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Future directions for resuscitation research. III. External cardiopulmonary resuscitation advanced life support[1]

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Abstract

This discussion about advanced cardiac life support (ACLS) reflects disappointment with the over 50% of out-of-hospital cardiopulmonary resuscitation (CPR) attempts that fail to achieve restoration of spontaneous circulation (ROSC). Hospital discharge rates are equally poor for in-hospital CPR attempts outside special care units. Early bystander CPR and early defibrillation (manual, semi-automatic or automatic) are the most effective methods for achieving ROSC from ventricular fibrillation (VF). Automated external defibrillation (AED), which is effective in the hands of first responders in the out-of-hospital setting, should also be used and evaluated in hospitals, inside and outside of special care units. The first countershock is most important. Biphasic waveforms seem to have advantages over monophasic ones. Tracheal intubation has obvious efficacy when the airway is threatened. Scientific documentation

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of specific types, doses, and timing of drug treatments (epinephrine, bicarbonate, lidocaine, bretylium) are weak. Clinical trials have failed so far to document anything statistically but a breakthrough effect. Interactions between catecholamines and buffers need further exploration. A major cause of unsuccessful attempts at ROSC is the underlying disease, which present ACLS guidelines do not consider adequately. Early thrombolysis and early coronary revascularization procedures should also be considered for selected victims of sudden cardiac death. Emergency cardiopulmonary bypass (CPB) could be a breakthrough measure, but cannot be initiated rapidly enough in the field due to technical limitations. Open-chest CPR by ambulance physicians deserves further trials. In searches for causes of VF, neurocardiology gives clues for new directions. Fibrillation and defibrillation thresholds are influenced by the peripheral sympathetic and parasympathetic nervous systems and impulses from the frontal cerebral cortex. CPR for cardiac arrest of the mother in advanced pregnancy requires modifications and outcome data. Until more recognizable critical factors for ROSC are identified, titrated sequencing of ACLS measures, based on physiologic rationale and sound judgement, rather than rigid standards, gives the best chance for achieving survival with good cerebral function.

Keywords: Adrenergic agents; Anti-arrhythmic agents; Buffer agents; Cardiac arrest; Cardiopulmonary resuscitation; Defibrillation; Maternal resuscitation; Neurocardiology; Vagotonia; Ventricular fibrillation

1. Introduction

1.1. Ornato

This discussion session concerns external cardiopulmonary resuscitation (CPR)-advanced cardiac life support (ACLS). Most experts would agree that in cases of ventricular fibrillation (VF) early defibrillation is the most effective weapon we have for resuscitating the adult cardiac arrest victim. The real challenge has been to determine the true value of everything else, such as advanced airway control measures and pharmacotherapeutic agents.

1.2. Paradis

When considering ACLS for restoration of spontaneous circulation (ROSC), what is the problem in the inability to defibrillate? Is it the poor state of the myocardium and its perfusion? All VF eventually ceases. What should we do to get the myocardium into a condition that makes countershocks in VF achieve a spontaneous heartbeat, rather than pulseless electric activity (PEA), i.e., electromechanical dissociation (EMD)?

During cardiac arrest, the pharmacokinetics of low-flow may be such that drugs do not reach significant tissue levels rapidly enough (Appendix 1, 1A). Specifically, it is hard to imagine that during standard external CPR, intravenously administered drugs reach therapeutic myocardial tissue levels for a relatively prolonged period. Do peripherally administered buffer agents and antiarrhythmic agents achieve adequate myocardial levels in minutes during the low-flow state of CPR? Probably not. This needs a better laboratory study.

What laboratory studies are useful in designing clinical trials? There are those that have been designed to be very sensitive and specific for a given hypothesis, those that might be considered hypothesis generating, and those that explore physiology. What we must not forget is that the laboratory studies are designed to generate specific data, and that even a statistically significant result may not merit a clinical trial. In all probability, only dramatic breakthrough therapies merit clinical trials, as their power is often limited [1–4].

Maybe we need to consider some type of alternative approach to this problem. Just as the first atom bomb was tested only once before its use, there still is occasionally a clinical case report or a clinical study with a small sample size that merits our attention. Maybe we need to broaden our methodological horizons. We might reconsider sequential (temporal) studies in which one employs a certain dose of a drug for 20 min of arrest, and then switches to another dose or drug, getting a result you would not have expected in 20 min. Is that convincing as to cause and effect? Although not amenable to standard statistical analysis, such types of experiments are used in other areas of science.

One should consider two stages in resuscitation from VF — first, preparation for defibrillation,

and second, actual defibrillation. The objective is countershock followed by ROSC.

What is the best pharmacological agent? Would a pure α-receptor agonist be preferable to epinephrine? For example, phenylephrine improves coronary flow without exacerbating myocardial oxygen consumption [5]. This may not be optimal, as the β-receptor agonist effect of epinephrine may be beneficial at the moment of countershock. After ROSC, you can still run into problems. We should discuss not only epinephrine and buffer agents as therapies to restore circulation, but also their effects on spontaneous circulation early after ROSC.

Maybe a better approach to ACLS steps D (drugs)–E (electrocardiography)–F (fibrillation treatment) [6] should be an escalation in therapy, rather than going through the same cycles over and over again. Clinicians currently cycle through ACLS without an appropriate sense of time. In the laboratory, when we are looking for cerebral recovery, as clinicians should, panic starts to set in, if the animal is still in arrest after a few minutes. Maybe we should try to convince clinicians to get as excited as we are in the laboratory. It is often not appreciated that ACLS provides diagnostic information. When one provides a cycle of a certain therapy, and that does not result in ROSC, one can conclude that the therapy was inadequate. Maybe we should not do exactly the same thing on the next go around.

1.3. Pepe

We in Houston are responsible for trying to resuscitate about 1200 out-of-hospital cardiac arrest patients per year [7]. We have begun to ask: 'How well does ACLS really work?' [8] (Appendix 1, 6A). We also think about the cost of giving the care, such as ambulances, salaries, equipment, and supplies; and the cost of training the personnel [9].

Over the past 25 years, 'reanimatologists' developed elaborate systems of care, with physician- or paramedic-staffed units [10–16]. We went into the streets to conquer sudden death. We have focused on VF which seems to be the major cause of sudden death, and have delivered defibrillation attempts with much success [15–19]. However, in many situations we have found that when we arrived, and defibrillated, that the patient remained pulseless with or without ECG complexes [20]. As a result, we empirically tried to combat acidemia, hypoxemia, or hypercapnia [21–24]. After tracheal intubation [25], we provided $NaHCO_3$ and epinephrine, also empirically, to try to re-stimulate the heart. But we did not succeed in most cases [20–26]. Most of us will agree that at this time, in *clinical* studies, only bystander CPR and early defibrillation have altered the outcome to a major extent [17]. We have not clinically proven the individual value of any of the other interventions [8,9].

Let us look at the usefulness of endotracheal intubation. I do not know of a study in which we have *proven statistically* that tracheal intubation is effective [9,27,28]. For example, with a univariate analysis of intubation and outcome, we would find that intubation correlates with poor outcome, since all nonsurvivors eventually get a tracheal tube, while many people who have ROSC accomplished rapidly, will not get intubated. As a result, tracheal intubation correlates with poor outcome due to the confounding factor of early CPR and defibrillation [9].

1.4. Dick

Nobody has (statistically) proven that endotracheal intubation during CPR is superior to the laryngeal mask or to simply administering mouth-to-mouth or mouth-to-nose ventilation. All we know is that tracheal intubation is the 'gold standard' [6,25,27,28]. Would it be ethically justified under these circumstances to run such a study? I personally feel 'no.' We know that direct mouth-to-mouth ventilation is less effective and may be more risky than ventilation via endotracheal tube, because the former offers no protection against aspiration of gastric contents. Aspiration has been found in over 80% of failed CPR attempts. We probably have to accept certain methodologies and procedures even if they cannot be documented by controlled, randomized clinical studies.

1.5. Pepe

I agree that *we* are not prepared to do such a study. I also believe that endotracheal intubation

is the gold standard and will stay with us. My point is that we may have to forego some of our science and rely a little more on the art in our quest to improve resuscitation.

There are other examples for skepticism. In spite of the documentation of the benefit of *epinephrine* in animal studies of cardiac arrest [21–23,29–32], we have so far not done well in the documentation of its value in clinical cases [26,33–35]. Even with high-dose epinephrine, we have not had *clinical* proof that it made a difference [26,33,34]. There has not even been a published clinical study yet to compare epinephrine vs. no epinephrine, although an abstract has been published on the subject [35].

There have been several studies recently which suggest that *lidocaine* may be deleterious if given prior to ROSC [36–39]. The positive and negative papers about $NaHCO_3$ treatment are another example [24,40–42]. Clinically, there has been no scientific proof that $NaHCO_3$ is needed or effective in cardiac arrest patients.

Defibrillation is no longer limited to ACLS, as automatic external defibrillators (AEDs) have been put into the hands of 'first responders,' such as firefighters and police officers, without expert training [17,19,43–45]. As a result, there are implications that we may not need physicians, nurses, or paramedics, if other ACLS interventions are unproven. This has a major economic impact because we would not have to go through ACLS training for first responders. But what about tracheal intubation? There are now recommendations calling for the use of the Combi-tube® by emergency medical technicians [28,45].

Having raised such a provocative question, let us take a step back and review some studies that show that ACLS *is* effective [7,46]. Cardiac arrest victims who never received a countershock, who presented with non-VF ECG patterns, constituted a large percentage of survivors; in one study [46], 44 of 193 survivors of out-of-hospital arrest did not present with VF, and 40 of these 44 never received a countershock. Something other than countershock within the ACLS regimen must have been effective.

In the future, we should rethink resuscitation procedures and the animal models used to evaluate them. Laboratory data are from animals with good coronary arteries. This, of course, differs from the use of epinephrine in clinical studies. Also, in most of the animal studies, epinephrine was given prior to countershock [47]. In the future we might look at a real-time spectrum or scale of the VF waveform [48] — say of 1 to 10. If there is an 8 we might shock first, if there is a 4 we might give a drug first, like high-dose epinephrine or a 'cardiac cocktail' [49]. How difficult would it be to re-evaluate a drug such as lidocaine? We have to rethink our models.

In the high-dose epinephrine study by Brown et al. [26], we found no statistically significant difference in outcome between standard-dose and high-dose groups (5% vs. 4%). This was statistically not significant when we are talking about 30 vs. 24 patients among 600. If, however, we had 10 000 patients, a significant difference may have been found. Extrapolating across the US alone, thousands of lives may have been saved every year by such a 1% difference. Thus, one of the problems with clinical trials is the need for very, very large numbers.

The majority of patients whom we save do not ever receive adrenergic drugs. When examining the effects of ACLS drugs, we are starting with a group of patients who have a very low survival rate. In the non-significant high-dose epinephrine study by Brown et al. [26], we had six large cities that participated with all their applicable cardiac arrest cases over 1 year's time. There were only 1200 patients. It would be even more difficult to get enough patients to do subgroup analyses (e.g. by ECG rhythm or neurologic outcome).

In the case of lidocaine, it is even more difficult to test subgroups among those few who receive this agent. A question concerning lidocaine is whether one should give it early in refractory VF or only after countershock and ROSC to prevent re-fibrillation, or whether to avoid it altogether. To get into such multiple arms of a study would be difficult. Unless there is overwhelming drug efficacy, we will have problems with interpreting the results of clinical trials.

1.6. Ornato

In cases of cardiac arrest without VF, we

sometimes get into trouble if we do not clarify terminology. It may be useful to subgroup patients into those who have a flat ECG tracing with no pulse, those who are bradycardic with no pulse, and those who have normal or rapid ECG complexes but no pulse. Do the majority of these patients have a relatively slow rate?

2. Pharmacology

2.1. Bircher

I would like to illustrate how resuscitation is done in our dog model of VF [50–55] and compare this with clinical resuscitation (Appendix 1, 2A). The preparation of the animal, with catheters in place, etc., differs from the clinical setting. In the previously healthy dog, the electrically induced VF changes its pattern during 10 min of no flow. A timer on the physiologic chart recorder allows us to keep track of interventions during ACLS and before ROSC. We monitor femoral arterial pressure, right atrial pressure, and pulmonary artery pressure continuously. This allows us to monitor the quality of chest compressions. After 10 min of no flow, we first give a countershock, then we inject epinephrine through the right atrial catheter, and then $NaHCO_3$. The buffer agent will have an effect on the pressor effect of epinephrine if both are given at the same time, but not if the buffer is given 10 min after the pressor agent (Appendix 1, 7A). The mechanical chest compressor is adjusted to the point of creating a femoral artery pressure peak of at least 80 mmHg. Then we observe what drugs do. After 2 min of VF no-flow, the first countershock is usually ineffective before drugs, which is characteristic of this kind of cardiac arrest canine model. Even after chest compressions and ventilation are started, the second, third, or fourth countershock may not be effective. If a countershock defibrillates successfully before drugs are given, the animal is typically asystolic. If norepinephrine infusion is not titrated skillfully after ROSC, the animal will usually develop hypotension and will re-arrest.

It is important to study different arrest time intervals. For example, in dogs after 5 min of VF no-flow, the addition of $NaHCO_3$ to epinephrine has no additional effect on ROSC [52]. There may be a slight neurological advantage at 24 h. After 10 min of VF no-flow, the addition of $NaHCO_3$ makes a difference in terms of ROSC and neurologic outcome [52]. After 15 min of VF no-flow there is a dramatic difference in both parameters [52]. Thus, it is important to look at short, medium, and long cardiac arrest no-flow intervals. In a clinical prehospital study, to be able to see such distinctions, one would have to have a very large sample size.

I now want to examine the molecular framework in which we used to think about the potential advantages of a buffer agent. The binding of α-1 and β adrenergic receptors are exquisitely sensitive to pH, although they have different second messengers [56]. We do not know about second messenger behavior during ischemic acidosis. We do, however, know that we can alter the effects simply by altering receptor binding at alpha or beta adrenergic receptors. Then, with respect to correcting intracellular acidosis, particularly in the brain and myocardium, if the intracellular hydrogen ion concentration is roughly equal to the extracellular concentration, the sodium proton pump — where proton flow outward is equal to sodium flow inward — is strongly inhibited by extracellular acidosis, particularly when it is of equal magnitude to intracellular acidosis. If, however, you can lower the extracellular proton concentration, this pump becomes active in terms of correcting intracellular pH. We can thus explain how sodium bicarbonate does not need to get into the cell to alter the catecholamine effect, and simple alteration of extracellular pH assists the cell significantly in regulating its own intracellular pH.

2.2. Paradis

Let us combine our thinking about automatic defibrillation and the need for pressor support immediately after countershock as discussed by Bircher. Would there be benefit if automatic defibrillators had a component of pressor support after defibrillation by, for example, attaching to the electrode over the sternum a device which would administer a bone marrow dose of pressor? Would this be of benefit to patients with post-

ROSC hypotension, without harming those that are normo- or hypertensive?

2.3. Bircher

Post-ROSC hypotension and rearrest are frequent in clinical trials, and they often are not treated adequately.

Concerning the question of whether hypertonic saline should be compared with the equally hyperosmolar sodium bicarbonate solution — hypertonic solutions have the disadvantage that they are potent vasodilators. We have been able to determine that there is no change in the level of serum sodium using titrated $NaHCO_3$. Weil has demonstrated the negative effect of hyperosmolality on coronary perfusion pressure in the absence of epinephrine.

2.4. Weil

There is little doubt that there is a correlation between the administration of epinephrine during external CPR, and aortic pressure, or coronary perfusion pressure, or achieving ROSC. This is supported by a large series of experimental and clinical data, with good correlation in patients with sudden death in the coronary disease age group who develop VF [57–59]. I do not think that epinephrine may be the ultimate drug of choice for resuscitation. The concept that we would not administer a countershock because the patient may have brady- or asystolic cardiac arrest on arrival at the scene, or that there is a small error in the intelligence of an AED, is less concerning than are the potential benefits.

2.5. Neumar

Based on the current literature, it appears that the effectiveness of $NaHCO_3$ therapy is not only dependent on the duration of cardiac arrest, which the studies by Vukmir and Bircher have shown very nicely [52], but is also dependent on the epinephrine dose given during cardiac arrest. All of the studies which show a beneficial effect of $NaHCO_3$ during CPR used at least 0.05 mg/kg of epinephrine [23,52,60–62]. In our rat model of asphyxial cardiac arrest [63], 1.0 mEq/kg $NaHCO_3$ during CPR had no effect on coronary perfusion pressure or ROSC in rats given 0.0, 0.01, or 0.1 mg/kg of epinephrine, but there was a trend towards improved survival in the 0.1 mg/kg epinephrine group with $NaHCO_3$ therapy [62].

The observation that $NaHCO_3$ therapy may be effective only when high doses of epinephrine are given during CPR raises the hypothesis that $NaHCO_3$ treats a side effect of epinephrine, in particular metabolic acidosis. In our rat asphyxial cardiac arrest model, the severity of postresuscitation metabolic acidosis increases as a function of epinephrine dose [62]. This is likely due to prolonged vasoconstriction in non-essential vascular beds resulting in continued end- organ ischemia following ROSC. It remains to be determined, however, if aggressive treatment of the postresuscitation effect of high dose epinephrine will allow the improved rates of ROSC to be translated into improved long-term survival.

2.6. Paradis

One must be careful in interpreting the results of laboratory models. By adjusting CPR steps ABC, the insult time, and the way we administer drugs, we can alter the results. We need to agree on what is clinically meaningful to mimic in the laboratory. Simply weighing the number of studies on either side of an argument is probably not going to be fruitful, because it depends on how people adjust their study designs to reflect the prevailing bias.

2.7. Ornato

The issue of $NaHCO_3$ administration is still somewhat controversial. It may or may not have incremental value. Dr Bircher has presented intriguing data [50–52,62].

2.8. Rubertsson

We conducted the following study concerning the effect of epinephrine on instantaneous blood flow variations with the compression and relaxation phases of CPR (Appendix 1, 7A): after tracheostomy and insertion of arterial, right atrial,

and pulmonary arterial catheters, thoracotomy was performed in 22 anesthetized piglets with placement of a pulmonary arterial, aortic, and left anterior descending (LAD) coronary arterial (extended study group) flow probe and a left atrial catheter. Blood flow was studied using transit-time ultrasound flowmetry. VF for 2 min was followed by 10 min of either open-chest ($n = 10$) or closed-chest CPR ($n = 12$). Seven min after CPR initiation all piglets received 0.5 mg epinephrine i.v. At 12 min, DC shocks were used to revert the heart to sinus rhythm. Open-chest CPR generated greater systemic perfusion pressure, especially during the relaxation phase, resulting in greater mean blood flow. With both open and closed-chest CPR, antegrade pulmonary arterial and aortic flow occurred during compression while antegrade LAD coronary arterial flow occurred during relaxation. Retrograde flow was found during relaxation in the pulmonary artery and aorta, and it occurred during compression in the LAD coronary artery. Epinephrine: (1) increased the systemic perfusion pressure more during open than closed-chest CPR; (2) increased the relaxation systemic perfusion pressure more than the compression perfusion pressure; (3) decreased mean pulmonary arterial and aortic flow but substantially increased mean LAD coronary arterial flow; and (4) reduced retrograde flow in the LAD coronary artery. We concluded that open-chest CPR generates greater systemic perfusion pressure and blood flow than closed-chest CPR. Epinephrine increased LAD coronary arterial flow, but decreased cardiac output to such a degree that cerebral perfusion might be endangered.

2.9. Traystman

We conducted the following study concerning the effect of $NaHCO_3$ administration on brain bioenergetics during CPR in dogs (Appendix 1, 8A): with no prior arrest time, a 30 mmHg (suboptimal) cerebral perfusion pressure (CPP) during CPR maintains brain ATP but not brain pH. With a 6 min arrest time, a 30 mmHg CPP has variable success in restoring brain ATP. We investigated the effects of adding $NaHCO_3$ on brain ATP and pH, in a 6-min arrest model with a CPP of 30 mmHg. The dogs were anesthetized with pentobarbital and fentanyl. Vascular catheters were placed for microsphere cerebral blood flow (CBF) determinations. Brain ATP and pH were measured using ^{31}P magnetic resonance spectroscopy using a 4.7 Tesla magnet. CPR was performed for 70 min with an inflatable vest, adjusted to produce a CPP of 30 mmHg after 6 min of VF arrest no-flow. $NaHCO_3$ was administered to 17 dogs to maintain arterial pH at pre-arrest levels, but it was not given to 14 control dogs. Both groups had ventilation adjusted to normalize arterial P_{CO_2}. There was no difference in the number of dogs able to achieve a CBF of 15 ml/100 g/min in the $NaHCO_3$ group (10/17) versus the control group (8/14). CBF, cerebral metabolic rate ($CMRO_2$), brain ATP recovery, and brain pH were compared over 70 min in the two groups among the animals that had achieved CBF of >15 ml/100 gm/min. $NaHCO_3$ did not affect the ability to restore CBF or ATP. The level of CBF and brain pH were improved in animals that had CBF restored.

3. Defibrillation

3.1. Ornato

I expect that there will be little debate over the use of automatic defibrillators, since there are overwhelming data to support their efficacy [64,65]. The next issue is how to get them into more widespread use. In many EMS systems we have begun to find solutions to that question. Paradoxically, the in-hospital environment is still a relatively untapped territory for automatic defibrillation, with few exceptions [66].

3.2. Kaye

Several outcome studies over the past 30 years of *in-hospital resuscitation* attempts, outside special care units, have shown that survival to hospital discharge remains at 15% [67,68]. In the United Kingdom, a study of in-hospital cardiac arrests, published in 1992, which included over 3000 patients [69] reported a similar outcome of 15% survivors to hospital discharge. This study was done

before they had an organized protocol-driven ACLS program. Concerning training needs, a study by Lowenstein et al. [70] and one by Saunders et al. [71] failed to show significant improvement in survival and hospital discharge rates following ACLS training of house staff and nurses.

Outcome may be poor for several reasons [72]. In-hospital arrests, outside of the CCU, usually occur in sick patients with single or multiple organ dysfunction. Despite better acceptance of policies for withholding CPR, the federal law mandating advanced directives, and a growing body of data that allow prediction of poor outcome following arrest, many patients still receive inappropriate CPR [73]. There may be difficulty in identifying the patient in cardiac arrest in unmonitored areas of the hospital; the arrest may have occurred minutes to hours before recognition. Finally, the question remains about the benefit of ACLS training beyond defibrillation [74].

The incidence of primary VF in a monitored unit such as CCU or ICU is high. In the CCU, survival following VF arrest may approach 90% [75]. The incidence of VF in resuscitation cases on medical or surgical wards is difficult to determine because most patients will be asystolic by the time the resuscitation team gets there. I suspect that the most common cause of cardiac arrest, even in those found asystolic, is still VF [76].

The American Heart Association (AHA) has recommended early defibrillation by all first responders using AEDs as standard of care [77]. Should this not be practiced both out-of-hospital as well as in-hospital? With automated external defibrillation available in unmonitored units in the hospital, the first responder could easily provide defibrillation rather than only CPR while awaiting the arrival of the ACLS team. We conducted a study in which we trained BLS nurses to use AEDs, and demonstrated that nurses can easily be taught and will retain the skills [66]. Similar data for student nurses have been provided by McKee et al. [78].

In-hospital resuscitation should start with countershock rather than CPR steps A-B-C. We eliminated initial ventilations during the assessment steps, even though the AHA protocol says 'check responsiveness, check breathing, if absent give two breaths, and then get the AED.' But in the hospital, because of the reluctance to perform mouth-to-mouth ventilation, first responders usually run to get a bag-valve-mask device before ventilating [79]. I would rather have them get the AED! We have re-defined CPR training for all first responders as CPR-AED, and teach the use of the AED in addition to BLS to all nurses, house staff, respiratory therapists and technicians (Appendix 1, 3A). The algorithms are as follows: 'If the patient looks dead and resuscitation is appropriate, run and get the AED and call for help. If you are by yourself do not waste time with CPR steps A-B-C first, but attach and activate the AED, and if indicated, defibrillate. If someone else is there to assist, or if there is a delay in getting the AED, or the AED does not recognize a shockable rhythm, or the patient is still pulseless after defibrillation, of course do CPR steps A-B-C. But, defibrillation takes priority over CPR steps A-B-C.'

We are now looking at the effect of in-hospital defibrillation by first-responders using AEDs, on the time to the first shock and on outcome. We believe that automated external defibrillation by first responders should be practiced in all hospitals [80].

3.3. Paradis

Several years ago, when I was in Detroit, we introduced AEDs on a limited basis. Increasing survival rates with the addition of AEDs did not reach statistical significance, but we did achieve an organized ECG pattern in a significant number of patients. In a subset of patients, the amplitude of the ECG's QRS complex widened and then the heart would re-fibrillate. The AED did not work as effectively in that group, and this prevented the study from reaching statistical significance. I suspect that these patients' adrenal glands had degranulated at or before arrest, and that post-ROSC hypotension had led to re-arrest. It may not be enough to defibrillate patients rapidly if we cannot maintain them in a perfusing state. Is there something we can do for these patients?

3.4. Kaye

I cannot answer that question. In the hospital, I would hope that after the first series of countershocks by the first responder with the AED, the ACLS team would arrive to control the airway and continue treatment with the relevant algorithm [81].

3.5. Paradis

If we put AEDs into the hands of all first responders, is there anything that these providers could do, using drugs before arrival of the ALS team, for patients who respond to defibrillation attempts, but need protection against re-arrest? These patients experience what many animals in Dr Bircher's and my laboratory do, specifically, re-arrest after ROSC, if we delay vasopressor support. It is my belief that this may be more common in patients than in the laboratory because patients frequently have pre-arrest morbidity.

3.6. Brown

One of the main reasons for failure of CPR in patients is the fact that we do not treat the *underlying problem*. If the patient is in primary VF and ROSC is accomplished, why do we wait so long to give thrombolytic therapy? There seems to be a fear or trepidation about giving thrombolytics in the prehospital setting.

3.7. Vostrikov

In worldwide resuscitation practice, most of the defibrillators used at present generate *monophasic impulses*. The impulses are critically damped sinusoidal waveforms. At the same time in Russia, the quasi sinusoidal asymmetrical *biphasic impulse* is widely used [82–84].

Naum Gurvich of the Institute of General Reanimatology in Moscow was the first, in the 1940s, who suggested bipolar waveforms [85]. My report is devoted to the results of a comparison of the efficacy and safety of these two waveforms in dogs (Appendix 1, 10A). The monophasic defibrillator 'Life-pack 7' (Physio-Control Corporation, Redmond, CA) and the biphasic defibrillator of the Scientific Industrial Corporation REMA (Lviv, Ukraine) were used in this study [86,87]. The criterion of effectiveness was the transthoracic defibrillation threshold, that is, the lowest peak current and delivered energy that would terminate electrically induced VF. The duration of VF was 30 s.

Dogs weighing 14–39 kg had an average threshold current of about 11 A with the biphasic impulse and 18 A with the monophasic impulse (i.e., 64% higher). The delivered energy with the biphasic impulse was 27 J and that with the monophasic impulse was 56 J (i.e., twice as high). Thus, the biphasic impulse was more effective.

When studying statistically the relationship between body weight of dogs (range 7–39 kg) and the threshold peak current, there was a close correlation between body weight and threshold current for both impulse groups ($r = 0.86$ and 0.80, respectively). At the same time, regression analysis showed that the coefficient of the biphasic impulse regression is significantly less than that of the monophasic impulse (0.32 and 0.72, respectively). This means that when the body weight is 10 kg higher, the threshold defibrillation current for the monophasic impulse increases 7 A, and for the biphasic impulse only 3 A.

The pathologic effect of defibrillating shocks on cardiac function is also important. The criterion used to evaluate the functional damage to the heart was the duration of (reversible) ventricular asystole between countershock and first heartbeat [87]. The average duration of asystole was 1 s, after having passed the biphasic impulse through chest paddle electrodes with a diameter of 10 cm. The monophasic impulse was followed by 6 s of asystole. When we decreased the diameter of the electrodes to 4.5 cm, the inter-electrode resistance increased from 50 to 100 ohms. The peak current causing asystole was decreased significantly. With increased chest resistance, the duration of asystole with the monophasic impulse also increased. The average duration of asystole in the first group of monophasic impulses was 5 s longer than with biphasic impulses, and in the second group it was 11 s longer.

With increased resistance from 50 to 100 ohms,

the duration of the monophasic impulse doubled. The total duration of the first and second phases of the bipolar impulse did not change. In the intact heart, with unsynchronized shocks, monophasic impulses caused VF 15 times in 13 of 100 dogs, while biphasic impulses did so only four times in three of 100 dogs. Jones and Jones [88] studied excitation threshold and arrhythmias caused in cultured myocardial cells from chick embryos.

We also studied prospectively 32 patients (unpublished new data). They received 66 countershocks. Twenty-six patients received these shocks for spontaneous VF, and six patients had induced VF [83,84]. Most patients received biphasic shocks. The operator selected an initial shock energy of 10–65 J. Delivered energy ranged between 12 and 190 J, with an average of 73 ± 39 J. The average peak current was 18.6 A, ranging between 8 and 34 A. Defibrillation was successful in all patients.

According to Kerber et al. [89], monophasic impulses with peak currents of less than 18 A did not generally defibrillate, while the success rate with peak currents of 54 A or more was only 50%. The average maximal delivered energy was more than 300 J [90]. We used biphasic impulses of only 170 J. According to Gascho et al. [91], more than 240 J delivered energy causes the defibrillation rate to decline. The authors attributed this negative effect of higher energy to electrical damage of the myocardium.

In *conclusion*, our experimental and clinical results demonstrate a considerably greater efficacy and safety of the biphasic impulse, which is widely used for transthoracic defibrillation in Russia. At present, several electrophysiology laboratories in the USA are carrying out studies on the comparative efficacy of mono- and biphasic impulses for induced VF and VT, in conducting transthoracic countershocks [92]. Our studies in collaboration with Physio-Control are continuing.

3.8. Paradis

Clinically, we often underestimate the importance of the first countershock. It is not only crucial that we defibrillate the patient, but when we do it. Putting maximal effort into the very first countershock is, in my opinion, the key to a favorable outcome. There may be some injury associated with electrical countershock, so that multiple countershocks may be deleterious beyond the time delay.

3.9. Dick

Neither I nor Dr Pepe believe in the 100% efficacy of AEDs. This is for two reasons. First, when we tried to extrapolate the results which have been obtained in the US with the use of AEDs in the hands of emergency medical technicians, concentrating on the prehospital setting, we launched a study and compared under controlled randomized conditions defibrillation attempts by physicians in the prehospital setting with such attempts by paramedics or emergency medical technicians. We predicted that the nonphysicians would do better because they would arrive at the scene earlier than the physicians. This was not the case [93]. The groups were almost identical as far as outcome was concerned, with about 30% long-term survivors, despite the fact that the critical intervals in the physician group were almost twice those in the nonphysician group. Apparently this did not change the survival rate. Secondly, as we are talking about data supporting something, I would doubt today that it is justified to provide almost everybody with an AED because it has not been proven yet that this may increase long-term survival rates of patients overall.

3.10. Martens

Previous prospective European studies about prehospital defibrillation by ambulance personnel in a two-tiered system failed to reach a statistically significant improvement in the number of patients discharged alive. We conducted the following study concerning out-of-hospital defibrillation (Appendix 1, 4A): We classified 367 out-of-hospital VF patients registered by the Belgian CPCR study group during 1991 and 1992 into two groups: (1) Those who received a first defibrillatory shock by the first tier (n = 111 or 30%). (2) Those who received a first defibrillatory shock by the second tier (n = 256 or 70%). Twenty-six patients of the first group (23%) were discharged from the hospital alive, compared to only 35 (14%)

of the second group ($P = 0.02$). The patients of the 1st group were defibrillated significantly earlier, at 8.5 ± 4.4 min vs. 14.5 ± 7.5 min after the call. Percentages of witnessed arrests and bystander CPR were higher in the first group, but failed to reach statistical significance. No significant differences in the other demographic characteristics (sex, age, number of shocks delivered, time from call to first drug injection, days discharged post-CA) were found between the two groups. In our population, seven patients achieved ROSC before arrival of the second tier, of whom six were discharged from the hospital. These data confirm that rapid defibrillation is the major determinant of survival in out-of-hospital cardiac arrest due to VF.

3.11. von Planta

We conducted a study concerning VF amplitude in rats (Appendix 1, 9A). Studies in the laboratory and clinical practice have demonstrated that VF amplitude decreases during prolonged VF and that high-amplitude VF facilitates defibrillation. The purpose of this study was to determine whether precordial chest compressions (PCC) increase VF amplitude in a rodent CPR model. Ventilation was controlled in 10 invasively monitored rats. VF was induced for 4 min and followed by PCC for another 4 min. VF amplitude was determined at 3 and 4 min after onset of VF and every min during precordial chest compressions (5–8 min). Coronary perfusion pressure (CPP) was monitored continuously. During PCC we could not find a significant linear correlation between CPP and VF amplitude. VF amplitude decreased during untreated VF, but it increased during PCC. During PCC, a low CPP was associated with an increased VF amplitude. No correlation between VF amplitude and coronary perfusion pressure was observed.

4. Neurocardiology

4.1. Ornato

A number of unsolved mysteries in resuscitation relate to brady-asystole. In most cases, brady-asystole is not just vagally mediated. This may account for the poor response to atropine. There is a new discipline called neurocardiology, that concerns the connections between the central nervous system and the heart. As we think about new ideas to study, I would encourage resuscitation researchers to scan the neurocardiology literature and look at mechanisms linking derangements in the central nervous system with cardiac arrhythmias. There are interesting clues and avenues to explore.

4.2. Levine

Everything important that has been accomplished in CPR occurred by the end of the 1960s. During that time, most of the empiric regimens for drug use that we have today were described by Redding et al. [21–23,32,61,94–96] and others [6,13,18,60]. Survival rates have not improved since the first guidelines issued by the American Heart Association [13,18]. It is my opinion that in order to improve our ability to resuscitate victims of sudden cardiac death, we need to step back and look at the pathophysiology of this event. We must change the paradigm we use to understand the events that lead to cardiac arrest, as well as the factors that prevent us from resuscitating those who die from this syndrome.

As an example, we have lost track of how to treat VF, perhaps because we do not understand the process that leads to it. Lidocaine and bretylium have never been shown to be effective in cardiac arrest. Low, medium, or high-dose epinephrine does not clearly make a difference in our ability to resuscitate. Even something as simple as which buffer to use is not immediately obvious. But all of these agents are still used in our protocols. When to defibrillate, the proper energy level and form of delivery, and even who needs defibrillation is still unknown. Most investigators in the field of resuscitation are not familiar with the cellular and subcellular effects of these interventions. Perhaps it is time to call a moratorium on research that does more of the same, and call for a return to the basic science of sudden death. As an example, consider the effects of the autonomic nervous system of the heart. The anatomical distribution of the autonomic afferents and efferents has been well described and would lead us to suspect that ischemia would have a pro-

found effect on their function. In fact, the influence of the sympathetic and parasympathetic nerve supply of the heart during ischemic states has been studied extensively. On a crude level, researchers have studied the effects of cardiac denervation by ablating the vagus nerve or by ablating the left or right stellar ganglion, or both [97]. These studies have shown that gross interruption of these pathways can provoke or protect from ischemia-induced arrhythmias. These results have been confirmed in studies that more selectively interrupt autonomic pathways.

Martins et al. [98] and Zipes et al. [99,100] have demonstrated that cardiac parasympathetic fibers run under the endocardium, while the sympathetic fibers run under the epicardial surface [101]. By selectively ablating the sympathetic or parasympathetic innervation, they demonstrated that denervation clearly affects fibrillation and defibrillation thresholds. The effects vary with the type of denervation and could be protective or render the animal more vulnerable to ischemia-induced VF [98–103]. Finally, clinical evidence of autonomic instability exists. In 1972, Webb et al. [104] reported that 92% of patients had evidence of autonomic disturbances at the onset of myocardial infarction manifested as sympathetic or parasympathetic over-activity. Which effect predominates varies with the location of the infarct. Sympathetic over-activity, defined as tachycardia or hypertension, is more common with anterior infarcts. Posterior infarcts are more likely to develop sinus bradycardia, AV block, and other vagal effects.

Stepping back from the localized effects of the autonomic nervous system to a more global picture, there is a large body of evidence demonstrating a significant heart-brain interaction in sudden death [105–116]. Clinically, the influence of stress on the development of VF is well known [105–108,114–116]. Similarly, the existence of circadian rhythms for angina, infarction, and sudden death has been described [109–111]. Skinner et al. [115,116] have extended these observations and demonstrated the direct effect of the central amygdaloid nuclei on the development of cardiac ischemia-induced VF. These pathways were inhibited reversibly in a pig model using implanted cryoprobes that chilled but did not freeze the brain. Inhibition of output from this area of the brain is believed to have blocked sympathetic activity and prevented VF. When the brain was allowed to rewarm, cardiac ischemia would once again induce VF. When we cooled the area again, the pig did not fibrillate. In other experiments, adaptation to stress prevented VF as did injection of L-propranolol into the lateral ventricle of the brain [113]. Conversely, at the subcellular level, psychological stress was shown to activate intra-myocardial phosphorylase, an effect that progressively declined with adaption to the novel environment, as did vulnerability to ischemia-induced VF [115,116].

In *conclusion*, in this brief overview of neurocardiology, I have tried to demonstrate the brain's powerful effects on the heart and our susceptibility to ischemia-induced VF. Through neural cellular and subcellular mechanisms, the brain can protect or render us vulnerable to sudden death. My hypothesis is that these same pathways are involved when we try to resuscitate victims of sudden death. Through better understanding of these pathways I believe we can increase our ability to fulfill the promise of cardiopulmonary resuscitation.

4.3. Ornato

There are many novel areas that need to be investigated further. For example, we used to think that sudden death in epileptics were the result of aspiration. In many cases, the autopsy did not provide evidence of aspiration and it is tempting to speculate that it was an arrhythmia-related death. The epilepsy service at our institution just published a study [117] confirming that 15–20% of patients who are admitted to the hospital with status epilepticus are found to also have myocardial infarction and/or serious cardiac arrhythmias. Those who develop arrhythmias have a high incidence of sudden death over the next 6–12 months. Resuscitation researchers should learn more about this phenomenon.

5. CPR in obstetrics

5.1. Patel and Ramanathan

There are special situations in which the normal rules for ACLS must be modified. One of these is

the pregnant woman who goes into cardiac arrest (Appendix 1, 5A). There is a paucity of research related to cardiac arrest and CPR in pregnancy [118]. CPR in pregnancy is important because successful resuscitation results in the saving of two 'hearts and brains too good to die.' CPR is required in about one in 30 000 pregnancies [119]. About 50% of maternal deaths are due to acute potentially treatable causes, including hemorrhage, pulmonary embolism, trauma, congenital or acquired cardiac disease and iatrogenic causes including anesthesia and drug therapies. The differences between CPR in adults in general and CPR in late pregnancy are underemphasized in the resuscitation literature. The altered anatomy and physiology of pregnancy affects every step of resuscitation.

There are no systematic studies on the hemodynamics of external CPR [120] — as performed in pregnant animals or humans. Most of what is known clinically relies on the physiology of pregnancy. Aorto-caval compression by the pregnant uterus in the supine position impedes venous return, produces hypotension in the supine position, and decreases the effectiveness of thoracic compressions. The enlarged uterus poses an obstruction to forward blood flow, especially when arterial pressure is low during cardiac arrest and CPR. To increase venous return, the uterus must be displaced to the left. Unfortunately, this also causes the torso to roll. Optimal chest compressions in the supine position, even in the non-pregnant patient, produce a cardiac output of 30% or less of normal [121]. It is not known whether cardiac output produced by chest compressions with the patient in the lateral position is sufficient for maternal or utero-placental circulation.

Further, what is the best method for achieving uterine displacement? What is the angle of deflection from the horizontal that optimizes venous return and still allows for effective chest compressions? What about the use of mechanical chest compression devices in this type of setting? Is there any role for open-chest CPR in pregnancy?

Another topic is drug therapy. Drugs administered during maternal CPR, especially epinephrine and $NaHCO_3$, can interfere with the transplacental gas exchange. What is the role of $NaHCO_3$ in this situation? Given the maternal propensity for hypoxemia and hypercapnia, which lead to decreases in utero-placental perfusion and resulting acidosis in the baby, perhaps the pregnant patient benefits from $NaHCO_3$ sooner than the normal adult. Could the administration of $NaHCO_3$ to the mother result in increased fetal acidosis as a result of the transfer of CO_2 across the placenta? The answers to these questions are not known.

The most important consideration in maternal CPR is that of (perimortem) cesarean section. The recommended timing and sequence of resuscitation are based on clinical reports. There are no experimental studies on this subject. Clinical algorithms for the performance of ACLS in pregnancy should be developed, for the management of cardiac arrest in pregnancy related to gestational age. This information should be disseminated throughout the community to those who are involved in the care of pregnant patients. Hospitals in which deliveries are performed should have policies, personnel, and equipment necessary for the performance of maternal CPR. The responding resuscitation team should consist of an anesthesiologist, obstetrician, and neonatologist. Obstetrical and neonatal ICU nurses should also be available to provide care for the mother and baby.

5.2. Paradis

The prehospital EMS personnel treating a pregnant woman at term who develops cardiac arrest, act as in a traumatic emergency, using a scoop and run approach. Because of anatomic and hemodynamic changes associated with pregnancy standard external chest compressions may not be effective. I wonder why, during the time the obstetrician is trying to get the baby out, we do not advocate open-chest CPR for the mother. This may be particularly important because of the high incidence of pulmonary embolism in such cases.

5.3. Patel

The major problem is what is practical. If you have all needed personnel immediately available, open-chest CPR is possible. In circumstances in which cardiac arrest in a pregnant patient usually occurs, as during the night, with only obstetrician

and anesthesiologist in-house, open-chest CPR may be problematic. The most definitive way to improve the maternal circulation is to deliver the baby rapidly, and to continue with external CPR during delivery of the baby while the cesarean section is in progress. Under these circumstances, the incision would be a rapid vertical midline incision through skin, fascia, and the uterus as well.

5.4. Kaye

Several discussants favor initiation of open-chest CPR very early and immediate cesarean section. In these situations the tools for open-chest CPR are immediately available. I do not understand why obstetricians, who are surgeons, could not be taught open-chest CPR.

5.5. Ramanathan

I do not think it is a mistake to take the baby out first, as quickly as possible. In maternal cardiac arrest the baby needs to be delivered. I take exception to first initiating open-chest CPR before cesarean section. We do teach how to do cesarean section first. If you do not get the baby out within 5 min, you are not going to save the mother or the baby. The inferior vena cava is completely compressed. I would open the abdomen first, not the chest. Once the baby is born and the maternal circulation is restored, there may be no need for thoracotomy.

5.6. Weil

We have heard many opinions. Are there data on survival? If you do not resuscitate successfully, and leave the infant in situ, that infant cannot survive. The 5-min period (of maximal cardiac arrest duration to be reversible) is documented. I do not think anything else is documented. We have heard about the supine hypotensive syndrome, a well documented impediment to venous return in the pregnant patient.

6. Comments

6.1. Paradis

I would like to describe a brief scenario for you to respond to. It involves the ACLS steps D-E-F, the subject of this session. You arrive at the scene of a cardiac arrest where the paramedics have arrived before you. The arrest happens right in front of them in a person who appeared to be in no significant distress before the event. When you arrive, the patient is intubated and the paramedics have begun to ventilate him. They have placed an antecubital i.v. infusion which is working properly. They applied quick-look paddles and found course VF. They looked at the patient's wrist and saw a bracelet saying 'If found in cardiac arrest, please do not follow standard guidelines, do what you think is optimal therapy.' What would be the optimal therapy you would use? What dose of epinephrine, where would you place the defibrillator electrodes, etc.?

6.2. Ornato

Presently I would escalate countershocks and epinephrine and push more forcefully on the chest if I have nothing else available.

6.3. Bircher

I would like to underscore the importance of rapid escalation of drugs and countershocks. If what you are doing is not working, move on quickly to something else. Move on to a higher dose of epinephrine. In this case I would not give $NaHCO_3$ because there is low probability of significant metabolic acidosis. If in the prehospital setting you know you can rapidly transport him rapidly to a place where emergency cardiopulmonary bypass is available, you should support him maximally during transport.

We are still in the realm of unproven, unavailable methods. Wave-form analysis may help in judging whether the heart is in good form for countershock to be effective, and could also guide the administration of epinephrine.

6.4. DeLooz

I want to mention another case, one I have witnessed recently in my department [122]. The patient, a 29-year-old man, had collapsed during rugby training, regained consciousness, and was brought by car to the emergency department by

one of his fellow players. On admission the patient was agitated and in profound shock, without palpable peripheral pulse. He reported no pain. Chest radiograph showed a slightly enlarged heart. The ECG showed an idioventricular rhythm, with runs of VT. Arterial pH was 7.25, P_{CO_2} 14 mmHg, bicarbamate −6.1, and PO_2 174 mmHg. When echocardiography became available, the patient's pupils dilated and CPR had to be initiated. The cardiac rhythm showed electromechanical dissociation. Without any firm diagnosis, but with the tentative diagnosis of pulmonary embolism, the patient was put on extracorporeal membrane oxygenation. On opening the chest, an old anterior and an old posterior wall myocardial infarction were found, but the pulmonary artery was patent. Because the patient's pupils reacted to light and the patient required anesthesia, a biventricular assist system was installed. Without assist the patient could not be weaned from bypass. The understanding was that only if the patient was fully conscious the next morning, would he be put on the emergency cardiac transplant list. The patient regained consciousness during the night. A cardiac transplant was performed the following evening. He recovered completely and 20 months later he was fully active.

6.5. Safar

Standard external CPR-ALS can achieve ROSC in previously healthy dog hearts after up to 20 min normothermic VF [53] or asphyxia-induced no-flow [54]. In diseased human hearts such ROSC attempts fail in over 50% of cases [1–3,6,13, 18,123]. 'Ultra-advanced' methods for achieving ROSC are needed for cases of long no-flow time or diseased hearts. These methods include open-chest CPR [50,121,124] and emergency cardiopulmonary bypass (CPB) [125–128]. The latter can achieve ROSC in dogs after up to 20 min normothermic VF no-flow [125].

Open-chest CPR is superior to closed-chest CPR not only in terms of perfusion pressure, cardiac output, and ROSC in patients [121,124], but also in terms of outcome in dogs [50] and patients [124]. Recently, in out-of-hospital cardiac arrest patients in Belgium, after 20–30 min of unsuccessful external ACLS attempts at ROSC by ambulance physicians, open-chest CPR achieved ROSC (unpublished data by L. Corne and P. Idrissi of Brussels; and A. Mullie et al. of Brugge). Due to prolonged external CPR preceding thoracotomy, conscious survival was not achieved in these patients. Open-chest CPR attempts in the field were accepted positively by observers. Out-of-hospital and in-hospital trials are justified of switching immediately to open-chest CPR when a brief attempt at external ACLS fails to achieve ROSC.

Closed-chest emergency CPB by veno-arterial pumping via oxygenator, with use of a portable device, proved superior to standard ACLS in dog models, in terms of ROSC and neurologic outcome [125]. CPB might be used to 'bridge' over hours or days, the sick arrested hearts of out-of-hospital victims of sudden cardiac death, to evaluation, recovery from stunning, coronary vascularization, or heart replacement [125–127]. Clinical feasibility trials of CPB in the emergency department had so far only limited success because of late decisions to switch from external ACLS attempts to CPB, and because of an average vessel access time by cutdown on the groin of over 10 min [128]. A more rapid method for vessel access is needed. Out-of-hospital trials of emergency CPB by ambulance physicians are justified.

6.6. Ornato

These additional comments remind us not to forget lessons which can be learned from individual cases.

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Appendix 1

Abstracts of the International Resuscitation Research Conference in Pittsburgh, May 1994, available from P. Safar, SCRR, University of Pittsburgh, 3434 Fifth Avenue, Pittsburgh, PA 15260, USA.

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