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Coronary Perfusion Pressure and the Return of Spontaneous Circulation in Human Cardiopulmonary Resuscitation

Norman A. Paradis, MD; Gerard B. Martin, MD; Emanuel P. Rivers, MD; Mark G. Goetting, MD; Timothy J. Appleton; Marcia Feingold, PhD; Richard M. Nowak, MD

Coronary perfusion pressure (CPP), the aortic-to-right atrial pressure gradient during the relaxation phase of cardiopulmonary resuscitation, was measured in 100 patients with cardiac arrest. Coronary perfusion pressure and other variables were compared in patients with and without return of spontaneous circulation (ROSC). Twenty-four patients had ROSC. Initial CPP (mean $\pm$ SD) was 1.6 ± 8.5 mm Hg in patients without ROSC and 13.4 ± 8.5 mm Hg in those with ROSC. The maximal CPP measured was 8.4 ± 10.0 mm Hg in those without ROSC and 25.6 ± 7.7 mm Hg in those with ROSC. Differences were also found for the maximal aortic relaxation pressure, the compression-phase aortic-to-right atrial gradient, and the arterial P_{O_2} . No patient with an initial CPP less than 0 mm Hg had ROSC. Only patients with maximal CPPs of 15 mm Hg or more had ROSC, and the fraction of patients with ROSC increased as the maximal CPP increased. A CPP above 15 mm Hg did not guarantee ROSC, however, as 18 patients whose CPPs were 15 mm Hg or greater did not resuscitate. Of variables measured, maximal CPP was most predictive of ROSC, and all CPP measurements were more predictive than was aortic pressure alone. The study substantiates animal data that indicate the importance of CPP during cardiopulmonary resuscitation.

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STUDIES of cardiac arrest in animal models have shown that the pressure gradient between the aorta and the right atrium during the relaxation phase is coronary perfusion pressure (CPP) during standard external cardiopulmonary resuscitation.^{1,2} Other work in animals has demonstrated that this gradient is correlated positively with return of spontaneous circulation (ROSC) and survival.²⁻⁶ Since CPP has been measured in only a limited number of patients during cardiac arrest,⁷⁻¹¹ only a small number of whom developed

ROSC, insufficient data exist to evaluate the relationship between this gradient and outcome in humans. Despite this, CPP has been assumed to be as important in human cardiac arrest as in animal models, and studies of alternative types of cardiopulmonary resuscitation have used it as an end point.^{7-9,11} We undertook this study to evaluate the relationship between CPP and ROSC in humans during cardiopulmonary resuscitation and the usefulness of CPP as a predictor of ROSC.

PATIENTS AND METHODS

We studied all adults with normothermic, nontraumatic, cardiopulmonary arrest in the prehospital or emergency department setting who remained in arrest after placement of

pressure monitoring catheters. *Down time* was defined as the time from collapse to initiation of basic life support. *Prehospital time* was the time from collapse to arrival at the hospital. *Total arrest time* equaled prehospital time plus catheterization time. Time data were used only if the arrest was witnessed. Cardiac arrest was diagnosed initially by absence of palpable pulses. On-duty physicians performed clinical treatment of the patients in accordance with Advanced Cardiac Life Support guidelines.¹² The only exceptions to this were 49 patients who received high-dose epinephrine (0.2 mg/kg) at the end of resuscitation as part of a concurrent study. Clinicians did not change therapy based on CPP. Rectal temperature was obtained when the history or physical examination indicated possible hypothermia.

A double-lumen, 20-cm, 7.5F catheter (Cook, Bloomington, Ind) was placed in the right atrium via the subclavian vein by guidewire technique. The proximal port was used for drug and fluid administration, the distal port for pressure monitoring. Chest compression and ventilation were performed in all patients by a pneumatic device (Thumper, Michigan Instruments, Grand Rapids, Mich). Members of an on-call research team placed a 60-cm, 5.8F catheter (Bunegin-Albin, Cook) into the aortic arch via the femoral artery either percutaneously or by cutdown. Cardiac arrest was then confirmed by absence of a spontaneous central aortic pulse. Placement of these catheters is part of standard therapy during cardiac arrest in our department.¹³ Initial studies that used the aor-

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tic catheter had been approved by our institutional review board⁷ under the concept of deferred consent.¹⁴ Catheter positions were confirmed by contrast-enhanced radiograms of the chest and by appropriateness of blood gas measurements (ie, $\text{PaO}_2 > 70$ mm Hg for the aortic catheter). Specimens for arterial blood gas measurement were obtained from the aortic catheter. The catheters were connected to transducers (Sorenson Transpac, Abbott Systems, Bloomington) through a heparinized-fluid flush system. This was set up and calibrated in advance. Transducers were zeroed to the midaxillary line on patient arrival. The resulting signals were amplified (78205D, Hewlett Packard, Sunnyvale, Calif) and simultaneous pressure tracings were recorded (7758 Multi-Channel, Hewlett Packard) throughout resuscitation. *Catheterization time* was the interval from hospital arrival to the first pressure measurements.

The CPP at each time point was calculated by subtraction of the right atrial pressure from the aortic pressures for five consecutive relaxation phases (one ventilation-to-ventilation cycle) and taking the mean. *Relaxation and compression phases* during mechanical cardiopulmonary resuscitation have been defined previously.¹⁵ Relaxation phase has also been called "cardiopulmonary resuscitation diastole." The aortic and right atrial pressures were measured toward the end of the relaxation phase, when oscillations caused by catheter movement had decreased. Comparison to micromanometer-tipped catheters had shown this method to be consistently accurate. Aortic relaxation pressures and compression-phase aortic-to-right atrial pressures are also the mean of five cycles. These were measured at the time of highest CPP. *Return of spontaneous circulation* was defined as development of spontaneous aortic pulse waveforms, with a systolic blood pressure greater than 60 mm Hg sustained for more than 2 minutes. Patients who had ROSC before pressure measurement followed by a period of relative hemodynamic stability and then a repeated arrest were considered to have 0-minute total arrest times. Patients not in cardiac arrest at the time of catheter placement who later experienced cardiac arrest were treated similarly.

The CPP measured immediately after catheter placement is the *initial CPP*. The *maximal CPP* is the largest aortic-to-right atrial relaxation-phase gradient during resuscitative attempts. Continued arrest was confirmed at the time of maximal CPP by the absence of

spontaneous aortic waveforms. Maximal CPP was not measured during the increase that occurs just before ROSC. The CPP at 5 minutes after catheter placement was subtracted from the initial CPP to obtain the *CPP trend* during initial resuscitative measures.

STATISTICAL METHODS

We compared variables with two-sided, two-sample *t* tests when applicable. Where necessary, Welch's Test or Wilcoxon Two-Sample Test were used instead. Pearson χ^2 statistics were employed to test proportions. A value of $P < .05$ was defined prospectively as statistically significant. No explicit correction for multiple tests was used.

Positive predictive value for a given CPP was calculated by dividing the number of resuscitated patients with gradients equal to or above the given pressure (true positives) by the sum of this group and the patients without ROSC who had gradients equal to or above this CPP (true positives and false positives). The negative predictive value for a given CPP was calculated by dividing the number of patients without ROSC who had gradients below the value (true negatives) by the sum of this group and the resuscitated patients with gradients below this CPP (true negatives and false negatives).

Multivariate analysis was performed by using stepwise logistic regression.¹⁶ Specifically, this was done to determine which variables were most predictive of ROSC. To directly analyze the predictive value of individual variables, receiver operating characteristic curves were generated for all variables found associated with ROSC using univariate tests.¹⁷ The receiver operating characteristic curve shows the relationship of sensitivity and specificity for a given variable as a predictor of ROSC using all possible cutoff points.¹⁷ The *sensitivity* of a variable using a given cutoff point is defined as the number of resuscitated patients with values equal to or above the cutoff point divided by the total number of resuscitated patients. The higher the sensitivity, the more likely a test is to identify the presence of an event (in this case, ROSC) at the chosen cutoff. The *specificity* of a variable is defined as the number of nonresuscitated patients with values below the cutoff divided by the total number of nonresuscitated patients. The higher the specificity, the more likely a test is to identify the absence of an event at the chosen cutoff. The screening value of two variables can be evaluated by comparing their receiver operating characteristic curves. The better the sensitivity and specificity of a variable the

closer the curve lies to the left-hand and top axes of the graph.

The predictive abilities of individual variables were evaluated by comparing their receiver operating characteristic curves graphically. Additionally, the area under the receiver operating characteristic curve, known as the "c-index,"¹⁸ was used for comparison of different variables as predictors of ROSC. The c-index quantifies the predictive ability of each receiver operating characteristic curve; a value of 1.0 indicates perfect prediction while a value of 0.5 implies only a random association of that variable with ROSC.

RESULTS

One hundred patients were studied. Patients received only basic life support before arrival at the hospital. Arrest was witnessed in 51 patients. Four patients experienced a repeated arrest after catheter placement and were considered to have had 0-minute total arrest times. The times from arrest to initial CPP measurement ranged from 0 to 74 minutes. The presenting rhythm at the hospital, as reported on the patient's chart, was ventricular fibrillation in 28%, electromechanical dissociation in 25%, asystole in 45%, and unrecorded in 2%. Measured variables, divided into ROSC and no ROSC groups and ranked by statistical significance, are presented in Table 1.

Twenty-four patients had ROSC; 20 maintained spontaneous circulation for longer than 1 hour; and no patient survived to hospital discharge, the majority dying of the sequelae of ischemic encephalopathy.

Recorder tracings showed little variability (< 3 mm Hg) between relaxation phases within one respiration-to-respiration cycle except during the first compression phase after each respiration, which was usually augmented. The initial CPP was 1.6 ± 8.5 mm Hg in patients without ROSC and 13.4 ± 8.5 mm Hg in those with ROSC ($P < .0001$) (Fig 1). The maximal CPP recorded during cardiopulmonary resuscitation was 8.4 ± 10.0 mm Hg in patients without ROSC and 25.6 ± 7.7 mm Hg in the group with ROSC ($P < .0001$) (Fig 2). In most cases of ROSC the maximal CPP was recorded within 2 minutes of ROSC. Aortic and right atrial pressure tracings and the CPPs from two typical patients, with and without ROSC, are shown in Figs 3 and 4.

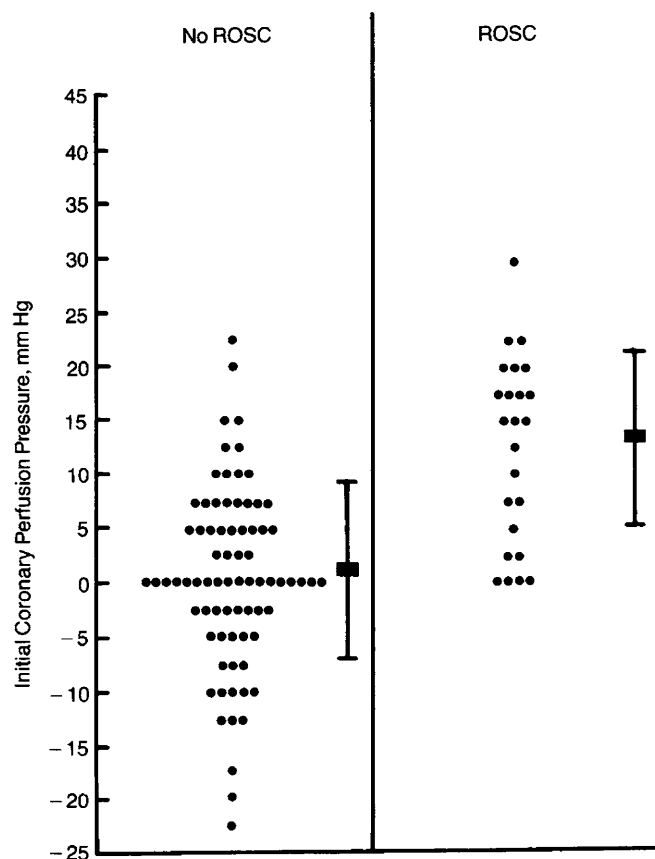
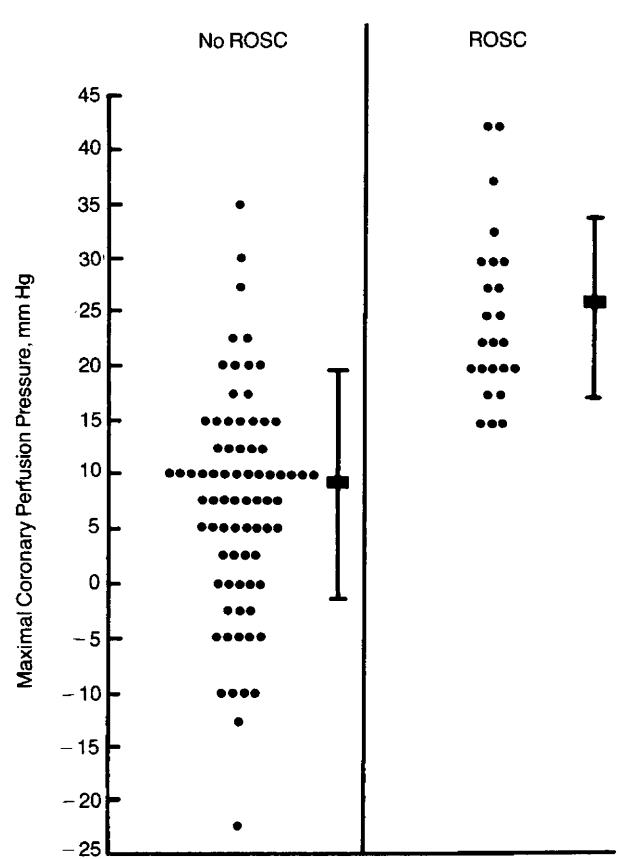
In addition to initial and maximal CPPs there were significant differences between patients with and without ROSC for CPP at 5 minutes, maximal aortic relaxation pressure, aortic-to-right atrial gradient during compres-

Table 1.—Comparison of Variables (Mean $\pm$ SD) for Patients With and Without Return of Spontaneous Circulation (ROSC), Ranked by Statistical Significance*

	Patients Without ROSC	Patients With ROSC	Sample Size	P
Initial CPP, mm Hg	1.6 $\pm$ 8.5	13.4 $\pm$ 8.5	100	<.0001
Maximal CPP, mm Hg	8.4 $\pm$ 10.1	25.6 $\pm$ 7.7	100	<.0001
5-min CPP, mm Hg	2.0 $\pm$ 9.6	16.6 $\pm$ 10.0	92	.0001
Maximal aortic relaxation pressure, mm Hg	24.1 $\pm$ 15.2	35.2 $\pm$ 11.5	100	.002
Compression-phase aortic-to-right atrial gradient, mm Hg	2.5 $\pm$ 13.0	12.5 $\pm$ 13.0	100	.002
Catheterization time, min	13 $\pm$ 6	10 $\pm$ 5	85	.02
Arterial Po ₂ , mm Hg	219 $\pm$ 169	303 $\pm$ 141	88	.05
Initial aortic relaxation pressure, mm Hg	17.6 $\pm$ 12.0	22.8 $\pm$ 10.7	100	.06
Prehospital time, min	19 $\pm$ 11	15 $\pm$ 12	48	.28
Age, y	66 $\pm$ 15	62 $\pm$ 17	82	.30
Down time, min†	12 $\pm$ 11	8 $\pm$ 7	51	.32
Arterial Pco ₂ , mm Hg	43 $\pm$ 44	29 $\pm$ 16	88	.36
Initial CPP trend, mm Hg	0.5 $\pm$ 7.0	-0.9 $\pm$ 12.2	92	.60
Arterial pH	7.20 $\pm$ 0.25	7.17 $\pm$ 0.27	88	.61
Total time, min†	25 $\pm$ 17	24 $\pm$ 16	48	.89

*CPP indicates coronary perfusion pressure.

†Down time and total time are for the 51 patients with witnessed arrests only.

Fig 1.—Distribution of initial coronary perfusion pressures among patients without and with return of spontaneous circulation (ROSC). Each dot represents a patient. The bar is the mean $\pm$ SD.Fig 2.—Distribution of maximal coronary perfusion pressures among patients without and with return of spontaneous circulation (ROSC). Each dot represents a patient. The bar is the mean $\pm$ SD.

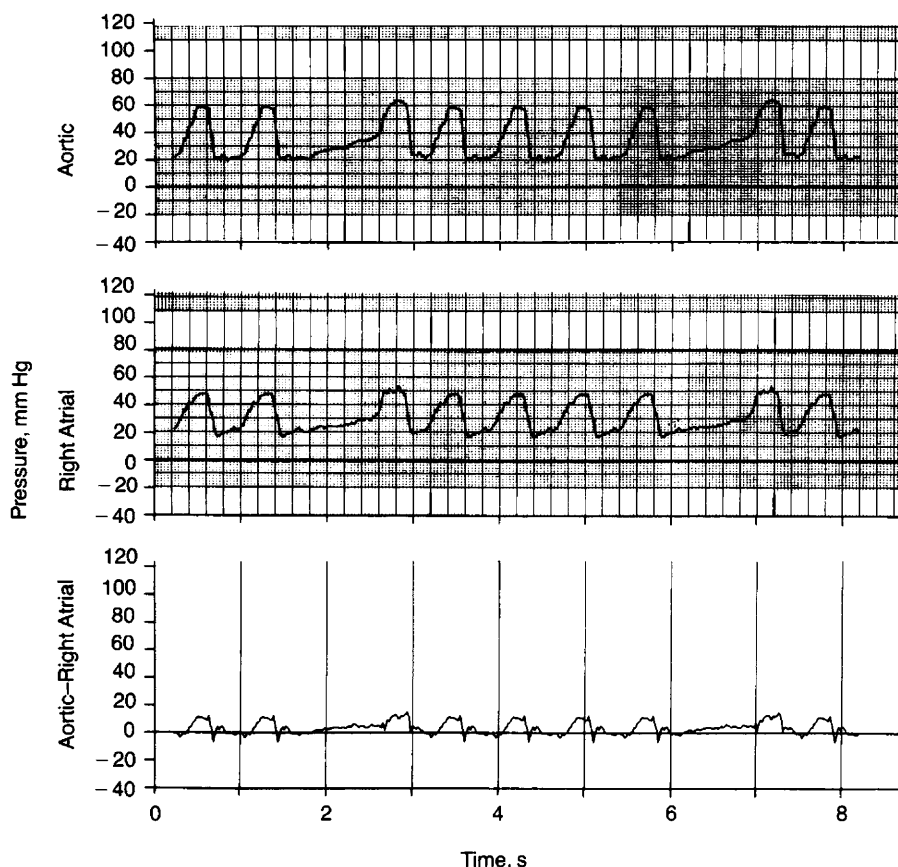


Fig 3.—Aortic and right atrial waveforms from a typical patient who did not have return of spontaneous circulation. The lower tracing is a computer-generated subtraction circuit showing the aortic-to-right atrial pressure gradient. Coronary perfusion pressure is this gradient during the relaxation phase. In this patient, the coronary perfusion pressure averages 0 mm Hg.

sion, PaO_2 , and time required for catheter placement. The minimum aortic relaxation pressure in a patient with ROSC was 17 mm Hg. Thirty-four patients had compression-phase aortic-to-right atrial gradients greater than 10 mm Hg. Thirty-three patients had negative compression gradients. Although resuscitated and nonresuscitated patients had a significant difference in the compression gradient, there were 7 patients with ROSC whose compression gradients were 0 mm Hg or less. Variables that did not differ significantly between patients with and without ROSC included initial CPP trend, PaCO_2 , and down time. The proportion of patients who received high-dose epinephrine was not statistically different in the two groups (χ^2 , $P = .41$).

Among the 27 patients with initial CPP less than 0 mm Hg (negative perfusion pressures), none developed ROSC. This is a negative predictive value of 1 for an initial CPP below 0 mm Hg. These patients tended to have longer down times (17 ± 13 vs 9 ± 9 minutes in patients with positive CPPs [$P = .08$]) and

a higher proportion of unwitnessed arrests. Patients whose maximal CPP never became 15 mm Hg or greater did not have ROSC (Fig 2) (negative predictive value of 1 for CPP less than 15 mm Hg). Only 17 patients had a CPP above 15 mm Hg at initial catheter placement (Fig 1); 25 others had an increase in their CPP to 15 mm Hg or greater during resuscitation. A CPP above 15 mm Hg did not guarantee ROSC, as 18 patients with a CPP greater than 15 mm Hg did not have ROSC. This is a positive predictive value of 0.57. The positive predictive value increased with the CPP, and at 25 mm Hg it was 0.79. Positive and negative predictive values for other initial and maximal CPPs can be derived using the above definitions and the data in Figs 1 and 2. The percentage of patients with ROSC increased as the maximal gradient increased above 15 mm Hg; of the 14 patients who had gradients of 25 mm Hg or greater at some time during their resuscitation, 79% had ROSC (Fig 5).

Stepwise logistic regression demonstrated that the maximal CPP during

resuscitation was the best single predictor of ROSC ($P < .0001$) and that no other variable added any predictive information once maximal CPP was accounted for ($P = .28$ for all other variables combined). Because of the high correlation of initial CPP with maximal CPP ($r = .74$), initial CPP can also be considered to be a good predictor of ROSC.¹⁶

Figure 6 shows the receiver operating characteristic curves of the initial and maximal CPPs matched with curves for initial and maximal aortic relaxation pressures. The CPPs for certain sensitivity/specificity intercepts are also shown. As one moves down the receiver operating characteristic curve from the upper right to the lower left the CPP increases. This means that with greater CPPs, the sensitivity decreased and the specificity increased. A maximal CPP of -1 mm Hg had a sensitivity of 1 and a specificity of 0.16, while a maximal CPP of 25 mm Hg had a sensitivity of 0.46 and a specificity of 0.96. A maximal CPP of 15 mm Hg, which had perfect negative predictive value, had a sensitivity of 1 and a specificity of 0.8. The receiver operating characteristic curves also indicate that, except at the upper and lower ends of the pressure range, CPP is more sensitive and specific than aortic relaxation pressure alone. Sensitivity and specificity of other CPPs and aortic pressures can be interpolated from Fig 6.

The comparison of individual variables as predictors of ROSC can be done using Table 2, which lists all variables for which ROC curves were generated together with the c-index for each curve. As with stepwise logistic regression, the c-indexes indicate that the maximal CPP was most predictive of ROSC. The indexes also indicate that the initial and 5-minute CPPs also have good predictive ability. Other variables, including aortic pressure, were not good predictors of ROSC.

COMMENT

The initial objective of therapy during cardiac arrest is restoration of spontaneous circulation. This must be achieved promptly if maintenance of cerebral viability is to be achieved.¹⁸ In patients not responding to ventilation and defibrillation, therapy must be directed toward improving the metabolic state of the myocardium. During acute ischemia this is largely determined by the oxygen supply/demand equilibrium. Cardiopulmonary resuscitation is performed to improve supply by inducing coronary blood flow and correcting the metabolic abnormalities of the arterial blood.¹²

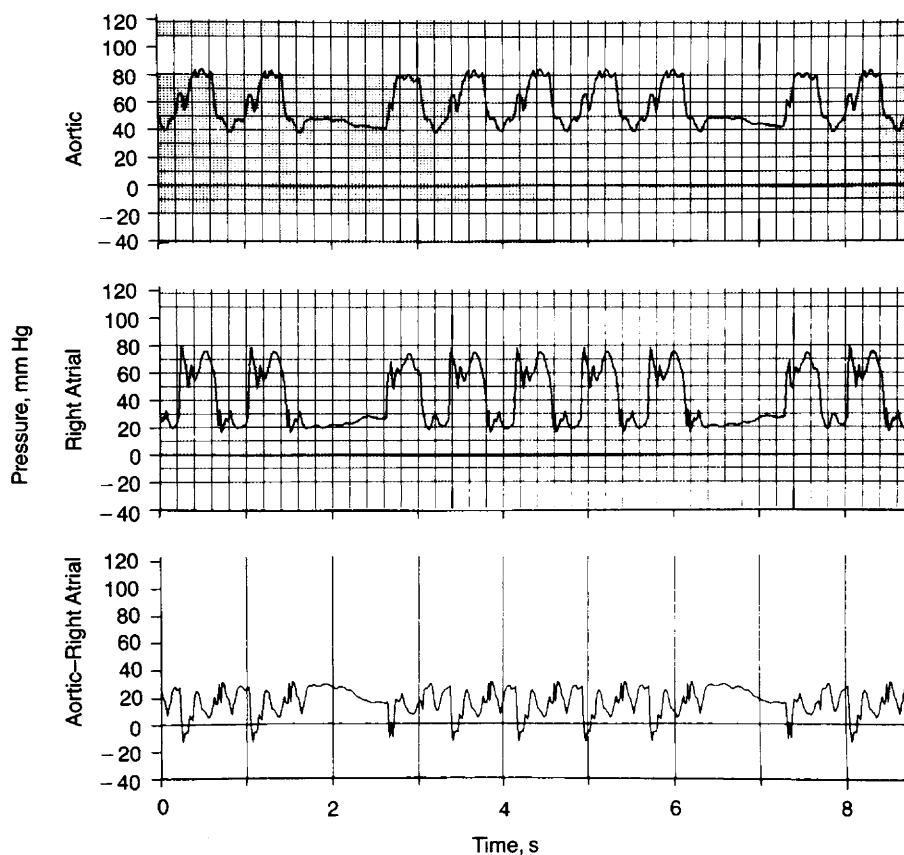


Fig 4.—Aortic and right atrial waveforms from a patient who had return of spontaneous circulation. The lower tracing is the aortic-to-right atrial gradient. This patient's overall pressures are higher than those shown in Fig 3, and the coronary perfusion pressure is about 30 mm Hg.

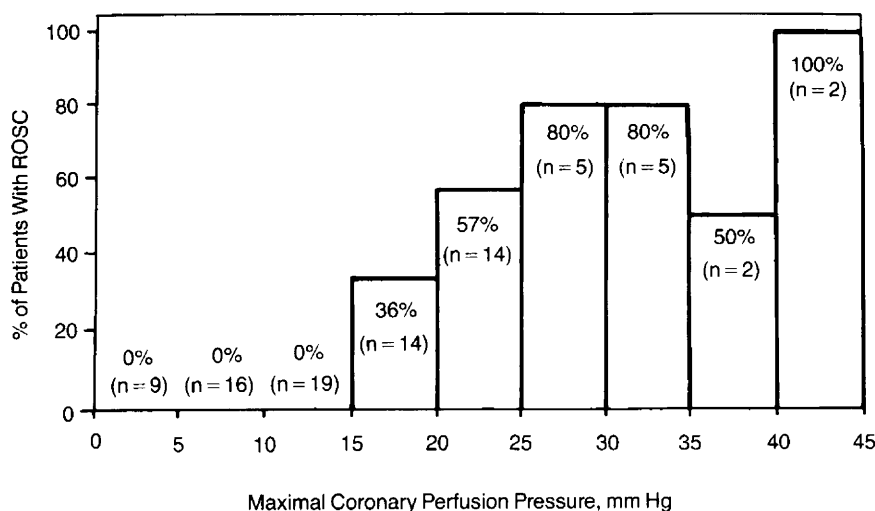


Fig 5.—Percentage of patients with return of spontaneous circulation (ROSC) as a function of the maximal coronary perfusion pressure.

In 1906 Crile and Dolley¹⁹ observed that the ability to resuscitate animals from cardiac arrest was related to the

diastolic pressure during rhythmic compression on the chest. This relationship was also noted by Redding and Pearson³

during the 1960s. Recent work in animal models has demonstrated that there is a minimum myocardial blood flow necessary for ROSC²⁰ and that this is a function of the aortic-to-right atrial pressure gradient during the relaxation phase of cardiopulmonary resuscitation.^{1,4,21} This gradient has become accepted as the CPP during cardiopulmonary resuscitation.¹⁰ In animal models without coronary artery disease, studies have found a CPP of 15 to 20 mm Hg to be predictive of successful resuscitation.^{2,22,23} In a model of ventricular fibrillation, Niemann et al⁶ found peak CPPs between 12 and 17 mm Hg to be perfectly predictive of ROSC. This was unexpected in that one animal study found that a pressure of greater than 28 mm Hg is needed for blood flow to the endocardium during ventricular fibrillation.²⁴ However, this study was not during cardiopulmonary resuscitation, and its results may not be applicable. It is also possible that intramyocardial pressure decreases with prolonged arrest or that coronary blood flow occurs during the asystole that often initially follows defibrillation. The same study found that only 15 mm Hg of pressure was needed for blood flow to the outer myocardium. It is intriguing to consider that endocardial blood flow may not be necessary for ROSC.

Studies that examined alternative types of cardiopulmonary resuscitation have used changes in the CPP as an end point.^{7-9,11} Extrapolation of animal studies to humans led to the assumption that increasing CPP would improve rates of cardiac resuscitation and overall patient survival.^{2,10,25} Previous studies in humans, however, have contained insufficient numbers of successfully resuscitated patients to evaluate the relationship between CPP and ROSC.⁷⁻¹¹

Our results substantiate the conclusions from animal models. Initial, 5-minute, and maximal CPPs were higher in patients with eventual ROSC. Logistic regression found that CPP was highly predictive of ROSC, and no additional predictive power was obtained by adding any other variable. The results are similar to those from animal models in that there seems to be a threshold gradient of approximately 15 mm Hg that must be obtained before ROSC occurs.⁶ The basis of this threshold CPP may be the "critical level" of myocardial blood flow that Ralston et al²⁰ identified as being necessary for ROSC after prolonged cardiopulmonary resuscitation. It is also remarkable that the threshold in humans is so similar to that in animals⁶ when many patients would be expected to have coronary artery disease. Most animal studies have used ventricu-

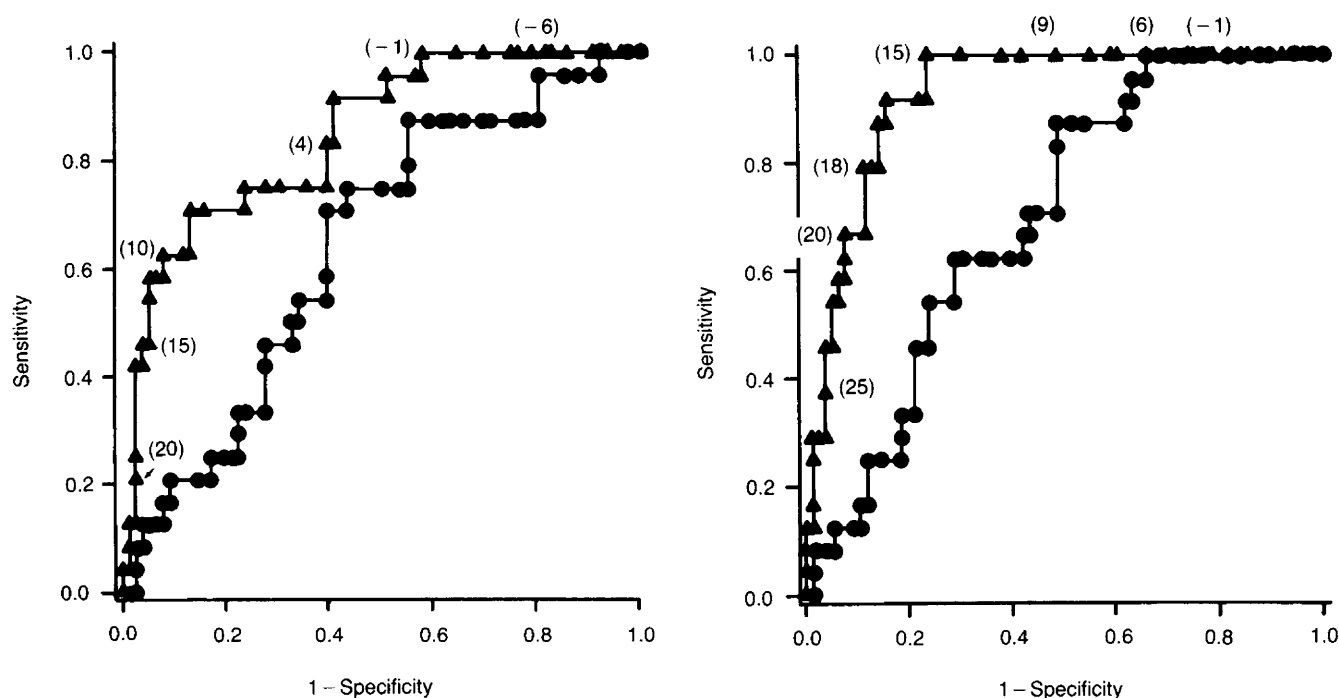


Fig 6.—Receiver operating characteristic curves of initial (left) and maximal (right) coronary perfusion pressures (triangles) and aortic relaxation pressures (circles) as predictors of return of spontaneous circulation. Actual coronary perfusion pressures at certain sensitivity/1 – specificity intercepts are in parentheses. See the "Statistical Methods" section for explanation.

Table 2.—The c-Indexes^{17,44} for Variables Associated With Return of Spontaneous Circulation*

Variable	c-Index†
Maximal CPP	0.930
5-min CPP	0.868
Initial CPP	0.837
Maximal aortic relaxation pressure	0.708
Compression aortic-to-right atrial gradient	0.685
Catheterization time	0.685
Pao ₂	0.646
Initial aortic relaxation pressure	0.631

*CPP indicates coronary perfusion pressure.
†The c-index is derived from the receiver operating characteristic curve¹⁷ for each variable and represents the area under the curve. The index allows comparison of the variables as predictors of return of spontaneous circulation. A value of 1 indicates perfect prediction, while 0.5 indicates only random association.

lar fibrillation. Patients with electromechanical dissociation or asystole may require lower CPPs for ROSC because of lower intramyocardial pressure. That there were patients with CPPs above 15 mm Hg who did not have ROSC is not surprising. Humans, unlike most animals that have been studied, have pre-existing disease, possibly fixed coronary lesions or acute thrombosis. A high CPP will not result in ROSC if resistance to flow is high.

Typical pressure tracings (Figs 3 and 4) reveal a CPP of approximately 0 mm Hg in the patient without ROSC. In the patient with eventual ROSC the CPP is

more than 20 mm Hg. The gradient also seems greater during the relaxation phase. This was the common pattern in patients with positive gradients, and it is consistent with animal studies demonstrating that the limited coronary blood flow during cardiopulmonary resuscitation occurs predominantly during the relaxation phase.¹

The increasing percentage of patients with ROSC as the CPP increased above 15 mm Hg, and the high predictive value of CPP, supports the hypothesis that it is physiologically related to outcome. However, these results should not be taken as proof that CPP is related causally to ROSC. It may be that the overall vascular status of the patient, of which CPP is a measure, is better in patients who go on to ROSC. Nonetheless, it seems reasonable to conclude that therapies that improve CPP probably will increase the fraction of patients with successful cardiac resuscitation. Its use as an end point in clinical studies seems valid.

No patients with negative CPPs or aortic relaxation pressures had ROSC, a perfect negative predictive value. Negative pressures were more common in patients with unwitnessed arrests who may have had long arrest times. Occasionally, a patient with massive aspiration would have a right atrial pres-

sure considerably higher than the aortic pressure, resulting in a large negative CPP. Measurement of a negative CPP may have a role in rational termination of resuscitation efforts.

The negative and positive predictive values of a CPP of 15 mm Hg may make it a good therapeutic cutoff. Because of the perfect negative predictive value of a CPP of 15 mm Hg, therapeutic measures that fail to achieve it indicate the patient may not be resuscitated successfully. The positive predictive value of 0.57 indicates that continued therapy for patients with CPPs of at least 15 mm Hg will achieve ROSC more than half the time.

Animal studies have shown that aortic relaxation pressure alone is correlated with coronary blood flow and ROSC.^{4,26} Niemann et al⁶ found that while peak CPP was perfectly predictive of ROSC, aortic end-relaxation pressure was less useful. Despite this, aortic relaxation pressure has been used to evaluate cardiopulmonary resuscitation in some studies.²⁷ The maximal aortic relaxation pressure was higher in our patients with ROSC, and a pressure of at least 17 mm Hg was needed for resuscitation. However, statistical analysis found that aortic pressure alone was not as good a predictor of ROSC as was CPP. This indicates that a

relatively low right atrial pressure, which would increase CPP, is helpful during cardiopulmonary resuscitation. It is consistent with the observation by Ditchey and Lindenfeld²⁸ in dogs that volume loading can decrease organ blood flow. No patient with a negative initial aortic relaxation pressure had ROSC. However, the difference in initial aortic pressure between resuscitated and nonresuscitated patients did not reach statistical significance, and the *c*-index indicates poor predictive value for aortic pressure early in resuscitation.

Although the PaO₂ was statistically different between patients with and without ROSC, both partial pressures are above that necessary for maximum hemoglobin saturation, so the difference is unlikely to be causally related to outcome. It may reflect greater pulmonary and systemic blood flow in patients with eventual ROSC, a result of some combination of higher vascular tone and more effective cardiopulmonary resuscitation in these patients. The poor ability of arterial blood gas measurements to predict ROSC is interesting in light of the effort that is directed toward their improvement in most clinical situations. Patients with unwitnessed arrests were not included in the statistical analysis for time variables. It can be reasonably assumed that this group of patients had longer arrest times. Had their down times been known, and included in the statistical analysis, the difference may have reached significance. The difference in catheterization times between patients with and without ROSC may reflect the ease of catheter placement in patients with higher intravascular pressure and greater vascular tone.

Even among patients with witnessed arrests, time measurements were not highly predictive of ROSC. Clinical experience has confirmed laboratory studies²⁹ showing that duration of cardiac arrest has a profound effect on the probability of ROSC.³⁰ To some extent, our results may reflect inaccuracy in determining the time the patient lost spontaneous circulation. Although we only used witnessed arrests in analysis of time variables, the moment of collapse does not necessarily indicate complete loss of blood pressure. The long mean arrest times may also explain the lack of predictive value. It has been shown in animal models of cardiac arrest,²² and is widely believed to be true in humans, that vascular tone deteriorates with time after cessation of circulation. It may be that after prolonged arrest, the state of the vasculature (as reflected in the CPP) is more important than the time since arrest. Factors such as technique of compression, responsiveness to

administration of pressors, oxygenation, and prearrest state also may be important. After 25 minutes of arrest these may be better reflected by CPP than by total down time. Regardless of the mechanism, the absence of a significant difference in down times between the two groups indicates that CPP is a better predictor of ROSC than is down time in patients with prolonged arrest and suggests that it may be one of the primary determinants of ROSC in such patients.

The selection of patients was biased by the circumstances of the study, and, therefore, our sample does not represent the typical population of patients with cardiac arrest. Most of our patients experienced cardiac arrest out of the hospital, resulting in a delay of therapy because our institution is in a city with only limited prehospital advanced life support. The time required for catheter placement also precluded the study of patients who responded to initial therapy. This group would be expected to have higher pressures, a greater incidence of ventricular fibrillation, and a better long-term prognosis. Therefore, our results should be applied with caution to patients with short arrest times. It may be that in the first few minutes of cardiac arrest, outcome is more a function of the inciting hemodynamic or cardiac rhythm disturbance than the CPP. Patients who experienced a repeated arrest after catheter placement also required a CPP of 15 mm Hg, but it is not clear that they are similar to patients who experience cardiac arrest for the first time. This study, however, could not have been performed in cities with prehospital advanced life support. Measurement of perfusion pressures in patients who have had prolonged therapy before transport to the hospital would be unlikely to result in meaningful data because those remaining in arrest would not be expected to have ROSC.

The proportion of patients who presented with ventricular fibrillation is lower, and with asystole is higher, than that in other series.³¹ This is also most likely a result of our prehospital system and the delay before entry into the study. In most emergency medical systems the initial rhythm is obtained by paramedics in the field. Our patients had to be transported to the hospital before this was obtained. Some patients initially in ventricular fibrillation probably had their rhythm decay to asystole during transport.

The absence of long-term survivors is understandable in light of the minimum arrest time required before CPP measurement. This does not necessarily mean that the time needed to measure

CPP precludes a good outcome. Almost all patients in this study suffered cardiac arrest before arrival at the hospital. Most were in cardiac arrest on arrival of emergency personnel and had not received basic life support. Although we measured CPP, we did not respond to this information during the study by changing therapy. Indeed, the researchers measuring the gradient were not those treating the patient. It is possible that early measurement of CPP, such as in a patient who experiences cardiac arrest within the hospital, with resultant changes in therapy, might lead to earlier ROSC and improved neurological outcome. This needs further study. The usefulness of CPP compared with other diagnostic modalities, especially end-tidal carbon dioxide,³² has not been studied prospectively. Recent work, however, indicates that efficacious doses of epinephrine may actually lower end-tidal carbon dioxide.³³

Controversy exists as to the mechanism by which external compression creates perfusion gradients during cardiopulmonary resuscitation. The widely accepted thoracic pump model,^{34,35} in which perfusion is believed to result from the rise in intrathoracic pressure, has been questioned recently by investigators who concluded that blood flow results from direct compression of the heart.³⁶ We recently studied pressures across the thoracic outlet during human cardiopulmonary resuscitation and concluded that the thoracic pump and cardiac pump mechanisms may not be mutually exclusive.¹⁵ The present study does not directly address this question, but the higher compression-phase aortic-to-right atrial gradients in patients with ROSC may indicate cardiac compression and a resultant benefit to the patient. However, this interpretation has been questioned by Weisfeldt and Halperin.³⁷ They observe that if there is a positive relaxation-phase gradient between the aorta and the right atrium then a general rise in intrathoracic pressure may add equally to both arterial and venous pressures, and a positive gradient will be maintained during compression. Thus, patients may have high compression-phase gradients simply as a result of high CPPs. On the other hand, there were a number of patients with zero or negative gradients across the heart during compression who had high CPPs and ROSC. Thus, absence of a compression-phase gradient, and presumably cardiac compression, does not necessarily mean cardiopulmonary resuscitation is not working.

Patients who received high-dose epinephrine at the end of resuscitation were included because it is thought to

function by raising aortic pressure and CPP.^{33,38} However, use of high-dose epinephrine was not predictive of ROSC under this protocol. Its administration at the end of resuscitation may have obscured any relationship to outcome.

That there is a threshold CPP necessary for ROSC has important clinical ramifications. In patients not responding to initial treatment, measurement of CPP may allow therapy to be adjusted based on real-time information. Presently, cardiac arrest is managed by protocols based on the rhythm disturbance. This has had disappointing results in patients with longer arrest times. A number of therapies are being studied that have the potential to improve CPP. Among these are interposed abdominal-compression cardiopulmonary resuscitation,³⁹ high-impulse cardiopulmonary resuscitation,⁸ high-dose epinephrine,³⁸ open-chest cardiac compression,^{40,41} vest cardiopulmonary resuscitation, and cardiopulmonary bypass.⁴² Measurement of CPP may provide a rational basis for use of these therapies.

Clinical use of CPP during cardiac arrest may be feasible. Since many patients will have a right atrial catheter placed as part of standard therapy,⁴³ measurement of CPP may only involve the insertion of a single additional catheter. Precalibrated equipment for monitoring pressure and extra personnel are needed, but these should not be a problem in large hospitals. Some skill is required to place the aortic arch catheter quickly.

In summary, this study substantiates animal data that indicate the importance of CPP as a predictor of return of spontaneous circulation, as well as the assumption that therapies that improve CPP increase the probability of ROSC. In patients with prolonged arrest, CPP is a better predictor of outcome than is aortic pressure alone. A CPP of 15 mm Hg seems to be necessary for ROSC and may represent a therapeutic goal during resuscitative efforts. It seems valid to use CPP as an end point in evaluating alternative methods of cardiopulmonary resuscitation in humans.

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