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.

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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

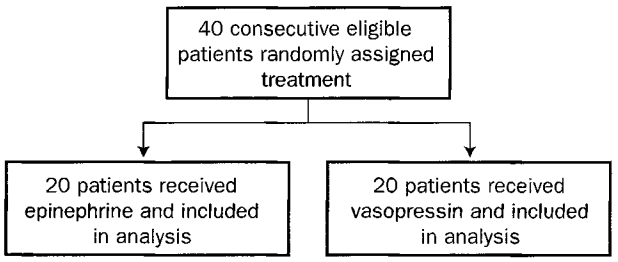
value of vasopressin treatment during cardiopulmonary resuscitation arose after the observation that there is a large release of vasopressin immediately after a cardiac arrest.[3] We have previously reported that the higher the endogenous vasopressin concentration, the greater the chances of restoration 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 advanced cardiac life support (including epinephrine). All patients were included in the outcome analyses.



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**

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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