Original article

# Transient occult cardiotoxicity in children receiving continuous beta-agonist therapy

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***Background:*** **Continuous beta-agonist therapy, typically in the form of inhaled albuterol, is the first line therapy for the treatment of acute and severe bronchospasm in children. Although this treatment is commonly used, concerns about cardiotoxicity have been raised. We aimed to investigate the cardiotoxic effects of continuous beta-agonist therapy in children.**

***Methods:*** **We conducted a retrospective review of children admitted to the intensive care unit (ICU) between May 2008 and April 2009, who were treated with continuous beta-agonist therapy (intravenous and nebulized).**

***Results:*** **Twenty of the 36 children treated with continuous albuterol had repeated serum troponin-T and lactate levels measured. Eleven patients (55%) were also treated with continuous intravenous terbutaline. Elevated levels of troponin-T levels were found in 25% of children, and elevated lactate levels were found in 60%. However, all returned to normal levels within 48 hours of ICU admission, despite continued beta-agonist therapy. No children experienced arrhythmias during therapy. There was no association between intravenous terbutaline use and elevated troponin-T [odds ratio (OR), 1.3; 95% CI, 0.2-10.3] or with elevated serum lactate (OR, 0.6; 95% CI, 0.1-3.7). There was also no association between elevated troponin-T or lactate and ICU or hospital length of stay.**

***Conclusions:*** **In this small study, a significant proportion of children had elevated serum troponin-T and lactate levels while receiving inhaled continuous beta-agonist therapy, irrespective of intravenous therapy. However, these abnormal values all returned to normal within 48 hours of ICU admission and were not associated with increased duration of hospitalization.**

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***Key words:*** **asthma;**
**beta-agonist;**
**pediatric**

## Introduction

Acute asthma is commonly treated with beta-agonist therapy, typically in the form of inhaled albuterol.[1-4] Initially, in children, this therapy is delivered via intermittent aerosol, then increased to continuous delivery if there is insufficient response to therapy.[1-4] Relatively high doses (20-30 mg/hour) are routinely used for hours to days in hospitalized children.[1,5] If there is continued failure in response, intravenous (IV) beta-agonist therapy is frequently used in children with poor air exchange.[1-3] In the United States, IV terbutaline is the most frequently used IV beta-agonist.[1-2] We have previously reported that in children admitted to the intensive care unit (ICU) with acute asthma at our institution, the median duration of continuous albuterol was 5 days, and almost 50% of children received IV terbutaline for a median duration of 47 hours.[5]

Although this treatment is widely delivered, concerns about potential occult cardiotoxicity have been raised for some time.[6,7] In adults, several investigators have noted that beta-agonists can have significant adverse effects, in particular, cardiotoxicity with cardiac arrhythmias and myocardial ischemia.[8,9] These effects may be magnified in dehydrated patients with inadequate intravascular volume.[9] In children, several investigators[7,10-13] have published reports about the safety of beta-agonist therapy in those treated for status asthmaticus. However, with increased use of high-dose inhaled and IV beta-agonist therapy at many institutions, some authors[14] have begun to again question the safety of these medications in children.

The purpose of this study was to investigate the incidence of cardiotoxicity associated with the use of continuous beta-agonist therapy in children. Because of

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concerns in the literature, between May 2008 and April 2009, our institutional practice was changed to measure lactate and troponin-T levels in all children with acute asthma admitted to the ICU and treated with continuous beta-agonist therapy. In this review, the goal was to measure the incidence of elevated serum lactate levels and troponin-T levels in this population of critically ill children with status asthmaticus and to compare these elevations with clinical outcomes.

## Methods

This study was conducted at Connecticut Children's Medical Center in a cohort of children admitted to the ICU with asthma between May 2008 and April 2009. During the study period, it was the local practice of our institution to have routine levels of troponin and lactate assessed every 12-24 hours in all children admitted to the ICU at Connecticut Children's Medical Center who were also receiving continuous beta-agonist therapy. Serum levels of troponin-T are well established markers of myocardial damage in children and they have been used previously to assess toxicity associated with IV beta-agonist therapy.[7,15,16] Similarly, elevations in serum lactate levels are commonly used as an indicator of tissue hypoperfusion and have also been previously used to assess toxicity in this population.[14,17,18]

All children aged 2 to 18 years who were admitted to the ICU with an asthma exacerbation and who had > 2 assessments of serum troponin-T and lactate during the study period were included in this study. There were no exclusion criteria. Data were then collected retrospectively for this observational study. The study was approved by Connecticut Children's Institutional Review Board, and informed consent was waived due to its retrospective nature.

All children were treated according to a previously published standard clinical protocol that adjusted beta-agonist therapy, first inhaled and then IV, based on a validated clinical asthma score, the modified pulmonary index score (MPIS).[19,20] The MPIS, a pediatric asthma severity of illness score that ranges from 0 to18, has previously been shown to be a valid indicator of severity of illness in children with asthma and highly reproducible across groups of medical professionals.[20] IV terbutaline was the IV beta-agonist used in this cohort.

Demographic, historical and clinical data were collected from the medical chart including patient age, gender, race/ethnicity, and asthma history. National Heart, Lung and Blood Institute classification of baseline asthma was determined at the time of admission by the attending intensivist or pulmonologist.[6] Data were also collected regarding the hospital course, treatments received and the durations of these therapies. All children also had continuous cardiac monitoring while in the ICU.

Measurements were grouped into pre-defined 12-hour intervals according to the patient's time since admission to the ICU (0 hour, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, and 84 hours). Elevations in serum lactate and troponin-T levels were defined according to the upper limits of normality for the laboratory at the Connecticut Children's Medical Center. For lactate, a level of >2.2 mmol/L was considered elevated. For troponin-T, a level of >0.03 ng/mL was considered elevated.

### Statistical analysis

Data were analyzed using JMP statistical software (version 8.0.1; Cary, NC) along with consultation from statisticians in the Office of Research at Connecticut Children's Medical Center. Demographic and clinical characteristics of children with and without elevated troponin-T and lactate levels were compared using appropriate parametric tests and non-parametric tests, including Student's *t* test and the Mann-Whitney *U* test for continuous variables and the Chi-square test for categorical variables. The Shapiro Wilk test was used to assess normality. *P* values of <0.05 were considered statistically significant. The data were reported as frequencies (%), as mean±standard deviation or as median with 25%-75% interquartile range (IQR) depending on the type and distribution of the variables.

## Results

During this study period, 229 children were admitted to the hospital with acute asthma. Of these, 36 were admitted to the ICU for continuous beta-agonist therapy. Unfortunately, due to limitations in performing phlebotomy in this population, only 20 of the 36 children treated with continuous albuterol during the study period had repeated serum troponin and lactate levels measured every 12-24 hours. All children who had >2 levels of troponin also had >2 levels of serum lactate (i.e. there were no children excluded for having >2 measurements of one value and not >2 measurements of the other).

The median age of these 20 children was 8.1 years (25%-75% IQR, 5.0-12.1 years), 60% were male and 55% had public insurance. The race/ethnicity of the cohort was Caucasian (40%), African-American (20%), Hispanic (35%), and others (5%). On admission, the NHLBI asthma classification was 40% intermittent, 25% mild persistent, 25% moderate persistent, and 10% severe persistent. More than half had previously been

admitted to the hospital with an asthma exacerbation (60%), 20% had previously been admitted to an ICU with asthma, and 10% had been previously intubated for asthma.

All of the children received continuous albuterol therapy of at least 20 mg/hour for at least some duration. The median duration of the continuous albuterol therapy was 40 hours (25-75% IQR, 15-114 hours). Eleven of these 20 patients (55%) were also treated with continuous intravenous terbutaline. The median duration of IV terbutaline for these 11 children was 63 hours (25-75% IQR, 32-104 hours) and the median highest dose of terbutaline used was 1.6 mcg/kg/min (25-75% IQR, 0.8-2.5 mcg/kg/min). Three children were intubated and mechanically ventilated.

All children had significantly elevated clinical



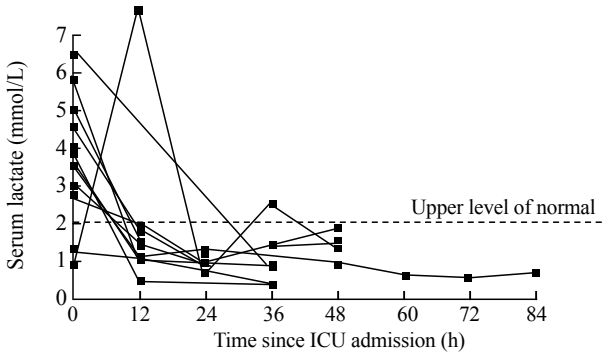


**Fig. 1.** Serum lactate levels over time in those children with at least one level >2.2 mmol/L (*n*=8).

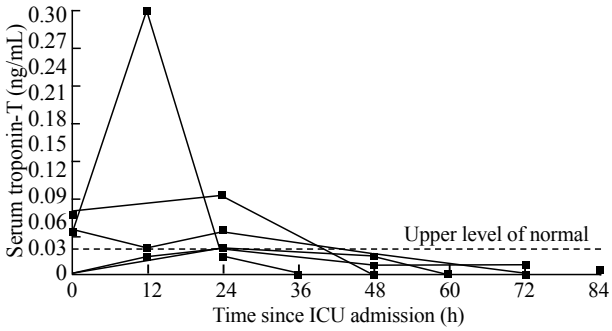


**Fig. 2.** Serum troponin-T levels over time in those children with at least one level >0.03 ng/mL (*n*=5).

**Table 1.** Clinical and hospitalization outcomes telated to elevated lactate levels

| Variables | Elevated lactate (*n*=12) | No elevation (*n*=8) | *P* value |
|---|---|---|---|
| Demographic data | | | |
| Age (y) | 8.1 (3.1-12) | 8.1 (5.3-15.1) | 0.30 |
| Male gender | 67% (*n*=8) | 50% (*n*=4) | 0.65 |
| Race/Ethnicity | | | |
| Caucasian | 50% (*n*=6) | 25% (*n*=2) | 0.37 |
| African-American | 25% (*n*=3) | 13% (*n*=1) | 0.62 |
| Hispanic | 17% (*n*=2) | 63% (*n*=5) | 0.06 |
| Other | 8% (*n*=1) | 0% (*n*=0) | 1.00 |
| Public insurance | 50% (*n*=6) | 63% (*n*=5) | 0.67 |
| Asthma history | | | |
| Asthma severity | | | |
| Intermittent | 33% (*n*=4) | 50% (*n*=4) | 0.65 |
| Mild persistent | 17% (*n*=2) | 38% (*n*=3) | 0.27 |
| Moderate persistent | 42% (*n*=5) | 0% (*n*=0) | 0.055 |
| Severe persistent | 8% (*n*=1) | 13% (*n*=1) | 1.00 |
| Previous hospitalization | 58% (*n*=7) | 63% (*n*=5) | 1.00 |
| Previous ICU admission | 25% (*n*=3) | 13% (*n*=1) | 0.62 |
| Previous intubation | 17% (*n*=2) | 0% (*n*=0) | 0.49 |
| Hospitalization data | | | |
| Admission MPIS | 15 (13-15) | 15 (13-15) | 0.75 |
| ICU stay (d) | 4 (2-7) | 4 (2-7) | 0.88 |
| Hospital stay (d) | 7 (4-9) | 6 (4-10) | 0.97 |
| Duration of continuous albuterol (h) | 33 (14-96) | 53 (36-129) | 0.28 |
| Received IV terbutaline | 67% (*n*=8) | 75% (*n*=6) | 1.00 |
| Duration of IV terbutaline, h | 75 (40-113) | 53 (26-99) | 0.52 |
| Maximum terbutaline dose (mcg/kg/min) | 1.5 (0.7-2.5) | 1.7 (0.9-2.5) | 0.65 |
| Intubated | 17% (*n*=2) | 13% (*n*=1) | 1.00 |

Data expressed as a median (25-75% interquartile range) or as a frequency (%). ICU: intensive care unit; IV: intravenous; MPIS: modified pulmonary index score.

**Table 2.** Clinical and hospitalization outcomes related to elevated troponin-T levels

| Variables | Elevated troponin-T (*n*=5) | No elevation (*n*=15) | *P* value |
|---|---|---|---|
| Demographic data | | | |
| Age (y) | 5.5 (5.1-13.5) | 9.2 (4.7-12.1) | 0.91 |
| Male gender | 80% (*n*=4) | 53% (*n*=8) | 0.60 |
| Race/Ethnicity | | | |
| Caucasian | 40% (*n*=2) | 40% (*n*=6) | 1.00 |
| African-American | 20% (*n*=1) | 20% (*n*=3) | 1.00 |
| Hispanic | 20% (*n*=1) | 40% (*n*=6) | 0.61 |
| Other | 20% (*n*=1) | 0% (*n*=0) | 0.25 |
| Public insurance | 60% (*n*=3) | 53% (*n*=8) | 1.00 |
| Asthma history | | | |
| Asthma severity | | | |
| Intermittent | 20% (*n*=1) | 47% (*n*=7) | 0.60 |
| Mild persistent | 0% (*n*=0) | 33% (*n*=5) | 0.27 |
| Moderate persistent | 60% (*n*=3) | 13% (*n*=2) | 0.07 |
| Severe persistent | 20% (*n*=1) | 7% (*n*=1) | 0.45 |
| Previous hospitalization | 80% (*n*=4) | 53% (*n*=8) | 0.60 |
| Previous ICU admission | 20% (*n*=1) | 20% (*n*=3) | 1.00 |
| Previous intubation | 0% (*n*=0) | 13% (*n*=2) | 1.00 |
| Hospitalization data | | | |
| Admission MPIS | 15 (14-16) | 14 (13-15) | 0.31 |
| ICU stay (d) | 6 (4-9) | 3 (2-5) | 0.15 |
| Hospital stay (d) | 8 (6-12) | 5 (4-8) | 0.10 |
| Duration of continuous albuterol (h) | 46 (29-145) | 35 (15-100) | 0.32 |
| Received IV terbutaline | 40% (*n*=2) | 80% (*n*=12) | 0.13 |
| Duration of IV terbutaline, h | 112 (107-116) | 60 (30-94) | 0.07 |
| Maximum terbutaline dose (mcg/kg/min) | 1.7 (0.8-2.5) | 1.6 (0.7-2.5) | 1.00 |
| Intubated | 20% (*n*=1) | 13% (*n*=2) | 1.00 |

Data expressed as a median (25-75% interquartile range) or as a frequency (%). ICU: intensive care unit; IV: intravenous; MPIS: modified pulmonary index score.

asthma scores on admission with a median MPIS of 15 (25%-75% IQR, 13-15). These children were also hospitalized for significant durations with a median ICU stay of 3.5 days (25%-75% IQR, 2-7 days) and a median hospital stay of 7 days (25%-75% IQR, 4-9 days).

The median baseline lactate level was 1.95 mmol/L (25%-75% IQR, 0.98-3.83 mmol/L). Elevated lactate levels were found in 60% of the children sometime during their hospitalization (maximum values range: 2.6-7.5 mmol/L), but all also normalized within 48 hours of ICU admission (Fig. 1). There was no association between intravenous terbutaline use and elevated serum lactate (OR, 0.6; 95% CI, 0.1-3.7), nor was there any association between elevated lactate levels and any of the demographic or clinical parameters measured, including no association between elevated lactate and illness severity on admission (admission MPIS) or with ICU or hospital length of stay (LOS) (Table 1).

Elevated troponin-T levels were found in 25% of children (maximum values range: 0.03-0.3 ng/mL). However, all returned to normal levels within 48 hours of ICU admission, despite continued high-dose beta-agonist therapy (Fig. 2). There was no association between intravenous terbutaline use and elevated troponin-T (OR, 1.3; 95% CI, 0.2-10.3), nor was there any association between elevated troponon-T levels and any of the demographic or clinical parameters measured, including no association between elevated troponin-T and illness severity on admission (admission MPIS) or with ICU or hospital LOS (Table 2).

Three children had elevations in both troponin-T and lactate levels. None of these children were intubated and only one of them received IV beta-agonist therapy.

All children in the ICU had continuous cardiac monitoring. Other than sinus tachycardia, there were no arrhythmias in any children. Despite a practice that all children with elevated troponin-T have a 12-lead electrocardiogram (ECG) performed, only three children had 12-lead ECGs performed. These ECGs were normal.

## Discussion

Continuous beta-agonist therapy is commonly used in the treatment of severe asthma in children. In this small cohort of critically ill children with status asthmaticus, a significant proportion had elevated levels of serum troponin and lactate while receiving continuous beta-agonist treatment. However, these elevations were transient, all returned to normal levels within 48 hours of ICU admission and were not related to IV beta-agonist use. Our data suggested that there is a subset of children receiving continuous beta-agonist therapy that have transient occult cardiotoxicity.

Lactic and metabolic acidosis has been previously reported in patients with status asthmaticus. In adults, metabolic acidosis is fairly common, occurring in more than a quarter of episodes,[21] but thought to be significantly less so in the pediatric population.[13,17] Few studies[13-14,17,22] have been conducted in children with severe asthma. In a review by Yousef,[13] only 1% of children admitted with status asthmaticus had elevated lactate. However in this review, only a fraction of children had serum lactates measured (only those with a serum pH <7.35). The most common acid-base abnormality in acute asthma is respiratory alkalosis,[21] so with this compensation, assessment of pH alone would likely result in an underreporting of metabolic acidosis and thus an undermeasurement of elevated lactates in the study by Yousef. In a paper by Meert et al,[14] 15 of 53 children (28%) with status asthmaticus developed metabolic acidosis with hyperventilation within 30 hours of presentation. Four of these were noted to have increased serum lactate, but not all patients had assessment of serum lactate. Meert et al[14] were criticized for providing care that contributed to the reporting of metabolic acidosis at an incidence far greater than the previously reported. However, the results of our study support these findings by Meert et al.[14] Although we did not assess blood gas samples in our study, our findings of transiently elevated lactate in 60% of all our population were consistent with their findings.

In our population of critically ill children with asthma, we found that more than half of the children had an increased lactate level, although the level returned to normal within 48 hours. Children with asthma have been theorized to have increased lactate from a variety of etiologies, including overuse of respiratory muscles under hypoxic conditions, reduced cardiac output due to elevated intrathoracic pressures, skeletal muscle hypoperfusion, and decreased lactate metabolism by the liver.[14,17,18] Hypovolemia may exacerbate these conditions.[14,18] Even when delivered via inhalation, beta-agonist therapy has systemic effects, stimulating beta-adrenergic receptors and causing tachycardia, nausea and sympathomimetic symptoms.[1] Activation of these receptors may also lead to lactic acid production through increased gluconeogenesis, glycogenolysis, glycolysis, and lipolysis.[14,17] These etiologies may have played a part in the initial elevated lactates in some of the children. Unfortunately, we did not obtain blood gas measurements or serum glucose levels along with serum lactate and troponin-T levels in this study. These measurements would have provided more information

of the acid-base balance in this population and might have potentially shed some light on the mechanisms for elevated lactate.

Several investigators[7,8,10-12,23-26] have attempted to assess whether myocardial injury is associated with beta-agonist therapy in adults and children. High-dose beta-agonist therapy, such as that routinely used for status asthmaticus, can potentially contribute to myocardial strain through several mechanisms.[1] First, activation of beta-adrenergic receptors can lead to tachycardia, which can induce myocardial strain in certain patients.[1] Additionally, disease related physiology can contribute to the risk of beta-agonist therapy. Increased intrathoracic pressure from air-trapping during acute asthma episodes can contribute to impaired venous return and decreased preload, which in conjunction with tachycardia leads to diastolic hypotension and a further increase in myocardial oxygen consumption.[1] In children, these myocardial effects may be less pronounced than in adults, but concerns regarding toxicity persist.

In our cohort, a quarter of the children had an elevation in their serum troponin-T levels, indicating some degree of myocardial strain and cardiotoxicity. However, these were transient, and unrelated to whether the patient received IV beta-agonist therapy. IV beta-agonist therapy is frequently given in this population due to a theoretically decreased absorption in critically ill asthmatics despite lack of supporting evidence that IV therapy provides better drug delivery than inhaled therapy.[27] Some authors[27] have suggested that in addition to the potential cardiac effects, the use of this high dose and intravenous beta-agonist therapy may actually worsen a patient's clinical status by increasing myocardial oxygen demand. In the pediatric population, Chiang et al[7] was one of the first to assess cardiotoxicity associated with IV beta-agonist therapy in children admitted with severe asthma. However, the overall cardiotoxicity was relatively low in this population. In a cohort of 29 critically ill children with status asthmaticus who were receiving IV terbutaline, only 3 of the children had a detectable serum troponin-T level during the study.[7] This frequency (10%) is similar to the frequency of elevated troponin levels found in our study (25%). In both studies, the elevations in troponin-T were clinically insignificant and transient.

There are several limitations to our study. First, our sample size was small and reflected only a subset of the larger cohort admitted with acute asthma. Therefore generalizing these results should be done cautiously. In addition, we performed a convenience sampling of children with status asthmaticus. Due to limitations in phlebotomy in this population, only 20 of the 36 children admitted to the ICU had these repeated measures obtained. These 20 children likely reflected the more acutely ill children in our cohort and therefore the incidence of elevated lactate and troponin in the general population of children with acute asthma is likely significantly lower. Also, because of the retrospective, observational nature of this study, there were additional tests that we did not perform that may have provided a clearer picture of the pathophysiology in this population. For example, after repeated normal levels, children did not continue to have levels drawn while they remained on beta-agonist therapy. It may be that these levels rose again but were not tracked. Performing these laboratory assessments for a longer duration may have been helpful. However, these laboratory assessments are not routinely performed in this population, and these assessments reflected a change in local practice that has not continued following this review.

In this small cohort of critically ill children with status asthmaticus, a significant proportion of children had transient elevated levels of serum troponin-T and lactate while receiving inhaled continuous beta-agonist therapy, irrespective of intravenous beta-agonist use. These abnormal lab values were transient in this small population, all returning to normal levels within 48 hours of ICU admission, and were not associated with the increased duration of hospitalization.

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