reported for the pediatric ARS between January 1990 and February 2009.[13] Seven of the tools were triggered because of a single parameter, and the remaining were initiated using a weighted aggregate system. Five of the 10 tools were composed of age-dependent and objective criteria: heart rate, pulse rate, blood pressure, oxygen saturation, and mental status. In particular, the single-parameter system of the Royal Children's Hospital, developed by Tibball and colleagues, consisted of seven objective and three subjective findings.[3] Bradycardia was distinctly presented as a single criterion. In addition, this tool was simpler than the others, and after modification, was consequently adopted by a number of hospitals, the results of which demonstrated the benefits of ARS.[14,15] However, according to previous studies, it was suggested that this single-parameter system may have a high sensitivity and low specificity.[4,5] Edwards and colleagues[5] introduced Cardiff and Vale Pediatric Early Warning System (C&VPEWS) criteria similar to that of our study, and revealed that the sensitivity and specificity were 89.02% and 63.89%, respectively, when activated by a single abnormal parameter. In our study, the analysis of the patient, activated by ARS with bradycardia alone, showed both lower sensitivity and specificity, compared with the previous study. Furthermore, considering that maximum AUC was 0.51 for such patients, it could be difficult to separately apply for the bradycardia criterion to the screening system.

Through studies on pediatric cardiopulmonary arrest cases, the most common precipitating causes of cardiac arrest are respiratory failure and shock in hospitalized children.[16,17] Initially, patients who suffer from respiratory failure or circulatory shock usually present with tachycardia, tachypnea, increasing work of breathing, or decreased urine output as a mechanism of compensation. Then, they progress to asystole or pulseless electrical activity due to decreased cardiac output.[6] Since bradycardia is commonly a terminal result of progressive tissue hypoxia and acidosis in deteriorating children, it is not solely observed but is associated with any sign of hypoperfusion.[1,17]. In our study, bradycardia with hypotension or hypoxemia was intervened, while there were no deteriorating cases activated owing to bradycardia alone. Therefore, bradycardia without any symptoms or signs has a lesser meaning in the criteria for ARS activation.

Bradycardia in children is less common than in adults. Nevertheless, healthy children can show bradycardia incidentally, regardless of cardiopulmonary arrest. In a retrospective review of 67,375 ECGs performed in asymptomatic patients < 25 years old, up to 35% had sinus bradycardia at rest.[18] The results of our study showed that there was an incidence of bradycardia in about 30% of all ARS cases. It is suggested that because of close monitoring, bradycardia is more often observed in hospitalized children. According to a study in Taiwan on a healthy population, severe bradycardia < 30-40/min was found in 0.025% of 400,000 cases and resulted in no life-threatening conditions.[19] Healthy children with bradycardia are expected to have favorable outcomes; however, there is a limit for hospitalized children. In our study, 36 patients (11.6%) had underlying heart disease that could cause arrhythmia, related to bradycardia. Only one patient revealed a pre-determined Mobitz type I secondary-AV block. Thus there were no significant differences in evaluation, management, reversible causes, or outcome between patients with or without heart disease. Throughout this study, regardless of underlying disease, there were no adverse outcomes in the patients who activated the ARS with bradycardia but underwent no interventions; thus, the outcomes of hospitalized children only with bradycardia may be similar to that of healthy children.

Bradycardia can lead to severe complications, so physicians should discriminate whether the case requires intervention. Bradycardia occurs under extrinsic causes with reversibility as well as intrinsic cardiologic causes. The heart rate lowers due to conditions such as a hypervagotonia state, medications, hypothyroidism, hypothermia, increased intracranial pressure, or an electrolyte imbalance.[8] Patients with bradycardia can be studied with ECG to evaluate possible cardiologic diseases. In addition, history taking and basic physical examinations should be performed to define precipitating factors. In our study, arrhythmia associated with bradycardia was found in 25 cases, but no case was treated with pacemaker insertion or with other interventions by a cardiologist. However, endocrinology department patients with bradycardia caused by clonidine required an additional fluid supply if they had simultaneous hypotension. In the gastroenterology department, numerous patients had anorexia nervosa or poor oral intake, which led to a low BMI and bradycardia. Some patients in the hemato-oncology department showed bradycardia during the night, which was associated with sleep. None of them received any intervention. A few cases received electrolyte correction, because the electrolyte imbalance was found through the blood test. Our study was conducted at a tertiary care hospital where most of the patient suffered from intensive problems, requiring the administration of various medications. An electrolyte imbalance caused by a disease process, medications, or poor nutrition was also commonly observed. Hence, we assume that the reversible causes were found in a great number of cases. Ultimately, physicians should suspect preceding causes of bradycardia in hospitalized children, and further management should be determined based on that suspicion.

A recent study found the high false-positive rate when bradycardia was considered as a parameter in the ARS, as a new perspective.[7] The heart rate of hospitalized children was characterized as a broad range, that is, there were more cases of tachycardia and bradycardia than in healthy children out of the hospital. The authors proposed that a standard limit for heart rate in ARS criteria should be re-established for in-patients. On the basis of a heart rate limit for in-patient, a higher specificity in pediatric ARS would be expected. However, further studies should be performed to determine which level of heart rate is adequate for ARS activation. Several findings on the implementation of pediatric ARS have been reported, and a variety of tools have been evaluated about its sensitivity and specificity. However, to the best of our knowledge, there are no other reports on the effectiveness of a detailed parameter in the pediatric ARS.

This is the first study to question whether bradycardia alone is useful. We indicated the limit of using bradycardia as a single parameter in the pediatric ARS criteria and suggested a few ways to overcome this limitation. However, this study has several limitations. We did not compare cases of bradycardia with other criteria. This retrospective study also did not clarify the causal relationship between bradycardia and its reversible causes. Lastly, this study lacks long-term outcomes because of the short follow-up time (24 hours after ARS activation).

In conclusion, bradycardia as a single parameter in pediatric ARS is not appropriate for detecting deterioration in patients or the progression of cardiopulmonary arrest. To improve the predictive value of bradycardia as an early parameter for ARS activation, it can be applied with other parameters that simultaneously activate ARS.

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