

Coronary perfusion pressure during cardiopulmonary resuscitation

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Coronary perfusion pressure (CPP) generated during cardiopulmonary resuscitation (CPR) is a key component for successful resuscitation. Defined as the pressure gradient between the aorta and the right atrium during the 'diastolic' or decompression portion of chest compression-decompression, this gradient has been correlated with both myocardial blood flow generated with CPR and ultimately with resuscitation outcome. Several unique features of cardiac arrest physiology, specifically the loss of vascular auto-regulation, make this pressure gradient even more important and the principal determinant of myocardial blood flow during CPR. Additionally, the loss of the ability to selectively vasoconstrict and vasodilate before and after an intra-coronary lesion results in increased significance of any coronary obstruction (even lesions less than 50%) with profound compromising effects on distal flow. Although CPP has been measured in patients undergoing CPR it remains difficult to acquire, secondary to the time needed to insert the pressure-measuring catheters. Alternative non-invasive measures of coronary perfusion are needed. Expired end-tidal carbon dioxide has been one suggested possibility.

Key words: cardiac arrest; myocardial perfusion; CPR blood flow; resuscitation success.

INTRODUCTION

The purpose of cardiopulmonary resuscitation (CPR) is to provide blood flow to the vital organs during cardiac arrest. Experimental evidence suggests that CPR can generate forward blood flow, although the actual levels of perfusion are typically well below those found during normal sinus rhythm. Closed-chest CPR techniques generally provide central nervous system blood flows of 20–40% of control levels, but provide only 10–20% of normal myocardial blood flow.^{1–6} Perfusion of other organs is even worse with minimal perfusion of all arterial beds below the diaphragm.^{3,5} This selective perfusion of only the most important organs, i.e. the myocardium and the brain, is critical for resuscitative efforts to succeed and if the long-term results are to be worthwhile.

DETERMINANTS OF CPR SUCCESS

A number of factors have been identified as contributing to the success of any resuscitation effort (Table 1). Foremost is the duration of the cardiac arrest. The longer

Table I. Determinants of CPR success.

Duration of cardiac arrest
Aetiology of cardiac arrest
Co-morbid conditions
Early basic life support (BLS) CPR
Quality of BLS CPR
Early defibrillation for ventricular fibrillation cardiac arrest

the insult of cardiac arrest with its associated no flow/ischaemic state, the more difficult it is to reverse the underlying and initiating process.⁷⁻⁹

Although it is true that the longer the cardiac arrest lasts the poorer the outcome, such results can be affected by the early use of CPR and defibrillation. Classic data from the Seattle area in the late 1970s⁷ demonstrate the importance of both these modalities for improving outcome from cardiac arrest.

The aetiology of the cardiac arrest is another important factor influencing the success of resuscitative efforts. Ventricular fibrillation is generally more amenable to therapy than asystole or pulseless electrical activity. The availability of automatic external and implantable internal defibrillators has made it possible to rapidly treat ventricular fibrillation, and where this is done within seconds to several minutes excellent long-term outcomes have been achieved. The commonly quoted concept that for every minute of untreated ventricular fibrillation survival declines by 10% has recently been prospectively validated by several public access automatic external defibrillator (AED) programmes.¹⁰⁻¹³ Figure 1 illustrates survival rates per time to defibrillation from several AED programmes.

Concurrent co-morbid conditions at the time of cardiac arrest have profound effects on the ultimate outcome seen with cardiopulmonary resuscitation.¹⁴ Individuals who suffer cardiac arrest while suffering from pneumonia, renal failure, or cancer have very poor prognoses, even if excellent CPR is performed.

Finally, the quality of cardiopulmonary resuscitation can affect its effectiveness and ultimately its success or failure.^{15,16} Quantifying the quality of CPR can be difficult, but the goal of 'quality CPR' is relatively straightforward, namely to provide 'adequate' blood flow to the heart to allow the resumption of spontaneous circulation, and to the brain to allow the recovery of central nervous system function. Myocardial perfusion can be best estimated by measuring the 'coronary perfusion pressure' (CPP) achieved during resuscitation. The importance of this myocardial perfusion pressure has been well studied in both the laboratory and in some clinical CPR series.

DETERMINANTS OF CORONARY PERFUSION PRESSURE DURING CPR

Crile and Dolley¹⁷ were the first to write about the importance of an adequate perfusion pressure for resuscitation from cardiac arrest. In 1906 after studying resuscitation from anaesthetic overdose in dogs and cats they noted, 'the basic problem, then, in resuscitations seems to us to be that of securing some means of some infusion – a coronary pressure, approximately amounting to 30–40 mmHg'.

Redding and Pearson expanded on this concept some 60 years later. Much of their early work demonstrated the importance of generating an aortic diastolic pressure of

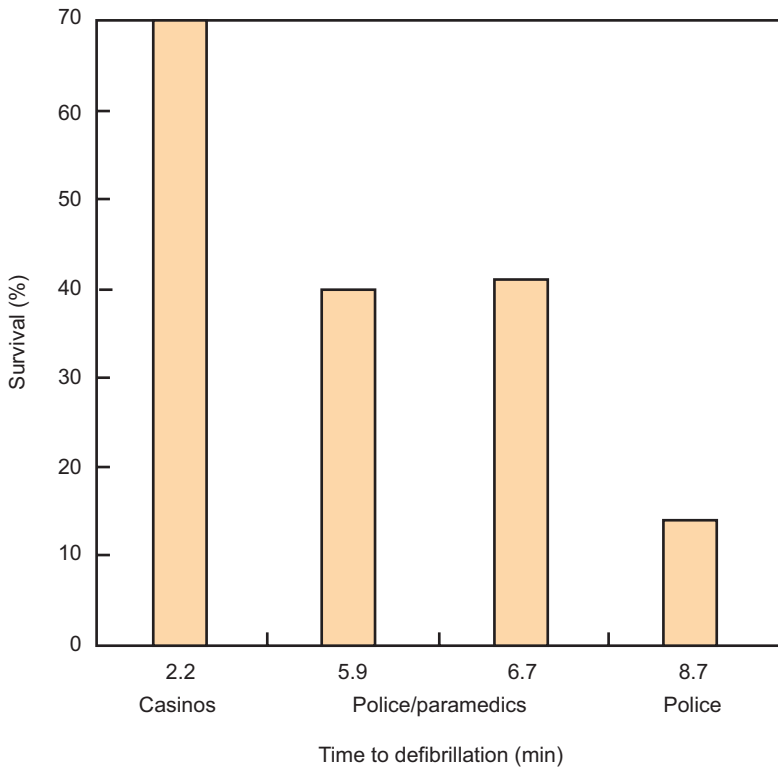


Figure 1. Survival from cardiac arrest as a function of time to defibrillation with automatic external defibrillators (AEDs) used by non-traditional, non-medical first responders.

at least 40 mmHg for successful resuscitation to occur.^{18–21} When such an aortic diastolic pressure was not accomplished successful resuscitation did not occur. They noted that drugs like epinephrine were often required to achieve such aortic pressures during CPR. From this early work they postulated that the mechanism of action of such α adrenergic agonists was by peripheral vasoconstriction resulting in increased central aortic diastolic pressures.¹⁹ This insight has become one of the central foundations upon which current resuscitative strategies are based. Follow-up studies by Otto and Yakaitis^{22–24} using more sophisticated selective α and β adrenergic blocking agents have confirmed this early work. These investigators found that if α adrenergic blockers were administered in conjunction with epinephrine in an asphyxia-induced cardiac arrest model, almost no survival could be achieved. Whereas, if a β adrenergic blocker and epinephrine were given concurrently, survival was not compromised and was equal to those receiving epinephrine alone (Figure 2).^{22–24} They concluded that, ‘the effectiveness of a pharmacological dose of epinephrine used during CPR in the canine asphyxial model is due entirely to its alpha adrenergic stimulating properties. Beta adrenergic stimulation of the heart and/or nonadrenergic effects of epinephrine have no effect on the outcome. Alpha adrenergic stimulation may increase peripheral vascular resistance, diastolic blood pressure and, thus, coronary perfusion allowing resumption of spontaneous cardiac function’.²² As predicted by Crile and Dolley as well as by Redding and Pearson, an average aortic diastolic pressure of

37 mmHg was seen in those animals that were successfully resuscitated.²³ Otto and Yakaitis also studied the effect of predominately α versus β adrenergic agonists (without adrenergic blockade) compared to placebo in both asphyxial and ventricular fibrillation cardiac arrest. The importance of α adrenergic stimulation, producing increased aortic diastolic pressure, was again demonstrated by increased resuscitation success (Figures 2(A) and (B)).

Further understanding of CPP during CPR followed in the 1980s. Data began accumulating showing that although aortic diastolic pressure was important as a 'perfusing pressure', in fact a perfusion pressure 'gradient' was even more accurate in describing acute myocardial perfusion during CPR. Investigators at Purdue University measuring regional blood flow to the central nervous system, myocardium and other peripheral organs noted that the arteriovenous gradient was important during the compression phase of CPR for cerebral blood.²⁵ They postulated that such a gradient would likewise be important for myocardial blood flow during the relaxation phase of chest compressions (CPR 'diastole'). Thus began the concept of defining CPP as the aortic diastolic pressure minus the simultaneously measured right atrial diastolic pressure. Figure 3 illustrates this concept graphically, with a driving pressure for perfusing the myocardium arising from the aortic diastolic pressure, with the simultaneous right atrial pressure acting as an impediment or resisting force to antegrade coronary flow by decreasing the transmural flow gradient. Early reports from both Neimann et al²⁶ and Ditchey et al¹ suggested that coronary perfusion results from differences in pressures between the aortic and right atrial chambers. Differences of opinion still exist on whether it is best to use mean or diastolic pressure in calculating this arteriovenous gradient. Ditchey and co-workers, using a small number ($n = 6$) of data points gathered at the lower end of the aortic to right atrial mean pressure difference, found a correlation coefficient of 0.97 for coronary blood flow and the perfusion pressure gradient.¹ The majority of resuscitation researchers have used the diastolic pressure difference between the aortic and right atrial chambers, generally with equally superb correlation between myocardial blood and the diastolic CPP gradient.²⁻⁴

Further evidence concerning the importance of right atrial diastolic pressure during CPR was found indirectly when abdominal binding was combined with some newer forms of external chest compression CPR. The addition of abdominal binding resulted in higher peak intra-thoracic pressures and improved carotid blood flow. However, an unanticipated effect was an increase in right atrial diastolic pressure compared to aortic diastolic pressure, thereby decreasing the diastolic CPP gradient. In an experimental study by Sanders et al²⁷ abdominal binding with simultaneous compression-ventilation CPR resulted in a lower CPP (10 mmHg versus 25 mmHg) and a worse resuscitation rate compared to standard CPR (0/6 versus 5/6).

CPP is defined differently during CPR than during normal sinus rhythm. Typically during normal physiological conditions (i.e. normal sinus rhythm) coronary perfusion occurs during diastole and is generally defined by aortic diastolic pressure minus left ventricular end-diastolic pressure. Wall stress can also affect such perfusion but is generally adequately accounted for by using left ventricular end diastolic pressure (LVEDP). Vascular resistance is an important determinant of perfusion.

Regional perfusion is determined by the pressure gradient across a vascular (capillary) bed divided by the vascular resistance ($Q = \Delta P/R$; where Q is flow; ΔP is the pressure gradient; and R is the resistance). Under normal physiological conditions, i.e. normal sinus rhythm, coronary vascular resistance is made up of three distinct components. These are termed R_1 , R_2 and R_3 . R_1 is the resistance of the epicardial

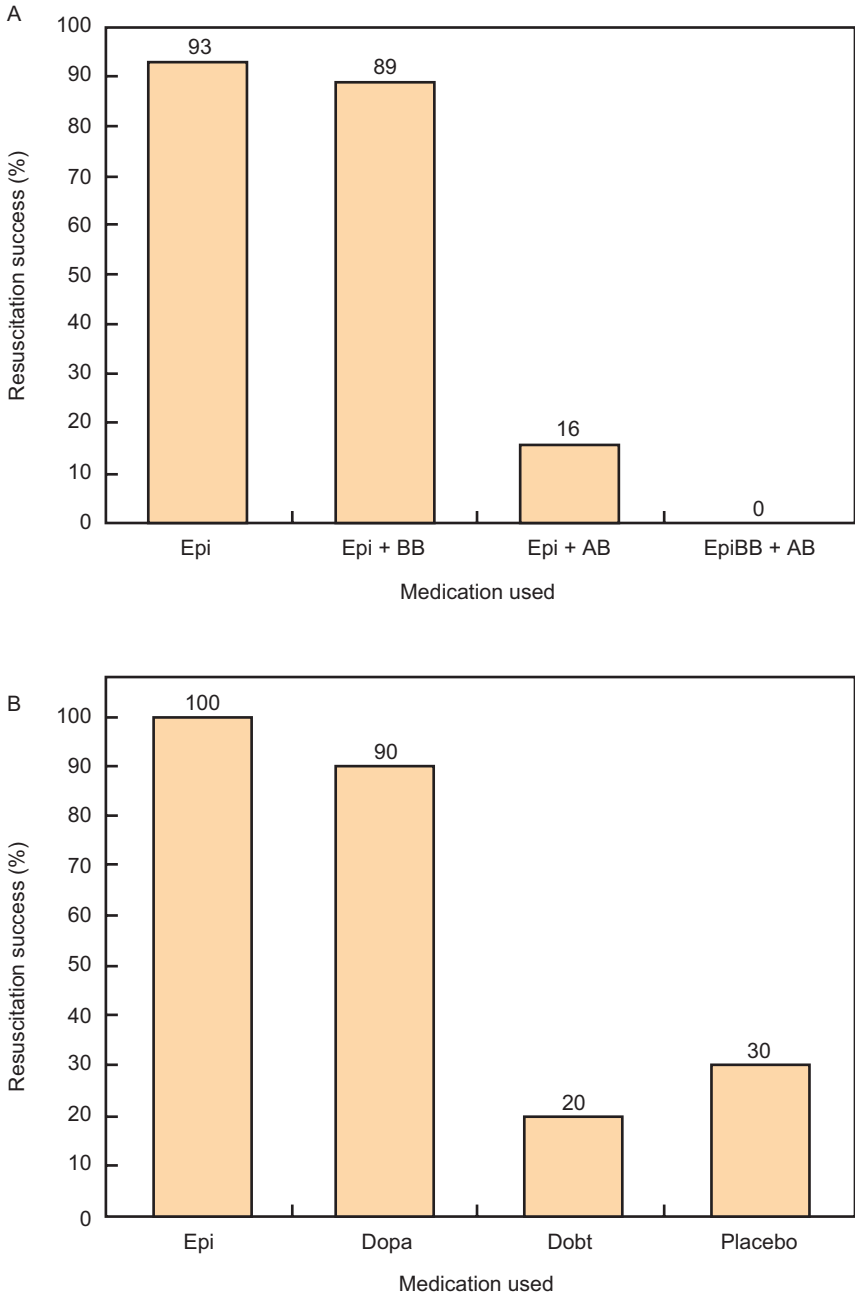


Figure 2. Resuscitation success as a function of medication usage during resuscitative efforts for both (A) asphyxial and (B) ventricular fibrillation cardiac arrest. Epi, epinephrine; Epi + BB, epinephrine plus beta-blocker; Epi + AB, epinephrine plus alpha-blocker; Dopa, dopamine; Dobt, dobutamine.

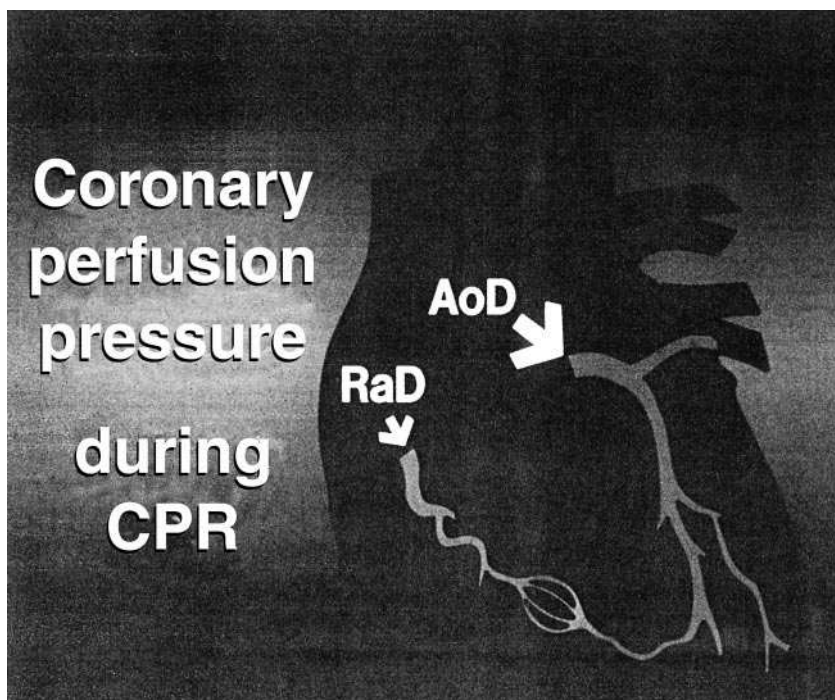


Figure 3. Coronary perfusion pressure is the pressure gradient difference between the ascending aortic (AoD) and right atrial (RaD) pressures during the relaxation or decompression phase of CPR.

vessel itself. The size and health of the coronary artery are the main determinants of this resistance. In the absence of vasospasm or fixed intra-coronary lesions, R_1 contributes very little to the total coronary resistance in normal physiological states.²⁸ R_2 , the autoregulatory resistance factor, is the major contributor to coronary resistance during normal sinus rhythm. This R_2 component is determined by the smooth muscle tone of the arteriolar bed (including but not limited to the epicardial vessel). The R_3 factor, called the compressive resistance factor, is created during the systolic phase of the cardiac cycle when the intra-myocardial capillary bed is literally squeezed closed, obliterating all blood flow run-off. The R_3 vascular resistance factor is the reason that coronary flow and myocardial perfusion is nearly always a 'diastolic' phenomenon in the normal cardiac cycle.

During cardiac arrest, coronary vascular resistance is dramatically different from the description above. First and foremost, the R_2 factor is markedly altered. The ischaemic insult associated with cardiac arrest results in a generalized vasodilatation. The myocardial vascular bed is maximally dilated within approximately 15–30 seconds. Postulated mediators are assumed to be similar to those seen with regional ischaemia, such as extracellular acidosis, adenosine and nitric oxide. The result of this maximal vasodilatation of both the epicardial coronary and the myocardial arteriolar bed is that the primary factor of coronary resistance is negligible. This profoundly affects the way coronary blood flow is generated and regulated during CPR. Myocardial blood flow now becomes almost entirely a function of the 'driving' pressure (the aortic pressure) impeded only by the 'resisting' pressure in the downstream venous reservoir (the

coronary sinus or right atrial pressure). Coronary vascular resistance during cardiac arrest is determined by any intra-coronary lesions (R_1) and the compressive resistance generated by CPR (R_3).

Several investigators have questioned whether coronary flow could occur during the compression phase of CPR.^{1,26,29} Positive aortic to right atrium pressure gradients (aortic peak pressure exceeding right atrial peak pressure) have been recorded with some resuscitation techniques, including open chest direct cardiac massage, and in some studies using epinephrine with closed chest compressions. Because of this positive 'perfusion pressure gradient' some have concluded that the diastolic gradient as an index of coronary flow during CPR may be incomplete.²⁹ Total 'net flow' during CPR may require consideration of any positive aortic to right atrial pressure gradient, regardless of whether it occurs during systole (compression) or diastole (relaxation). We therefore studied this possibility by measuring intra-coronary flow velocity direction during normal sinus rhythm and CPR.³⁰ Using a Doppler flow catheter inserted into the proximal portion of the left anterior descending coronary artery we were able to determine the direction of coronary flow throughout the cardiac cycle, whether spontaneous or during the chest compression or chest relaxation phase of resuscitation. We found that retrograde coronary flow (flow from the coronary back towards the aorta) routinely occurred during the compression phase of CPR. Even if the aortic peak pressure exceeded the peak right atrial pressure, suggesting a positive pressure gradient, no antegrade flow (from the aorta into the coronary) was seen. Such antegrade flow occurred exclusively during the relaxation phase of chest compression CPR and correlated with a positive diastolic perfusion pressure gradient between the aorta and right atrium. The greater this diastolic gradient the larger the antegrade coronary flow velocity. Positive systolic CPP gradients occurring during the compression phase of CPR do not signify antegrade coronary flow, but rather can be associated with substantial retrograde flow. Only diastolic pressure gradients determined forward or antegrade myocardial perfusion during resuscitation.

CPP AND MYOCARDIAL BLOOD FLOW DURING CPR

Defining CPP as the pressure gradient between the aorta and right atrium during the relaxation phase of chest or cardiac compression has allowed the direct measurement of this gradient if the pressures in both chambers can be simultaneously measured during resuscitation. This is routinely done in the experimental laboratory. Only with great effort, and usually after substantial elapsed time, have such measurements been obtained during clinical cardiac arrest.^{31–38}

A number of different resuscitation laboratories have measured coronary perfusion pressure while also measuring myocardial blood flow, usually with radioactive or coloured microspheres.^{2–4,39} Correlation coefficients ranging from 0.82–0.89 have been reported. Ralston et al² from Purdue University found a coefficient of 0.89 when no epinephrine was used, and 0.85 with the use of epinephrine during CPR. Investigators at Johns Hopkins University found coefficients of 0.84 and 0.88^{3–4} and we found similar results in our University of Arizona resuscitation research laboratory with a correlation coefficient of 0.82.³⁹ The higher the CPP generated during CPR, the greater the resultant myocardial blood flow. Evident from these separate but collaborating studies is that at the range of typical CPP generated with standard closed-chest compression CPR (10–20 mmHg), resultant blood flow is typically poor, averaging only 15–25 ml/min/100 g (with normal coronary blood flow being 125–150 ml/min/100 g). However, if a

better CPP can be achieved, say 30–40 mmHg, then myocardial blood flow is markedly better, ranging between 40–80 ml/min/100 g. This range is close to 50–60% of ‘normal’ control levels during normal sinus rhythm.⁴⁰ If CPPs of > 50 mmHg are achieved, myocardial blood flow can equal and even exceed the usual ‘normal’ control levels. This is possible since coronary flow in non-diseased arteries during CPR is totally ‘pressure gradient’ driven with minimal vascular resistance following the loss of auto-regulation and resultant maximal coronary vascular bed dilatation. The previously documented plateau of blood flow seen with increasing coronary pressure during normal sinus conditions is not found during cardiac arrest with this loss of autoregulation.²⁸ In these circumstances the incremental increase in myocardial blood flow for every increase in CPP seems to continue without limit.

These insights into myocardial blood flow during CPR have been obtained by using standard canine and porcine cardiac arrest models. These animals have been normal without any coronary artery disease nor left ventricular dysfunction. The typical patient suffering cardiac arrest, however, is markedly different in this respect, almost always having significant organic heart disease. Over 90% of cardiac arrest victims have coronary artery lesions and, currently, more and more have a background of prior myocardial infarction and left ventricular dysfunction.^{41–43} Realizing that the major coronary artery resistance factor during cardiac arrest is not R_2 but could be R_1 if coronary disease is present, we studied the relationship between coronary perfusion pressure and myocardial blood flow in an in vivo porcine model with implanted intra-coronary artery lesions. Using percutaneous techniques, so as to avoid the complications of doing external chest compression CPR after a thoracotomy, fixed coronary stenoses were placed in the mid left anterior descending epicardial coronary artery. A single stenosis was first utilized, which reduced the coronary diameter by 33%. In half the animals the stenosis was kept patent with aggressive anti-coagulation, and the other half were allowed to thrombose and occlude. In this porcine model, with minimal collaterals, we found that complete coronary occlusion resulted in negligible distal myocardial perfusion, regardless of how much CPP was generated during CPR.³⁹ In those animals where the stenosis was kept patent myocardial blood flow measured during CPR continued to show a high correlation with CPP, although with significantly less myocardial blood flow for every mmHg of CPP generated. In the presence of intra-coronary lesions, the pressure–flow relationship becomes much less steep in its slope. Within the range of CPPs of 20–60 mmHg the blood flow distal to the stenosis was only about half of what was seen proximal to the 33% fixed stenosis. This reduction occurred over a wide range of CPPs generated with CPR. Such data suggest that previously determined levels of adequate perfusion pressure during CPR in models without coronary artery disease may not be applicable to patients with coronary disease.

The importance of coronary artery lesions in victims of cardiac arrest has not been routinely considered in previous CPR research. Intuitive reasoning would suggest that any coronary lesion that compromises myocardial blood flow under normal physiological conditions would do so as well during CPR. But that a lesion of only 33%, that was previously thought of as ‘insignificant’, would do so was not anticipated. When blood flows proximal and distal to this stenosis were measured during CPR we found a significant drop-off in distal perfusion. Early on, at 3 minutes of CPR, there was a marked difference in endocardial blood flow that later, at 8 minutes of CPR, was even more accentuated.⁴⁴

Intrigued by these results with a 33% diameter lesion we studied additional degrees of coronary stenoses, including 50%, 25% and 10%. What was surprising was that each,

including the mere 10% stenoses, had effects on distal endomyocardial blood flow during CPR.⁴⁵ Although there was a gradation of effect, with the 50% stenosis having a larger effect, compromising both epicardial and endocardial flow distally, even the 10% lesion decreased flow to the endocardium distal to the stenosis.

We concluded that fixed intra-luminal coronary lesions, even those deemed to be 'insignificant' during normal physiological conditions, have a profound effect on distal myocardial perfusion and alter the previously established relationship between CPP and resultant myocardial blood flow.

The potential ramifications of these findings are startling. Under the altered physiology of cardiac arrest, any fixed coronary lesion is likely to have a detrimental effect on myocardial perfusion distal to the site of that coronary disease. Such a discovery highlights the importance of optimizing CPP as early as possible with any resuscitation effort.

Another important concept is apparent with careful study of the data illustrating the relationship between CPP and myocardial blood flow during CPR. Notable is the lack of any myocardial blood flow until a minimum CPP of approximately 5–10 mmHg is achieved. This corresponds to the 'critical closing pressure', the CPP below which flow stops secondary to intrinsic smooth muscle tone in the arteriole wall literally causing physical closure of the arteriolar vessels.²⁸ Under normal physiological conditions it is estimated that this critical closing pressure is about 30–40 mmHg, and that during intense vasodilatation it decreases to approximately 10–12 mmHg.²⁸ Data gathered during actual cardiac arrest, suggest that during maximal vasodilatation this closing pressure may fall as low as 5–10 mmHg, but does not become zero as some have previously postulated.⁴⁶ This 'closing pressure', below which no flow seems to occur is a key concept in understanding the importance of limiting interruptions to chest compressions/relaxations during which the CPP inevitably falls.

Diastolic CPP is the key to producing adequate myocardial blood flow during CPR. Recent interest has centred around improving the myocardial perfusion achieved during resuscitation by decreasing interruptions to CPP generation. Recent prospective observations of laypersons performing standard basic life support CPR with 15 compression-relaxation cycles followed by two ventilations have revealed significant interruptions of chest compression-relaxations for the delivery of these ventilations.⁴⁷ In a cohort of 258 laypersons taught standard CPR then asked at the end of their training course to demonstrate basic life support (BLS) CPR using a recording Resusci-Anne mannikin we found that the average time for the interruption of chest compressions was 16 seconds. Each time they stopped to ventilate it took 16 seconds before they began chest compressions again. The result of these lengthy interruptions is that although they did follow the taught instructions to compress at 100 times/minute, the actual delivered compressions and hence relaxation cycles were at only 43 times/minute. Since chest compression-relaxation cycles (i.e. specifically the relaxation phase) are responsible for blood flow generation to the heart such a decrease in the delivered chest compression cycles can markedly decrease the total amount of myocardial perfusion generated with the resuscitation effort. In addition, these interruptions of chest compression-relaxation have direct effects on the amount of CPP generated during the period of 15 compression cycles. We found that at the beginning of each cycle of 15, the first 5–10 compressions-relaxations are 'building-up' the coronary perfusion gradient and that it is not optimal until at least one-third of the series has been completed.⁴⁸ Then, with the cessation of chest compressions-relaxations this diastolic gradient falls off rapidly, often returning to near zero within 5–10 seconds. Often the CPP gradient falls even sooner to below the 'critical closing

pressure' predicting no forward flow after just a few seconds of interruption to the chest compression-relaxation cycle. If more than 5–10 seconds elapse from the last compression to the next in order to perform the recommended two ventilations, when chest compressions do resume the CPP must be re-built starting from ground zero again. Careful examination in the experimental porcine model of standard CPR (15:2 compression to ventilation ratio) suggests that less than one-third of all resuscitation time is spent with optimal CPP being produced ([Figure 4](#)). These observations have led to the current emphasis among resuscitation researchers for simplifying BLS CPR and eliminating these lengthy interruptions of chest compression-relaxation. One bold thought that is still a controversial suggestion is to eliminate lay rescuer attempts at mouth-to-mouth ventilation for the victim. Although provocative, this suggestion is clearly gaining momentum and is being studied by numerous CPR investigators around the world.

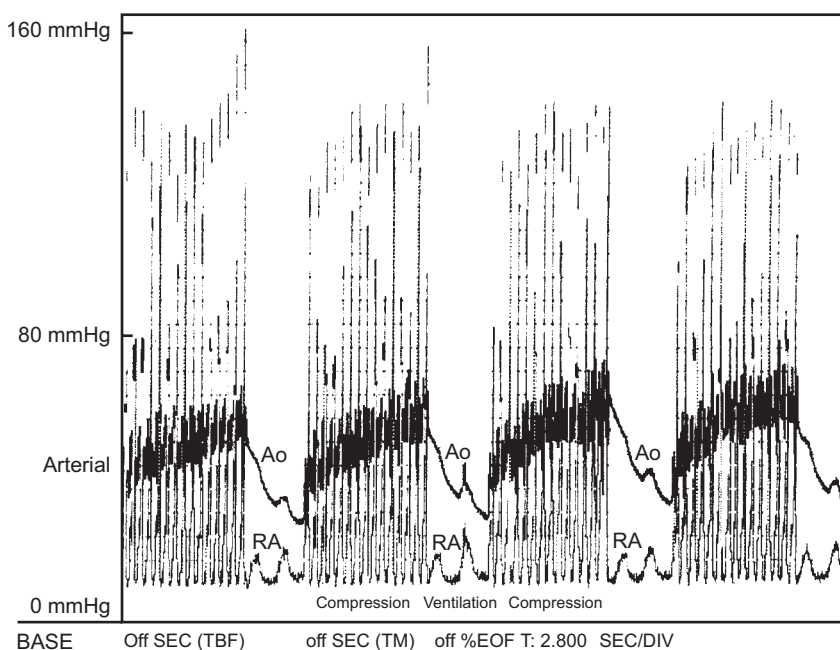


Figure 4. Aortic and right atrial pressures measured during standard closed-chest CPR (15:2 compressions to ventilations ratio). The interruptions of aortic diastolic pressure (lower border of the dark band) during ventilation are easily recognized. Such interruption causes the coronary perfusion pressure (CPP) gradient (the area from the lower edge of the dark band to the bottom of the tracing) to fall. Substantial time is required to 'build' back up to the previous level of perfusion pressure during each cycle of 15 compressions-relaxations. Maximal CPP occurs for only one-third of each compression-relaxation cycle. (Reproduced from Kern et al⁴⁸, with permission).

CPP AND SUCCESSFUL RESUSCITATION FROM CARDIAC ARREST

Laboratory experiments have shown an excellent correlation between CPP and myocardial blood flow during CPR. But is there a relationship among coronary perfusion, myocardial blood flow and successful resuscitation? Indeed, there is.

Investigators at both Purdue University and Johns Hopkins University have, again, independently shown excellent correlation between CPP during CPR, resultant myocardial blood flow generated and successful resuscitation results.^{2,3} Ralston and colleagues² showed that the amount of myocardial blood flow generated during CPR was directly proportional to the ease of resuscitation. Animals that resuscitated easily, generally with a single defibrillation shock restoring a perfusing rhythm, had CPR-generated myocardial blood flows greater than 40 ml/min/100 g, whereas animals that could be resuscitated only with great effort had myocardial blood flows of 15–40 ml/min/100 g. Animals that could never be resuscitated regardless of effort had myocardial blood flows of less than 15 ml/min/100 g. Investigators at Johns Hopkins found a similar relationship between both CPP and myocardial blood flow with resuscitation success.³ They found that the mean CPP for those animals that were successfully resuscitated from prolonged cardiac arrest was 32 mmHg with a corresponding myocardial blood flow range of generally 30–50 ml/min/100 g. Animals that could not be resuscitated had a mean CPP of 8 mmHg with myocardial blood flows of less than 10 ml/min/100 g.

CPP has also been correlated with longer-term outcomes including from 1 to 24-hour survival^{49–58} and even 7-day survival.⁵⁹ Since the higher the CPP the greater the myocardial blood flow and the better the ultimate outcome result, it would seem then to be a reasonable goal during CPR to produce the highest CPP achievable. However, the production of higher and higher levels of CPP is not without its cost. An effort to produce higher and higher CPP with closed-chest CPR generally translates into increasing the force of compressions, and such can result in significant life-threatening injuries.⁵⁷ In this example from our laboratory at the University of Arizona using an animal model with normal coronary arteries, we found that a CPP of 30 mmHg was best for producing long-term survival. CPPs of 10 mmHg or less did not allow successful resuscitation to happen, while CPPs of 20 mmHg allowed for initial resuscitation, but the animal often died within 24 hours. Interestingly, when efforts to increase CPP to 40 mmHg were made, decreased survival resulted. The trauma associated with such effort actually decreased long-term outcome! These results suggest that CPP can be used as a guide to optimizing resuscitation efforts both by achieving the necessary myocardial perfusion needed for successful resuscitation and for avoiding unnecessary injury by not trying to exceed that optimal level. No data yet exist for what the optimal level of CPP is in patients with coronary artery disease. Such data would be useful and may even suggest that certain resuscitation techniques are futile since they might not produce such levels without excessive injury.

Experimental studies have been very useful in one other aspect of understanding the role and importance of CPP during CPR. If a certain CPP is needed for successful resuscitation, how long does one need to maintain such a level? This question is crucial for determining how long to persist with CPR prior to attempting defibrillation. It appears that an optimal CPP for a period of as little as 3 minutes is sufficient to then allow successful defibrillation and return of spontaneous circulation. In a series of experiments where closed-chest CPR was unable to produce CPPs greater than 20 mmHg and where continued closed-chest efforts typically resulted in poor survival, we randomized some animals to receive 3 minutes of open-chest direct cardiac massage. CPP rose dramatically during the performance of open-chest CPR and after a period of only 3 minutes successful defibrillation was accomplished with excellent long-term (24-hour or 7-day) survival.^{52,59} Thus it appears that even after just a short period of optimized CPP generation outcome can be improved.

CLINICAL EXPERIENCE WITH CPP

Although not an easy task secondary to the need for pressure measuring catheters in the aorta and right atrium, CPP has been measured in nearly 200 human victims of cardiac arrest.³¹⁻³⁸ Early reports basically just confirmed that with effort such measurements could be obtained in clinical cardiac arrest. Most were accomplished quite late in the resuscitation effort; hence very low levels of perfusion pressure were recorded. Sanders and colleagues at the University of Arizona found a mean CPP in seven patients receiving CPR of $0(\pm 3)$ mmHg³¹, while investigators at the University of Washington found a mean level of $9(\pm 11)$ mmHg in a small series of clinical cardiac arrests.³⁵ Consistent with these low values of CPP none of these individuals survived. However, there have been some reports of successful resuscitation in humans where CPP has been measured. McDonald reported that 1 out of 12 patients survived who had CPP measured during CPR.³² That individual had the highest CPP in his series (16 mmHg). Paradis et al³⁸ have collected the largest series of patients in whom CPP was measured during the actual performance of CPR. Utilizing an in-hospital resuscitation team, especially trained to insert arterial and right atrial lines during the resuscitation effort, they reported on 100 patients in whom CPP coronary perfusion pressure was successfully measured. Twenty-four of these patients had successful initial resuscitations with return of spontaneous circulation. Comparison of CPP between those resuscitated and those not resuscitated showed a significant difference with the maximal CPP gradients being $26(\pm 8)$ mmHg versus only $8(\pm 10)$ mmHg. These data substantiated those obtained from animal models showing that CPP during CPR can predict success and failure from resuscitation efforts. Of interest, Paradis et al noted that in patients with prolonged cardiac arrest, CPP was a better predictor of resuscitation outcome than was aortic diastolic pressure alone.

INCREASING CPP DURING CPR

Recognition of the importance of CPP has led to numerous approaches to increase it during CPR. These include the development of new CPR techniques and extensive efforts to pharmacologically improve CPP, chiefly through the manipulation of peripheral vascular resistance.

Table 2. New CPR methods devised to increase coronary perfusion pressure.
Closed-chest techniques
Piston CPR
Rapid manual compression CPR
Interposed abdominal compression CPR
Vest CPR
Active compression-decompression (ACD) CPR
ACD plus impedance threshold valve CPR
Phased chest and abdominal compression-decompression CPR
Invasive techniques
Open-chest massage
Minimally invasive direct cardiac massage

Many newer techniques of resuscitation have been designed primarily to enhance CPP. Table 2 is a partial list of such CPR variations, each of which has been touted as increasing CPP. Unquestionably, the most potent alternative CPR technique for increasing CPP is the use of invasive direct cardiac massage. Several independent investigators have shown that open-chest cardiac massage can double and even triple the CPPs obtained with closed-chest CPR.^{51,52,59–61} Bircher et al⁶⁰ have shown in a canine model of prolonged cardiac arrest that even after 2 hours of closed-chest CPR a switch to open-chest internal massage raised CPP from $11(\pm 16)$ mmHg to $44(\pm 22)$ mmHg. Sanders et al⁵² at the University of Arizona found similar results when they studied open-chest CPR after 15 minutes of standard closed-chest BLS CPR. CPP rose from $5(\pm 9)$ mmHg to $59(\pm 22)$ mmHg after the initiation of open-chest massage. In follow-up studies we found in collaboration with investigators at Purdue University that open-chest CPR begun after variable periods of no CPR, always produced excellent CPPs, sometimes even a magnitude better than alternative closed-chest techniques.⁶² However, such improvements, if occurring late in the resuscitation course, do not produce improved outcome, presumably secondary to the extent of preceding injury.

Other noteworthy newer CPR techniques designed specifically to increase CPP include: interposed abdominal compression CPR (IAC); vest CPR; active compression-decompression CPR (ACD) and its latest version, ACD plus the addition of the impedance threshold valve (ACD-ITV); phased chest and abdominal compression-decompression CPR (LifeStick[®]); and minimally invasive direct cardiac massage CPR (MID-CM[®]).

Interposed abdominal compression CPR was designed to improve diastolic pressure by attempting to augment arterial pressure during the decompression or relaxation phase of CPR. Some studies have found this promise fulfilled, others have not.^{54,63,64}

Vest CPR in some studies found that CPP was increased for the majority of, though not all, cardiac arrest victims.^{2,50,55}

More recently developed CPR methods, centred on the concept of increasing CPP, include a number that involve active compression and decompression of the chest alone^{65,66} or of both the chest and abdomen.⁶⁷

Less invasive or minimally invasive techniques for direct cardiac compression have been developed and are reported to raise CPP.⁶⁸

One of the major avenues for increasing CPP is the use of α -adrenergic agonists. Such medications raise CPP by causing vasoconstriction of the peripheral arterial vasculature resulting in increases in the central aortic pressure. A greater increase in aortic pressure than in right atrial pressure results in an improved CPP gradient.

Epinephrine is the time-honoured agent used during CPR to increase CPP by this α -adrenergic agonist mechanism. The β -adrenergic effects seen with epinephrine are generally considered to be a detriment due to its increased myocardial oxygen consumption and vasodilatation effects. Ditchey and Lindenfeld⁶⁹ have shown that epinephrine, although increasing the CPP, also increased myocardial lactate concentration and decreased myocardial ATP stores, particularly when large doses were used.

Although theoretically more attractive, other more selective α -adrenergic agents, e.g. phenylephrine, have been tried in a limited fashion, but thus far have not shown any superiority over epinephrine.⁷⁰

The optimal dose for epinephrine during cardiac arrest remains unknown. Numerous experimental animal studies suggest haemodynamic improvements with 'higher' doses (0.2 mg/kg) of epinephrine administered during CPR.^{71–73} However, numerous

randomized clinical trials have failed to show an increased survival after high dose^{74–76}, and some animal studies suggest high dose could even decrease 24-hour survival.⁷⁷

Several non-adrenergic pharmacological agents have recently been studied for their ability to increase CPP without activation of the α -adrenergic receptor. Two examples are vasopressin and endothelin. Vasopressin has been systematically studied in the experimental resuscitation laboratory. Lindner and colleagues have shown vasopressin to be superior to epinephrine for increasing CPP, for increasing myocardial blood flow and for improving resuscitation outcome.^{78,79} Endothelin-I is another potent vasoconstrictor via a non-adrenergic receptor pathway. Impressive rises in CPP can be seen with the use of endothelin-I during CPR. But caution is advised. Some experimental work has shown that the vasoconstriction effect of endothelin-I, so desirable during CPR, is persistent and becomes a potential problem post-resuscitation. In one experimental study, pulse pressure diminished so dramatically after restoration of spontaneous circulation that haemodynamic collapse occurred, resulting in death.⁸⁰ An important lesson concerning increasing CPP should be appreciated, namely that this may come at a cost of worsening post-resuscitation myocardial dysfunction and causing death!

NON-INVASIVE ALTERNATIVES TO CPP

CPP provides unique feedback to the rescuer during the performance of CPR because of its correlation with both the myocardial blood flow produced and ultimate resuscitation success. Unfortunately, due to its invasive requirements for pressure measuring catheters in the aorta and right atrium it is not practical for most resuscitations. Searching for a non-invasive surrogate for measuring CPP has led to monitoring expired end-tidal carbon dioxide during CPR. Laboratory and clinical trials have shown an excellent correlation between end-tidal carbon dioxide levels (PetCO₂) and cardiac output, CPP and survival.^{81–89} Several clinical studies have found similar results in defining a minimal level of PetCO₂ below which successful resuscitation seems highly unlikely. The ease and facility of such measurements during CPR make monitoring PetCO₂ very attractive. There are a few pitfalls, namely some resuscitation therapies altering the level of end-tidal CO₂. Administration of sodium bicarbonate can raise the PetCO₂ level transiently. Potent vasoconstrictors temporarily cause a decrease in end-tidal CO₂^{90,91}, probably because they decrease forward flow or cardiac output secondary to the increase in systemic resistance. Despite these shortcomings, monitoring expired end-tidal CO₂ can be used as a non-invasive alternative to measuring CPP and gives 'real-time' feedback information concerning ongoing resuscitation efforts.

SUMMARY

Coronary perfusion pressure (CPP) is the pressure gradient between the ascending aorta and right atrium during the chest relaxation or decompression phase of CPR. Monitoring CPP during the performance of CPR can give immediate feedback concerning the resuscitation effort, specifically whether adequate myocardial blood flow is being generated and whether successful resuscitation can be expected if current efforts continue. If the CPP is low, suggesting that success is unlikely, efforts can be made to change the resuscitation strategy and see if perfusion pressure improves. The

loss of autoregulation during CPR makes any coronary lesion even more important in its effect on CPP and resuscitation-generated myocardial blood flow. Optimal CPR methods are most sorely needed in those with coronary artery disease if adequate perfusion is to be obtained, allowing successful resuscitation. Antegrade myocardial perfusion only occurs during the 'relaxation' phase of chest compression-decompression CPR. Interruptions of chest compressions-decompressions have profound effects on the generation of CPP. Significant time is required after each such interruption to rebuild the optimal perfusion pressure gradient. Efforts to decrease or limit such interruptions are paramount for providing the best perfusion during CPR. Clinically measuring CPP is difficult secondary to the necessity of inserting pressure monitoring catheters in the right atrium and aorta. The time required to place such catheters after the onset of cardiac arrest is generally prohibitive. However, occasionally such victims of cardiac arrest are already instrumented with an arterial line and a pulmonary artery catheter. In such circumstances CPP can be obtained easily by switching the monitoring site on the pulmonary artery catheter to the 'proximal' port and subtracting that pressure from the simultaneous arterial pressure during the relaxation portion of chest compressions. A non-invasive alternative to measuring CPP is to monitor expired end-tidal carbon dioxide. With ventilation kept reasonably constant, $P_{et}CO_2$ reflects cardiac output and pulmonary blood flow generated during CPR. Correlation

Practice points

- coronary perfusion pressure can guide CPR efforts
- follow the aortic and right atrial pressure difference during the chest relaxation phase
- limiting interruptions to chest compression-decompressions can greatly enhance CPP production
- increase CPP by:
 - increasing the force of compression
 - vasoconstrictive agents administered during CPR
 - newer techniques of advanced cardiac life support (ACLS) such as:
 - interposed abdominal compression CPR
 - active compression-decompression CPR
 - invasive CPR
- consider monitoring end-tidal carbon dioxide as a non-invasive alternative to CPP

Research agenda

- new short-acting vasoconstrictors to enhance CPP without worsening post-resuscitation myocardial function
- enhancing venous return to promote forward flow as better methods (i.e. invasive) are developed for emptying the arrested left ventricle
- innovative strategies to eliminate or minimize compression-decompression interruptions
- alternative, less invasive, monitoring techniques for real-time assessment of the quality of resuscitation effort

between PetCO₂ and successful resuscitation has been established, much like the relationship between CPP and resuscitation outcome. Very few individuals have been successfully resuscitated if the PetCO₂ is less than 10 mmHg during the active CPR period. CPP can be increased in a variety of ways including the use of vasoconstrictor medications, increased force of compression, active decompression and improved techniques of basic life support CPR.

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