平成１８年度（財）救急振興財団調査研究助成事業

病院外心停止症例に対する救急救命士による

エピネフリン投与の効果の検討

病院外心停止症例に対する救急救命士による

エピネフリン（アドレナリン）投与の効果の検討

報告書

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【背景】

　急性心筋梗塞症による死亡の半数から 2／3 は院外死であると報告されるなど、心疾患による死亡の多くは病院外での突然死であり、日本では年間 2〜3 万例の心臓突然死が発生しているとされる。その多くは、発症当初心室細動（VF, ventricular fibrillation）の状態であり、院外心停止症例を救命するためには、早期の心肺蘇生開始とともに、早期除細動がもっとも重要であるとされている。わが国においても、救急救命士による包括的指示下での除細動の実施、自動体外式除細動器（AED, automated external defibrillator）の非医療従事者による使用の解禁など、BLS の充実が図られ、院外心停止症例の救命率は徐々に向上してきているがいまだ不十分な状態である。

　BLSに反応しない症例に対しては、気管挿管、薬剤投与などの二次救命処置（ALS, advanced cardiac life support）が行われる[1]が、早期除細動が可能な体制下では、ALSによる救命率の向上は見込めないと報告されるなど[2]、ALSの有効性を示した報告は少ない。ALS時に使用する薬剤として、古くからアドレナリン（エピネフリン）が使用されており、ALSの際に使用する薬剤のゴールデンスタンダードとなっているが、高容量アドレナリンの効果の検討[3,4]、バゾプレシンとの効果の比較[5,6,7]などはなされているものの、アドレナリンの効果自体を証明した研究はなく、エビデンスは不十分な状態である。こうした中、わが国においても病院前救護体制の整備が進み、平成 17 年 4 月より、一定の研修を終えた救急救命士による院外心停止症例に対するアドレナリンの投与が開始され、BLSに反応しない院外心停止症例の救命率向上が期待されている。

　我々は、1998 年 5 月より、大阪府全域（対象人口 880 万人）を網羅する形で救急隊員の関わる全ての院外心停止症例の蘇生に関する記録を国際的に標準化されたフォーマットに基づいて、記録・集計するプロジェクト（ウツタイン大阪プロジェクト）を継続し、院外心停止に関するさまざまな疫学的なデータを報告するとともに、地域の救急システムの検証を行ってきた[8-12]。本研究では、この地域を網羅した大規模な院外心停止症例の登録プロジェクトを生かし、救急救命士によるアドレナリン投与の効果を検討することとした。

【目的】

　院外心停止症例に対する救急救命士によるアドレナリン（エピネフリン）投与が心停止症例の転帰を改善するか否かを検証すること。

【方法】

●研究デザイン：コホート研究（前向き集計、population-based）

●対象・サンプリング
　１．対象地域：大阪府全域（人口 880 万人、年間院外心停止約 5000 例）
　２．対象期間：2005 年 1 月 1 日から 2006 年 12 月 31 日
　３．ウツタイン大阪プロジェクトでのレジストリ：
　　　本プロジェクト用に、病院外心停止症例の蘇生記録に関する国際的に標準化されたフォーマットであるウツタイン様式[13, 14]にのっとった記録用紙を作成。救急隊員の関わるすべての病院外心停止症例の蘇生に関する記録を前向きに集計した。居合わせた市民による心肺蘇生実施の有無及び種別は現場で救急隊員が情報を収集し判断した。
　　　１ヶ月生存の有無、脳神経学的機能までの蘇生経過に関する情報を、蘇生に関わった救急隊員が搬送先医療機関の担当医師の協力のもと記録し報告。
　４．本研究における対象症例の適格基準
　　以下のすべてを満たすもの：
　　　①18 歳以上
　　　②心原性心停止と判断されたもの
　　　③心停止現場を居合わせた市民により目撃されたもの

●主たる要因：救急救命士によるアドレナリン（エピネフリン）投与の有無

●調整すべきその他の要因：
　性別や年齢、心停止発生場所など生物学的に本質的な事項
　居合わせた市民が実施した心肺蘇生法
　　（胸骨圧迫＋人工呼吸／胸骨圧迫のみ／心肺蘇生未実施）
　蘇生の時間経過
　　（虚脱～覚知時間／覚知～心肺蘇生開始までの時間／覚知～電気ショックまでの時間／覚知～病院到着までの時間、等）

●主たるアウトカム指標
　① 病院到着前の心拍再開の有無
　② 神経学的機能良好な状態での１ヶ月生存

●解析方法

　救急救命士によるアドレナリン（エピネフリン）投与が行われた症例の背景、心肺蘇生の時間経過を、同時期のアドレナリン非投与症例と比較。主たるアウトカムである病院到着前の心拍再開の有無、神経学的機能良好な状態での1ヶ月生存の有無については、年齢、性別、心停止発生場所、初期心電図調律、居合わせた市民による心肺蘇生法実施の有無（胸骨圧迫のみ／人工呼吸付／心肺蘇生なし）、救急隊による心肺蘇生開始までに要した時間、等の調整要因をロジスティック回帰モデルに投入して、多変量調整オッズ比およびその95％信頼区間を算出した。統計学的解析はいずれも両側検定、有意水準：0.05。使用ソフトウェア：SPSS
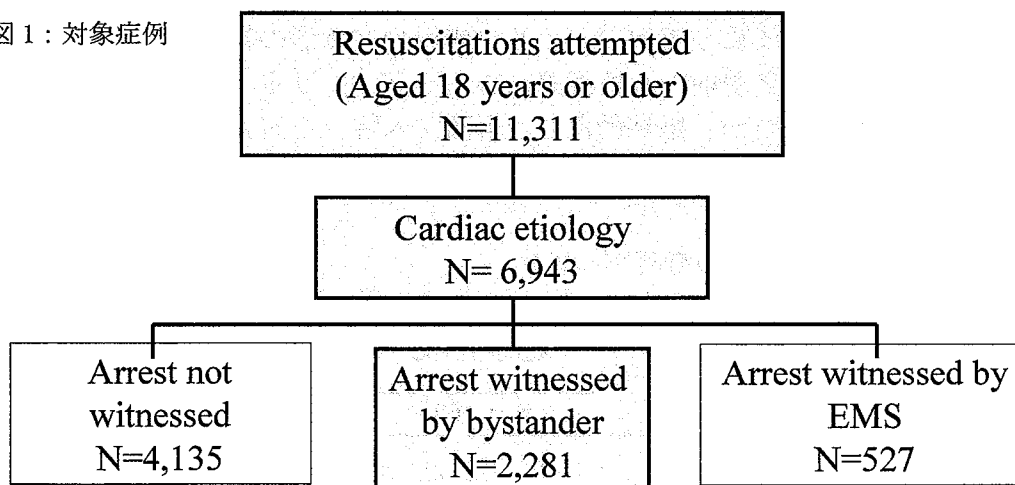
●倫理的配慮

　本研究は、ヘルシンキ宣言および疫学研究に関する倫理指針を遵守して実施した。集計・解析にあたっては、対象者特定情報は削除し、匿名化を行った。本プロジェクトは大阪大学医学部医学倫理委員会の承認を得ている。

【結果】

　対象期間に、救急隊が蘇生処置を行った18歳以上の病院外心停止のうち、心原性心停止と診断され、居合わせたものにより心停止現場を目撃されていた2,281例を分析の対象とした（図1）。

図1：対象症例

```
┌─────────────────────────────┐
│  Resuscitations attempted   │
│   (Aged 18 years or older)  │
│        N=11,311             │
└─────────────────────────────┘
              │
┌─────────────────────────────┐
│      Cardiac etiology       │
│        N= 6,943             │
└─────────────────────────────┘
    │          │          │
┌────────┐ ┌────────┐ ┌────────┐
│Arrest  │ │Arrest  │ │Arrest  │
│not     │ │witnessed│ │witnessed│
│witnessed│ │by      │ │by EMS  │
│N=4,135 │ │bystander│ │N=527   │
│        │ │N=2,281 │ │        │
└────────┘ └────────┘ └────────┘
```

　対象期間内に、アドレナリンを使用されていた症例は、108例（4.7％）であった。救急救命士によるアドレナリン使用の有無別の患者背景を表1に示す。男性の割合がアドレナリン群で高いほか、心停止発生場所、初期心電図調律が両群で異なる傾向を認めた。バイスタンダーCPR、覚知から救急隊による心肺蘇生開始、除細動までに要する時間に差は認めなかった。覚知から病院到着までに要する時間はアドレナリン群で有意に長かった。

表1. 患者背景と蘇生処置

		Adrenarine N = 108	Control N = 2173	P value
Age, mean, SD		71.1±14.9	72.0±14.9	0.55
Male, N (%)		83 (76.9)	1373 (63.2)	0.002
Location, N (%)	Home	76 (70.4)	1465 (67.4)	
	Public	14 (13.0)	380 (17.5)	
	Work place	3 (2.8)	71 (3.3)	0.08
	Care facility	8 (7.4)	204 (9.4)	
	Others	7 (6.5)	53 (2.4)	
Bystander CPR, N (%)	No CPR	70 (64.8)	1396 (64.2)	
	Cardiac-only	15 (13.9)	340 (15.6)	0.87
	Conventional	23 (21.3)	437 (20.1)	
VF, N (%)		30 (27.8)	508 (23.4)	0.18
Call to CPR, mean, SD		7.7±2.3	7.9±2.9	0.69
Call to Shock, mean, SD		9.0±2.5	8.6±2.9	0.44
Call to Hospital arrive, mean, SD		31.8±9.9	26.3±7.7	<0.001

VF; ventricular fibrillation

　表2に、救急救命士によるアドレナリン使用の有無別の転帰を示す。アドレナリン使用群では、病院到着前の心拍再開が22%とアドレナリン非使用群（11%）と比較して有意に高かったが、最終的な心拍再開、入院、一ヶ月生存、社会復帰の割合に差は認めなかった。

表2. アドレナリン使用の有無別の転帰

	Adrenarine N = 108	Control N = 2173	P value
ROSC before arrival, N (%)	24 (22.2)	248 (11.4)	0.001
ROSC (total), N (%)	40 (37.0)	843 (38.8)	0.4
Admission, N (%)	33 (30.6)	702 (32.3)	0.4
1-month surviveal, N (%)	10 (9.3)	240 (11.0)	0.74
Neuro favorable outcome, N (%)	5 (4.6)	119 (5.5)	0.46

　次に、救急隊到着時の初期心電図調律が VF であった症例と非 VF 症例に分けて転帰を検討した。VF 症例では、転帰はむしろアドレナリンの非使用群で良好な傾向を認めた（Table3A）。一方、非 VF 群では、病院到着前の心拍再開がアドレナリン群で非アドレナリン群と比較して有意に高く（24.4% vs 5.5%, p<0.001）、社会復帰もアドレナリン群で高い傾向を認めた（3.8% vs 1.9%, p=0.19）（Table3B）。

表3. 初期心電図別、アドレナリン使用の有無と転帰
A）初期心電図 VF

	Adrenarine	Control	P value
	N = 30	N = 508	
ROSC before arrival, N (%)	5 (16.7)	155 (30.5)	0.08
ROSC (total), N (%)	13 (43.3)	282 (55.5)	0.13
Admission, N (%)	12 (40.0)	260 (51.2)	0.16
1-month surviveal, N (%)	7 (23.3)	148 (29.1)	0.71
Neuro favorable outcome, N (%)	2 (6.7)	88 (17.4)	0.09

B）初期心電図 non-VF

	Adrenarine	Control	P value
	N = 78	N = 1660	
ROSC before arrival, N (%)	19 (24.4)	91 (55)	<0.001
ROSC (total), N (%)	27 (34.6)	558 (33.6)	0.47
Admission, N (%)	21 (26.9)	439 (26.4)	0.51
1-month surviveal, N (%)	3 (3.8)	91 (5.5)	0.78
Neuro favorable outcome, N (%)	3 (3.8)	31 (1.9)	0.19

VF; ventricular fibrillation, ROSC; return of spontaneous circulation

非 VF 群における、アドレナリン投与の病院到着前の心拍再開、社会復帰に対する多変量調整オッズ比は、それぞれ、6.21（95%信頼区間, 3.45-11.2）、2.79（95%信頼区間, 0.78-9.97）であった。

【考察】

　本研究は、大規模なpopulation-based cohort studyで蓄積された臨床データをもとに、救急救命士による院外でのアドレナリン投与の有用性を示したはじめての報告である。二次救命処置におけるアドレナリンの投与は、すでに標準的な治療となっており、多くの地域で救急救命士（あるいはそれに準ずるシステム）によって投与されているため、その効果の客観的な検証は困難となっている。これまでに報告されたアドレナリンの効果に関する検討は、高容量と標準量の検討[3, 4]、バゾプレシンとの比較[5, 6, 7]などに限られてきた。最近、院外心停止例に対するアドレナリン投与の効果を、アドレナリンの投与が始まった期間の前後で比較検討した報告がシンガポールからなされたが、この報告ではアドレナリンの効果は示されなかった[15]。こうした中、わが国では、平成17年度から救急救命士によるアドレナリンの投与が開始された。ウツタイン大阪プロジェクトでは、アドレナリン投与開始前から、ウツタイン様式にのっとった院外心停止例の蘇生記録を継続的に登録しているため、アドレナリン投与の効果を、非投与群と比較・検討する非常に重要な機会を得たといえる。

　本研究では、初期心電図がVFであった症例では、アドレナリン投与の効果が認められなかったのに対し、非VF例では、病院到着前の心拍再開を著名に改善し、早期心拍再開によって社会復帰率の向上をもたらす可能性があることを示唆している。VF症例では、除細動による治療が薬剤投与に優先され、除細動に反応しなかった症例に対してのみアドレナリンが使用されるため、アドレナリンの効果が観察されなかったものと思われる。今後は、症例を積み重ね、除細動に反応しなかった症例におけるアドレナリン投与の効果を検討する必要がある。

　Marcusらによってシンガポールから報告されたデータでは、初期心電図波形にかかわらず、アドレナリン投与の効果が示されなかったが、この研究では、覚知から救急隊員が患者の傍らに到着するまでに平均11分以上を要しており、内因性院外心停止からの救命率が 1%台であるなど、救急システムが不十分な状態での比較であったことが、効果を示すことができなかったひとつの要因と思われる[15]。

　本研究は観察研究であり、アドレナリンの使用はコントロールされたものではない。現在、アドレナリンは特別に訓練をつんだ救急救命士のみに許されており、アドレナリンの効果だけでなく、特別に訓練をつんだ救命士の効果を反映している可能性がある。また、アドレナリン群は除細動を含むBLSに反応しなかった群となるため、もともと転帰が不良であるというバイアスが入っている可能性が高い。いずれの群でも、生存例は非常に少ないため、アドレナリンの効果をさらに確認するためには症例の蓄積が必要である。

【結語】

　院外心停止症例に関する大規模な地域網羅的コホート研究により、救急救命士による院外でのアドレナリン投与が、非 VF における病院到着前の早期心拍再開をもたらし、社会復帰率の向上をもたらす可能性があることが示唆された。効果の確認のためには、更なる症例の蓄積が必要である。

【謝辞】

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【参考資料】

1）ウツタイン大阪プロジェクト　病院外心肺停止患者登録コード表
2）参考文献

病院外心肺停止患者記録（大阪版）コード表

No.	項目名	コード
1	本部コード	
2	救急隊コード	
3	発生年	発生年月日の年
4	事例No	
5	プロトコールA	0:なし、1:あり
6	プロトコールB	0:なし、1:あり
7	プロトコールC	0:なし、1:あり
8	プロトコールD	0:なし、1:あり
9	プロトコールE	0:なし、1:あり
10	プロトコールF	0:なし、1:あり
11	発生年月日	YYYYMMDD
12	救急救命士乗車	1:気管挿管認定救命士が乗車 2:薬剤投与認定救命士が乗車 3:気管挿管・薬剤投与認定救命士ともに乗車 4:上記以外の救急救命士が乗車 5:救急救命士乗車なし
13	ドクターカー出場	0:なし、1:現場、2:ドッキング、3:両方
14	医師同乗	N:未選択、0:なし、1:あり
15	患者性別	1:男、2:女
16	患者年齢	
17	患者年齢推定区分	N:未選択、1:推定
18	初期治療病院名	
19	心疾患の既往症	1:あり、2:なし、3不明
20	心疾患の既往症内訳 虚血性心疾患(狭心症・心筋梗塞)	0:なし、1:あり
21	心疾患の既往症内訳 ペースメーカー植込み	0:なし、1:あり
22	心疾患の既往症内訳 その他	0:なし、1:あり
23	普段の生活状態	1:良好 2:中等度障害(片麻痺、構語障害等)あるも自立 3:重度障害あり要介助(ねたきり) 4:植物状態 5:不明
24	現場での傷病判断	1:内因性、2:外因性
25	現場での傷病判断内訳	N:未選択 1:前駆症状あり 2:前駆症状なし 3:不明
26	心肺停止の目撃	1:心肺停止の瞬間を目撃、または音を聞いた 2:既に心肺停止(心肺停止の状態で発見)
27	心肺停止の時分	mmss 例)8時7分 → 0807
28	心肺停止の目撃者	N:心肺停止の目撃＝2の場合 1:家族 2:その他(友人) 3:その他(同僚) 4:その他(通行人) 5:その他(その他) 6:消防隊員 7:救急隊員 8:救急救命士隊

29	心肺停止場所	1:家 2:道路上 3:職場 4:公衆の出入りする場所 5:救急車内 6:医院内 7:老人ホーム 8:学校 9:その他
30	心肺停止場所公衆内訳	N:心肺停止場所≠4の場合 1:公的施設 2:鉄道駅 3:空港 4:スポーツ施設 5:その他
31	心肺停止場所その他備考欄	心肺停止場所=9の場合 必須
32	心肺停止時の状況	1:運動中 2:入浴中 3:就労中 4:就寝中 5:その他 6:不明
33	口頭指導	0:なし、1:あり
34	口頭指導内訳	N:口頭指導=0の場合 1:人工呼吸のみ 2:心臓マッサージのみ 3:人工呼吸と心臓マッサージ
35	バイスタンダーCPR	0:なし、1:あり
36	バイスタンダーCPR内訳	N:バイスタンダーCPR=0の場合 1:人工呼吸のみ 2:心臓マッサージのみ 3:人工呼吸と心臓マッサージ
37	バイスタンダーCPR開始時刻	mmss 例)8時7分 → 0807
38	バイスタンダーCPR開始時刻区分	1:確定、2:推定、3:不明、4:バイスタンダーCPR=0の場合
39	市民等による除細動	0:なし、1:あり
40	市民等による除細動開始時刻	mmss 例)8時7分 → 0807
41	市民等による除細動開始時刻区分	1:確定、2:推定、3:不明、4:市民等による除細動=0の場合
42	市民等による除細動実施者	N:市民等による除細動=0 0:医療従事者 1:非医療従事者 2:不明
43	市民等による除細動 除細動実施者AED講習会受講歴の有無	N:市民等による除細動=0 1:あり 2:なし 3:不明
44	時間経過1(覚知から患者接触まで) 覚知時刻	mmss 例)8時7分 → 0807
45	時間経過1(覚知から患者接触まで) 出場時刻	mmss 例)8時7分 → 0807
46	時間経過1(覚知から患者接触まで) 現場到着時刻	mmss 例)8時7分 → 0807
47	時間経過1(覚知から患者接触まで) 患者接触時刻	mmss 例)8時7分 → 0807
48	救急隊到着時の状態	1:心肺停止 2:心機能のみ停止 3:呼吸機能のみ停止 4:心・呼吸機能ともあり
49	救急隊員によるCPR	1:施行 2:施行せず 3:人工呼吸のみ
50	救急隊員によるCPR開始時間	mmss 例)8時7分 → 0807
51	救急隊到着時の医師による2次救命処置	0:なし、1:あり

52	初期心電図波形	1:心室細動 2:無脈性心室頻拍 3:無脈性電気活動(PEA) 4:心静止 5:その他 6:装着できず
53	初期心電図波形その他備考欄	初期心電図波形＝5の場合　必須
54	初期心電図波形モニター装着時刻	初期心電図波形≠6の場合 必須 mmss 例)8時7分 → 0807
55	除細動	0:実施せず 1:実施
56	除細動実施	0:除細動＝0の場合 1:二相性 2:単相性
57	除細動実施者 救急救命士	N:除細動＝0の場合 0:実施せず 1:実施
58	除細動実施者 救急隊員	N:除細動＝0の場合 0:実施せず 1:実施
59	除細動実施者 消防隊員	N:除細動＝0の場合 0:実施せず 1:実施
60	除細動実施者 その他	N:除細動＝0の場合 0:実施せず 1:実施
61	除細動施行回数	除細動＝1の場合有効
62	除細動適応波形確認時刻	除細動＝1の場合　必須 mmss 例)8時7分 → 0807
63	初回除細動実施時刻	除細動＝1の場合　必須 mmss 例)8時7分 → 0807
64	特定行為気道確保	0:実施せず 1:実施
65	特定行為気道確保実施区分	0:特定行為気道確保＝0の場合 1:LM 2:食道閉鎖式エアウェイ 3:挿管チューブ
66	食道閉鎖式エアウェイ	0:特定行為気道確保＝0 and 特定行為気道確保実施区分 ≠ 2 の場合 1:スミウェイ 2:コンビチューブ 3:ラリンゲアルチューブ 4:その他
67	最終気道確保器具挿入時刻	特定行為気道確保＝1の場合　必須 mmss 例)8時7分 → 0807
68	静脈路確保	0:施行 1:施行せず 2:施行できず
69	薬剤投与	0:実施せず 1:実施
70	薬剤投与回数	
71	薬剤投与時刻	薬剤投与＝1の場合　必須 mmss 例)8時7分 → 0807
72	時間経過2(搬送開始から病院到着まで) 搬送開始時刻	mmss 例)8時7分 → 0807
73	時間経過2(搬送開始から病院到着まで) 病院到着時刻	mmss 例)8時7分 → 0807
74	病院到着前の心拍再開	1:あり 2:なし
75	初回心拍再開時刻	mmss 例)8時7分 → 0807
76	病院到着時患者状況 脈拍	1:あり 2:なし

77	病院到着時患者状況 呼吸	1：あり 2：なし
78	病院到着時心電図	1：心室細動 2：心室頻拍 3：心静止 4：無脈性電気活動 5：その他
79	病院到着時心電図その他備考	
80	二次救命処置	0：施行 1：施行せず
81	二次救命処置未施行理由	N：二次救命処置＝0の場合 1：医学的社会的理由 2：全身状態改善
82	CPAに至った原因	1：心原性 2：非心原性
83	CPAに至った原因心原性内訳	N：CPAに至った原因＝2の場合 1：確定（疑い含む） 2：除外診断
84	CPAに至った原因非心原性内訳	N：CPAに至った原因＝1の場合 1：脳血管障害 2：呼吸器 3：悪性腫瘍 4：外因性 5：その他
85	CPAに至った原因非心原性 外因性内訳	N：CPAに至った原因非心原性内訳≠4の場合 1：交通事故 2：墜落・転落 3：縊首 4：溺水 5：窒息 6：中毒 7：不明
86	CPAに至った原因非心原性 外因性内訳 窒息理由	0：餅以外　or CPAに至った原因非心原性外因性内訳≠5の場合 1：餅
87	CPAに至った原因非心原性その他備考	CPAに至った原因非心原性内訳＝5の場合　必須
88	病院到着後心拍再開	0：あり 1：なし 2：病院到着時既に心拍再開
89	搬入後心拍再開時刻	mmss　例）8時7分　→　0807
90	病院搬入後の状態	0：ICU／病棟入院 1：外来処置室で死亡
91	発症1ヶ月予後の回答	1：あり 2：なし 3：回答待ち
92	発症1ヶ月後生存	1：あり 2：なし 3：回答待ち
93	発症1ヶ月後生存あり内訳	N：発症1ヶ月後生存≠1の場合 1：入院中 2：生存退院
94	発症1ヶ月後生存なし 死亡年月日	発症1ヶ月後生存＝2の場合　必須 YYYYMMDD
95	発症1ヶ月後または退院時の機能評価 全身機能評価	0：発症1ヶ月後生存＝3の場合 1：良好 2：中等度障害あるも自立 3：重度障害あり要介助 4：植物状態 5：死亡又は脳死 or 病院到着後心拍再開＝1の場合

96	発症1ヶ月後または退院時の機能評価 脳機能評価	0:発症1ヶ月後生存＝3の場合 1:良好 2:中等度障害あるも自立 3:重度障害あり要介助 4:植物状態 5:死亡又は脳死 or 病院到着後心拍再開＝1の場合
97	発症1年後生存	N:発症1ヶ月後生存≠1の場合 1:あり 2:なし
98	発症1年後生存あり内訳	N:発症1年後生存≠1の場合 1:入院中 2:生存退院
99	発症1年後生存なし 死亡年月日	発症1年後生存＝2の場合　必須 YYYYMMDD
100	発症1年後の機能評価 全身機能評価	0:発症1ヶ月後生存＝3の場合 1:良好 2:中等度障害あるも自立 3:重度障害あり要介助 4:植物状態 5:死亡又は脳死 or 病院到着後心拍再開＝1の場合
101	発症1年後の機能評価 脳機能評価	0:発症1ヶ月後生存＝3の場合 1:良好 2:中等度障害あるも自立 3:重度障害あり要介助 4:植物状態 5:死亡又は脳死 or 病院到着後心拍再開＝1の場合
102	メモ	
103	登録状態	0:仮登録、1:本登録
104	削除フラグ	0:有効、1:削除

※　各項目は可変長のカンマ区切りとなります。また、1件分のデータは改行コードを終端記号としてください。
　　（各項目はダブルクォーテーションで囲む必要はありません）
※　データ中にカンマが含まれる場合はASCIIコード1の文字に置き換えてください。

Survival Outcomes With the Introduction of Intravenous Epinephrine in the Management of Out-of-Hospital Cardiac Arrest

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Study objective: The benefit of epinephrine in cardiac arrest is controversial and has not been conclusively shown in any human clinical study. We seek to assess the effect of introducing intravenous epinephrine on the survival outcomes of out-of-hospital cardiac arrest patients in an emergency medical services (EMS) system that previously did not use intravenous medications.

Methods: This observational, prospective, before-after clinical study constitutes phase II of the Cardiac Arrest and Resuscitation Epidemiology project. Included were all patients who are older than 8 years, with nontraumatic out-of-hospital cardiac arrest conveyed by the national emergency ambulance service. The comparison between the 2 intervention groups for survival to discharge was made with logistic regression and expressed in terms of the odds ratio (OR) and the corresponding 95% confidence interval (CI).

Results: From October 1, 2002, to October 14, 2004, 1,296 patients were enrolled into the study, with 615 in the pre-epinephrine and 681 in the epinephrine phase. Demographic and EMS characteristics were similar in both groups. Forty-four percent of patients received intravenous epinephrine in the epinephrine phase. There was no significant difference in survival to discharge (pre-epinephrine 1.0%; epinephrine 1.6%; OR 1.7 [95% CI 0.6 to 4.5]; adjusted for rhythm OR 2.0 [95% CI 0.7 to 5.5]); return of circulation (pre-epinephrine 17.9%; epinephrine 15.7%; OR 0.9 [95% CI 0.6 to 1.2]), or survival to admission (pre-epinephrine 7.5%; epinephrine 7.5%; OR 1.0 [95% CI 0.7 to 1.5]). There was a minimal increase in scene time in the epinephrine phase (10.3 minutes versus 10.7 minutes; 95% CI of difference 0.02 to 0.94 minutes).

Conclusion: We were unable to establish a significant survival benefit with the introduction of intravenous epinephrine to an EMS system. More research is needed to determine the effectiveness of drugs such as epinephrine in resuscitation. [Ann Emerg Med. 2007;xx:xxx.]

Editor's Capsule Summary

What is already known on this topic

There are few human data supporting the current use of intravenous epinephrine for patients with out-of-hospital cardiac arrest.

What question this study addressed

Does the introduction of a single dose of 1 mg intravenous epinephrine improve outcomes from out-of-hospital cardiac arrest in a system that previously did not use this drug?

What this study adds to our knowledge

Only 44% of eligible subjects received epinephrine in this 1,296-patient before-after trial in Singapore. No benefit in initial survival or other common short-term resuscitation metrics occurred.

How this might change clinical practice

Given the study's limitations, the role of epinephrine remains unclear. This study highlights the difficulties in establishing the value of standard EMS resuscitative care.

INTRODUCTION
Background and Importance
In the chain-of-survival concept,[1,2] provision of early access, early cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced care, including intravenous drugs, should improve survival in sudden cardiac arrest. Survival rates for out-of-hospital cardiac arrest vary in published reports from 2% to more than 20%.[3]

Intravenous epinephrine (adrenaline) has been used since 1906 to treat cardiac arrest.[4] However, since then, there have been few formal evaluations of the value of epinephrine, and these studies are more than 10 years old.[5] Clinical trials have not been able to show any benefit with intravenous epinephrine in the field.[6,7] In fact, some suggest that harm is actually associated with its use in cardiac arrest.[8,9] Extensive clinical trials comparing high-dose epinephrine (>5-mg boluses) with standard-dose epinephrine (1 mg) have shown that there is no improvement in survival with increasing doses of epinephrine.[10-16]

The current International Liaison Committee on Resuscitation Advanced Cardiac Life Support Guidelines (2005)[17] acknowledges that there is no placebo-controlled evidence that use of any vasopressor during cardiac arrest improves survival to hospital discharge. However, acknowledging the current standard clinical practice, they state that it is reasonable to continue to use vasopressors routinely.[17] Because the use of epinephrine is ingrained in clinical practice in North America and Europe, it would probably not be possible to conduct controlled evaluations of epinephrine in these settings.

Goals of This Investigation
In this study, we aimed to evaluate the incremental benefit of introducing intravenous epinephrine in the out-of-hospital setting on the survival outcomes of cardiac arrest patients in the Singapore emergency medical services (EMS), a system that previously did not use out-of-hospital intravenous medications. Specific outcomes examined included survival to discharge, survival to hospital admission, return of spontaneous circulation, and functional status on discharge.

MATERIALS AND METHODS
Study Design
The Cardiac Arrest and Resuscitation Epidemiology Study is a prospective multiphase, before-after study of all eligible out-of-hospital cardiac arrest patients in Singapore. During phase II, intravenous epinephrine was introduced in the treatment protocols of all out-of-hospital cardiac arrest patients conveyed by the Singapore Civil Defence Force ambulance service. The Singapore Civil Defence Force operates the national 995 emergency telephone service; private ambulance operators do not convey emergency cases. The study period was October 1, 2002, to October 14, 2004.

Setting
Singapore is a city-state with a land area of 699.4 km^2 and a population of 4.35 million.[18,19] The population is multiracial, with the major ethnic groups being Chinese, Malay, and Indian. The island's EMS system is run by the Singapore Civil Defence Force, which currently operates 32 ambulances based in 15 fire stations and 14 satellite stations in a single-tier system. Emergency ambulance patients are delivered to 6 major public hospitals in the country that are equipped with modern emergency departments (ED).

Singapore EMS is activated by a universal, centralized, enhanced, 995 dispatching system run by the Singapore Civil Defence Force and using computer-aided dispatch, medical dispatch protocols, global positioning satellite automatic vehicle locating systems, and road traffic monitoring systems.

Since 1996, ambulances in Singapore have been manned by specifically trained paramedics (roughly equivalent to North American EMT-I), replacing the nurses who previously served as ambulance officers. The paramedics undergo an 18-month training, including theory and hospital and ambulance attachments. They are able to provide basic life support and defibrillation with automated external defibrillators. Before this study, cardiac arrest protocols followed basic life support guidelines and included the use of automated external defibrillators in a "shock first" protocol. Intravenous medications were previously not in use by ambulance crews. The crews are not certified to perform endotracheal intubation and do not give epinephrine by the endotracheal tube. Mechanical CPR is not used.

The Cardiac Arrest and Resuscitation Epidemiology Study Group includes representatives from the 6 major public hospitals in Singapore, the Singapore Civil Defence Force,

Health Sciences Authority, and the Clinical Trials and Epidemiology Research Unit, Singapore. The Cardiac Arrest and Resuscitation Epidemiology phase I study described out-of-hospital cardiac arrest epidemiology in Singapore and served as a baseline for phase II.[20]

For this study, the investigators initiated a series of intravenous cannulation and drug administration workshops during a 9-month period for Singapore Civil Defence Force paramedics, which included didactic teaching, demonstrations and training using simulators, and an attachment to EDs in hospitals for practical training in intravenous cannulation and drug administration. Paramedics had to log 10 supervised intravenous drug administrations in the hospitals to be certified competent to give intravenous epinephrine. The Singapore Civil Defence Force maintained a register of paramedics certified to give intravenous drugs.

The Singapore Civil Defence Force ambulance service implemented intravenous epinephrine for the out-of-hospital management of cardiac arrest, with approval from the Ministry of Health and under the supervision of the Singapore Civil Defence Force Medical Advisory Committee from October 15, 2003. Treatment followed strict protocols approved by Ministry of Health and Medical Advisory Committee. Intravenous epinephrine was given after initiation of CPR and initial defibrillation (if appropriate) according to advanced cardiac life support (ACLS) guidelines. Paramedics were given 2 attempts or 2 minutes for successful intravenous placement at the scene. If intravenous placement was unsuccessful, the protocol emphasized not to delay transport any further but to transport the patient. Another 2 intravenous attempts were allowed in the ambulance en route. Only 1 dose of prediluted epinephrine 1:10,000 in 10 mL solution was given if intravenous insertion was successful according to approved protocols.

Selection of Participants

Patients older than 8 years were included. Patients older than 8 years were considered suitable for automated external defibrillator use, as well as the 1-mg dose of epinephrine used in the study. Exclusion criteria were traumatic cardiac arrest patients and those "obviously dead" as defined by the presence of decomposition, rigor mortis, or dependent lividity.

Methods of Measurement and Data Collection and Processing

Patient characteristics (age, sex, race, medical history), cardiac arrest circumstances (arrest location, witnessed, bystander CPR, defibrillation, epinephrine given), ECG rhythms, EMS response times, and outcomes were prospectively recorded in a standard report filled out by EMS and EDs according to the Utstein style.[21] ECG recordings were captured using the Lifepak 12 (Medtronic, Physio-Control, Redmond, WA) and subsequently verified by physician reviewers. EMS timings were automatically recorded by the computerized central dispatch system and ambulance automated external defibrillators. All watches and automated external defibrillators

were synchronized with the central dispatch clock at the beginning of each shift. Institutional review board approval was obtained from all participating institutions.

Outcome Measures

The primary outcome measure for the study was survival to hospital discharge, which was defined as the patient leaving the hospital alive or survival to 30 days post–cardiac arrest, whichever came first. Outcomes were obtained by hospital medical record review or patient assessment by physicians in the study team. Functional assessment of survivors was performed by reviewing physicians using standardized cerebral performance category and overall performance category scores according to Utstein guidelines.

Primary Data Analysis

For sample size, it was anticipated that the introduction of epinephrine would improve the primary outcome variable "survival to discharge" from the hospital from 1% to 5%. Using a 2-sided test size of 5% and a power of 90% suggested that approximately 450 patients would be needed in each arm. It was anticipated that within the practical contingencies of the design, the 1-year trial period without and 1-year period with epinephrine would allow this number of patients to be recruited.

Data management was carried out with the Clintrial application software, version 4.2. All data analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL), presenting descriptive statistics and frequencies. The comparison between mean scene times for the 2 periods was made with a t test. The comparison between the 2 intervention groups for the binary variable "survival to discharge from hospital" was made with logistic regression and expressed in terms of the odds ratio (OR) and the corresponding 95% confidence interval (CI), an OR greater than 1 indicating an advantage to the epinephrine group. In view of the low prevalence of the outcome, this analysis was adjusted by a single covariate (each in turn) from 4 of those suggested by Stiell et al,[22] that is, patient age, bystander witness arrest, bystander CPR, response time, and presenting rhythm. In any event, adjustment for rhythm had the largest influence, and so this was also used for comparisons between groups according to the secondary endpoints of "survival to hospital" and "return of spontaneous circulation."

RESULTS

Characteristics of Study Subjects

From October 1, 2002, to October 14, 2004, 1,296 patients were enrolled into the study, with 615 in the pre-epinephrine and 681 in the epinephrine phase (Figure). One hundred seventeen patients in both phases had trauma arrests, and these were excluded.

Table 1 shows the characteristics of patients in pre-epinephrine and epinephrine phases. Characteristics such as age,
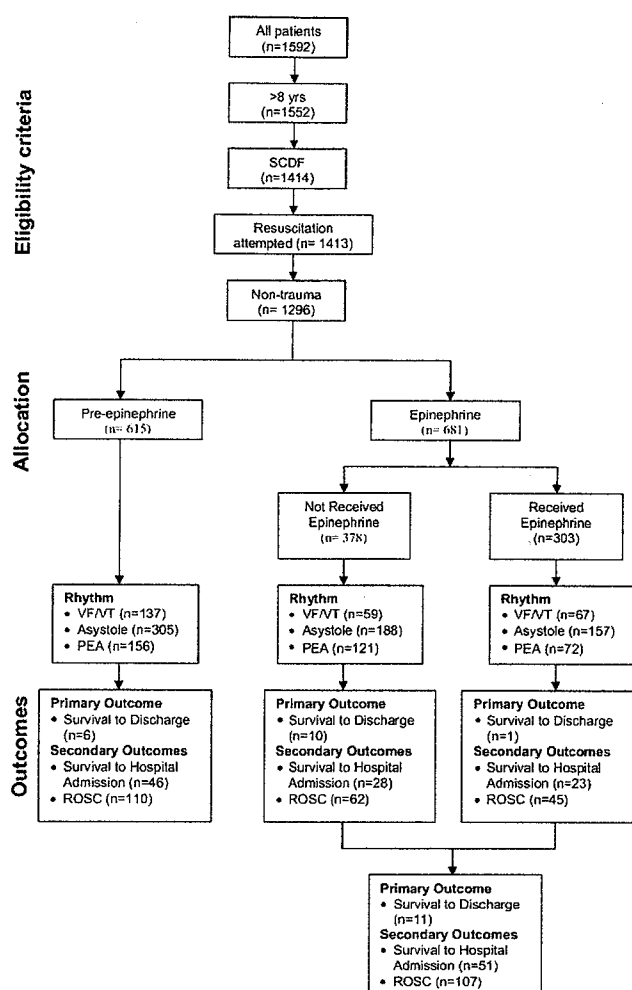
Figure. Trial profile. *SCDF*, Singapore Civil Defence Force; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *PEA*, pulseless electrical activity; *ROSC*, return of spontaneous circulation.

Table 1. Characteristics of patients in the pre-epinephrine and epinephrine phases.

Characteristics	Pre-epinephrine (N=615)	Epinephrine (N=681)
Mean age, y (SD)	63.3 (15.5)	63.7 (15.5)
Male (%)	435 (70.7)	456 (67.0)
Race		
Chinese	421 (68.5)	483 (70.9)
Malay	97 (15.8)	101 (14.8)
Indian	73 (11.9)	75 (11.0)
Others	24 (3.9)	22 (3.2)
Arrest location (%)		
Residence	383 (62.3)	431 (63.3)
Other	232 (37.7)	250 (36.7)
Collapse witness		
By bystander (%)	350 (57.0)	390 (57.3)
EMS witnessed (%)	59 (9.6)	72 (10.6)
Not witnessed (%)	205 (33.4)	219 (32.2)
Bystander CPR (%)	120 (21.6)	131 (21.5)
Initial rhythm		
Ventricular fibrillation (%)	134 (22.0)	120 (17.8)
Ventricular tachycardia (%)	3 (0.5)	6 (0.9)
Asystole (%)	305 (50.1)	345 (51.0)
Pulseless electrical activity (%)	156 (25.6)	193 (28.6)
Defibrillated (%)	156 (25.4)	162 (23.8)
Call receipt to vehicle stops, min (SD)	9.2 (3.5)	9.1 (4.3)
Call receipt to arrival at patient's side, min (SD)	11.6 (3.8)	11.4 (4.7)
Vehicle arrival at patient's side to leaving location, min (SD)	10.3 (4.00)	10.7 (4.4)
Vehicle leaving location to arriving at hospital, min (SD)	11.4 (7.4)	11.4 (5.9)
Medical history		
Heart disease	214 (42.1)	258 (44.8)
Diabetes	160 (31.5)	179 (31.1)
Hypertension	184 (36.2)	257 (44.6)
Stroke	38 (7.5)	46 (8.0)
Cancer	44 (8.7)	57 (9.9)
Others	73 (14.4)	125 (21.7)
% actually received IV epinephrine	0 (0)	301 (44.2)

race, witnessed by bystander, bystander CPR, initial rhythm, EMS response times, and out-of-hospital defibrillation were similar in both groups. There was a slightly higher incidence of hypertension and "other" medical history in the epinephrine group compared with the pre-epinephrine group. There was a minimal increase in scene time in the epinephrine phase (10.3 minutes versus 10.7 minutes; 95% CI of difference 0.02 to 0.94; *P*=.04).

Main Results

Table 2 shows the subgroup analysis for study outcomes stratified by presenting rhythm, witnessed, bystander CPR, and response time. Table 3 shows the functional status of survivors in both phases.

Table 4 shows the comparison of outcomes in the pre-epinephrine and epinephrine phases. There was no significant difference in survival to discharge (pre-epinephrine 1.0%;

epinephrine 1.6%; OR 1.7 [95% CI 0.6 to 4.5], adjusted for rhythm OR 2.0 [95% CI 0.7 to 5.5]). There was no significant improvement in return of circulation (pre-epinephrine 17.9%; epinephrine 15.7%; OR 0.9 [95% CI 0.6 to 1.2]) or survival to admission (pre-epinephrine 7.5%; epinephrine 7.5%; OR 1.0 [95% CI 0.7 to 1.5]). Analysis of survival to discharge, adjusted by a single covariate (each in turn), namely, by patient age, bystander witness arrest, and response time, did not greatly change the results. The 2 covariates that had the greatest effect on the ORs (rhythm and bystander CPR) are shown in Table 4.

LIMITATIONS

Limitations of this study include that it was a before-after clinical study and not a placebo-controlled, randomized study, and thus results may be affected by secular trends. Variations in postresuscitation care can affect survival to discharge status, and variations between institutions or individual hospital providers are difficult to account for. During this period, we were

Table 2. Subgroup analysis for study outcomes.

		Return of Spontaneous Circulation				Hospital Admission				Hospital Discharge			
Subset	N	Pre-epinephrine (%)	Epinephrine (%)	OR	95% CI	Pre-epinephrine (%)	Epinephrine (%)	OR	95% CI	Pre-epinephrine (%)	Epinephrine (%)	OR	95% CI
Initial rhythm													
VF/VT	263	25 (18.2)	23 (18.3)	1.000	(0.54–1.87)	9 (6.6)	16 (12.7)	2.069	(0.88–4.87)	4 (2.9)	9 (7.1)	2.558	(0.77–8.52)
PEA	349	35 (22.4)	41 (21.2)	0.933	(0.56–1.55)	17 (10.9)	18 (9.3)	0.841	(0.42–1.69)	1 (0.6)	1 (0.5)	0.807	(0.05–13.01)
Asystole	650	49 (16.1)	35 (10.1)	0.590	(0.37–0.94)	20 (6.6)	16 (4.6)	0.693	(0.35–1.36)	1 (0.3)	1 (0.3)	0.884	(0.06–14.19)
Witness to collapse													
Bystander	740	66 (18.9)	56 (14.4)	0.721	(0.49–1.07)	25 (7.1)	32 (8.2)	1.162	(0.67–2.00)	2 (0.6)	6 (1.5)	2.719	(0.55–13.56)
EMS	131	19 (32.2)	30 (41.7)	1.504	(0.73–3.09)	11 (18.6)	13 (18.1)	0.961	(0.40–2.34)	3 (5.1)	5 (6.9)	1.393	(0.32–6.09)
None	424	25 (12.2)	21 (9.6)	0.764	(0.41–1.41)	10 (4.9)	6 (2.7)	0.549	(0.20–1.54)	1 (0.5)	0 (0.0)	—	—
Bystander CPR													
Yes	251	22 (18.3)	22 (16.8)	0.899	(0.47–1.72)	6 (5.0)	16 (12.2)	2.643	(1.00–7.00)	0 (0.0)	5 (3.8)	—	—
No	914	69 (15.8)	55 (11.5)	0.692	(0.47–1.01)	29 (6.7)	22 (4.6)	0.677	(0.38–1.20)	3 (0.7)	1 (0.2)	0.303	(0.03–2.92)
Response time													
≤8 min	590	45 (17.1)	56 (17.1)	1.001	(0.65–1.54)	24 (9.1)	24 (7.3)	0.789	(0.44–1.42)	2 (0.8)	7 (2.1)	2.855	(0.59–13.86)
>8 min	706	65 (18.5)	51 (14.4)	0.743	(0.50–1.11)	22 (6.3)	27 (7.6)	1.239	(0.69–2.22)	4 (1.1)	4 (1.1)	0.994	(0.25–4.01)

Table 3. Cerebral performance category/overall performance category of survivors at 30 days in the pre-epinephrine and epinephrine phases.

Performance Categories (%)	Pre-epinephrine (n=5)*	Epinephrine (n=11)
CPC 1	3 (60.0)	8 (72.7)
CPC 2	1 (20.0)	1 (9.1)
CPC 3	0	1 (9.1)
CPC 4	1 (20.0)	0
CPC 5	0	1 (9.1)
OPC 1	2 (40.0)	6 (54.5)
OPC 2	2 (40.0)	3 (27.3)
OPC 3	0	1 (9.1)
OPC 4	1 (20.0)	0
OPC 5	0	1 (9.1)

CPC, Cerebral performance category; *OPC*, overall performance category.
*One patient's CPC and OPC are unknown.

unaware of any major change in ED protocols or in ICU treatment. Nevertheless, it is possible that variations in individual and hospital practice could affect the study results in ways that are difficult to determine.

This study was performed in an EMS system that previously did not use intravenous drugs and endotracheal intubation, which differs greatly from the practice, for example, in North American EMS systems. Thus, care should be taken when the results are extrapolated to other EMS systems.

A related limitation is the relatively low rate of successful intravenous drug delivery[23] during the epinephrine phase, which may have been due to a variety of reasons. Intravenous placement may not have been successful, because of ambulance crew inexperience and our insistence on not delaying transport for more than 2 minutes or 2 attempts at intravenous insertion, after which "load and go" would be initiated. This practice was reflected in that the scene time increased by only half a minute during the 2 phases. However, nondelivery may also have been due to the patient's recovering a pulse after initial CPR and defibrillation. Our protocols would not have allowed delivery of intravenous epinephrine in those circumstances. Finally, nondelivery may have also been due to noncompliance with protocol, although we were unable to detect many instances of this.

Also, this study examined only the effect of a single dose of epinephrine. No repeated dosing of epinephrine was allowed according to protocols until after arrival at the ED. Also, no other drugs usually given in ACLS, such as atropine, amiodarone, or lidocaine, were given out-of-hospital in this study, which differs from current EMS practice, for example, in North America.

DISCUSSION

Epinephrine has been standard of ACLS care since its inception. Before this study, there were few formal evaluations, and there have not been any large-scale clinical studies that have been able to demonstrate a survival benefit associated with the

Table 4. Comparison of outcomes in the pre-epinephrine and epinephrine phases.

Outcomes	Phase		Unadjusted		Adjusted for Rhythm		Adjusted for Bystander CPR	
	Pre-epinephrine (n=615)	Epinephrine (n=681)	OR	95% CI	OR	95% CI	OR	95% CI
Survival to discharge/at 30 days postarrest (%)	6 (1.0)	11 (1.6)	1.666	(0.61–4.53)	1.975	(0.72–5.46)	1.843	(0.46–7.43)
Survival to hospital admission (%)	46 (7.5)	51 (7.5)	1.001	(0.66–1.52)	0.983	(0.65–1.49)	0.991	(0.62–1.59)
Return of spontaneous circulation (%)	110 (17.9)	107 (15.7)	0.856	(0.64–1.15)	0.810	(0.60–1.09)	0.739	(0.53–1.03)

use of epinephrine in cardiac arrest.[5] This deficit may have be due to the early, widespread adoption of intravenous epinephrine as the standard of care for cardiac arrest in EMS. Thus, it has been ethically difficult to justify any randomized controlled trials comparing epinephrine and placebo in cardiac arrest. A formal evaluation today would be impossible because it is seen as standard of care and is ingrained in practice. Our effort is notable in that it examines the effect of individual interventions in a setting untainted by customary practice.

In Singapore, ambulance crews were not previously using intravenous epinephrine in cardiac arrest, which gave us a unique opportunity to observe any effect that introduction of intravenous epinephrine in cardiac arrest protocols would have on survival outcomes. In current clinical practice, such a study would be possible only outside North America or Europe. In this study, we were unable to show a significant survival benefit with the introduction of intravenous epinephrine to an EMS system. The limitation of this study is its setting in Singapore, with relatively inexperienced rescuers.

Epinephrine is thought to aid resuscitation, mainly by its α-adrenergic effects.[24-28] However, the potential adverse effects of epinephrine include decreased total forward cardiac output, increased myocardial oxygen consumption, myocardial dysfunction postresuscitation,[28-32] and increased intrapulmonary shunting.[29,33-35] Postresuscitation, patients who received greater than 15-mg cumulative dose had significantly lower cardiac index, lower systemic oxygen consumption, lower systemic oxygen delivery, and significantly higher systemic vascular resistance index, higher lactic acid, and lower 24-hour survival.[36] Two studies, by van Walraven et al[8] and Roberts et al,[9] have suggested that use of epinephrine is a strong early predictor of mortality in cardiac arrest. However, these were both retrospective, noninterventional studies. Weaver et al[6] studied 199 patients in persistent ventricular fibrillation who were given epinephrine or lignocaine and compared them with historical controls given bicarbonate (not placebo). They found no difference in the proportion of patients resuscitated with either epinephrine or lignocaine and lower survival in both groups compared to bicarbonate. Woodhouse et al[7] compared high-dose epinephrine (10 mg), standard-dose epinephrine, and placebo in cardiac arrest. This study showed no significant difference in survival with high-dose or standard-dose epinephrine or placebo.

In our study, we believe that care should be taken when comparing outcomes according to whether epinephrine was actually given or not (see the Figure) because intravenous epinephrine may not have been given for a variety of reasons during the epinephrine phase, as elaborated previously. In the instance in which patients did not receive epinephrine because of early return of spontaneous circulation (and this group tends to have better survival), this may give a "survival bias" to the no-epinephrine group compared to the epinephrine group. Thus, we advocate an intention-to-treat approach to avoid the Van de Werf effect.[37] Perhaps the survivors who actually received intravenous epinephrine might be thought of as the additional responders to those who would not have return of spontaneous circulation after initial CPR and defibrillation (Figure).

There was also a trend in the subgroup analysis (Table 2) to suggest that the effect of epinephrine on survival might have been greater in those with response times less than or equal to 8 minutes and those presenting with ventricular fibrillation, although these were not statistically significant, because of sample size. We believe that there is some evidence to suggest that the effectiveness of any intervention in cardiac arrest is closely linked to response times and presenting rhythm.[3,22,38-44] If EMS response times are long, it is unlikely that any intervention will be able to show a difference in outcomes.

In conclusion, we were unable to establish a survival benefit with the introduction of intravenous epinephrine to an EMS system that previously did not use intravenous medications.

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Editor's Capsule Summary: *What is already known on this topic:* There are few human data supporting the current use of intravenous epinephrine for patients with out-of-hospital cardiac arrest. *What question this study addressed:* Does the introduction of a single dose of 1 mg intravenous epinephrine improve outcomes from out-of-hospital cardiac arrest in a system that previously did not use this drug? *What this study adds to our knowledge:* Only 44% of eligible subjects received epinephrine in this 1,296-patient before-after trial in Singapore. No benefit in initial survival or other common short-term resuscitation metrics occurred. *How this might change clinical practice:* Given the study's limitations, the role of epinephrine remains unclear. This study highlights the difficulties in establishing the value of standard EMS resuscitative care.

Review

Epinephrine and vasopressin during cardiopulmonary resuscitation

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Abstract

Epinephrine (adrenaline) and vasopressin have been by far the most commonly studied vasopressors in experimental cardiac arrest. Despite animal experimental studies suggesting improved outcomes in experimental cardiac arrest, clinical trials of pressor agents have failed to show clear cut benefit from either vasopressin or epinephrine, although few, if any, trials compared pressor agents to a placebo.

The action of vasopressors in the heart, particularly β_1-Adrenergic stimulation, is associated with adverse cardiac effects including post-resuscitation myocardial dysfunction, worsening ventricular arrhythmias, and increasing myocardial oxygen consumption. α_2-Adrenergic agonists, in experimental studies, show great promise in improving outcomes in experimental cardiac arrest, but have not been studied in humans. The combination of epinephrine and vasopressin may be effective, but has been incompletely studied. Clinical trials of vasopressor agents, which minimize direct myocardial effects are needed.
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Keywords: Cardiac arrest; Cardiopulmonary resuscitation (CPR); Epinephrine; Vasopressin

Contents

1. Introduction

Cardiac arrest remains a major health problem in Western countries. There are an estimated 300,000 cardiac arrests yearly in the USA and Canada [1], and more and more

patients die of cardiac arrest in developing countries such as China. The *sine qua non* of successful resuscitation is prompt restoration of effective blood flow to the most vulnerable organs, the brain and the heart. Most out-of-hospital cardiac arrests are caused initially by ventricular fibrillation (VF) [2], but the initial rhythm found by EMS responders is increasingly frequently asystole or pulseless electrical activity (PEA) [3]. Limitations of current advanced cardiac life support (ACLS) techniques include relatively low cardiac output despite standard CPR [4,5], frequent shock resistant

VF and "re-fibrillation" [6], and poor myocardial function following defibrillation or resuscitation, as a consequence of cellular ischemia and acidosis during cardiac arrest. The lack of reliable and simple monitoring tools for the efficacy of continuous CPR partly constrains resuscitation strategy.

Vasopressors are believed to improve the outcome of patients with cardiac arrest by improving cardiac and brain blood flow during CPR [7,8], increasing the ability to restore spontaneous circulation (ROSC), and increasing spontaneous organ perfusion post-resuscitation [9–15]. Although epinephrine has been used as a standard first-line drug in cardiac arrest for several decades, it has not been shown to be superior to placebo in any clinical trial, and has potential adverse effects [4,5].

Vasopressin is an alternative vasopressor that has been tested clinically and experimentally in cardiac arrest. Interpreting the data regarding the effectiveness and relative efficacy of epinephrine and vasopressin is complicated by differences in the experimental models, study designs, drug doses, clinical settings, and adjunctive therapies [16,17], especially in the different situations of the three main categories of adult cardiac arrest (persistent VF, PEA and asystole). There are no convincing data that vasopressin is superior to epinephrine in VF; however, other vasopressors, not yet tested in humans, offer substantial promise. We attempt to review the available data on vasopressors to place into perspective their risks, benefits, and potential clinical usefulness.

Understanding the potential roles of vasopressors also requires a consideration of the specific role of pharmacologic agents that act on vasoactive receptors. During experimental and clinical cardiac arrest, endogenous catecholamine concentrations are extremely high; for example, in an animal model of VF, interstitial fluid epinephrine concentrations are increased to levels 170 times baseline pre VF levels [18]. Cardiac β_1-receptors, in particular, may be already maximally stimulated by the time exogenous agents are administered, usually after more that 10–15 min of no spontaneous circulation in most EMS settings.

Vasopressors can lead to increased coronary perfusion pressure (CPP) during CPR by increasing coronary arterial resistance and increasing the "diastolic" (during decompression) pressure gradient between the epicardial coronary arteries and the right atrium. Increases in perfusion pressure are presumably associated with increases in flow, although pressure–flow relationships in this setting have not been well studied. Improving cardiac blood supply not only protects the myocardium from ischemic damage but also may indirectly lower energy requirements for defibrillation or make refibrillation less likely. On the other hand, the direct action of β_1-stimulation is to increase defibrillation energy requirements [19–21]. In the case of PEA or asystole, adrenergic stimulation can also increase impulse formation directly.

Since the rhythm is frequently in transition from VF to asystole/PEA and vice versa in many patients in cardiac arrest, and VF reoccurs ("refibrillation") in more than 50% of episodes [6], the multiple effects of adrenergic stimulation can be helpful in some states but not in others. For example, it is likely that β_1-adrenergic stimulation promotes refibrillation in ischemic myocardium.

Long-term survival will depend on the interplay between therapy and residual left ventricular function, organ damage as a consequence of the cardiac arrest, and drug effects or the mediation of cell injury and death that become pertinent in the "third phase" of cardiac arrest [22].

2. Epinephrine

2.1. Epinephrine in experimental studies

Epinephrine is a mixed adrenergic agonist, acting on α- (α_1 and α_2) and β- (β_1 and β_2) adrenergic receptors. The important actions of epinephrine for ROSC are mostly mediated by the α-adrenergic properties. Epinephrine increases CPP via systemic arteriolar vasoconstriction, which maintains peripheral vascular tone and prevents arteriolar collapse. Aortic diastolic pressure can be increased by any potent α-adrenergic agonist [23].

If initial defibrillation has failed, the ACLS and ALS guidelines for CPR recommend periodic intravenous administration of epinephrine [4,5]. During prolonged cardiac arrest, CPP and forward blood flow are the major determinants of successful resuscitation. When CPP is too low, successful resuscitation is unlikely. When the CPP is marginal, resuscitation may be possible; however, 24 h survival is unlikely [24]. When CPR is able to generate CPP above 30 mmHg, as reflected in an adequate end-tidal CO_2, the 24 h survival rate is greatly improved [24].

In contrast to the α-receptor effects, β-receptor stimulation may have a deleterious effect [25]; β-adrenergic stimulation increases the oxygen consumption of the fibrillating myocardium, reduces subendocardial perfusion [20], and is associated with poorer post-resuscitation myocardial function [26].

The β-antagonist esmolol administered immediately following defibrillation, but before CPR, improved ROSC and 4 h survival after prolonged VF in pigs. Esmolol may protect from cardiac cytotoxicity caused by β_1- and β_2-stimulation in the setting of the high catecholamine concentrations seen during cardiac arrest [18]. Ditchey et al. [27] found β_2-blockade may result in increases in CPP during experimental cardiac arrest. However, Hilwig et al. [28] investigated the effect of intravenous β-blockers given during CPR after 1 min of untreated VF, followed by 6 min of basic life support, in combination with a variety of adrenergic agonists including standard dose epinephrine, high dose epinephrine, and phenylephrine, for their effects on long-term survival in pigs. There was no survival advantage to adding β-blockade during the performance of CPR to treatment with a variety of vasopressors.

Both α_1- and β-adrenergic agonists increase the severity of global myocardial ischemic injury; α_1-agonists increase myocardial oxygen demands [29] and therefore may increase the severity of post-resuscitation myocardial dysfunction. α_1-Adrenergic agonists may have other deleterious effects, causing intramyocardial coronary arteriolar vasoconstriction with the potential of further reductions in myocardial blood flow. The effects of α_1-adrenergic stimulation in clinical cardiac arrest are not clear. Pearson and Redding and Roberts et al. compared the effects of epinephrine with those of a selective α_1-agonist, methoxamine, in the setting of VF in dogs [30,31]. In contrast to the hypothesis of potential harm from α_1-adrenergic stimulation, they found that methoxamine significantly increased myocardial and cerebral blood flow during CPR compared to epinephrine, and was associated with significantly improved post-resuscitation cardiac output and survival when compared with epinephrine.

In contrast to α_1-adrenergic receptors, no α_2-adrenergic receptors have been identified in the myocardium [32]. Pellis et al. [33] hypothesized that combined β- and α_1-adrenergic blockade would improve initial resuscitation and post-resuscitation myocardial and neurological functions. They randomized pigs to receive central venous injections of equipotent pressor doses of (1) epinephrine; (2) epinephrine in which both α_1- and β-adrenergic effects were blocked by previous administration of prazosin and propranolol; and (3) vasopressin, during CPR. Following epinephrine, significantly better cardiac output and neurological function was observed after defibrillation in the α_1- and β-adrenergic blockade group. They concluded that "equipotent pressor doses of epinephrine, epinephrine combined with α_1- and β-adrenergic blockade, and vasopressin were equally effective in achieving ROSC after prolonged VF. However, combined α_1- and β-adrenergic blockade, which would result in a predominantly selective α_2-vasopressor effect, resulted in improved post-resuscitation cardiac and neurological recovery" [33]. Another animal experimental study using α-methylnorepinephrine, a selective α_2-adrenergic agonist, showed significantly fewer post-resuscitation ventricular arrhythmias and better post-resuscitation myocardial function than after epinephrine [34]. When the α_2-actions of epinephrine were blocked with yohimbine, the therapeutic benefits of epinephrine were diminished [34].

Post-resuscitation myocardial function after epinephrine and α-methylnorepinephrine were compared in a swine model of cardiac arrest due to VF [20]. Either α-methylnorepinephrine (100 μg/kg) or epinephrine (20 μg/kg) was administered as a bolus after 7 min of untreated VF and 2 min of CPR. After an additional 4 min of precordial compression, defibrillation was attempted. All animals were successfully resuscitated; epinephrine and α-methylnorepinephrine were equally effective in achieving ROSC. However, ejection fraction was reduced by 35% by epinephrine from baseline and only 14% by α-methylnorepinephrine ($P < 0.01$).

These experimental observations have not been validated in humans, and epinephrine remains as the adrenergic agent of first choice in the international ACLS guidelines [4,5,16,17].

2.2. Clinical studies using epinephrine

Although epinephrine has been used as a standard first-line drug in cardiac arrest for several decades [4,5,16,17], there is no good evidence to show that it improves outcome in humans [4,5]. Furthermore, the optimal dose (assuming any dose is beneficial) of epinephrine for the three main categories of adult cardiac arrest (persistent VF, PEA and asystole), has also not yet been definitely determined.

No randomized clinical studies have compared standard dose epinephrine to placebo in cardiac arrest. In a small randomized trial, high dose (10 mg) epinephrine was not superior to placebo (immediate survival of 29% with epinephrine, 42% with placebo, $P = $NS), although more patients converted to sinus rhythm or ventricular tachycardia (VT) with epinephrine (26% versus 12%, $P = 0.01$) [35]. In the same study, a historical control group treated with 1 mg epinephrine had "immediate survival" of 50%, not different from placebo [35].

In a randomized but not blinded comparison of epinephrine (0.5 mg) to lidocaine (100 mg) in 199 patients with pre-hospital VF [36], the outcomes were similar with respect to survival, although significantly more patients treated with lidocaine developed asystole (25% versus 7%, lidocaine and epinephrine, respectively, $P < 0.02$). Resuscitation success, but not survival rates, were higher during the prior 2-year period when sodium bicarbonate or no drug therapy was administered after failed defibrillation. The authors concluded that "currently recommended doses of epinephrine and lidocaine are not useful for improving outcome in patients who persist in VF" [36].

Herlitz et al. [37] compared outcomes in 417 patients with out-of-hospital VF who received epinephrine to 786 patients who received no epinephrine (the EMS personnel in attendance were not authorized to administer epinephrine). Among those successfully defibrillated, admission to hospital alive was the same in the epinephrine treated patients versus controls (36% versus 36%), but hospital discharge rates were higher in the no epinephrine group (12% versus 19%, respectively). Using a different study design, van Walraven et al. [38] performed multivariate analysis on factors associated with improved or worse outcome after in-hospital cardiac arrest in 773 patients. After controlling for patient variables (etiology, rhythm) and other treatment factors, epinephrine administration (compared to no epinephrine) was still associated with a lower probability of successful resuscitation.

A Swedish study related out-of-hospital cardiac arrest results to whether epinephrine was given and whether patients were intubated [39]; 10,966 patients with cardiac arrest receiving CPR were included. Survival was defined as survival 1 month after cardiac arrest. Epinephrine was given in 42.4% and 47.5% were intubated. Treatment with

epinephrine and intubation were associated with a lower survival when all patients were evaluated. Among patients with bystander witnessed cardiac arrest found in VF and requiring more than three defibrillatory shocks, neither treatment with epinephrine nor intubation was associated with higher survival rates. Among patients with a non-shockable rhythm, treatment with epinephrine was a significant independent predictor for lower survival (OR 0.30, CI 0.07–0.82). Neither in the total nor in any subgroup did they find results indicating beneficial effects of either of these two interventions [39].

A meta-analysis of studies comparing standard (1 mg or 0.02 mg/kg) versus high dose (5–15 mg) epinephrine (3199 patients received high dose and 3140 patients received standard dose), failed to demonstrate a significant beneficial effect of high and/or escalating dose of epinephrine for hospital discharge [40]. Although ROSC tended to be higher after the high dose, there was a tendency for greater in-hospital attrition after the higher dose [40]. These trials likely suffer from bias in that patients with longer arrest duration and poorer prognosis are almost certainly more likely to receive epinephrine. However, the accumulated evidence does not suggest (although does not rule out) that epinephrine is likely to be beneficial in out-of-hospital cardiac arrest in patients.

Babbs et al. [41], considering the evidence detailed above, concluded that a high initial intravascular dose of epinephrine in victims of cardiac arrest may increase CPP and ROSC, but may also exacerbate post-resuscitation myocardial dysfunction. They suggested that high doses of epinephrine do not improve long-term survival and neurological outcome, and may cause harm, and that routine use of high doses of epinephrine is not recommended [41].

3. Vasopressin

3.1. Vasopressin in experimental studies

Vasopressin is an endogenous pressor peptide, which has pharmacologic properties that seem well suited to use as an adjunct to resuscitation. Theoretically vasopressin is a desirable vasopressor for use in cardiac arrest and CPR, producing selective vasoconstriction of resistance vessels in non-vital tissues whilst preserving blood flow to vital organs including heart and brain [42].

Endogenous vasopressin levels were found to be higher in survivors of cardiac arrest than in patients who died, suggesting that vasopressin could be beneficial in cardiac arrest [44,45]. The effect of vasopressin on cardiac arrest and CPR in animal models has been extensively investigated [11–15,43]. In a porcine open-chest CPR model, blocking endogenous vasopressin resulted in poor CPP and left ventricular myocardial blood flow. In comparison, pigs with effective endogenous vasopressin and additional exogenous vasopressin had good left ventricular myocardial blood flow and survived the 1 h post-resuscitation phase [11]. In adult pigs with VF or post-countershock PEA, vasopressin improved

left ventricular myocardial blood flow, cerebral blood flow and resuscitability, and neurological recovery better than epinephrine [9–15].

In a meta-analysis [46] of human and animal trials comparing vasopressin with epinephrine or placebo in the management of cardiac arrest, 33 animal experiments (totaling 669 animals) were examined. Intravenous vasopressin dosage was 0.2–0.8 U/kg, epinephrine dosage was 0.03–0.2 mg/kg. In animals with VF, vasopressin appeared superior to both placebo and epinephrine in achieving ROSC ($P < 0.001$). Subgroup analysis showed vasopressin was associated with significantly higher rate of ROSC in comparison to epinephrine (ROSC, $P < 0.001$), but was not significantly superior to epinephrine in the subgroup of non-VF cardiac arrest ($P = 0.16$). In a pediatric porcine model of asphyxial cardiac arrest, epinephrine was superior to vasopressin with respect to left ventricular myocardial blood flow and ROSC [47].

Cardiovascular adverse effects of vasopressin in humans were first reported in 1947 [48]. Other adverse effects reported include transient ischemia, transmural myocardial injury without infarction, acute myocardial infarction and ventricular arrhythmias including VF [49]. In contrast to epinephrine, which induces potent platelet aggregation, especially in high doses [50], vasopressin has no effect on platelet aggregation [50], although there are conflicting studies [51,52]. However, vasopressin and its analogue desmopressin induce coagulatory activity in healthy individuals, in patients with haemophilia [51], renal and hepatic disease [54], and after cardiac surgery [53]. Whether vasopressin promotes clinically relevant procoagulant effects during cardiac arrest is currently unknown and must be examined in future studies, especially since thrombolysis in cardiac arrest appears to increase the rate of ROSC [52]. Persistent vasoconstriction resulting in an increased systemic resistance in the post-resuscitation period could be detrimental. In a pig model of prolonged VF, vasopressin use during CPR resulted in worse post-resuscitation left ventricular function compared to epinephrine, although it did not compromise 24 h outcome [55]. The morbidity associated with vasopressin has led to the investigation of synthetic analogues, such as terlipressin [56]. Vasopressin has a longer half-life than epinephrine (10–20 min versus 4 min) and remains effective during acidosis.

3.2. Clinical studies with vasopressin

ACLS guidelines recommend vasopressin as a "class IIb intervention" (acceptable, not harmful, supported by fair evidence), in the treatment of VF or pulseless VT refractory to defibrillation [4,5]. The initial recommended dose is 40 IU intravenously.

A small out-of-hospital trial [56] of 40 patients showed that vasopressin was superior to epinephrine, but a larger in-hospital trial of 104 patients failed to show any significant difference in clinical outcomes between vasopressin and epinephrine [57,46].

In a more recent multicenter trial, 1186 adult patients, with out-of-hospital cardiac arrest due to VF, PEA, or asystole requiring CPR and vasopressor therapy were randomly assigned to receive either intravenous vasopressin ($n = 589$) or epinephrine ($n = 597$) [7]. Open label epinephrine was used, after study drug, if deemed necessary. The effects of vasopressin were similar to those of epinephrine in the management of VF and PEA, but vasopressin was superior to epinephrine in asystole (29.0% hospital admission with vasopressin, versus 20.3% with with epinephrine, $P = 0.02$ and 4.7% hospital discharge with vasopressin, versus 1.5% with epinephrine, $P = 0.04$). Thus, vasopressin may be a better option than epinephrine for patients with asystole, who normally have the worst chance of survival of all patients with cardiac arrest.

Aung and Htay [58] performed a meta-analysis of vasopressin trials in cardiac arrest. They concluded that 'there is no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest'. Unfortunately, such an analysis does not answer the question whether either drug is superior to placebo, or if there are subgroups (for example, asystole) for which vasopressin may be superior.

3.3. Epinephrine combined with vasopressin

In experimental models of VF, epinephrine combined with vasopressin resulted in a more rapid rise in CPP [59], higher levels of left ventricular myocardial blood flow during CPR [60], and higher resuscitation rates, compared to epinephrine or vasopressin alone [60,61]. However, cerebral blood flow was decreased significantly by the combination compared to vasopressin alone in adult pigs [62]. In piglets, both vasopressin alone and the combination of epinephrine with vasopressin, but not epinephrine alone, improved cerebral blood flow during CPR [63].

In a clinical retrospective out-of-hospital cardiac arrest study, 231 patients received epinephrine only and 37 patients received a combination of epinephrine with vasopressin [8]. When asystole was the initial rhythm, ROSC was more common for the combination group (6/15, 40%) than for subjects in the epinephrine-only group (17/127, 13%), whereas ROSC did not differ between groups when VF or PEA was the initial rhythm [8]. In a secondary analysis of the study by Wenzel et al. [7], a minority of the patients received two doses of initial study drug (vasopressin or epinephrine) and open label (additional) epinephrine. ROSC was more common for the group randomized to vasopressin and receiving subsequent epinephrine (137/373, 36.7%) than for subjects in the epinephrine-only group (randomized to epinephrine and receiving further epinephrine) (93/359, 25.9%; $P = 0.002$); the rates of survival to hospital discharge were significantly higher among patients who were treated with vasopressin and epinephrine, than among those who were treated only with epinephrine (23/369, 6.2% versus 6/355, 1.7%; $P = 0.002$).

Vasopressin has greater activity than epinephrine under the hypoxic and acidic conditions of a prolonged cardiac arrest

[15] and the V_2 receptor mediated vasodilatory effect of vasopressin may improve the end-organ hypoperfusion that results from multiple doses of epinephrine. The combination of the two agents may limit the dose of either agent and reduce the risk of unwanted end-organ hypoperfusion and dysrhythmia [8]. Vasopressin decreases endogenous catecholamine plasma concentrations, possibly contributing to the apparent usefulness of the combination of epinephrine and vasopressin during asystole [64].

Applying the above findings, Krismer et al. [65] suggest a pressor regimen of 1 mg of epinephrine first, followed by 40 IU of vasopressin alternating with 1 mg of epinephrine every 3 min, regardless of the initial electrocardiographic rhythm.

4. Summary

The vast literature accumulated on vasopressors in cardiac arrest is difficult to interpret. This is in part because of the large variety of animal models of cardiac arrest, the differences between the pathophysiological mechanisms of cardiac arrest in animal experiments and in humans, and the complexity of the "trajectories" of cardiac arrest in humans (involving multiple transitions between VF, asystole, and PEA), a situation unlike that in the typical animal studies [6]. As there are multiple mechanisms for cardiac arrest, expecting one drug to be suitable for all cardiac arrests may not be appropriate.

One other important reason for the potential lack of applicability of many animal experimental studies to the clinical setting of out-of-hospital cardiac arrest is that CPR, in humans, is often not performed or poorly performed. Recent clinical studies have highlighted the inconsistent, and generally poor performance of CPR in out-of-hospital cardiac arrest, even when performed by expert personnel [66]. Drugs such as epinephrine and vasopressin, for which benefits, in experimental models, are largely due to improved coronary blood flow during CPR, may apply imperfectly to the typical clinical setting of basic and advanced cardiac life support.

Perhaps because of these factors, decades of research using epinephrine have been unable to demonstrate a clinical benefit, and have indeed suggested harm, at least at higher doses. To the extent that epinephrine is beneficial, it appears to be largely due to its α_2-agonist actions, with the β_1-actions likely to be harmful.

Vasopressin, for its part, although theoretically and experimentally attractive as a vasopressor, has not been validated as an effective vasopressor in clinical trials.

Given the poor correlation between animal experimental and human clinical trials with vasopressors, it is imperative that large scale randomized controlled clinical trials of vasopressors be undertaken. Alternative vasopressors or combinations of drugs are clearly needed. New vasopressor agents or combinations are likely to show optimal efficacy if, and only if, CPR is optimized by minimizing "no compression time" [66] and by preventing excessive ventilations [67], which

diminish effective coronary and brain blood flow during CPR. A clinical trial of effective α_2-agonists, or "broad spectrum" adrenergic agonists combined with beta blockers and alpha agonists, or a combination of relatively low dose epinephrine and vasopressin (such a trial is currently underway) seem to be a good beginning for controlled trials of vasopressors in human out-of-hospital cardiac arrest. Collaborative group efforts, such as made possible by the Resuscitation Outcomes Consortium [68] seem the ideal research environment for such trials to be conducted. Despite decades of disappointment, it is premature to dispense with vasopressors in cardiac arrest.

Acknowledgements

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Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial

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Summary

Background Survival rates for cardiac arrest patients, both in and out of hospital, are poor. Results of a previous study suggest better outcomes for patients treated with vasopressin than for those given epinephrine, in the out-of-hospital setting. Our aim was to compare the effectiveness and safety of these drugs for the treatment of in-patient cardiac arrest.

Methods We did a triple-blind randomised trial, in the emergency departments, critical care units, and wards of three Canadian teaching hospitals. We assigned adults who had cardiac arrest and required drug therapy to receive one dose of vasopressin 40 U or epinephrine 1 mg intravenously, as the initial vasopressor. Patients who failed to respond to the study intervention were given epinephrine as a rescue medication. The primary outcomes were survival to hospital discharge, survival to 1 h, and neurological function. Preplanned subgroup assessments included patients with myocardial ischaemia or infarction, initial cardiac rhythm, and age.

Findings We assigned 104 patients to vasopressin and 96 to epinephrine. For patients receiving vasopressin or epinephrine survival did not differ for hospital discharge (12 [12%] vs 13 [14%], respectively; p=0·67; 95% CI for absolute increase in survival −11·8% to 7·8%) or for 1 h survival (40 [39%] vs 34 [35%]; p=0·66; −10·9% to 17·0%); survivors had closely similar median mini-mental state examination scores (36 [range 19–38] vs 35 [20–40]; p=0·75) and median cerebral performance category scores (1 vs 1).

Interpretation We failed to detect any survival advantage for vasopressin over epinephrine. We cannot recommend the routine use of vasopressin for inhospital cardiac arrest patients, and disagree with American Heart Association guidelines, which recommend vasopressin as alternative therapy for cardiac arrest.

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Introduction

There are an estimated 300 000 cardiac arrests yearly in patients in hospital throughout Canada and USA.[1] We have previously recorded[2] that the survival rate of hospital patients who required epinephrine was only 6%. Results of clinical trials have failed to show improved survival with high doses of epinephrine and other adrenergic agents (phenylephrine and methoxamine). Because of the high drug concentrations required and the potential side-effects of adrenergic agents, non-adrenergic vasoactive drugs are sought to maintain vascular tone and blood flow during cardiac arrest.

Several laboratory and clinical studies have documented high concentrations of endogenous vasopressin during cardiac arrest.[3,4] Additionally, Lindner and colleagues[5] showed that arginine vasopressin increased arterial and coronary pressures as well as myocardial and cerebral blood flows compared with standard doses of epinephrine in experimental models of cardiac arrest. In two small case series,[6,7] patients failed standard epinephrine therapy but survived after receiving vasopressin. In one randomised controlled clinical trial,[8] the investigators compared the effect of 40 U vasopressin with 1 mg epinephrine in 40 prehospital patients who had not responded to three countershocks. Compared with epinephrine, the group that received vasopressin had a 50% increase in the number of admitted patients and a 66% increase in patients alive at 24 h.

The American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guidelines[9] recommend vasopressin as an alternative to epinephrine for treatment of cardiac arrest. This recommendation could lead to use of vasopressin for millions of cardiac arrests worldwide. We did a randomised controlled clinical trial of vasopressin or epinephrine as the initial vasopressor, to compare survival outcomes and safety for patients who had cardiac arrest in hospital.

Methods

Patients

We did our study in the emergency departments, critical care units, and general wards of two tertiary-care hospitals affiliated with the University of Ottawa, Ottawa, Canada, and with one tertiary hospital affiliated with the University of Western Ontario in London. Patients were eligible if they were admitted to hospital, had a cardiac arrest, and required epinephrine according to AHA ACLS protocols for asystole, pulseless electrical activity, or refractory ventricular fibrillation. We excluded patients who: were younger than 16 years; had a documented terminal illness (life expectancy <6 weeks) or do not resuscitate status; were admitted to hospital less than 24 h after traumatic injury; had a cardiac arrest secondary to obvious exsanguination such as ruptured aortic aneurysm and massive gastrointestinal bleeding; had a cardiac arrest before arrival at hospital; had been previously entered into the study; or had a cardiac arrest in the operating, recovery, or delivery rooms. Informed consent was not obtained because the experimental treatment had to be given urgently. The research ethics committees of the participating hospitals approved the study.

Study protocol

We did a triple-blind, randomised controlled trial in which patients who had a cardiac arrest received one dose of vasopressin or epinephrine, which was given at the outset of resuscitation. All patients who failed to respond to initial drug administration received, as rescue therapy, standard doses of epinephrine every 3–5 min. Study drugs were randomly distributed to all cardiac arrest carts in all designated study areas. The distribution of study drugs on the cardiac arrest carts was done by consecutive allocation from a computer-generated random listing stratified by centre and prepared by the data coordinating centre. A patient was judged as randomly assigned after the study package was opened. Once opened, the entire cardiac arrest box was returned to the hospital pharmacy and another study box was released in the appropriate sequence according to the randomisation schedule. Allocation of patients was therefore based on the random occurrence of cardiac arrests in specific locations and on the random allocation of study drugs. We successfully used this process in previous clinical trials.[2,10]

We treated all patients according to the ACLS protocols recommended by the AHA,[1] and the study was supervised by senior medical residents on the wards and critical-care units and staff physicians in the emergency departments. We gave patients one intravenous dose of vasopressin (40 U) or epinephrine (1 mg) at the point in standard ACLS protocols at which epinephrine was first indicated. If there was no return of pulse after this initial dose, patients in both groups received intravenous epinephrine 1 mg every 3–5 min. We did not give drugs via the endotracheal tube. All drugs were prepared by the pharmacy of the Ottawa Hospital in identical preloaded 10 mL syringes. Concentrations of vasopressin and epinephrine, measured by high performance liquid chromatography, were at least 98% of original values during 2 months of storage at room temperature. Study syringes were packaged in special cardiac-arrest trays and boxes at multiple sites throughout the study hospitals.

Before the start of the trial, we instructed all nursing, respiratory therapy, and medical staff about the rationale for the study and the protocol, by a series of rounds and teaching sessions. All new staff were instructed on study procedures. Once enrolment was underway, the research nurses at the study institutions attended the arrests or contacted the physician in charge to assess compliance with protocols.

Our primary outcome was the continuous presence of a measurable pulse and blood pressure for at least 1 h from the time resuscitation was discontinued, irrespective of the need for vasopressor or antiarrhythmic treatments. Patients who arrested again were not randomised a second time. Ascertainment of survival at 1 h was done from the cardiac-arrest record by the research nurses, hospital investigators, and the study co-ordinator who were unaware of treatment allocation. Secondary outcomes included survival to hospital discharge, defined as leaving the acute-care institution alive, and neurological function measured with the modified mini-mental state examination (MMSE)[11] and a five-point scale of cerebral performance[12] assessed at hospital discharge. We also ascertained the return of spontaneous circulation, defined as the documented presence of a measurable pulse and blood pressure at any time after administration of the study drug, and the frequency of adverse events including tachyarrhythmias, uncontrolled hypertension, and mesenteric infarction.

Statistical analysis

Because the results of the only other randomised trial of vasopressin, which enrolled only 40 patients, were for

Characteristic	Vasopressin (n=104)	Epinephrine (n=96)
Age (mean [SD]) (years)	70 (12)	70 (14)
Sex		
Male	65 (63%)	61 (64%)
Female	39 (37%)	35 (36%)
Hospital		
Ottawa Civic	61 (59%)	50 (52%)
Ottawa General	32 (31%)	34 (35%)
Victoria	11 (11%)	12 (13%)
Location of cardiac arrest		
Emergency department	17 (16%)	21 (22%)
ICU/CCU	17 (16%)	26 (27%)
Ward	69 (66%)	46 (48%)
Other	1 (1%)	3 (3%)
Witnessed cardiac arrest	81 (78%)	81 (84%)
Initial rhythm		
Ventricular fibrillation	21 (20%)	15 (16%)
Ventricular tachycardia	3 (3%)	3 (3%)
Pulseless electrical activity	43 (41%)	52 (54%)
Asystole	35 (34%)	26 (27%)
Other	2 (2%)	0
Suspected cause of cardiac arrest		
Myocardial ischaemia or infarction	32 (31%)	33 (34%)
Respiratory	10 (10%)	11 (11%)
Pulmonary embolism	5 (5%)	3 (3%)
Sepsis	4 (4%)	5 (5%)
Lethal arrhythmia	3 (3%)	2 (2%)
Metabolic	2 (2%)	4 (4%)
Congestive heart failure	1 (1%)	3 (3%)
Unknown	28 (27%)	26 (27%)
Other	19 (18%)	9 (9%)
Current diagnoses*		
Ischaemic heart disease	34 (33%)	33 (34%)
Circulatory disease	35 (34%)	44 (46%)
Postoperative event	36 (35%)	21 (22%)
Respiratory disease	13 (13%)	13 (14%)
Digestive disease	14 (13%)	7 (7%)
Genitourinary disease	5 (5%)	10 (10%)
Neoplasm	15 (14%)	12 (13%)
Past medical diagnoses*		
Neoplasm	21 (20%)	18 (19%)
Diabetes mellitus	25 (24%)	24 (25%)
Hypertension	26 (25%)	32 (33%)
Ischaemic heart disease	52 (50%)	46 (48%)
Circulatory disease	48 (46%)	52 (54%)
Respiratory disease	27 (26%)	29 (30%)
Necropsy	29 (28%)	34 (35%)

*Patients might have had more than one diagnosis. ICU=intensive care unit, CCU=critical care unit.

Table 1: **Baseline characteristics**

patients not admitted to hospital, our study was designed as a preliminary assessment of vasopressin for survival after inhospital cardiac arrest. As such, our study was not designed to have adequate power to detect clinically meaningful absolute differences in survival in the range 1–5%. Based on the inhospital results of a trial of high-dose epinephrine[2] and the Ontario trial of active compression-decompression,[10] we estimated baseline survival at 1 h to be 30%. Assuming a two-sided alpha of 0·05 and a power of 80%, a total sample size of 200 patients would allow us to detect a 20% absolute difference in survival to 1 h. Our protocol had a carefully laid out description of what results would constitute an important trend favouring vasopressin and would therefore justify larger and more expensive clinical trials.

An adjudication committee, unaware of treatment allocation, assessed patients who were randomised but who did not meet the inclusion criteria (eg, respiratory arrest only or ventricular fibrillation not requiring epinephrine), or had clear exclusion criteria. Patients judged ineligible were not included in the final analysis. Eligible patients not randomised and ineligible patients excluded post hoc were compared with those included in the analysis. All survival

Characteristic	Vasopressin (n=104)	Epinephrine (n=96)
Time to treatment (mean [SD]) (min)		
Collapse to CPR	1·9 (2·8)	1·4 (1·3)
CPR to ACLS	1·3 (2·3)	1·1 (2·0)
Duration of CPR	23·4 (18·9)	21·4 (19·2)
Duration of ACLS	22·1 (19·0)	20·3 (19·3)
ACLS to study group	3·5 (4·6)	3·0 (4·2)
Drug administration		
Additional epinephrine	90 (87%)	79 (81%)
Atropine	87 (84%)	81 (85%)
Sodium bicarbonate	39 (38%)	33 (34%)
Calcium	26 (25%)	24 (25%)
Lidocaine	23 (22%)	27 (28%)
Bretylium	8 (8%)	4 (4%)
Procainamide	1 (1%)	1 (1%)

CPR=cardiopulmonary resuscitation, ACLS=advanced cardiac life support.

Table 2: **Treatment characteristics**

rates including survival at 1 h, survival to hospital discharge, and the return of spontaneous circulation and rates of adverse outcomes were compared by an unadjusted χ^2 test. Furthermore, 95% CI around the absolute increase in survival were calculated.[13] The cerebral performance categories and the modified MMSE were compared with the Wilcoxon rank-sum statistic.

Before the study, we decided to compare survival outcomes in clinically important subgroups, including initial rhythm at time of advanced life-support, age older and younger than 70 years, and cause of cardiac arrest, including myocardial ischaemia or infarction, respiratory, &c. Two investigators (IGS, PCH) unaware of treatment allocation, assessed all clinical records including electrocardiogram and necropsy reports to ascertain whether the initiating cause of arrest could be attributed to myocardial ischaemia or infarction. Fisher's exact test was used for all comparisons of subgroup survival rates. Absolute p values and 95% CI are reported as appropriate. We made no corrections for multiple comparisons.

Results

From July 3, 1997, to Nov 30, 1998, we enrolled and successfully followed up 200 patients (figure). During the trial, a further 50 eligible patients were not entered into the study by attending clinicians because of the urgency and stress of treating an immediately life-threatening condition. Clinical and demographic characteristics of these individuals were closely similar to those of the enrolled patients. Furthermore, 74 ineligible patients received the study drug and were excluded afterwards for the following predefined exclusion criteria: prehospital cardiac arrest (n=50), exsanguination (eight), incorrect use of study drug (six),
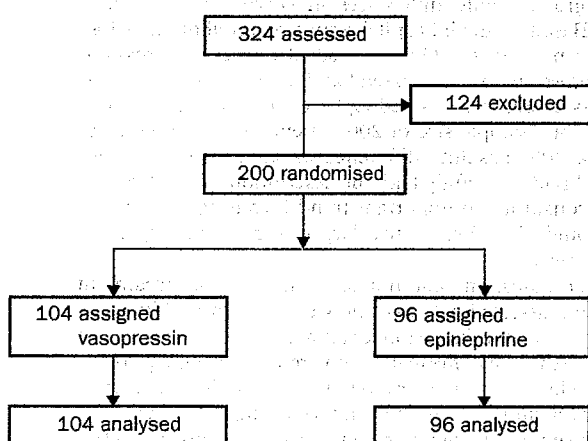
Outcome measure	Vasopressin (n=104)	Epinephrine (n=96)	p	Percentage absolute difference (95% CI)
Primary survival measures				
1 h	40 (39%)	34 (35%)	0·66	3·1 (−10·5 to 17·3)
Hospital discharge	12 (12%)	13 (14%)	0·67	−2·0 (−11·6 to 7·8)
Other survival measures				
Any return of pulse	62 (60%)	57 (59%)	0·97	0·2 (−14·0 to 14·5)
Pulse >20 min	45 (43%)	38 (40%)	0·60	3·7 (−10·6 to 17·9)
24 h	27 (26%)	23 (24%)	0·74	2·0 (−10·6 to 14·6)
30 days	13 (13%)	13 (14%)	0·83	−1·0 (−11·0 to 8·9)
Adverse outcomes				
Tachyarrhythmias	10 (10%)	8 (8%)	0·75	1·3 (−7·2 to 9·8)
Uncontrolled hypertension	0	0	..	..
Mesenteric infarction	0	0	..	..

Table 3: **Survival and adverse outcomes**

terminal illness (four), acute trauma (four), and subsequent cardiac arrest in patient previously randomised (two).

Table 1 shows demographic and clinical characteristics of study patients, and table 2 shows treatment characteristics. Overall, enrolled patients had a mean age of 70 years, had a witnessed cardiac arrest in 81% of cases, were uncommonly in ventricular fibrillation (18%), and had lethal arrhythmia or myocardial ischaemia as the cause of arrest in 35% of cases. On average, estimated times from collapse to treatment were rapid: 1·6 min to cardio-pulmonary resuscitation, 2·8 min to ACLS measures, and 6·1 min to administration of study drug. The demographic, clinical, and cardiac arrest treatment characteristics were closely similar for the 104 patients on vasopressin and the 96 on epinephrine, although more individuals were given vasopressin on the wards than elsewhere.

In the vasopressin and epinephrine groups, outcomes did not differ for survival to hospital discharge or for 1 h survival (table 3). Similarly, there were no differences between study groups for any of the secondary survival outcomes, including any return of pulse, or survival for 24 h or for 30 days, or in adverse outcomes. The neurological state and quality of life of survivors was good in both groups. Scores for MMSE were high in both groups, and over 80% of patients in the two groups were in the best cerebral performance category at discharge (table 4).

We assessed 1 h and hospital discharge survival outcomes for several predefined subgroups, and identified no benefit of vasopressin, irrespective of initiating cause, initial rhythm, or age (table 5). In particular, when comparing vasopressin with epinephrine for the myocardial ischaemia and infarct cases, survival did not differ for discharge (p=0·96; 95% CI for absolute increase in survival −18·9% to 19·9%) or for 1 h (p=0·48; −16·3% to 32·8%) survival. Finally, we detected no difference between groups for adverse outcomes including tachyarrythmias, uncontrolled hypertension, and mesenteric infarction.

Discussion

We failed to show any improvement with vasopressin compared with epinephrine for either short-term or long-term survival. Furthermore, in several clinically important

324 assessed → 124 excluded → 200 randomised → 104 assigned vasopressin → 104 analysed; 96 assigned epinephrine → 96 analysed

Figure 1: **Trial profile**

Outcome measure	Vasopressin (n=12)	Epinephrine (n=13)
Mini-mental state examination score* (median [range])	36 (19–38)	35 (20–40)
Cerebral performance category score		
1	10 (83%)	11 (85%)
2	0	2 (15%)
3	2 (17%)	0
4	0	0

*Maximum score=40.

Table 4: **Neurological outcomes and quality of life of patients who survived to hospital discharge**

Subgroup	Number of patients	Percentage survival to 1 h		Percentage survival to discharge	
		Vasopressin	Epinephrine	Vasopressin	Epinephrine
Cause of cardiac arrest					
Myocardial ischaemia or infarction	65	28	36	16	15
Respiratory depression	21	60	73	10	18
Sepsis	9	75	40	25	0
Pulmonary embolism	8	40	33	0	33
Metabolic	6	50	25	0	25
Lethal arrhythmias	5	33	100	33	100
Congestive heart failure	4	0	0	0	0
Unknown	54	39	12	7	4
Other	28	37	56	11	11
Initial rhythms					
Pulseless electrical activity	95	33	29	9	10
Asystole	61	37	31	6	8
Ventricular fibrillation or tachycardia	42	54	61	25	33
Age (years)					
≤70	81	44	40	10	23
>70	119	35	32	13	7

Table 5: **Survival in clinically important subgroups**

subgroups, vasopressin was not associated with improved outcomes. We recognise that, because of our small sample size and the wide confidence intervals around the treatment effect estimates, our results do not exclude the possibility of a clinically important benefit for vasopressin. Nevertheless, we detected no trends favouring vasopressin and suspect that the magnitude of any potential benefit would be small if present at all.

Previous reports provided much evidence to support the hypothesis that vasopressin could improve outcomes in cardiac arrest. Endogenous arginine vasopressin is thought of as a stress hormone in that it is released in response to various stimuli including pain, syncope, surgery, and shock.[14] Arginine vasopressin causes peripheral vasoconstriction and maintains perfusion pressures during acute haemorrhage in animals.[15] Concentrations of arginine vasopressin are raised in people who have myocardial infarction and cardiogenic shock,[16,17] and in people with haemorrhagic and septic shock.[18,19] Paradis and colleagues[3] showed, in a canine model of cardiac arrest, that arginine vasopressin concentrations increased greatly during resuscitation. In a study of 34 cardiac arrest patients, Lindner and colleagues[4] measured high concentrations of vasopressin and noticed that concentrations were much higher in patients who were successfully resuscitated than in those who were not. More recently, the same research group showed that plasma concentrations of endothelin, catecholamines, arginine vasopressin, and adreno-corticotropin rose quickly in patients with cardiac arrest.[20] Concentrations of the last two hormones were much lower in patients who were not successfully resuscitated. The researchers speculated that arginine vasopressin and adrenocorticotropin were essential for achieving adequate cerebral and coronary perfusion pressures in those patients who were resuscitated.

The effects of exogenously administered vasopressin in animals in cardiac arrest have been described. In pigs, Lindner and co-workers[5] noted that administration of vasopressin during resuscitation increased myocardial blood flow. Compared with epinephrine, in pigs, vasopressin led to higher arterial pressures and greater coronary perfusion pressures, and had more longlasting effects than epinephrine.[21-23] Coronary perfusion pressure correlates with return of spontaneous circulation in human cardiac arrest.[24] Vasopressin administration increases cerebral blood

flow and oxygenation and raises blood flow to other vital organs.[25-27] Results of one study suggest improved survival in animals treated with vasopressin.[28] The mechanisms by which vasopressin might improve blood flow in vital organs during cardiac arrest remain unknown. The drug might increase peripheral vasoconstriction directly via the V1 receptor or by potentiating the effects of endogenous cate-cholamines.[5,29-31] Paradis and colleagues[3] have speculated that ideal vasomotor therapy might involve a combination of adrenergic and non-adrenergic (ie, vasopressin) vasomotor agents. However, the combined effects of epinephrine and vasopressin are not clear.[32-34]

Previous human experience with exogenously administered vasopressin is limited. Morris and colleagues[6] compared the haemodynamic effects of vasopressin and epinephrine in prehospital cardiac arrest patients who had had long resuscitation and who were judged unsalvageable. Although no patient responded to epinephrine, four of ten showed a substantial rise in coronary perfusion pressure with a mean increase of 28 mm Hg. In a case series,[7] eight patients who had cardiac arrest in hospital were given one or more doses of vasopressin 40 U after they had failed to respond to standard ACLS therapy that included countershocks and at least one dose of epinephrine. All eight patients regained spontaneous circulation after vasopressin and three were later discharged from hospital neurologically intact. The investigators suggested that vasopressin might be more effective than epinephrine because of a greater vasoconstrictor effect in the presence of hypoxia and acidosis and because of longer lasting effects. Furthermore, epinephrine, but not vasopressin, might have serious deleterious effects by increasing myocardial oxygen consumption during cardiac arrest.

Before our study, only one randomised trial had assessed the effect of vasopressin in human cardiac arrest, and this was for out-of-hospital patients.[8] Lindner and co-workers compared 40 U vasopressin with 1 mg epinephrine in 40 pre-hospital patients who had not responded to three countershocks. In the vasopressin group many more patients were admitted to hospital than the epinephrine group (70% vs 35%, p<0·05), more patients were alive after 24 h (60% vs 20%, p<0·05), and there was a trend towards more patients alive to hospital discharge (40% vs 15%, p=0·08).[8] No adverse effects were seen in the vasopressin group. However, this pilot study had too few patients to show an improvement in long-term survival.

Our results for inhospital patients differ greatly from those of Lindner and colleagues for out-of-hospital patients, even though the study drug protocols and interventions were identical. Clearly, our response times were much more rapid than in Lindner and co-workers' study and our patients were different in that our case mix included those with greater comorbidity from various chronic diseases. In only a third of our patients could cardiac arrests be clearly attributed to myocardial ischaemia or infarction, and only a fifth presented with ventricular fibrillation or tachycardia. We note discouraging similarities to the situation with high-dose epinephrine in the early 1990s, when large randomised controlled trials failed to confirm the promise of earlier and smaller studies.[2,35,36] Nevertheless, the value of vasopressin might be different for inhospital and out-of-hospital patients.

With a planned sample size of 200 patients, our study was deliberately under-powered to assess the outcome of alive to hospital discharge. We estimated that a study adequately powered to assess a 1% difference in hospital discharge rates would require more than 50 000 patients, and one powered to assess a 5% difference in 1 h survival would require more than 2000 patients. By contrast with Lindner and colleagues' trial, which only included

40 patients, we believed that the expense of a large study assessing a non-patent drug could not be justified and would not be funded by any peer-review agency at this time. Nevertheless, our study enrolled five times more patients than the only other randomised trial of vasopressin.

We believe that our findings, although disappointing, are difficult to refute. We employed a strictly blinded and rigorously controlled design that incorporated a typical inhospital mix of cardiac arrest patients in three large tertiary-care hospitals. We failed to detect even a modest trend favouring vasopressin, even in the pure subgroups of myocardial ischaemia or infarction, or ventricular fibrillation or tachycardia. We strongly disagree with the decision of the AHA to recommend vasopressin as an alternative to epinephrine. Their ACLS guidelines are used worldwide and will affect the care of millions of patients with cardiac arrest both inside and outside of hospital. We believe that vasopressin cannot be recommended unless further larger clinical trials show evidence of improved survival to hospital discharge.

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pronounced in these three patients. The preservation of the Piper-band sound during movement in some parkinsonian patients is not surprising. In healthy subjects the sound is usually louder during movement than in sustained postures of the hand.

Discussion

Piper-style rhythms are lost in untreated Parkinson's disease. They are replaced by a series of pulses with a frequency of around 10 Hz. This is a familiar finding in EMG records,[12] but, owing to the partial fusion of muscle activity at this frequency, such parkinsonian action tremor is not readily visible, and is usually clinically detectable only on auscultation. The sound heard is rather like that picked up over the thigh muscles in primary orthostatic tremor,[13] in which the sound may be diagnostic. In Parkinson's disease, however, the pulsatile action tremor does not appear nor, more significantly, does the Piper-band sound of normal muscle discharge cease, until the diagnosis is clinically apparent.

Auscultation has shown that muscle discharge in the Piper band is diminished in Parkinson's disease, but may return after dopaminergic treatment, suggesting that this mode of muscle activation is partly dependent on activity within pallidal projections to the motor areas of the cortex. Without treatment, patients with Parkinson's disease are left with a 10 Hz pulsatile mode of muscle discharge which is not, by itself, pathological, but is suboptimal when fast or powerful contractions are necessary. Muscle driven at 10 Hz is only partially fused and is also subject to the ramp effect, in which muscle tension increases slowly over several seconds.[14] The result is bradykinesia, and low ultimate strength.[3]

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Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation

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Summary

Background Studies in animals have suggested that intravenous vasopressin is associated with better vital-organ perfusion and resuscitation rates than is epinephrine in the treatment of cardiac arrest. We did a randomised comparison of vasopressin with epinephrine in patients with ventricular fibrillation in out-of-hospital cardiac arrest.

Methods 40 patients in ventricular fibrillation resistant to electrical defibrillation were prospectively and randomly assigned epinephrine (1 mg intravenously; n=20) or vasopressin (40 U intravenously; n=20) as primary drug therapy for cardiac arrest. The endpoints of this double-blind study were successful resuscitation (hospital admission), survival for 24 h, survival to hospital discharge, and neurological outcome (Glasgow coma scale). Analyses were by intention to treat.

Findings Seven (35%) patients in the epinephrine group and 14 (70%) in the vasopressin group survived to hospital admission (p=0·06). At 24 h, four (20%) epinephrine-treated patients and 12 (60%) vasopressin-treated patients were alive (p=0·02). Three (15%) patients in the epinephrine group and eight (40%) in the vasopressin group survived to hospital discharge (p=0·16). Neurological outcomes were similar (mean Glasgow coma score at hospital discharge 10·7 [SE 3·8] *vs* 11·7 [1·6], p=0·78).

Interpretation In this preliminary study, a significantly larger proportion of patients treated with vasopressin than of those treated with epinephrine were resuscitated successfully from out-of-hospital ventricular fibrillation and survived for 24 h. Based upon these findings, larger multicentre studies of vasopressin in the treatment of cardiac arrest are needed.

Introduction

Intravenous epinephrine is currently the recommended drug of choice for the treatment of ventricular fibrillation when direct-current shock therapy is ineffective.[1,2] Because of the poor clinical outcome in patients in cardiac arrest who require epinephrine treatment, other pharmacological therapies have been examined. Interest in the possible

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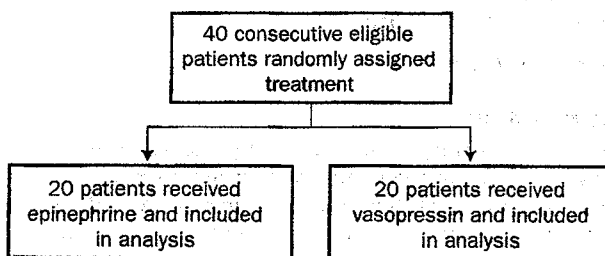
value of vasopressin treatment during cardiopulmonary resuscitation arose after the observation that there is a large release of vasopressin immediately after a cardiac arrest.[3] We have previously reported that the higher the endogenous vasopressin concentration, the greater the chances of restoration of spontaneous circulation.[4] In cardiac arrest of long duration associated with severe hypoxia and acidosis, vasopressin seems to be more effective than epinephrine in restoration of spontaneous cardiovascular function.[5] These findings are consistent with data from studies in animals, demonstrating greater efficacy of vasopressin than of optimum doses of epinephrine in restoration of vital-organ blood flow.[6,7] In a randomised, double-blind study, we have directly compared vasopressin (40 U) with epinephrine (1 mg) as the initial intravenous drug therapy for treatment of out-of-hospital ventricular fibrillation.

Methods

The study was approved by the Institutional Review Board of Ulm University. Waiver of informed consent was accepted under the requirements of German law. Patients were prospectively enrolled in the study if they were treated for out-of-hospital cardiac arrest by the Emergency Rescue Team of Ulm University and if they required epinephrine, according to standard treatment protocols, for advanced cardiac life support according to the guidelines of the European Resuscitation Council and the American Heart Association.[1,2]

Patients enrolled in this study lived in the greater metropolitan area of Ulm (population 100 000). The study began in July, 1994, and ended in December, 1995. The first response team in Ulm consists of a mobile intensive-care unit, staffed 24 h by paramedics and a physician specialising in emergency care.

Cardiac arrest was defined as the absence of both spontaneous respiration and palpable carotid pulse. Patients with cardiopulmonary arrest were included in the study if the initial electrocardiogram showed ventricular fibrillation, and the patient remained in ventricular fibrillation despite repeated direct-current shocks. Exclusion criteria were age under 18 years, cardiac arrest associated with trauma or terminal illness, pregnancy, and the endotracheal administration of epinephrine. After unsuccessful direct-current shocks and persistence of ventricular fibrillation, the patients were randomly assigned either epinephrine (1 mg intravenously) or arginine vasopressin (40 U intravenously) by means of numbered and coded syringes that had previously been placed in computer-generated random order. So that the rescue team was not aware of the study drug, we provided precoded, prefilled 10 mL syringes that were identical in appearance. The study drug was administered into a peripheral venous vein or into the external jugular vein, followed by flushing with Ringer's lactate solution. Further direct-current shocks were adminstered 60–90 s after drug administration. If the study drug failed to restore spontaneous circulation, resuscitation was continued according to the standard guidelines.[1,2] Patients remaining in cardiac arrest after receiving the study drug followed by direct-current countershocks then continued to receive conventional

40 consecutive eligible patients randomly assigned treatment

20 patients received epinephrine and included in analysis

20 patients received vasopressin and included in analysis

Trial profile

Characteristic	Epinephrine group (n=20)	Vasopressin group (n=20)
M/F	15/5	14/6
Mean (SE) age in years	66 (4)	64 (3)
Number of patients with		
Witnessed arrests	12 (60%)	13 (65%)
CPR instituted by bystander	5 (25%)	4 (20%)
Mean (SE) treatment times		
EMS response time (min)	6·1 (0·7)	6·5 (0·7)
From start of CPR to study drug (min)	7·8 (0·8)	8·6 (1·0)
From start of CPR to ROSC (min)	14·5 (1·5)	12·2 (1·5)

CPR=cardiopulmonary resuscitation; ROSC=restoration of spontaneous circulation.

Table 1: Characteristics of study patients

advanced cardiac life support (including epinephrine). All patients were included in the outcome analyses.

Outcome measures and time intervals were recorded according to the guidelines for uniform reporting of data from out-of-hospital cardiac arrest recommended by the Utstein conference report.[8] A study protocol check, by means of an onset tape recording of all resuscitation-related events, was made by a supplementary member of the rescue team. The call-response interval is the time from receipt of the call for help by the dispatcher to the moment when the emergency vehicle stops at the site of the accident. In witnessed cardiac arrests, the time from collapse to start of cardiopulmonary resuscitation was recorded. Restoration of spontaneous circulation was defined as the return of a spontaneous palpable carotid pulse (ie, a systolic blood pressure of about 60 mm Hg for an undefined period at any time after administration of the study drug). Successful resuscitation was defined as a return of spontaneous circulation, and on admission to hospital spontaneous circulation and measurable blood pressure with or without vasoactive drugs. Additional endpoints were survival at 24 h, discharge from the hospital, and neurological outcome (Glasgow coma score at hospital discharge).[9]

Fisher's exact test was used for categorical data and Student's t test for continuous data. The primary endpoint of the study was successful resuscitation, defined as survival to intensive-care unit admission without the need for closed-chest cardiopulmonary resuscitation after return of spontaneous circulation. Before the study we calculated the sample size required based on the assumption that the study should be able to detect with 80% probability, at a one-sided significance of 0·05, an increase in successful resuscitation rate from 30% with standard epinephrine treatment to 45%; the calculation indicated that 19 patients in each group would be required.

Results

40 consecutive patients (29 men, 11 women) with a mean age of 65 (SE 4) years and out-of-hospital ventricular-fibrillation cardiac arrest resistant to direct-current shocks were enrolled into the investigation during an 18-month period (figure). Table 1 shows the demographic characteristics of the patients and response times of the emergency medical services system. Eight patients in the epinephrine group and seven in the vasopressin group had a history of myocardial infarction. Seven other patients in each group had angina pectoris; in the remaining cases the

Endpoint	Epinephrine group (n=20)	Vasopressin group (n=20)	p
Return of spontaneous circulation	11 (55%)	16 (80%)	0·18
Successful resuscitation (to hospital admission)	7 (35%)	14 (70%)	0·06
Survival ≥24 h	4 (20%)	12 (60%)	0·02
Survival to hospital discharge	3 (15%)	8 (40%)	0·16
Mean (SE) Glasgow coma score at hospital discharge	10·7 (3·8)	11·7 (1·6)	0·78

Table 2: Outcome by treatment group

medical history remained unclear. 63% of the arrests were witnessed, but cardiopulmonary resuscitation was initiated by a bystander at the site of the incident in only 23% of cases. There were no significant differences in demographic characteristics or times to treatment between the groups (table 1).

Return of spontaneous circulation, for any length of time, was achieved in 11 patients in the epinephrine group and in 16 patients in the vasopressin group but the difference was not significant (table 2). However, more patients in the vasopressin group than in the epinephrine group were successfully resuscitated (to hospital admission) and a significantly greater proportion survived for at least 24 h (table 2). The proportions surviving to hospital discharge did not differ significantly. No differences in neurological outcome were apparent.

After administration of the study drug alone (without further advanced cardiac life support), there was a return of spontaneous circulation and successful resuscitation in two (10%) epinephrine-treated and seven (35%) vasopressin-treated patients (p<0·001). Immediately after resuscitation and during the further clinical treatment, we observed no side-effects (such as sustained splanchnic hypoperfusion) that could be attributed to vasopressin administration. No patient required pacing for bradycardia before reaching the hospital.

Discussion

Consistent with previous studies in animals and in patients with refractory cardiac arrest, in this study, among patients with out-of-hospital ventricular fibrillation resistant to direct-current shocks, a significantly higher proportion of those treated with vasopressin than those given epinephrine as the initial vasopressor during cardiopulmonary resuscitation and advanced cardiac life support survived for 24 h.

The results of this preliminary study are encouraging, especially because there is no proof that use of intravenous epinephrine is effective in the treatment of patients in ventricular fibrillation resistant to direct-current countershock. Standard epinephrine treatment in human beings in cardiac arrest is based on data from studies in animals and from case reports.[1,2] Large multicentre clinical trials with various doses of epinephrine have shown no significant advantage of high-dose epinephrine.[10,11] Studies of patients in cardiac arrest suggest that epinephrine may have no benefit over placebo.[12] These findings, though controversial, may be due to the well-known physiological observations that epinephrine increases myocardial oxygen consumption, cardiac ischaemia, coronary vasoconstriction, and lactate production in the fibrillating myocardium.[13,14]

The dose of vasopressin used in this study (40 U) was chosen, partly, because of results from patients with refractory cardiac arrest in whom vasopressin was given when all other resuscitation efforts had failed.[5] In that series of case reports, eight patients with in-hospital cardiac arrest had restoration of spontaneous circulation after receiving 40 U vasopressin after arrest of long duration resistant to standard doses of epinephrine. Although the prognosis was poor in all cases and all conventional measures had failed, return of spontaneous circulation was achieved in all eight patients after vasopressin; three patients survived to hospital discharge with little or no neurological deficit.

Our study had some limitations. Since no previous investigation of vasopressin for resuscitation of the fibrillating human heart was available, we used only one dose of vasopressin in our algorithm. At present, nothing is known about the pharmacokinetics of repeated vasopressin administration during cardiopulmonary resuscitation in human beings. Because of the lack of information, epinephrine was administered in the vasopressin group when spontaneous circulation was not restored within 3 min of vasopressin infusion. Since vasopressin has a longer duration of action than epinephrine, the apparent efficacy of subsequent epinephrine administration may be due, in fact, to the combination of agents, which work by different mechanisms. Outcomes may also have been affected by inpatient clinical management, for which we did not control in this study. We were unable to look for potential detrimental effects of vasopressin on the coronary and splanchnic circulation. The population of patients in this initial study was limited to those in resistant ventricular fibrillation. The effects of vasopressin in out-of-hospital arrest with an initial rhythm of asystole or pulseless electrical activity are not known.

A larger multicentre comparison of vasopressin with adrenaline therapy is needed before widespread use of vasopressin can be recommended for treatment of patients with ventricular fibrillation refractory to direct-current cardioversion.

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High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest

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Abstract

This trial compared blinded 10 mg aliquots of adrenaline with placebo in 194 cardiac arrest patients treated in hospital using American Heart Association guidelines. In-hospital and out-of-hospital arrests were included. Of the 339 eligible patients a large proportion (145 (45%)) were not randomised and received open 1 mg aliquots of adrenaline. This group is also analysed. Supervising physicians gave significant preference for males, patients with no previous cardiac history and without multiple organ disease to be given open 1 mg adrenaline. Patients in asystole at the time of consideration for entry were preferentially placed in the trial group (114 (69%) vs. 170 (88%)) and patients in ventricular fibrillation were preferentially given open 1 mg adrenaline (31 (21%) vs. 24 (12%) $P < 0.03$). The most beneficial rhythm changes which led to survival were sinus rhythm and ventricular tachycardia. Analysis of rhythm changes resulting from the dosing showed a significant ($P = 0.01$) change to a beneficial rhythm with 10 mg adrenaline but not for 1 mg adrenaline or placebo. This was not reflected by an improvement in immediate survival. No significant differences in immediate survival (IS) or hospital discharge (HD) exists between open 1 mg adrenaline (IS 14 (9.7%), HD 3 (2%)) or the 10 mg adrenaline (IS 9 (9.6%), HD 0) vs. placebo (IS 7 (7%), HD 0) trial arms. Patients reaching the point of use of adrenaline have a uniformly poor immediate survival (8.8%) and hospital discharge rate (0.9%). Dosing with 10 mg or 1 mg adrenaline does not influence outcome compared with placebo.

Keywords: Cardiac arrest; Adrenaline; Placebo controlled trial

1. Introduction

Patients who remain in ventricular fibrillation (VF) after defibrillation or who are in asystole are treated with adrenaline according to American Heart Association (AHA) guidelines [1].

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Favourable data from canine and pig models of cardiac arrest [2,3] have been extrapolated to the human without due consideration of the differences particularly regarding weight [4]. Recently, high dose (10 mg or more) of adrenaline has come into vogue based on non-human [5–7] and human haemodynamic studies [8,9]. This enthusiasm was developed further by anecdotal case reports [10–13] and a large trial in pre-hospital arrest sug-

gesting an advantage for high dose adrenaline over standard 1 mg doses [14]. More recently three prehospital arrest based trials have compared the 10 mg dose with 1 mg doses and failed to show any advantage either in immediate survival or hospital discharge for the two dose regimes [15–17]. One of these [17] also had a noradrenaline arm which again showed no benefit over low or high dose adrenaline. There are no trials directly comparing adrenaline in any dose with placebo [18]. We have previously published data obtained from our database of prospectively collected data which suggested that adrenaline at best produced no benefit and at worst was detrimental [19].

This trial was justified on the basis of our published data and was designed to compare placebo with high dose adrenaline (10 mg) in human cardiac arrest. End points used were immediate survival, discharge from hospital rates and favourable rhythm changes.

2. Subjects and methods

The trial had full ethical approval from the hospital ethics committee and extended from July 1989 until December 1992. The protocol followed AHA guidelines [1] except that two (instead of three) defibrillations preceded the use of adrenaline for VF, but asystole was treated early with adrenaline. Out-of-hospital arrests reaching the hospital still in ventricular fibrillation or in asystole were included with arrests occurring in the hospital. CPR by trained personnel was maintained throughout, conforming with AHA guidelines. Patients in asystole were immediately randomised and those in VF were defibrillated twice. If still in VF or defibrillated into asystole they were randomised into the trial. Only primary cardiac arrests were entered and patients were excluded if secondary causes were suspected as per the Utstein style [20]. No patient received adrenaline prior to randomisation. When the trial was considered, a blinded randomised box containing two 10-ml ampoules was opened. Both ampoules contained either saline or 10 mg of adrenaline. For ethical reasons, once both ampoules had been administered, mean of 5 min (but up to 10 min)

apart, open 1 mg aliquots of adrenaline were allowed as recommended by the AHA guidelines.

Data was recorded during the resuscitation and rhythm strips were taken from the monitors and subsequently analysed and recorded. Utstein style data was also collected on time delays. Following the resuscitation the supervising medical practitioner completed a summary sheet which has been previously validated and reported on [21]. Data sheets were sent to a central area where the data was validated, in a blinded fashion, against the records and the medical practitioner was contacted if data required further validation. Immediate survivors were defined as patients who were in a stable cardiac rhythm with a palpable pulse at the time the cardiac arrest team was disbanded. Their conscious state or need for ventilatory support was not considered for the definition of an immediate survivor. Patients could only be entered into the trial once. To ensure no group was disadvantaged, ongoing monitoring of results was undertaken by the investigators and members of the ethics committee while remaining blinded. Results were analysed using chi-squares and analysis of variance (ANOVA).

3. Results

There were 406 cardiac arrest patients treated during the trial period. Fifty-three (53) were excluded; 10 for protocol violations, 7 had inadequate records and 36 were terminated prematurely (cancers, severe multiple organ disease, extreme old age). The remaining 353 patients were eligible. Fourteen patients with 16 episodes, although eligible, were not given open adrenaline or entered into the trial. Six of these were in the emergency department, 4 in wards and 4 in the coronary care unit. There were 8 in VF (10 episodes) with 9 initial survival episodes and 5 discharged alive and 6 in asystole with 6 initial survivors and 3 patients discharged alive. No clear reason could be found either for not choosing adrenaline or for the good outcome. This group was not included in the analysis and so 339 patients remain. It is of note however that if these eligible patients were included there was an immediate survival for VF of 17%

with 14% discharged from hospital. For asystole the immediate survival was 12.4% and hospital discharge rate was 2.1%. For all eligible patients with cardiac arrests there were 47 (13%) initial survivors of whom 15 (4.2%) were discharged alive.

This trial was undertaken in a general hospital setting and cardiac arrests were supervised by numerous middle level medical staff who remained unhappy about the use of placebo. In consequence, rather than risk placebo in the trial, many chose to use open 1 mg aliquots of adrenaline using the AHA guidelines. There were 145 of these patients (45%) leaving 194 to be randomised.

Of the 194 patients in the trial 94 were randomised to receive 10 mg adrenaline and 100 to receive placebo (saline). Because of the similarity of the data and because some benefit arises from examining the group who received open 1 mg adrenaline we analysed this group to show comparisons with the trial group.

The baseline characteristics are in Table 1. There were no significant differences between the arms of the trial but there were significant preferences for males, patients without a cardiac history and without multiple organ disease to be given open adrenaline. The site of the arrest showed no preference for patients entering the trial or given open adrenaline — 44% of trial patients and 46% of open, 1 mg, adrenaline patients were out-of-hospital arrests (Table 2). The first rhythm and

Table 1
Demographics of trial arms and eligible patients who received open 1 mg aliquots of adrenaline

	Standard adrenaline	Trial 10 mg adrenaline	Trial placebo
Number of patients	145	94	100
Age (years)	68 ± 13	70 ± 12	67 ± 14
Sex (M/F)	2.56*	1.6	1.8*
Previous cardiac history	56%**		70%**
Combined organ disease	34%***		44%***
Initial rhythm VF	37%		39%

*P = 0.004; **P = 0.007; ***P = 0.05.

Table 2
Site where arrest initiated. Comparison of all patients entered into trial and those eligible patients treated with 1 mg aliquots of adrenaline

	Total	Ward	Out of Hospital	Emergency dept	CCU
Trial	194	47%	44%	4%	5%
Open 1 mg adrenaline	145	40%	46%	8%	4%

the rhythm on entry are shown in Table 3. Of the patients given 1 mg adrenaline, 53 (37%) had VF as the initial rhythm but 31 (21%) were in VF when given the adrenaline. Of those patients entering the trial 76 (39%) had VF as the initial rhythm but 24 (12%) were in VF on entry into the trial. Patients in asystole, no matter what the initial rhythm, were preferentially entered into the trial and those still in ventricular fibrillation were preferentially given open (1 mg) adrenaline ($P < 0.03$). The protocol allowed the use of standard adrenaline after the trial material and there was no difference between the study arms for this (43% vs. 47%) or the number of trial patients where both ampoules were used (70% vs. 71%).

Utstein style documentation [20] was collected on all patients. Thirty-nine % (57) of patients given open 1 mg adrenaline received immediate, bystander CPR compared with 32% (30) in the 10-mg group and 33% (33) in the placebo group ($P = $ NS). CPR delay between 1 and 5 min occurred in 21% (31) of the 1-mg group, 26% (24) of

Table 3
Initial rhythm and rhythm of eligible patients on trial entry or when given open 1 mg aliquots of adrenaline

Initial rhythm	Entry rhythm	Standard adrenaline	Trial
VF	Asystole	22 (15%)*	52 (27%)*
VF	VF	31 (21%)**	24 (12%)**
Asystole	Asystole	92 (64%)	118 (61%)

*P = 0.01; **P = 0.026.

Table 4
Outcome — immediate survival and hospital discharge of all patients by rhythm on trial entry and change of rhythm after receiving 10 mg adrenaline/placebo or 1 mg aliquots of adrenaline

Rhythm at trial entry	Total	Immediate survival	Hospital discharge
Asystole (284)			
No change	156	1.9%	—
E.M.D.	43	2.3%	—
V. fibb	34	6.0%	—
Sinus rhythm	39	49%	8%
V. tachy	12	25%	—
Vent. fibb (55)			
No change	21	—	—
E.M.D.	11	—	—
Asystole	14	—	—
Sinus rhythm	7	14%	—
V. tachy.	2	50%	—

the 10-mg group and 17% (17) of the placebo group (P = NS). The percentages of patients in whom the delay to defibrillation was less than 10 min, in the ventricular fibrillation group, in the 1-mg, 10-mg and placebo groups were 67%, 64% and 58% respectively. The delay to defibrillation was greater than 30 min in only 4 patients; 1 in the placebo group and 3 in the 10-mg adrenaline group.

Rhythm changes occurred with the use of the drugs and placebo and all rhythm changes were analysed in order to determine rhythms which had significant impact on immediate survival. We were able to define rhythm changes following the trial drugs, however, it was not possible to identify changes after administering each of the two trial ampoules. This is because the rhythm after the first ampoule and before the second was not always recorded and in some cases defibrillation and other drugs (particularly atropine) were administered at the same time. It is shown in Table 4 that immediate survival, defined as patient alive and in sinus rhythm when the resuscitation team left, occurred significantly more often, when the rhythm changed to either sinus rhythm or ventricular tachycardia as opposed to other rhythms

(2.5% vs. 40% — P < 0.00001). Changes to these rhythms were therefore analysed (Table 5). Significant rhythm changes occurred between the two trial arms (P = 0.01). This increase in beneficial rhythm change by 10 mg doses of adrenaline was not seen with the 1 mg doses as compared with placebo. The percentage of immediate survivors from the converted rhythms seem to be reduced when 10 mg doses are used although this trend did not reach statistical significance.

The final results on immediate survival and hospital discharge are in Table 6, analysed by intention to treat principles. There is no significant difference between the trial arms or those patients treated with standard dose, 1 mg adrenaline (P = 0.30). This is true whether analysed by initial rhythm or rhythm on entry to the trial, or, in the open group, the rhythm when the adrenaline was given. Combining this data, therefore, provides an immediate survival rate of 8.8% and a hospital discharge rate of 0.9%.

4. Discussion

We have shown previously [19], that in a large group of patients with prospectively collected data, the use of 1 mg doses of adrenaline at worst had an adverse effect and at best had no effect. At this time it was suggested that the dosing was insufficient and 10 mg doses were considered. This was based on animal data and anecdotal experiences with this dose [8-13]. It was using this and the published data that we felt ethically

Table 5
Patients converted to sinus rhythm or ventricular tachycardia and outcome. Comparison of open 1 mg aliquots of adrenaline and blinded 10 mg adrenaline or placebo

	Standard 1 mg adrenaline	Trial 10 mg adrenaline	Trial placebo
Group total	145	94	100
Converted	24 (17%)	24 (26%)*	12 (12%)*
Immediate survival	12 (50%)	7 (29%)	5 (42%)
Hospital discharge	3 (13%)	—	—

*P = 0.01.

Table 6

Outcome — immediate survival and hospital discharge based on initial presenting rhythm and rhythm when eligible for trial entry. Comparison of open 1 mg aliquots of adrenaline, blinded 10 mg adrenaline and placebo

Initial rhythm	Entry rhythm	Standard 1 mg adrenaline	Trial 10 mg adrenaline	Trial placebo	Group total	Immediate survivors
VF	Asystole	22 (2–3)	29 (0–3)	23 (0–0)	74 (2–6)	8%
VF	VF	31 (0–0)	10 (0–1)	14 (0–1)	55 (0–2)	4%
Asystole	Asystole	92 (1–11)	55 (0–5)	63 (0–6)	210 (1–22)	10.5%
		145	94	100	339	
	Immediate survival	14 (9.7%)	9 (9.6%)	7 (7%)*	30 (8.8%)	
	Discharge from hospital	3 (2%)	—	—	3 (0.9%)	

Brackets (numbers of patients discharged from hospital, number of immediate survivors).
*P = 0.3 (NS).

justified to develop the protocol for this study. We have subsequently shown that adequate levels of adrenaline are maintained in patients having good CPR, although deficiencies in noradrenaline may exist [24].

Recently, human trials using out-of-hospital arrest patients have shown no differences between differing doses of adrenaline [15,16]. A direct comparison of high dose and standard dose adrenaline with nor-adrenaline has similarly shown no difference [14]. In this latter study there was a suggestion that more patients regained a pulse early with the high doses of adrenaline but there were no effects on short and long-term outcome.

These trials differ from this trial in the type of patients entered but they will all have heterogeneity of patients. It is therefore not surprising that the outcomes of first and second defibrillations are similar to that we have recently detailed [25]. The outcome from subsequent use of adrenaline is uniformly poor. We have a group of patients who did not receive adrenaline for reasons unknown, who when included in the trial data give comparative survival and discharge rates to other published data. This important group is too small for analysis but has a large impact on survival rate and would have been entered in the other published trials.

Trials during cardiac arrest comparing current procedures with alternative ones have major pro-

blems. Once a protocol is established it is more likely that paramedics will enter patients and comply with requirements. In a hospital setting, medical practitioners, driven either by personal, medico-legal, or ethical considerations will select patients, based on current opinion. This trial shows this effect and indeed indicates that current selection bias may not be valid. Patients in ventricular fibrillation after two defibrillations seem to do worse than those in asystole. This effect remains unexplained. In spite of these biases toward patients in ventricular fibrillation, male sex, lack of previous cardiac disease or lack of previous multiple organ disease this group, selected to receive open 1 mg adrenaline, did no better than the placebo group in the blinded trial.

The use of adrenaline in cardiac arrest, based on animal studies, was to increase the rate of slow ventricular fibrillation to enhance the likelihood of successful defibrillation [2–4] and to maintain effective cerebral and coronary blood flow [5–9]. In this study we show that in the human cardiac arrest setting adrenaline in 10 mg doses can effectively change the rhythm to sinus rhythm or ventricular tachycardia. These rhythm changes can, however, occur with time and good CPR as shown in the blinded placebo group. During resuscitation these rhythm changes have often been taken as an indication of effectiveness of the last therapy given. The trend in this study was, how-

ever, to reduce the effective immediate survival rate of patients in whom rhythm changes were induced by high dose adrenaline. The overall outcome therefore remained the same. Similar findings have been suggested in several uncontrolled studies [22,23].

In the high dose adrenaline vs. placebo trial arms there was no significant difference between the baseline characteristics of either arm, including CPR and defibrillation delays. The immediate outcome survival was no different between the arms (9.6% vs. 7%) ($P = 0.3$) and none of these 16 immediate survivors out of 194 initial patients were discharged alive from hospital. It was not our intention to assess neurological outcome or long-term survival and given the paucity of survivors no statistically useful information could be gained from such analysis.

In the group who received open standard dose adrenaline the immediate survival rate (9.7%) was no different from either arm of the blinded trial ($P = 0.3$). Of the 145 patients in this group there were 14 immediate survivors and 3 patients left hospital.

The power of this study has been severely limited by the number of eligible patients not entered. In the initial calculations of numbers required, based on previously existing data, the expected survival outcomes were too high. It is only after careful stratification based on time, type of rhythm and delays to both CPR and defibrillation that we have reached the realisation that the groups entering adrenaline trials based on the AHA guidelines have a uniformly poor outcome. It is unlikely that any agent currently in use will induce a large difference in outcome, and any trial looking for small differences will require several thousand patients entered. Of this whole group of 339 patients still in cardiac arrest after two defibrillations for ventricular fibrillation or in asystole and having adequate CPR, there is an immediate survival rate of less than 10% and a hospital discharge rate of less than 2%. The use of adrenaline in this group of patients showed no clinically significant benefit and may only interrupt the application of effective CPR and repeated defibrillation of those patients still in ventricular fibrillation. We believe that a large trial to show small differences in this group is not a valid option.

The economics of current drug dosing in hospital cardiac arrest are dubious, with less than 10% immediate survivors and less than 2% of patients leaving hospital. Any improvement in immediate outcome must be reflected in an improved hospital discharge rate in order to justify use of limited resources. It would seem that early CPR and defibrillation must remain the best hope for improved outcomes, and strategies must be developed to provide this. New CPR techniques may also provide for improved outcomes possibly in combination with more widespread use of mechanical supports, pacing for asystole and continued defibrillation for ventricular fibrillation without the use of adrenaline, unless specifically indicated because of slow rate. We believe that the previous ethical requirement to use adrenaline will now give way to more controlled trials using the modalities outlined.

Acknowledgements

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