

Single, short-time exposure to heat in a car during sunny day can decrease epinephrine concentration in autoinjectors: a real-life pilot study

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Clinical Implications

- Difficult to avoid in summer months, exposure to heat in a car can decrease epinephrine concentration in epinephrine autoinjector, without any recognizable change in solution appearance. If such decreases are progressive or cumulative, this could potentially lead to underdosage of epinephrine in case of anaphylaxis.

TO THE EDITOR:

Intramuscular adrenaline is the first-line treatment of anaphylaxis, and epinephrine autoinjectors (EAI)s are currently recommended in all patients at risk of this condition.¹⁻³ According to prescribing information, EAI)s should be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).⁴ However, those recommendations appear in conflict with the idea of ensuring prompt accessibility to epinephrine in out-of-hospital setting, where strict adherence to storage conditions may not always be possible. Especially summer season, which is reported to be the time of highest incidence of anaphylaxis,⁵ can be associated with high risk of extreme heat exposure.

The aim of this pilot study was to assess the effect of a single, 12-hour-long heat exposure on adrenaline concentration in EAI left inside a parked car on a sunny summer day.

We strived to perform the study in conditions reflecting real-life settings. On the basis of the local weather forecast for Lodz (central Poland, 51°46'N 19°27'E, warm-summer humid continental climate according to Köppen climate classification; mean summer temperature 17.57°C [63.63°F] over the last decade⁶), we selected August 9, 2018, as an optimal day to carry out our experiment, due to predicted high temperature and variable cloud coverage.

In the early morning on the day of measurement, we purchased twelve 0.3 mg EpiPen Senior autoinjectors (Meda Pharma GmbH & Co. KG, Bad Homburg, Germany) from a local certified pharmaceutical wholesaler. After unpacking and confirming that all EAI)s came from a single lot, with expiration date of 16 months (valid through November 2019) and no discoloration or cloudy appearance present on visual inspection, we proceeded to place them in a black sedan car (2003 Volvo S60), parked in a treeless area in the center of Lodz, Poland.

We selected 3 locations inside the vehicle: glove compartment, cabin shelf under the rear window, and the trunk, as areas commonly used for the first aid kit storage (Figure 1). Nine

autoinjectors, each inside its carrier tube, were distributed inside the car—3 in each zone, with no direct sunlight exposure. Three remaining EAI)s, used as control, were stored in a dark, air-conditioned room with a constant temperature of 20°C (68°F). Each storage location was equipped with an Elitech RC-5 temperature data logger (Elitech Ltd, London, United Kingdom), set to register ambient temperature in 5-minute intervals. The autoinjectors were left inside the car for 12 hours, between 8:30 AM and 8:30 PM.

After removing the EAI)s from the car, epinephrine was cooled down to room temperature, injected into test tubes, inspected, and measured. The identification of epinephrine concentration was performed using a high-performance liquid chromatography (HPLC) system (Dionex, Sunnyvale, Calif), equipped with a photodiode-array detector.⁷ Separation of the compounds was achieved on an RP column (C18 Hypersil GOLD aQ 150 × 4.6 mm) linked with a guard column (Hypersil GOLD aQ 10 × 4 mm).

All data were presented as mean and standard deviation. Reductions in concentrations were expressed in percentages.

On the day of experiment, the ambient temperature ranged from 24°C to 32°C (75.2°F to 89.6°F). The mean temperature was 27.3°C ± 2.69°C (81.14°F ± 36.84°F). The weather was clear and sunny for the first 6 hours of measurement, with high cloud cover from around 3 PM until the end of the day, with no precipitation. We recorded the highest temperature in the cabin, which reached 62°C (143.6°F).

When removing autoinjectors from the car, we observed that all 3 devices placed in the glove compartment were noticeably warmer to touch, unlike the rest of the samples. We inspected contents of each EAI visually, observing no discoloration, cloudiness, or any visible particles. We observed no malfunction of delivery mechanism when injecting each EAI's contents into separate tubes and all obtained volumes were equal (0.3 mL).

HPLC analyses revealed a 3.3%, 13.3%, and 14.33% reduction in epinephrine concentration in samples placed in the trunk, cabin, and glove compartment, respectively (Table I, Figure 1).

The data on the stability of epinephrine in autoinjector devices after exposure to extreme heat are scarce.⁸ In the single study available on this topic, Rachid et al⁹ reported significant degradation in EAI)s stored at 70°C (158°F) in an incubator over several days. To our knowledge, this pilot study is the first to report real-life data on the effects of excessive temperature on epinephrine delivered by autoinjectors. We chose the car for our experiment, as one of the most likely places of unintentional exposure to extreme heat in real-life setting, especially during summer. Considering the climate changes predictions, which project a rise in temperature over the 21st century,¹⁰ the issue appears significant even in relatively temperate climate areas.

The HPLC analysis showed sufficiently repeatable measurements. We observed a decline of epinephrine concentrations in all exposed autoinjectors. Concerningly, we observed the most significant drop in adrenaline dose in EAI)s stored in the glove compartment, which is commonly considered the safest storage space for the first aid kit, due to convenience and air-conditioned gloveboxes present in an increasing number of

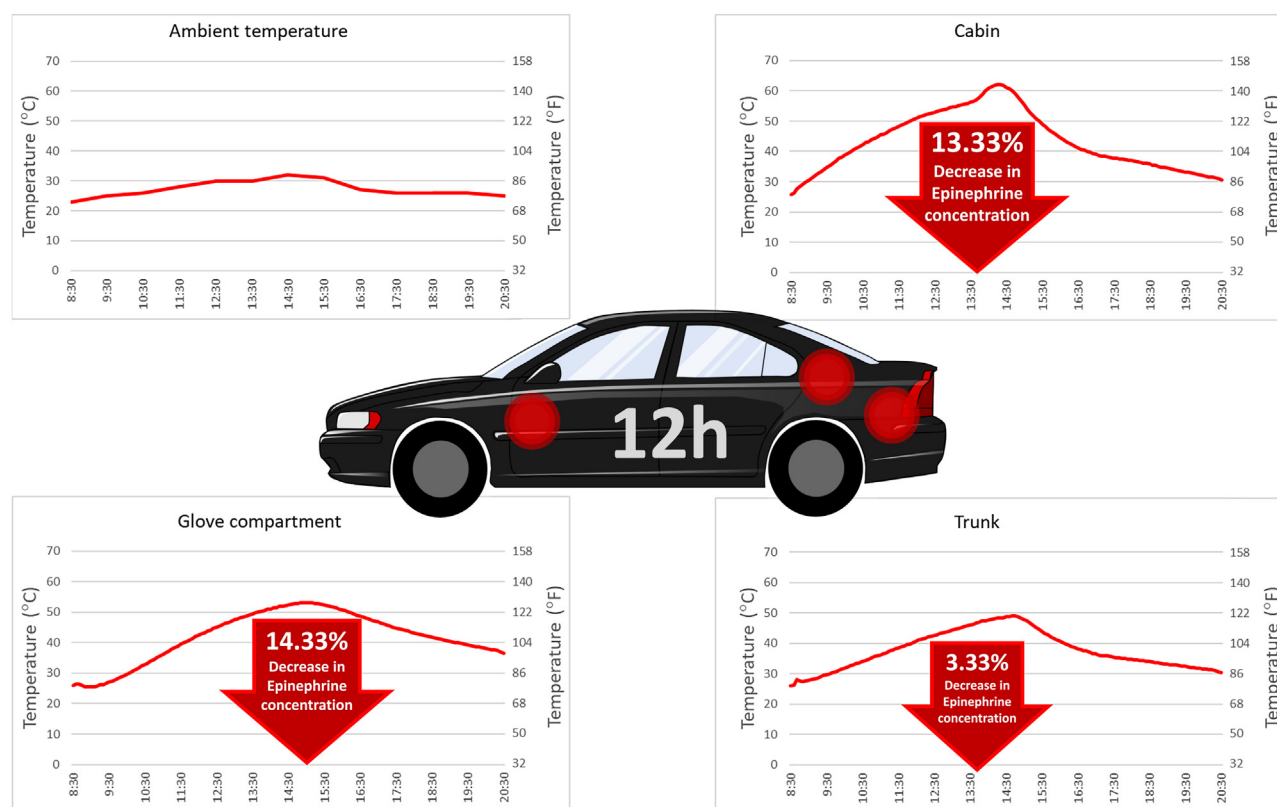


FIGURE 1. Visual summary of the study methods and results.

TABLE I. Solutions of epinephrine in EAI after a single, 12-hour-long exposure to heat in a car

Location	Temperature, °C (°F)		Epinephrine concentration, mg/0.3 cm ³
	Range	Mean ± SD	Mean ± SD
Cabin	25.8-62.0 (78.44-143.6)	43.21 ± 10.00 (109.78 ± 50)	0.26 ± 0.01
Trunk	26.1-49.0 (78.98-120.2)	37.47 ± 6.53 (99.45 ± 43.75)	0.29 ± 0.002
Glove compartment	25.5-53.1 (77.9-127.6)	41.5 ± 8.82 (106.7 ± 47.88)	0.257 ± 0.004
Control	Constant, controlled room temperature of 20°C (68°F)		0.3 ± 0.004

EAI, Epinephrine autoinjector; SD, standard deviation.

modern cars. This observation can be possibly explained by the fact that temperature in this closed space remained relatively high even after the ambient temperature began to drop, presumably due to worse heat dissipation compared with other, open spaces evaluated in our study. Consecutively, we observed the smallest decrease in the EAI stored in the trunk, in which we recorded the lowest range of temperatures. Concerningly, these changes were not associated with any visible changes in the solution appearance. It is worth noting that although Epi-Pen prescribing & patient information⁴ available online contains a direct warning against glovebox storage, we did not find this information in the leaflet enclosed to EAI used in our study. Moreover, our results show that other parts of the vehicle can be similarly detrimental to autoinjectors, making the whole car a hazardous environment.

On the basis of our observations, we can hypothesize that even a single exposure to excessive heat in a car can decrease epinephrine concentration in an autoinjector below the recommended dosage. Although the decreases measured after this 1-day

heat exposure would be unlikely to affect the effectiveness of the administered dose, further studies are needed to evaluate if such degradation is progressive or cumulative, which could lead to clinically ineffective underdosing. Furthermore, epinephrine in low concentrations (eg, 0.1 µg/kg) can paradoxically produce vasodilation, hypotension, and increased release of inflammatory mediators,¹¹ potentially worsening prognosis in anaphylaxis. Moreover, those observations may indicate the need for development of a new, heat-resistant storage solution or formulation, to delay epinephrine degradation in hot environments.

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