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BRIEF REPORT

General Medicine

Frequency of cardiotoxicity following intramuscular administration of epinephrine in emergency department patients with anaphylaxis

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Abstract

Objectives: Epinephrine can be a life-saving treatment for patients with anaphylaxis. Potential cardiovascular side effects of epinephrine may contribute to clinician hesitancy to use it. However, the frequency of cardiotoxicity resulting from epinephrine treatment for anaphylaxis is not well described. We sought to describe the frequency of cardiotoxicity following intramuscular (IM) administration of epinephrine in adult emergency department (ED) patients with anaphylaxis.

Methods: We conducted a retrospective observational study at a single, quaternary care academic ED in Tennessee. We identified consecutive ED visits with the diagnosis of anaphylaxis from 2017 to 2021 who received at least one intramuscular (IM) dose of epinephrine in the ED. Analysis was primarily descriptive. The primary outcome was cardiotoxicity, the occurrence of any of the following after epinephrine administration: ischemic electrocardiogram changes, systolic blood pressure >200 mmHg, or cardiac arrest ≤4 h; elevated troponin ≤12 h; or percutaneous coronary intervention or depressed ejection fraction ≤72 h.

Results: Among 338 included patients, 16 (4.7%; 95%CI: 2.8–7.6%) experienced cardiotoxicity. Cardiotoxic events included eight (2.4%) ischemic electrocardiogram changes, six (1.8%) episodes of elevated troponin, five (1.5%) atrial arrhythmias, one (0.3%) ventricular arrythmia, and one (0.3%) depressed ejection fraction. Patients with cardiotoxicity were significantly older, had more comorbidities, and were more likely to have received multiple doses of epinephrine or an epinephrine infusion compared with a single IM dose of epinephrine.

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Conclusions: Among 338 consecutive adult ED patients who received IM epinephrine for anaphylaxis during a recent 4-year period, cardiotoxic side effects were observed in approximately 5% of patients.

KEYWORDS
anaphylaxis, cardiotoxicity, epinephrine

1 | INTRODUCTION

1.1 | Background

Anaphylaxis is a common, life-threatening disease in the emergency department (ED), characterized by a sudden, systemic reaction to an allergen involving multiple organ systems. Manifestations of anaphylaxis may include airway compromise, hypotension, skin changes, and/or gastrointestinal symptoms. The estimated lifetime incidence of anaphylaxis is 0.05–7.9% for U.S. adults.[1,2] Common triggers include food, insect stings, and medications.[1] A nationwide cross-sectional survey found that 36% of patients who reported an episode of anaphylaxis went to a hospital, 13% went to a doctor's office, 12% called 911, 11% self-administered epinephrine, and 28% received treatments other than epinephrine.[1] The mainstay of anaphylaxis treatment in the ED is epinephrine administered intramuscularly (IM).[3] Epinephrine treats anaphylaxis by increasing peripheral vascular resistance through alpha receptors and causing bronchodilation through beta receptors.[4] Potential cardiovascular toxicities of epinephrine stem from alpha-1 mediated vasoconstriction and beta-1 mediated enhancement of cardiac contractility.[3]

1.2 | Importance

Timely administration of IM epinephrine can be a life-saving treatment for anaphylaxis. Some clinicians in the ED delay or avoid the administration of epinephrine due to concerns that its vasoactive properties may contribute to serious cardiovascular sided effects ("cardiotoxicity").[5] Clinician hesitancy to administer IM epinephrine for anaphylaxis has deleterious effects for patients.[5] However, there is a lack of high-quality studies describing the frequency of cardiotoxicity following the use of epinephrine for the treatment of anaphylaxis, with appropriate dose and route of administration.

1.3 | Goals of this investigation

We sought to estimate the frequency of cardiotoxicity following administration of IM epinephrine given to adults for the treatment of anaphylaxis in the ED. Additionally, we sought to identify potential risk factors for cardiotoxicity after receipt of epinephrine for anaphylaxis in the ED.

2 | METHODS

2.1 | Study design, setting, and selection of participants

This was a retrospective observational study to identify the frequency of cardiotoxicity among ED adult patients treated for anaphylaxis with IM epinephrine. We included ED encounters between November 2, 2017 and December 31, 2021 to a quaternary care academic medical center during which an adult (≥18 years old) patient received any dose of IM epinephrine and the encounter included a diagnostic code (International Classification of Diseases version 10; [ICD-10]) for allergic reaction or anaphylaxis. This time period reflects the availability of data following the implementation of a comprehensive electronic health record (Epic, Inc). All ICD-10 codes are listed in Supplemental Data. This list includes conditions that were not relevant to this project and were consolidated by manual review process and those associated with epinephrine administration. Patients who receive out of hospital epinephrine were not excluded as long as they received at least one dose of IM epinephrine in the ED. Manual medical record review was completed to confirm eligibility for every included patient. The local institutional review board approved this study as exempt as it was minimal risk.

2.2 | Measurements

Emergency medicine residents were trained to perform chart reviews for this study as part of a new educational program to immerse them into emergency care research. The chart review team was trained in data collection methods according to the guidelines by Kaji et al.[6] via in-person and recorded training sessions led by senior researchers. Chart reviews were used to collect patient data, including demographics, clinical presentation details, route and dose of medication administration, and outcomes. Abstractors were not blinded to the outcome. All ED encounters that met eligibility criteria for this study were reviewed by one of the resident chart abstracters to confirm eligibility and collect data. Secondary review was conducted by a more senior researcher for 7% of abstracted charts. Data were collected and stored in REDCap,[7] a research electronic data tool hosted by our institution.

2.3 | Outcomes

The primary outcome was cardiotoxicity following the administration of IM epinephrine for anaphylaxis, which was broadly defined as

adverse cardiovascular effects following treatment with epinephrine.[8] Patients were classified as having a cardiotoxicity if they experienced any of the following: (1) ischemic electrocardiogram (EKG) changes within 4 h of IM administration per the ED physician interpretation as specified in their electronic health record clinical documentation including ST-depression or ST-elevation; (2) ventricular arrhythmia or atrial arrhythmia within 4 h; (3) elevated troponin (greater than or equal to the 99th percentile cut-off) within 12 h; (4) cardiac catheterization with percutaneous coronary intervention within 72 h; (5) newly depressed ejection fraction on transthoracic echocardiogram within 72 h; or (6) SBP >200 within 4 h. Secondary outcomes included radiologic evidence of pulmonary edema or intracranial hemorrhage within 72 h.

2.4 | Data analysis

Central tendencies and dispersion were reported as medians and interquartile ranges, respectively, for continuous variables. Categorical variables were reported as frequencies and percentages. The proportion of patients who experienced the primary outcome (cardiotoxicity) was calculated by dividing the number of patients who met the criteria for cardiotoxicity by the total number of patients in the analysis, who all received at least one dose of IM epinephrine for suspected anaphylaxis.

In exploratory analyses, we assessed the unadjusted association between patient characteristics and the primary outcome (cardiotoxicity) using the Wilcoxon–Rank Sum test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Patient characteristics assessed for association with cardiotoxicity included age, sex, ethnicity, insurance status (as a surrogate for social determinants of health[9]), chronic medical conditions, reported history of cocaine or methamphetamine use, a urine drug screen test positive for cocaine or methamphetamine, the number of epinephrine doses received, and whether an epinephrine continuous infusion was stated. Two-tailed *p* values less than 0.05 were considered statistically significant. Given the anticipated small number of patients with cardiotoxicity and the exploratory nature of this analysis, an adjusted analysis was not performed. All statistical analysis was performed using SAS version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

Our electronic data search identified 512 ED encounters between November 2, 2017 and December 31, 2021 with an ICD-10 code for anaphylaxis or allergic reaction and an electronic order for IM epinephrine. Upon manual chart review, 174 of these patients were identified as not having received IM epinephrine in the ED for anaphylaxis and were excluded, resulting in an analytical population of 338 patients. Among these 338 patients, median age was 32 years, 63 (18.6%) had chronic hypertension, 12 (3.6%) had coronary artery disease, and three (0.9%) had a positive urine drug screen for cocaine or methamphetamines.

The Bottom Line

The adverse cardiovascular effects of epinephrine administration for anaphylaxis are not well described. In this retrospective analysis of 338 patients who received epinephrine for anaphylaxis over a four-year period, only 16 (5%) experienced cardiovascular adverse effects. Risk factors included older age and comorbid conditions like hypertension and multiple doses of epinephrine.

Among the included 338 patients, 33 patients had the chart review completed by a second abstractor. Among these patients with duplicate chart reviews, percent agreement for data entered by the two chart reviewers was 100% for the presence of elevated troponin, 100% for ischemic EKG changes, 97% for ventricular arrythmia, 100% for atrial arrythmia, 100% for depressed ejection fraction, and 100% for systolic blood pressure >200 mm Hg.

3.2 | Main results

Among the 338 patients, 16 (4.7%, 95% CI: 2.8–7.6%) experienced at least one cardiotoxic event. These 16 patients experienced 22 cardiotoxic events, including 6 (1.8%) with elevated troponin, eight (2.4%) with ischemic EKG changes, one (0.3%) with a ventricular arrhythmia, five (1.5%) with atrial arrhythmias, and one (0.3%) with a depressed

TABLE 1 Cardiotoxicity and extracardiotoxicity following epinephrine treatment for anaphylaxis.

Cardiotoxicity	
Ischemic changes on 12-lead EKG (*n*, %)	8 (2.4%)
Elevated troponin I (*n*, %)	6 (1.8%)
Median (IQR) initial troponin I	0.17 (0.01, 0.43)
Median (IQR) maximum troponin I	0.22 (0.07, 1.91)
Atrial arrhythmia (*n*, %)	5 (1.5%)
Ventricular arrhythmia (*n*, %)	1 (0.3%)
Ejection fraction < 55% on TTE (*n*, %)	1 (0.3%)
SBP > 200 mmHg (*n*, %)	0 (0.0%)
PCI (*n*, %)	0 (0.0 %)
Cardiac arrest (*n*, %)	0 (0.0%)
Extracardiotoxicity	
Pulmonary edema (*n*, %)	1 (0.3%)
Intracranial hemorrhage (*n*, %)	0 (0.0%)

EKG, electrocardiogram; IQR, interquartile range; TEE, transthoracic echocardiogram; SBP, systolic blood pressure; PCI, percutaneous coronary intervention.

TABLE 2 Description of 16 patients who experienced cardiotoxicity among 338 consecutive patients treated with epinephrine for anaphylaxis in a single ED.

Age (years)	Sex	Hispanic	Comorbidities	ED disposition	# of doses	Extra-cardiotoxicity	Cardiotoxicity
20–29	M	Yes	None	Floor	2 IM doses in ED	None	New atrial arrhythmia
20–29	F	Yes	None	ICU	4 IM doses in ED, infusion	None	New ST elevation or depression
30–39	M	No	Smoking, amphetamine use	ICU	2 IM doses in ED, infusion	None	Elevated troponin[a] (peak 1.91 ng/mL)
30–39	F	No	Prior dysrhythmia (Sick Sinus Syndrome)	Floor	1 IM dose in ED	None	Elevated troponin (peak 1.95 ng/mL), new ST elevation or depression, new atrial arrhythmia, Reduced EF of 52% (normalized in 1 month)
30–39	F	No	None	Floor	2 IM doses in ED	None	New atrial arrhythmia
30–39	F	No	Mast Cell Activation Syndrome	ICU	2 prehospital, 1 IM dose in ED	None	Ventricular arrhythmia (60 s of ventricular tachycardia, self-resolved)
40–49	M	No	Obesity, hypertension, hyperlipidemia	Discharge	1 IM dose in ED	None	New ST elevation or depression
40–49	F	No	Hypertension, hyperlipidemia, diabetes	ICU	1 prehospital, 2 IM doses in ED, infusion	None	New ST elevation or depression
60–69	F	No	None	ICU	1 prehospital, 2 IM doses in ED, infusion	None	New ST elevation or depression
60–69	M	No	Congestive heart failure, hypertension,	ICU	1 IM dose in ED	None	Elevated troponin, New ST elevation or depression
60–69	F	No	None	Floor	1 IM dose in ED, infusion	Pulmonary edema	Elevated troponin (peak 0.28 ng/mL)
60–69	F	Yes	None	Floor	1 IM dose in ED	None	New ST elevation or depression, New atrial arrhythmia
60–69	M	No	Hypertension	ICU	2 IM doses in ED, infusion	None	Elevated troponin (peak 0.07 ng/mL)
70–79	M	No	Obesity, hypertension, diabetes	ICU	2 IM doses in ED, infusion	None	New ST elevation or depression
70–79	M	No	Hypertension	ICU	2 IM doses in ED, infusion	None	Elevated troponin (peak 0.41 ng/mL)
80–89	F	No	Hypertension, prior dysrhythmia	ICU	1 IM dose in ED, infusion	None	New atrial arrhythmia

[a]Normal troponin value < 0.04 ng/mL. ARCHITECT STAT Troponin-I assay used. Abbreviations: ED, emergency department; ICU, intensive care unit; IM, intramuscular.

ejection fraction as interpreted on comprehensive echocardiogram within 72 h (Table 1). The details for each patient who developed cardiotoxicity are presented in Table 2. No patients experienced systolic blood pressure greater than 200 mm Hg or cardiac arrest within 4 h of IM epinephrine administration. Two patients (0.6%) had cardiac catheterization performed but neither underwent percutaneous coronary intervention. Regarding secondary outcomes, one (0.3%) patient was diagnosed with pulmonary edema and no patients had an intracranial hemorrhage.

3.3 | Association between patient characteristics and cardiotoxicity following epinephrine

Patients who experienced cardiotoxicity, compared with those without cardiotoxicity, were older (median age 55 years vs. 31 years, $p < 0.01$), more likely to have a past medical history of hypertension (43.8 vs. 17.4%, $p < 0.01$), and more likely to have positive urine drug screen for cocaine or methamphetamine (12.5 vs. 0.3%, $p = 0.09$) (Table 3. Additionally, patients who experienced cardiotoxicity were more likely to

TABLE 3 Patient characteristics overall and stratified by the primary outcome (cardiotoxicity following receipt of IM epinephrine for anaphylaxis).

Variable	All $n = 338$	Cardiotoxicity $n = 16$	No cardiotoxicity $n = 322$	p value
Median age (IQR, years)	32 (23, 49)	55 (34, 67)	31 (24, 48)	<0.01
Female (*n*, %)	218 (64.5)	9 (56.3)	209 (64.9)	0.48
Ethnicity (*n*, %)				0.06
Non-Hispanic or LatinX	310 (91.7)	13 (81.3)	297 (92.2)	
Hispanic or LatinX	24 (7.1)	3 (18.8)	21 (6.5)	
Missing	4 (1.2)	0 (0.0)	4 (1.2)	
Comorbidities (*n*, %)				
Hypertension	63 (18.6)	7 (43.8)	56 (17.4)	0.01
Obesity	47 (13.9)	2 (12.5)	45 (14.0)	0.99
Smoking	27 (8.0)	1 (6.3)	26 (8.1)	0.99
Diabetes	25 (7.4)	2 (12.5)	23 (7.1)	0.34
Dysrhythmias	25 (7.4)	2 (12.5)	23 (7.1)	0.34
Hyperlipidemia	23 (6.8)	2 (12.5)	21 (6.5)	0.30
Coronary artery disease	12 (3.6)	0 (0.0)	12 (3.7)	0.99
Heart failure	10 (2.7)	2 (12.5)	8 (2.5)	0.08
Peripheral vascular disease	1 (0.3)	0 (0.0)	1 (0.3)	0.99
Insurance (*n*, %)				0.12
Commercial	231 (68.3)	8 (50.0)	223 (69.3)	
Medicaid	29 (8.6)	1 (6.3)	28 (8.7)	
Medicare	42 (12.4)	6 (37.5)	36 (11.2)	
Other government	2 (0.6)	0 (0.0)	2 (0.6)	
Self-pay	28 (8.3)	1 (6.3)	27 (8.4)	
Worker's compensation	6 (1.8)	0 (0.0)	6 (1.9)	
History of cocaine or methamphetamine abuse (*n*, %)	2 (0.6)	1 (6.3)	1 (0.3)	0.09
UDS positive for cocaine or methamphetamine (*n*, %)	3 (0.9)	2 (12.5)	1 (0.3)	<0.01
Home medications (*n*, %)				
Stimulants	10 (3.0)	0 (0.0)	10 (3.1)	0.99
TCA	2 (0.6)	0 (0.0)	2 (0.6)	0.99
Monoamine oxidase inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0.99
Prehospital epinephrine doses (*n*, %)				0.47
0	289 (85.5)	13 (81.3)	276 (85.7)	
1	38 (11.2)	2 (12.5)	36 (11.2)	
2 or more	9 (2.7)	1 (6.3)	8 (2.5)	
Missing	2 (0.6)	0 (0.0)	2 (0.6)	
# of IM epinephrine doses in the ED (*n*, %)				<0.01
1	280 (82.8)	7 (43.8)	273 (84.8)	
2 or more	58 (17.2)	9 (56.3)	49 (15.2)	
Epinephrine intravenous infusion (*n*, %)	30 (8.9)	9 (56.3)	21 (6.5)	<0.01

IQR, interquartile range; UDS, urine drug screen; TCA, tricyclic antidepressants; IM, intramuscular; ED, emergency department.

TABLE 4 Anaphylaxis characteristics and ED disposition stratified by cardiotoxicity.

Variable	Cardiotoxicity $n = 16$	No cardiotoxicity $n = 322$	p Value
Anaphylaxis signs and symptoms (n, %)			
Dermatologic	11 (68.8)	249 (77.3)	0.43
Gastrointestinal	9 (56.3)	118 (36.7)	0.11
Hypotension	9 (56.3)	18 (5.6)	<0.01
Dyspnea	8 (50.0)	173 (53.7)	0.77
Angioedema	4 (25.0)	196 (60.9)	<0.01
Lip swelling	2 (12.5)	79 (24.5)	0.38
Syncope	0 (0.0)	4 (1.2)	0.99
Suspected etiology of anaphylaxis (n, %)			0.03
Medications	8 (50.0)	69 (21.4)	
Unknown	3 (18.8)	61 (18.9)	
Food	2 (12.5)	151 (46.9)	
Iodinated contrast	2 (12.5)	12 (3.7)	
Insects	1 (6.3)	10 (3.1)	
Other	0 (0.0)	13 (4.0)	
Environmental	0 (0.0)	5 (1.6)	
Exercise	0 (0.0)	1 (0.3)	
Latex	0 (0.0)	0 (0.0)	
Disposition from ED (n, %)			<0.01
Admitted to ICU	10 (62.5)	26 (8.1)	
Admitted to floor	5 (31.3)	57 (17.7)	
Discharged	1 (6.3)	231 (71.7)	
AMA	0 (0.0)	6 (1.9)	
Other[a]	0 (0.0)	2 (0.6)	
Deceased	0 (0.0)	0 (0.0)	

ICU, intensive care unit; AMA, against medical advice; IM, intramuscular; ED, emergency deparment.
[a]Other: admitted to stepdown unit; sent to the operating room.

have received a more than one dose of IM epinephrine (56.3 vs. 15.2%, $p < 0.01$) or started a continuous intravenous epinephrine infusion (56.3 vs. 6.5%, $p < 0.01$).

3.4 | Characteristics of anaphylaxis episodes

Patients who experienced cardiotoxicity, compared with those who did not, were more likely to have anaphylaxis-associated hypotension (56.3 vs. 5.6%, $p < 0.01$) and less likely to have angioedema (25.0 vs. 60.9%, $p < 0.01$) (Table 4). The most common suspected etiology of anaphylaxis was a medication among patients who developed cardiotoxicity and food in those without cardiotoxicity. Among those with cardiotoxicity, 15 out of 16 (93.8%) were admitted to the hospital at the end of their ED stay, while among those without cardiotoxicity, 83 out of 322 (25.8%) were admitted to the hospital. Within the group of patients who did not experience cardiotoxicity, two had dispositions marked as "Other." One patient was admitted to the stepdown unit, and one went to the operating room for emergent tracheostomy management in the setting of angioedema.

4 | LIMITATIONS

Our study should be interpreted in the context of its limitations. First, known limitations to retrospective studies exist that we attempted to mitigate through training of the chart abstractors and duplicate data abstraction for a random sample of patients. Second, the single center nature of the study for patients who were seen at an academic institution in a large metropolitan area without a control group may limit the generalizability of this study to other settings and populations. Third, there was no standard diagnostic evaluation for patients treated with epinephrine in the study ED which likely contributed to variability in clinical assessments. For example, some providers may have ordered

troponin testing for a patient when others would not have ordered troponin testing. Additionally, echocardiogram was only performed in seven patient encounters, limiting our assessment for depressed ejection fraction. Fourth, small sample size of patients who experienced cardiotoxicity prevented multivariable models to assess for risk factors for cardiotoxicity such as older age and additional cardiovascular risk factors. Fifth, anaphylaxis itself can cause cardiotoxicity, such as elevated troponin levels; no attempt was made to distinguish cardiotoxicity caused by anaphylaxis as opposed the epinephrine treatment.

5 | DISCUSSION

In this study of 338 consecutive adult patients treated with IM epinephrine for analysis at a single ED over a recent 4-year period, we found that approximately 5% of patients likely had cardiovascular side effects associated with epinephrine. Over half of the 16 patients who had cardiotoxicity received more than one dose of epinephrine. While the frequency of cardiotoxicity was low overall, the risks were higher amongst patients who were older, had hypertension, and who had evidence of receipt cocaine or methamphetamine use. After receipt of epinephrine, no patients in this study underwent percutaneous coronary intervention or had cardiac arrest in the following 72 h.

We present, to our knowledge, the first study to systematically describe cardiotoxicity associated with IM epinephrine administration for the treatment of anaphylaxis in the emergency care setting. Prior literature describing adverse cardiac events following epinephrine treatment for anaphylaxis was limited to case reports. We identified 43 case reports with 48 total patients that described adverse cardiac effects following epinephrine administration in the treatment of anaphylaxis in adults. Of these case reports, only 13 described cardiotoxicity following administration of epinephrine using a correct dose, concentration and route. Thirteen of the 14 total patients described in these reports had an elevated troponin and 11 had new ST-elevation or depression.[10–21] Other side effects described included decreased ejection fraction, diagnosis of cardiomyopathy, and coronary artery thrombus that was diagnosed on cardiac catheterization.[19–22] The other case reports described 34 patients in total who received an intravenous bolus dose of epinephrine inadvertently, or an inappropriately high IM dose.[23–52] This led to a wide array of side effects including arrhythmias, cardiomyopathy, thrombus, and cardiac arrest. Our study adds to the literature by providing an estimate for the frequency of cardiovascular events correlated with appropriately doses IM epinephrine.

In summary, we found that the frequency of cardiotoxicity associated with epinephrine treatment for anaphylaxis was approximately 5% and primarily in those with history of hypertension and who received multiple doses or an infusion of epinephrine. These findings support the practice of rapidly treating adults with anaphylaxis with IM epinephrine.

AUTHOR CONTRIBUTION

E. P. conceived the study and designed it with W. H. S., W. B. S., M. W., and J. W. S. B., M. C., Z. C., T. D., T. J., P. K., C. N., F. P., L. S., S. S., M. S., and B. W. performed data collection and drafted the manuscript. J. H. H. and J. W. assisted with statistics and data analysis. E. P., J. H. H., W. H. S., W. B. S., M. W., and J. W. supervised data collection and revised the manuscript. All authors approved of the final manuscript.

CONFLICT OF INTEREST STATEMENT

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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