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Concepts

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ABSTRACT

When the abdomen is compressed manually in counterpoint to the rhythm of chest compression, in the performance of interposed abdominal compression-CPR, artificial circulation is approximately doubled in animal experiments and in electronic models of the circulatory system. These studies suggest that external manual compression of the abdominal aorta acts like an intra-aortic balloon pump to increase aortic pressure, whereas external manual compression of the abdominal veins acts to prime the right heart and pulmonary vessels before the next chest compression. As a result, perfusion pressures and flows are increased. Several clinical studies of this technique have shown promising results, including improved hemodynamics, resuscitation success, and survival. The history of interposed abdominal compression-CPR research suggests a number of principles that may be useful in the development of other new methods for the management of cardiac arrest, including the virtues of vigorously pursuing a new idea suggested by serendipitous observations, developing and refining a working hypothesis as to pathophysiologic mechanisms, working in interdisciplinary groups, refining a novel technique in stages as experience is gained, and recognizing the need for staged phase 1, 2, and 3 clinical trials in the context of the approximately ten-year gestation period from laboratory inspiration to clinical practice.

Key words: abdominal, cardiac arrest, cardiopulmonary, history, research, resuscitation

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INTRODUCTION

During the past decade, cardiac arrest research at several centers led to a successful phase 3 clinical trial of a new technique of CPR: interposed abdominal compression (IAC)-CPR. IAC-CPR includes all the steps of standard CPR with the addition by a second rescuer of manual abdominal compressions in counterpoint to the rhythm of chest compression. Abdominal pressure is applied over the mid-abdomen with two hands during the interval between chest compressions. Abdominal pressure always is released when the chest is being compressed actively, so that the liver is not injured by entrapment beneath the sternum and ribs, as may occur with continuous abdominal compression or binding.[1-3] During IAC-CPR, abdominal compression also is maintained during ventilatory pauses, thus reducing the probability of gastric insufflation.[4] Experimentally, a folded blood pressure cuff that is placed between the hands and the abdomen and connected to an aneroid manometer may be used to monitor the applied pressure. Good hemodynamic results have been obtained with negligible trauma in animals using applied abdominal pressures of 120 to 150 mm Hg.[5, 6] Physiologically, the technique produces a form of manual external counterpulsation of the abdominal aorta and great veins, which has been shown in animal studies[5-7] and theoretical models[8, 9] to produce genuine augmentation of blood flow and diastolic arteriovenous pressure gradients during cardiac arrest and CPR, which are critical determinates of initial success in resuscitation.[3, 10]

The current state-of-the-art of IAC-CPR is particularly exciting for the field of cardiac arrest research. Recent large-scale clinical studies in more than 200 patients have shown essentially that twice as many people are resuscitated initially and that twice as many people survive to leave the hospital when IAC-CPR is applied instead of standard CPR (Table 1).[11] The first 156 resuscitation attempts in this series have been reported in full.[11] The study group comprised only intubated patients in an ICU setting. Initial resuscitation success was declared after three minutes of a palpable pulse accompanied by systolic blood pressure of more than 80 mm Hg. Complications were comparable for the two treatment groups (Table 2). In particular, there was no evidence of increased incidence of emesis or abdominal trauma after IAC-CPR compared with standard CPR. The success of IAC-CPR in clinical environments other than the ICU (e.g. the prehospital setting) remains unproven, and further clinical studies are needed to confirm and extend these initial findings. Nevertheless, IAC-CPR represents a promising new technique.

The evolution of IAC-CPR provides an interesting case study that may guide others in discovering further refinements in resuscitation methodology. Several principles have helped investigators develop the use of IAC from the status of a laboratory discovery to that of a promising clinical technique. These principles include the value and importance of following up on serendipitous observations; developing a working hypothesis regarding physiologic mechanisms; working in interdisciplinary groups; revising both the hypothesis and the technique in stages as experience is gained (the iterative method of engineering design and analysis); understanding the need for phase 1 and 2 clinical trials before attempting definitive phase 3 clinical trials, just as is classically done in the course of drug development; and patiently recognizing, without cynicism or despair, the approximately ten-year gestation period needed to advance a new technique from the preclinical laboratory into clinical practice. These principles are discussed briefly in the context of the history of IAC-CPR.

Table 1.
Efficacy of IAC-CPR versus standard CPR in human beings[11]

End Point	Frequency in IAC-CPR (%)	Frequency in Standard CPR (%)
Return of spontaneous circulation	60	25
24-Hour survival	33	13
Survival to hospital discharge	25	7
Neurologically intact survival	17	6

*Forty-eight patients received IAC-CPR during 71 resuscitation attempts, and 55 patients received standard CPR during 64 resuscitation attempts.

Table 2.
Complications during IAC-CPR versus standard CPR in human beings[11]

Complication†	Frequency in IAC-CPR (%)	Frequency in Standard CPR (%)
Emesis (before and after EET*)	7	9
Emesis (after ETT)	17	25
Abdominal trauma	0	0

*Endotracheal intubation.
†Most recent available data are from 135 resuscitations in 103 patients. Necropsy data were obtained on 11 patients—six from the standard CPR group and five from the IAC-CPR group. No evidence of abdominal organ damage or additional morbidity could be found in the patients who underwent IAC-CPR.

SERENDIPITY

The hemodynamic effects of abdominal counterpulsation were discovered independently by several research teams searching for something else. Ohomoto and coworkers were interested in mechanical CPR, not manual CPR.[12] They described an arrangement of two mechanical pistons--one that compressed the chest and a second that compressed the abdomen. They called the technique "countermassage" and reported that phased abdominal compression combined with chest compression improved carotid flow, mean aortic pressure, and short-term survival in anesthetized dogs with ventricular fibrillation. Rosborough and coworkers[13] were attempting to develop an animal model of cough-CPR, as previously described by Criley et al.[14] They combined simultaneous high-pressure lung inflation with abdominal compression and found that

abdominal compression and ventilation alone could maintain carotid flow and aortic blood pressure during ventricular fibrillation in dogs. They suggested phasic abdominal compression as a new CPR modality. Coletti and coworkers were studying the intra-aortic balloon pump and tried the manual technique of external aortic counterpulsation in desperation one day when the standard balloon pump broke down.[15]

In our laboratory, a graduate student in physiology, Sandra Ralston, was studying the effects of intrapulmonary epinephrine.[16] She discovered the ability of interposed abdominal compressions to raise systolic and diastolic arterial pressure while attempting a manual version of sustained abdominal binding as an adjunct to mechanical chest compression and ventilation by a Thumper® (Michigan Instruments, Inc, Grand Rapids, Michigan) in dogs. To avoid liver damage, which is common with simultaneous abdominal and chest compression,[1-3] she tried applying manual abdominal pressure only when chest compression was being released. To our surprise, the interposed abdominal compressions dramatically improved brachial arterial blood pressure without a comparable increase in central venous pressure.[5]

At that time, the author challenged Ralston to forsake her thesis research for a few months to follow up on a potentially new form of CPR. She accepted the challenge and performed the first systematic study of the method[5], which showed significantly improved cardiac output and diastolic arterial pressures. This research spawned a series of reports on the physiology of IAC-CPR that set the stage for future clinical studies. Ralston's willingness to seize on a new observation in the laboratory with enthusiasm and to take the risk of delaying pursuit of her original goals turned out to be crucial in establishing the preclinical momentum that paved the way to future clinical studies.

PHYSIOLOGIC MECHANISMS

Another key to preclinical acceptance of IAC-CPR was the identification of a credible physiologic mechanism. The physiology of blood flow during CPR has turned out to be complex, unconventional, and controversial[9, 17, 18] The major controversy among resuscitation researchers concerned the issue of what makes blood flow during ordinary CPR.[17] Fortunately, there was the precedent of the intra-aortic balloon pump,[18, 19] which suggested an initial hypothesis about why IAC-CPR might augment artificial circulation. We expanded this notion in the interdisciplinary studies to be described next to include two probable mechanisms for the beneficial effects of abdominal counterpulsation. The first is similar to that of the intra-aortic balloon pump: compression of the abdominal aorta during chest recoil squeezes blood retrograde toward the heart and brain. The resultant augmentation of aortic diastolic pressure encourages greater peripheral perfusion. The second mechanism is priming of the intrathoracic pump mechanism in a manner analogous to the action of the cardiac atria when the heart is beating normally. These initial hypotheses were tested and refined during several cycles of interdisciplinary research at our center during the mid-1980s.

THE INTERDISCIPLINARY APPROACH

Working with a veterinary radiologist, William Blevins, we were able to perform contrast angiocardiographic studies in dogs that confirmed improved hemodynamics during IAC-CPR, compared with standard CPR in the same animal. We constructed a special frame for mounting a Thumper® on an up-tilted radiograph table, allowing spot films in the lateral projection during CPR at four and 13 seconds after injection of contrast medium into the left ventricle. The films at four seconds showed much greater regurgitation of contrast into the left atrium and pulmonary veins with standard CPR than with IAC-CPR. The 13-second films showed faster clearance of contrast from both the heart and the aorta, suggesting greater blood flow. These radiographic studies provided direct, visual evidence that confirmed our previous physiologic studies. They gave a psychological lift to the research team that helped to sustain enthusiasm for the project. Such direct visualization of mechanisms is extremely valuable in building credibility for a new technique.

Following an entirely different path of interdisciplinary research, we studied an electrical model of the circulation,[8, 9] in which the heart and blood vessels were modeled as resistive-capacitive networks, pressures as voltages, blood flow as electric current, blood inertia as inductance, and the cardiac and venous valves as diodes. Pressurization of the chest and abdomen, as would occur in IAC-CPR, was simulated by half-sinusoidal voltage pulses applied to the vascular capacitances. The specific motivation for developing such a model was the criticism that early results with IAC-CPR might be an artifact of the particular anatomy of the dogs, which is, after all, in some ways quite unlike that of a human being. The electronic model of the circulation, patterned after Guyton's original work,[20] was completely independent of the geometric nuances of canine versus human anatomy, such as the shape of the chest or the position of the liver. The model included only functional elements representing vascular resistances and compliance and the inertial masses of blood columns in the vascular tree. It was configured typically to simulate thoracic pump CPR[17], in which blood is impelled by compression of all intrathoracic vascular structures. IAC added to chest compression in this model produced flow augmentation according to the following expression

$$\text{Flow} = \alpha P_c + \beta P_a \ ,$$

where P_c is peak intrathoracic pressure, P_a is peak abdominal pressure, and α and β are constants ($\alpha > \beta$). IAC enhanced the simulated blood flow to the heart and brain as well as total flow in the electrical model. In typical simulations, a doubling of total flow occurred, similar to the flow augmentation measured in early animal studies.[5, 6] We therefore concluded that the peculiarities of dog anatomy were not critical to the observed effects of abdominal counterpulsation. The model also allowed us to test independently the effects of aortic compression versus caval compression (both improved the circulation)[8] and the effects of valvular stenosis and incompetence.

In addition to confirming in general the "manual balloon pump" mechanism, simulations with the electronic model also showed that IAC potentially is synergistic with peripheral vasoconstriction such as might be produced by catecholamines--a phenomenon not yet well studied in the animal laboratory or clinic. Simulated IAC-CPR with epinephrine effect (high peripheral resistance in non-vital organs) generated flow to the head and neck portions of the model corresponding to approximately 70% of normal flow, the highest value obtained in any simulation. Other theoretical models created by Dinnar and coworkers at the Technion Institute, Haifa, Israel, also demonstrate the value of abdominal counterpulsation during CPR.[21] Dinnar et al's model required solution of simultaneous differential equations describing the circulatory system on a digital computer. Their results showed that the greatest flow augmentation occurs when abdominal pulsation is 180 degrees out of phase with chest compression.

The use of imaging technologies and engineering models are just two diverse examples of an interdisciplinary approach to a research and development problem in the field of resuscitation. Other colleagues at our center and elsewhere contributed their own approaches to physiologic data acquisition, including a special apparatus for measuring total body oxygen delivery during CPR[6] and regional perfusion to the cerebral cortex,[22, 23] each with relatively low cost, custom made hardware in the absence of major federal funding. Requesting help from interested colleagues and the application of "mind over matter" to develop low cost methods of making key measurements proved to be crucial in sustaining preclinical research on IAC-CPR. Walker et al.'s study of cerebral blood flow, for example, demonstrated values averaging 0.06 ml/min/g in animals receiving chest compression alone immediately after beginning CPR compared with 0.27 ml/min/g in animals receiving chest compressions with IAC.[22] This value obtained with IAC-CPR was approximately 50% of pre-arrest cerebral perfusion in the dog. Voorhees et al, using the radioactive microsphere technique in dogs with ventricular fibrillation, found cerebral perfusion of 0.28 ml/min/g with IAC-CPR,[24] a value significantly greater than that during standard CPR and nearly identical to that reported by Walker et al. However, Voorhees and coworkers did not demonstrate statistically improved myocardial perfusion with IAC, which leads to the next principle--the engineering approach of guided trial-and-error.

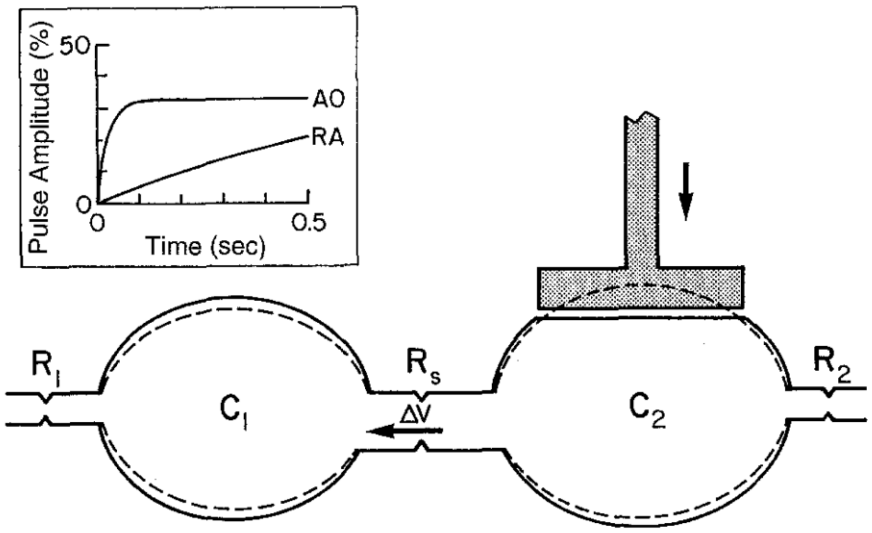

Figure. Conceptual model of fluid transfer from abdominal to thoracic compliances. At time zero, the piston travels a fixed distance to compress abdominal compliance (C_2). Fluid volume ΔV therefore is transferred to the thoracic compliance (C_1). With different values of compliance, the system can represent either arterial or venous elements. Inset: calculated pressures in compartment 1 (thorax) as a percentage of the abdominal pressure for hypothetical values of aortic and venous compliance. AO, thoracic aorta; RA, right atrium.

THE ITERATIVE METHOD

When the goal of a research project is to develop a practical method, as well as to test specific scientific hypotheses, application of engineering approaches becomes of value. A long tradition in engineering is the process of guided trial-and-error: 1) Get an idea for a better mousetrap; 2) build a prototype; 3) test it; 4) analyze test results; and 5) go back to step 1. Using this approach, one builds a prototype, tests it, analyzes the results, determines the problems, and redesigns or modifies the prototype accordingly to eliminate the problems and improve performance.

One example of engineering analysis in the history of IAC-CPR, which may serve as a useful precedent, relates to the problem of inconsistent augmentation of coronary perfusion pressure. It was, of course, known from a wide variety of studies that the prime determinant of artificial circulation during cardiac arrest and CPR is the central arteriovenous pressure difference during chest recoil, or "diastole". Such a diastolic pressure difference is crucial for coronary perfusion during CPR[16] and appears to be the key to restoration of spontaneous circulation when CPR lasts more than two to four minutes.[3, 16, 25] Abdominal counterpulsation clearly was able to induce measurable intrathoracic pressure pulses in both arteries and veins. The studies just discussed suggested that in both animal models and electronic models, the induced arterial pulses typically are greater than the induced central venous pulses. In occasional animals, however, we noted that

the central venous pulses caused by IAC were greater than the thoracic aortic pulses; these instances included two of the ten animals in Ralston et al.'s study and three of the 19 animals in Voorhees et al.'s study.[6, 24] To further refine IAC for clinical application, it was clear that we needed to better understand the factors governing the balance between the intrathoracic arterial and venous pressure pulses induced by manual abdominal compression. Insight came from a conceptual simplification of the problem, which can be visualized with the aid of the Figure.

Two sections of an elastic tube are represented as compliance joined by a small value of resistance (R_s). On the one hand, the drawing can be understood as a simplified representation of the thoracic and abdominal segments of the aorta (compartments l and 2). Peripheral vascular resistances (R_1 and R_2), both much larger than R_s, lead to distant organs. On the other hand, the same diagram can represent the abdominal veins that are compressed by IAC (compartment 2) and the remaining central veins that are not compressed (compartment 1). The essential feature of IAC is that external pressure is applied to the abdominal vascular compartment, forcing blood through the small in-line resistance, R_s, to augment intrathoracic blood pressure. The blood volume shift from abdomen to thorax is the critical phenomenon in this process, which is especially relevant to perfusion of the coronary vascular bed.

After some thought and reference to engineering and physiology textbooks, the author was able to analyze this blood volume shift, either from the abdominal aorta to the thoracic aorta, or from the abdominal veins to the thoracic veins, in terms of a simple differential equation.[26] The solutions for the pressure pulses induced by abdominal compressions in the thoracic aorta (superscript a) and vena cava (superscript v) as a function of time (t) after the onset of abdominal compression are as follows:

$$\Delta P_1^a = \Delta P_{t=0}^a \left(\frac{C_2^a}{C_1^a + C_2^a} \right) \left(1 - e^{-\frac{1}{R_s^a}\left(\frac{1}{C_1^a}+\frac{1}{C_2^a}\right)t} \right) \approx \Delta P_{t=0}^a \left(\frac{C_2^a}{C_1^a + C_2^a} \right) \qquad (1)$$

and

$$\Delta P_1^v = \Delta P_{t=0}^v \left(\frac{C_2^v}{C_1^v + C_2^v} \right) \left(1 - e^{-\frac{1}{R_s^v}\left(\frac{1}{C_1^v}+\frac{1}{C_2^v}\right)t} \right), \qquad (2)$$

where ΔP is the pressure pulse, C is aortic or caval compliance, and subscripts 1 and 2 represent the thoracic and abdominal compartments, respectively. Because both of the aortic compliance values (C_1^a and C_2^a) are much smaller than the venous compliance values (C_1^v and C_2^v), the rising exponential term in Equation (1) for the intrathoracic arterial pressure pulse quickly reaches the plateau value (Figure, inset), whereas the venous pressure pulse has a longer rise time. The delayed rise in venous pressure induced by IAC in this model system permits the generation of positive arteriovenous pressure differences in response to abdominal compression.

Inspection of Equations (1) and (2) for the induced arterial and venous pressure pulses provided several insights into optimization of IAC-CPR. The goal is to make the induced arterial pressure pulse (ΔP_1^a) as large as possible and the induced venous pressure pulse (ΔP_1^v) as small as possible. This result will maximize the diastolic arteriovenous pressure gradient necessary for generating forward flow as well as myocardial perfusion through the coronary arteries. Equation (1) indicates that two variables are critical on the arterial side--the pressure applied to the abdomen and the proportion of total aortic compliance that is compressed by the abdominal thrust. One reasonable modification of the IAC technique to maximize the ratio of $\frac{C_2^a}{C_1^a + C_2^a}$ involves placing the heels of the hands side by side on the abdomen (thumbs interlocking and fingers raised) and slightly to the left of midline to compress as long a segment of the abdominal aorta as possible. This subtle change in technique compared with the original method (in dogs) of placing one of the hands compressing the abdomen on top of the other may have the effect of increasing the effective C_2^a. In turn, the fraction of the aortic compliance $\frac{C_2^a}{C_1^a + C_2^a}$ that is compressed during counterpulsation and the induced thoracic aortic pressure pulse (ΔP_1^a) would be increased. In dogs, no special effort is required because the longitudinal span of the dog's abdominal aorta is little more than a hand's width from the first to fifth digit. In human beings, however, who are larger, special care may be required to ensure that the abdominal laying on of hands takes place over as much of the length of the aorta as possible.

Inspection of Equation (2) suggested ways to minimize the pressure induced in the right atrium (ΔP_1^v). One strategy is that of minimizing the compressed venous capacitance (C_2^v). Because veins are more widely distributed in the abdomen than arteries, the use of a long, narrow zone of compression just to the left of the abdominal midline may also decrease the venous capacitance ratio $\frac{C_2^v}{C_1^v + C_2^v}$, while it is increasing the aortic capacitance ratio. That is, by restricting abdominal pressure to a narrow zone to the left of the midline, lateral abdominal veins may be compressed less effectively and so may become part of C_1^a rather than C_2^a. Thus, the volume displaced from the central abdominal veins can move into the lateral abdominal veins as well as into the thorax, so the induced venous pressure pulse is smaller. Obversely, one might speculate that occasional failure to generate positive arteriovenous pressure differences with IAC in animal studies may have been due to poor hand position that missed compressing the abdominal aorta but significantly compressed the abdominal veins.

Turning to the exponential term, in Equation 2, it would be desirable to make this term as close as possible to $e^0 = 1$, so that ΔP_1^v will be as close as possible to zero. One way to do this is to avoid excessive fluid loading, which tends to distend veins and reduce their compliance. Venous compliance is a highly nonlinear function of venous blood volume, and stretching veins with fluid can make them stiffer by an order of magnitude or more.[27] This notion that central venous distension by fluid loading is inimical to coronary perfusion during CPR appears to apply to

standard as well as to IAC-CPR, as shown by Ditchey and Lindenfeld[28] and Voorhees et al,[29] who found reduced coronary perfusion during CPR after fluid loading. Another way to improve the arteriovenous difference, suggested by Equation 2, may be to shorten the compression time, t. This might be done by increasing the overall rate of CPR, thus reducing the absolute duration of abdominal compression on each cycle. The efficacy of this approach has not been evaluated fully but was suggested to be effective in Sack et al.'s successful clinical study[11] of IAC-CPR, in which a rate of 80 to 100 per minute rather than 60 per minute was used.

In this way, the evolution of IAC-CPR appeared to benefit from application of the engineering style analysis of failure modes and the identification of opportunities for improved system performance. New methods are rarely, if ever, born perfect. Some degree of trial-and-error, or trial-and-analysis, is a normal and desirable part of the research and development process. Often, clinical scientists act as evaluators rather than creative participants in the research and development process. They tend to ask the question, "Is this new method any good?" in which case the answer may, of course, be either "yes" or "no." The engineer, on the other hand, tends to ask, "How can we make this new method work really well?" or "Why did the system fail, and what can we do about it?" In response to such questions, answers may be forthcoming that would be missed by the evaluator who is perfectly willing to accept a "no" and blame failure on presumed inherent shortcomings of the technique. In the present case of IAC-CPR, the cross disciplinary application of a simple, first order differential equation has provided mechanistic insights that may help to maximize both systemic and coronary perfusions during IAC-CPR.

PHASED CLINICAL TRIALS

Just as it is rare to achieve perfection on the first try in preclinical studies, it is virtually impossible to achieve perfection in initial clinical studies. In the pharmaceutical industry, it is well recognized that clinical studies must evolve in phases--formally identified as phase l, phase 2, phase 3, and phase 4 clinical studies.[30] Phase l studies involve the first drug administration to small numbers of human beings to determine biologic activity and potential toxicity. Phase 2 studies determine potential usefulness and dosage ranges in human beings. It is not until phase 3 that broad, randomized, controlled trials are done in large populations of specified patients to determine efficacy and safety. These are followed by phase 4 data collection, which involves limited marketing to multiple centers and then widespread marketing with post-marketing surveillance of untoward effects. The tedious, multistep process of phased clinical trials may easily require more than ten years before a promising new drug is carried from the laboratory to general clinical use.

It may be helpful to apply the paradigm of drug development to the process of resuscitation research, especially to avoid the perils of perfectionism and cynicism in the early stages. If a sufficient number of authorities are too critical of early clinical studies, interpreting them as failed phase 3 trials rather than as useful and limited phase 1 or phase 2 trials, then the process of innovation may be aborted prematurely. The phased approach to clinical research may be especially relevant to the problem of cardiac arrest, which arguably is the ultimate emergency situation. Although it is relatively easy to do well-controlled physiologic experiments on

animals, it is quite another thing to do the all-inclusive, ultimate study of a new method in the sometimes chaotic environment of the emergency department or ICU.

In the early clinical studies of IAC-CPR, there were necessary compromises with clinical reality and limitations of time, resources, and funding. Although results were mixed, these early clinical studies showed that success was possible in certain clinical environments, and they probably are best interpreted as phase 1and phase 2 studies. Berryman and Phillips' phase 1study, for example, involved patients who presented to the ED in cardiac arrest.[31] Standard CPR was alternated with IAC-CPR at approximately two-minute intervals, and in each period stable blood pressures were obtained. Chest compression was standardized using a Thumper® IAC-CPR raised mean arterial pressure and arteriovenous pressure difference; the latter was measured in only one patient.[31]

Subsequently, Howard and coworkers measured coronary perfusion pressure in a small group of 14 patients during alternate two-minute trials of IAC compared with standard CPR.[32, 33] They found that perfusion pressures were approximately doubled by the addition of IAC, as had been shown in previous animal studies.[5, 6] In addition, three patients had return of spontaneous circulation during IAC-CPR, applied with high compression force, after an average of 54 minutes of asystole with standard CPR. Although the hemodynamic effects were promising, none of these investigations showed improved patient survival with IAC. However, it is important to recognize that the design of these early trials was never intended to answer definitively the question of whether consistently applied IAC-CPR produced long-term survival different from that of standard CPR; all patients involved had prior standard CPR.

A more extensive prehospital study in Milwaukee showed that IAC-CPR applied briefly by paramedics in the field to patients unresponsive to initial defibrillation did not alter resuscitation success.[34] This study was convincing in suggesting safety of the method (no increase in the incidence of emesis or abdominal trauma) but disappointing in terms of efficacy. In retrospect, today it might be best interpreted as a phase 2 study, focusing on safety. One reason is that because of practical limitations obviating use of IAC-CPR during transport in the ambulance, the study actually compared patients receiving a combination of IAC and standard CPR with those receiving standard CPR alone. At the time, however, many in the resuscitation research community tended to view this Wisconsin experience as a "negative" phase 3 study. As a result, the resuscitation research community as a whole, including the author, tended to back away from the idea of IAC-CPR. After all, results were mixed, and a pessimist might rightly conclude that there was little virtue in the new technique.

PATIENCE AND PERSISTENCE

Fortunately, the patience and enthusiasm required to accomplish most any innovation continued unabated at a few centers. Howard and coworkers continued their clinical studies and developed interesting new physiologic principles related to the effects of venous pressure and critical closing pressure on coronary perfusion during resuscitation,[35] Einagle and coworkers in Canada confirmed that IAC-CPR in dogs produced approximately double the carotid blood flow of standard CPR and showed that this phenomenon was robust with respect to changes in the timing of abdominal compressions--early versus late onset--and changes in fluid loading of the animals,

neither of which altered the flow augmentation produced by IAC.[36] Ward and coworkers, then at Tulane University in New Orleans, studied end-tidal P_{CO2} in 33 adult patients resuscitated with either standard or IAC-CPR in a randomized, cross-over design in which each patient served as his or her own control.[37] Carbon dioxide excretion, an indicator of the rate of venous blood return to the right heart, increased in every patient switched from standard to IAC-CPR and decreased in every patient switched from IAC-CPR to standard CPR.

In Germany, Lindner and coworkers compared standard CPR with IAC-CPR in anesthetized pigs. Circulatory arrest was initiated by either asphyxia or ventricular fibrillation.[38] In either arrest model, none of seven animals could be resuscitated by standard CPR, whereas seven of seven were resuscitated by IAC-CPR, which produced diastolic arterial blood pressures twice those of standard CPR during resuscitation.

Most recently, Sack and coworkers performed a well controlled phase 3 study in the ICU setting, as previously described, and found a clinically meaningful and statistically significant doubling of both short-term and long-term survival when modified IAC-CPR was compared with standard CPR. In retrospect, it appears that what was required of the resuscitation research community as a whole to bring IAC-CPR to the stage of a successful phase 3 clinical study was a sustained interdisciplinary effort over the course of a decade, characterized by persistence, intellectual risk taking, and the willingness to modify and improve concepts and techniques in the course of the development process. Further refinements and modifications of IAC-CPR are likely to be discovered as additional clinical experience is gained.

SUMMARY

The engineering approach to discovery, research, and development provides a variation of the classic scientific method of hypothesis testing that is well suited to practical innovation in emergency medicine. The process begins with recognition of a practical problem (or opportunity) and a creative idea for solution of the problem. The next stage involves the feasibility study, the creation of a prototype for testing. The prototype may be hardware, such as a novel sensor, catheter, surgical instrument, or endoscope; or it may be software, such as a novel technique like IAC-CPR. As soon as possible, the engineer tests the prototype to determine whether the underlying idea has merit. The tests identify problems and trigger a new cycle of creative solutions, often involving many scientific disciplines, which lead to a refined prototype. Many such development cycles are needed to develop a final working system, just as many cycles of hypothesis refinement and testing are needed to develop a well-established theory in basic science. In modern research and development, basic understanding of anatomic and physiologic mechanisms and the engineering approach of guided trial-and-error become unified in a single creative process.

True optimization of a novel device or method requires clear and detailed knowledge of the pathophysiology of patients to whom the new method will be applied. In the case of IAC-CPR, evolving ideas about mechanisms of blood flow during resuscitation[8, 9, 17, 26, 38] led to validation and refinement of the method. This process is still ongoing, and further insights and refinements in the technique are likely as clinical research and application continue.

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