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Cardiac Function in Pediatric Septic Shock Survivors

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Objective: To evaluate the long-term effects of septic shock on cardiac function in children treated with inotropic and/or vasoconstrictive agents for 24 hours or longer.

Design: Cohort study.

Setting: Tertiary pediatric intensive care unit and outpatient follow-up clinic.

Participants: One hundred eight of 144 eligible children who were admitted to our tertiary pediatric intensive care unit with septic shock from 1995 through 2005 and were alive in 2006 were invited to participate and visit our outpatient follow-up clinic. Fifty-two healthy controls were included.

Main Exposure: Septic shock survival.

Outcome Measures: History, physical examination, electrocardiogram during rest and exercise, 24-hour electrocardiography registration, and left and right ventricular function.

Results: No children had abnormalities when histories were taken or during physical examination that were attributable to cardiac dysfunction. Six children (6%) had cardiac abnormalities: polymorphic premature ventricular contractions during exercise and 24-hour electrocardiography registration (2 patients), decreased left ventricular function (2 patients), decreased left ventricular function and polymorphic premature ventricular contractions (1 patient), and decreased right ventricular function (1 patient).

Conclusions: In this small and diverse group of pediatric septic shock survivors, we found an excellent recovery of cardiac performance in most patients. In a limited number of patients, we found rhythm disturbances and decreased ventricular function. We believe that, against the background of aging, long-term cardiac follow-up of these patients is important.

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SEPSIS IS ONE OF THE LEADING causes of death in children. Mortality ranges from 4% to 20%.[1] Septic shock is characterized by myocardial dysfunction, loss of vascular tone, and capillary leak leading to diminished organ perfusion and the development of multiple organ system failure. Myocardial dysfunction—caused by hypoperfusion, myocardial cell death, and/or cardiodepressant circulating substances, such as tumor necrosis factor α, IL-1 (interleukin 1), and nitric oxide—is a key factor in the development of circulatory failure during septic shock.[2-4] Treatment includes adequate fluid resuscitation and the administration of inotropic and/or vasoconstrictive agents.[5,6]

Mortality due to septic shock has decreased owing to advances in pediatric intensive care practices, such as improved use of inotropic and vasoconstrictive agents and early goal-directed fluid therapy.[6-8] Follow-up studies of children with septic shock have mainly focused on mortality and short-term morbidity.[9-11] Particularly in children, long-term follow-up studies may be important against the background of the development and maturation of organs. Consider, for example, respiratory distress syndrome of the prematurely born infant (idiopathic respiratory distress syndrome) and acute lung injury in older children. Both have long-term pulmonary consequences. The primary insult occurs when the lung is exposed to a damaging process (idiopathic respiratory distress syndrome or acute lung injury); the secondary insult is caused by mechanical ventilation.[12,13] In children treated with inotropic and/or vasoconstrictive agents because of septic shock, the primary insult on the myocardium may be the septic shock and the secondary insult may be treatment with these agents. This may result in permanent damage to the developing heart. The aim of this study was to evaluate the late (>6 months after pediatric intensive care unit [PICU] discharge) effects of septic shock on cardiac function in children and to analyze risk factors for cardiac abnormalities.

METHODS

The study was performed in the PICU of the Emma Children's Hospital/Academic Medical Center Amsterdam. This is a tertiary multidisciplinary PICU with 14 beds serving the greater Amsterdam area.

PARTICIPANTS

Patients were included if they had been admitted to the PICU for septic shock between 1995 and 2005, had received inotropic and/or vasoconstrictive agents for 24 hours or longer (dopamine, dobutamine, epinephrine, and/or norepinephrine), were alive in 2006, and had been followed up for longer than 6 months after PICU discharge. Exclusion criteria were preexisting cardiac disorders and serious psychomotor retardation. The hospital's institutional review board approved the study protocol, and written consent was obtained for all included patients and/or their parents.

STUDY DESIGN

Cardiac function was evaluated in our outpatient follow-up clinic by patient history, physical examination, and electrocardiogram (ECG) recorded during rest. Electrocardiogram recording during exercise was performed when the child was older than 7 years at follow-up. Twenty-four-hour ECG recording and echocardiography were performed as well.

A structured checklist was used for history taking and the physical examination. Special attention was paid to syncope, chest pain, skipped beats and heart palpitations, peripheral pulsations, liver size, edema, and heart murmurs. Exercise testing was performed in children aged 7 years and older, as summarized in the Bruce protocol (younger children cannot perform this test owing to their size and lack of adequate concentration).[14]

Echocardiography was performed to evaluate systolic function of the left and right ventricles. Systolic function of the left ventricle was determined by measuring left ventricular end-diastolic diameter (LVEDD) and shortening fraction. Shortening fraction is the percentage of change in the left ventricular cavity dimension during systole ([(LVEDD – left ventricular end-systolic dimension)/LVEDD] × 100). In many studies, left ventricular function is measured by the ejection fraction. In normally shaped left ventricles, shortening fraction and ejection fraction are comparable. We chose to report shortening fraction. In pediatric literature, normal values for systolic function of the left ventricle differ from shortening fraction by more than 28% or more than 30%.[15-18] Systolic function of the right ventricle was determined by measuring tricuspid annular plane systolic excursion (TAPSE). There are no known reference data in the pediatric literature for TAPSE. As in adult literature, a TAPSE longer than 15.0 mm is considered normal.[19] We also studied systolic cardiac function in a control group of 52 healthy children with a benign murmur. Echocardiography was performed to exclude cardiac abnormalities. Diastolic function of the left ventricle was evaluated as well and will be published separately.

During septic shock, sedation was administered when the patient needed artificial ventilation, according to our sedation protocol (morphine and midazolam). Patient characteristics at PICU admission were obtained from medical records and the patient data management system. In our PICU, it was not standard procedure to perform echocardiography to evaluate systolic function of the left ventricle or to perform an ECG during PICU admission. Echocardiography was performed when the pediatric-intensivist on duty wanted additional information on cardiac function or if one was clinically indicated. Electrocardiogram recordings were performed only when rhythm disturbances were suspected. Echocardiography to evaluate systolic function of the right ventricle was not performed.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS (SPSS Inc, Chicago, Illinois). Mann-Whitney and χ^2 tests were done to compare participants with nonparticipants and the control group with the patient group with regard to patient characteristics. The worst shortening fraction during admission was compared with shortening fraction at follow-up using paired *t* tests. Shortening fraction less than 30% and less than 28% during PICU admission and at follow-up were compared by using the Fisher exact test. A significance level of $P < .05$ was used in all tests.

To analyze risk factors for cardiac abnormalities, patients with cardiac abnormalities (rhythm disturbances, decreased left ventricular function, and/or decreased right ventricular function) were clustered because of the small number of patients. Mann-Whitney and χ^2 tests were used to compare characteristics of patients with and without cardiac abnormalities, such as sex, age at PICU admission, age at follow-up, follow-up time, risk of mortality (Pediatric Index of Mortality 2), length of ventilation, and length of PICU stay. Furthermore, nonparametric correlations were performed to test the association between cardiac abnormalities and the use of different inotropic and/or vasoconstrictive agents, and the dosage and duration of treatment with these agents. A significance level of $P < .001$ was used in these tests to compensate for multiple testing.

RESULTS

One hundred forty-four patients who were admitted to our PICU for septic shock from 1995 through 2005 and survived fulfilled the inclusion criteria. Eleven patients refused to participate and 25 patients could not be located. One hundred eight of 144 eligible patients (75%) were evaluated. No statistically significant differences were found between participants and nonparticipants, except for sex (**Table 1**). The age of PICU patients ranged from newborns (with a birth weight >2 kg) to 18 years. Median follow-up time was 6.3 years (range, 0.8-12.7 years).

The exercise test was performed in 87 of 108 patients (81%) aged 7 years or older. Twenty-four-hour ECG recording was successfully performed in 86 of 108 patients (80%). Evaluations of systolic function of the left and right ventricles were successfully performed in 105 of 108 patients (97%) and 86 of 108 patients (80%), respectively.

Medical history and physical examination revealed no abnormalities in all but 1 patient (1%). This patient complained of dyspnea while at rest and had a limited exercise capacity due to respiratory obstruction caused by an, until then, unknown tracheal stenosis, which was probably due to intubation. All patients had normal ECG results at rest and a good exercise capacity. Episodes of premature ventricular contractions (PVCs) were seen in 7 of 87 patients (8%) during and after exercise (3 patients [3.5%] had monomorphic PVCs during exercise, 3 patients (3.5%) had monomorphic PVCs during rest after exercise, and 1 patient (1%) had a series of polymorphic PVCs during exercise). In 3 of the aforementioned patients (3.5%), episodes of PVCs were seen on

Table 1. Characteristics of Study Participants and Nonparticipants

Characteristic	Median (Range)		P Value
	Participants (n=108)	Nonparticipants (n=36)	
Age at PICU admission, y	3.5 (0.0-17.9)	5.7 (0.0-16.5)	.38
Length of PICU stay, d	6.0 (1.0-64.4)	5.0 (1.0-19.0)	.29
Age at follow-up, y	9.9 (2.4-27.1)		
Follow-up time, y	6.3 (0.812.7)		
Length of artificial ventilation, d	4.0 (0.0-40.0)	2.5 (0.0-18.0)	.15
Risk of mortality, PIM 2, %	7.0 (0.3-42.9)	6.5 (1.0-21.3)	.98
Highest lactic acid, µmol/L	3.5 (0.7-23.0)	3.7 (1.1-14.4)	.67
Highest creatinine, mg/dL	0.67 (0.15-4.81)	0.66 (0.23-4.97)	.92
Worst shortening fraction during PICU admission, %[a]	27.0 (14.3-48.9)	28.7 (22.0-45.6)	.18
Female sex, No. (%)	49 (57)[b]	12 (35)	.02
Artificial ventilation, No. (%)	67 (78)	23 (68)	.12
Organism, No. (%)			
Neisseria meningitidis	77 (71)	20 (56)	.06
Other	31 (29)	16 (44)	

Abbreviations: PICU, pediatric intensive care unit; PIM, Pediatric Index of Mortality.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] Of 67 participants and 19 nonparticipants.

[b] $P < .05$, participants vs nonparticipants.

Table 2. Cardiac Abnormalities in Pediatric Septic Shock Survivors at Follow-Up

Characteristic	Patients, No. (%)
History (n=108)	1 (1)
Physical examination (n=108)	0
ECG during rest (n=108)	0
Exercise (n=87)	
Exercise capacity	0
PVCs on ECG	7 (8)
Polymorphic PVCs	1 (1)
24-h ECG (n=86)	
PVCs	3 (3)
Polymorphic PVCs	2 (2)
Sinus arrest	1 (1)
Echocardiography	
Left ventricular function (n=105)	
Shortening fraction, median (range), %	35.9 (25.0-47.2)
Shortening fraction <30%	13 (12)
Shortening fraction <28%	3 (3)
Right ventricular function (n=86)	
TAPSE, median (range), mm	20.7 (13.5-32.3)
TAPSE <15 mm	1 (1)

Abbreviations: ECG, electrocardiogram; PVCs, premature ventricular contractions; TAPSE, tricuspid annular plane systolic excursion.

the 24-hour ECG recording (polymorphic PVCs in 2 and monomorphic PVCs in 1). One patient (1%) had a sinus arrest of 2.6 seconds (**Table 2**).

The median shortening fraction at follow-up in 105 patients was 35.9% (range, 25.0%-47.2%); 13 of 105 children (12%) had a shortening fraction of less than 30%, and 3 of 105 children (3%) had a shortening fraction of less than 28%. One of the children (1%) with a shortening fraction of less than 28% had reduced left ventricular function (shortening fraction of 25%) with paradoxical movement of the intraventricular septum and a series of PVCs during exercise. This patient had a shortening fraction of 25% at PICU discharge. He is an active athlete and has no complaints (Table 2). All the other children had normal wall motion of the left ventricle.

Table 3. Longitudinal Systolic Function During PICU Admission and at Follow-up in 65 of 108 Patients

Systolic Fraction	Time of Assessment		P Value
	PICU Admission	Follow-Up	
Shortening fraction median (range), %	27.0 (14.3-48.9)	36.2 (25.0-47.2)	<.001[a]
Shortening fraction <30%, No. (%)	36 (80)	6 (9)	.21[b]
Shortening fraction <28%, No. (%)	34 (52)	2 (3)	.49[b]

Abbreviation: PICU, pediatric intensive care unit.

[a] Paired *t* test.

[b] Fisher exact test.

The median TAPSE at follow-up in 86 patients was 20.7 mm (range, 13.5-32.3 mm); 1 of 86 children (1%) had a TAPSE shorter than 15 mm. No other abnormalities at echocardiography were found (Table 2).

In 65 of 108 patients (60%), we compared shortening fraction measured during PICU admission and at follow-up (**Table 3**). During admission, the worst median shortening fraction was 27.0% (range, 14.3%-48.9%); at follow-up, the median shortening fraction was 36.2% (range, 25.0%-47.2%). A statistical difference was found between worst median shortening fraction during admission and median shortening fraction at follow-up. During admission, 36 of these 65 children (55%) had a worst shortening fraction of less than 30%; 34 (52%) of them had a worst shortening fraction of less than 28%. At follow-up, 6 of these 65 children (9%) had a shortening fraction of less than 30% and 2 children (3%) had a shortening fraction of less than 28% (Table 3). The children with a shortening fraction of less than 30% and those with a shortening fraction of less than 28% during admission were compared with children with a shortening fraction of less than 30% and those with a shortening fraction of less than 28%, respectively, at follow-up by Fisher exact test. No association was found (Table 3).

The control group of 52 healthy children consisted of 22 girls and 30 boys with a median age of 5.9 years (range, 0.8-17.3 years). The median shortening fraction was 36.2% (range, 28.1%-44.9%), and the median TAPSE was 19.9 mm (range, 16.1-31.0 mm). The median age of the control group was significantly less than that of the patient group (**Table 4**).

Cardiac abnormalities were detected in 6 patients (shortening fraction <28% in 2, shortening fraction <28% and polymorphic PVCs in 1, TAPSE <15 mm in 1, and polymorphic PVCs in 2). No statistically significant differences were found between children with and without cardiac abnormalities with respect to sex, age at PICU admission, age at follow-up, follow-up time, risk of mortality (Pediatric Index of Mortality 2), length of ventila-

Table 4. Shortening Fraction and TAPSE in Patients and 52 Healthy Children

Characteristic	Median (Range)	
	Controls (n=52)	Patients (n=108)
Female sex, No. (%)	22 (42)	49 (57)
Age, y	5.9 (0.8-17.3)	9.9 (2.4-27.1)[a]
Shortening fraction, %	36.2 (28.1-44.9)	35.9 (25.0-47.2)
TAPSE, mm	19.9 (16.1-31.0)	20.7 (13.5-32.3)

Abbreviation: TAPSE, tricuspid annular plane systolic excursion.
[a] $P < .05$, control group vs patient group.

tion, and length of PICU stay. No correlations were found between cardiac abnormalities and inotropic and/or vasoconstrictive agents used or duration of treatment with or dosage of these agents (**Table 5**).

Table 5. Characteristics of Inotropic and Vasoconstrictive Treatment of 108 Patients and Correlation Between Cardiac Abnormalities and Inotropic and Vasoconstrictive Treatment in 6 Patients

Characteristic	Median (Range)	Correlation With Cardiac Abnormalities	*P* Value
Patients undergoing treatment, No. (%)			
Dopamine	103 (95)	0.053	.58
Dobutamine	78 (72)	0.120	.21
Epinephrine	24 (22)	0.162	.09
Norepinephrine	71 (66)	0.005	.96
Duration of treatment, d			
Dopamine	3 (1-41)	0.132	.19
Dobutamine	3 (1-41)	0.312	.005
Epinephrine	2 (1-39)	0.215	.31
Norepinephrine	1 (1-41)	0.261	.03
Maximum dose, µg/kg/min			
Dopamine	20 (5-30)	0.061	.54
Dobutamine	10 (2-30)	0.114	.31
Epinephrine	0.30 (0.02-5.00)	0.001	>.99
Norepinephrine	0.20 (0.03-10.00)	0.126	.29
Total duration of inotropic and/or vasoconstrictive treatment, d	3 (1-41)	0.102	.29

COMMENT

In this study of 108 pediatric septic shock survivors, 6 children had cardiac abnormalities consisting of PVCs during exercise with 24-hour ECG registration (2 patients), decreased left ventricular function (2 patients), decreased left ventricular function and PVCs (1 patient), and decreased right ventricular function (1 patient). Surprisingly, only 1 patient had abnormalities according to medical history and physical examination. These complaints were caused by tracheal injury due to the endotracheal tube and not cardiac dysfunction.

The rhythm disturbances found in this study are difficult to interpret. Because ECG recording at PICU admission was not standard procedure, we could not compare our findings with ECG data in the acute phase. Studies of healthy ambulatory children have documented various rhythm disturbances with a range of incidences. Monomorphic PVCs are benign; polymorphic PVCs may form a risk for ventricular tachycardia and sudden cardiac death.[20-24] Only 3 children had polymorphic PVC. The incidence of rhythm disturbances in our study is probably not higher than that found in the normal population. Literature on incidences and clinical relevance of rhythm disturbances in healthy children is scarce. Additional studies in pediatric septic shock survivors and healthy control groups have to be done. Our findings, however, are reassuring and suggest excellent recovery after septic shock with inotropic and/or vasoconstrictive support.

Septicemia is associated with acute myocardial failure. In adult studies, myocardial function during septic shock is evaluated predominantly with echocardiography. In these studies, reduced ejection fraction was found in 40% to 50% of patients with septic shock. Right heart dilation and decreased right ventricular function have also been described in the acute phase. The decrease in left ventricular function was reversible with full recovery of cardiac function in 7 to 10 days.[25,26] Theoretically, it is conceivable that myocardial damage due to the inflammatory response, cell death, and apoptosis with remodeling does not repair completely and leads to impaired myocardial function.[27,28] Furthermore, shock combined with inotropic and/or vasoconstrictive agents may cause cardiovascular damage.[4,29-31] It is conceivable that children are even more at risk for tissue damage because of their still-developing organ systems.[32-34] In our study, left and right ventricular function was normal in almost all patients (only 3 patients had shortening fraction <28% and 1 patient with TAPSE <15 mm). The implications for future cardiac function in children with decreased function are unknown and need further research. Because correlations with possible risk factors were not found, the data do not support our hypothesis. However, analysis of risk factors is only possible to formulate hypotheses for future studies owing to the small number of children with abnormalities. We believe that against the background of aging, long-term cardiac follow-up of septic shock survivors and a healthy control group is important.

A number of limitations to this study should be taken into account. First, the response rate of our study was 75%. Although other follow-up studies in the PICU have had similar response rates, this could have biased our results. Second, the number of studied children is small; owing to differences in age at PICU admission and follow-up and in follow-up times, strong conclusions are difficult. Follow-up times varied between 0.8 and 12.7 years; evaluation of late effects is not possible 0.8 years after discharge and thus our results may have been biased by including patients with the shortest follow-up times. As damaging effects of septic shock may only be seen much later in life, our follow-up time may have been too short. Third, we only had a healthy control group for cardiac function. The median age of this control group was significantly younger than the median age of the study patients. The prevalences of rhythm disturbances and decreased right ventricular function in healthy children are not well documented in the literature. The median TAPSE

in our healthy controls was 19.9 mm (range, 16-31 mm). The cutoff for a normal TAPSE of 15 mm in children was possibly too low. Fourth, because this is a retrospective cohort study, it was not possible to analyze fluid at the same time echocardiography was performed. It was also not possible to evaluate the effect of other cardiodepressant medication possibly given in the acute phase. Fifth, the risk factor analysis is statistically questionable because of the small number of children with abnormalities. A prospective study with an adequate control group is necessary to analyze risk factors for cardiac damage.

CONCLUSIONS

In this small and diverse group of pediatric septic shock survivors, we found excellent recovery of cardiac performance in most patients. In a limited number of children, we found rhythm disturbances and decreased left ventricular function. We believe that long-term cardiac follow-up in these patients is important.

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