Imperial College London

Does size matter ?

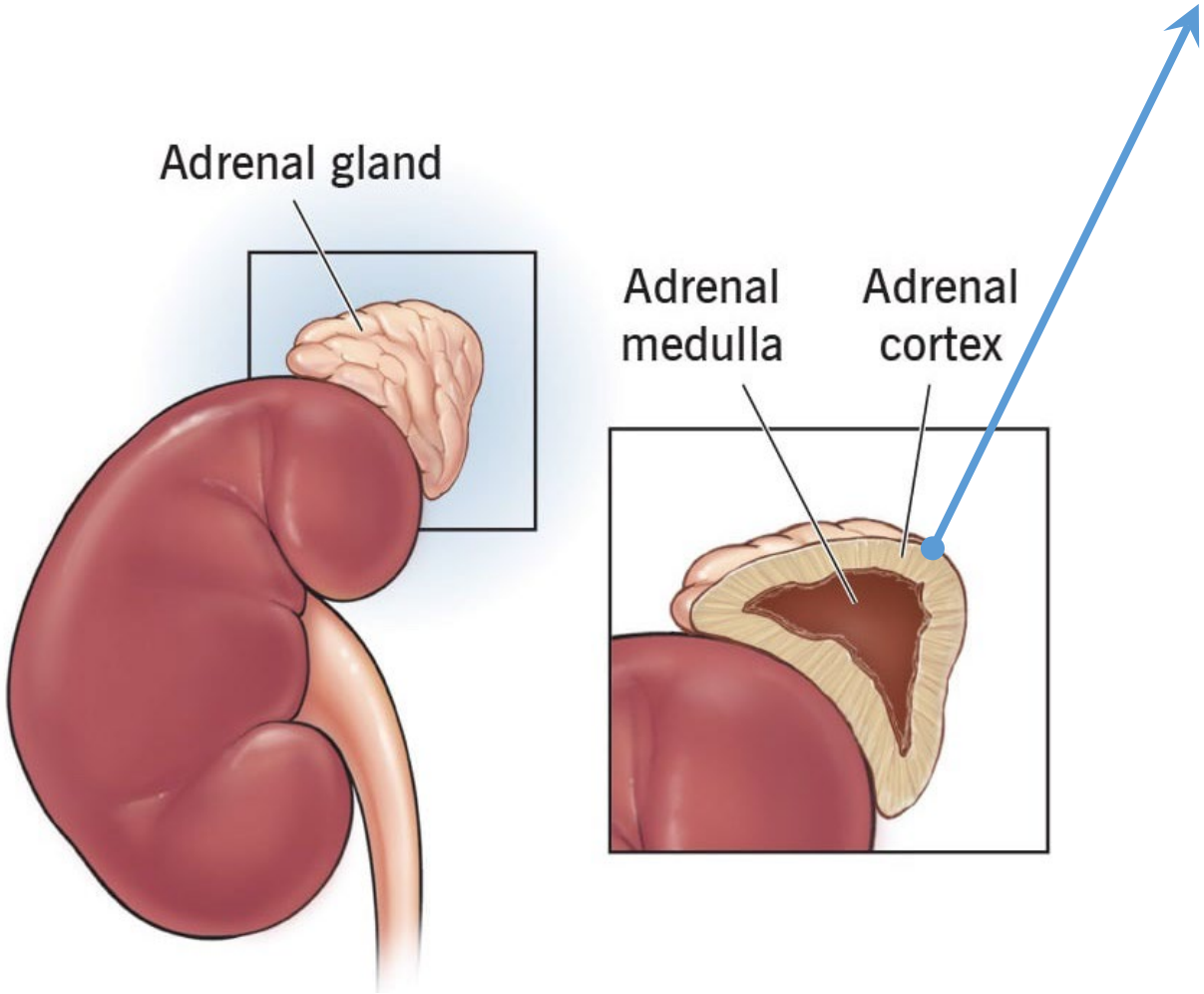
Conundrums over epinephrine and risk management

Dr Paul Turner
National Heart & Lung Institute, Imperial College London, London, UK

Type	Company
Employment full time / part time	Imperial College London / Imperial College Healthcare NHS Trust UK Health Security Agency
Spouse / Family member employment / engagement	None
Research Grant (PI, collaborator or consultant; pending and received grants)	Medical Research Council National Institute for Health Research European Commission Horizon 2020 JM Charitable Trust Aquestive Therapeutics
Other research support	Aimmune Therapeutics DBV Technologies
Speakers Bureau / Honoraria	ALK ILSI Europe
Ownership interest (stock, stock-options, patent or IP)	Allergenis
Consultant / advisory board	Allergenis Aimmune Therapeutics Novartis UK Food Standards Agency WHO/FAO Codex Expert Committee on Allergens Ex Chair, BSACI Paediatric Committee Chair, EAACI European TF on Food allergy Thresholds and Severity Chair, WAO Anaphylaxis Committee Joint lead, UK Resuscitation Council Anaphylaxis Guideline

What's in a name?

Otto von Fürth (Strasbourg) isolated suprarenin (1897)



Parke, Davis & Co cocaine with adrenalin. Photograph courtesy of the Wood Library-Museum, Schaumburg, Illinois.

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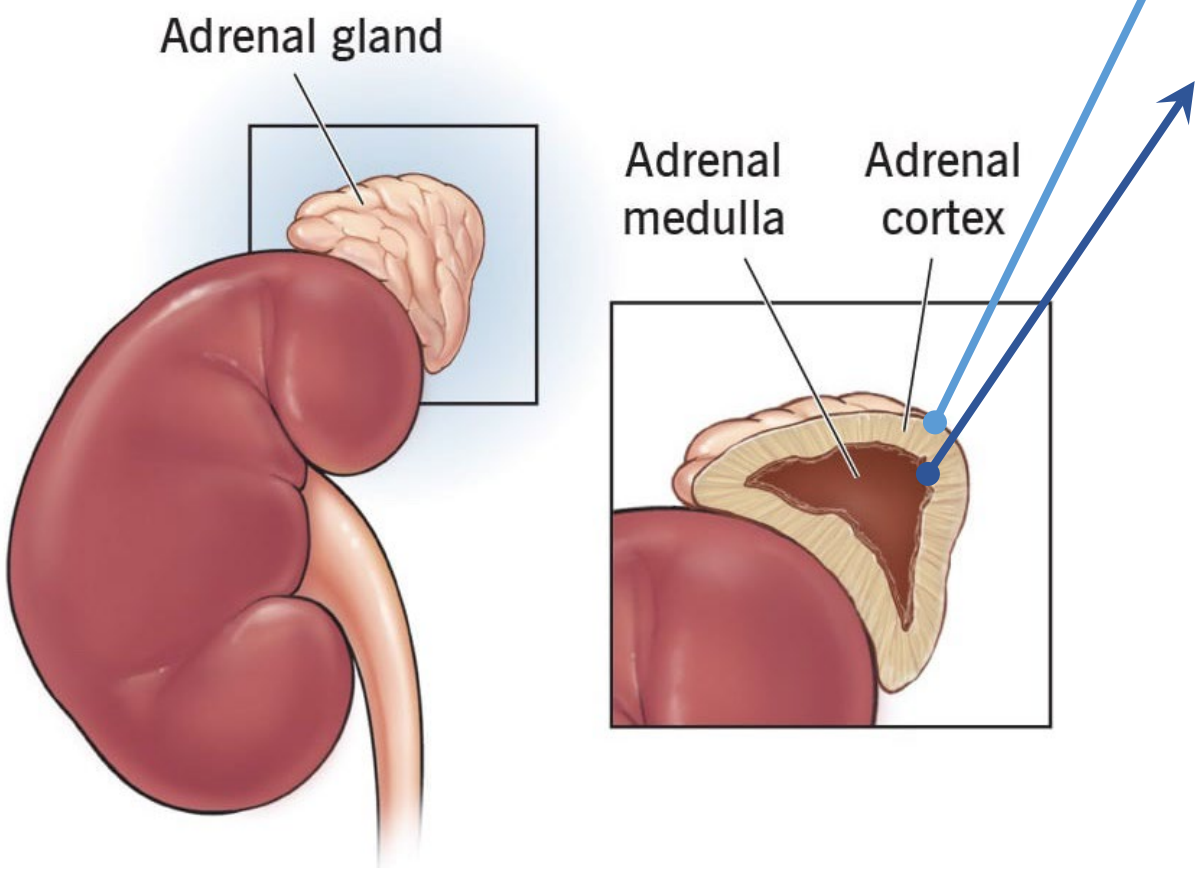

Otto von Fürth (Strasbourg) isolated suprarenin

John Jacobs Abel (Johns Hopkins) isolated epinephrine from the epinephric gland (1897)

Parke, Davis & Co cocaine with adrenalin. Photograph courtesy of the Wood Library-Museum, Schaumburg, Illinois.

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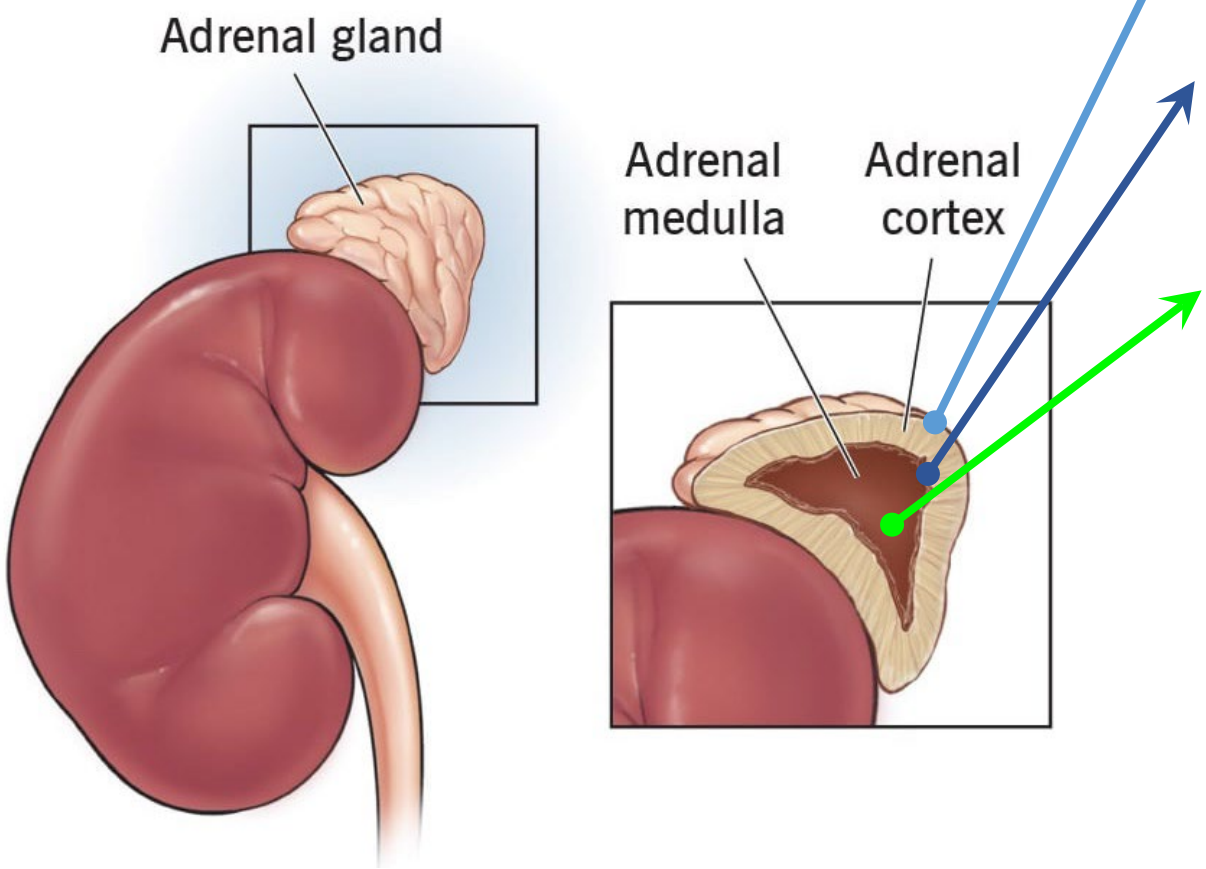

Otto von Fürth (Strasbourg) isolated suprarenin

John Jacobs Abel (Johns Hopkins) isolated epinephrine

Jokichi Takamine (Japan), working with Parke, Davis & Co Laboratories, isolated a pure crystalline substance from the adrenal medulla, 2000 times stronger than either suprarenin or Abel's epinephrine (1900)

= **A**drenaline

Parke, Davis & Co cocaine with adrenalin. Photograph courtesy of the Wood Library-Museum, Schaumburg, Illinois.

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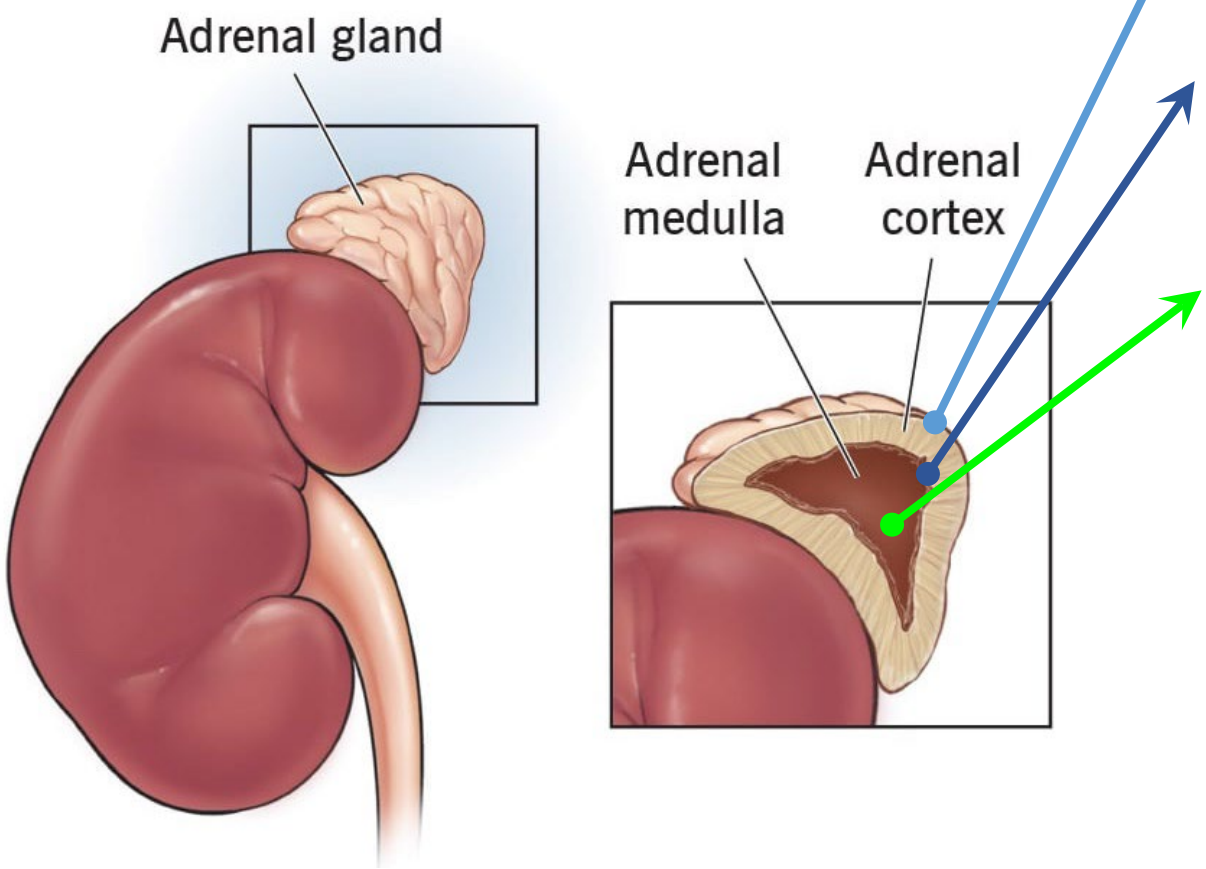

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= **A**drenaline

Parke, Davis & Co cocaine with adrenalin. Photograph courtesy of the Wood Library-Museum, Schaumburg, Illinois.

adrenaline ≠ epinephrine

What's in a name?

- 1910: Sir Henry Dale published that anaphylaxis was due to the host-response to the toxin, and not the toxin itself.
- 1906: Dale wrote a paper on the pharmacological effects of ergot alkaloids
  - including experiments with adrenaline.
- Henry Wellcome objected to "adrenaline" because Adrenalin was a registered trade-name of Parke, Davis & Co, suggesting that Dale should use "epinephrine"
- Dale argued (successfully) that "adrenaline" was used to describe the physiologically active principle of the adrenal glands, and did not imply a specific commercial preparation. Furthermore, epinephrine was a different substance and therefore refused to change his manuscript, threatening to withdraw it altogether.

Letter from Henry Dale to Henry Wellcome, 1906:

“There is among English medical men and particularly among physiologists, a strongly marked prejudice against any connection with commerce. That prejudice I am earnestly and constantly trying to break down on my own behalf, and on that of any pharmacological workers in your laboratories. I have great hope of success: but the position I am striving for, on your behalf as well as my own, would be seriously imperiled by a breath of suspicion that the publication of my work was hampered or modified by other than scientific considerations”

Imperial College London

- Poppy Harvey died in 2010 after accidentally eating some cake containing peanut, despite using both her Epipens.

- The Coroner raised a concern that the Epipens resulted in a subcutaneous injection, which might have contributed to the outcome.

MHRA
Regulating Medicines and Medical Devices

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2015
EMA/478468/2015
Committee for Medicinal Products for Human Use (CHMP)

Adrenaline Auto-injectors:
A Review of Clinical and Quality Considerations

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Adrenaline auto-injectors (AAIs)

International non-proprietary name: adrenaline (epinephrine)

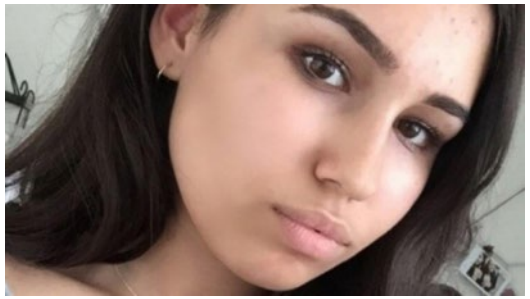
Procedure number: EMEA/H/A-31/1398

04 June 2014

Medicines and Healthcare Products Regulatory Agency

2018

- Natasha Ednan-Laperouse died from anaphylaxis while on board a flight to France
- Both her Epipens were administered
- The coroner concluded that:



“the use of needles which access only subcutaneous tissue and not muscle is in my view inherently unsafe…

“The combination of … an inadequate dose of adrenaline and an inadequate length needle raises serious safety concerns.”

Does epinephrine work?

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

REVIEW ARTICLE

Management of anaphylaxis: a systematic review

S. Dhami[1], S. S. Panesar[2], G. Roberts[3,4,5], A. Muraro[6], M. Worm[7], M. B. Bilò[8], V. Cardona[9], A. E. J. Dubois[10], A. DunnGalvin[11], P. Eigenmann[12], M. Fernandez-Rivas[13], S. Halken[14], G. Lack[15,16], B. Niggemann[17], F. Rueff[18], A. F. Santos[15,16,19], B. Vlieg-Boerstra[20], Z. Q. Zolkipli[3,4] & A. Sheikh[2,21] on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group*

"The only trial[s]… have been undertaken in patients who were at the time not experiencing anaphylaxis. Taken together with the methodologically lower quality evidence from case-series and fatality registers, there is some evidence to support the use of adrenaline for the emergency management of anaphylaxis."

Allergy 2014;69:168–17

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

US Parachute Association reported
821 injuries and 18 deaths out of
2.2 million jumps in 2007

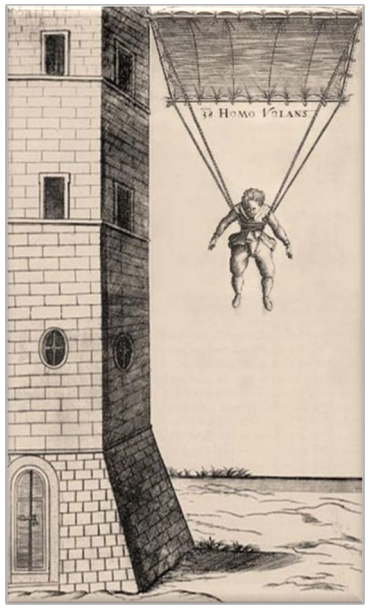
Relative risk reduction:
….> 99.9 % (1/100,000)

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

BMJ, 2003

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



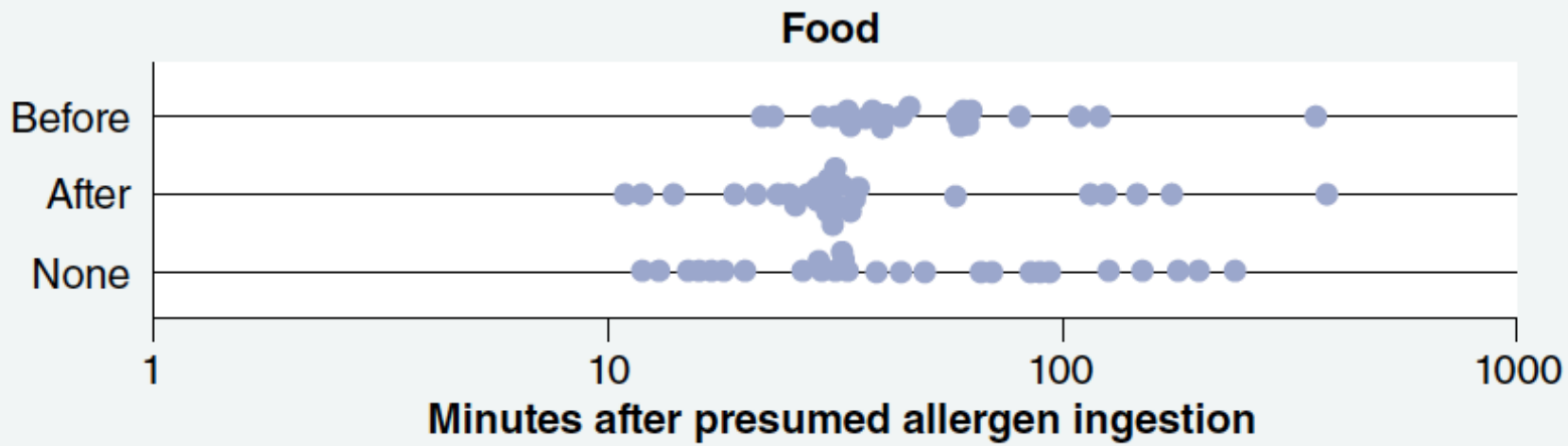
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

BMJ, 2003

But anaphylaxis/epinephrine is different…

- People die despite getting timely epinephrine…

Figure 3.4. Timing of epinephrine with respect to time of first arrest.



One third of UK fatalities were administered epi correctly and in a timely manner

Pumphey & Gowland, JACI 2007;119(4):1018-9.
Pumphrey & Sturm, Advances in Anaphylaxis Management, Future Medicine 2014.

Significant underuse of epinephrine, yet…

UK survey of 869 teenagers[1]

- 83% of (245) teenagers with anaphylaxis don't use their EAI

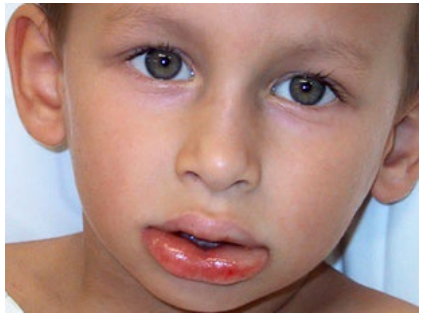
European Anaphylaxis Registry[2]

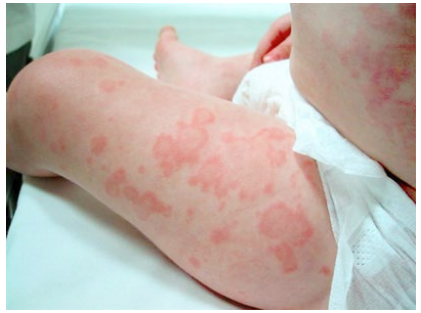
- 59 centres reported 3333 cases of anaphylaxis…
- Only 13.7% of lay- or self-treated reactions to food and 27.6% of insect anaphylaxis received epinephrine.

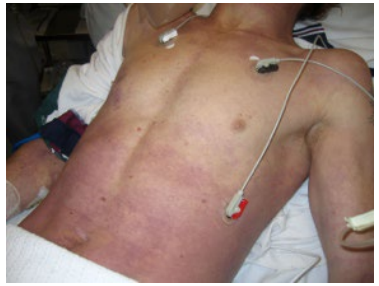
[1]Noimark et al, CEA 2012;42:284-92.

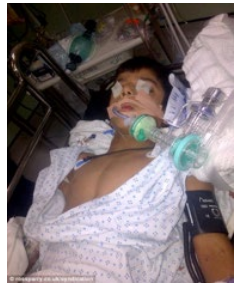
[2]Worm et al, Allergy 2014;69:1397-1404

Most people having anaphylaxis do not die…









Mild, localized symptoms

Generalized skin reaction +/- tummy symptoms

ANAPHYLAXIS

Severe anaphylaxis

Death

1 in 10 | 1 in 100 | 1 in 1000 | 1 in 10,000 | 1 in 100,000 | 1 in 1 million

- Emergency hospital visit due to a motor vehicle accident
- Death (any cause)
- Death due to an accident
- Death due to a fire

Umasunthar et al, Clin Exp Allergy. 2013;43:1333-41.

Yet some tragically do…

Pret has power to stop more food allergy deaths, says coroner

Report into death of teenager concludes current system of monitoring 'highly inadequate'

▲ Natasha Ednan-Laperouse died in 2016 after eating a baguette with sesame seeds. Phot
handout/PA

Megan Lee: Pair guilty of girl's takeaway allergy death

26 October 2018 Share

Megan Lee died two days after she was admitted to Royal Blackburn Hospital

Two men have been found guilty of the manslaughter of a 15-year-old girl who suffered an allergic reaction to a takeaway meal.

13-year-old boy dies of allergic reaction after having 'cheese thrown down his T-shirt', inquest hears

Karanbir Cheema died 10 days after incident at school in Greenford

Adam Forrest | @adamtomforrest | Wednesday 19 September 2018 16:41 | 52 comments

News > UK > Home News

Mother-of-five died after eating Pret a Manger vegan wrap contaminated with traces of milk, coroner rules

Celia Marsh, 42, suffered anaphylaxis shortly after eating super-veg rainbow flatbread while on post-Christmas shopping trip with her family in Bath

Chiara Giordano • Thursday 22 September 2022 20:57 BST

Dental nurse Celia Marsh died after eating a Pret a Manger vegan wrap *(Leigh Day/PA)*

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

REVIEW ARTICLE

Can we identify patients at risk of life-threatening allergic reactions to food?

P. J. Turner[1], J. L. Baumert[2], K. Beyer[3], R. J. Boyle[1], C.-H. Chan[4], A. T. Clark[5], R. W. R. Crevel[6], A. DunnGalvin[7], M. Fernández-Rivas[8], M. H. Gowland[9], L. Grabenhenrich[10], S. Hardy[11], G. F. Houben[12], J. O'B Hourihane[13], A. Muraro[14], L. K. Poulsen[15], K. Pyrz[7], B. C. Remington[12], S. Schnadt[16], R. van Ree[17], C. Venter[18,19], M. Worm[20], E. N. C. Mills[21], G. Roberts[19,22] & B. K. Ballmer-Weber[23]

[1]Section of Paediatrics (Allergy and Infectious Diseases) & MRC and Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London, London, UK; [2]Food Allergy Research and Resource Program, Department of Food Science and Technology, University of Nebraska, Lincoln, NE, USA; [3]Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany; [4]Food Standards Agency, London, UK; [5]Cambridge University Hospitals NHS Foundation Trust, Cambridge,UK; [6]Safety and Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedford, UK; [7]Applied Psychology and Paediatrics and Child Health, University College Cork, Cork, Ireland; [8]Servicio de Alergia, Hospital Clínico San Carlos, IdISSC, Madrid, Spain; [9]Allergy Action, Farnborough, UK; [10]Institute for Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Berlin, Germany; [11]Food Standards Agency, London, UK; [12]TNO, Zeist, The Netherlands; [13]Paediatrics and Child Health, University College Cork, Cork, Ireland; [14]Department of Paediatrics, Centre for Food Allergy Diagnosis and Treatment, University of Padua, Veneto, Italy; [15]Allergy Clinic, Copenhagen University Hospital at Gentofte, Copenhagen, Denmark; [16]German Allergy and Asthma Association (Deutscher Allergie- und Asthmabund (DAAB)), Mönchengladbach, Germany; [17]Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [18]School of Health Sciences and Social Work, University of Portsmouth, Portsmouth; [19]The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK; [20]Allergy-Center Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany; [21]Institute of Inflammation and Repair, Manchester Academic Health Science Centre, Manchester Institute of Biotechnology, The University of Manchester, Manchester, UK; [22]NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust and Human Development and Health Academic Unit, University of Southampton Faculty of Medicine, Southampton, UK; [23]Allergy Unit, Department of Dermatology, University Hospital, University Zürich, Zürich, Switzerland

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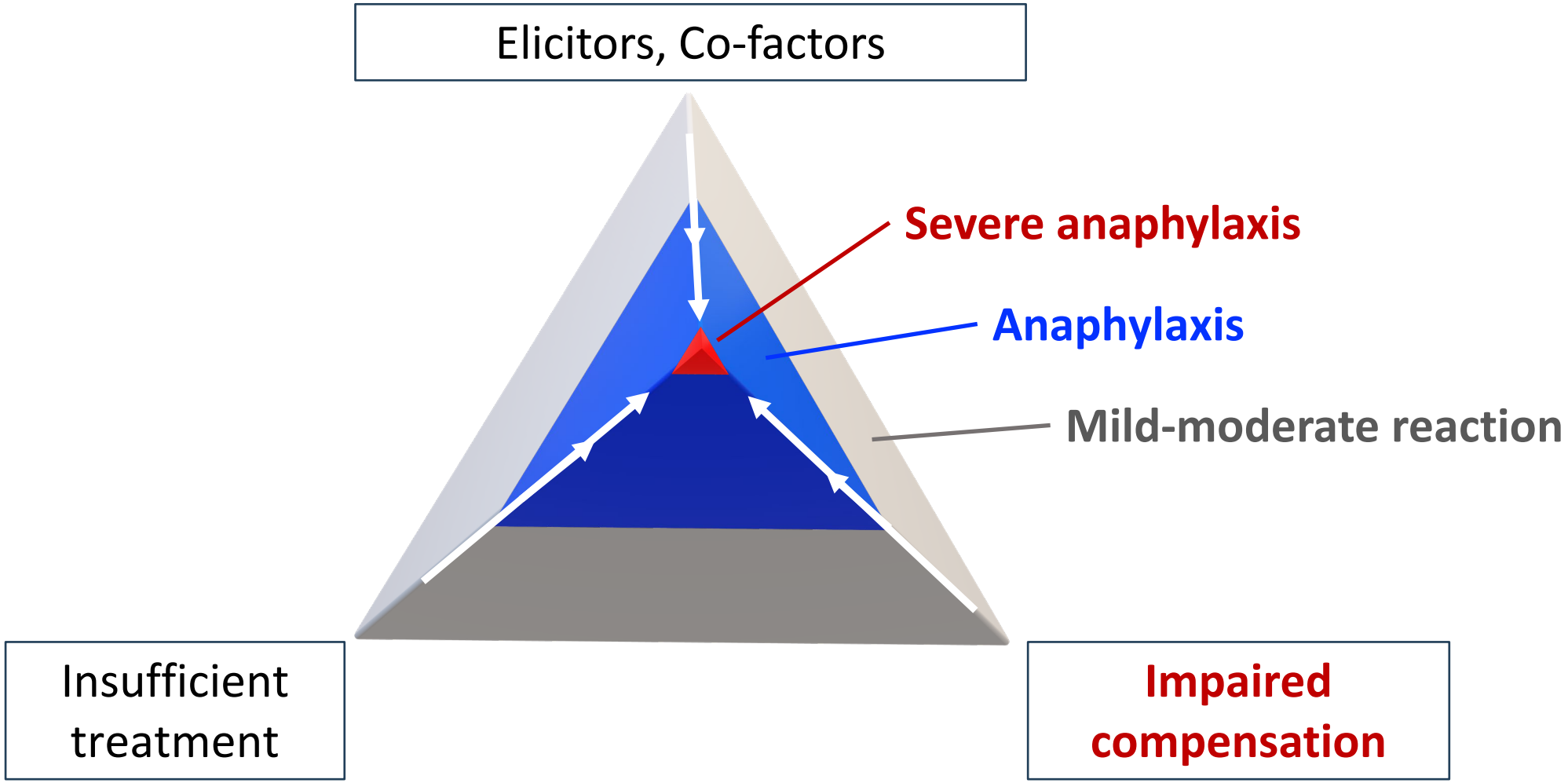
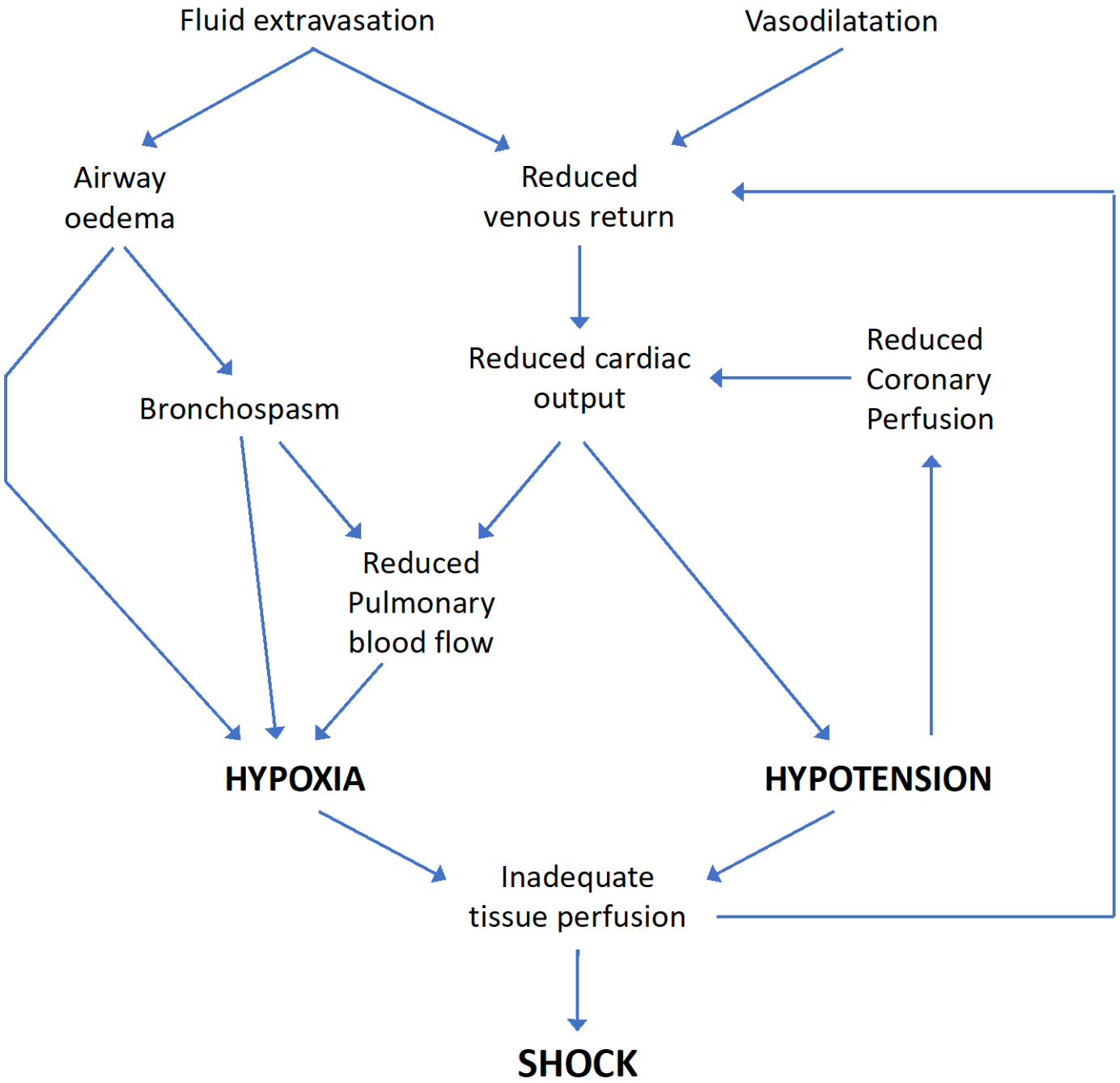
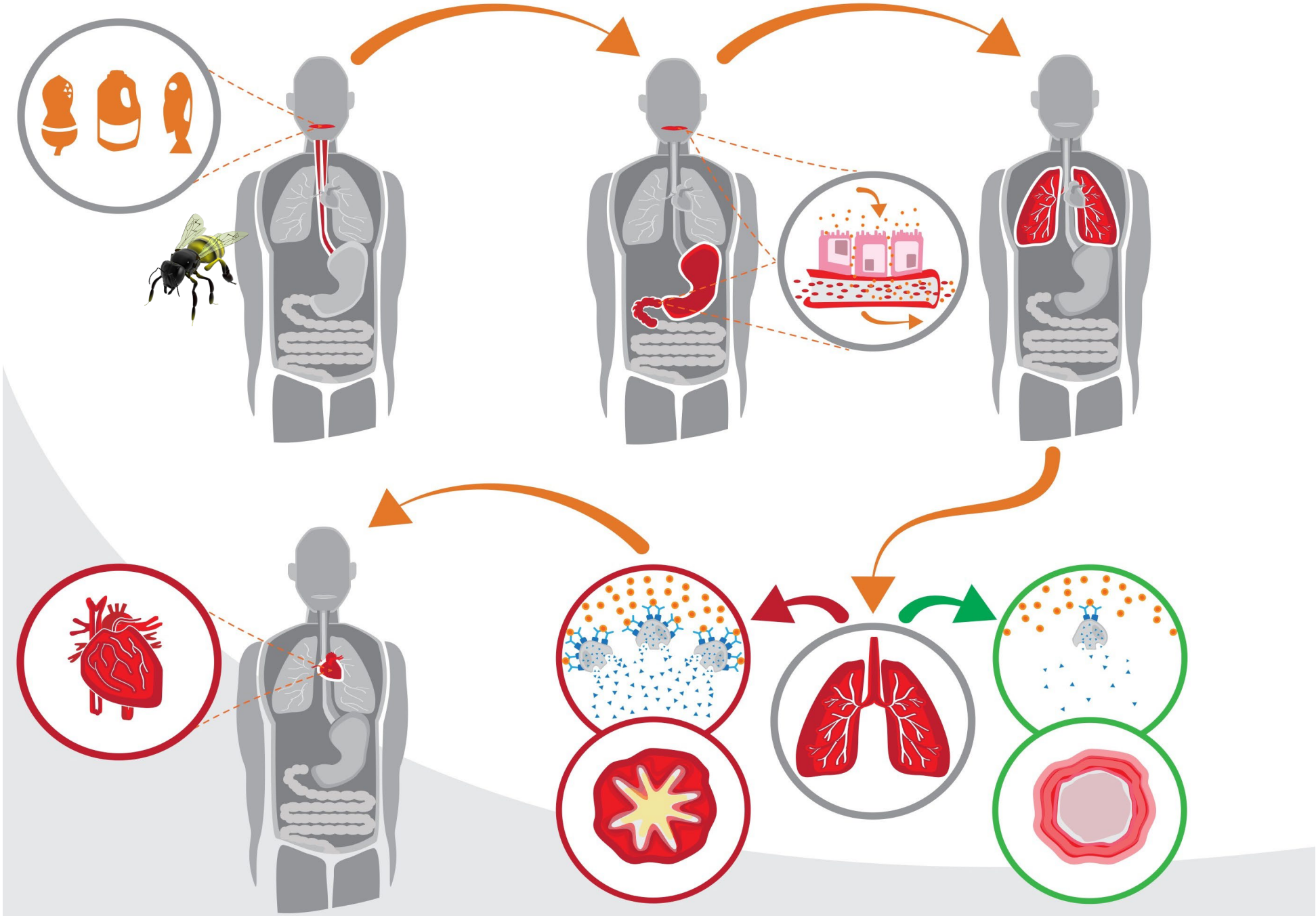
NO!

What are the drivers of severity?



So what *really* happens during anaphylaxis?


Fluid extravasation
Vasodilatation
Airway oedema
Reduced venous return
Reduced cardiac output
Reduced Coronary Perfusion
Bronchospasm
Reduced Pulmonary blood flow
HYPOXIA
HYPOTENSION
Inadequate tissue perfusion
SHOCK



Not all anaphylaxis is the same…

Anaphylaxis: Clinical patterns, mediator release, and severity

Simon G. A. Brown, MBBS, PhD, FACEM,[a,b,c,d] Shelley F. Stone, PhD,[a,b] Daniel M. Fatovich, MBBS, FACEM, PhD,[a,b,c] Sally A. Burrows, BMath Grad Dip Med Stat,[b] Anna Holdgate, MBBS, MMed, FACEM,[e] Antonio Celenza, MBBS, MClinEd, FCEM, FACEM,[b,f] Adam Coulson, MBBS, FACEM,[g] Leanne Hartnett, MBBS, FACEM,[d,h] Yusuf Nagree, MBBS, FACEM,[d,i] Claire Cotterell, BSc(Hons),[a] and Geoffrey K. Isbister, MBBS, MD, FACEM[j,k]

Perth, Crawley, Fremantle, Sydney, Nedlands, Bunbury, Rockingham, Armadale, and Newcastle, Australia

- 315 episodes of acute anaphylaxis
- 97 severe reactions:
  - 45 (46%) hypotensive (sBP<90mmHg/LOC/incontinence)
  - 23 (24%) hypoxemic (O_2 sats < 92%)
  - 29 (30%) mixed

Brown et al, JACI 2013;132:1141-9

Not all anaphylaxis is the same…

	Hypotensive reaction (n = 50)	Hypoxemic reaction (n = 38)
Age*	1.02 (1.01-1.04) [.011]	1.04 (1.02-1.06) [<.001]
Male	0.72 (0.38-1.36) [.317]	1.18 (0.58-2.41) [.646]
Lung disease	0.89 (0.42-1.90) [.760]	3.33 (1.47-7.56) [.004]
Causation†		
Oral medicine	3.79 (1.52-9.47) [.004]	2.55 (0.95-6.89) [.064]
Injected	4.20 (1.21-14.60) [.024]	4.26 (1.20-15.20) [.025]
Venom	1.34 (0.48-3.77) [.575]	1.38 (0.49-3.91) [.542]
Unknown	1.65 (0.56-4.90) [.364]	0.45 (0.10-2.04) [.302]
Hypotensive reaction		
Hypoxemic reaction		

All values are odds ratios (95% CI) [*P* value].

*Odds ratio per year of increment in age.

†Odds ratios for causation are relative to food causation as a baseline. Overall *P* values (Wald test) for cause as a categorical variable

Brown et al, JACI 2013;132:1141-9

Table 4. Differences in the epidemiology and pathophysiology of anaphylaxis because of food versus nonfood causes

	Food	Medication/iatrogenic causes	Venom sting
Age distribution: anaphylaxis (all severity)	Most common in preschool children, less common in older adults	Predominantly older ages	All ages
Age distribution: fatal anaphylaxis	Young adults into fourth decade of life. Rare in younger children	Unusual until fifth decade of life	Fourth to sixth decade
Symptoms	Respiratory	Cardiovascular (respiratory less common)	Cardiovascular (respiratory less common)
Asthma/atopy	Common	Uncommon	Uncommon
Onset	Less rapid	Rapid	Rapid
Site of antigen presentation	Usually orogastric route	Usually parenteral route	Parenteral
Triggering threshold dose	++ Interperson variability (up to 4 log)	Poor data for medications	Less variability for insect stings
Mechanism	No or relatively modest increases in MCT generally observed	Increased MCT often seen	Increased MCT often seen
Sex	M=F	M=F	M>>F
Ethnic distribution	Possible higher risk in persons of Asian decent My be more common in male children of African American decent	More common in persons of African-American decent	More common in Caucasians

MCT, mast cell tryptase.

Turner & Campbell. Curr Opin Allergy Clin Immunol. 2016;16:441-50.

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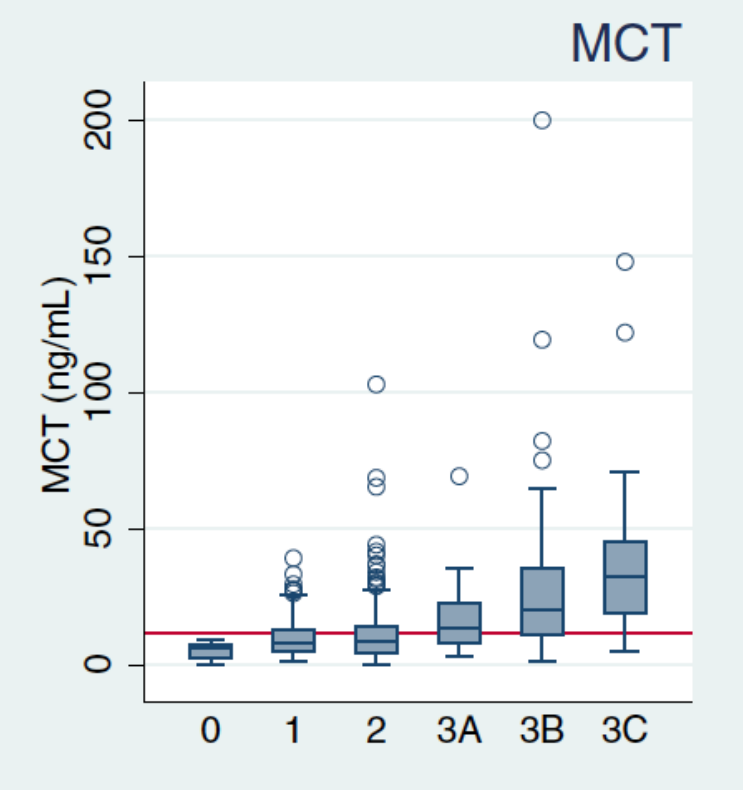
Turner & Campbell. Curr Opin Allergy Clin Immunol. 2016;16:441-50.

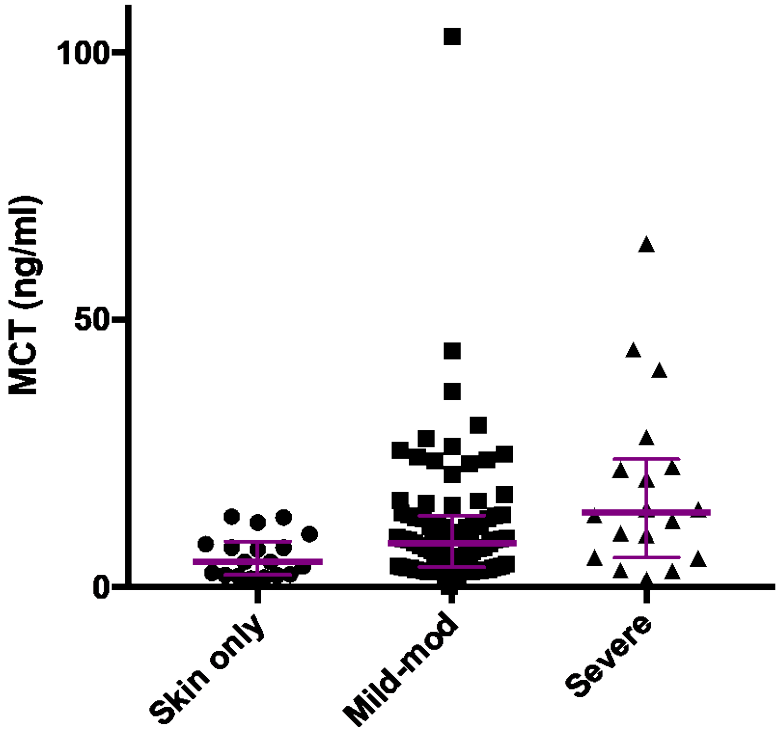
Anaphylaxis: Clinical patterns, mediator release, and severity

Simon G. A. Brown, MBBS, PhD, FACEM,[a,b,c,d] Shelley F. Stone, PhD,[a,b] Daniel M. Fatovich, MBBS, FACEM, PhD,[a,b,c] Sally A. Burrows, BMath Grad Dip Med Stat,[b] Anna Holdgate, MBBS, MMed, FACEM,[e] Antonio Celenza, MBBS, MClinEd, FCEM, FACEM,[b,f] Adam Coulson, MBBS, FACEM,[g] Leanne Hartnett, MBBS, FACEM,[d,h] Yusuf Nagree, MBBS, FACEM,[d,i] Claire Cotterell, BSc(Hons),[a] and Geoffrey K. Isbister, MBBS, MD, FACEM[j,k]

Perth, Crawley, Fremantle, Sydney, Nedlands, Bunbury, Rockingham, Armadale, and Newcastle, Australia



All cause (n=315)



Food only (n=123)

Anaesth Intens Care (1986), 14, 17-21

Clinical Observations on the Pathophysiology and Treatment of Anaphylactic Cardiovascular Collapse

M. McD. Fisher*
Intensive Therapy Unit, Royal North Shore Hospital, Sydney, New South Wales

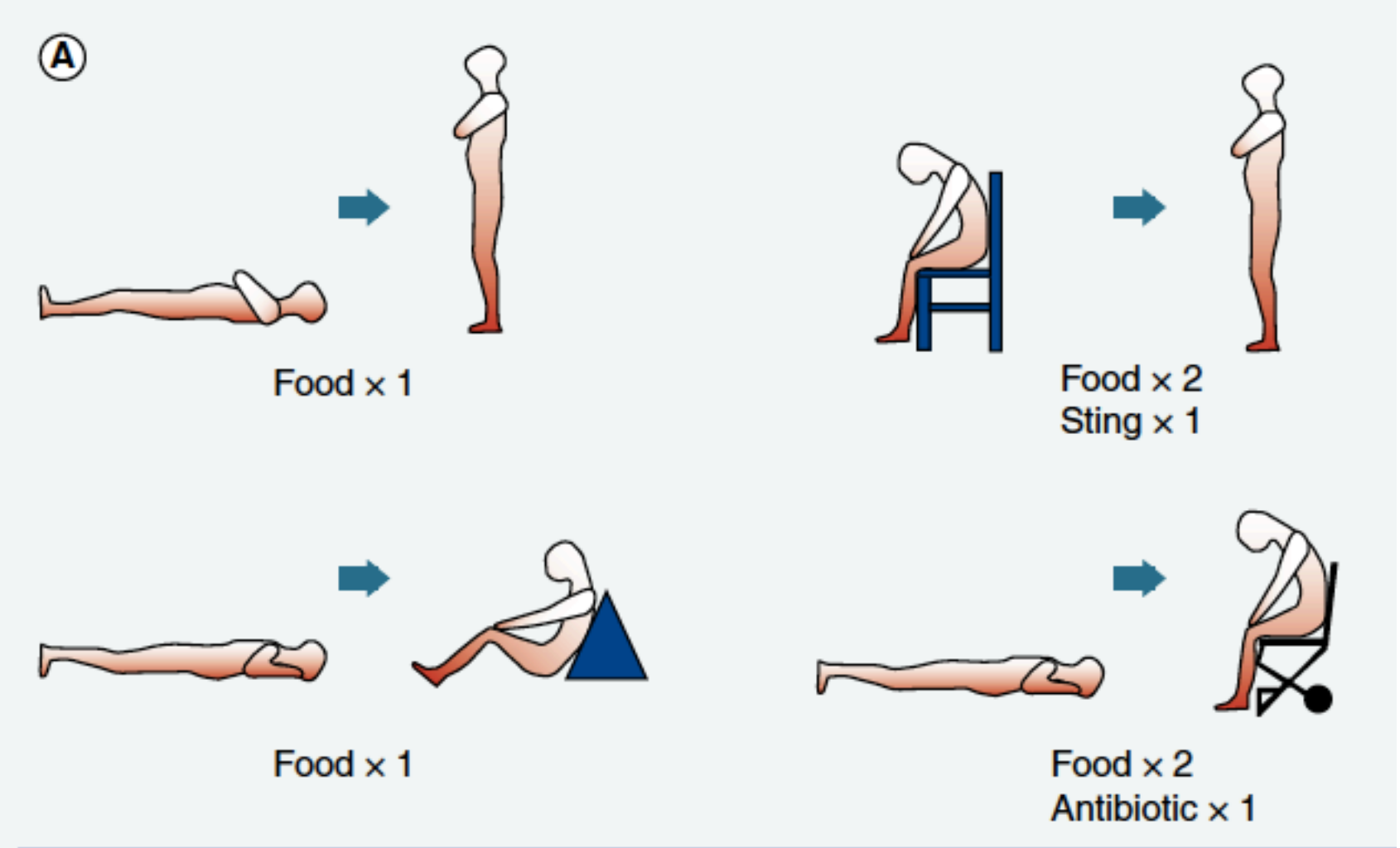
---

Perioperative anaphylaxis, n=227

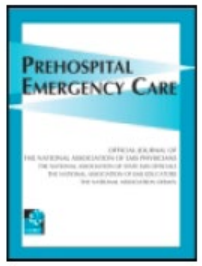
- 204 cases had sBP <40mmHg

1. Arrhythmia
2. Cardiac (myocardial) dysfunction
3. Plasma extravasation: serial Hb measurements (n=22)
   - ❖ loss in circulating volume of up to 35%

Posture and fatal anaphylaxis



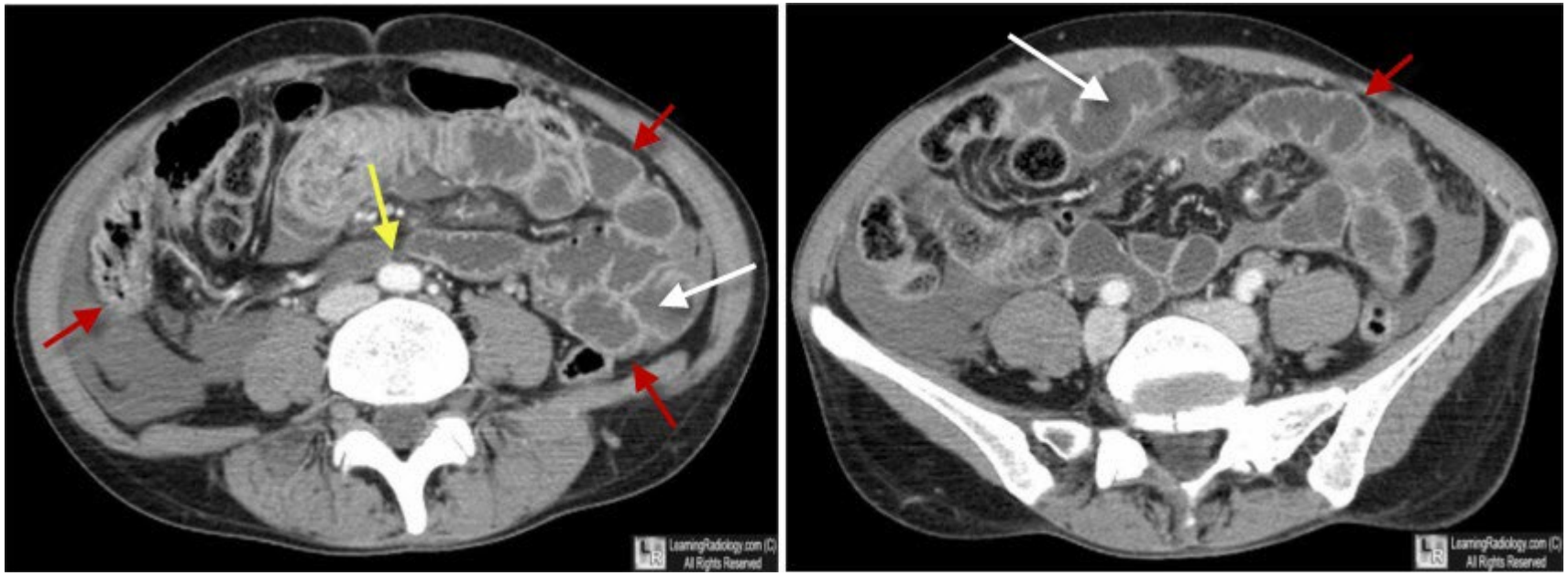
Pumphrey & Sturm 2014



A Case of Unrecognized Prehospital Anaphylactic Shock

Ryan C. Jacobsen, MD, EMT-P, Matthew C. Gratton, MD

PREHOSPITAL EMERGENCY CARE 2011;15:61–66

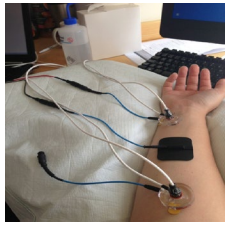


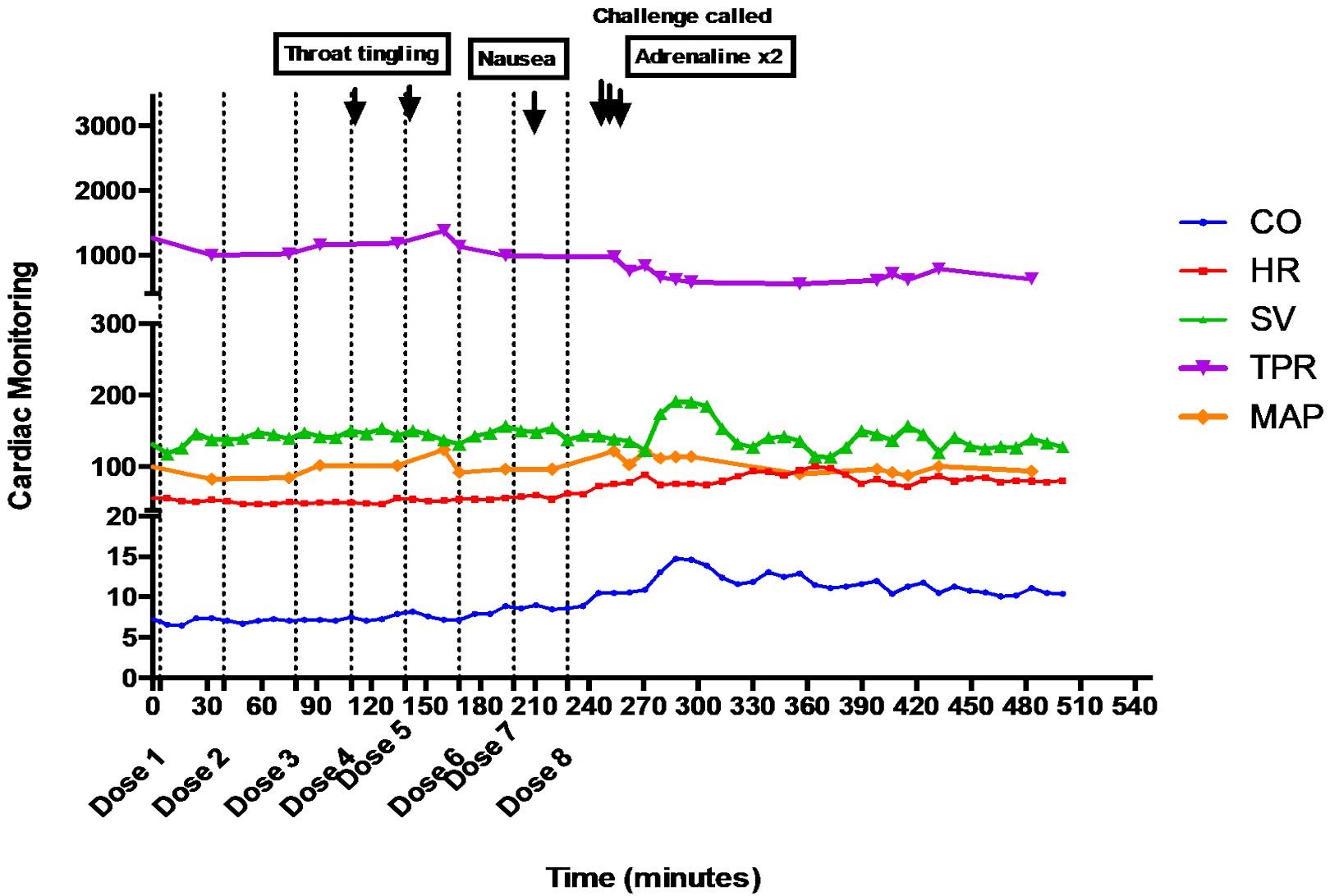
Hypotension (<80mmHg) with lactic acidosis (7.7mM)

Diffuse hives noted ~30mins later

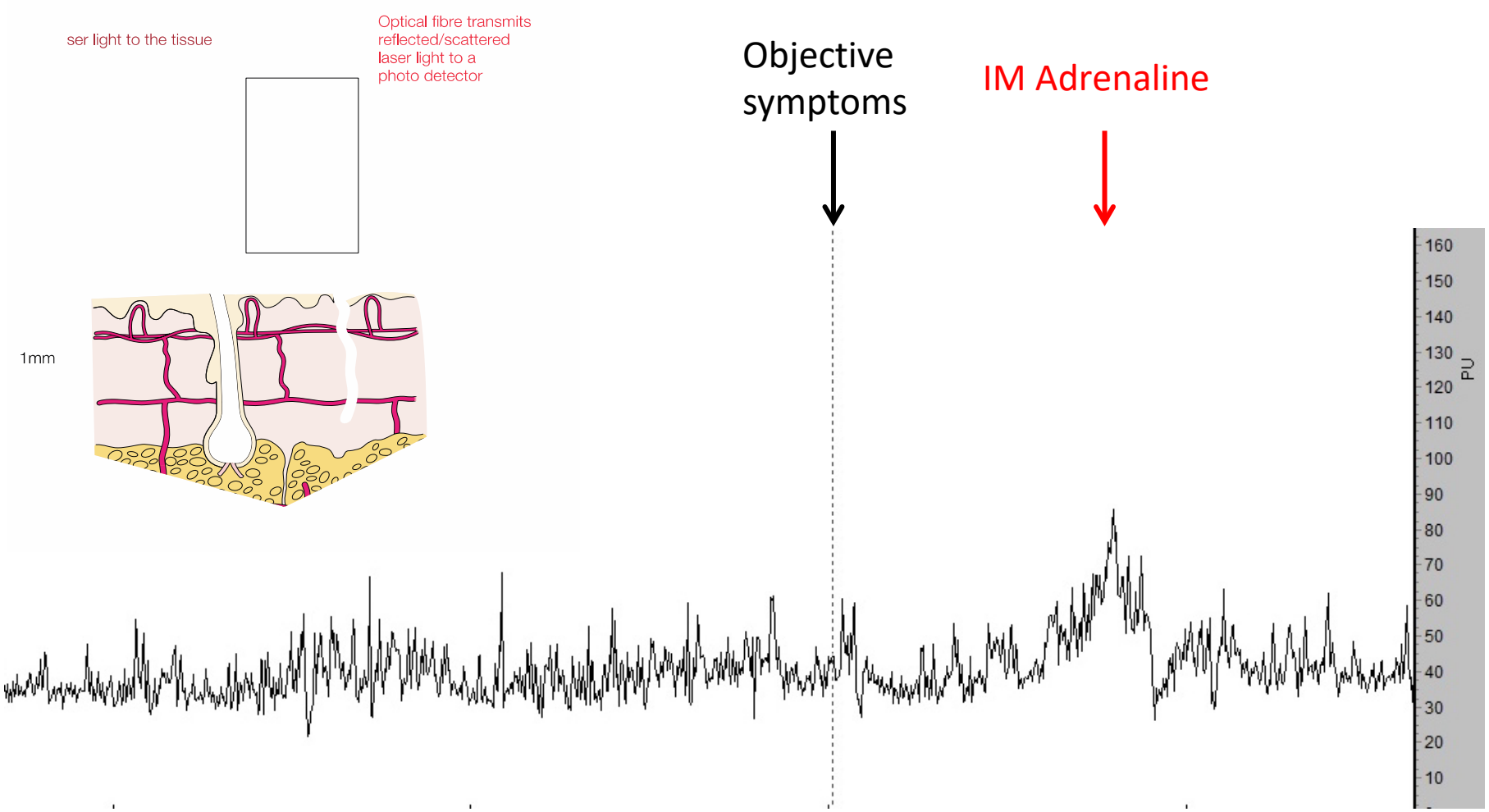
Drug-induced reaction (oral route)

What about more typical anaphylaxis?

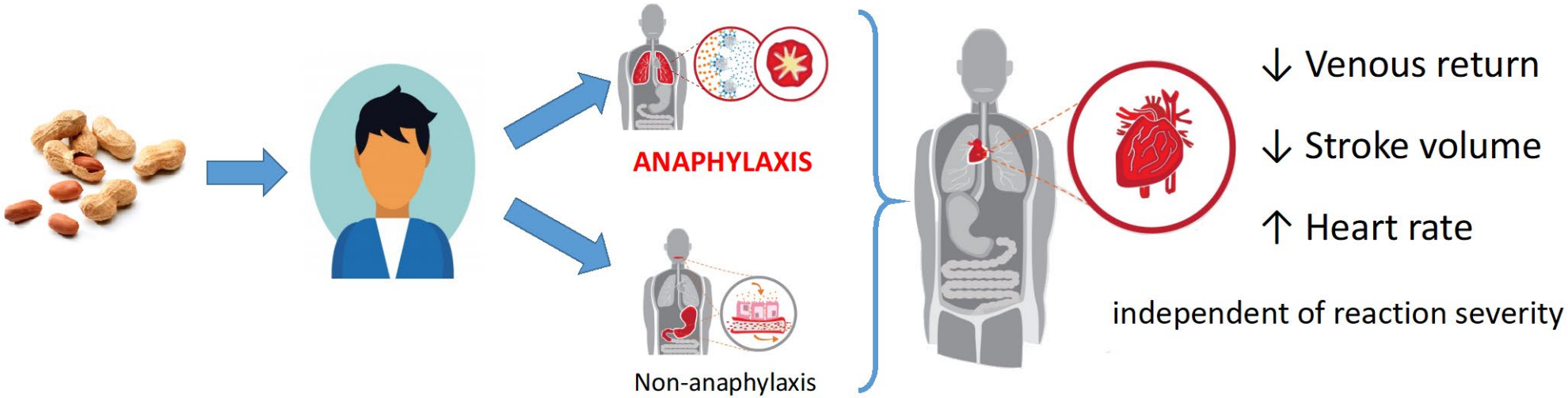




Blood flow

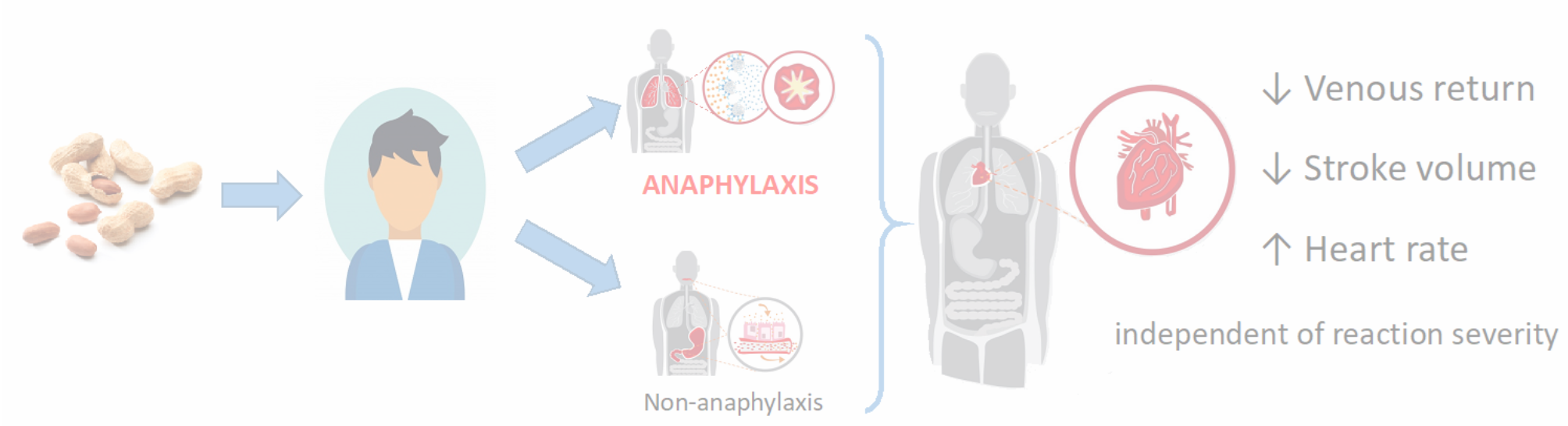

ser light to the tissue
Optical fibre transmits reflected/scattered laser light to a photo detector
1mm
Objective symptoms
IM Adrenaline
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
PU

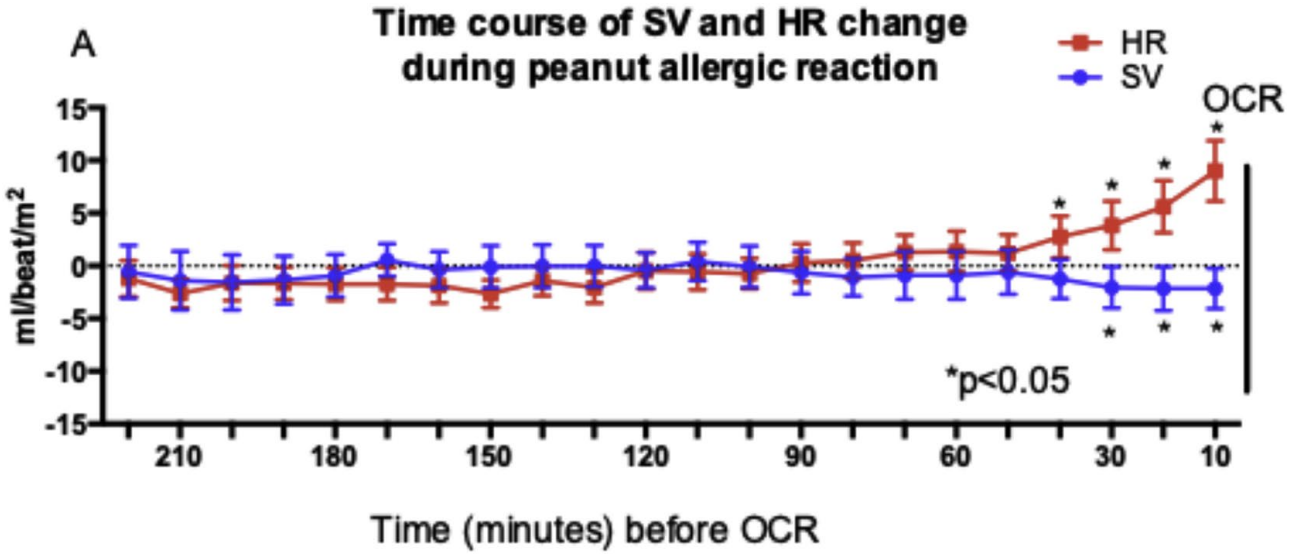
What about more typical anaphylaxis?



Ruiz-Garcia et al, JACI 2020
doi: 10.1016/j.jaci.2020.06.033

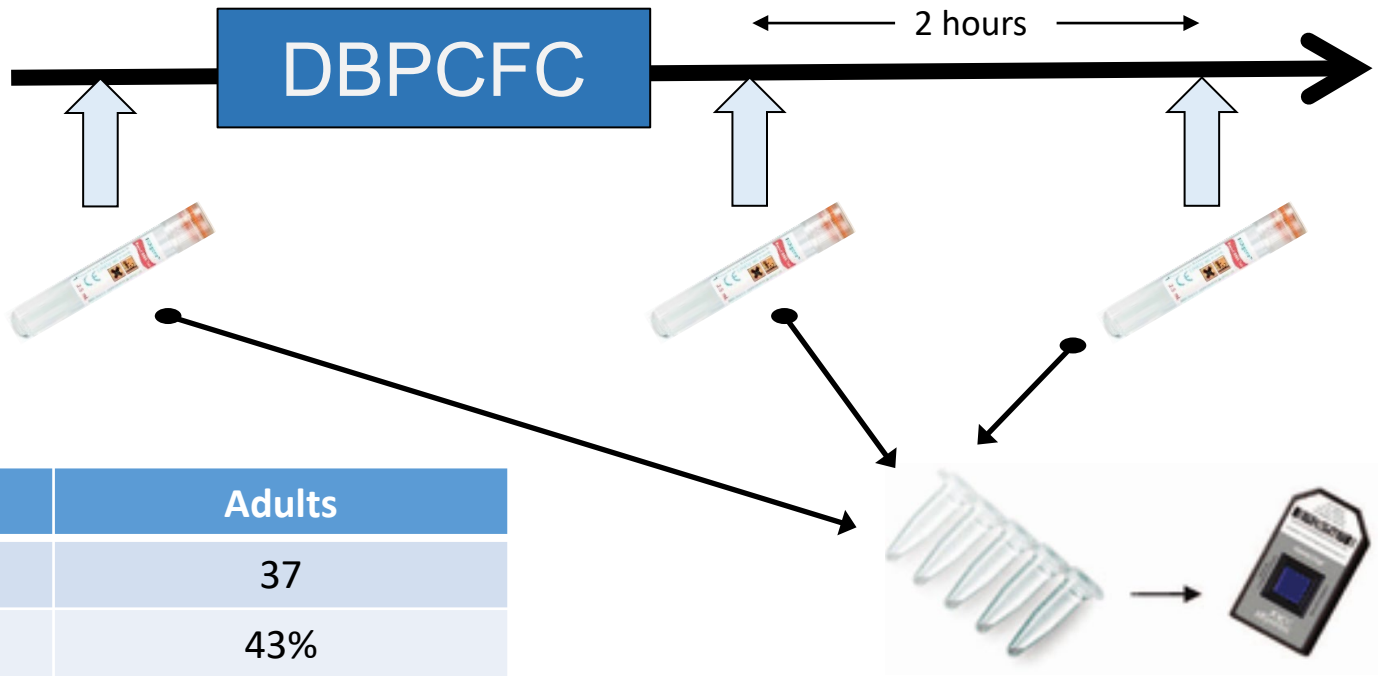
What about more typical anaphylaxis?





Ruiz-Garcia et al, JACI 2020
doi: 10.1016/j.jaci.2020.06.033

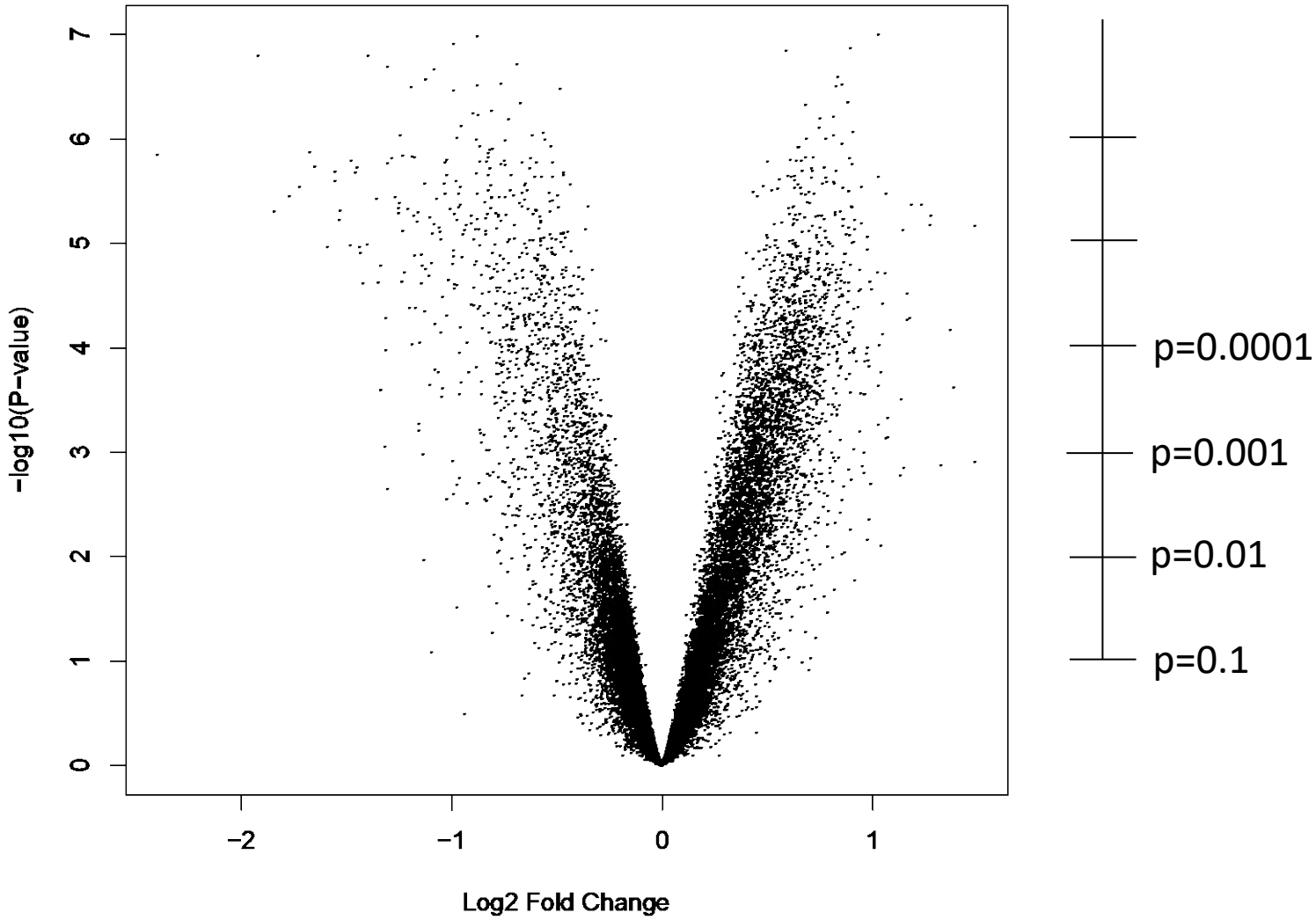
What's driving reactions?



	Children	Adults
n	57	37
% male	54%	43%
SPT to peanut	8mm (7 - 11)	11mm (9½ - 13)
sIgE to: • Peanut • Ara h 1 • Ara h 2 • Ara h 3 • Ara h 8	38.7 (5.1-136) 4.9 (0 - 40.3) 18.0 (2.3-68.7) 0.4 (0 - 11.7) 0.1 (0 - 5.5)	10.7 (3.3-41.7) 0.7 (0 - 10.7) 6.2 (1.6-17.9) 0.1 (0 - 3.7) 0.1 (0 - 1.5)
ED at index DBPCFC	143mg (43-443)	133mg (33-433)
Anaphyalxis at FC: • NIAID • Respiratory/CVS	 27 (47%) 17 (30%)	 31 (84%) 17 (46%)

Affymetrix HTA 2.0 platform
(>6million probes)

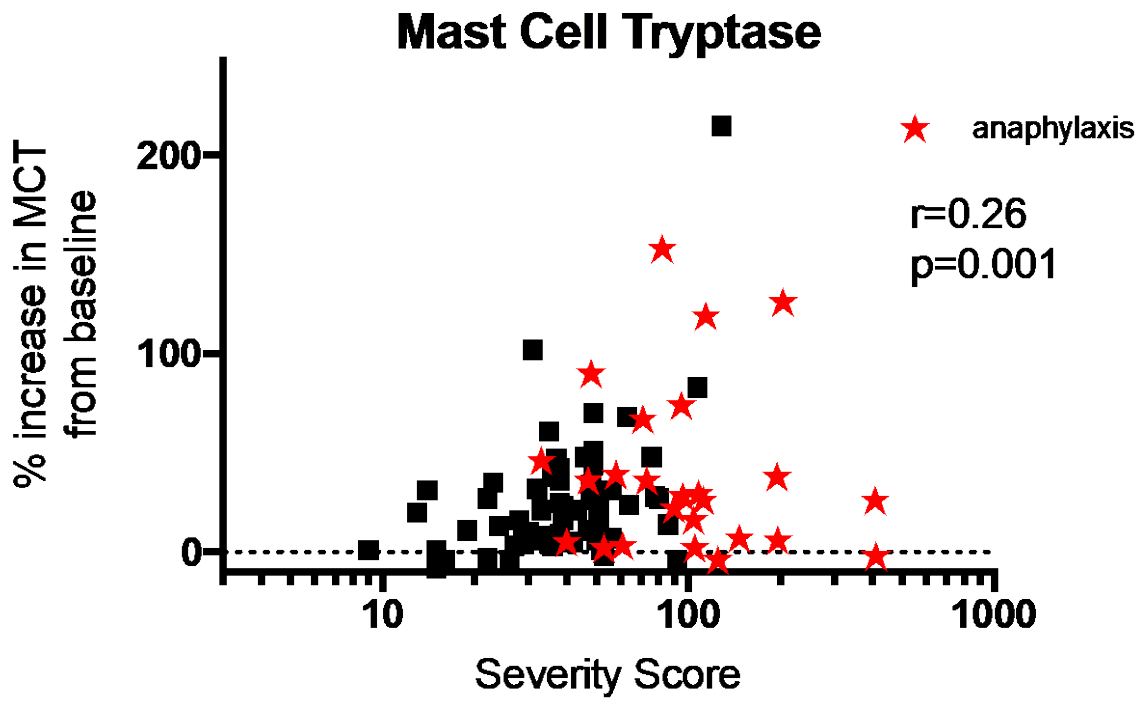
Changes in gene expression with anaphylaxis:

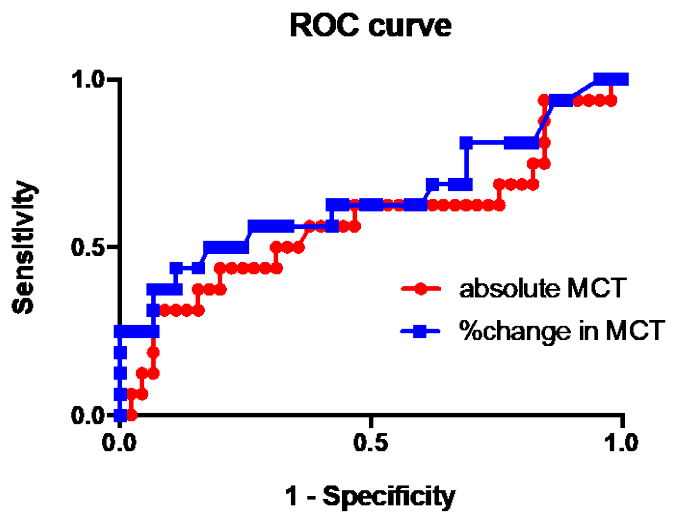


Results: unpaired analysis

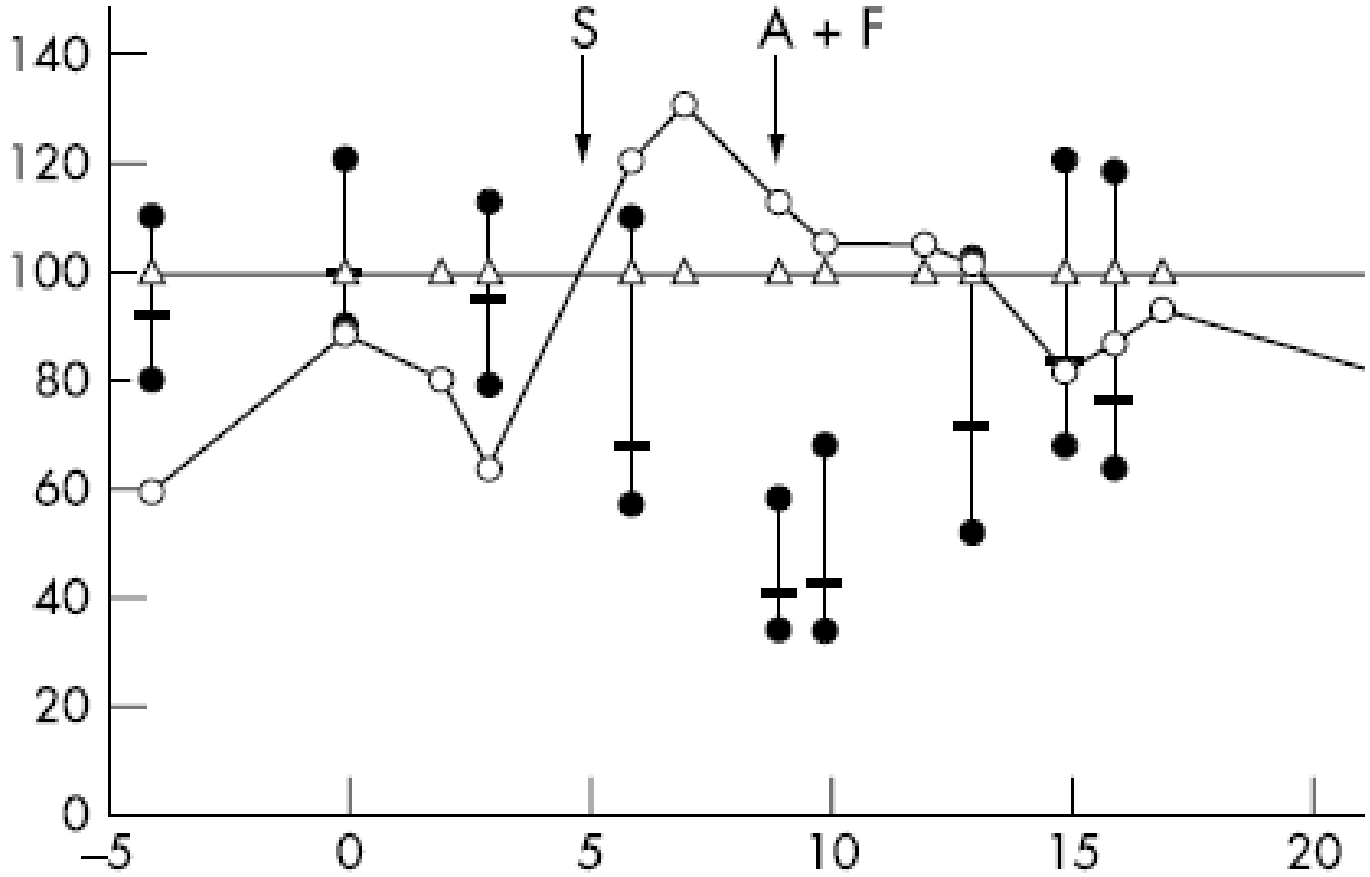
Grade	Reaction vs baseline	2hrs post vs baseline	2hrs post vs reaction
❶ n=11	nil	nil	nil
❷ *not* anaphylaxis n=35	nil	4449 genes	4927 genes
❷ anaphylaxis (NIAID) n=20	nil	646 genes	2042 genes
❸ n=16	nil	2646 genes	1343 genes
❹ n=19	nil	2505 genes	1751 genes
(Placebo) n=20	nil		

What's driving reactions?





Efficacy of epinephrine in human anaphylaxis



Brown et al, Emerg Med J 2004;21:149-54

Why doesn't epinephrine (always) work?

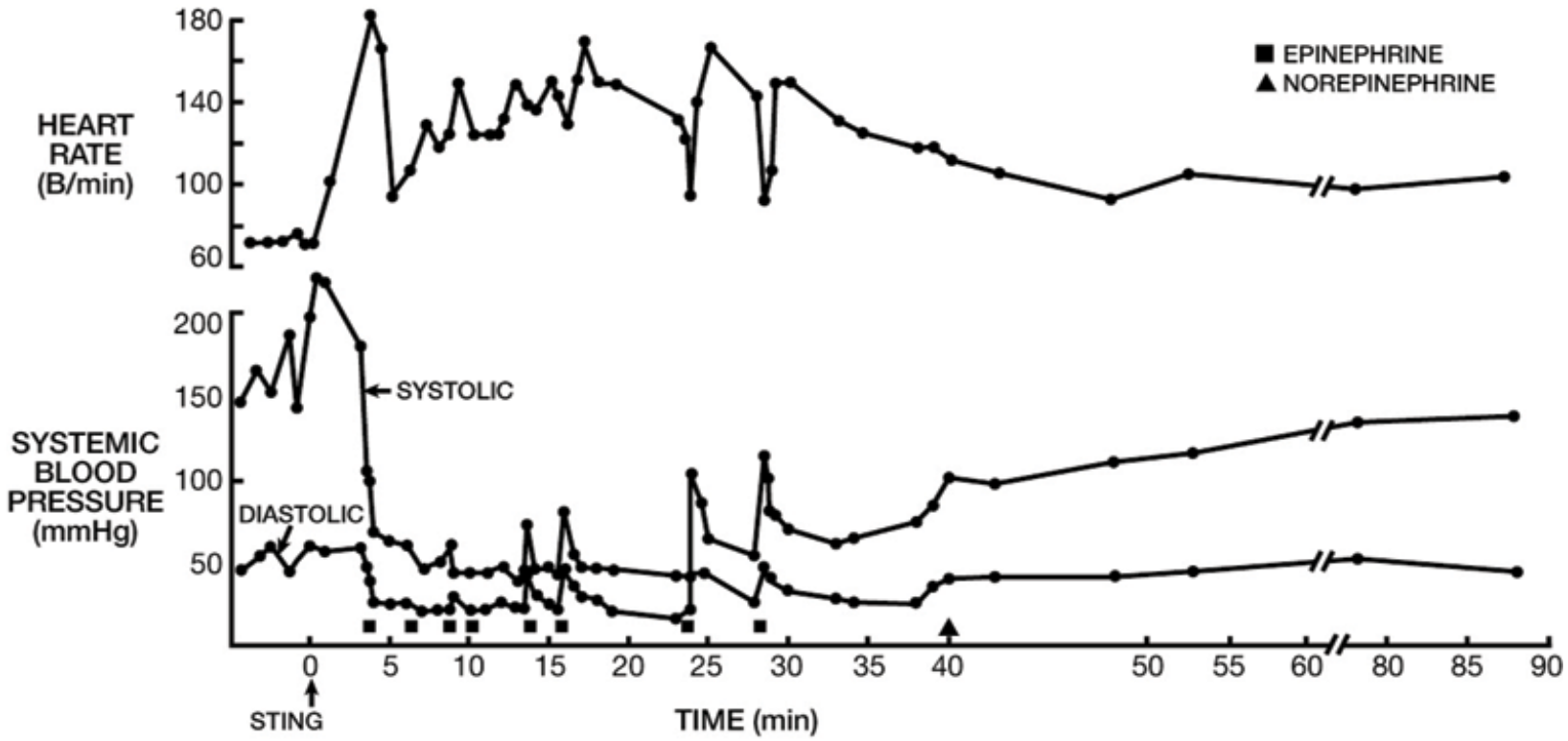


Figure 2: Severe Anaphylaxis Following an Insect Sting in Patient 2—The time of the sting is indicated on the abscissa. Blood pressure is shown by the ● and the pulse rate by the ×. Each ■ denotes IV administration of 4–5 mL of 1:10,000 epinephrine (0.4–0.5 mg) as a bolus over 10 to 15 seconds. The ▲ denotes the start of a 2-minute infusion of norepinephrine.

Smith et al, J Clin Invest 1980;66:1072-80

Does needle length matter?

Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen Autoinjector in Healthy Volunteers

Thierry Duvauchelle, MD[a], Philippe Robert, PhD[b], Yves Donazzolo, MD[c], Sabrina Loyau, PharmD[d], Bernard Orlandini, MSc[d], Philippe Lehert, PhD[e,f], Jeanne-Marie Lecomte, PhD[a], and Jean-Charles Schwartz, PhD[a]

Paris, Saint Gregoire, Gières, and Massy, France; Louvain, Belgium; and Melbourne, Victoria, Australia

Characteristic	Normal weight men (n = 18)	Overweight women (n = 12)
Age (y)	31.50 ± 9.23	33.25 ± 9.07
Height (cm)	179.17 ± 7.85	161.92 ± 6.52
Weight (kg)	75.03 ± 10.48	78.07 ± 7.91
BMI (kg/m^2)	23.28 ± 1.87	29.73 ± 1.89

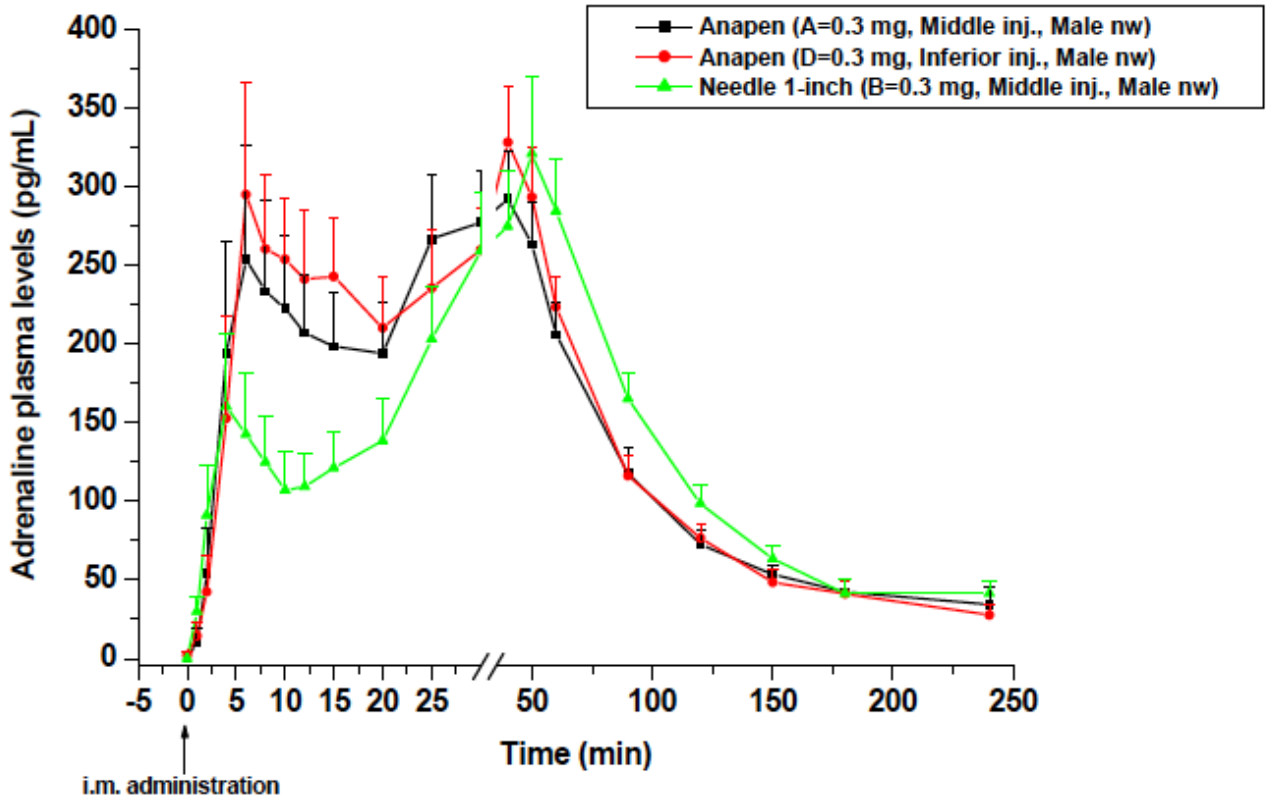
	Injection site	Dose	Cohort
A	Mid thigh	300mcg, Anapen	♂ normal BMI
B	Mid thigh	300mcg, needle	♂ normal BMI
C	Mid thigh	500mcg, needle	♂ normal BMI
D	Inferior	300mcg, Anapen	♂ normal BMI
E	Inferior	300mcg, Anapen	♀ overweight

JACI IP 2018;6:1257-63

Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen Autoinjector in Healthy Volunteers

JACI IP 2018;6:1257-63

Mean ± SEM plasma adrenaline concentration-time profiles in linear scale



	Site	Dose	
A	Mid	300mcg, Anapen	♂
B	Mid	300mcg, needle	♂
C	Mid	500mcg, needle	♂
D	Inferior	300mcg, Anapen	♂
E	Inferior	300mcg, Anapen	♀

Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen Autoinjector in Healthy Volunteers

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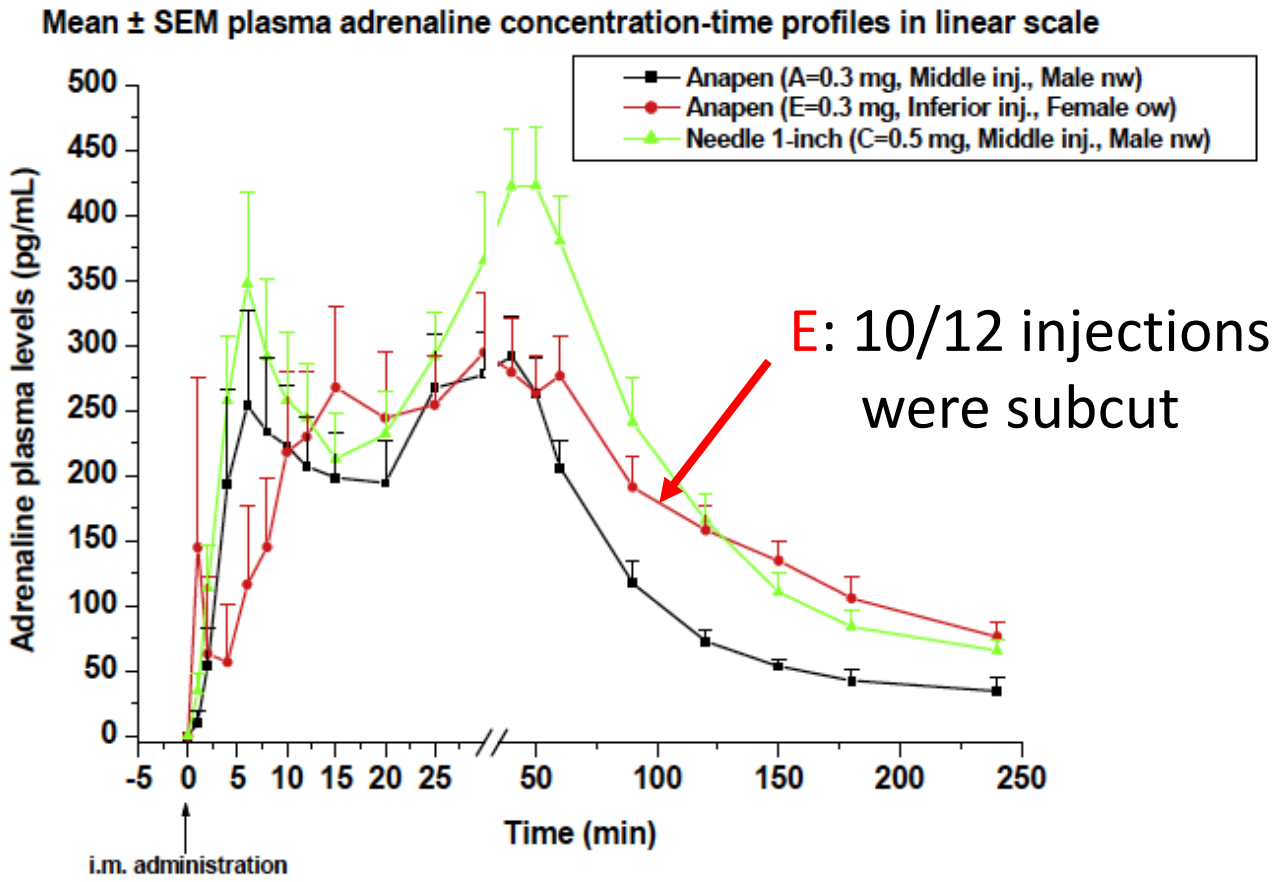


E: 10/12 injections were subcut

	Site	Dose	
A	Mid	300mcg, Anapen	
B	Mid	300mcg, needle	
C	Mid	500mcg, needle	
D	Inferior	300mcg, Anapen	
E	Inferior	300mcg, Anapen	

Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen Autoinjector in Healthy Volunteers

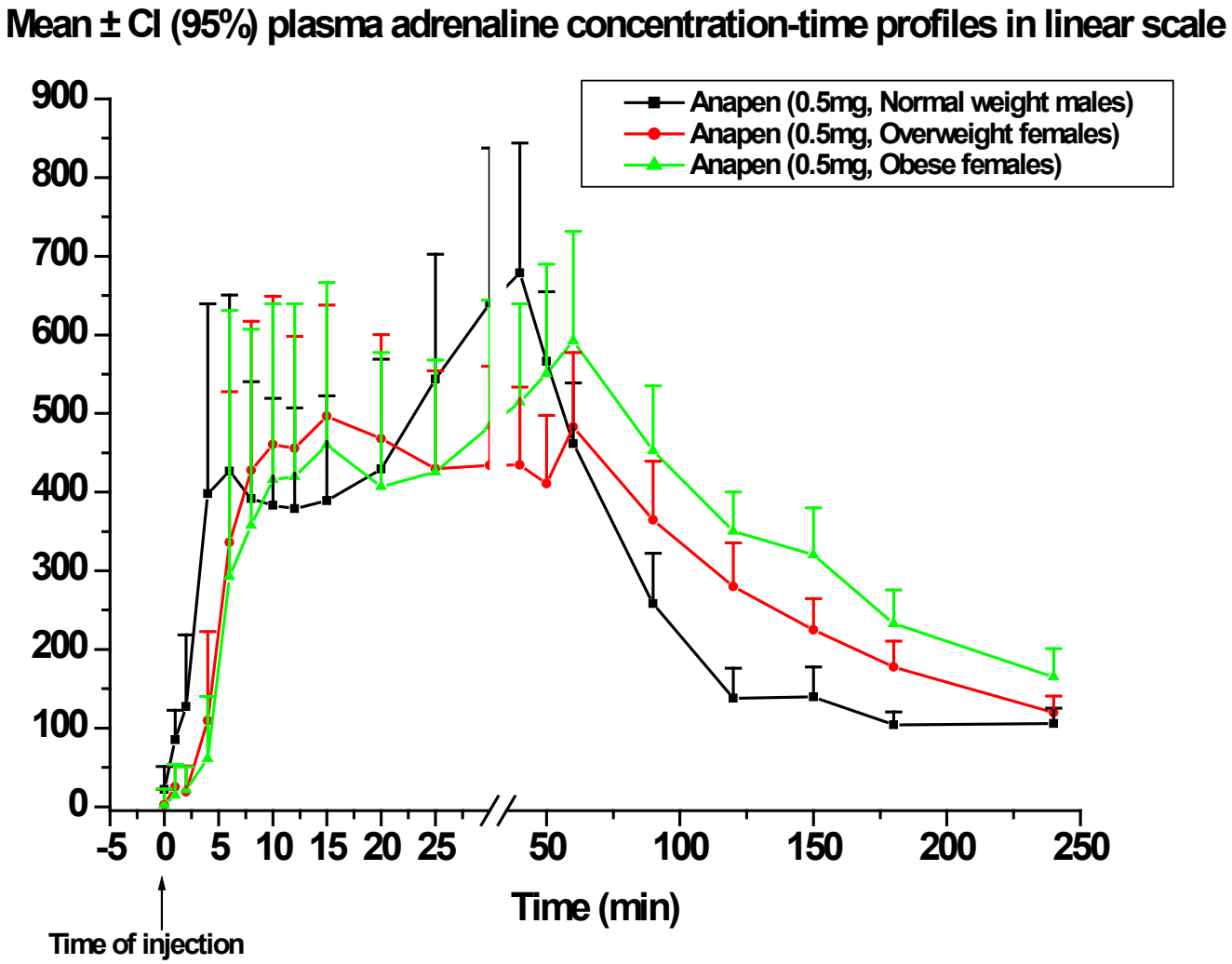
JACI IP 2018;6:1257-63

"…needle length alone was insufficient to predict bioavailability and that intramuscular injections might not be a critical prerequisite for the successful administration by autoinjectors in anaphylaxis."

Does dose matter?

- International guidelines recommend 500 mcg in adults…

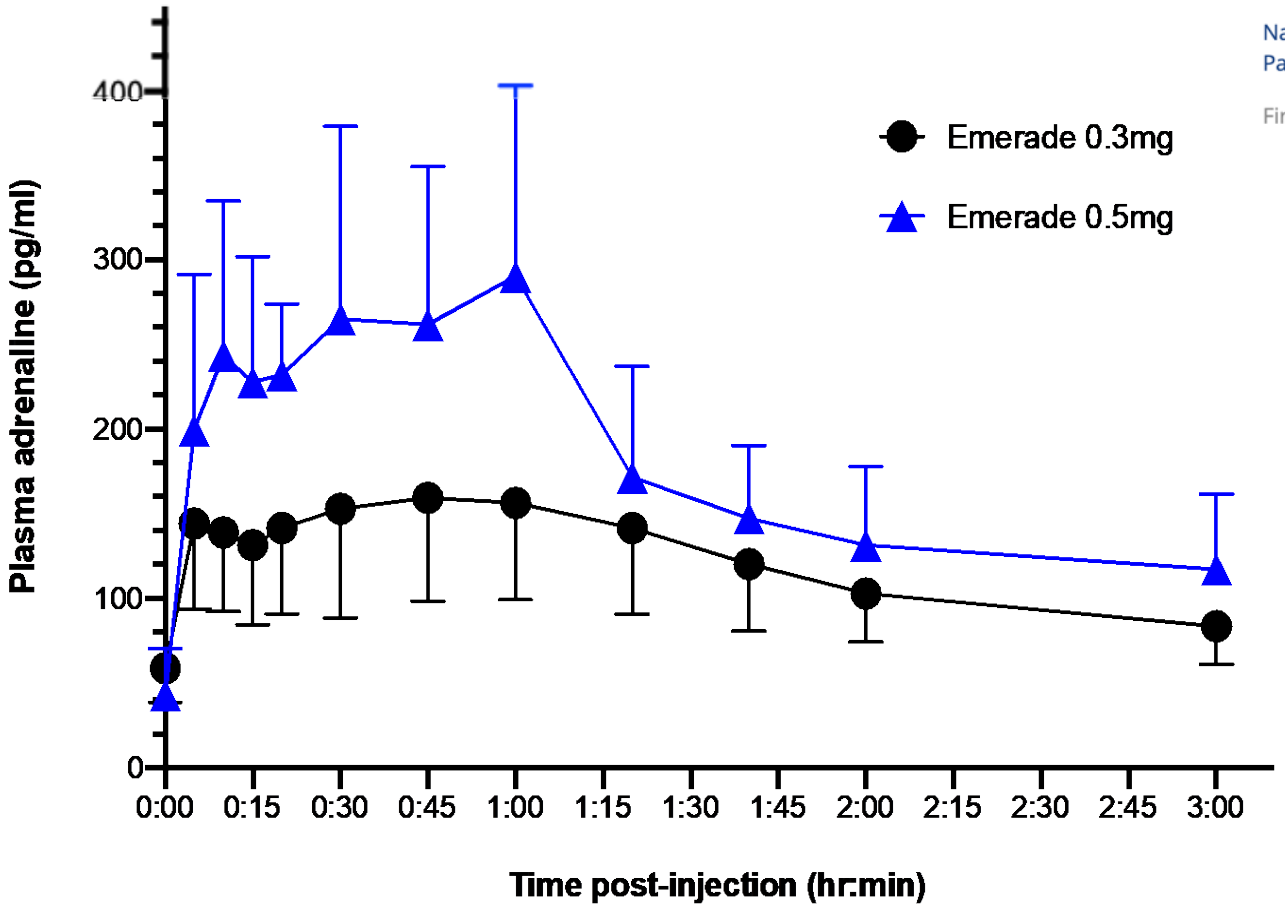
Anapen 300 vs 500 (separate studies)



Duvauchelle 2018, doi: 10.1016/j.jaip.2017.09.021

Duvauchelle 2023, doi: 10.1111/bcp.15545

Emerade 300 vs 500



Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI

ORIGINAL ARTICLE | Open Access

Optimal dose of adrenaline auto-injector for children and young people at risk of anaphylaxis: A phase IV randomized controlled crossover study

Nandinee Patel, Emily Isaacs, Bettina Duca, Nanthagopan Nagaratnam, Jackie Donovan, Sara Fontanella, Paul J. Turner

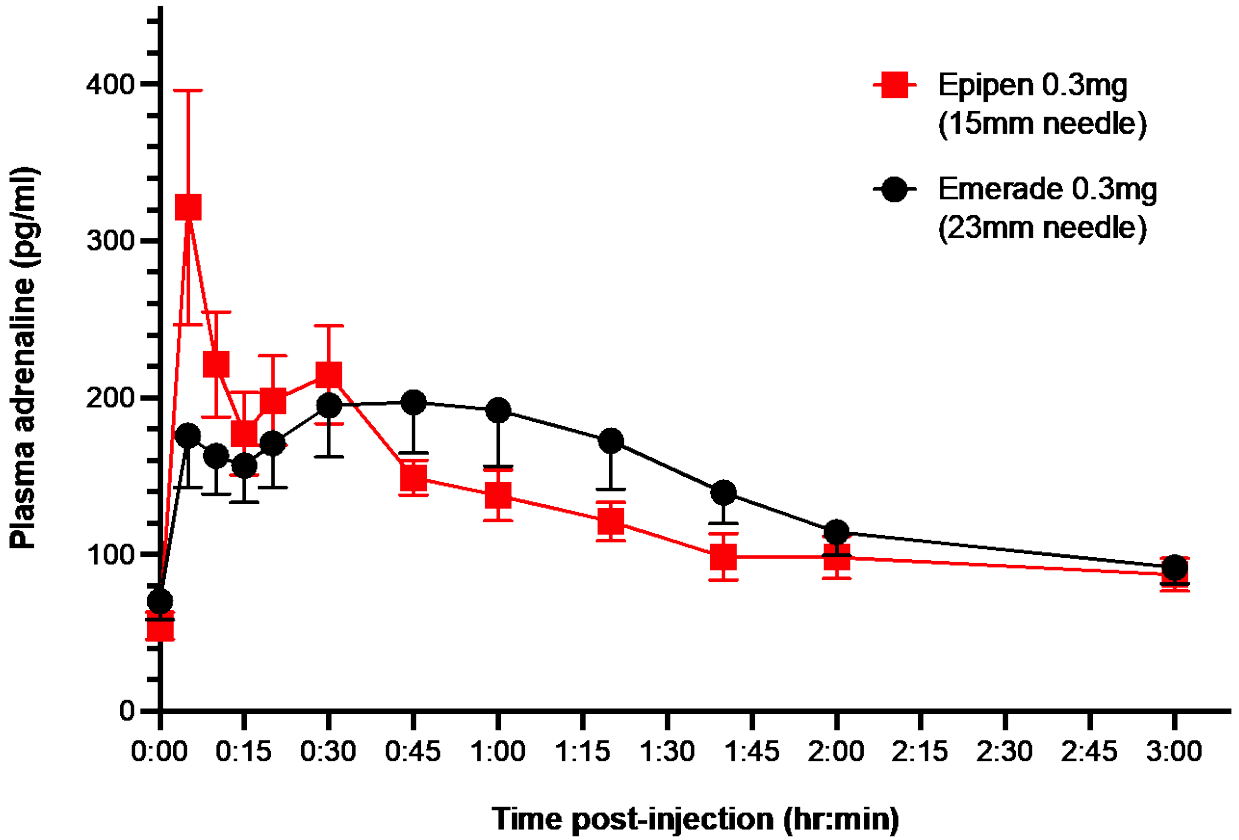
First published: 16 February 2023 | https://doi.org/10.1111/all.15675 | Citations: 1

PIMAT Study
NCT03366298
n=12
Cross-over

So how important is dose?

- For any given AAI device, a higher dose results in more favourable PK profile

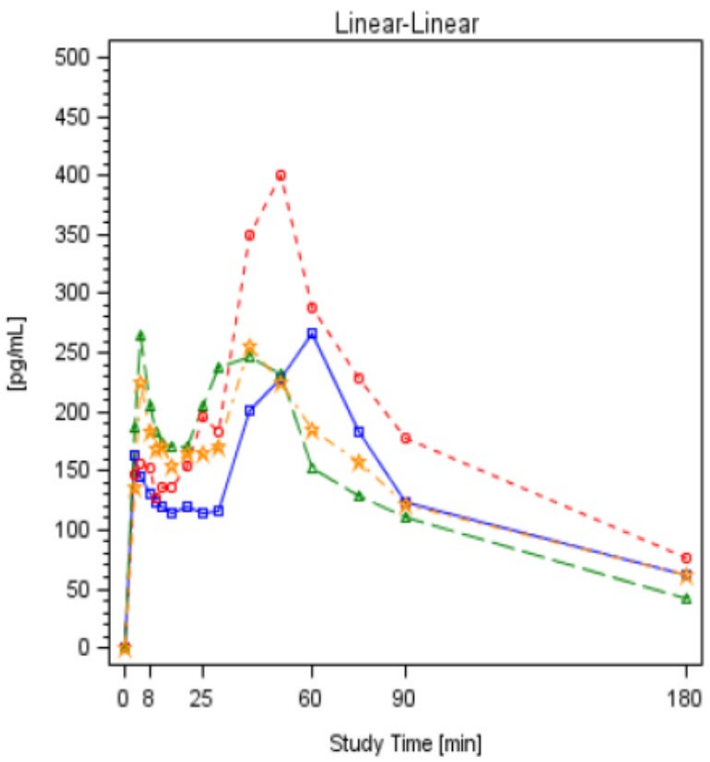
- But how do devices compare to each other?

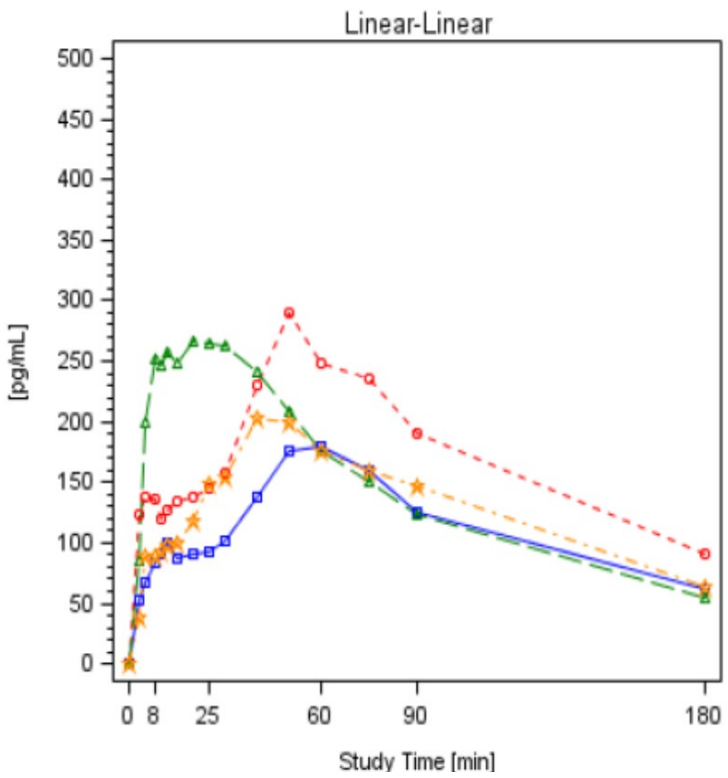

Plasma adrenaline (pg/ml)
400
300
200
100
0
0:00
0:15
0:30
0:45
1:00
1:15
1:30
1:45
2:00
2:15
2:30
2:45
3:00
Time post-injection (hr:min)
Epipen 0.3mg
(15mm needle)
Emerade 0.3mg
(23mm needle)

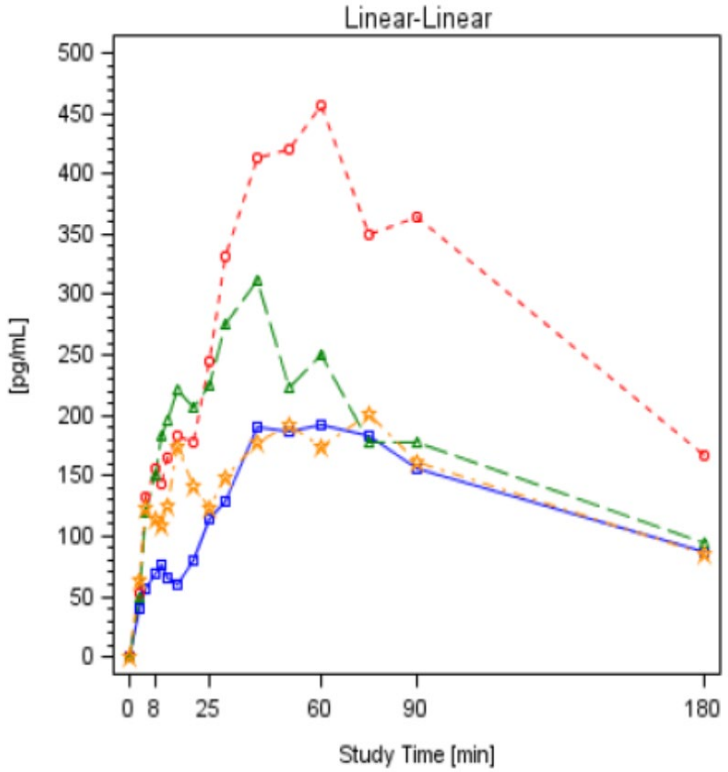
n=12

Emerade vs Epipen/Jext

STMD: <15mm 15-20mm >20mm







STMD C Emerade 300

ıort: >= 15 Emerade 500

= 20 mm Epipen 300

Jext 300

Allergy EAACI WILEY

ORIGINAL ARTICLE

Optimal dose of adrenaline auto-injector for children and young people at risk of anaphylaxis: A phase IV randomized controlled crossover study

Nandinee Patel[1] | Emily Isaacs[1] | Bettina Duca[1] | Nanthagopan Nagaratnam[2] | Jackie Donovan[2] | Sara Fontanella[1] | Paul J. Turner[1]

[1]

[2]

Correspondence

Funding information

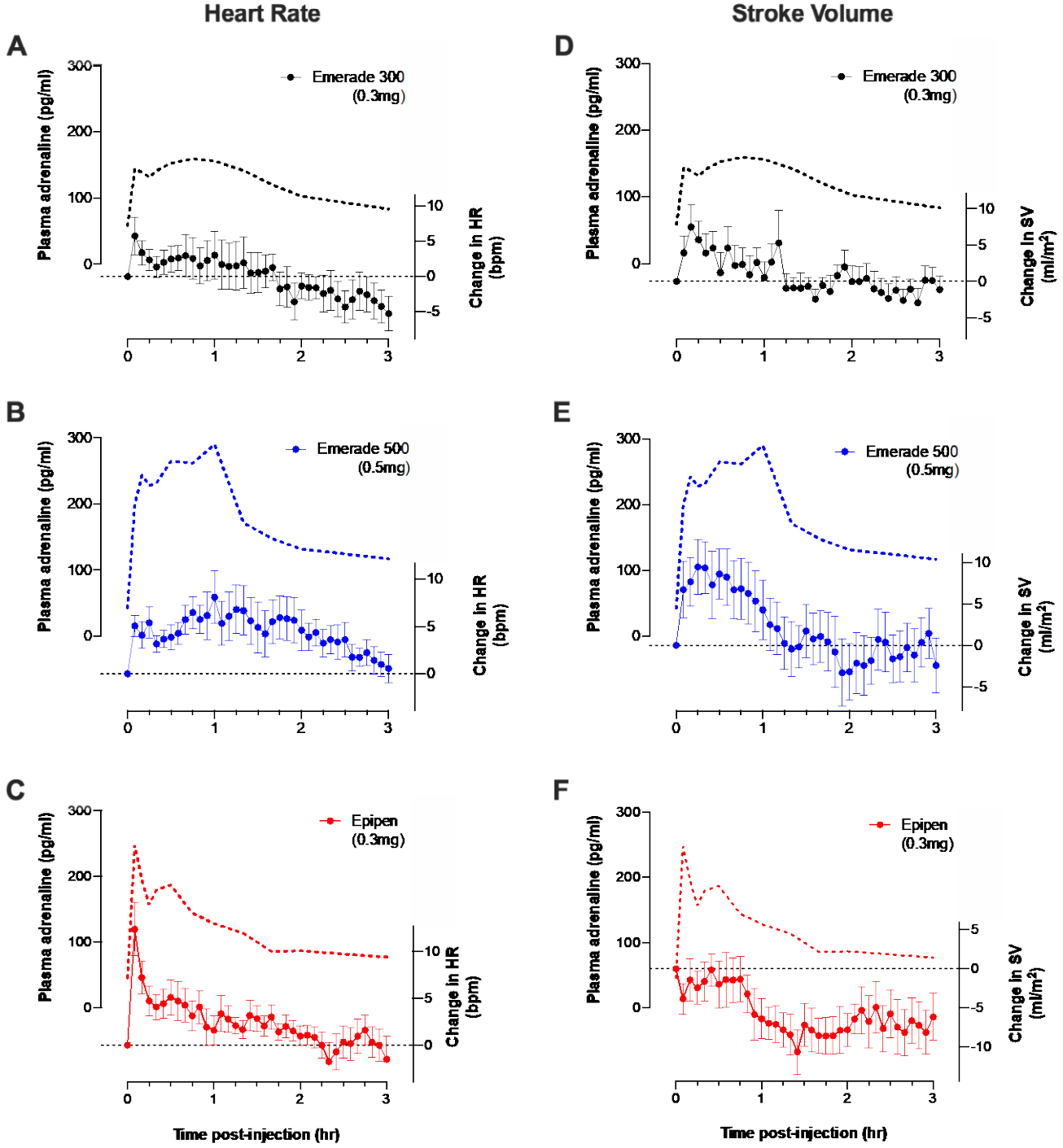
Abstract

Background:

Methods:

Results:

Conclusions:

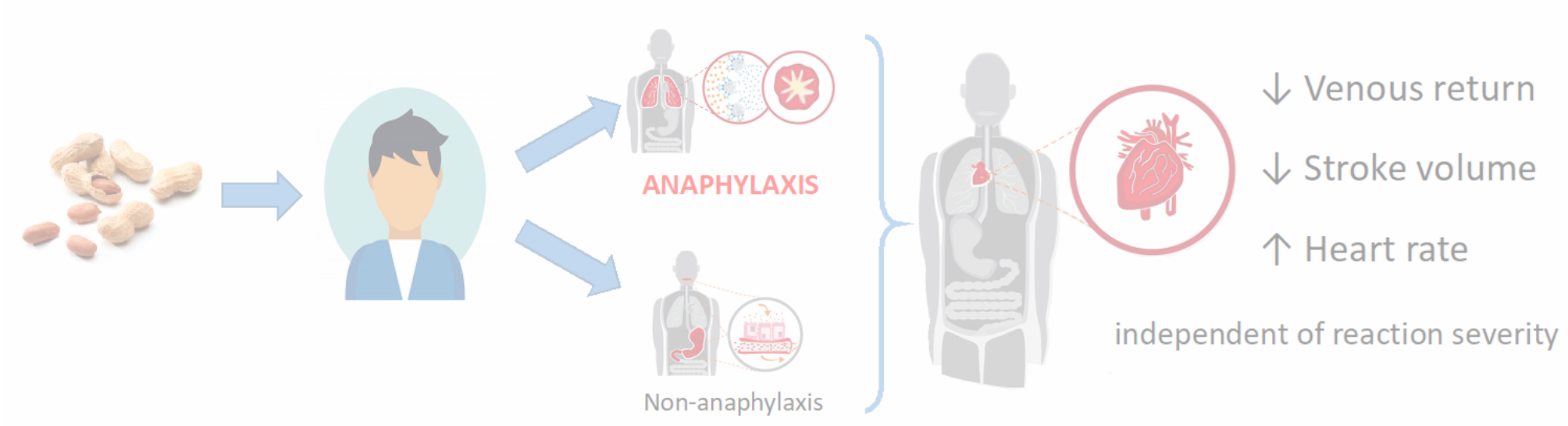


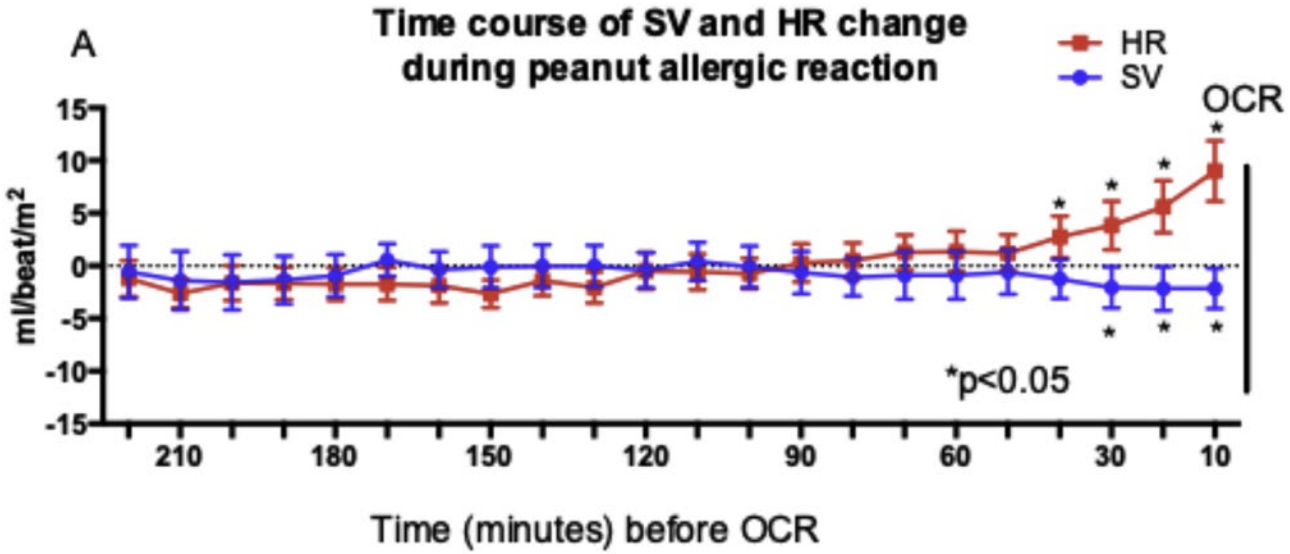
Stress (Takotsubo) cardiomyopathy

- FDA Black box warning in Epipen SmPC from April 2017
  - 113 cases (4 deaths) reported in patients receiving adrenaline administration
  - 10 following Epipen use (all hospitalized, 1 critical)

- At ‘low and medium’ doses, adrenaline is a positive inotropes via β_1AR-Gs and β_2AR-Gs signalling but are high doses it becomes a negative inotrope via β_2AR-GI signalling
  - this is probably why adrenaline can cause Takotsubo syndrome.

What about epinephrine given *during* anaphylaxis?





Ruiz-Garcia et al, JACI 2020
doi: 10.1016/j.jaci.2020.06.033

The Journal of Allergy and Clinical Immunology: In Practice

doi: 10.1016/j.jaip.2020.08.041

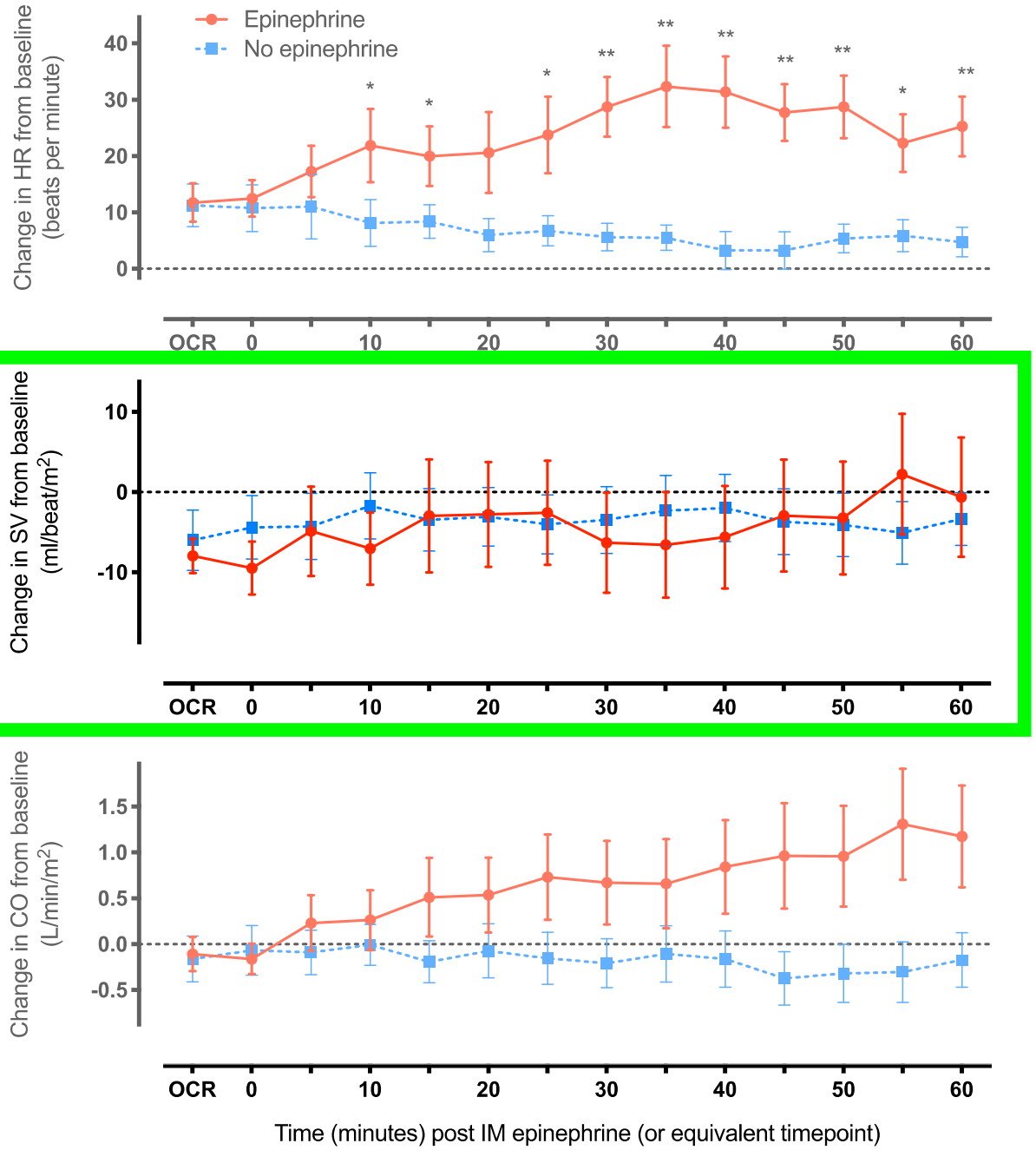
Clinical Communications

Limited effect of intramuscular epinephrine on cardiovascular parameters during peanut-induced anaphylaxis: An observational cohort study

Paul J. Turner, FRCPCH, PhD[a],
Monica Ruiz-Garcia, MD, PhD[a],
Stephen R. Durham, MD, FRCP[a,b], and
Robert J. Boyle, MD, PhD[a]

Clinical Implications

- Intramuscular injection with epinephrine had limited impact in reversing the decrease in stroke volume caused by peanut-induced anaphylaxis. These data question the effectiveness of intramuscular epinephrine alone to treat cardiovascular compromise during anaphylaxis and support the need for guidelines to incorporate effective adjuvant treatments in addition to intramuscular epinephrine in the management of refractory anaphylaxis.



So what can we conclude?

- **IM epinephrine is preferable to subcutaneous**
  - Subcut associated with delayed peak, but data limited
- **Where STMD>20mm, injection (presumably subcutaneous) still results in relatively good absorption**
  - Is this due to vascularization of subcut tissue?
- **Concern over –ve inotropic effect of some AAI?**
- **Studies need to evaluate ”proper” PD data, not just PK-equivalence**

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- Sarah Lindsley
- Nanth Nagaratnam (RBHT)
- **Nandinee Patel**
- Monica Ruiz Garcia
- Emily Isaacs
- Marta Vazquez-Ortiz

With special thanks to:

All our wonderful patients

Simon Brown (Perth, Australia)
Richard Pumphrey (UK)

MRC Medical Research Council