

UNCERTAINTIES PAGE

Is adrenaline effective in out of hospital cardiac arrest?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic, please email us at practice@bmj.com

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Previous articles in this series

- ▶ What is the most effective operation for adults with severe and complex obesity? (*BMJ* 2014;348:g1763)
- ▶ How effective is tranexamic acid for acute gastrointestinal bleeding? (*BMJ* 2014;348:g1421)
- ▶ Does depression screening improve depression outcomes in primary care? (*BMJ* 2014;348:g1253)
- ▶ Should children who have a cardiac arrest be treated with therapeutic hypothermia? (*BMJ* 2014;348:f7672)
- ▶ Should women with HIV, or at high risk of contracting HIV, use progestogen-containing contraception? (*BMJ* 2013;347:f6695)

Adrenaline (epinephrine) has been an integral component of advanced resuscitation algorithms since the early 1960s. Initial guidelines for the treatment of cardiac arrest recommended the use of intracardiac adrenaline (0.5 mg) or high dose intravenous adrenaline (10 mg), repeating with larger doses if required.¹ The mechanism of action for adrenaline in cardiac arrest is attributed to stimulation of α_2 receptors in vascular smooth muscle, causing vasoconstriction. This increases aortic diastolic pressure, which in turn leads to increased coronary perfusion pressures, which improves short term survival. Experimental studies, however, suggest that adrenaline impairs cerebral macrovascular² and microvascular blood flow,^{3 4} increases ventricular arrhythmias, and increases myocardial dysfunction after return of spontaneous circulation.⁵ This creates the paradox of better short term survival but at the potential cost of worse long term outcomes.

What is the evidence of uncertainty?

We searched Medline, Embase, the Cochrane Library, and trial registries for systematic reviews, randomised controlled trials, and observational studies relating to the use of adrenaline in the treatment of cardiac arrest.

A systematic review linked to the International Liaison Committee for Resuscitation 2010 evidence appraisal of vasoactive drugs in the treatment of cardiac arrest⁶ identified 53 articles, of which five compared adrenaline with placebo (three randomised trials⁶⁻⁸ and two observational studies^{9 10}). The review concluded that adrenaline is associated with improved short term survival compared with placebo, but no long term survival benefit was seen. A more recent systematic review,¹¹ which focused solely on adrenaline in cardiac arrest, identified 10 studies (two randomised trials^{6 8} and eight observational studies^{9 10 12-17}). Meta-analysis found no significant effect on long term survival in randomised trials (odds ratio 2.33, 95% confidence interval 0.85 to 6.40) or observational studies with unadjusted data (odds ratio 1.17, 95% confidence interval 0.67 to 2.07). Adrenaline was associated with decreased long term survival in observational studies that included adjustment for potential confounders (odds ratio 0.43, 95% confidence interval 0.40 to 0.48).

The first randomised controlled trial compared high dose (10 mg) adrenaline with placebo after cardiac arrest both in and out of hospital.⁸ The study found no difference in short or long term survival between groups, although meaningful interpretation is impossible as there were multiple protocol violations, off label use of 1 mg doses of adrenaline, and evidence of selection and performance bias.

A subsequent randomised prehospital trial compared 1 mg doses of adrenaline with placebo.⁹ Short term survival was higher in the adrenaline group (64/272 (23%) v 22/262 (8%); odds ratio 3.4, 95% confidence interval

2.0 to 5.6). Long term survival did not differ significantly between groups and did not exclude the possibility of harm (adrenaline, 11 survivors (4%) v placebo, five survivors (2%) (odds ratio 2.2, 95% confidence interval 0.7 to 6.3). Study limitations were that only 12.0% (601/5000) of the planned sample was recruited and 11.1% (n=67) of patients were lost to follow-up.

A further randomised study compared intravenous cannulation and injection of drugs versus no intravenous cannulation or drugs among 851 patients with out of hospital cardiac arrest.¹⁰ The study found a similar pattern of outcomes (improved short term survival, but uncertainty about the effect on long term survival). Reanalysis according to whether patients received adrenaline (n=367) showed a higher rate of admission to hospital (odds ratio 2.5, 95% confidence interval 1.9 to 3.4) but worse survival to hospital discharge (0.5, 0.3 to 0.8) and worse neurologically intact survival (0.4, 0.2 to 0.7).¹¹ These effects persisted after adjustment for confounding factors.

The randomised trials published to date, singly and together, lack sufficient power to draw meaningful inferences about the long term effectiveness and safety of adrenaline. The trials have focused primarily on measures of effectiveness (return of spontaneous circulation, longer term survival, and gross neurological function). None of the studies have provided data on the frequency of adverse events, effect on quality of life, cost effectiveness, or long term safety. The studies span three decades, during which changes in patient characteristics and improvements in initial and post-resuscitation care have taken place that may further limit interpretation.

Observational studies enable large quantities of data to be collected but are often limited by bias and confounding. Statistical adjustment is often used to compensate for this; however, unmeasured confounders (for example, precise time of drug being administered, clinician perceptions about the likelihood of success, the number, type, and training of clinicians at the arrest) may still lead to biased results. The limitations of reliance on such data are exemplified in two recent analyses of data from the Japanese Out of Hospital Cardiac Arrest Registry.^{13 18} Both studies used propensity matched analysis, a technique that controls for the effects of a large number of potential confounding variables and therefore should give the most reliable results. Small adjustments to the same statistical methods produced opposing results, with one study showing noticeably reduced long term neurologically intact survival (odds ratio 0.21, 95% confidence interval 0.1 to 0.44),¹³ whereas the other study showed marginal benefit (1.57, 1.04 to 2.37).¹⁸

The International Liaison Committee for Resuscitation Consensus on Science and Treatment Recommendations synthesised the available evidence in 2010.¹³ It similarly found evidence that vasopressors (adrenaline or vasopressin) improved return of spontaneous circula-

RECOMMENDATIONS FOR FUTURE RESEARCH

Population

- Adults
- Children
- In-hospital cardiac arrest
- Out of cardiac arrest
- Shockable rhythms
- Non-shockable rhythms

Interventions

- Bolus adrenaline every 3-5 minutes

Comparators

- Placebo or adrenaline administered by infusion or with other drugs

Outcomes

- Survived event
- Long term neurological outcomes
- Patient reported outcome measures
- Quality of life
- Cost effectiveness
- Adverse events or safety

tion and short term survival. Evidence was insufficient to suggest that they improve survival to discharge and neurological outcome and some evidence suggested that they may worsen these outcomes. The International Liaison Committee for Resuscitation identifies the need for placebo controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest. At the current time, adrenaline continues to be included in European and American guidelines.

Is ongoing research likely to provide relevant evidence?

We searched clinicaltrials.gov and current controlled trials and were unable to identify any ongoing studies.

Personal communication with global research groups indicated that investigator led studies including further placebo controlled trials, variable dose or timing, and use of adjunctive agents (for example, β blockers¹⁴) are currently in the planning stage. The box summarises recommendations for future research.

What should we do in the light of the uncertainty?

Evidence based interventions for cardiac arrest are summarised in the International Liaison Committee for Resuscitation Consensus on Science and Treatment Recommendations.¹⁹ A systematic review of data from observational studies found that bystander cardiopulmonary resuscitation improves survival.²⁰ Trained rescuers should perform high quality cardiopulmonary resuscitation with compressions and ventilations.²¹ Rescuers who are unable or unwilling to provide ventilations should perform compression only cardiopulmonary resuscitation.²¹ Meta-analysis of randomised trials supports ambulance dispatchers providing instructions focusing on compression only cardiopulmonary resuscitation.²² Prompt defibrillation improves survival and may be facilitated by public access defibrillation programmes.¹⁹

If adrenaline is recommended as part of local treatment policies, specific attention should be given to minimising interruptions in cardiopulmonary resuscitation while vascular access is obtained and adrenaline is administered. Effective post-resuscitation care,²³ which includes targeted temperature management, early percutaneous coronary intervention, and careful neuroprognostication should be provided to patients, especially where adrenaline has been used.

Competing interests and references are in the version on bmj.com

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10-MINUTE CONSULTATION

Diagnosis and management of chronic heart failure

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An 80 year old woman who rarely attends your surgery presents with a two month history of difficulty getting her shoes on due to swollen feet and breathlessness going upstairs.

What you should cover**Ask about**

- How far can she walk before feeling breathless? Does she wake at night feeling breathless? How many pillows does she use? Has she ever had chest pain or been told she's had a heart attack? Any palpitations or feeling faint?
- Risk factors or causes of heart failure:
 - Any history of myocardial infarction or angina, hypertension, valvular heart disease, atrial fibrillation, diabetes, smoking, excessive alcohol intake, or family history of ischaemic heart disease or cardiomyopathy?

– Coronary heart disease is the most common cause of heart failure and requires a specialist referral within two weeks (see box).

- Precipitating factors for heart failure:
 - Any recent symptoms of tachyarrhythmias, hyperthyroidism, or anaemia?
 - Is she taking any drugs that might exacerbate heart failure (such as non-steroidal anti-inflammatory drugs, steroids, diltiazem, or verapamil)?
- Differential diagnoses:
 - Consider other causes of breathlessness such as pulmonary emboli, lung malignancy, chronic obstructive pulmonary disease, and chest infection. Any cough, haemoptysis, pleuritic chest pain, smoking, or weight loss?
 - Consider other causes of ankle swelling such as dependent oedema due to sleeping in a chair all night.

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This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

Clinical examination

- Check pulse rate and rhythm (for tachycardia or atrial fibrillation), blood pressure, and listen for murmurs suggesting valvular heart disease.
- Check respiratory rate and listen for bilateral basal crepitations.
- Assess volume overload including extent of peripheral oedema and weight. Assess overall severity (see box).

What you should do**Talk to the patient**

- Explain her heart may not be pumping very efficiently. She may have heart failure, which is a common, treatable condition affecting about one in 20 people her age.
- Arrange for her to have blood tests and an electrocardiogram this week and to see you in 7-10 days with the results. Depending on these, you plan to refer her for an echocardiogram and to see a specialist at the heart failure clinic.

Establish the diagnosis*Blood tests*

- B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT pro-BNP), as per NICE guidance to assess likelihood of heart failure:
 - BNP >400 pg/mL or NT pro-BNP >2000 pg/mL suggests strong probability of heart failure. Specialist referral within two weeks is recommended (box).
 - BNP 100–400 pg/mL or NT pro-BNP 400–2000 pg/mL suggests moderate probability of heart failure and requires specialist referral within six weeks.
 - BNP <100 pg/mL or NT pro-BNP <400 pg/mL suggests an alternative cause (see differential diagnoses above).
- Full blood count and thyroid status to exclude anaemia or thyroid disease which may precipitate heart failure.
- Renal and liver function tests alongside a urinary dipstick to exclude renal or liver failure as a cause of oedema.
- Lipid profile and fasting glucose or HbA_{1c} to assess cardiovascular risk.

Other tests

- Arrange an electrocardiogram—Evidence of previous myocardial infarction requires a specialist referral within two weeks (box). A normal electrocardiogram and BNP make a diagnosis of heart failure unlikely.
- Refer for echocardiography and specialist heart failure clinic within six weeks unless BNP <100 pg/mL or NT pro-BNP <400 pg/mL suggests an alternative diagnosis.
- Consider chest radiography and lung function tests, especially if there is a history of smoking.

Make a management plan*Drug treatment*

- Diuretics (such as furosemide 20 mg once daily) can be started immediately. They can be titrated up or

Indications for urgent specialist assessment within two weeks

Any one of:

- Previous myocardial infarction on electrocardiogram or medical history
- Inability to perform simple daily activities because of severe breathlessness or breathlessness at rest (NYHA class 4*)
- Valvular heart disease
- B-type natriuretic peptide >400 pg/mL or N-terminal pro-B-type natriuretic peptide >2000 pg/mL
- Baseline blood creatinine concentration >250 µmol/L

*New York Heart Association classification of severity of heart failure symptoms: class 1=no symptoms, 2=mild limitation of physical activity, 3=marked limitation of physical activity, 4=symptoms at rest.

down according to the degree of oedema. Diuretics improve symptoms but not mortality.

- Angiotensin converting enzyme (ACE) inhibitors
 - ACE inhibitors and β blockers improve prognosis and symptoms in heart failure due to left ventricular systolic dysfunction (diagnosed by echocardiography), but evidence for their use in heart failure with preserved ejection fraction is currently inadequate.
 - ACE inhibitors may be started at follow-up once the diagnosis is established and you have results of baseline renal function tests. Prioritise ACE inhibitors (initially low dose, such as ramipril 1.25 mg daily) over β blockers. Repeat renal function tests within 1-2 weeks.
- β blockers (such as bisoprolol 1.25 mg daily) can be started (usually by the specialist) in addition to ACE inhibitors as long as no severe asthma or chronic obstructive pulmonary disease, pulmonary oedema, or bradycardia. “Start low, go slow.”
 - If patients are already taking a β blocker for hypertension, this should be switched to one licensed for heart failure (such as bisoprolol).
- Review or stop medications that could worsen heart failure (such as non-steroidal anti-inflammatory drugs).

Further monitoring (may be by the heart failure team depending on local arrangements)

- At each review (for example, every 2-4 weeks) assess clinical status (such as exercise tolerance and oedema), heart rate and blood pressure (ensure patient is not hypotensive or feeling faint). Only increase one drug at a time.
- Uptitrate ACE inhibitor (for example, double the dose every 2-4 weeks) until target dose is achieved (such as ramipril 5 mg twice daily or highest tolerated dose). Arrange renal function tests within 1-2 weeks of each dose increment to check that blood creatinine levels and estimated glomerular filtration rate are stable and there is no hyperkalaemia.
- Uptitrate β blocker (for example, double the dose every four weeks) until target dose is achieved (such as bisoprolol 5 mg twice daily or highest tolerated dose). Check no significant bradycardia or lethargy.

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Previous articles in this series

- ▶ Baby with an abnormal head
(*BMJ* 2014;348:f7609)
- ▶ A feeling of a lump in the throat
(*BMJ* 2014;348:f7195)
- ▶ Tremor
(*BMJ* 2013;347:f7200)
- ▶ Dental pain
(*BMJ* 2013;347:f6539)
- ▶ Flashes, floaters, and a field defect
(*BMJ* 2013;347:f6496)

- Patients should be encouraged to monitor their weight and to inform you if they gain ≥ 2 kg over three days.

Treatment of comorbidities

- Optimise treatment for hypertension, coronary heart disease, diabetes, and atrial fibrillation.

Long term health promotion and rehabilitation

- Where appropriate advise on smoking cessation, exercise and weight loss, and avoidance of excessive salt or alcohol intake.
- Recommend referral to local community heart failure clinic and exercise based rehabilitation programme. Heart failure nurses can optimise treatment and provide psychosocial support.

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USEFUL READING**For patients**

British Heart Foundation. Heart failure. www.bhf.org.uk/heart-health/conditions/heart-failure.aspx

For health professionals

Kotecha T, Fox K. Investigating suspected heart failure. *BMJ* 2013;346:f2442

Arroll B, Doughty R, Andersen V. Investigation and management of congestive heart failure. *BMJ* 2010;341:c3657

Al-Mohammad A, Mant J, Laramie P, Swain S; the Chronic Heart Failure Guideline Development Group. Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. *BMJ* 2010;341:c4130.

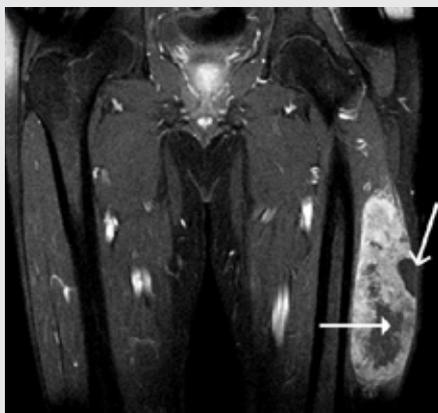
National Institute for Health and Care Excellence. NICE Pathways: Chronic heart failure overview. <http://pathways.nice.org.uk/pathways/chronic-heart-failure>

ANSWERS TO ENDGAMES, p 38

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PICTURE QUIZ**A man with a mass in the thigh**

- 1 Benign causes of a large lump in an extremity include haematoma, chronic muscle tear, an abscess, and lipoma. Malignant causes include sarcoma, lymphoma, and soft tissue metastasis from an occult tumour.
- 2 The four cardinal clinical signs that are suggestive of cancer in a soft tissue mass are a lump larger than 5 cm in diameter, which is increasing in size, deep to the fascia, and painful. The magnetic resonance imaging scan shows a large mass in the left lateral thigh, which displays a pseudocapsule with heterogeneous enhancement and a lack of central enhancement (figure), suggestive of necrosis.
- 3 The next most appropriate step is to take a core needle biopsy. The diagnostic accuracy of fine needle aspiration is poor, and incision biopsy is associated with a higher rate of complications.
- 4 Surgery is the mainstay of treatment for



Magnetic resonance imaging scan showing a large heterogeneously enhancing mass in the left lateral thigh, which displays a lack of central enhancement (lower arrow with solid arrowhead) and a pseudocapsule (upper arrow)

localised disease and is based on complete excision of the tumour, with a margin of about 1 cm of normal tissue. Limb salvage surgery allows for good postoperative quality of life with acceptable resection margins. Such surgery has become the standard of care in patients with soft tissue sarcomas of the extremity.

ANATOMY QUIZ**Sites of tendon insertion on a shoulder radiograph**

- A: Trapezius (lateral one third of clavicle; insertion)
- B: Long head of biceps brachii (supraglenoid tubercle of the scapula; origin)
- C: Short head of biceps brachii and coracobrachialis (apex of coracoid process; origin)
- D: Supraspinatus (greater tuberosity of the humerus; insertion)
- E: Subscapularis (lesser tuberosity of the humerus; insertion)
- F: Long head of triceps brachii (infraglenoid tubercle of the scapula; origin)

STATISTICAL QUESTION**What is an “n-of-1” trial?**

Statements *a*, *b*, and *c* are true, whereas *d* is false.