Towards cardiopulmonary resuscitation without vasoactive drugs

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Purpose of review
Whereas there is clear evidence for improved survival with cardiopulmonary resuscitation (CPR) and defibrillation during cardiac arrest management, there is today lacking evidence that any of the recommended and used drugs lead to any long-term benefit for the patients. In this review, we try to discuss our current view on why advanced life support (ALS) today can be performed without the use of drugs, and instead gain all focus on improving the tasks we know improve survival: CPR and defibrillation.

Recent findings
Previous and recent cardiac arrest drug studies have been reviewed. These are mostly consisting of retrospective register data, some experimental data and a few new randomized trials. The alternative drug-free ALS concept is also discussed with relevant studies.

Summary
There is currently no evidence to support any specific drugs during cardiac arrest. Good-quality CPR, early defibrillation and goal-directed postresuscitation care is more important. Healthcare systems should not prioritize implementation of unproven drugs before good quality of care can be documented. More drug studies are indeed required, and future research needs to incorporate better diagnostic tools to test more specific and tailored therapies that account for underlying causes and individual responsiveness.

Keywords
advanced life support, cardiac arrest, cardiopulmonary resuscitation, catecholamines, vasoactive drugs

INTRODUCTION

Advanced life support (ALS) during cardiac arrest management consists of cardiopulmonary resuscitation (CPR), defibrillation, airway management and administration of vasoactive drugs [1,2]. Whereas there is clear evidence for improved survival with CPR and defibrillation, there is still no definitive evidence that any of the currently recommended vasoactive drugs improve long-term survival [1,2]. The rationale for using epinephrine, vasopressin and amiodarone is to improve haemodynamics and the heart's responsiveness to defibrillation, but so far none of these drugs have demonstrated improved survival-to-hospital discharge in randomized controlled clinical (RCT) trials [1,2]. In this review, we will present important previous and recent data on vasoactive drug research, and discuss our view on why ALS should evolve beyond routine use of standardized drugs with a 'one size fits all' philosophy. The most important ALS treatment during ALS remains to optimize CPR and defibrillation. Additionally, there are some new concepts that might provide a more tailored therapy during resuscitation and improve outcome in cardiac arrest management.

VASOPRESSORS

The rationale for using vasopressors during ALS is to increase the aortic pressure without a concomitant increase in the right atrial pressure, thereby improving both coronary and cerebral perfusion, with the goal of successful defibrillation and return of spontaneous circulation (ROSC), leading to neurologically intact survival [3–5]. The peripheral

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KEY POINTS

- There is currently no evidence to support any specific drugs during cardiac arrest.
- Good-quality CPR and early defibrillation is more important, and future ALS might evolve beyond routine use of standardized drugs with a 'one size fits all' philosophy.
- There are some new concepts that might provide a more tailored therapy during resuscitation and improve outcome in cardiac arrest management.
- Future research needs to incorporate better diagnostic tools to test more specific and tailored therapies that account for underlying causes and individual responsiveness.

vasoconstriction with epinephrine is primarily due to its α-adrenergic effects. Studies have reported decreased microcirculatory cerebral blood flow with epinephrine given during CPR [6,7]. Animal and registry studies have also indicated increased myocardial oxygen consumption [8], post-defibrillation ventricular arrhythmias [9,10▪] and increased post-ROSC myocardial dysfunction [11,12] attributed to epinephrine's β-adrenergic effects.

Arginin vasopressin is a peptide with strong non-adrenergic peripheral vasoconstrictive effects. It has been reported to improve haemodynamics and vital organ blood flow compared to epinephrine [13–15], without the unwanted negative effects from epinephrine on microcirculation [6]. In pig experiments, vasopressin increased survival with better neurologic outcome compared to epinephrine [14,16], but clinical studies and meta-analyses have failed to find any improvement in favourable survival compared with epinephrine [17–21]. In addition to vasopressin, high-dose epinephrine, norepineprine, phenylephrine and methoxamine have all been investigated without showing any benefit compared to standard epinephrine [22–27].

RECENT CLINICAL STUDIES

Two RCTs have attempted to prove a causal relationship between epinephrine and survival [28,29]. The first study ($n = 851$ patients) was designed to test the hypothesis that intravenous (i.v.) drug administration would lead to inferior quality of CPR and thereby inferior outcome. This hypothesis could not be confirmed as both no-i.v. drug and i.v. drug arms of the study had good CPR quality. Significantly more patients in the i.v. drug arm were hospitalized alive compared to the no-i.v. drug arm, but with no difference in long-term survival. The improvements in ROSC rate occurred in patients with initial non-shockable rhythms, with no difference for initial shockable patients [28].

The second study was a double-blind, randomized, placebo-controlled trial which ended up underpowered to detect smaller differences in survival to hospital discharge. Again, the rate of ROSC increased with epinephrine, but with no significant difference in hospital discharge rate [29].

Later, several registry studies have attempted to shed additional light on the effects of epinephrine during resuscitation. Most noteworthy are studies from the impressive approximately 400 000 patient All Japan Registry. Hagihara *et al.* [30▪] first suggested epinephrine might be associated with poor outcome, supporting the equipoise many believe to surround the use of epinephrine during cardiac arrest. In an effort to overcome some of the limitations of their non-randomized data, the authors used propensity matching to select comparable groups within their registry [30▪]. A later publication from the same registry demonstrated conflicting results after revising their propensity matching criteria [31▪]. Further, there has been a debate whether early epinephrine administration is important for a better total effect, but so far, these retrospective clinical registry data show conflicting results without any clear conclusion [32–36]. A lot of confounding factors also complicate interpretation. The conservative interpretation of current epinephrine evidence is that larger RCTs are needed to provide definitive answers.

The most recent attempt to prove vasopressin's usefulness is a RCT from Singapore comparing vasopressin and epinephrine at hospital admission in cardiac arrest patients. Although there were no differences in ROSC (30 vs. 32%) or survival to hospital discharge (2 vs. 3%) between the epinephrine and vasopressin groups, the patients who received vasopressin were significantly more likely to survive to hospital admission (17 vs. 22%; $P = 0.05$) [37▪].

ANTI-ARRHYTHMICS

Amiodarone is a class III anti-arrhythmic drug, mainly blocking potassium channels, and prolonging re-polarization [38]. Two previous randomized trials showed increased rate of ROSC compared to placebo or lidocaine in out-of-hospital patients with shock-resistant ventricular fibrillation (VF) without improved long-term outcome [39,40]. Similar results were reported from the previously discussed i.v. drug trial [28]: trends to improved ROSC, but no differences in final survival (not published, data from the authors). Amiodarone also

has β-blocking properties [38] and is likely dependent on co-administration of epinephrine for any beneficial effect. In a recent experimental pig study, administration of amiodarone alone expectedly had adverse effects on the coronary perfusion pressure compared to a combination of amiodarone and epinephrine, but seemed to stabilize the heart sufficiently in the early post-ROSC period [41]. A new RCT comparing amiodarone, lidocaine and placebo is underway in the US Resuscitation Outcome Consortium (ROC) (NCT0140164), using a new amiodarone solution.

COMBINATION OF VASOACTIVE DRUGS

The absence of significant improvements in long-term outcome with the current recommended drugs indicates that we still have not found the optimal drug use. Due to epinephrine's negative effects on micro-circulation, unwanted arrhythmias and post-resuscitation myocardial dysfunction [6–9,10▪,11,22], combining epinephrine with a β-blocker agent has been suggested in patients with initial VF [42]. By blocking both epineprine's α_1-effects and β_1-effects with propanolol, Pellis *et al.* [43] showed that the post-resuscitation myocardial function was improved, with no haemodynamic differences. Two recent pig studies have confirmed these findings; one study showed better outcomes and post-resuscitation myocardial function by combining esmolol with epinephrine vs. epinephrine alone [44], and another study showed better ROSC rates with metoprolol, but not labetalol [45]. Indeed, the type of β-blocker is important, and today esmolol and metoprolol seem to be the most promising ones. Importantly, current studies have never compared β-blockers and epinephrine to amiodarone and epinephrine.

Other drug combinations have been studied. Two randomized studies with a total of 4300 patients compared the combination of vasopressin and epinephrine vs. epinephrine alone, with no improvements in rates of ROSC, long-term survival or neurologic recovery [46,47]. However, in a recent randomized double-blinded trial among in-hospital cardiac arrest patients, Mentzelopoulos *et al.* [48▪▪] documented that the combined use of vasopressin+epinephrine and methylprednisolone during CPR, compared with epinephrine alone, and stress-dose hydrocortisone in post-resuscitation shock patients, compared with saline placebo, improved favourable survival to hospital discharge. The interpretation of this trial is complicated as the two arms received various combinations of four different drugs during and after cardiac arrest. Yet, the results are compelling with improvements in blood pressures during CPR, presumably generating a higher coronary perfusion pressure reflected in shorter resuscitation efforts and less need for epinephrine. The drug cocktail studied in this trial is tailored to the in-hospital cardiac arrest cohort, where the causes of arrest differ from the more common out-of-hospital cardiac arrests [1,2]. Caution must be used when extrapolating these findings to other cardiac arrest cohorts, also since there seemed to be some differences in the causes of the arrests in the two arms, favouring the drug-combination group [48▪▪].

Other promising drug combinations are epinephrine and glycerylnitrate [49]; vasopressin, epinephrine and glycerylnitrate [50]; epinephrine, vasopressin and levosimedane [51]; or sodium nitroprusside and epinephrine [52], which all have shown promising results in experimental animal models. A recent small clinical study showed no haemodynamic improvement with the combination of vasopressin, epinephrine and glyceryl nitrate compared with epinephrine alone [53].

SUMMARY VASOACTIVE DRUGS

There are no indications that epinephrine administered alone or in combination with amiodarone as currently recommended has a major impact on survival, and we certainly lack information on the optimal dose [1,2] or optimal timing of any vasoactive drug during ALS. A recent retrospective study from Seattle indicated that less frequent average epinephrine dosing than recommended was associated with improved survival [54]. Similarly, it might not only be a matter of drug dose, or early vs. late drug administration; it might very well be delivering the right drug at the right time for each individual. A thought-provoking experimental study showed convincing effects of administering vasopressors guided by coronary perfusion pressure rather than algorithm [55]. Perhaps, even an infusion of epinephrine is a better solution than a higher dose in intervals [56]. More drug research including experimental animal studies, prospective clinical studies and especially RCTs are definitively needed.

A prerequisite for the efficiency of any drug during cardiac arrest is generation of adequate blood flow. This has been eloquently demonstrated by a porcine experiment showing no effect of epinephrine administered during CPR, mimicking what had been demonstrated clinically, whereas 'laboratory quality' CPR produced the expected improvements in haemodynamics [57]. Interestingly, both cerebral and coronary perfusion was better with good-quality CPR without epinephrine

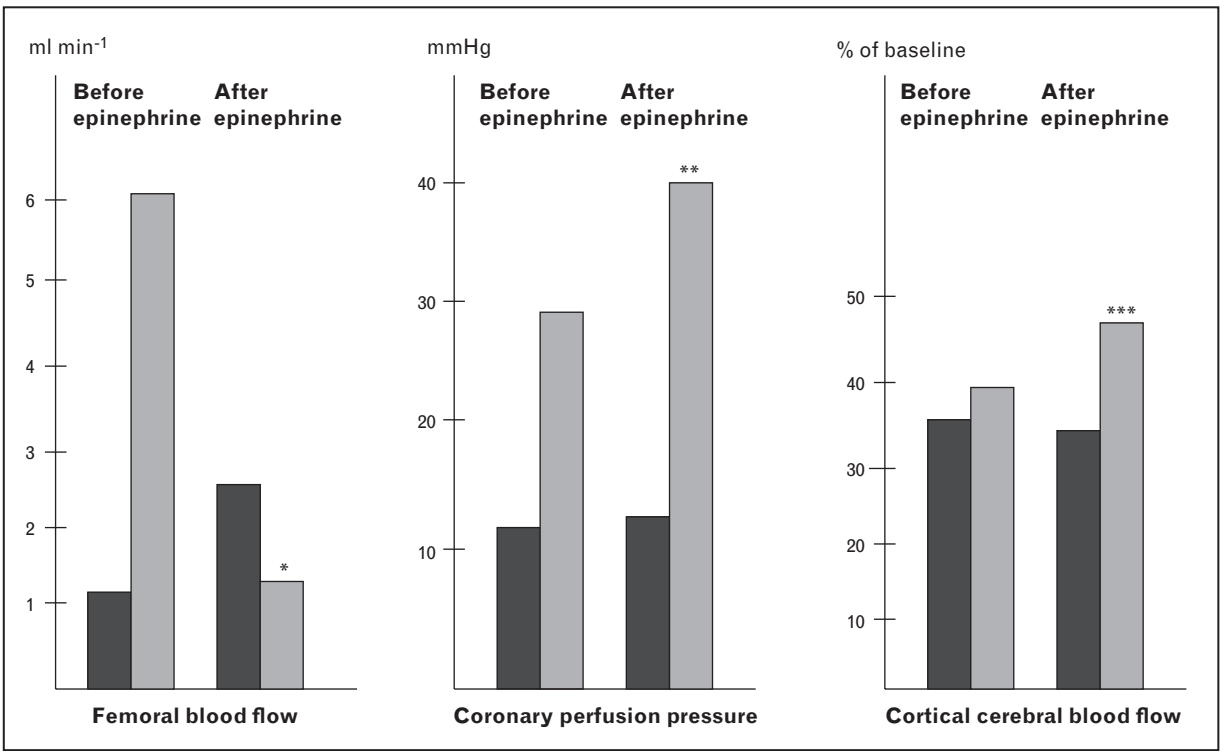

FIGURE 1. Median values of femoral blood flow, coronary perfusion pressure, and cortical cerebral blood flow before and after epinephrine administration and at the time of peak plasma concentration of epinephrine in an experimental pig study ($n = 14$) (Pytte *et al.* [57]) during different quality of CPR. Black bars indicate bad-quality CPR, and grey bars good-quality CPR. (*)$P = 0.02$, (**)$P = 0.01$, (***)$P = 0.04$ vs before epinephrine administration. CPR, cardiopulmonary resuscitation.

compared to bad-quality CPR with epinephrine (Fig. 1). Very few clinical drug trials performed in the cardiac arrest setting provide data on chest compression quality, and there is a real possibility that poor resuscitation quality has confounded negative drug trials leaving the drugs in the peripheral vein they were administered due to lack of generated blood flow. Whereas it is possible to administer drugs without compromising chest compression quality [28], we still have no clear evidence which drugs in what doses to use.

THE CONCEPT OF CARDIOPULMONARY RESUSCITATION WITHOUT DRUGS

Although not verified by randomized controlled trials, healthcare systems that have implemented rigorous training and monitoring systems have arguably had the greatest impact on survival from cardiac arrest [58–61]. It stands to reason that no healthcare system should prioritize implementation of unproven drugs before good quality of care can be documented. We would argue that the all-important first step is to ensure optimal quality of care with high-quality chest compressions, early defibrillation before ROSC, and good post-resuscitation care after ROSC. Secondly, we should expand our diagnostic capabilities exploring the feasibility of utilizing technologies such as capnography, near-infrared spectroscopy (NIRS), VF analysis, and ultrasound assessment to allow targeted therapy (while maintaining adequate CPR). When good quality of care and improved diagnostics have been ensured, more tailored drug approaches could eventually be tested based on underlying causes.

End-tidal carbon dioxide

End-tidal carbon dioxide ($ETCO_2$) mirrors cardiac output, and the positive correlation between $ETCO_2$ and outcome in cardiac arrest has been well described in several animal and clinical studies [62–66,67▪]. During ALS, it will give feedback about quality of CPR over time, prognosis and discriminate pulseless electric activity from ROSC after shock delivery [1,2,62,64,65]. In a clinical study by Qvigstad *et al.* [68▪], capnography was used to seek for the optimal sternal compression site, which varied between individuals. Use of epinephrine [69,70] and factors like cause of arrest, initial rhythm, presence of bystander CPR and time from arrest impact and complicate capnography

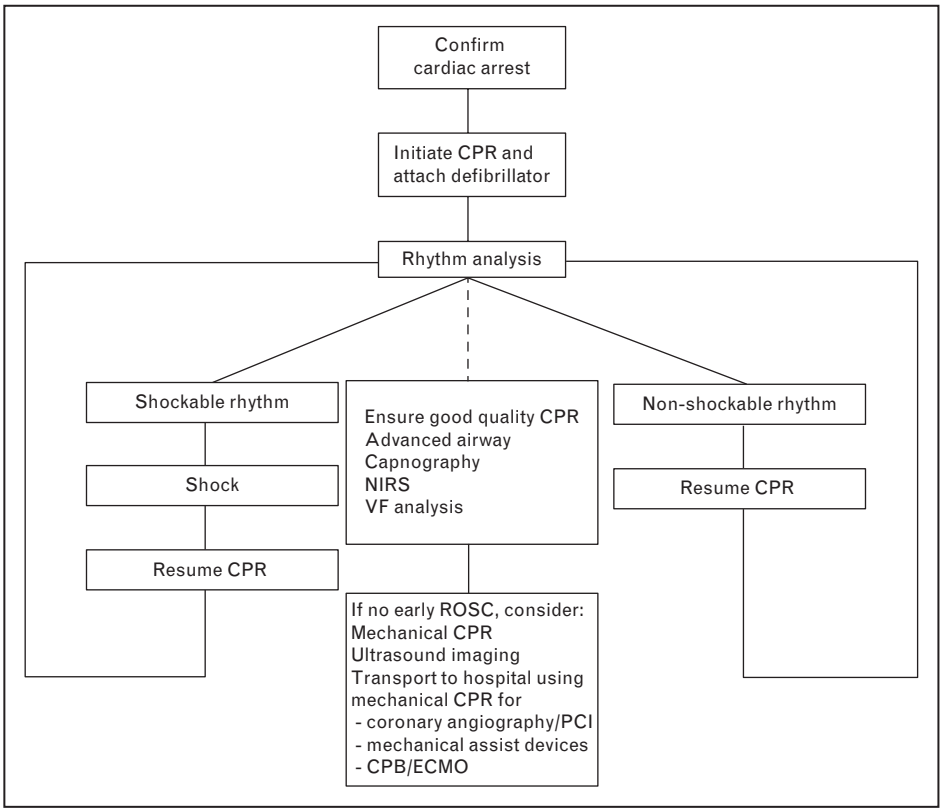

FIGURE 2. An alternative advanced drug free ALS algorithm. Note there is no time recommendation for the CPR interval between rhythm analysis or shocks, because this might differ based on monitoring, diagnosis, response to treatment and other individual circumstances. CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; NIRS, near-infrared spectroscopy; PCI, percutaneous coronary intervention; VF, ventricular fibrillation.

interpretation during ALS, but might also provide us with underutilized clues of cause [66,67▪]. As an example, pulmonary embolism will reduce the return of CO_2 from the lungs reflected in lower and 'non-responsive' $ETCO_2$ values [67▪], whereas asphyxia would be expected to generate high CO_2 values prior to cardiac arrest with high initial $ETCO_2$ values and gradually decrease regardless of chest compression effort [66,67▪].

Near-infrared spectroscopy

Another exciting tool is near-infrared spectroscopy (NIRS), which measures oxygen saturation in a specific volume of the brain, where low measurements might indicate ischaemia or hypoxia [71]. Although we have limited clinical data, some exciting minor studies indicate that NIRS might provide data on quality of CPR, and patients with a NIRS rise seem to have a higher ROSC rate [72▪,73,74]. Randomized trials are needed with the use of both capnography and NIRS as quality indicators during chest compressions resulting in more individualized cardiac arrest management compared with standard guideline algorithm.

Ventricular fibrillation analysis

By using VF analysis incorporated in the defibrillators, timing of the defibrillation attempt will lead to more targeted shock delivery, avoidance of unnecessary shocks and further reduction of the hands-off ratio [75]. Although this concept is not quite yet ready for worldwide commercial use, some interesting studies have recently been published [76▪,77▪]. Although a recent RCT could not prove any survival benefit from delivering shocks guided by an a priori waveform threshold, the VF-cohort is still heterogeneous and had varying responsiveness to additional chest compressions [78▪▪]. In two recent large retrospective registry studies, the VF analysis predictor amplitude spectrum area (AMSA) was judged to be a useful tool to guide CPR interventions and predict the optimal timing of shocks [76▪], and a positive median change between shocks was associated with favourable neurologic survival

[77▪]. It is important to emphasize that the cause of arrest impacts on the VF spectrum [79], as well as drugs like β-blockers [45], making clear cut-off values difficult to use in the clinical setting.

Ultrasound imaging

Other diagnostic clues might be found from direct ultrasound imaging [80–84], importantly incorporated into the treatment without interrupting chest compressions more than a few seconds at a time. Especially a tamponade, dilated right ventricle as a possible sign of pulmonary embolism, and the contractility in general can be diagnosed, and might provide guidance in selecting patients eligible for more advanced therapies like pericardocentesis, use of thrombolytics or mechanical chest compressions as a bridge to coronary angiography/percutaneous coronary intervention (PCI) during ongoing CPR [85–87], cardiopulmonary bypass [88] or better extracorporeal membrane oxygenation (ECMO) [89,90▪]. Two recent large multi-centre RCTs with the LUCAS- [91▪▪] and AutoPulse [92▪▪] mechanical chest compression device, have both shown similar survival compared with manual CPR. Obviously, mechanical CPR is the preferred CPR method during transport [93,94]. There are no data to support the use of any of the available mechanical chest compression devices over another. Optimal strategies for different causes are likely to be different, and it is difficult to see how significant progress might be made without any attempt to provide more tailored treatment. As an example, in prolonged, refractory VF, transport of the patient with mechanical CPR to a centre with mechanical assist systems and/or coronary angiography/PCI might be better than doing unsuccessful standard ALS at the scene. Again, RCTs are needed.

In the absence of scientifically proven drug therapies, we propose an alternative advanced drug-free ALS algorithm (Fig. 2).

CONCLUSION

There is currently no evidence to support any specific drugs during cardiac arrest. Healthcare systems should not prioritize implementation of unproven drugs before good quality of care can be documented. More drug studies are indeed required, and future research needs to incorporate better diagnostic tools to test more specific and tailored therapies that account for underlying causes and individual responsiveness.

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Conflicts of interest

K.S. has received travel grants and lecture payment from Bard Medical in 2013 (no specific conflicts related to this manuscript).
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- ▪ of special interest
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