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31st Bethesda Conference

Emergency Cardiac Care (1999)
September 13–14, 1999

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BETHESDA CONFERENCE REPORT

31st Bethesda Conference: Emergency Cardiac Care (1999)*

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This Conference, sponsored by the American College of Cardiology, was held at the Heart House, Bethesda, Maryland, September 13–14, 1999.

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31ST BETHESDA CONFERENCE

Emergency Cardiac Care: Introduction

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There are more than five million visits to Emergency Departments in the U.S. each year for evaluation of chest discomfort or other symptoms suggesting acute cardiac ischemia. These evaluations generate over $10 billion in hospital costs alone. In addition, over one million Americans have an acute myocardial infarction each year, and >250,000 people die of sudden, unexpected cardiac arrest.

Treatment of these conditions can be broadly termed "Emergency Cardiac Care." The American College of Cardiology has recognized this specialized area for decades. In fact, the 13th Bethesda Conference in 1981 was devoted to this subject (1). At that time, the principal focus was on the identification and management of patients with an acute cardiac emergency. Consensus guidelines were developed for "optimal emergency cardiac care before hospital admission, in the Emergency Department, and in the 6 h after hospital admission."

Since then, there have been major advances in the prehospital and in-hospital treatment of patients who have an acute coronary syndrome or who experience sudden, unexpected cardiac arrest. Prehospital care has improved markedly with the development of effective Emergency Medical Services (EMS) systems. Out-of-hospital defibrillation capability, in its relative infancy in 1981, has become the standard of care of first-responding fire engine companies and ambulances in most urban and suburban locales. Now some cities, such as Rochester (Minnesota), Pittsburgh and Cincinnati, even equip law enforcement officers with automated external defibrillators. We now have security officers in most Las Vegas casinos and airline flight attendants aboard many U.S. commercial aircraft who are trained and equipped to defibrillate cardiac arrest victims.

The 31st Bethesda Conference represents consensus opinions and recommendations of experts from a variety of disciplines on 1) the initial management of patients with sudden, unexpected cardiac arrest; 2) the initial evaluation and treatment of patients who present with symptoms suggesting the presence of an acute coronary syndrome; and 3) the facilitation of emergency cardiac care research requiring a waiver of informed consent. The principal focus of the conference was not on the development of clinical practice guidelines, but rather on a modified Delphi approach used to develop consensus opinions and recommendations on critical questions for which absolute or hard data are incomplete. Conference deliberations occurred in each of the three areas just noted. Specific discussions on the initial evaluation and treatment of patients with symptoms suggesting the presence of an acute coronary syndrome were divided into prehospital and in-hospital components.

Since 1981, there have been significant advances in cardiopulmonary resuscitation (CPR) and defibrillation. Although there is now clear evidence showing that bystander CPR significantly increases neurologically intact survival from cardiac arrest, several studies have documented reluctance on the part of the general public to perform mouth-to-mouth resuscitation on a stranger (2–4). A major topic of discussion at the 31st Bethesda Conference was whether the current national CPR guidelines for lay persons should be simplified, by not including a recommendation for bystanders to perform mouth-to-mouth resuscitation. Surprisingly, there is an increasing body of scientific evidence suggesting that it may not be essential to provide such ventilation during the first few minutes of cardiac arrest due to ventricular fibrillation (VF) (5–7). The present state of knowledge supports consideration of an etiology-based approach for CPR: 1) ABC CPR for asphyxial cardiac arrests and 2) chest-compression-only CPR for initial treatment of VF by the lay public. Perhaps the advancement that will have the greatest impact has been the development of the automatic external defibrillator. Specific recommendations are made (see later outline).

There have also been major advances in the recognition and treatment of patients with an acute coronary syndrome. Several of these advances were discussed in detail at the 31st Bethesda Conference, and several new recommendations were made regarding application of these new therapies in the prehospital and Emergency Department setting. There are detailed discussions on the complex issue of how to evaluate patients with chest discomfort, as well as a review of the diagnostic technologies and approaches to the initial management of patients with a suspected acute coronary syndrome.

Despite these advances, further progress has been hindered by the difficulty of performing emergency care research on impaired human subjects who are not able to give informed consent. This is particularly problematic in the area of cardiac arrest research, where all of the patients are unconscious and where promising new drugs or devices must be used early if they are to have any hope of success. In most cases, there is insufficient time to contact the family member to get consent. In 1996, Congress issued "Final Rules" (21 CFR 50.24) allowing for a waiver of informed

consent under very limited circumstances. Unfortunately, these rules have also created a new set of obstacles for researchers. Specifically, they require a vaguely defined community consultation and a public disclosure program. At the 31st Bethesda Conference, there were extensive discussions on this topic, and substantive new recommendations have emerged.

Finally, perhaps the most significant element of this exciting conference was the multidisciplinary representation of its participants. In 1981, cardiologists dominated the conference. In 1999, cardiologists still accounted for the largest percentage of participants. However, for the first time at a Bethesda Conference, there were a large number of emergency physicians. In addition, the conference included internists, family practitioners, prehospital care and/or fire service personnel, representatives of government agencies (including the National Heart, Lung, and Blood Institute of the National Institutes of Health and the Food and Drug Administration [FDA]), pediatricians, specialists in nuclear cardiology and echocardiography, basic science researchers, nurses, epidemiologists and educators. The recommendations derived from this exciting conference truly represent a broad range of relevant perspectives.

The Steering Committee of the 31st Bethesda Conference recommends that the American College of Cardiology formally endorse the following:

1. An educational program for the public and Institutional Review Boards (IRBs) on the importance of and the means to obtain a waiver of informed consent for research on patients who have emergency cardiac conditions.
2. Physician education on how to cost-effectively risk stratify the heterogeneous groups of patients who present with signs and/or symptoms of an acute coronary syndrome.
3. Patients with myocardial infarction and hemodynamic compromise, cardiogenic shock or other high risk criteria should be triaged to medical facilities that have 24 h staffed cardiac care services including emergency revascularization (percutaneous coronary intervention and coronary artery bypass graft surgery) and hemodynamic support available, provided ambulance transport duration is not excessive (>30 min). Triage should be performed as soon as possible, preferably in the field or in the nearest Emergency Department, depending on the medical community.
4. There is now compelling evidence that automatic external defibrillators (AEDs) can be safe and effective when used by first responders, particularly if the time for traditional EMS response is too long.
5. Continued research is needed in all areas of emergency cardiac conditions, including each link in the chain of survival.

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TASK FORCES

Task Force 1: Cardiac Arrest

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Out-of-hospital or prehospital sudden cardiac arrest accounts for an estimated 250,000 events each year (8). The majority occur secondary to cardiac arrhythmias. A small number, however, are due to asphyxia. The importance of bystander CPR and early defibrillation in survival from out-of-hospital cardiac arrest has been well documented. Survival rates as high as 90% have been seen with early defibrillation within the first minutes of cardiac arrest (9). The likelihood of meaningful survival to hospital discharge decreases by ~10% per minute thereafter. This has led to the concept of the "chain of survival": early access, early CPR, early defibrillation and early advanced life support. Each link is needed to improve cardiac arrest survival rates. Geographic constraints, population density and EMS organizations are associated with meaningful survival rates from out-of-hospital cardiac arrest from as low as 0% to as high as 44% (10). Survival rates of ≤10% are the norm in many areas.

Recent studies have shown the changing demographics of out-of-hospital cardiac arrest (11–13). The incidence of primary VF is declining, whereas the initial cardiac arrest rhythm is increasingly bradyasystolic. This parallels an increase in both the age-related and concurrent comorbid heart diseases, especially congestive heart failure, in the population of cardiac arrest victims.

BASIC LIFE SUPPORT CPR: IMPROVING BYSTANDER CPR BY LAY RESCUERS

Standard, basic CPR (ABC CPR) is a coordinated integration of **A**irway management, rescue **B**reathing and chest compression-induced **C**irculation. This technique has proven to be life saving. However, CPR is performed infrequently by bystanders, and when it is performed, the quality is often disappointing. Insufficient force, inadequate rate and interruption of chest compressions are particularly significant problems. It is increasing clear that ABC CPR is a complex psychomotor technique, and therefore it is difficult to teach, learn, remember and perform under the best set of circumstances. New educational approaches, including video-based and home-learning systems, with more opportunity for skill mastery, are under investigation to address this dilemma (14). A significant effort to educate family members of high risk individuals is also warranted. The need to simplify basic life support (BLS) CPR is now well recognized. It has been documented that lay persons can neither remember nor perform ABC CPR as presently taught (15–18). Accordingly, proving the efficacy of simplified techniques should be a high priority.

Routes to CPR simplification. Existing data support several simplifications in BLS. Instruction to place the rescuer's hands "in the middle of the victim's chest and push" have resulted in hand positioning comparable to that of the previous method of careful landmark identification and measurement from the xiphoid process (19). European studies have shown the futility of asking lay persons, paramedics and even some physicians to judge the presence or absence of a pulse in assessing for adequate circulation (19,20). Elimination of the pulse check seems reasonable.

Cardiopulmonary resuscitation with chest compressions only (i.e., no assisted ventilation) has been proposed as one simplified technique that may encourage increased bystander CPR. Such a modification makes CPR easier to learn and to master, and it alleviates the fears and concerns associated with mouth-to-mouth contact. Animal studies have established that prompt initiation of chest compressions without assisted ventilation for 8 to 12 min can be as effective as ABC CPR with respect to 24 h survival and neurologic outcome after VF (21–25). Immediately after an acute fibrillatory cardiac arrest, aortic oxygen and carbon dioxide concentrations do not vary from the prearrest state, because there is no blood flow and aortic oxygen consumption is minimal. When effective chest compressions are initiated, this oxygenated blood flows from the aorta to the coronary circulation. Moreover, chest compression–induced gas exchange and active gasping during CPR are well documented (22,23,25). Importantly, these studies have documented no outcome disadvantage with less than optimal gas exchange from chest compressions alone, particularly when associated with active gasping during CPR.

Two important clinical studies support the use of chest-compression-only CPR for VF cardiac arrest. The Belgian Cerebral Resuscitation Group (26) prospectively evaluated 3,053 prehospital cardiac arrest victims. Physicians on the ambulance evaluated the quality and efficiency of bystander CPR. Good-quality chest-compression-only CPR and good-quality chest compressions plus mouth-to-mouth rescue breathing were comparably efficacious, and both were more effective than no bystander CPR.

Hallstrom et al. compared chest compressions alone to chest compressions plus assisted ventilation in the setting of dispatcher-directed telephone-assisted bystander CPR when the dispatchers determined that the bystander or caller did not know CPR (A. Hallstrom, personal communica-

tion, September 9, 1999). They randomly instructed these nearly 500 bystanders to provide chest compressions alone or chest compressions plus assisted ventilation. Survival to hospital discharge was 10% after chest compressions plus assisted ventilation and 14.5% after chest compressions alone ($p = 0.09$). Chest compressions alone was certainly not worse than chest compressions plus assisted ventilation, and the trend suggests it might be better.

Optimal BLS for asphyxial arrests is quite different. Asphyxia results in progressive oxygen consumption and carbon dioxide and lactate production before cardiac arrest. Therefore, adequate myocardial oxygen delivery during CPR for an asphyxial cardiac arrest requires re-establishment of arterial oxygenation and improvement of pH through adequate gas exchange in the lungs, as well as myocardial perfusion. Chest compressions plus rescue breathing is the treatment of choice for asphyxial arrest. However, laboratory and clinical experience suggests that patients with asphyxial cardiac arrest can sometimes be resuscitated with ventilation alone or compressions alone, despite a history of pulselessness and unresponsiveness (i.e., it is better to do "something" than "nothing") (27).

The present state of knowledge supports consideration of an etiology-based approach for CPR: 1) ABC CPR for asphyxial cardiac arrests and 2) chest-compression-only CPR for the initial treatment of VF by the lay public. Patients with witnessed sudden collapse and adults with unwitnessed arrests could be assumed to have VF, whereas patients with a submersion event or a foreign body aspiration or children with an unwitnessed arrest should be assumed to have an asphyxial arrest.

Defibrillation first versus CPR first by the lay health care provider. Ventricular fibrillation is uniformly fatal without defibrillation. Immediate defibrillation is the treatment of choice for a short episode of VF; the success of defibrillation decreases dramatically with the passage of time, presumably because of continued ischemia and progressive imbalance of myocardial oxygen supply and demand. Conversion to a perfusing rhythm with the first series of countershocks is a major determinant of survival from VF (28), yet the rate of such conversion with the first shock diminishes over time. Should a brief period of CPR be provided before defibrillation attempts for prolonged VF? Experimental animal studies have suggested that precountershock CPR for prolonged cardiac arrest can improve the defibrillation rate and rate of initial successful resuscitation as compared with immediate defibrillation attempts (29).

A recent prospective, observational investigation suggests that precountershock CPR for 90 s improves survival (30). After routine availability of AEDs, the overall survival rate from prehospital VF did not improve in Seattle, despite a 3 to 4 min shortened time to defibrillatory shock in most cases. Accordingly, Cobb et al. (30) compared an EMS protocol to provide an initial period of ~90 s of CPR before automated analysis of cardiac rhythm with defibrillation first. Survival improved from 24% (155 of 639) to 30% (142 of 478) ($p = 0.04$). As predicted, the survival benefit was more impressive when the initial response interval was >4 min (17% [56 of 321] vs. 27% [60 of 220]) ($p = 0.01$).

MANAGEMENT OF VF/VT

Before Hospital Admission

Need for prospective, randomized trials. Prospective, randomized trials need to be designed and funded to assess the effectiveness of BLS/defibrillator capability in diverse settings. Studies should follow the Utstein style and must determine the effect of any changes on the eventual survival of an integrated functioning individual; for this, particular attention needs to be given to the reporting of neurologic outcomes. The characteristics of the population being served by the EMS system must be well defined. Intervals from collapse to bystander CPR and collapse to defibrillation must be carefully assessed. Finally, all aspects of the links in the "chain of survival" need to be carefully documented. All these data points, in the Utstein template, are required if we are to compare the results of one study with those of another. Armed with such data, the medical profession will be in a better position to advise government and private industry as to the most efficacious and cost-effective manner of addressing the challenge of out-of-hospital cardiac arrest.

Early defibrillation. USE OF AEDS BY FIREFIGHTERS AND EMERGENCY MEDICAL TECHNICIANS. The development of AEDs has been a major medical advance. Their development not only holds the promise of early defibrillation, but also decreases the level of training necessary for personnel to defibrillate the out-of-hospital cardiac arrest victim. Since 1979, emergency medical technicians (EMTs) have been trained to use either manual or automated defibrillators. At about the same time, the use of AEDs by minimally trained first responders (usually firefighters) became more frequent. A review of pertinent studies evaluating firefighters and others using AEDs is given in Table 1. In general, adding firefighter or EMT defibrillator capability to existing advanced cardiac life support (ACLS) paramedic response led to improved survival rates, although these data are mainly derived from studies done in Seattle and King County, Washington. It is unclear whether all areas will achieve similar benefit.

USE OF AEDS BY LAW ENFORCEMENT PERSONNEL. Law enforcement personnel provide cardiac arrest first-responder care in an increasing number of communities. Recently, this has often included training and equipping with AEDs. The number of published studies evaluating law enforcement defibrillation is limited. Table 1 reviews these studies. The two published studies have shown variable results in time response intervals and survival with law enforcement AED use (28,36). Use of AEDs by law enforcement personnel needs to be supported by the chain of survival if benefits are

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Table 1. Automatic External Defibrillators by Nonmedical First Responders

Provider	Intervention	Study Type	Outcome	References
Firefighter	BLS/ defibrillation	Meta-analysis	Improved survival to hospital discharge	31–33
Police	Defibrillation	Historic control	Improved survival as compared with baseline	28,34–39
Airline personnel	AED	Observational study	Significant survival rate (33%)	40–42
Casino personnel (trained security guards)	AED	Observational study	Significant ROSC rate (70%)	43,44

ROSC = return of spontaneous circulation.

to be realized. In areas where time intervals to defibrillation are not altered with law enforcement AED use, no benefit should be expected.

DEFIBRILLATION ABOARD COMMERCIAL AIRCRAFT. The number of deaths per year on commercial airlines due to medical emergencies is not well defined, but estimates range from 72 to 1,000 per year, with most of them being sudden (40,45).

A number of factors unique to airline travel may exacerbate medical conditions, including stress of flying, exertion in getting from one gate to another (especially when carrying luggage), circadian disruption and reduced oxygen in the cabin (equivalent to 6,000 to 8,000 feet). Furthermore, the aircraft cabin is poorly designed for recognition and treatment of cardiac arrest. The most important limitation in delivering treatment to cardiac arrest victims has been the lack of access to defibrillation. Under the best of circumstances, it takes 20 min to divert for an emergency landing and another 10 to 15 min to reach a gate.

In 1990 and 1991, Virgin Atlantic and Qantas airlines, respectively, began placing AEDs on their aircraft. There were 27 deaths on Qantas aircraft, and only 16 (59%) of these were "witnessed." The initial rhythm was asystole or pulseless idioventricular rhythm in 21 arrests (78%). Six passengers were in VF, with five immediately converted and two surviving long term (40). In addition, Qantas placed AEDs near its terminal gates. There were 19 arrests in the terminal, all witnessed, with 17 (89%) revealing VF as the initial rhythm. Four of these patients (24%) survived long term. In comparison with the experience aboard aircraft, the higher percentage of those with VF as the initial rhythm and the longer term survival reflect the fact that cardiac arrest in the terminal is more likely to be recognized and treated immediately.

In July 1997, American Airlines became the first U.S. carrier to place AEDs aboard its aircraft, with flight attendants trained in AED use. In the first nine months of the program, the AED was used on cardiac arrest victims aboard the aircraft 42 times and in the terminal on six occasions. Seven individuals were in cardiac arrest: four were in asystole or agonal rhythm and three had VF. One of the three patients with VF has survived long term. It is important to note that the device was placed during stable rhythms in 41 individuals, but no inappropriate shock was advised or delivered (41).

EXTERNAL DEFIBRILLATORS IN CASINOS. Security officers in the gaming establishment can use AEDs to achieve collapse-to-defibrillation intervals shorter than those feasible with traditional prehospital EMS systems. Security officers trained by the Clark County Fire Department (Nevada) yielded mean collapse-to-defibrillation intervals of 2.2 min in 10 cases of witnessed VF. Seven (70%) of the 10 victims survived to hospital discharge (43). The program has subsequently been expanded, with the result that later adopters of the program have demonstrated longer collapse-to-defibrillation intervals and lower rates of survival after witnessed VF. The following conclusions can be drawn from this experience:

1. Rapid defibrillation can be achieved by appropriately trained and motivated casino security officers, resulting in high rates of survival.
2. Sufficient devices must be installed and located on site to enable the arrival of an AED at the victim's side in $\leq$3 min.
3. The interval from call for assistance to arrival of an AED must be tested prospectively from a representative set of locations on each site.
4. Optimal initial and refresher training intervals for nontraditional defibrillation providers remain to be established.
5. Integration of rapid defibrillation programs with local EMS services is necessary.
6. Physician oversight of casino defibrillation programs needs to be addressed.

USE OF AEDS AT GATED COMMUNITIES, RESORTS AND LARGE PUBLIC GATHERINGS. Public access to AEDs has been implemented in a number of Palm Springs country clubs under the auspices of a Coachella Valley-Wide Resuscitation Project (M. Weil, personal communication,

1999). Over the past four years, 10 golf resorts have acquired AEDs as part of this community resuscitation program. A total of 233 security and club personnel were trained (23.3 persons per site); 29 defibrillators are currently in use (2.9 defibrillators per site). A population of 16,640 individuals is covered (averaging 1,664 persons for each site). The mean age of this population is 63.7 years (range 54 to 82). One defibrillator covers 574 individuals. There is one defibrillator for an average of eight trained rescuers. The cost of implementation was $11,030 per club, including training, or ~$6.62 per member. Annual expenses were ~10% of the implementation cost ($1,100 per club and 66 cents per member). Club personnel arrive at the scene within 3.5 min (range 1 to 5), and professional rescuers after an additional interval of 6 min (range 4 to 8). The AEDs have been used on six occasions. Defibrillation was required and successfully resuscitated one victim before the arrival of professional rescuers. The victim survived with hospital discharge and no neurologic impairment. The remaining five cases represented preparedness to defibrillate in settings of acute dyspnea (n = 4) and syncope (n = 1).

LAY PUBLIC DEFIBRILLATION—BARRIERS AND SOLUTIONS. Although the concept of lay public defibrillation is appealing, there are certain barriers to consider. Is it possible that use of AEDs by lay rescuers may harm either the patient or the operator? What is the likelihood that some collapse will be misdiagnosed as VF? Previous work has shown that the rhythm detection algorithms in the AED devices are excellent for distinguishing VF and non-VF rhythms. In one out-of-hospital cardiac arrest series, 103 of 106 "shockable" rhythms were recognized and a shock was delivered (46). The three cases of VF that were not shocked were all in-patients with pacemakers, where the pacer spikes were superimposed during VF. In contrast, no shock was advised or delivered in all 950 cases of "nonshockable" rhythms, including asystole (427 [45%] of the 950). How much harm is done to a cardiac arrest victim who is shocked mistakenly? These and a number of other questions also remain. Can VF be caused by a mistaken shock? What level of defibrillation should be used for children? If a lay person is harmed by improper defibrillation, who is liable?

It is probable that the selected lay person who is highly motivated and capable of operating a defibrillator will need to undergo retraining. Laws need to be passed to indemnify individual operators, training centers and their personnel and locations where defibrillators are used. Such "good Samaritan" laws are currently in place in some states, but not all. Federal statutes may also be needed.

An additional cadre of questions arises around the actual administration of lay public defibrillation programs. Who will control the development and implementation of defibrillator programs for the lay public? Organizations with appropriate physician expertise, such as the American College of Cardiology (ACC) and American Heart Association (AHA), could assume leadership.

USE OF AEDS BY NONTRADITIONAL PROVIDERS. The potential efficacy of early defibrillation by nonmedical first responders has been demonstrated by numerous studies. There now exists compelling evidence that AEDs can be safe and effective when used by first responders, including police, firefighters and first-tier EMS providers. However, although the results are largely favorable, they are not uniformly so. The studies without favorable results highlight the importance of the incremental time gained by employing nontraditional providers of AEDs, as well as the importance of all links in the "chain of survival," to obtain improved results with early CPR and early defibrillation. One important yet unresolved issue is the proper interposition of CPR and incorporation of AEDs. Should defibrillation always take precedent or should a period of CPR sometimes be done before defibrillation attempts? Experimental laboratory studies, as well as one recently published study in humans by Cobb et al. (30), indicated that for individuals with cardiac arrest >5 min, a short duration (60 to 90 s) of chest compression is indicated before attempting defibrillation.

The need for AEDs in large populations will depend on the number of those at risk. In 1986, AEDs were made available at the World's Fair in Vancouver, British Columbia. With 22 million visitors, there were only five cardiac arrests, two of which were due to VF and were successfully treated (47). The AEDs will be most effective in high risk populations.

An example of a high risk population appears to be elderly patients at casinos. It appears that AEDs can be effectively used in these special circumstances by nontraditional first responders. The use of AEDs by spouses and family members of patients at high risk for cardiac arrest has been tried, but has been largely superceded by the development of effective implantable cardioverter-defibrillators.

Much work remains to be done before we can confidently suggest the optimal method for 1) deployment of defibrillators; 2) training of nonmedical responders; and 3) methods of control and supervision of AEDs. The answers to these problems will vary widely depending on geographic constraints and population density, as well as population risks. Rural, suburban and urban systems will undoubtedly need to be designed very differently.

Use of AEDs in ambulatory care facilities. There are no specific guidelines from accrediting organizations that provide recommendations for types of equipment and training requirements in nonhospital-affiliated outpatient facilities. Ambulatory care centers attached to hospitals fall under the auspices of the Joint Commission for the Accreditation of Health Care Organizations (JCAHCO) and use its new guidelines for hospital-based resuscitation practices.

Little research has been done, to date, regarding emergency cardiac care practices and preparedness in the outpatient setting. A study of primary care provider offices revealed that only 65% of offices had a physician or nurse

trained in BLS, and only 39% had anyone trained in ACLS (48). Defibrillation capability was only present in 6% of offices. Thirty-five percent of offices had at least one medical emergency in the two years before the study. Cardiopulmonary resuscitation was required in two cases and one death occurred. A cost analysis of providing AEDs and training of two personnel in BLS/defibrillation over a 10-year period only came to an additional 3 cents per outpatient visit.

Ambulatory care centers connected to hospitals typically do not have adequate on-site resuscitation capabilities. Appropriate equipment is lacking in many cases, and there are significant personnel issues. Most physicians and nurses in this setting are not trained in either BLS/defibrillation or ACLS. Much of the physician staff is transient throughout the day, which leaves the nursing staff as the only consistent presence. It is imperative that the personnel most likely to witness a cardiac arrest have the appropriate equipment and training to respond promptly. The most likely way to accomplish this is with the use of AEDs.

There is an emerging expectation from the public that early defibrillation capabilities be widely available. Given that the volume and acuity of patients seen in the ambulatory care setting are increasing, that staff has variable presence and training, that early defibrillation is the intervention most likely to improve survival in adult cardiac arrest and that cost is relatively low, all outpatient facilities should review their current preparedness for cardiac arrest and consider implementation of an early defibrillation program utilizing AEDs.

Hospital-Based Resuscitation

It has often been assumed that hospitals function as self-contained EMS systems with respect to their management of cardiac arrest, because there is an abundance of health care providers in a defined environment. Unfortunately, because of this incorrect assumption, the process of resuscitation in the hospital has traditionally received less attention. The JCAHCO developed standards related to in-hospital resuscitation that were released in December 1998, effective January 1, 2000. The new standard TX.8 mandates that effective resuscitation practices be available throughout the hospital. The intent of TX.8 is that the mechanisms for effective resuscitation include:

1. Appropriate policies, procedures, processes or protocols governing the provision of resuscitation services.
2. Appropriate equipment placed strategically throughout the hospital close to areas where patients are likely to require resuscitation services.
3. Appropriate staff who are trained and competent to recognize the need for and use of designated equipment in resuscitation efforts.
4. Appropriate data collection related to the process and outcomes of resuscitation.
5. Ongoing review of outcomes related to resuscitation, in the aggregate, to identify opportunities for improvement of resuscitation efforts.

It is likely that these new guideline requirements for ongoing accreditation will stimulate hospitals to critically evaluate the process by which resuscitation is performed, as well as outcomes. The majority of U.S. hospitals are deficient in one or more of these areas and will require significant restructuring of their resuscitation efforts, including early defibrillation capability with AEDs.

A comprehensive hospital-based resuscitation program requires administrative and clinical support. A committee should be formed consisting of members representing different areas of participation in the resuscitation effort. This committee needs to have direct-line authority to someone within the hospital administrative structure who cannot only support improving the process of resuscitation from both the financial and procedural standpoint, but who can also follow through to make sure that appropriate policies are enforced. The committee also needs to have a strong quality improvement program to ensure that the process of resuscitation is appropriate and to provide a basis for feedback to personnel on the resuscitation team. The JCAHCO now requires both of these processes.

The physical layout of the institution must be evaluated, along with the patient population and staffing, to determine the best way to provide timely defibrillation. Hospital practice must shift from having CPR as the sole form of BLS to including defibrillation as a BLS skill. Delayed defibrillation occurs much less frequently in critical care areas than on general floors, and this should be taken into account when equipment choices are made. The AHA recommends that hospitals should aim for a goal of delivering the first shock within 2 min of when the arrest was determined in noncritical care areas (49).

There are adequate published data detailing that nurses can be trained to use an AED appropriately and that they can retain these skills over time. However, merely having AEDs and nursing staff trained to use them is not enough. From the clinical perspective, there appears to be significant reluctance by many nurses to use the devices. One barrier that must be overcome for a successful hospital-based AED program is re-education and an "unlearning" of previously learned behavior. The magnitude of this process should not be underestimated.

Documentation of resuscitation efforts in the hospital is typically inadequate and often inaccurate. Hospitals should develop a documentation form specifically designed to collect information on the process of resuscitation, as well as any other information pertinent to their local quality improvement. There needs to be widespread education on documentation of events during a cardiac arrest. This education needs to include training on how to use the specific documentation record, as well as the importance of accurate information. Because the form used becomes a medicolegal record, it is imperative that steps be taken to

ensure completeness and accuracy. The same documentation form should be used throughout the hospital and should include critical care areas as well.

The timing of events during in-hospital resuscitation is one of the most important and least accurate parts of documentation. There are typically several time intervals used to document events during in-hospital resuscitation efforts. Typically, someone from the hospital begins timing events with their watch while waiting for the official code team to arrive. There is also likely to be an initial time event that gets documented by the hospital page operator as the official start time. When the person responsible for documentation arrives on scene, a third time piece is often used to document events.

There will be considerable inaccuracies, unless these time pieces are synchronized. This has significant ramifications from both a medicolegal as well as a quality improvement perspective. The vast majority of hospitals have no method of time synchronization, and therefore most data regarding time to therapy may not be accurate.

Quality improvement and feedback are an integral part of the resuscitation process in the hospital and are now required by the JCAHCO. Many hospitals currently do not support this process and must quickly change their ways to be in compliance with the new standards. A good quality improvement process includes complete and accurate documentation, retrieval of documentation forms from all areas of the hospital (including intensive care units), personnel trained to understand the process of ACLS who can critically review the documentation record, a data base for collection and trending of data and a method for providing feedback to those performing resuscitation.

The National Registry of Cardiopulmonary Resuscitation offers, for a small fee, an electronic data base specifically designed for data collection of in-hospital cardiac arrest events. It is based on the Utstein Guidelines for Documentation and Reporting of Events for In-Hospital Resuscitation, but is also applicable for pediatric populations. The Registry provides precise definitions for all entries and thus lessens the confusion when comparing data from different institutions. Participating hospitals enter data from each cardiorespiratory arrest into the electronic data base. This information is sent confidentially to the coordinating center, which will then prepare quarterly reports for each hospital. Reports not only include information pertinent to each hospital's quality improvement program, but also provide benchmark information comparing similar institutions. This is the first large-scale data base of information and will likely be able to fuel data-driven guidelines on hospital-based resuscitation and ACLS. The process of improving resuscitation in the hospital remains in its infancy.

Pharmacologic Adjuncts to Defibrillation

The prognosis is ominous for a sizable proportion of patients with cardiac arrest in whom spontaneous circulation is not restored by the first few defibrillation shocks and in whom additional ACLS measures, such as endotracheal intubation, epinephrine and antiarrhythmic medications, are required.

Antiarrhythmic drugs. Antiarrhythmic drugs, including lidocaine, bretylium, magnesium and procainamide, have been classified as an "acceptable, probably helpful" treatment for cardiac arrest secondary to ventricular tachyarrhythmias unresponsive to three or more shocks under current ACLS guidelines. Although these drugs represent current clinical practice in the U.S., there is limited evidence supporting the benefit from use of these agents in treating cardiac arrest victims. Use of antiarrhythmic agents has not been universally embraced as an essential component of treatment algorithms for shock-refractory cardiac arrest.

Evidence supporting any clinical benefit from early administration of antiarrhythmic drugs in cardiac arrest is scarce. In early animal trials, either resuscitation of VF was not improved by the addition of procainamide or lidocaine, or any benefit was offset by worsened short-term survival attributed to the drugs' adverse circulatory depressant effects. Ironically, lidocaine, procainamide, quinidine, phenytoin and oral and higher doses of intravenous amiodarone (10 mg/kg body weight) have all been observed to increase the defibrillation threshold and, in theory, make it more difficult to resuscitate hearts from VF (50–55).

In the only published case-controlled clinical trial in which shock-refractory victims of out-of-hospital VF were stratified according to those who did and those who did not receive lidocaine, no significant differences were observed in the return of an organized rhythm, admission to the hospital or survival to hospital discharge between the treatment groups (56). A retrospective evaluation of antiarrhythmic drug use during a trial of active compression–decompression CPR found that lidocaine and bretylium were independently associated with a lower likelihood of survival to 1 h after cardiac arrest (57). Another retrospective study comparing outcomes from a time when ambulances were or were not staffed by personnel who were authorized to give medications found that recipients of lidocaine were more likely to have a return of spontaneous circulation and to be admitted to the hospital, although no survival benefit was demonstrated (58). In contrast, in a prospective, randomized trial comparing administration of lidocaine with standard doses of epinephrine in shock-refractory VF, not only was there absence of benefit, but survival actually worsened when such pharmacologic therapies served to delay defibrillation (59).

The current recommended use of magnesium in torsade de pointes is supported only by case reports. Two recent prospective, double-blind, randomized trials of cardiac arrest in patients in the hospital and in the Emergency Department found no benefit from routine treatment with magnesium (60,61). Finally, none of the reported randomized trials comparing bretylium with placebo or with lido-

Table 2. Biphasic Versus Monophasic Waveforms for Out-of-Hospital Defibrillation

Waveform	Study Type	Outcome	References
Monophasic-DS	Randomized: 175 J vs. 320 J	First shock defibrillation success rates 175 J = 61%; 320 J = 61%	Weaver et al. (65)
Biphasic-IC	Case series	First shock defibrillation rate 89% All shocks defibrillation rate 80% Return to pulse in 56%	Poole et al. (66)
Biphasic vs. monophasic	Case series, retrospective	First shock defibrillation rates: monophasic 75%; biphasic 83% All shocks defibrillation rate: monophasic 74%; biphasic 91%	Gliner et al. (67)
Biphasic vs. monophasic	Randomized, clinical trial	Defibrillation rate within three shocks: monophasic 67%; biphasic 98% Survival to hospital discharge: monophasic 32%; biphasic 28%	Schneider et al. (68)

DS = damped sinusoidal; IC = impedance compensating.

caine in victims of cardiac arrest demonstrated any significant differences in outcome between treatment groups (62).

In most studies to date, intravenous amiodarone has been administered only after failure of other antiarrhythmic medications to terminate malignant ventricular tachyarrhythmias. When compared with additional lidocaine and epinephrine in dogs with shock-refractory VF pretreated with prophylactic lidocaine, intravenous amiodarone significantly improved the success of subsequent defibrillation (63). The Amiodarone in out-of-hospital Resuscitation of REfractory Sustained ventricular Tachyarrhythmias trial (ARREST), a recently published randomized, prospective, double-blind, placebo-controlled trial, evaluated intravenous amiodarone in out-of-hospital cardiac arrest due to VF or pulseless ventricular tachycardia (64). In 504 randomized patients, a significant improvement in admission to hospital was observed in recipients of intravenous amiodarone as compared with placebo (44% vs. 34%, $p = 0.03$). The trial was underpowered to detect differences in survival to hospital discharge between the two treatment groups, which tended to favor recipients of intravenous amiodarone. However, this is the only randomized, placebo-controlled clinical trial ever to show a significant benefit from antiarrhythmic drug therapy during CPR.

Conclusions. With the possible exception of intravenous amiodarone, available evidence is inconclusive concerning benefit of antiarrhythmic drugs in cardiac arrest. Most studies addressing this question have been unpowered either to demonstrate or necessarily exclude benefit from such treatment or to have employed a positive but equally unproven control (lidocaine) comparison. The dose and manner in which to administer antiarrhythmic medications during cardiac arrest and the optimal variables by which to measure benefit from treatment (e.g., return of spontaneous circulation, admission alive to the hospital, 24 h survival, discharge from the hospital, neurologic function at hospital discharge, one-year survival) also remain controversial.

Emerging Defibrillation Technologies

Electrical defibrillation of the heart was first accomplished by using epicardial electrodes in the operating room. Subsequently, transthoracic defibrillation by using first alternating and then direct current was introduced, with the latter becoming the clinical standard. A damped sinusoidal monophasic waveform has been the most commonly used waveform in commercial external defibrillators. Experience with implantable cardioverter-defibrillators indicated that a biphasic waveform achieved lower defibrillation thresholds in many patients. External defibrillators that use biphasic waveforms have recently been introduced into clinical use. Experimental studies in animals and humans, including three clinical trials comparing biphasic with monophasic waveforms in out-of-hospital cardiac arrest, have shown that lower energy is required for successful defibrillation with biphasic waveforms (Table 2).

Both monophasic and biphasic defibrillation may employ a variety of waveforms (e.g., damped sinusoidal, monophasic truncated exponential), which may not necessarily have similar efficacy. Whether one waveform is more toxic than another has not been well established. Multiple, high energy transthoracic shocks can be associated with myocardial necrosis and electrocardiographic (ECG) changes. The latter appears to be less common with biphasic shocks of equivalent efficacy.

Conclusions. Defibrillation can be accomplished with transthoracic direct current shocks. The optimal waveform has not yet been determined, but biphasic shocks usually have lower energy requirements for conversion out of VF to another rhythm. It remains to be determined whether

Table 3. Guidelines for Economic Evaluations of Health Technologies

Comparison	Intervention should be compared to existing practice.
Time horizon	Long enough to capture all relevant future effects of intervention.
Design	Acceptable to use either modeling or direct observation of costs and effects.
Costs	Including costs of health care services, patient time expended for intervention, paid or unpaid caregiving, travel expenses and nonhealth impacts of intervention.
Effects	Morbidity and mortality should be accounted for by expressing effects as quality-adjusted life years.
Quality of life	Quality weights should be preference-based and measured on a scale from 0 (equal to dead) to 1 (equal to optimal health)
Discounting	Costs and effects should be discounted to present value.
Sensitivity analysis	Values of variables should be varied to assess whether uncertainty about key variables could have an impact on study conclusions.

biphasic shocks will be associated with better clinical outcomes in all situations, including pediatric cardiac arrest.

COST-EFFECTIVENESS OF PUBLIC ACCESS DEFIBRILLATION (PAD) STRATEGIES

Economic Evaluation of Treatments for Sudden Cardiac Arrest

Sudden cardiac arrest is debilitating and costly. Experts have debated which outcomes should be considered when evaluating treatments for this illness. Additional insights may be gained by considering the economics of treatments for sudden cardiac arrest.

Health economic evaluation considers the tradeoff between the costs and effects of interventions. The direct costs of treatment, the costs of subsequent medical care and the costs of long-term care should be considered. If one treatment is both more costly and more effective than another, then the difference between the two interventions is expressed as an incremental cost-effectiveness ratio. Although a variety of methods have been used to calculate incremental cost-effectiveness ratios, an expert panel has proposed guidelines that may be used to standardize these methods (Table 3) (69).

Furthermore, a treatment can be considered cost-effective in comparison with another if it is associated with an incremental cost of less than twice the average annual income per life year (i.e., approximately $50,000 per life year in the U.S.) (70).

The following data have been expressed in 1999 U.S. dollars.

Defibrillation. A decision analytic model combined effect estimates from a meta-analysis with cost and quality of life data to evaluate the incremental cost-effectiveness of decreasing the time to defibrillation (71). Decreasing the time to treatment by addition of firefighters able to provide CPR or defibrillation cost $63,700 per quality-adjusted life year. Decreasing the time to treatment by addition of ambulance-based providers cost $191,100 per quality-adjusted life year. These estimates were limited by the quality of the underlying effectiveness data.

Another decision analytic model estimated the incremental cost-effectiveness of decreasing time to defibrillation by implementing public access defibrillation (72). If this was implemented by using lay responders, the program cost $46,700 per quality-adjusted life year. If it was implemented by using police, the program cost $29,000 per quality-adjusted life year.

Also, decision analysis was recently used to assess the incremental cost-effectiveness of decreasing time to defibrillation by training and equipping security guards in a gaming establishment (73). Compared with usual care, early defibrillation cost $40,700 per life year, even after including all future costs.

As yet, there has been no comprehensive evaluation of the economics of defibrillation on passenger aircraft or in other public settings (e.g., golf courses).

Advanced life support. Two studies have evaluated the costs of advanced life support for sudden cardiac arrest. In the decision analysis described earlier, implementation of advanced life support cost $48,000 to $113,000 per quality-adjusted life year (71). On the basis of cost data collected from a retrospective case-series, advanced life support cost $13,200 per life year (74). The former analysis considered EMS costs and hospital costs, whereas the latter considered EMS costs alone.

Conclusions. Economic analyses of treatments for sudden cardiac arrest provide several insights into the economics of emergency cardiovascular care. First, interventions that shorten the time to defibrillation are likely to be cost-effective if achieved by a low intensity intervention such as police or lay responder defibrillation. Second, advanced life support is an effective treatment for cardiac arrest, but it is also expensive. There are conflicting data as to whether the additional benefit of ACLS justifies the additional expense. There are insufficient data to determine whether other treatments for cardiac arrest are economically attractive.

Finally, future economic evaluations of treatments of cardiac arrest should adhere to current standards for cost-effectiveness analysis.

CARDIAC ARREST: LEGAL AND LEGISLATIVE ISSUES

"Good Samaritan" laws were designed to protect and indemnify the unskilled provider administering BLS. The last decade, however, has shifted the burden of sophisticated patient care to the outpatient arena and to health care providers with lesser degrees of formal training. Several previously defined "ACLS" tasks (i.e., defibrillation) are now performed out of the hospital by nontraditional health care providers. These events have exposed the inadequacy of many existing Good Samaritan laws in dealing with current resuscitation practice and the potential liability for out-of-hospital health care providers and others.

In 1993, the AHA and other organizations endorsed early defibrillation. Despite this extremely strong recommendation, in 1996 and 1997, <30% of first responders nationwide were equipped with AEDs. One of the major roadblocks to implementing the AHA recommendation was that, in many states, the first responders (many times the EMT) was not *legally permitted* to defibrillate. Subsequently, numerous studies demonstrated the overall safety and efficacy of defibrillation (using AEDs) in the hands of nontraditional health care providers (31,33,75–82) and prompted several questions that warrant attention:

1. Who is a health care provider?
2. Who can defibrillate with an AED?
3. What is the legal risk for not only the user, but also the trainer or the owner of a facility with an AED?
4. Who "regulates" or monitors such PAD programs?
5. What is the manufacturer's liability if the device is used "off-label"?

Who is a health care provider? The AHA sponsored conferences on PAD and defined the traditional health care provider as an individual with a duty to respond as part of their professional job description (e.g., nurse, EMT). The nontraditional health care responder, on the other hand, was defined as someone who may encounter a medical emergency but is not required to respond as part of their job (e.g., airline personnel, police, security guards). It was suggested that all individuals trained in a physician-monitored AED program be allowed to defibrillate.

Indemnification. Individuals, however, may be fearful of litigation when using an AED or developing an AED program. Along with effective AED training, it becomes necessary to have mechanisms for immunity of not only the user, but also the provider, trainer or person who owns the AED (i.e., the AED acquirer). Both state and federal legislation has introduced immunity for AED use when implemented in programs under physician authorization.

Federal and state legislation. Over 42 states (as of September 10, 1999) have passed legislation that provides immunity for the traditional and the nontraditional health care provider when using an AED. Some of these laws extend this protection to trainers, acquirers, owners and other relevant individuals. These laws also support school CPR training and authorization for AED use by EMTs. All these statutes recommend that PAD programs remain under physician authorization.

If state legislation has been so effective, what is the value for additional federal legislation? The two should not be thought of as mutually exclusive, but rather as mutually supportive. State programs are limited in their scope, vary in their provisions from state to state and do not have jurisdictional control over federal facilities (e.g., military bases, Veterans Affairs hospitals, the National Institutes of Health, Indian reservations, national parks, courthouses). Federal programs, however, are able to define minimal national standards of excellence, and thus serve to standardize the quality of care nationwide. This is not a new concept, but is evident when one examines programs from the National Highway Traffic Safety Administration. In addition, federal legislation is important for identifying future jurisdictional control (i.e., issues pertaining to cardiac arrest) by virtue of being applicable nationwide, and outcomes impacted nationwide should reside at the national level.

ADVANCED CARDIAC LIFE SUPPORT

Use of Pressor Agents in the Treatment of Refractory Cardiac Arrest

Patients in VF or ventricular tachycardia (VT) who fail defibrillation and those in bradyasystolic states who fail BLS need immediate therapy to reverse the metabolic effects of ischemia on the myocardium if CPR is to be successful. Basic life support, including ventilation and chest compression, is intended to generate an adequate coronary perfusion pressure to provide improved flow of blood to the myocardium. However, BLS efficacy is limited, and frequently the clinician will need to proceed to therapy with drugs that might increase myocardial blood flow.

The immediate goal of pressor therapy is to increase vasomotor tone and increase coronary perfusion pressure to improve blood flow to the heart and brain, improving the chance of return of spontaneous circulation (ROSC) and preventing continued brain injury.

Alpha-adrenergic receptor agonists, such as phenylephrine, are powerful peripheral vasoconstrictors that redistribute blood to the brain and heart during CPR. Their effect is principally on the arterial side of the circulation, and in laboratory models they increase the rate of ROSC. Beta-adrenergic agents, such as isoproterenol, cause significant vasodilation and can worsen coronary perfusion pressure during CPR. They can also increase myocardial oxygen utilization, and thereby exacerbate the metabolic effects of ischemia. When the beta receptor is blocked before admin-

istration of epinephrine, a mixed alpha- and beta-receptor agonist, the resulting coronary perfusion pressure is increased.

Stimulation of vasopressin's V_1 receptor results in vasoconstriction that is mediated through a secondary messenger system different from that used by adrenergic agonists. This holds the promise of synergy when vasopressin is combined with a catecholamine. Vasopressin may decrease oxygen utilization by the myocardium, an effect that is theoretically attractive.

Agent of Choice

Epinephrine has been the pressor of choice in the treatment of refractory cardiac arrest (83,84). There are theoretic reasons to consider the pure alpha agonists, such as phenylephrine, because they raise intravascular pressure without the potentially negative effect on myocardial oxygen utilization. However, animal studies have failed to show a survival advantage when phenylephrine was compared with epinephrine (85). This potential advantage has not resulted in adequate clinical investigation, and at this time, they are rarely used.

Epinephrine, a catecholamine with mixed alpha- and beta-agonist properties, is the agent of choice after failure of defibrillation. Although laboratory and clinical investigations clearly indicate that it can raise perfusion pressure and the rate of ROSC, it has not been unequivocally shown to increase long-term survival. It may be that the paucity of data supporting the use of epinephrine results from the drug being the de facto standard of care for a disease in which performance of placebo-controlled trials is problematic. However, it is possible that the failure of epinephrine, in a range of dosages, to improve long-term survival, may represent a poorly defined toxicity. Clinical trials that indicate toxicity are difficult to interpret because the epinephrine dosage is a strong marker for duration of arrest, which itself is the best predictor of poor outcome.

Recently, there has been considerable interest in the potential utility of vasopressin in the treatment of refractory cardiac arrest. In a series of laboratory and clinical investigations, Lindner et al. (86–90) appear to have demonstrated significantly better outcomes with vasopressin than with epinephrine. There is also the possibility of using vasopressin in combination with adrenergic agonists (91). Further studies are needed.

Route and Dosage

In choosing a route of administration, the clinician must balance timeliness against the potential of greater efficacy. In most cases, epinephrine will be administered as a bolus of 1 mg by peripheral intravenous catheter, followed by a large volume saline flush to assume rapid delivery of the epinephrine into the central circulation.

Although it may be possible to administer the drug more quickly by endotracheal injection, bioavailability may not be adequate. It is possible that increasing the endotracheal dosage may overcome the decreased serum levels obtained by this route. Intracardiac injection is not recommended because intramural administration can reportedly cause intractable VF.

There has been interest in dosages of epinephrine greater than the traditional 1 mg. Laboratory investigations have indicated that higher dosages may improve myocardial blood flow and the rate of ROSC, but that survival may actually be decreased (92). There have been a number of randomized clinical trials of "high dose" epinephrine; in none of these trials was there increased survival, although a meta-analysis has shown improved rate of return of spontaneous circulation (93–95) (Stiell IG. Meta-analysis for high dose epinephrine during CPR. Personal communication, 1999). Epinephrine duration of action is short-lived, so that every 3-min dosing is recommended, although the efficacy of subsequent doses is not well proven.

Potential Alternatives to Standard Closed-Chest Compression

Standard chest compression produces ~25% to 35% of normal cardiac output. There have been exciting developments in CPR adjuncts, for use by health care providers, that appear to improve hemodynamic measurements during resuscitation. These new developments include interposed abdominal compression (IAC) CPR, active compression–decompression CPR, vest CPR, phased chest and abdominal compression–decompression CPR and open-chest CPR.

These techniques have been difficult to study and evaluate definitively for the following reasons: 1) they are often used only late in resuscitation; 2) controversies persist regarding study end points; 3) some of the devices used have not yet received FDA approval; 4) the current health care environment favors conventional therapy and limits experimental procedures; and 5) costs of prospective, randomized trials can be prohibitive.

These alternative forms of resuscitation have solid laboratory data, with some limited clinical data, supporting their efficacy. They also demonstrate an acceptably low incidence of adverse effects. Consideration of the use of these techniques, when approved by the FDA, should come early in the resuscitation effort. Successful use of these techniques requires a commitment to adequate training and follow-up. There is a continual need for randomized trials of such alternatives to prove their efficacy as compared with standard CPR.

Interposed abdominal compression CPR. This type of CPR requires the addition of mid-abdominal compressions by an extra rescuer during the intervals between the chest compressions of conventional CPR (96). The abdominal compression point is located in the midline, halfway between the xiphoid process and the umbilicus. The recommended force of abdominal compression is that sufficient to generate ~100 mm Hg of external pressure on the abdom-

Table 4. Results of Clinical Studies of Interposed Abdominal Compression Cardiopulmonary Resuscitation (CPR)

Outcome Measure	Studies	IAC CPR	Standard CPR	p Value
Return of spontaneous circulation in or out of the hospital	Mateer (103)	40/145 (28%)	45/146 (31%)	0.54
	Ward (101)	6/16 (38%)	3/17 (18%)	0.19
	Sack (100)	29/48 (60%)	14/55 (25%)	0.00014
	Sack (102)	33/67 (49%)	21/76 (28%)	0.0067
	All four studies	108/276 (39%)	83/294 (28%)	
Return of spontaneous circulation after in-hospital resuscitation	Ward (101)	6/16 (38%)	3/17 (18%)	0.19
	Sack (102)	29/48 (60%)	14/55 (25%)	0.00014
	Sack (104)	33/67 (49%)	21/76 (28%)	0.0067
	All three studies	68/131 (52%)	38/148 (26%)	
Survival to discharge, neurologically intact, after in-hospital resuscitation	Ward (101)	1/16 (6%)	0/17 (0%)	0.3017
	Sack (102)	8/48 (17%)	3/55 (5%)	0.0700
	Both studies	9/64 (14%)	3/72 (4%)	

IAC = interposed abdominal compression.

inal aorta and vena cava and is equivalent to that required to palpate the aortic pulse optimally when the heart is beating normally. Interposed abdominal compression mathematic models generate additional artificial circulation that is approximately equal to that created by chest compressions only (97,98), potentially doubling blood flow during CPR. The positive hemodynamic effects of IAC during CPR have been confirmed in 16 of 17 animal studies using canine and porcine models (99).

Three randomized clinical trials of IAC CPR for in-hospital cardiac arrest have been done (100–102), two of which have shown statistically significant improvement of outcome measures (100,102). One randomized trial of prehospital IAC CPR, combined when possible with standard CPR in the field, showed no difference in outcome (103). These clinical studies are summarized in Table 4. Pooled analysis of all available data for both prehospital and in-hospital resuscitations shows statistically significant improvement in the return of spontaneous circulation with IAC CPR. When only in-hospital studies are examined, the effect of IAC becomes much greater. Pooled data from two studies that examined long-term, neurologically intact survival after in-hospital resuscitations show a positive benefit of IAC CPR as compared with standard CPR. Thus, strong preclinical and clinical evidence supports the use of IAC CPR for in-hospital resuscitations.

Practical implementation of IAC CPR is straightforward and inexpensive. If the chest compressor counts "one—AND—two—AND—three—AND . . . ," the abdominal rescuer applies pressure during "AND." In the hospital, the availability of an extra trained rescuer is rarely a problem.

The safety of IAC, as reviewed previously (104), has been well documented in 426 humans, 151 dogs and 14 pigs. Only one isolated case report of traumatic pancreatitis in a child describes local trauma from abdominal compression during CPR (105). These data compare favorably with the well-known and frequent incidence of rib fracture and pulmonary contusion from chest compression during CPR. Increased emesis and aspiration from IAC have not been reported, and there is evidence that if positive abdominal pressure is applied during ventilations from the beginning of an arrest, the rate of gastric inflation before endotracheal intubation is reduced (106). Review of the available data, therefore, suggests that there is much to be gained and little to be lost from application of IAC CPR during in-hospital resuscitations. Because the most favorable clinical results have been obtained when IAC CPR is applied from the beginning of resuscitation, early application of the technique is to be encouraged. Use of IAC CPR as a last-ditch effort after prolonged, failed ACLS is not recommended.

Active compression–decompression CPR device. Active compression–decompression CPR is a method of CPR utilizing a hand-held suction device to actively compress and then decompress the chest during cardiac arrest. Although chest wall compression achieves the same hemodynamic effect as closed-chest manual CPR, active decompression with the device decreases intrathoracic pressures, leading to enhanced minute ventilation and venous blood return to the thorax. Arterial systolic blood pressure, diastolic blood pressure, coronary perfusion and vital organ perfusion have been shown to be improved in nearly all animal models of VF when ACD CPR is compared with standard CPR (107–110). This increase in overall CPR efficacy led to the development of both a new device (Ambu CardioPump) and the performance of a number of clinical in-hospital and out-of-hospital studies evaluating the potential benefits of this approach.

Results from the clinical trials have been mixed. Although some studies demonstrated no difference between standard CPR and ACD CPR, other clinical trials point to a significant improvement in resuscitation rates and 1 h survival, especially in patients with witnessed cardiac arrests. The most positive results come from Paris, where data demonstrate that one-year survival is doubled with the use of the CardioPump (5%) as compared with standard CPR (<2.0%) (111). In contrast, other large studies have failed to demonstrate any significant outcome improvement with

ACD (112–115). No study has shown a worse outcome when using ACD CPR as compared with standard CPR. Although ACD CPR has been adopted by the EMS in some countries, preliminary research has shown that the benefits of ACD CPR can be improved by the use of an inspiratory threshold valve (ITV) (116). This valve blocks inspiratory gas exchange during the decompression phase of CPR, thereby augmenting blood return to the chest and overall efficiency of CPR. In patients in prolonged cardiac arrest, use of the combination of ACD CPR plus the ITV resulted in a higher and more rapid rise in end-tidal carbon dioxide and significantly higher systolic and diastolic pressures as compared with ACD CPR alone.

Vest CPR. With vest CPR, a bladder-containing vest (analogous to a large blood pressure cuff) is placed circumferentially around the patient's chest (117). The bladder is inflated and deflated by an automated pneumatic system to cyclically compress the chest. Adherent defibrillation pads can be placed on the chest before applying the vest to allow for defibrillation without the need to remove the vest or interrupt CPR.

Vest CPR was developed as a means of circumferentially compressing the chest with the intention of reducing the thoracic volume and increasing intrathoracic pressure (by Boyle's law) to an extent greater than that which could be achieved with standard manual CPR (118–127). This circumferential compression allows for a large amount of force to be applied without the trauma inherent in applying force to a single point, as with standard chest compression. Laboratory data showed substantial improvement in hemodynamic data and survival.

With the latest improved vest CPR system, hemodynamic measurements in humans were improved significantly over those of standard external chest compression (117). Peak aortic pressure was nearly doubled (up to an average of 138 mm Hg), and coronary perfusion pressure increased by 50%. In addition, 4 of the 29 patients had return of spontaneous circulation during vest CPR, despite their late (50 ± 22 min) resuscitation. In a second phase of the study, patients were randomized to either vest CPR or standard external chest compression after initial resuscitation efforts had failed (11 ± 4 min). There was a trend toward improved initial resuscitation in the vest CPR group, but the trial was too small to show a statistically significant benefit. These data formed the basis for a large-scale, randomized trial of vest CPR immediately after cardiac arrest, which was performed on 81 patients in Europe and showed a trend toward improved survival with vest CPR (128).

Vest CPR requires a sophisticated device for its administration. The technique will obviously be limited to locations where the device would be readily available, although a portable device may be possible. Application of the vest itself is not difficult and can be performed successfully by nurses given only a few minutes of instruction on its use. It is likely that if vest CPR proves successful in improving survival from cardiac arrest, it will remain predominately in the hands of health care professionals. Currently, the vest CPR system is too heavy and consumes too much energy to be easily portable, as would be needed for treating out-of-hospital cardiac arrest victims. The final utility of vest CPR will be determined by the outcomes of larger clinical trials and by whether the device can be miniaturized sufficiently for routine clinical use.

Phased chest and abdominal compression–decompression CPR. This technique incorporates chest compression–decompression and ACD. A manually operated Lifestick Resuscitator (Datascope, Fairfield, New Jersey) is employed. The chest and abdomen are reciprocally compressed and decompressed in a see-saw fashion.

Experimental studies demonstrated impressive hemodynamic efficacy. The coronary perfusion pressure generated by the Lifestick Resuscitator was threefold greater than that generated by conventional precordial compression after 7 min of untreated VF. This was associated with improved initial resuscitability and 72 h survival (129). Experimental studies also indicated that the Lifestick Resuscitator markedly improves efficiency and achieves greater myocardial blood flow, cerebral blood flow (130) and minute ventilation (131), with significantly lower compression force. Hemodynamic efficacy was also demonstrated in a human case series (132).

Open-chest CPR. Open-chest CPR, once the only treatment option for victims of sudden cardiac arrest, quickly fell out of favor with the advent of closed-chest resuscitation techniques. Recognition of the generally poor hemodynamic support generated with closed-chest CPR has spurred a resurgence of interest in invasive forms of CPR.

Previous experimental work in both animals and humans has shown improved CPR-generated hemodynamic data and blood flow with direct cardiac massage. The fundamental unresolved issue is whether the improved hemodynamic data will translate into an improved resuscitation outcome. A number of laboratory experiments have shown an improved outcome with the use of open-chest cardiac massage. An important aspect in employing any invasive CPR method is the time of application within the course of cardiac arrest and the preceding resuscitation efforts. Although open-chest massage may be superior to all forms of closed-chest efforts, because of the inherent morbidity of the associated emergent thoracotomy, it seems most reasonable to try an initial period of closed-chest compressions followed, as soon as possible, by external defibrillation attempts. If successful, the morbidity of the emergent entry into the chest is avoided. Experimental studies of cardiac arrest with open-chest CPR have documented improved coronary perfusion pressures, regardless of when it was begun, but outcome was only improved when invasive CPR was begun within 15 min of the onset of cardiac arrest (133). These findings indicate that invasive techniques such

as open-chest massage must be applied early, before extensive myocardial injury occurs.

Limited human trials have confirmed the importance of this "window of efficacy" for the successful use of invasive CPR after unsuccessful standard closed-chest compressions. Geehr et al. (134) reported a small series of 49 patients with out-of-hospital cardiac arrest who were randomized to standard closed-chest CPR versus initial closed-chest CPR followed by emergent thoracotomy and open-chest massage on arrival to the hospital. In this study, no survival benefit was seen with the addition of open-chest massage. Scrutiny of the times elapsed before the institution of invasive CPR shows that none of the subjects received open-chest cardiac massage within the first 20 to 25 min of their cardiac arrest. Two recent nonrandomized human studies of open-chest resuscitation confirm the superiority of open-chest direct cardiac massage for hemodynamic support during cardiac arrest and highlight the importance of total cardiac arrest time on successful outcome with invasive CPR (135,136).

Alternative invasive techniques for resuscitation have been developed, many of which have been carefully studied in the past. With either direct mechanical ventricular assistance or emergency cardiopulmonary bypass, the principal issue remains the time to successful application in the arrested patient. Generally, the more sophisticated the device, the more difficult it is to use in a timely fashion during cardiac arrest. One simplified concept that has evolved recently is "minimally invasive direct cardiac massage." Using only a limited 2-cm thoracotomy, a wand-like device is inserted to directly compress the heart. The hope is that by avoiding the necessary thoracotomy of typical open-chest massage, the morbidity will be less and the technique more acceptable. Studies of efficacy are currently under way.

EVALUATION AND CARE AFTER RESUSCITATION

Most patients who are initially resuscitated die within 72 h from persistent postresuscitation cerebral or myocardial dysfunction. Efforts to understand and successfully treat this postresuscitation syndrome are under way.

THE BRAIN DURING AND AFTER CARDIAC ARREST

Support of the brain during the postischemic period is essential to survival after cardiac arrest. Most treatments commonly administered after global brain ischemia have not been formally tested in prospective, randomized clinical trials. Generally accepted postresuscitation therapeutic goals for brain preservation include the following.

Cerebral reperfusion. Maintenance of normal to high cerebral perfusion (based on the individual patient's baseline blood pressure before arrest) is a mainstay of treatment. Normally, cerebral blood flow is autoregulated so that blood flow is independent of perfusion pressure over a wide range of blood pressures (between ~50 and 150 mm Hg, mean arterial pressure). During and after ischemia, autoregulation is compromised, if not lost. Perfusion of ischemic tissue then becomes passively dependent on arterial pressure. As a result, the occurrence of postischemic hypotension compromises cerebral blood flow and may result in significant additional brain damage. Therefore, after restoration of spontaneous circulation, arterial pressure should be rapidly normalized using intravascular volume administration and vasopressors, as needed (137), but may come at the risk of increasing postresuscitation myocardial dysfunction by increasing both preload and afterload.

Ventilation. Although the cerebral circulation may lose its ability to adjust to blood pressure changes after ischemia, responsiveness to arterial carbon dioxide and oxygen levels is usually maintained and may lead to increased intracranial pressure in the presence of hypercapnia or hypoxemia. Hyperventilation may be effective in correcting postischemic tissue acidosis and is important for excretion of the carbon dioxide load generated from bicarbonate administration, which may be given during CPR. Although the usefulness of hyperventilation after global brain ischemia has never been demonstrated, slight hyperventilation is usually recommended after cardiac arrest to guarantee that hypercarbia and the associated increase in intracranial pressure are prevented.

Oxygenation. Adequate tissue oxygenation is necessary to preserve cellular function and to allow postischemic reparative processes to occur. The maintenance of moderate hyperoxia (partial pressure of oxygen [P_{O_2}] >100 mm Hg) seems judicious to prevent transient pulmonary problems from causing a significant deterioration of oxygenation in already compromised tissues. Adequate partial pressure of oxygen in the arterial blood (Pa_{O_2}) levels should be maintained using the lowest inspired oxygen fraction (F_{IO_2}) possible with carefully titrated minimal levels of positive end-expiratory pressure. Because hypoxia and hypercapnia must be avoided, controlled ventilation, with muscle relaxation and sedation, if needed, has been recommended for at least several hours after resuscitation.

Correction of acidosis. After brain ischemia, the decline of pH correlates with the extent of cellular necrosis (138,139). Cell damage is further accentuated by hypercapnia and hyperglycemia. Treatment of severe acidosis is generally believed to be clinically beneficial. Because the capacity of respiratory compensation for a metabolic acid load is limited, administration of a buffer base is tempting, but controversial. Unless effectively removed, increased carbon dioxide production from bicarbonate neutralization can lead to intracellular acidosis. Currently, the correction of intracellular acidosis remains a clinical challenge.

Immobilization and sedation. The comatose brain can and does respond to external stimuli, such as physical examination and airway suctioning, with increases in cerebral metabolism. This elevation of regional brain metabo-

lism requires increased regional cerebral blood flow at a time when the oxygen demand-to-perfusion ratios are, at best, precariously balanced. Protection from afferent stimuli with administration of titrated doses of anesthetic drugs and muscle relaxants may prevent the supply–demand imbalance and improve the chances of neuronal recovery. All activity that increases intracranial pressure, such as straining or coughing, should be suppressed, and tracheal suction should be performed with care.

Anticonvulsant therapy. Seizure activity can increase the cerebral metabolic rate by 300% to 400%. This extreme increase in metabolic demand may tip the tissue oxygen supply–demand balance unfavorably, resulting in additional tissue damage. Although the prophylactic use of anticonvulsant drugs (e.g., before a seizure occurs) is controversial, it is generally agreed that the occurrence of a postischemic seizure should be treated quickly and effectively. Commonly used drugs include barbiturates, benzodiazepines and phenytoin.

Glucose. Postischemic hyperglycemia has detrimental effects on cerebral blood flow, metabolism, edema formation and neurologic outcome (140–142). Thus, after global brain ischemia, hyperglycemia should be avoided and, if present, treated aggressively. The administration of glucose should be avoided, except in cases of verified hypoglycemia.

Corticosteroids. Although steroids are commonly administered to patients with intracranial pathology of any etiology, available clinical studies of steroid use after cardiac arrest suggest no benefit of this therapy (143,144).

Temperature control. The cerebral metabolic rate increases ~8% per degree Centigrade of body temperature elevation. Because the regional cerebral metabolic rate determines regional blood flow requirements, elevation of temperature above normal creates the possibility for a significant imbalance between oxygen supply and demand. Thus, temperature elevation should be treated aggressively in the postischemic period, perhaps aiming at a slightly subnormal body temperature.

Hypothermia, in contrast, suppresses cerebral metabolic activity effectively and has been reported to have a protective effect in global and focal ischemia (145–149). It has been shown experimentally that temperature changes of only 2 to 3°C may limit the extent of ischemic brain injury. Hypothermia, although not yet proven to be of clinical benefit, is probably the most promising brain resuscitation therapy currently on the horizon.

Conclusions. In the quest to improve survival after cardiac arrest, concerns have been raised about the possibility of increasing success in the resuscitation of patients while creating increased numbers of survivors with severe residual neurologic disabilities. However, available outcome data from recent large-scale clinical trials allay these fears (150,151). With very few exceptions, long-term survivors demonstrated recovery of good neurologic function and were able to lead independent lives.

Current rates of survival and recovery of intact neurologic function after cardiac arrest are low. However, there is reason for optimism. Not only are neurons more resistant to ischemia than had been believed previously, but important secondary mechanisms of tissue injury have also been identified. These include generation of oxygen free radicals, increased free intracellular calcium and excessive production of excitatory amino acids and other neurotransmitters. Because these secondary processes occur during postischemic reperfusion, they allow opportunity for clinical intervention. Potentially beneficial agents are now being developed and tested. Unfortunately, none has yet been proven clinically effective.

MYOCARDIAL DYSFUNCTION AFTER RESUSCITATION

Postresuscitation myocardial dysfunction has been recognized by resuscitation researchers for decades. Clinical resuscitation trials have substantiated the importance of postresuscitation myocardial dysfunction and its sometimes fatal outcome. Myocardial postresuscitation dysfunction may manifest itself as fatal recurrent ventricular arrhythmias or persistent low cardiac output and shock. There is laboratory evidence suggesting that the severity of postresuscitation myocardial dysfunction is related to the duration of cardiac arrest, the residual effects of potent vasoconstrictors used during resuscitation efforts and the use of high energy defibrillation.

Experimental evidence of myocardial dysfunction after successful resuscitation has come from a number of independent investigators over the last decade. Decreases in myocardial contractile function and left ventricular compliance after resuscitation after 4 min of VF has been documented in both isolated, perfused rat hearts (152) and in domestic pigs (153,154). Global left ventricular systolic and diastolic dysfunction has been demonstrated in experimental models after 10 to 15 min of untreated VF and subsequent resuscitation. This global dysfunction has been shown to be classic "stunning," with profound mechanical compromise in the presence of normal levels of myocardial blood flow with spontaneous recovery if death does not occur (153).

Treatment and support of myocardial dysfunction after resuscitation is just beginning to be explored. Because left ventricular "stunning" is so reminiscent of what occurs with recently transplanted hearts, similar treatments should be effective. Dobutamine, which is often used to stabilize patients who have had a heart transplant, has been studied in animal models of prolonged cardiac arrest and induced postresuscitation myocardial dysfunction. Left ventricular systolic and diastolic dysfunction improves with dobutamine treatment (155). No survival benefit has yet been established.

Searching for a mechanism of this postresuscitation phenomenon has suggested a role of the potassium adenosine triphosphate channel. Experimental laboratory studies have found less myocardial dysfunction after resuscitation

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and increased postresuscitation 48 h survival in animals given a potassium adenosine triphosphate channel activator (cromakalin) (156).

Conclusions. Postresuscitation myocardial dysfunction is a common problem following prolonged cardiac arrest. It appears to be a "stunning" phenomenon and is transient. However, there is substantial morbidity and even mortality associated with this period. An effective approach to treatment of this postresuscitation left ventricular systolic and diastolic dysfunction, once found, has the potential of improving long-term survival from cardiac arrest.

Task Force 2: Acute Coronary Syndromes: Section 2A—Prehospital Issues

Adolph M. Hutter, Jr., MD, MACC, *Co-Chair*, W. Douglas Weaver, MD, FACC, *Co-Chair*

Coronary heart disease (CHD) is the most common cause of mortality for American men and women, accounting for 481,287 deaths in 1995 (8). Annually, an estimated 1,100,000 Americans experience a new or recurrent acute myocardial infarction (AMI) due to CHD, and one-third of them will die from that event (8). Although difficult to quantify, it is estimated that annually 250,000 individuals will die within 1 h of the onset of symptoms and before they reach the hospital owing to cardiac arrest. Out-of-hospital deaths account for more than one-half of all CHD mortality, and many of these victims have no history of CHD (157). Coronary heart disease is prevalent, with ~14 million Americans having a history of myocardial infarction or angina pectoris, or both, with African American men and women bearing a disproportionate burden (158).

Over the past 40 years, there has been a dramatic decline in age-adjusted CHD mortality, which began in the mid-1960s and continues today. From 1965 to 1994, the average age-adjusted CHD decline was 2.8% per year (158). The decline has lessened since 1990 (1.5%). Similarly, although less dramatic, CHD incidence (new cases) and case fatality have fallen, resulting in a rising prevalence of CHD (159–162). These trends have led to a significant increase in the expected life span of Americans (158). Less recognized is the observation that absolute mortality has fallen only slightly, as people still succumb to CHD, although now at older ages.

The postulated reasons for this age-adjusted decline in incidence, case fatality and CHD mortality are many (157,163,164). However, it is clear that traditional risk factor–based prevention and advances in medical therapy for AMI and follow-up care have played an important and increasing role in the decline. The advent of the coronary care unit with intensive monitoring and treatment of complications, along with reperfusion therapies such as thrombolysis, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery (CABG), has contributed (157,165–167).

Among the more important goals in early care of CHD is making these effective treatments available to patients in a timely fashion (168). This is obvious for the victim of cardiac arrest, but is also critical in reperfusion and other therapies, where outcomes are improved when treatment is delivered early.

PATIENT DELAYS

Several sources of delay inhibit the early application of beneficial therapies. Widespread availability of these treatments and recognition of the importance of timely application have led to greater scrutiny of sources of delay and programs to reduce delay.

The delay from the onset of symptoms of AMI to definitive therapy (usually reperfusion) is commonly divided into three periods (174). The first is from symptom onset to the patient's action to seek treatment, such as going to the hospital or calling the emergency medical service (EMS). This is the longest component of delay and constitutes from 60% to 70% of the total time.

The first step in this process is teaching patients and their families the basic information they need to live successfully with heart disease and to respond to unexpected symptoms. A summary of educational goals is presented in Table 1 (169–171). Three categories of information are important: 1) practical information; 2) medications; and 3) risk factors. Practical, concrete information is desired by patients more so than detailed descriptions of the mechanism of ischemia (172). This information includes how to avoid a heart attack, what types of symptoms are worrisome and exactly what to do when it is experienced (e.g., stop what you are doing, rest and take up to three nitroglycerin tablets).

Many patients with heart discomfort report that their symptoms were different from the sudden and dramatic event they had expected (175). Longer delays in seeking

Table 1. Summary of Education/Instruction Goals by Physicians

What Should Be Taught?	Supplemental Materials	How Should Teaching Occur?
Practical, concrete information (e.g., specific symptoms to look for)	Miniature electrocardiographic copies	Timing is important (no more than 15 min)
What to do when experiencing chest discomfort and how to avoid it	Wallet medication cards	Avoid confrontation in preference for empathy (174)
Minimize information on pathophysiology of chest discomfort	Carefully selected brochures	Avoid fear or paternalism
Medication profile	Fifth-grade reading level (173)	Combination of approaches (written and verbal) will help achieve goal
Risk factor modification goals	Videotaped materials for functionally illiterate	Solicit and respond to questions
	Computer health risk appraisals	

treatment have been reported when the expected symptoms did not match the experience (176). This discordance led to a tendency to attribute symptoms to some other source or condition (Finnegan et al., 1998). Women, in general, do not view themselves at risk for a heart attack (Finnegan et al., 1998). Misconceptions such as these need to be suspected and clarified.

The second period is from deciding to seek attention to arrival at the hospital. This is transport time whether by ambulance, automobile or other means and is routinely 3% to 8% of the total delay.

Finally, the time from arrival at hospital to definitive therapy is the third period. Hospital assessment and treatment decision comprises 25% to 33% of the total delay.

The delay period of patient symptom recognition and decision making is long and has undergone considerable study in recent years (177–180). A number of characteristics are associated with longer delay, including older age, female gender, African American race, low socioeconomic group and no insurance. Surprisingly, an important characteristic associated with prolonged delays is a history of CHD or AMI. This counterintuitive observation is unexplained. Environmental factors associated with increased delay include symptom presentation at home, having a spouse at home, being with family members and attempting to contact a physician. Factors associated with decreased delay include symptom severity, typical symptoms and the belief that CHD is preventable. Even when a decision is made to seek medical help, most patients do not dial 911 for EMS transport.

These associations may operate through a variety of individual knowledge, beliefs, attributions and practical barriers to taking action. A patient must recognize the presence of abnormal symptoms, attribute them to a condition requiring medical attention, decide to seek care, arrange transportation and travel to the hospital. Barriers to this process may arise from inadequate knowledge of heart attack symptoms, maladaptive coping strategies, misattribution of the symptoms to noncardiac causes, denial, fear or other characteristics (180,181). Patient denial is a particular issue in those with known CHD. Any attempts to reduce patient delay must confront these many factors.

There are considerable published data on the period for prehospital delay. A review of data from 12 U.S. and European studies published from 1969 to 1987 found that median prehospital delay times ranged from 2.5 to 7 h, with many patients waiting 12 to 24 h or more, with hospital arrival at a time when reperfusion therapy was of unproven benefit. Cooper et al. (182) describe a 6 h median delay time for African Americans in 1983 to 1984. More recently, however, the median delay time of 2.7 h for patients with acute infarction with ST segment elevation in the U.S. was unchanged over a two-year period (183). The Rapid Early Action for Coronary Treatment (REACT) study found a median delay time of 2.2 h at baseline in 20 cities (180).

PATIENT EDUCATION EFFORTS

Prodromal symptoms frequently are present in the days or even weeks prior to the onset of AMI. Educational programs targeting recognition of such symptoms and early action to seek help seem appropriate at this time. Because of substantial patient delays to presentation, attempts have been made to reduce this time. These methods have focused on mass-media strategies supplemented by smaller media and direct patient education. Ho et al. (184) utilized a two-month mass-media campaign using television, radio and newspaper in the Seattle metropolitan area. The median delay time decreased from 2.6 to 2.3 h, which was not statistically significant. Herlitz et al. (185) describe a one-year campaign of mass and specialized media in Sweden using newspaper, printed materials and radio. Patients admitted to the coronary care unit had a statistically significant decline in median delay, from 3.0 to 2.6 h. Those with confirmed AMI had an even greater decrease of 0.7 h. Gaspoz et al. (186), in a one-year mass-media and local media campaign with television, radio, newspapers and printed brochures in Switzerland, also demonstrated a median delay time decrease from 3 to 2.7 h.

Although none of these community studies was ideal in design, much was learned. It appears that a mass-media campaign, which is sustained, intense and supported by other forms of communication, can reduce delay time.

The REACT trial attempted to improve on these design differences with a randomized study of 20 cities with a population of ~100,000 each in a sustained campaign of over one year (180). It improved community awareness of the problem and the proper action to be taken. The median delay time (2.2 h) declined over the intervention; however, similar changes were observed in the "control" communities. Therefore, the differences were not statistically significant. However, there were statistically significant delay time declines in patients who called the 911/EMS system (20%), favoring the intervention communities. Encouragement by physicians to educate their patients with known CHD and those at high risk about reducing delay had little effect. The REACT trial provides evidence that community campaigns to alert citizens and patients of appropriate action for AMI can have an effect. However, a secular trend in delay time suggests the need for new strategies if we are to further reduce this delay. The cost-effectiveness of such programs is unknown.

EMERGENCY MEDICAL SERVICES AND ASSESSMENT OF CHEST DISCOMFORT

Current Emergency Medical Services

Access. Time is a critical factor for the cardiac patient. A single, nationwide emergency number for emergency services—fire, police and health care—is essential, and the number should be the same—911. Today, 911 covers 75% to 80% of the population. There are two types of 911 systems available. One version is the phone number 911, which connects the caller with an operator or dispatcher. A more sophisticated version is the "enhanced 911" system, which has automatic identification of the caller's telephone number and address. This has the advantage that the information required for an emergency response is immediately available. An enhanced 911 system throughout our country should be a goal (187–192). Cellular and digital telephones do not universally have location identification at the present time.

Dispatch. Centralized dispatch is required to provide fast and efficient EMS action. This is particularly important in areas where there are multiple agencies providing services. The dispatcher should be trained to determine what level and extent of services are required. Dispatchers need to quickly determine the nature of the emergency and the types of equipment and personnel required and provide first-aid ("prearrival") instructions over the telephone. It has been shown that untrained telephone callers can be instructed and will perform cardiopulmonary resuscitation (CPR) until the emergency rescuers can respond (190,191,193–198).

Levels of service. The Department of Transportation has developed guidelines for training four different levels of EMS personnel: 1) the first responder; 2) the emergency medical technician (EMT), basic; 3) the EMT, intermediate; and 4) the EMT, paramedic (191,199–202).

First responders with 40 h of training do not transport patients; they provide first-aid for most life-threatening emergencies and may use automated external defibrillators. Firefighters and security guards are often the first responders in the urban areas. In rural and smaller towns, law enforcement officers and volunteers are often the first responders providing treatment. They initiate therapy until another more skilled person or team can assume care and transport the patient (191,199–202).

A basic EMT (EMT-B) has about 120 to 150 h of training in basic first-aid skills. An EMT-B is trained to provide CPR, oxygen therapy and other types of first-aid skills. Most ambulance personnel are EMT-Bs (191,199–202).

The next higher level of training is the intermediate EMT (EMT-I). The amount of training varies from state to state. The Department of Transportation curriculum requires about 450 to 600 h of training and is similar to that of paramedics of a few years ago. The EMT-Is can usually provide intravenous therapy, drug therapy, defibrillation and tracheal intubation. These individuals provide service in rural areas, where it is not feasible to have paramedics (191,199–202).

The paramedic EMT (EMT-P) has the greatest extent of training, ranging from 900 to 1,500 h. Paramedics are trained to differentiate medical emergencies, provide defibrillation, administer cardiac drugs, infuse intravenous fluids and do endotracheal intubation as well as care for many other medical emergencies. Although EMT-Ps are less common than EMT-Bs, they are responsible for transporting the majority of patients in the U.S. (191,199–202).

Types of service. In the U.S., four major types of EMS systems are utilized: city government–based systems, hospital-based systems, public utility systems and competitive private systems (32,76,190,191,199–206).

City government–based systems are most often through the Fire Department. The Fire Department uses fire and rescue officers as dual-trained personnel (fire and medical). In some cities, the Fire Department provides both paramedics and transportation; in others, it provides only paramedics. The Fire Department may provide both basic treatment and transport, as well as a paramedic service (a two-level service system). The Fire Department has advantages by employing personnel with more extensive training in dangerous environments, extrication and rescue. The major potential disadvantage of using the Fire Department is the political environment in which it operates. Fire departments compete for funding with other city services and even within the Fire Department itself. There can be competition within the Fire Department for resources, recognition and promo-

tion, and at times there are hard feelings between firefighters and EMS personnel. The civil service system can sometimes make discipline difficult.

Police Department EMS systems are usually found in smaller towns. These systems provide first-aid and transport. Adjacent city services generally provide paramedic or basic service with transportation. Often, an adjacent city service is operated as a division of the city hospital. The major advantage of this system is that it circumvents intradepartmental politics and gives EMS the same emphasis as police and fire. A major cost may be housing and locations for the emergency units and for a communications system.

Another system is the hospital-based EMS system. These are generally found in smaller towns where one or two ambulances can service an area from the hospital. Some towns provide a subsidy to the hospital to provide the service.

The public utility model is one in which a single private provider is given a virtual monopoly in exchange for services, similar to that for public utilities. This service provides all ambulance transport, including all contracts with health maintenance organizations or preferred provider organizations, nonemergency transfers and emergency runs. The city frequently has to pay less into this system because nonemergency patient transportation is profitable. Patient charges pay for the system rather than tax dollars.

The final model is the competitive private model. In this model, competing companies either vie for business or are centrally dispatched on a rotating basis. This tends to be the least costly. However, response times can be long, and the level of service may only be basic. This model can lack coordination.

Public service versus business. The bulk of the public service systems is usually paid by the taxpayer, with the individual patient paying only a portion of the cost. Public service systems tend to respond to the victim and obtain only essential information. Thus, most public service systems only obtain adequate billing information for the minority of patients. In contrast, public utility and competitive private systems obtain funding from the patient, with only a small subsidy coming from the city for indigent losses. The bills are itemized with a response fee, a mileage fee for transport and fees for any service rendered, similar to a hospital and physician's bill combined. These systems tend to provide more billable services for a far greater number of patients than do public service systems.

When a system is managed as a public service, there are a number of differences in the service that may not be noticed by the casual observer. A public service system tends to offer uniform levels of service. A public service system will position units so that response time is uniform for most citizens. A system operated as a business will operate the ambulances so that the load per ambulance is similar, which may lead to longer response times in the periphery. Neither the average response times nor the percentage of calls handled within a period may reveal these differences, but they could greatly affect some citizens.

Another difference between the two major approaches is the problem of unusual load requirements. At the time of a rain storm or disaster, business types of systems may not be able to respond as promptly as a public service system, which tends to staff for disaster. Fire Departments often have extra personnel who can be moved quickly from fire suppression to EMS should the need arise.

Business types of systems can respond more quickly to changes in technology, because most new technology can be billed. Because public service systems are a part of the governmental bureaucracy, it can be difficult and time consuming for them to add new technology.

Medical Direction

Strong medical direction must be present for all EMS systems, regardless of the level of care provided, to ensure that patients receive appropriate care and are taken to the appropriate facility. This includes setting patient care standards through protocols. It also includes effective physician or physician-directed input by means of radio or telephone communications where indicated (190,191,200).

PREHOSPITAL ASSESSMENT

Prehospital identification of patients with AMI. The primary purpose for prehospital 12-lead electrocardiographic (ECG) diagnostic programs is the early detection of AMI with ST segment elevation (207), and communication of that information to the receiving emergency physician before patient arrival. Multiple studies have shown the feasibility of performing prehospital 12-lead ECGs (208,219). Diagnostic-quality ECGs can be acquired and successfully transmitted in about 4 min in ~85% of patients eligible for 12-lead electrocardiography (210,211,215,216).

It has been demonstrated that prehospital 12-lead ECGs improve prehospital diagnostic accuracy for patients with a final hospital diagnosis of AMI, angina or nonischemic chest pain (210). For patients with a final hospital diagnosis of AMI in one study, the specificity of the base physician's prehospital working diagnosis (incorporating both paramedic-acquired history and a prehospital 12-lead ECG) was improved from 68% to 95%, and the positive predictive value increased from 33% to 71%, as compared with single-lead telemetry (210). When the 12-lead ECG alone was used by base physicians to diagnose AMI, sensitivity was 42%, specificity increased to 99.7% and positive predictive value increased to 97%, demonstrating that the prehospital 12-lead ECG alone was more accurate in the prehospital diagnosis of AMI than the ECG and historic information (210).

The direct impact that improved prehospital diagnostic accuracy has on treatment and outcome for patients with

AMI, angina and nonischemic chest discomfort remains to be fully characterized.

Reduced hospital-based time to treatment. Many studies have demonstrated significant reductions in hospital-based time to treatment with reperfusion therapy for patients with AMI identified before patient arrival (213,215,216,220). Time savings in these studies ranged from 20 to 55 min (213,215,216,220).

A similar time reduction was demonstrated by transmitting the prehospital 12-lead ECG directly to the receiving hospital (215). Different methods of patient transport and communication of diagnosis have also been assessed (216). The median hospital delay to treatment in one such study was 64 min for patients transported by private automobile, 55 min for patients transported by local ambulance, 50 min for patients transported by the EMS with a prehospital ECG obtained but not transmitted to the receiving hospital and 30 min for patients transported by the EMS with a 12-lead ECG transmitted from the field (216).

These data support the contention that prehospital identification of patients with AMI reduces hospital-based door-to-drug time and assists receiving hospitals in meeting the National Heart Attack Alert Program's recommendation of treatment within 30 min of arrival (187).

The management and outcome of patients receiving and not receiving prehospital 12-lead electrocardiography were evaluated in the National Registry of Myocardial Infarction-2 data base (221). Although the median time from infarct onset to hospital arrival was longer among those having a prehospital ECG, this group experienced a significantly shorter median time to initiation of either thrombolysis or primary angioplasty. The prehospital ECG group was also more likely to receive thrombolytic therapy, primary angioplasty or CABG. The in-hospital mortality rate was 8% in patients with a prehospital ECG and 12% in those without a prehospital ECG ($p < 0.001$). Investigators concluded that the prehospital ECG is a valuable test that is underutilized nationally.

Identifying thrombolytic candidates by checklists. Patients with AMI identified by a prehospital 12-lead ECG can be further classified as thrombolytic-eligible candidates through the use of a checklist. Prehospital thrombolytic therapy trials provide experience that appears to be useful in reducing time to treatment (212,217,222–228). In the U.S., paramedics, not physicians, have used checklists to identify thrombolytic candidates (209,215,219,220,229). One U.S. study directly addressed the accuracy of a paramedic contraindication checklist (209). The positive predictive value of case selection was 100%. Paramedic scene time was increased by only an average of 4 min (209).

These data support the feasibility, accuracy and time-effectiveness of prehospital identification of thrombolytic candidates through focused contraindication checklists. Such a checklist should be part of the prehospital assessment of all patients with chest discomfort, as recommended in the American College of Cardiology/American Heart Association's Guidelines for the Management of Patients with Acute Myocardial Infarction (230).

Computerized ECG programs. Several computerized ECG programs have potential to assist in improving prehospital AMI diagnostic accuracy and clinical decision-making.

Electrocardiographic criteria for the automated ECG diagnosis of AMI has been evaluated using the 12-SL interpretive algorithm (Marquette Medical Systems, Inc.) (218). This automated program diagnosed acute evolving Q wave myocardial infarction with 71% sensitivity and 98% specificity. Specificity was 100% when patients with a known previous Q wave myocardial infarction were excluded.

In another large study, the positive predictive values of the computer- and physician-interpreted ECG were 94% and 86%, respectively, and the negative predictive values were 81% and 85% (231). Computerized ECG algorithms are not all the same and should be prospectively validated before implementation (232,233).

Predictive instruments. The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) has been prospectively validated for use in the Emergency Department (234) and retrospectively validated for prehospital use (235). This predictive instrument is incorporated into a computerized electrocardiograph. Using the patient's age, gender and presence or absence of chest discomfort on presentation, the ACI-TIPI predicts the likelihood of acute cardiac ischemia (AMI or angina), along with the ECG. In one study, the ACI-TIPI was associated with a reduction in false positive diagnoses and reduced the number of hospital admissions among patients without acute ischemia (234).

PREHOSPITAL STUDIES OF FIBRINOLYTIC THERAPY

Several studies have reported results of trials of fibrinolytic therapy initiated before hospital admission. Most have been designed to evaluate time savings, resulting left ventricular function, infarct size and mortality differences in patients treated in the prehospital setting as compared with in-hospital treatment. In an early, small, randomized Israeli trial of prehospital versus in-hospital treatment aimed at evaluating left ventricular function, there was no difference in resulting ejection fraction despite a 43 min time difference between the groups. Mortality was also similar (228). The findings from this, as well as other, studies led to several randomized, controlled trials. The largest trial—the European Myocardial Infarction Project (EMIP)—was carried out in 15 European countries and Canada. Anistreplase was given as a bolus in the prehospital setting to 2,750 patients, and their outcomes were compared with those of 2,719 patients treated in the hospital (222). Although the project initially planned to enroll 11,000 patients to have sufficient statistical power to show a 3% difference in

mortality, recruitment was slow and the study was terminated early. The prehospital treatment resulted in an average time savings of 55 min from the time of onset of symptoms to initiation of treatment (130 min for the prehospital group vs. 190 min for the in-hospital group). Total mortality was reduced by 12% ($p = 0.08$) and cardiac mortality by 16% ($p < 0.05$) in prehospital-treated versus hospital-treated patients. The greatest effect on mortality was when treatment differences were >90 min between the two strategies.

The Grampian Region Early Anistreplase Trial (GREAT) was a study of 311 patients aimed at evaluating prehospital-initiated fibrinolytic therapy, this time given by general practitioners in patients' homes as compared with after hospital arrival. The average time to treatment was 101 versus 240 min, respectively. At three-month follow-up, patients treated in the prehospital group had fewer Q wave myocardial infarctions and had improved left ventricular function (236). The one-year mortality was substantially lower in the prehospital treatment group (10.4% vs. 21.6%, $p = 0.007$).

The Myocardial Infarction Triage and Intervention (MITI) trial was the largest randomized prehospital trial in the U.S. It included 360 patients who were initially screened by paramedics utilizing a checklist and ECGs, which were transmitted by cellular telephone to a base station physician for the assignment of treatment. The trial only included patients with a short time to treatment for chest discomfort onset in both prehospital versus hospital initiated thrombolysis groups (92 vs. 120 min, respectively). The prehospital treatment strategy, therefore, provided only a modest time savings of 33 min. There was no significant difference in complication rates between treatment strategies, suggesting that paramedic-administered treatment could be safe. The primary end point of the trial was a ranked composite score that included death, stroke, serious bleeding and infarct size measured by sestamibi imaging. The composite score was similar for both strategies (53% vs. 54%), infarct size (6.1% vs. 6.5%) and mortality (5.7% vs. 8.1%). To further explore the effect of treatment time, a secondary analysis was performed on all randomized patients. There were marked differences in both infarct size and mortality between patients treated within 70 min and those treated between 70 min and 3 h (1.2% vs. 8.7%, $p = 0.04$).

In a meta-analysis of the three major trials and from five smaller trials, there was a significant reduction in mortality among patients randomized to prehospital therapy ($p = 0.002$). It was estimated that the benefit–time gradient at 35 days was 21 lives saved per thousand treated per hour (237). These trials have suggested that when long delays of 60 to 90 min or greater are routine, then prehospital initiation of fibrinolytic therapy should be considered. It is clear, however, that prehospital electrocardiography performed by paramedics appears to reduce the total time to treatment and allows for preparation of staff at the receiving hospital. Most data also suggest that the time benefit of treatment is not linear, and that the magnitude is much greater in patients seen in the first hour as compared with 2 to 12 h (238) (Fig. 1). Unfortunately, few patients present to hospital within the first 60 to 90 min, making this strategy less attractive. The current approach requires an extensive expenditure of resources and organization for the benefit of a relatively small fraction of patients. Hospitals have markedly reduced the time to treatment in recent years from hospital arrival to thrombolytic therapy, whereas symptom onset to hospital arrival was unchanged at 2.4 h in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes trials over a seven-year period (182). Similar observations were made in the National Registry of Myocardial Infarction registry in over 250,000 patients treated with fibrinolytic therapy over a five-year period. Some studies have recently shown that treatment times are now in the neighborhood of 15 to 20 min. Both the EMIP and MITI trials have shown a substantially declining benefit of fibrinolytic therapy as a function of time. They provide community emergency services and hospitals an impetus for improving critical care delivery to patients with AMI.

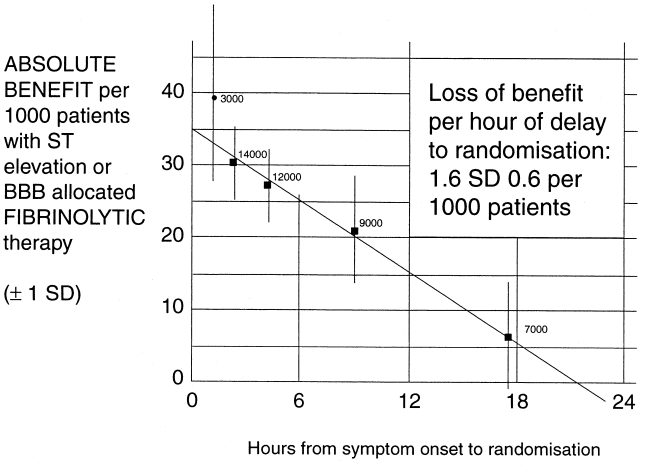

Figure 1. From Fibrinolytic trialists collaboration. Lancet 1994; 343:311–20.

REGIONAL PLANNING

Regional plans should be established to determine the manner of delivering emergency cardiac services. These plans should integrate the uses of various emergency resources, including both prehospital and hospital resources.

The regional plan should set out the appropriate criteria of how a patient is allocated to a particular hospital. Many systems currently require that the patient be taken to the closest facility. Other systems take the patient to the hospital of the patient's choice, as long as the system has the necessary resources to provide transport to another facility and the patient is stable. These simple policies fail to take into account how they affect the delivery of optimal care to

Table 2. Mortality Rates of Subsets of patients in Randomized Trhombolysis Trials

Variable	FTT	GUSTO-1	GUSTO-3
Age >75 years	25%	21%2	20%
HR >100 beats/min	20%	16%	18%
BP <100 mm HG	28%	16%	18%
Diabetes	14%	11%	12%

BP = blood pressure; FTT = Fibrinolytic Therapy Trialists; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes; HR = heart rate.

Table 3. Mortality Rates for the Two Forms of Reperfusion as Determined in a Meta-analysis of Randomized Trials (From Primary Coronary Angioplasty Thrombolysis Collaboration)

Variable	Primary PTCA	Thrombolysis
Anterior infarct location	8%	15%
Age >70 years	13%	24%
Previous MI	10%	23%
Diabetes	9%	19%

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

the cardiac patient. Transport to the closest facility may not be appropriate if the patient has been recently cared for at another facility or is at high risk of complications after myocardial infarction. In contrast, the closer facility may be able to provide care more quickly. Hospital crowding and bed availability should also be considered in the plan. These competing concepts must be considered in the planning process. A triage plan is particularly important for patients at high risk of death.

The hospital facilities in many urban and suburban areas vary widely, with some providing 24 h full tertiary cardiac services, others having inconsistent staffing with a catheterization laboratory but no surgery on site and still others having no tertiary cardiac services. Coronary care units, on the other hand, are common in all areas. The logical question, therefore, is should patients with AMI be diverted to places with full tertiary cardiac services? Unfortunately, this question has not been studied directly in any great detail. Throughout the U.S., patients with trauma are diverted depending on the severity of the illness and resources of the recovery hospital. This severity is gauged through assessment of various factors associated with type of injury as well as the initial clinical findings. Previous studies of elderly (Medicare) patients have suggested that the initial early treatment of AMI within the first day was the major determinant of survival at four years. In addition, this study showed that patients who lived within 2.5 miles of a hospital with cardiac catheterization facilities were substantially more likely to be admitted to a high volume AMI hospital (67% vs. 37%) and to undergo cardiac catheterization within seven days (21% vs. 11%), with a 1% absolute lower rate mortality at one year, as compared with patients living >2.5 miles away (239). These findings have been strengthened by the observations that patients admitted to a high volume hospital (>1.4 AMIs per week) had a lower mortality at one year (27% vs. 30%) than those admitted to a lower volume hospital (<1.4 AMIs per week). These findings were consistent across a variety of high and low risk criteria, but were not associated with a greater use of revascularization (240). However, the link between outcomes after AMI may be closely related to the more appropriate use of "evidence-based medicine" rather than the technology used (241). Large, randomized trials of thrombolytic therapy have shown that the 30-day and one-year mortality rates are closely related to certain baseline characteristics such as age, blood pressure, heart rate and signs of heart failure (167). The overall 30-day mortality rate from a variety of trials has been between 5% and 10%, whereas in certain subgroups the mortality has been substantially higher (Table 2) (242–244).

For patients with cardiogenic shock, the mortality has remained >50% in the majority of studies and has not changed over time (245). The same risk factors described earlier are also predictive for the development of cardiogenic shock, which typically occurs within the first 6 to 12 h after arrival to the hospital. These findings suggest that certain patient groups with heightened risk can be easily identified by simple measures.

Although individual randomized trials of thrombolysis versus primary PTCA have been done, a meta-analysis of the available data suggests that primary PTCA may be most advantageous among high risk patients (as defined earlier). The outcomes comparing one-year mortality from the meta-analysis (246) suggest particular benefit with primary PTCA among the high risk patients (Table 3).

Patients with cardiogenic shock represent the highest risk group. A prospective, randomized trial has identified a trend toward a reduction in 30-day mortality in patients randomized to emergency revascularization within 6 h of onset of shock as compared with a conservative approach (247). The benefit was seen across all groups, but was particularly apparent in patients <75 years old (41% vs. 57%). On the basis of these observations, it would appear that high risk patients with AMI should be triaged to a high volume AMI center that routinely (24 h service) offers emergency revascularization (PTCA and CABG) if the facility has a transport time of ≤30 min.

CONCLUSIONS AND RECOMMENDATIONS FOR PATIENTS WITH ACUTE CORONARY SYNDROMES

1. Public and professional education should be implemented to increase early recognition of symptoms,

reduce patient delay and enhance appropriate use of EMS systems.
2. The physician should ensure that those patients at risk for an acute coronary syndrome know when and how to react to their symptoms. Risk factor modification should be achieved for all patients.
3. When there is an emergency such as cardiac arrest, chest discomfort or other signs of acute coronary syndromes, 911 should be called directly and should be nationally available as the only emergency call number.
4. The 911 and EMS calls through cellular or digital telephones should have priority over nonemergent calls.
5. All types of telephones should have location identification that is transmitted to the 911 center.
6. All EMS dispatchers should be trained in medical dispatching, including prehospital instructions.
7. Communities should develop plans to optimize triage and treatment of patients with acute coronary syndromes.
8. The EMS providers should use a prehospital chest discomfort checklist.
9. Prehospital 12-lead ECG programs should be implemented in established urban and suburban paramedic systems.
10. Prehospital 12-lead ECG programs should communicate the prehospital findings to the receiving emergency physician before patient arrival.
11. Prehospital 12-lead computer-interpreted ECGs and predictive instruments should be prospectively validated.
12. Patients with myocardial infarction and hemodynamic compromise, cardiogenic shock or other high risk criteria should be triaged to medical facilities that have 24 h staffed cardiac care services that include emergency revascularization (percutaneous coronary intervention and CABG) and hemodynamic support available, provided ambulance transport duration is not excessive (>30 min). Triage should be performed as soon as possible, preferably in the field or in the nearest Emergency Department, depending on the medical community.
13. Routine prehospital thrombolytic therapy is currently not warranted, except possibly in systems with long transport delays and experienced EMS teams.

Task Force 2: Acute Coronary Syndromes: Section 2B—Chest Discomfort Evaluation in the Hospital

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RATIONALE

Reliable, cost-effective management of patients presenting to the Emergency Department (ED) with chest pain remains a major clinical challenge. There are over five million annual visits to EDs in the U.S. for this problem, resulting in two million hospital admissions at a cost of $8 billion (248), and three-fourths of these admissions for presumed myocardial ischemia or infarction prove to be incorrect (249). The primary goal in the management of patients presenting with chest pain is rapid recognition and management of a cardiac ischemic event. Secondary goals include assessment of risk in patients with suspected ischemia and minimization of unnecessary admissions for low risk conditions. Because of the focus on patient welfare and the litigation potential for failure to detect myocardial infarction (MI), a low threshold for admission has been applied in these patients, but 2% of patients with MI are discharged inadvertently, and the morbidity and mortality of this group are substantial (250). Underscoring this problem are data indicating that failure to diagnose MI has been the leading cause of medical malpractice awards against ED physicians (251).

Nontraumatic chest discomfort remains the primary stimulus triggering evaluation of patients for possible acute coronary syndrome (ACS) in the ED. The ACSs include unstable angina, non–Q wave MI and Q wave MI. To be included in the American College of Cardiology registry for ACS, ST segment changes must be present. However, for this report, ACS includes those patients with suggestive clinical presentations and/or positive biomarkers with or without ST segment changes (252). The clinician in the emergency setting must be suspicious, however, of atypical presentations for ACS. It is essential that emergency physicians be able to make a rapid, carefully focused clinical assessment to identify patients with ST segment elevation MI. Of patients presenting to the ED with chest pain, ~95% do not have electrocardiographic (ECG) evidence of evolving Q wave MI, and only 20% will ultimately have

evidence of unstable angina or non–Q wave MI (249). After the initial evaluation, including a directed history, physical examination and 12-lead electrocardiogram other methods must be used by the clinician to detect ACS in the ED. If the 12-lead ECG is nondiagnostic for ST segment elevation acute MI, patients with a possible ACS must be evaluated for 1) myocardial necrosis; 2) rest ischemia; or 3) exercise-induced ischemia (253). Many hospitals have developed a protocol-driven approach to achieve these objectives (254,255). Through efficient evaluations that take 6 to 12 h, myocardial necrosis is detected by cardiac biomarkers; rest ischemia is documented by serial ECG or ST segment trend monitoring and, if needed, echocardiographic or radionuclide studies; and exercise-induced ischemia is assessed by exercise testing, stress echocardiography or radionuclide testing.

A comprehensive, protocol-driven approach is essential because it minimizes variability in diagnosis and treatment of ACS and promotes optimal management. The evaluation must be complemented by careful documentation of diagnostic results and treatment. Communication with the patient's primary physician is essential to ensure appropriate evaluation and treatment in the ED, and care must also be coordinated with the cardiovascular specialist, when appropriate.

Evaluation in the hospital ED or chest pain center (CPC). Chest pain centers or programs were initially developed to facilitate therapy for patients with acute MI and other ACSs (253,256–259). Their number has grown continuously, and they have subsequently evolved to include safe, cost-effective management of low risk patients presenting with chest pain. It was recently estimated that 30% of hospitals in the U.S. have these units, which number ~1,200 (256).

The rapid increase in CPCs was stimulated in the early 1980s by the need to reduce time to coronary reperfusion therapy (257). The necessity for safer, more cost-effective management of low risk patients, who comprise the majority presenting to the ED with chest pain, has been a major factor in their continuing growth (206,260–262).

Chest pain units vary in form and may be based more on process and coordination of skilled personnel (cardiologists, emergency physicians and nurse specialists) and availability of dedicated equipment than on physical structure. Emphasis is on protocol-based, systematic management to promote optimal application of current standards of care. Guidelines, or critical care pathways, are commonly employed. There are few controlled trials on the utility of CPCs in the management of high risk patients, but the importance of rapid coronary reperfusion therapy is incontrovertible. Recent data demonstrate the efficacy of achieving this objective with a chest pain unit strategy (263). In addition, the importance of early stratification of patients into high and low risk groups is emphasized in the first published guideline for the management of unstable angina (264).

The emphasis of CPCs is variable. Some focus on high risk patients, whereas others primarily aim to decrease unnecessary admissions of low risk patients. In addition to a directed history, physical examination and administration of aspirin, current recommendations include ECG acquisition and interpretation within 10 min to detect myocardial ischemia and make a decision regarding coronary reperfusion therapy, which should be initiated within 30 min of presentation in appropriate patients (188,265,266). Many clinicians advocate briefer time limits for assessment and initiation of therapy (e.g., <20 min). Patients with non–ST segment elevation ischemic syndromes also require prompt identification and treatment. These two groups of patients are recognized as high risk and are transferred to the inpatient service for further management.

In contrast, low risk patients with chest pain, characterized by a stable clinical status and a normal or nondiagnostic ECG, have been increasingly managed by a variety of accelerated diagnostic protocols, usually 6 to 12 h of monitoring and serial cardiac biomarkers (254). If this evaluation is negative, exercise testing (or another noninvasive cardiac stress study) is usually performed, and the patient is discharged if there are no abnormalities. Multiple techniques are currently being assessed for detection of myocardial ischemia during accelerated diagnostic protocols. These include innovative ECG methods, clinical algorithms, new biomarkers, noninvasive cardiac imaging and immediate exercise testing (255). It has been amply demonstrated that accelerated diagnostic protocols utilizing one or more of these techniques in patients identified as low or intermediate risk on the basis of their initial presentation are safe and accurate. Length of stay has been consistently reduced, and subsequent risk in patients with negative evaluations is low. Initial data suggest this strategy is cost-effective, but controlled studies are few, and it is recognized that this approach has the potential for overutilization of expensive tests.

Link between the "chest pain ED movement" and the chest pain awareness educational program. One goal of the "Chest Pain ED Movement" has been development of a partnership between emergency physicians and cardiologists in a continuous quality-improvement process to enhance delivery of heart attack care through community penetration that links the CPC with an early symptom community awareness program. A major focus of this strategy is addressing reasons for delay when patients are having early symptoms. One focus should be on patients presenting with central chest discomfort, not necessarily perceived as chest pain, as well as those with chest pain. Thus, the CPC movement is a strategy to reduce the time to treatment in patients with evidence of early active ischemic heart disease. The new paradigm, as seen in this light, represents a shift in care to enhance present day management of patients with ischemic heart disease.

Operational plan of the CPC. The development and effective operation of a CPC require coordination at multiple levels within the institution, including 1) administrative support (budget, personnel); 2) development of a protocol by emergency physicians, cardiologists and nurses; and 3) integration of special services such as exercise testing, nuclear cardiology, echocardiography and pharmacy. Of primary importance, optimal management in CPCs is critically dependent on communication between the cardiologists and ED physicians.

STAFF. The location of the CPC typically determines the mix of personnel needed to staff the unit. If it is contiguous with the ED, emergency nurses often staff the program. This requires a nurse to patient ratio of approximately 1:4, similar to that of noncritical care areas of the ED or a coronary care unit (CCU) step-down unit. Special training of emergency nurses is necessary before working in a CPC environment. This may include information regarding biomarkers, serial 12-lead electrocardiography or ST segment trend monitoring, exercise testing, echocardiography and radionuclide testing. The CPC stay is also an excellent opportunity to educate patients about ACS, risk factors and the importance of timely follow-up with a cardiologist or other appropriate physician if the evaluation is negative.

Nurse practitioners and physician assistants may help to staff CPCs, but decisions to treat, admit or release the patient require physician involvement in every step of care and are the responsibility of the attending physician. Technicians who perform studies such as echocardiography or nuclear cardiology are essential and must have the flexibility to follow protocols. The availability of technicians at night or on weekends determines not only the frequency of testing, but also the ability of a CPC to extend service beyond the traditional scheduling limits.

PHYSICIANS. If the CPC is located in or next to the ED, emergency physicians are responsible for evaluating and monitoring patients, administering therapy and developing disposition plans for hospital admission or discharge. The CPC requires 15 to 20 patients at a time to justify the presence of a dedicated emergency physician at all times. Smaller CPCs are usually served by physicians with other responsibilities in the ED. Typically, two or more physicians working simultaneously in the ED are necessary to allow sufficient free time to attend to patients in the CPC.

In CPCs in or next to the ED, emergency physicians monitor symptoms and signs, interpret diagnostic tests and initiate therapy for patients admitted with ACS. As a functional component of an ED, the availability of an emergency physician 24 h per day, seven days per week remains an essential component. Offline discussions regarding protocols with referring physicians, clinical pathologists and cardiologists ensure a consistent approach to evaluation, treatment, patient education and follow-up plans for patients discharged. Such communication with cardiologists allows a coordinated approach to administering antiplatelet and antithrombotic agents, nitroglycerin and beta-blockers in a protocol-driven manner. For patients with ST segment elevation consistent with acute MI, fibrinolytic therapy is usually administered without previous consultation with a cardiologist. In hospitals where primary angioplasty is available, communication with the interventional cardiologist is necessary to decide between thrombolysis and primary angioplasty and to coordinate mobilization of the cardiac catheterization laboratory team if the latter therapy is selected.

In institutions where the CPC is located in the CCU or serves as a part of an inpatient step-down unit, cardiologists (or internists) are responsible for serial examinations, interpretation of diagnostic testing and, if such testing is positive for an ACS, therapeutic directives.

For CPCs adjacent to the ED or CCU, cardiologist involvement in the care of the patient at the end of a 6 to 12 h protocol is often necessary to interpret predischarge tests such as exercise electrocardiography or imaging. The decision to admit a patient to the hospital or discharge the patient often requires the collaboration of the cardiologist and the physician responsible for the patient in the CPC. In institutions without a structurally designated CPC, the goals of this strategy can be implemented by adhering to protocols that focus and coordinate the efforts of the diverse personnel noted earlier to provide optimal management of patients presenting with chest pain. In this approach, the CPC process remains foremost.

INITIAL TRIAGE

The goals of clinical assessment of the patient with chest pain are 1) to distinguish those patients with ischemia or infarction from those with other potentially serious (aortic dissection, pericarditis, pulmonary embolism) or less serious causes of chest pain; 2) to assess the risk of early adverse outcomes in patients with suspected ischemia or infarction; and 3) to initiate therapy rapidly in patients with serious clinical conditions. Initial evaluation of the patient with chest pain includes a careful history and physical examination and, in almost all cases, an ECG. It may be performed by emergency medical service personnel, the triage nurse, physician or other medical personnel. The evaluation may begin at home, at the work site or another location and continue during transfer and in the ED or outpatient facility. Patients with probable ischemic pain and patients with high risk features such as severe or prolonged pain or hemodynamic compromise should be transported to the ED by ambulance. Proper assessment at this point is critical to the efficacy and cost-effectiveness of subsequent testing.

Differential diagnosis of chest pain. Until recently, the description of the characteristic pain of myocardial ischemia was based almost exclusively on data from men. However, a number of patient groups commonly present with "atypical" symptoms. In women, ischemia may be manifested by symptoms such as fatigue, dyspnea or epigastric pain. Other groups commonly presenting with atypical symptoms in-

clude diabetics and the elderly. These factors must be incorporated into the clinical evaluation.

CORONARY ARTERY DISEASE (CAD). The key factors in recognizing ischemia in the ED are the characteristics of the symptoms, the ECG, a history of CAD and evidence of hemodynamic or electrical instability. The presence of coronary risk factors may be a helpful predictor, but is of limited utility and may even be misleading in this setting, as compared with other variables such as the ECG. However, in the absence of strong clinical or ECG evidence of ischemia, assessment of risk factors has value. The discomfort or pain of myocardial ischemia or infarction is generally described as tightness, heaviness, pressure, burning, aching, squeezing, constriction or "indigestion." It usually comes on gradually over a minute or two and lasts minutes rather than seconds. It is usually not affected by respiration or changes in position. It is usually felt in the central chest, with other common sites including the throat, jaw, back, epigastrium, left chest and arm (usually left). Associated symptoms include sweating, dyspnea, nausea, vomiting, lightheadedness, weakness and malaise.

Typical angina is precipitated by physical or emotional stress and is relieved by rest. The discomfort of stable angina (most often *not* described as pain) is often relieved or lessened within 2 to 5 min of the administration of sublingual nitroglycerin. Ischemic pain due to infarction may not be relieved by nitroglycerin. On physical examination, particular attention should be directed to signs of pulmonary congestion and the presence, during symptoms, of an S_3 or paradoxic splitting of S_2 (sign of systolic left ventricular dysfunction), an S_4 (sign of diastolic dysfunction) or a murmur of mitral regurgitation (sign of papillary muscle dysfunction). Peripheral pulse deficits, or bruits, are valuable clues to the presence of atherosclerosis, aortic dissection or, rarely, vasculitis.

Electrocardiographic tracings should be obtained whenever possible in both the presence and absence of chest pain. The ECG should be examined for evidence of a previous MI. ST segment elevation $\geq$1 mm is generally indicative of acute MI, but must be distinguished from other conditions (e.g., early repolarization, pericarditis). Lesser degrees of ST segment elevation are less specific for MI. Any ST segment or T-wave abnormalities that are observed in the presence but not in the absence of chest pain are suggestive of myocardial ischemia. Peaked T-waves may be due to hyperkalemia or may be a hyperacute manifestation of ischemia. Fixed ST segment and T-wave abnormalities are usually less specific, but are suggestive of myocardial ischemia or infarction if there is $\geq$1 mm ST segment depression or elevation or deep symmetrical T-wave inversion. In contrast, a normal ECG does not reliably exclude the diagnosis of myocardial ischemia (or even infarction). It is often helpful, and in some clinical presentations essential, to obtain frequent serial ECGs (266).

PERICARDITIS. Pericarditis may occur in patients with connective tissue disease, malignancy, previous radiation, recent MI or thoracotomy or uremia or in previously healthy individuals. The pain is usually sharp, midcentral in location and worsened by inspiration or lying down. It may be felt in the left chest, supraclavicular area, shoulder and, rarely, the back. Fever may be present; difficulty taking a deep breath should be distinguished from true dyspnea. A two- or three-component pericardial friction rub is pathognomonic of pericarditis. Pulsus paradoxus and jugular venous distention suggest pericardial tamponade. Diffuse ST segment elevation, as well as PR segment depression, strongly supports the diagnosis of acute pericarditis. Further evaluation includes a chest radiograph and echocardiogram.

AORTIC DISSECTION. Patients with hypertension, Marfan's syndrome, trauma or bicuspid aortic valve or previous aortic valve surgery and those who are pregnant are at risk for dissection of the thoracic aorta. The pain of dissection is usually abrupt in onset and is often described as ripping or tearing, but may be similar to the pain of myocardial ischemia. It is located in the chest or back, or both, and may radiate to the teeth. Associated symptoms are related to affected branches of the aorta and include angina, dizziness and other neurologic complaints. Physical examination may reveal unequal arm blood pressures, pulsus paradoxus (due to associated cardiac tamponade), signs of left pleural effusion, aortic insufficiency and pulse deficits. The ECG may reveal myocardial ischemia (usually in the distribution of the right coronary artery). When the initial assessment suggests aortic dissection, imaging with chest radiography, transesophageal echocardiography, computed tomography or magnetic resonance imaging, or a combination of these, is appropriate. Fibrinolytic therapy should not be initiated if the diagnosis of aortic dissection is being considered seriously in the differential diagnosis.

PULMONARY EMBOLISM. Patients at risk for pulmonary embolus include those with pelvic or leg trauma, previous surgery, immobility, obesity and hypercoagulable states. "Pleuritic" chest pain results from pulmonary infarction. Substernal pressure or discomfort may be due to right ventricular ischemia resulting from an increase in pulmonary vascular resistance and a decrease in systemic arterial pressure, and thereby coronary perfusion pressure. Tachypnea and tachycardia are common findings. In the presence of massive pulmonary embolus, the ECG may show an S_1-Q_3 pattern, a rightward axis and right precordial T-wave inversions. Further evaluation may include a $\dot{V}\dot{Q}$ scanning, contrast spiral computed tomographic scanning, pulmonary angiography and noninvasive evaluation of leg veins. Unless there is a contraindication, heparin is begun when the diagnosis is first discussed.

OTHER CAUSES OF CHEST PAIN. Exertional (and, rarely, rest) angina can occur in patients with aortic stenosis,

hypertrophic cardiomyopathy, pulmonary hypertension or pulmonic stenosis. Chest pain may be caused by a thoracic aortic aneurysm, pleuritis and pneumothorax. Of several gastrointestinal causes of chest pain, esophageal spasm is noteworthy in that it may be relieved by nitroglycerin. The pain of herpes zoster may bring patients to medical attention before bullae appear. Various musculoskeletal disorders, including arthritis of the cervical spine, costochondritis and chest wall muscle injuries may cause pain that mimics angina. Careful palpation of the chest wall may indicate point tenderness and reproduce the patient's presenting symptom.

LOW RISK PATIENTS

The low risk population can be readily recognized in most cases from the initial clinical presentation and the ECG. Patients with chest pain with a risk of MI <5% and a risk of cardiac complications <1% can be identified by this approach (267). Patients with negative findings after evaluation in the CPC of the ED usually have noncardiac etiologies of their symptoms and often require further outpatient studies to determine the cause of their symptoms so that appropriate therapy can be initiated. It is essential that further evaluation be done in conjunction with the patient's primary physician. Noncardiac conditions (e.g., gastrointestinal, musculoskeletal, pulmonary, psychological) may be responsible for chest pain symptoms that initiate a cardiac evaluation. Too often, evaluation ends with the negative cardiac workup. Identification of the etiology of symptoms in this sizable group of patients has the potential to ameliorate the patient's problem and avoid unnecessary return to the ED. In some patients, even the most thorough evaluation for noncardiac sources of pain is unrevealing. These patients rarely have a life-threatening problem, but their symptoms may be disabling. A physician expert in pain management may be helpful in such cases. Up to 40% of patients with a negative workup have chest pain related to panic attacks. This is infrequently recognized by physicians during the acute episode and on follow-up (268). Somatization syndrome (multiple symptoms across organ systems without an organic basis) is a relatively common noncardiac cause of chest pain in patients presenting to the ED. If patients meet the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (269) criteria for diagnosis, consideration of cardiac disease should be based on objective findings. Other patients with nonischemic pain may have what has recently been termed the "sensitive heart," in which normal physiologic stimuli (e.g., changes in intracardiac pressure, blood flow and heart rate) are sensed as discomfort or pain in the chest (270). In contrast, some patients with chest pain have myocardial ischemia with angiographically normal coronary arteries (syndrome X) (271).

ASSESSING LEVELS OF RISK AND APPROPRIATE INITIAL MANAGEMENT IN PATIENTS WITH MYOCARDIAL ISCHEMIA OR INFARCTION (HIGH RISK PATIENTS)

Once the diagnosis of myocardial ischemia or infarction is made, the clinician must assess the history, physical examination and ECG to determine 1) the pace of initial therapy, including acute reperfusion strategies, if indicated (266,272); and 2) the appropriate next step in evaluation if reperfusion therapy is not indicated.

Appropriate patients with ST segment elevation MI should receive coronary reperfusion therapy. Selected high risk individuals with non–ST segment elevation ACS should be admitted for intensive medical management or coronary angiography (264,266,272).

INTERMEDIATE RISK PATIENTS: FURTHER EVALUATION

Continuous ST segment ECG monitoring and nonstandard ECG lead systems: use in patients with chest pain who present to the ED. The rest 12-lead ECG is the standard of care in the diagnosis of patients with chest pain seen in the ED. Approximately 50% or less of patients with acute MI or ACS initially have a positive 12-lead ECG. Because early diagnosis is crucial to myocardial salvage, newer strategies have been advocated for increasing the sensitivity of the 12-lead ECG. These include serial electrocardiography, continuous ST segment ECG monitoring and the use of nonstandard lead systems, including posterior and right ventricular leads. Recommendations for the use of newer diagnostic technologies should rely on prospective, randomized studies that 1) clearly show an incremental benefit in terms of either diagnosis or prognosis; 2) take into account the availability, ease of use and applicability; and 3) demonstrate cost-effectiveness. Sensitivity and specificity are important measures of a diagnostic test, but positive and negative predictive values, which are highly dependent on the prevalence of disease in the population tested, are more important in determining the incremental value of a new test or procedure.

STANDARD ECG. A 12-lead ECG should be obtained on admission and repeated in 15 to 30 min if there is high suspicion of myocardial ischemia or if there is recurrent chest pain. In patients with negative accelerated diagnostic protocols, a repeat ECG should always be obtained before stress testing.

CONTINUOUS ST SEGMENT MONITORING. This technique for detecting ischemia has been studied predominantly in patients with established CAD. Its role in the detection of myocardial ischemia in patients who present to the ED is unclear. In one recent study in a CCU setting (with a high prevalence of CAD), there was a 40% false positive rate of ST segment shift. With the lower prevalence of CAD in

most patients with chest pain who present to the ED, this high incidence of false positive tests would be expected to reduce the positive predictive value of this method. In another study, the sensitivity for detecting acute MI and ACS was increased from 55.4% to 68.1% using continuous ST segment monitoring as compared with the initial ECG, with a corresponding increase in the likelihood ratio of 10.3 to 13.1. In one additional study performed in a CPC/ED protocol, the sensitivity of serial ST segment monitoring was 21.2%, and the positive predictive value was 64.7%. However, its additive value was unclear. In summary, the cost-effectiveness of ST segment monitoring used in concert with other measures has not been assessed directly, and thus its role in the ED for patients with chest pain is uncertain.

RIGHT-SIDED ECG LEADS. The sensitivity of the standard 12-lead ECG in diagnosing right ventricular and posterior infarction is extremely low. These limitations have given rise to the evaluation of a number of nonstandard lead placement systems. The most common of these are right ventricular leads, of which the most sensitive is V_4R. The sensitivity and specificity for diagnosis of right ventricular infarction with the V_4R lead is ~80% during the initial 24 h of infarction. A number of prospective studies have demonstrated that right ventricular MI is a significant negative prognostic factor in patients with coexistent inferior wall MI. A V_4R lead should be recorded at least once, as early as possible, in all patients with inferior or inferoposterior wall MI.

POSTERIOR LEADS. The 12-lead ECG is least sensitive for detection of posterior ischemia in the distribution of the left circumflex coronary artery (273). The use of leads V_7 through V_9 offers incremental benefit for diagnosing posterior MI. The use of posterior ECGs leads V_7 through V_9 is appropriate if there is suspicion of posterior infarction. It cannot be recommended routinely for all patients presenting to the ED with chest pain.

Biomarkers of cardiac injury for the treatment of low risk patients. Two strategies have competed in this area. The first relies on two markers—a rapid rising marker and a marker that takes longer to rise but is more specific. This strategy is predicated on the assumption that early diagnosis of MI will change care by:

1. Facilitating identification of patients who may be candidates for aggressive intervention.
2. Streamlining and improving flow within the CPC/ED setting.
3. Providing the ability to discharge patients earlier.
4. Facilitating the triage of patients who are admitted to various parts of the hospital.

Both myoglobin and isoforms of creatine kinase, MB fraction (CK-MB) have been proposed for this purpose. In the latest trial to date, no statistically significant differences were observed between these markers (274). Myoglobin is rapidly released from the myocardium and therefore is often elevated in the first sample after presentation. Definitive inclusion of infarction takes at least 6 h (274). The failure of myoglobin to change over time by some predetermined amount effectively excludes evolving infarction (275).

Isoforms of creatine kinase function on a different principle. Low levels are present in the blood normally. Thus, sensitive detection of a change can achieve earlier diagnosis.

This strategy allows the early identification of patients without infarction who may need stress testing or other follow-up evaluation. Individuals in whom biomarker levels are increasing require additional sampling for either CK-MB or troponin so that a definitive diagnosis of infarction can be made with markers that have a higher degree of specificity. Both myoglobin and CK-MB isoforms lack tissue specificity. Thus, subsequent samples to diagnose infarction may be needed at 6 and often 9 to 12 h. These samples also allow detection of a subset of patients who may have small amounts of necrosis as documented by a sensitive marker like troponin. This group may have had cardiac insults in the days before admission or a minimal amount of myocardial necrosis more sensitively detected by troponin. Regardless of the mechanism, this group is known to have an adverse short- and long-term prognosis (276–279), and preliminary data suggest that these patients may benefit from more intense therapy (280). Although CK-MB is frequently used at present for definitive "late diagnosis," eventually the troponin markers will replace CK-MB for this purpose.

The troponins (cardiac troponins I and T) are a new class of markers that have unique cardiac specificity (281). It is now clear that for both markers, elevations are indicative of cardiac injury only. In addition, at the present levels of assay sensitivity, the troponins are more sensitive than CK-MB for minor myocardial necrosis (282). Furthermore, continuing release of troponin occurs for many days or even weeks after cardiac injury (283). Inpatients who are at high risk for ischemic heart disease (e.g., patients with unstable angina, elevations) almost always have ischemic injury, and multiple studies have confirmed that elevations presage an adverse short- and long-term prognosis (276–279). Elevations are more problematic in low risk patients. Hamm et al. (284) have shown that elevations identified all of the patients at risk in a cohort of 733 patients with chest pain and nondiagnostic ECGs. Other investigators have shown a significant relation between positive troponins and underlying, severe CAD in otherwise low risk patients in the CPC (285). Elevation of troponins may also occur in a second group of patients who have nonischemic cardiac injury related to a transitory or chronic process. Thus, elevations in low risk patients would not always be associated with CAD.

The second strategy suggests that the urgency is less critical than suggested by the first strategy (286). The tactic involved is simply to measure a single CK-MB or cardiac troponin, with the understanding that definitive exclusion

or inclusion of infarction will take longer. At present, for the troponins, it appears that at least 9 h is required, depending on the cutoff value utilized, and for CK-MB, the general time is 12 h. These times can be altered somewhat by choosing different critical values for diagnosis. The logic of this strategy insists that marker proteins will not facilitate the evaluation of patients in need of an immediate intervention, because most of these patients present with clinical syndromes and ECG changes that are easily identified. It further argues that discharge and in-hospital triage will not suffer substantially from a 2 to 3 h delay. The advantage of this strategy is that it is definitive in both directions (to include and exclude infarction).

The strategy suggested by Hamm et al. (284) is to use a low cutoff value with troponin markers in serial samples obtained on admission and at least ≥6 h after the onset of symptoms. A low cutoff value uses the level of detectability of the assays, and with that criterion, all patients at risk for events during the first 30 days, even without additional stress testing, are identified. The benefit of this strategy is that it combines the early negative predictive value of rapidly appearing markers with a high level of positive predictive value. The disadvantage of this strategy is that minor elevations of troponin are frequent in patients who have hypertension, congestive heart failure and other clinical syndromes that may cause minimal amounts of myocardial damage.

The rapid availability of test results is essential. Most laboratories acknowledge that a turnaround time of 30 to 60 min for these tests is standard. If the availability of results takes substantially longer, point of care testing should be considered (287). At present, the devices available are not as accurate or as easy to use and interpret as they will likely become; they are also several fold more costly, and regulatory issues add to the difficulty of their use. Nonetheless, their use is advocated if laboratory turnaround times are inadequate for the needs of the patients. It is clear that strategies will need to be developed to accommodate local needs. No matter what strategy is employed initially, it is likely that in the long term, it will evolve into one predicated on troponin markers.

Predictive instruments. The major reasons for development of these decision aids are to standardize care and improve efficiency. Physicians, in general, tend to be risk adverse by nature, overestimate the probability of complications and have a low threshold for admitting low risk patients (288). Accurate estimates of patients' probabilities for complications might support physicians in their transfer of low risk patients to be treated at non-CCU facilities or at home. It has been shown, in patients presenting with chest pain, that ECG and other clinical data predict risk of acute MI (289), and these factors also predict which patients will have complications (267). On the basis of clinical features, patients can be stratified into four groups, with the risk of major complications in the first 72 h ranging from 0.7% to 20% (267). These data can also be used to stratify patients according to their risk of long-term complications (248). Decision aids have been adapted and incorporated into computerized ECG reports to help clinicians in the triage process (234,290).

Although studies continue to show that algorithms based on multivariate statistical techniques have the *potential* to improve medical decision-making (291), prospective trials have consistently shown minimal or no impact of attempts to use these algorithms in practice (292–294). Some data indicate that physicians do not use these algorithms because they are too busy or do not perceive their value (292), or because they are concerned about the medicolegal and clinical consequences of inappropriate discharges of patients (295,296). An important current focus of research is to integrate decision aids into routine data acquisition, such as through predictive instruments (234) or critical pathways (297).

Guidelines and critical pathways. Standards of care for the initial evaluation of patients with chest pain have been developed by several organizations, including the American College of Emergency Physicians (ACEP) (298). These guidelines stress that the decision to admit the patient must be primarily based on clinical judgment and do not make recommendations about levels of care (CCU versus intermediate care of CPC) for different patient subsets. The ACEP statement provides "rules" and "guidelines" about the data that should be obtained, and recorded, as part of the evaluation, as well as the actions that should follow from certain findings. "Rules" are considered actions that reflect principles of good practice in most situations. "Guidelines" in the ACEP document are actions that should be considered; there is no implication that failure to follow a "guideline" constitutes improper care. These guidelines also emphasize the need for a functional design of the program, appropriate staffing, quality assurance and outreach, in addition to the ability to diagnose and initiate therapy in patients with acute MI and unstable angina and to evaluate those low risk patients with chest pain.

The National Heart Attack Alert Program (NHAAP) has issued guidelines for specific functions related to evaluation and treatment of patients with chest pain aimed at improving the speed with which patients with acute MI are identified and treated (265). Guidelines for the care of acute MI and unstable angina are available to direct care for patients with clear evidence of those syndromes (266,272,299).

Guidelines from the Agency for Health Care Policy and Research (AHCPR) for unstable angina indicate that not all patients with this syndrome require admission, but recommend ECG monitoring patients with unstable angina during their evaluation; those with ongoing rest pain should be placed in bed rest during the initial phase of stabilization (264). The ACEP policy statement indicates that patients who are discharged should be provided a referral for

follow-up care, as well as instructions regarding the treatment and circumstances that require a return to the ED (298).

Institutional guidelines to increase efficiency have generally emphasized two strategies: 1) triage of low risk patients to non-CCU–monitored facilities such as intermediate care units or CPCs; and 2) shortened lengths of stay in the CCU and hospital. Recommendations regarding the minimal length of stay in a monitored bed for a patient who has no further symptoms have been decreasing over the last two decades from 24 h (300) to 12 h (301), to even shorter periods if exercise testing or other risk stratification technologies are available (254,297).

Several studies have shown inconsistent application and impact of guidelines. In one study, there was no effect on admission rates, triage decisions or length of stay (293). In another, a 26% reduction in length of stay resulted in use of the guideline (302).

One strategy for optimizing and streamlining care is through critical pathways (297,303). These predefined protocols outline and manage the crucial steps in defining a clinical problem and treating that patient and aim to improve quality of patient care, reduce variability and enhance efficiency. Data are collected to define the rate-limiting steps for each patient group and to provide feedback to health care providers and managers regarding the care rendered.

There are at least two important differences between a critical pathway and more traditional guidelines: 1) critical pathways define time goals for the performance of key tasks; 2) critical pathways should be used to collect information on rates at which these tasks are performed within the target period.

Data on the impact of critical pathways on efficiency and patient outcomes are not yet available. Such data are likely to have limited generalizability, because the effectiveness of a pathway depends heavily on the capacities of the institution in which it is implemented and whether data are fed back to clinicians as part of a quality-improvement process. Furthermore, pathways evolve quickly with the adoption of new technologies such as cardiac markers of injury.

Exercise testing. Recent studies have confirmed the safety, accuracy and utility of early treadmill exercise testing in low risk patients presenting to the ED with chest pain. These data stem primarily from investigations of patients with negative evaluations in accelerated diagnostic protocols (6 to 12 h of monitoring, negative serial cardiac biomarkers) who then undergo predischarge exercise testing. In this context, the test is used to determine the need for further inpatient evaluation (positive test) or suitability for discharge with follow-up (negative test). Accelerated diagnostic protocols, including exercise testing as a key element, have been associated with reduced hospital stay and lower costs. There have been no adverse effects of exercise testing in this setting, and a negative test has accurately identified low prognostic risk (i.e., patients with negative evaluations on accelerated protocols have had the same posthospital course as those with negative findings with traditional, longer hospital stays) (254,255). Exercise treadmill testing has been adequate for evaluation after a negative accelerated protocol. There are no data indicating that stress imaging tests add to predictive accuracy in this group.

One group has employed "immediate" exercise testing of low risk patients in the ED without previous evaluation by serial cardiac biomarkers (304,305). These patients were clinically stable and had normal or near normal ECGs and a negative screening evaluation (physical examination, chest radiograph). This method has been safe and effective, with no adverse effects of exercise testing in >1,000 patients (306), and has been used to identify patients who could be discharged directly from the ED and those who required admission. However, it has been associated with a low (<1%) rate of inadvertent testing of patients with inapparent non–Q wave MI (306). This approach requires further study.

Echocardiography. Left ventricular wall motion abnormalities in a patient with acute chest pain should be considered suggestive of ischemia (307). However, echocardiography cannot distinguish new abnormalities of wall motion or systolic wall thickening (due to either reversible ischemia or acute infarction) from those that are old (previous infarction), and it may detect abnormalities that are unrelated to ischemia in patients with conduction abnormalities such as paced rhythms and bundle branch blocks, thus limiting its specificity. In addition, with minimal or nontransmural myocardial involvement, even with acute MI, wall motion abnormalities may not be detected by early echocardiography (308).

In general, the sensitivity and specificity of the echocardiogram for detecting acute ischemia as the etiology of chest pain symptoms are best when it is used during or soon after an episode of pain. Small studies in highly selected groups without a previous infarction or other cardiac abnormalities have shown sensitivities and specificities of 86% to 92% and 53% to 90%, respectively, in this setting (207). In one unselected group with chest pain, 94% of patients had technically adequate images for assessment of ischemia, and even in these patients, the sensitivity and specificity were only 93% and 57%, respectively (309). However, echocardiography may provide information such as abnormalities of global left ventricular function or wall motion suggestive of previously unrecognized CAD. Localized wall motion abnormalities may also help identify the culprit artery in acute ischemia.

To be most useful for diagnosis and early risk stratification, the echocardiogram would need to be available immediately in the ED, with highly trained personnel to obtain and interpret the study (310,311). Ideally this service would be immediately available 24 h a day, seven days a week.

Technology to provide transtelephonic interpretation of digital images is available (312).

Finally, study of the economics of incorporation of echocardiography into routine evaluation of chest pain in the ED, or of basing triage decisions on its results, has yet to be done. In early 1997, the NHAAP Working Group on "Evaluation of Technologies for Identifying Acute Cardiac Ischemia in the ED" (207,233) concluded that even in highly selected groups, the sensitivity of echocardiography was not sufficient to warrant its use for triage and risk stratification in the ED. There remains a lack of comparative, prospective clinical trial information on the diagnostic performance, clinical outcomes and costs of using early echocardiography for risk stratification and triage decisions in chest pain evaluation in the ED (313–315).

Stress echocardiography. Stress echocardiographic testing may be useful for risk stratification of patients with negative cardiac markers or normal rest echocardiographic data before discharge. The incremental value of stress echocardiographic imaging over standard ECG stress testing remains to be determined. This is particularly true in patients with baseline normal ECGs and in other groups (e.g., women, young men) in whom false positive rates for ECG stress testing are relatively high (316,317).

Conclusions. Given the technical limitations, resource requirements and somewhat limited sensitivity and incremental value of echocardiography in the ED setting, this modality should have further prospective study in comparison with standard strategies before recommending its widespread use in acute chest pain evaluation.

Myocardial perfusion imaging in patients presenting to the ED with an ACS. Investigations from the late 1970s documented the power of planar thallium-201 imaging to predict outcomes in patients presenting with ACSs (318–320). New technetium-99m–based radiopharmaceutical agents for myocardial perfusion are better suited for early use by allowing "uncoupling" of the injection from imaging and providing concurrent evaluation of function (321–325). For optimal value, it is preferred that early perfusion imaging be provided daily on a 24 h basis. The principal barriers to providing this service around the clock are cost and timeliness of radiotracer availability. In patients with an ACS, the optimal value of imaging requires injection during or as soon as possible after symptoms start (326). This can only be accomplished if radiotracer is available in the ED and an in-house staff member is available to perform the injection at all times.

Clearly, the availability of imaging capability in or next to the ED is optimal. All imaging studies should be performed as gated tomographic acquisitions (327). Image interpretation should be performed by physicians with expertise in nuclear cardiology, using both static perfusion and gated functional images, as well as a cine film of the rotating acquisition to evaluate patient motion and artifact. In the case of a negative early imaging study, an appropriate follow-up evaluation is indicated.

Repeat presenters to the ED with negative findings or indications for coronary angiography. Among the low risk patients with chest pain who present to the ED, there is a subgroup with a pattern of repeat visits with consistently negative cardiac findings and unrevealing evaluations for noncardiac etiologies of their symptoms (328). These patients account for a disproportionate number of ED visits for chest pain among the entire group with negative findings. In these patients, it is reasonable to consider cardiac catheterization and coronary angiography to document the absence of cardiac disease or to identify an unsuspected cardiac condition. A normal evaluation may significantly relieve the cardiac focus and anxiety of many patients and thereby decrease the number of ED visits when symptoms arise. Negative findings also provide essential information to the physician for management decisions in subsequent ED visits by these patients with chest pain. In addition, the detection of unsuspected cardiac disease by catheterization affords the potential for definitive management.

SUMMARY

Safe, cost-effective management of patients presenting to the ED with chest pain is a continuing challenge. The traditional low threshold for admission of these patients, in order not to miss a life-threatening cardiac condition, has resulted in a <30% incidence of coronary events in those admitted for chest pain. This approach has been neither medically optimal nor cost-effective. It is now recognized that the high and low risk groups of patients presenting with chest pain can be recognized on presentation, facilitating urgent therapy for the former and more deliberate evaluation of the latter. Chest pain programs have been developed for systematic implementation of innovative approaches. Most CPCs focus on the low risk group and utilize accelerated diagnostic protocols, usually comprising 6 to 12 h of monitoring and serial cardiac biomarkers, which, if negative, are followed by stress testing (exercise ECG or noninvasive cardiac stress imaging). These methods have been safe and accurate and appear to be cost-effective. Most patients in the low risk group with negative evaluations have a noncardiac source of the chest pain, but follow-up evaluation for noncardiac etiologies has been inadequate and could improve care of these patients.

RECOMMENDATIONS

1. Nontraumatic chest pain in adults presenting to the ED should prompt evaluation for an ACS.
2. Evaluation of chest pain should follow a comprehensive, systematic, protocol-driven approach with the goals of identifying 1) myocardial necrosis; 2) ischemia at rest; and 3) stress-induced ischemia.

3. The goals of initial assessment of the patient with chest pain are 1) to distinguish patients with an ACS or other serious etiology; 2) to assess the level of risk of adverse outcomes in patients with a suspected ACS or other serious etiology; and 3) to initiate rapid treatment in patients with serious conditions, according to current published guidelines.
4. Patient evaluation in the ED should include documentation of diagnostic tests and management in coordination with the patient's primary care physician and, when appropriate, with a cardiologist.
5. Patients with negative evaluations for ACS should have further studies for noncardiac causes of chest pain.
6. Chest pain centers facilitate rapid, efficient management of high risk patients with an ACS and identification of lower risk patients who do not require hospital admission, by application of accelerated diagnostic protocols.
7. Chest pain centers may have a dedicated environment and the coordinated efforts of specialized personnel or may utilize personnel and process ("virtual units") to attain the objectives of safe, accurate and cost-effective management of patients presenting with chest pain.
8. Accelerated diagnostic protocols should include 6 to 12 h of observation, ECG monitoring, serial cardiac biomarkers and, in patients with negative findings, stress testing before discharge.
9. Expertise in the recognition of typical and atypical presentations of ischemic chest discomfort is mandatory for physicians managing patients with this presentation.
10. An ECG should be obtained and interpreted within 10 min or less of presentation of the patient with chest discomfort, and, when possible, it should be recorded in the presence and absence of chest discomfort.
11. Right-sided ECG leads should be recorded in patients with evidence of inferior or posterior MI.
12. Posterior ECG leads (V_7 through V_9) should be recorded in patients in whom posterior infarction is suspected.
13. The role of continuous ST segment monitoring in the ED has not been established.
14. The results of cardiac biomarker testing should be available within 30 to 60 min in patients presenting with a possible ACS.
15. Because of their superior sensitivity and specificity for identifying myocardial injury, the cardiac troponins are currently the biochemical markers of choice for this purpose.
16. Guidelines and critical care pathways are useful in that they emphasize a systematic program for the management of patients presenting with chest discomfort and provide a basis for quality assurance, but they do not replace clinical judgment. These guidelines also emphasize the need for a functional design of the program, appropriate staffing, quality assurance and outreach.
17. Standard echocardiography cannot be recommended for routine use in the ED evaluation of patients presenting with chest discomfort because of technical limitations, resource requirements and limited incremental diagnostic value.
18. Early rest nuclear imaging for risk stratification of patients presenting with a possible ACS can be effectively employed in institutions with appropriate resources and expertise and can be cost-effective if patient volume is sufficient.
19. The majority of patients presenting with acute chest discomfort who have negative cardiac findings have a noncardiac etiology of their symptom, which may be gastrointestinal, musculoskeletal, pulmonary or psychological. These patients require further evaluation to provide a basis for appropriate management.
20. Coronary angiography should be considered in selected patients with repeat presentations to the ED for chest discomfort with negative cardiac evaluations and no other identifiable source of symptoms.

Task Force 3: Special Aspects of Research Conduct in the Emergency Setting: Waiver of Informed Consent

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In the U.S., nearly 1,000 people die each day after experiencing a sudden, out-of-hospital cardiac arrest. Although standard-of-care resuscitation efforts are applied on behalf of most of these patients, the mortality rate is nevertheless as high as 99% in some urban areas. The American College of Cardiology (ACC) strongly advocates a vigorous program of

medical research directed at improving these very dismal outcomes. Because these patients are deprived of their autonomy by their sudden cardiac arrest, the ACC also believes it is essential to maintain these patients' rights as human beings during the course of their enrollment and treatment as research subjects. Although informed consent is one of the usual means of providing for such protection, it is usually impossible in such emergency situations where no "informing" or "consenting" can occur because of sudden death or critical illness. Because therapy is highly time dependent, and even 2 or 3 min can dramatically reduce survival, consent by family members or other surrogates is equally difficult.

Because critically ill and dying patients who are unable to give consent are often individuals for whom new advances are likely to be life-saving, the Food and Drug Administration (FDA) and National Institutes of Health (NIH) have recognized that conditions for the conduct of research in these patients must be specified (329). The recently promulgated FDA regulations stipulate the conditions for ethical research when the informed consent requirement is waived. Examples of abuse of patients' rights from the recent past, most notably from the Department of Energy's radioactive materials studies, have underscored that such oversight of the conduct of research is imperative (330).

Unfortunately, confusion and uncertainty about the application of these regulations are significantly impairing the national research community's efforts to improve the outcomes of these most severely ill Americans. Implementation at the local level of the new regulations for cardiac arrest victims and other emergency patients (329) is currently vague and burdensome. The nation's research projects, and thus its efforts to improve the outcomes of cardiac arrest, were stopped entirely between 1993 and 1996. During this period, no waiver of informed consent was valid. Furthermore, since the end of the moratorium and the adoption of these new regulations, new projects are proceeding very slowly, at a rate of less than two studies per year. The task of this working group was to address and attempt to establish clearer rules. We will begin by examining some of the history that has led to efforts to protect human subjects.

Table 1. Timeline of Events Surrounding Informed Consent

1932	U.S. Public Health Service begins the Tuskegee Syphilis Study (333).
1946–1947	Nuremberg Tribunal: "the voluntary consent of the human subject is absolutely essential."
1964	Declaration of Helsinki (334): recognized that a proxy decision-maker is ethical for subjects who lack decision-making capacity.
1972	Tuskegee Syphilis Study terminates (333).
1979	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: The Belmont Report (335): articulated three principles for research—respect for persons, beneficence and justice.
1992	Public outcry over testing without consent, as performed by the Department of Energy on subjects with ionizing radiation (330).
1993	"Dear Colleague" letter from OPRR at NIH warns Institutional Review Board chairs that deferred consent does not meet regulatory compliance for waiver of consent (336).
1994	The FDA terminates an ongoing human CPR study and sends marshals to the homes of investigators to confiscate devices.
	Rep. Ron Wyden, Chairman of the House Subcommittee on Regulation, Business Opportunities and Technology, holds a public hearing on waiver of consent in the emergency setting.
1995	FDA and NIH co-sponsor public meetings to discuss issues of informed consent.
	Initial draft of proposed new rules released in September (337).
1996	Final new rules released in October for waiver of consent criteria (337).
1997	President Clinton formally apologizes to the Tuskegee study subjects.

CPR = cardiopulmonary resuscitation; OPRR = Office of Protection from Research Risks.

PRE-1993 INFORMED CONSENT REGULATIONS

Much of the debate and confusion over informed consent begins with the first principle of the Nuremberg Code, which states that "the voluntary consent of the human subject is absolutely essential" (see the event timeline in Table 1 for important dates surrounding informed consent) (331). This document did not address the need for research on subjects who could not, for any number of reasons, give their own "voluntary consent" (332), but focused on unethical research conducted in Nazi Germany, which deprived healthy individuals of their autonomy. Research on subjects who cannot give informed consent requires other means to ensure that the research is ethical and the patients' rights are protected. It is widely recognized that informed consent is not always needed for research to be considered ethically acceptable. The World Health Organization's Declaration of Helsinki recognized that incompetent patients could be subjects of research if consent was obtained from a proxy, and went further to say that consent could be waived altogether "if the physician considers it essential not to obtain informed consent, the specific reasons for the proposal should be stated in the experimental protocol for transmission to the independent committee" (332).

The research community in the U.S. recognized the need for a waiver of consent to allow research on patients who could not give consent. Two major government regulatory agencies that dealt with research (Department of Health and Human Services [DHHS] and FDA) developed different but unfortunately inconsistent regulations on the criteria for waiver of informed consent. Under the regulations

Table 2. Pre-1993 DHHS Policy on Waiver of Informed Consent

The Department of Health and Human Services (i.e., NIH) allowed a waiver of consent only if all of the following were true:
1. The research involves no more than minimal risk to the subjects.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. The research could not practically be carried out without the waiver.
4. Subjects are provided with additional pertinent information after participation, as appropriate.

developed by DHHS, researchers could get a waiver of consent if four criteria were met (Table 2). However, a major problem developed because of the requirement that the research involve no more than minimal risk. This "no more than minimal risk" clause seemed to preclude almost all emergency research, because these situations were likely to involve more than minimal risk. However, some emergency research was carried out under this regulation when investigators interpreted minimal risk to mean the differential risk in outcome for the experimental treatment as compared with standard treatment, not the risk compared with the risks of daily life. In addition, "deferred consent" was used in some studies. Under deferred consent, a patient was initially entered into the study, and then later, when the patient became competent or a proxy was identified, consent (or no consent) to remain in the study after initiation of therapy was obtained. Different organizations interpreted these practices and regulations differently.

During this period, the FDA regulations allowed for a waiver of informed consent for nonresearch "compassionate use" purposes, only using different criteria (Table 3). A serious difficulty with these criteria was the use of the phase "necessary" to save the life of a patient, as this seemed to eliminate the use of control groups. It was impossible to claim that participation in the placebo arm of a trial was "necessary" to save a life. These ambiguities created multiple problems for researchers, Institutional Review Boards (IRBs) and regulatory agencies. Concerns were being expressed that studies were done "outside of the rules." Some IRBs would approve a study, whereas other IRBs would reject the same study. Some investigators and companies would not even consider initiating the efforts and resources to advance a proposal owing to the confusing situation. To make matters even worse, many studies required both NIH and FDA oversight and had to meet both sets of criteria.

Table 3. Pre-1993 Food and Drug Administration Regulation on Waiver of Informed Consent

The FDA permitted a waiver of consent for nonresearch "compassionate use" if all four of the following conditions were met:
1. The human subject is confronted with a life-threatening condition necessitating the use of a device or drug.
2. Informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject.
3. Time is not sufficient to obtain consent from the subject's legal representative.
4. There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the subject.

THE 1993 "MORATORIUM" ON EMERGENCY RESEARCH

The issue came to a crisis in 1993, when the Director of the Office of Protection from Research Risks (OPRR) at the NIH warned IRB chairs in a "Dear Colleague" letter that using deferred consent was not in compliance with DHHS rules on waiver of consent and that any type of consent mechanism that did not involve prospective waiver of consent was not in compliance (336). The effect of this letter was to place a moratorium on all human resuscitation research in the U.S. The fear of regulatory action against the research community became real when the FDA sent armed U.S. marshals to the homes of CPR investigators to confiscate suction-cup devices when the FDA terminated a study in progress because of concerns about informed consent. An IRB had approved this trial, and no apparent adverse effects had been noted at the time of the suspension. The FDA also terminated a study on head trauma owing to informed consent issues and only allowed enrollment of patients for whom informed consent could be obtained prospectively in an antioxidant study.

Multiple efforts began to develop new rules for waived consent that would permit emergency care research on impaired subjects. A national consortium of emergency care researchers was created. Rep. Wyden, Chairman of the House Subcommittee on Regulation, Business Opportunities and Technology, held a public hearing on waiver of informed consent in the emergency setting. A new set of rules was distributed in September 1995, additional hearings took place and a final rule was adopted in October 1996 (337). The 1996 final FDA rule allowed waiver of informed consent under a limited set of criteria (Table 4, abridged version).

AFTER THE 1996 FINAL RULE (21 CFR 50.24)

With the final rules for waiver of informed consent published in 1996, the way for a waiver of informed consent on new studies seemed to be clear. The FDA hosted a "National Conference on Implementation of the Waiver of Informed Consent in Emergency Situations" on September 29–30, 1997. The new rule and issues of implementation were described, and public commentary was solicited (338). There was substantial controversy over the new rules. Since then, most written statements in the published data have

Table 4. Abridged Highlights of the 1996 Food and Drug Administration Rule (21 CFR 50.24)

The central themes of the final 1996 rule were:
1. The patient has a life-threatening situation.
2. Available therapies are unproven or unsatisfactory.
3. Direct consent from the patient is not feasible because of the patient's condition and because therapies must be started before an authorized surrogate representative can be contacted.
4. The research cannot be reasonably conducted otherwise.
5. The risks and benefits of the experimental protocol are considered reasonable in light of the patient's condition and what is known about the other available therapies.
6. Participation in the research holds out the prospect of direct benefit to the subject.

been supportive of the final rules; some strong opposition was also voiced (337,339). Some critics suggested that the new rules were regressive and in violation of the Nuremberg Code. They also questioned the claim that the patient may benefit from experimental therapy (339).

Although these rules allow for waiver of informed consent under very limited circumstances, they also created a new set of obstacles for researchers: they require a vaguely defined community consultation and a public disclosure program (336,339–341). Santora et al. (340) described the stepwise process followed at the Allegheny University of the Health Sciences to comply with the requirement for public disclosure. This procedure required 80 person-hours to complete and included four public meetings, newspaper notices, radio public service announcements and a 24 h telephone hotline. Another report of efforts to comply with the new rules revealed that the institution had to increase community representation on their IRB, fund newspaper notices, create a call-in telephone line, hold public forums, make presentations to the Department of Medicine and Medical Boards, create a videotape presentation, provide literature in the physician lounge, put up large posters, put brochures in patient rooms and have charge nurses notify patients (342). A total of 25 people from a community of nearly 1.5 million people attended the public forum. The direct costs for the public disclosure was $5,600. A total of four patients were enrolled in the study over four months. The authors reported confusion as to what was sufficient for a broad community consultation/public disclosure criterion.

If the "public disclosure" dilemmas were not enough for researchers, a survey of what patients actually think about the 1996 FDA rule (21 CFR 50.24) suggests an even rockier road ahead for the rules. Smithline and Gerstle (343) surveyed a convenient sample of 212 emergency patients. Only half of the patients were in agreement with a waiver of consent for serious illness, using the new rules. This discordance between patient desires and regulatory requirements will likely lead to future conflicts for the research community.

In addition, the following new procedural protections are required: 1) consultation with the community in which the research will occur; 2) informing the subject, if feasible, representative or family member at the earliest point, including in the event of death; 3) public disclosure of the study results when completed; 4) use of an independent data safety board; and 5) approval of the study by the FDA.

STATEMENT OF THE PROBLEM

Traditional informed consent for human research is impossible or difficult in a number of common medical conditions. The Emergency Department or the prehospital care environment is often the site where such emergencies occur, even if one limits the focus to cardiovascular conditions. Informed consent is usually impossible to obtain during cardiac arrest, acute congestive heart failure, sepsis or hemorrhage, stroke syndrome, drug overdose with hemodynamic compromise, severe hypoxia related to acute or chronic pulmonary disease, severe metabolic acidosis and alteration in sodium or hydration with altered mental status. There are also a number of conditions for which "consent" can be obtained from the patient, even though it is likely that the detailed and prolonged explanation may not be fully understood by the patient. Such circumstances might include circulatory catastrophes requiring an immediate intervention (e.g., ruptured ventricle, valve or aorta), massive hemorrhage, pulmonary embolism with severe hypoxemia, congestive failure with shock, myocardial infarction with severe pain or dyspnea, life-threatening arrhythmia with hypotension or hypertensive crisis. A "standard of reasonableness" with regard to the adequacy of informed consent is often not met.

Research requiring informed consent or a waiver in such settings would include not only new therapeutic strategies but also studies involving a protocol approach to medical effectiveness, or implementation of care plans with a research focus that involves more than minimal risk. Minimal risk is usually limited to drawing a very small amount of venous blood, blood testing and data gathering.

ISSUES IN OBTAINING INFORMED CONSENT IN EMERGENCY SITUATIONS

The FDA requires that the investigators attempt to obtain informed consent from the patient "under all reasonable conditions" (337). A waiver of informed consent is only considered where informed consent is not possible.

Intense efforts to obtain informed consent before circumstances such as a cardiac arrest raise a number of issues worthy of consideration. These issues include whether informed consent from an individual who is not yet a candidate for a study and is not yet experiencing an emergency is a valid consent. A patient who is not yet a candidate may be more concerned about avoiding candidacy than receiving treatment should a catastrophe occur. Would an individual refuse consent in the belief that consent would

lead to less effort by the provider to avoid candidacy? Alternatively, would a subject agree to participate in a study if he or she believes their candidacy is unlikely, to please a physician or investigator and to gain more attention?

A second issue raised by an intense effort to obtain informed consent before an emergency situation is the number of informed consents needed to gain one patient candidate. What is the psychological impact on a patient of the approach for consent in the event of an adverse outcome that has only a 1 in 500 chance of occurring? If large numbers of patients are to be consented, how detailed does the consent need to be?

Finally, the ability of a patient to understand detailed information during an emergency may be severely compromised. Is there a role for an abbreviated consent procedure with a simple level of understanding, rather than a detailed form, which would be appropriate in the nonemergency setting? We believe it is not reasonable to attempt to obtain informed consent before medical circumstances that may come under study for many patients with cardiac disease.

JUSTIFIABLE RESEARCH AND CLINICAL EQUIPOISE

Imperatives during biomedical research include an improved understanding of illness and, through this knowledge, better diagnosis, treatment and prevention. However elegant and conclusive preclinical research on a new device, drug or concept may be, diagnostic and therapeutic strategies must be tested in patients before widespread use.

Publication of a clinical trial testing streptomycin as a treatment for tuberculosis nearly 50 years ago led to widespread use of clinical trial methodology in testing new drugs and surgical techniques (344,345). The demand for properly conducted, randomized, controlled animal experiments and clinical trials before general use has protected patients from useless or toxic therapy, although the ethical correctness of clinical trials has been debated periodically (346,347). The requirement for clinical equipoise and informed consent protects patients from exposure to poorly designed and dangerous clinical trials.

As noted earlier, clinical equipoise is the state in which the medical community, after careful review of the totality of evidence, is convinced that none of the therapies tested in a randomized trial are clearly established to be more effective (348). Trial design may compare a therapy with placebo or the best-established therapy (i.e., standard of care). Periodic review of the data developed during the course of a trial by a duly constituted Data and Safety Monitoring Board (DSMB) assures that clinical equipoise remains for the entire research period. If, at any time, one therapy is clearly shown to be superior to another, the DSMB has the duty to terminate the study.

A critical part of the Nuremberg Code (349) and the Declaration of Helsinki (350) is the requirement to inform all subjects involved in medical experimentation before entry into a study. They must know the goals of the experiment and the potential risks, benefits and alternatives. They have the right to withdraw from the study at any time. This is particularly true of vulnerable populations, such as children, those who are mentally impaired or prisoners.

Respect for a subject's autonomy is the underlying ethical principle of informed consent. An important aspect of informed consent is the capacity to understand the goals of the research effort and the attendant risks, benefits and alternatives. Patients brought to medical attention in the midst of a severe illness, particularly an illness that disables the central nervous system, may not be able to give informed consent and can be thought of as having a disability. This is particularly true for patients who have a cardiac arrest. Relatives or friends who might be able to communicate the patient's wishes are often not available in a time frame that would permit entry into a trial using time-sensitive treatments.

Such "disabled" men and women are unable to participate as subjects in a randomized, controlled study using traditional safeguards. The aggregate effect of intellectually disabled patients not getting into clinical trials has resulted in little or no progress in testing new, potentially effective treatments for such severe illnesses. These patients are desperately ill; some never recover; and many die. Holding informed consent in abeyance requires strict documentation of initial and continuing equipoise and may need the involvement of community leaders, including those without ties to medicine or research.

ETHICAL PERSPECTIVE ON WAIVING INFORMED CONSENT

Clinical research places individuals at risk to develop generalizable knowledge that can be used to improve societal health and well-being. By placing some at risk for the good of others, clinical research has the potential to exploit its subjects. To justify the risks of clinical research and ensure that subjects are not exploited, seven ethical requirements must be met (Table 5).

First, subjects should be placed at risk only when the research concerns a socially, scientifically or clinically important question—one that can improve overall health and well-being. In this sense, "me too" studies are not valuable and not ethically justifiable. Next, the research plan must be valid scientifically; it must offer a good chance of answering the question(s) posed. In this sense, only good clinical research can be justified ethically. Studies that are underpowered or not generalizable or that use biased statistical techniques are not ethical. Third, subjects must be selected in a fair manner. Fair subject selection requires that risky research not be limited to the underprivileged, nor that potentially beneficial research be extended to the privileged. Rather, inclusion and exclusion criteria and subject recruitment strategies must be based on scientific criteria relevant to the information sought. Fourth, research should offer the most favorable risk-benefit ratio possible. To meet this

Table 5. Seven Requirements That Make a Research Trial Ethical

Requirement	Explanation	Justifying Ethical Values
Social or scientific value	Evaluating a treatment, intervention or theory that will improve health and well-being or increase knowledge.	Scarce resources and avoidance of exploitation
Scientific validity	Stating a clear hypothesis, using accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data.	Scarce resources and avoidance of exploitation
Fair subject selection	Selecting subjects so that stigmatized and vulnerable individuals are not selected for risky research, while favored classes are offered potentially beneficial research.	Distributive justice
Favorable risk-benefit ratio	Minimization of potential risks and harms with maximization of potential benefits so that the risks to the subject are proportionate to the benefits to the subject and society.	Nonmaleficent, beneficence, nonexploitation
Independent review	Review of the design of the research trial, its proposed subject population and risk-benefit ratio by an individual who is unaffiliated with the research.	Minimizing potential conflicts of interest, public accountability
Informed consent	Provision of information to potential subjects about the purpose of the research, its potential risks, benefits and alternatives, so that the individual understands this information and can make a voluntary, uncoerced decision about participation in the study.	Respect for subject autonomy
Respect for potential and enrolled subjects	Respect for subjects by 1) permitting withdrawal from the research; 2) protecting privacy through confidentiality; 3) informing of newly discovered risks or benefits; and 4) informing about the results of clinical research.	Respect for subject autonomy and welfare

requirement, the risks of research must be minimized and the potential social and individual benefits maximized. When the potential benefits to individual subjects are proportionate or outweigh the potential risks they face, clinical research is ethical. When the potential benefits to individual subjects do not outweigh the risks to them, as in phase I research, then clinical research is justified only when its potential social benefits outweigh the "excess" risks to individual subjects. Although the first comparison of benefits and risks to the same individual is fairly clear and performed routinely, the comparison of social benefits to individual risks is more complex and lacks a clear methodology. Fifth, because investigators may have conflicts of interest between safeguarding subjects and completing their research, and because research must be accountable publicly, research studies should be reviewed by an independent body with the expertise to evaluate the study and the power to approve, revise or even stop it. Sixth, when possible, research subjects should provide informed consent before research enrollment, and continuing consent periodically throughout their participation. Finally, ethical clinical research requires that investigators respect potential and enrolled subjects. This includes respecting subjects' privacy, informing them of what is learned from the research and carefully monitoring their welfare, even if it means withdrawing them from the research if the harms and side effects become too great.

Valid informed consent requires the completion of four separate steps. The first three steps constitute the *informed* portion of the requirement. Subjects must be informed concerning the research study that they are being asked to participate in, including its objective, procedures, risks, potential benefits and alternatives. Second, they must understand this information. Third, physicians and researchers must inform subjects about their medical condition, including their diagnosis and prognosis; subjects must also understand this information. Finally, in the *consent* portion, subjects must make a voluntary decision whether to enroll on the basis of this information, and in light of their own preferences and values.

Why is informed consent important ethically and what are the special ethical concerns raised by conducting human subject research without it? Obtaining informed consent before research enrollment helps to respect subjects' autonomy by allowing them to decide whether or not to enroll. In addition, because individuals are typically in the best position to judge their own interests and values, requiring informed consent increases the chances that individuals will be enrolled in research only when it is consistent with their personal preferences and values. Therefore, conducting

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Table 6. How Well Do Food and Drug Administration Provisions Satisfy Requirements for Ethical Research and Address Ethical Concerns of Waiving Consent?

Provision	Ethical Requirement or Concern Addressed
1. IRB approval	Independent review
2. Life-threatening situation without satisfactory treatment	Value
3. Informed consent not feasible	Informed consent when possible
4. Prospect of direct benefit	Most favorable risk-benefit ratio
	Potential for unwanted research enrollment
5. Risks are reasonable	Most favorable risk-benefit ratio
	Potential for unwanted research enrollment
6. Impracticable to conduct research without waiver	Informed consent when possible
7. Commitment to contact legally authorized representative	Respect for enrolled subjects
8. Community consultation	Independent review
	Potential for especially risky research with waiver
9. Public disclosure of research plan	Independent review
	Potential for especially risky research with waiver
10. Public disclosure of research results	Respect for enrolled subjects
11. Independent oversight board	Independent review
	Respect for enrolled subjects
12. Investigator informs subject, representative or family member at earliest possible point	Respect for enrolled subjects
	Ethical concern that waiver of informed consent will diminish respect for subject autonomy
13. Investigator provides information about subjects who die before notification	Respect for enrolled subjects

IRB = Institutional Review Board.

research without informed consent raises two ethical concerns: 1) investigators may fail to respect subjects' autonomy; and 2) individuals may be enrolled in research that conflicts with their preferences and values.

The emergency setting frequently does not offer sufficient time to inform potential subjects of the nature of the research or obtain their consent. In addition, the ailments on which emergency research focuses—such as stroke, myocardial infarction and acute brain injury—frequently render individuals incapable of understanding during the time treatment must be initiated. For these reasons, research in the emergency setting often cannot meet the four conditions for informed consent. As a result, the ethical conduct of emergency research often depends on the possibility of waiving the requirement for informed consent.

Arguments in support of waiving informed consent in limited cases focus on three claims. First, because many emergency treatments are unproven or unsatisfactory, it is important to identify more effective alternatives. Second, in a related way, because many emergency interventions have dismal outcomes, subjects may benefit—or not be harmed, as compared with conventional care—from enrolling in emergency research.

Finally, by using other safeguards, it is possible to ensure that the interests of individuals who are enrolled in emergency research without their consent are protected and that they will not be exposed to excessively risky procedures.

The FDA regulations allow for a waiver of informed consent before enrollment in emergency research under the 13 conditions outlined in Table 6. The study and waiver are approved by the relevant IRB.

To what extent do these 13 conditions ensure that emergency research conducted without informed consent meets the seven requirements on ethical research? In addition, do these conditions satisfactorily address the special ethical concerns raised by waiving informed consent?

The FDA regulations address the requirement for social, scientific or clinical value by stipulating that subjects must have a life-threatening condition; available treatments must be unproven or unsatisfactory; and the collection of valid scientific evidence must be necessary to determine the safety and effectiveness of particular interventions (condition 2). Presumably, when these conditions are met, the development of alternative treatments has social value. However, two problems arise. First, there is some vagueness in this condition: how unsatisfactory must the treatments be to justify research without informed consent? Is a 10% success rate of the conventional intervention or a 25% success rate sufficiently bad? Is a 50% survival rate with 30% permanent brain injury sufficiently bad? The difficulty here is that the regulations do not require a minimal level of value to justify research without informed consent, nor would it be reasonable to provide such arbitrary limits.

The FDA regulations address the requirement that clinical protocols present the most favorable risk-benefit ratio possible by stipulating that participation must hold out the prospect of direct benefit to the subjects (condition 4) and risks must be reasonable (condition 5). These conditions ensure that subjects of emergency research do not face excessive risks or participate in research with no potential for benefit. However, these conditions do not fully address the special ethical concern that a waiver of informed consent

may lead to individuals being enrolled in research that conflicts with their preferences. Even if most individuals are willing to participate in research that offers the most favorable risk-benefit ratio, these conditions do not ensure that emergency research in which consent is waived meets this condition—a reasonable level of risk can outweigh an unspecified potential for direct benefit.

To address this concern, the American Medical Association guidelines (351), as well as the preamble to the FDA regulations, argue that informed consent should not be waived unless there is clinical equipoise (337). When it does, individuals enrolled in emergency research without their consent will not face a less favorable risk-benefit ratio than individuals who receive standard of care; hence, there is good reason to believe that such enrollment will not conflict with the individual's preferences. However, the FDA's stated conditions—that subjects must have a life-threatening condition, available treatments must be unproven or unsatisfactory and collection of valid scientific evidence must be necessary to determine the safety and effectiveness of particular interventions—are not equivalent to clinical equipoise. These conditions do not compare the experimental treatment being studied directly with any existing standard treatments, which are necessary to assess equipoise. As a result, they do not ensure that clinical equipoise exists.

Although it is very difficult to fully address the possibility of unwanted research enrollment, the regulations would need to address the possibility that some individuals may have idiosyncratic preferences and values that get left out of the assessment of equipoise. For example, the risks from a treatment arm that involved a blood transfusion might be deemed low by most individuals in our society, but would be considered extremely risky to many Jehovah Witnesses.

The FDA conditions provide for significant independent review in addition to the usual IRB review (condition 1). Investigators who request a waiver must establish an independent monitoring board (condition 11) and consult with community representatives (condition 8). In addition, they must disclose their research plan and results (conditions 9 and 10) publicly. Such a comprehensive level of independent review ensures that research without informed consent is not likely to expose subjects to excessive risks. Indeed, combining the conditions for a favorable risk-benefit ratio with this added level of independent review obviates an important concern that informed consent is meant to address—namely, that research could be so risky as to pose a threat to individuals and conflict with subjects' preferences.

The FDA regulations require that investigators obtain informed consent when possible, by stipulating that requests for a waiver may be approved only when the research could not be carried out practicably without the waiver (condition 6) and obtaining consent is not feasible (condition 3). In addition, they ensure that proxy consent is not possible, by requiring that investigators attempt to contact a legally authorized representative for each subject (condition 7).

The regulations define consent as not being "feasible" in terms of three conditions: 1) subjects are not able to give consent owing to their medical condition; 2) the intervention being tested must be administered before it is feasible to get proxy consent; and 3) it is not possible to identify subjects prospectively. Taken together, these conditions go a long way toward ensuring that research without informed consent is done only when necessary.

The FDA regulations address the need to respect potential and enrolled subjects by requiring investigators to attempt to contact a legally authorized representative or family member and that subjects be notified at the earliest time possible (condition 12). This last requirement also helps to address the special ethical concern that research without informed consent fails to respect individuals' autonomy. Finally, for subjects who die before notification, the regulations stipulate that information be provided to the legally authorized representative or family member when feasible (condition 13).

Overall, the FDA regulations go a long way toward ensuring that the ethical requirements for clinical research are fulfilled in emergency research where subject consent is not possible. In particular, attention to the risk-benefit ratio and comprehensive independent review beyond IRB review ensures that subjects unable to consent will not be enrolled in excessively risky research. Although there remain some areas of disagreement, mostly about how difficult it should be to obtain consent before the waiver can be invoked, the conditions do ensure that emergency research with the waiver will fulfill the other ethical requirements.

PROBLEMS RELATED TO THE FDA/DHHS REGULATIONS ALLOWING A WAIVER OF INFORMED CONSENT

Although the FDA/DHHS regulations have been assessed to be ethical in terms of their requirements for special patient protections, there still exist a number of ambiguities that make the application difficult, hence making them susceptible to misinterpretation and misapplication. A few specific examples of problems related to the interpretation of the regulations follow.

There must be disclosure to the community in which the clinical investigation is to be conducted. The question is, what constitutes adequate community notification? A wide variety of approaches to this difficult problem have been used, including newspaper advertisements, interviews with media, open discussions, meetings with concerned citizen groups, and many of these approaches involve considerable cost and considerable time and delay. What is adequate?

The FDA provisions also require community consultation. What constitutes reasonable consultation? What if there is limited objection to the study as a whole? It is important to point out that the FDA provisions do not

require public input into the study protocol. Instead, it requires community consultation, but what occurs during community consultation cannot by itself block the conduct of the study. Community consultation might raise issues that the IRB has not considered. It is up to the IRB, in conjunction with the investigator, to determine whether these community concerns are sufficient to warrant a change in the protocol. There is absolutely no requirement in the FDA regulations indicating that a community can have direct input into changing the study. Instead, a community's responsibility is to raise concerns that should then be considered by the IRB and the investigator.

Finally, these regulations governing waiver of informed consent have particularly imposing aspects for IRBs and institutional leaders. The regulations require provision of the information to the patient as soon as possible. When alert, the patient must be informed that he or she was included in a research study and provided the option for discontinuation of involvement. If the person does not resume consciousness or succumbs to the illness, the next of kin or immediate family member must be informed immediately of the patient's inclusion in a research study without informed consent. In the latter situation, there is great concern of litigation. It is interesting to note that the same provisions were developed when deferred consent was applied.

The risk of litigation would likely be reduced if there was very detailed documentation of appropriate adherence to the guidelines and regulations. Because the regulations for community notification and public input are currently extremely broad, it will be difficult to legally defend the measures taken as adequate.

PROPOSAL FOR A NATIONAL CONSENSUS ADVISORY BODY

The 31st Bethesda Conference on Emergency Cardiac Care proposes a national advisory consensus body (committee). There is precedent for the creation of a governmental advisory body related to an area of research in which there is significant public concern. The Recombinant Advisory Committee (RAC) was established in 1974 in response to public concerns regarding the safety of manipulation of genetic material through the use of recombinant deoxyribonucleic acid (DNA) techniques. This body was established as an advisory to the Director of the NIH and focused on concerns "that recombinant DNA technology would be associated with possible hazards relating to new types of organisms, some potentially pathogenic, that could be introduced into the environment without effective controls." The RAC developed a set of guidelines for the use of recombinant DNA materials that have been revised repeatedly since 1976. The guidelines include a comprehensive description of facilities and practices intended to prevent unintended release or exposure to genetically modified organisms. Compliance with these guidelines was made mandatory at institutions receiving NIH funds for research involving recombinant DNA. Many companies complied with the NIH guidelines voluntarily and had representatives that were part of the RAC draft meetings and deliberations. The Director of the NIH was required to seek the advice of the RAC before taking specific actions, including changing containment levels for types of experiments that are specified in the NIH guideline; assigning containment levels for types of experiments that are not explicitly considered in the NIH guidelines; certifying new "vector" systems; promulgating and amending a list of classes of recombinant DNA molecules to be exempt from NIH guidelines; adopting other changes in NIH guidelines; and interpreting and determining containment levels on the request of other regulatory bodies.

The RAC was described as a technical committee whose goals were to consider the current state of knowledge and technology regarding DNA recombinants, their survival in nature and the potential for transfer of genetic materials to the organism. It also considered hypothetical hazards and methods of monitoring and minimizing risk. Approximately one-third of the 25 members did not have scientific expertise, but represented public interest and attitudes. This balance was intended to provide a forum for open public debate of social and scientific issues associated with recombinant DNA research. The RAC is viewed as being overwhelmingly successful in achieving this goal. Recently, review of all protocols by the RAC was discontinued after 24 years, but the group maintains its advisory role. These statements are paraphrased from the Missions Statement of the Recombinant DNA Advisory Committee (352).

The issues surrounding a waiver of informed consent for the conduct of research with more than minimal risk bear similarity to the public concerns with regard to the use of recombinant DNA materials in human and other research efforts. First and foremost, such a national voluntary advisory body dealing with research to be conducted with a waiver of informed consent could provide quality control on the research itself. The advisory body would be composed of a significant number of scientific and physician experts in the areas of emergency cardiac care and would be available to assess the issue of importance of research to be conducted with a waiver of informed consent. Does the state of medical knowledge now allow an acceptance of equipoise between the proposed arms of the study? Is there a valid possibility that treatment of this disease will be improved through inclusion in the intervention arm of the study? Are the risks considered to be reasonable by broad and nationally respected groups of physicians and scientists? Will the study design that is proposed have a high probability of success in demonstrating which of the alternative strategies is more effective? Are the end points that are proposed measurable and important? Is the sample size reasonable for assessing the primary and secondary end points of the proposed study? Making such judgments could be either advisory to the local IRBs, the FDA, the NIH, or sponsors.

Because this proposed national advisory body would have a substantial group of public and community representatives, as well as scientific and physician leaders, the advisory committee itself could provide one form of community review and input with regard to the conduct of the study. This input, although remote from the specific community in which the research is to be conducted, would nonetheless provide a unique form of community information and response not available with only local information.

Finally, this national advisory body could provide advice on the methods used by the investigators to inform the local community and to provide the means for receiving community input. The body could also provide reasonable advice on how the local IRB and investigators should respond to objections or concerns expressed by the community or individuals within the community. The specific details of information provided to the community, a detailed listing of expressions of concern or support by the community and the reasonableness of the response would be disclosed to the advisory committee. A very difficult problem would be the serious objection to the conduct of the study by a very small group of individuals within a broader, well-informed community wishing to participate. A national advisory body could provide standards and reasonableness with regard to denying the objections made by a small number of individuals within a large community. A mandatory national advisory group review was not recommended, because it was viewed that this additional step would become another major delay in the conduct of straightforward research under a waiver.

CONCLUSIONS

1. The treatment of cardiac arrest is in desperate need of clinical research on how to improve survival and decrease disability outcomes.
2. The results of enormous efforts to salvage patients from cardiac arrest have been extremely disappointing. These patients are not likely to improve, unless there are fundamental and applied research efforts to produce major advances.
3. A critically important target for resuscitation research is avoidance of severe neurologic disability.
4. Patients in cardiac arrest are unable to provide informed consent. Their disease has deprived them of autonomy. Thus, a strong and thoughtful IRB is critical in assessing the need for and, ultimately, where appropriate, in granting a waiver of informed consent. Advance directives should always be honored.
5. As used in the FDA's regulations on waiver of informed consent, "prospect of direct benefit to the subject" should be taken to mean: 1) the therapy is directed to the patient's condition that required the waiver; 2) there is at least as good a chance of a beneficial result as a deleterious outcome from the intervention; 3) in randomized trials, there is clinical equipoise; and 4) in nonrandomized trials, the risks and benefits profile of the experimental treatment is at least as favorable as the current standard of care.
6. There is a need for a major educational effort to inform the public and the mass media of these issues, focusing on the importance of waivers of informed consent.
7. The IRBs and investigators should be provided with additional education and support toward implementation of the regulations on waiver of informed consent. The ACC, American Heart Association (AHA), Society for Academic Emergency Medicine (SAEM), American College of Emergency Physicians (ACEP), American Academy of Neurology (AAN), American Society of Anesthesiology (ASA), National Association of Emergency Medical Services Physicians (NAEMSP) and other professional societies should have a leadership role.

The final rule advanced by the FDA in 1996 provides researchers with an opportunity to do resuscitation studies in circumstances in which individual patients are unable to provide prospective informed consent. The final rule clearly states the criteria for applying the waiver of informed consent, but gives limited guidance for its implementation. The number of resuscitation studies for which waiver of informed consent apply is limited, and IRBs and principal investigators may not be familiar or have experience with the regulations providing for waiver of informed consent. A substantial number of questions concerning its implementation have arisen. In addition, to date, there has been limited experience with the new regulations, and no prototype for its implementation exists. Although the FDA promises a guidance statement giving suggestions for implementing the regulations, this statement is still in the process of final approval. Even after it is approved, it is likely that IRBs and investigators will need education and support to implement the regulations. Therefore, we believe that professional organizations such as the ACC, AHA, SAEM, ACEP, AAN, ASA and NAEMSP should develop strategies to educate and support researchers and IRBs in implementing the regulations regarding waiver of informed consent. One strategy might be for each organization to identify experts within its own membership who are familiar with the regulations, understand their purpose and spirit and have some knowledge of existing methods of implementing them. In addition, these organizations should advertise the availability of consultants within the organization who can assist investigators in determining the best methods of implementing the regulations on a protocol-by-protocol basis. These organizations should also make the availability of this expertise known beyond their membership, so that investigators with no official means of receiving such counsel might have the ability to discuss projects and implementation strategies with knowledgeable individuals representing the resuscitation research community as a whole. Organizations should develop didactic pro-

grams regarding implementing the waiver for presentation at national meetings and have literature available for researchers. The support and education regarding implementation of the regulations given by these various professional organizations may require some financial assistance of the organizations. This commitment is an important mission of these professional organizations, whose members include resuscitation researchers committed to advancing the emergency care of their patients and society.

The ACC should, as a consequence of this 31st Bethesda Conference, be positioned to rapidly provide input to the anticipated FDA-drafted guidance document on implementation of the regulation on waiver of informed consent.

The 1996 FDA regulations provide for waiver of informed consent in life-threatening emergencies. Unfortunately, there is a widespread misunderstanding among sponsors, clinical investigators and IRBs of some of the provisions of the regulations, particularly with respect to the degree to which participation in the study must provide a positive benefit to each individual subject and in the areas of community consultation and public notification. A draft guidance document that addresses all aspects of the informed consent waiver process is in final preparation at FDA. The ACC should actively participate in public comment on the draft guidelines.

8. An official advisory group should serve as an optional resource to local IRBs, the FDA, sponsors and individual or groups of investigators, and may be called on for advice by any of these sources. This group should be constituted under the auspices of a concerned federal government body.

Many IRBs are reported to be unfamiliar with or uncertain as to how to practicably apply the waiver of informed consent regulation. In addition, FDA staff, sponsors or groups of investigators may have internal disagreements on how to discharge their responsibilities with regard to a proposed investigation. The conferees believe that for these groups, and where a protocol will involve multiple centers and hence multiple IRBs, it would be valuable to have an authoritative independent national forum. This optional forum would provide broadly applicable evaluation and advice on how to meet the requirements of the waiver regulation before consideration of a given protocol on an institution-by-institution basis. Therefore, the conferees recommend that the federal government make available an advisory committee to provide review, on a request basis, of clinical investigations that plan to use the waiver of informed consent provisions. This committee, modeled after RAC, might be either an independent advisory committee for these specific issues or a panel constituted under the charter of an existing committee with appropriate jurisdiction (e.g., an FDA advisory committee supplemented with patient or public representatives and specialists in bioethics and communication). The advisory committee should, in conjunction with its secretariat, have the discretion to accept for review and discussion those topics which give rise to significant new issues and decline any issues believed to be settled by previous similar experience or better handled at the local IRB level. The scope of the advice offered should include the full range of likely controversial topics raised by the waiver regulations or available guidance on implementation of them. This would include the ethics of informed consent waiver in a given protocol, the scientific support for the proposed study, whether there is clinical equipoise regarding the treatments, trial design issues, the appropriateness and adequacy of the proposed mechanism for public input and informing the public of the trial.

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