# Effect of Cardiopulmonary Resuscitation on Restoration of Myocardial ATP in Prolonged Ventricular Fibrillation

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# Effect of Cardiopulmonary Resuscitation on Restoration of Myocardial ATP in Prolonged Ventricular Fibrillation

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ABSTRACT

## Effect of Cardiopulmonary Resuscitation on Restoration of Myocardial ATP in Prolonged Ventricular Fibrillation

**Background:** It is known that a short period of cardiopulmonary resuscitation (CPR) prior to defibrillation improves survival in patients with unwitnessed sudden collapse. However, there has been no report about whether CPR restores myocardial adenosine triphosphate (ATP) during prolonged ventricular fibrillation (VF). The aim of this study is to investigate the effect of CPR in restoring of myocardial high energy phosphate during prolonged VF.

**Methods:** Seventy two adult male Sprague-Dawley rats (330-400 g) were enrolled in the study. Baseline ATP and ADP prior to induction of VF were measured from 9 animals (No-VF group). Sixty three animals were subjected to 4 minutes of untreated VF. Then, animals were randomized into No-CPR group (n=37) and CPR group (n=26). In No-CPR group, ATPs and ADPs were measured 4 (No-CPR4, n=9), 6 (No-CPR6, n=10), 8 (No-CPR8, n=8), or 10 (No-CPR10, n=10) minutes after induction of VF, respectively. CPR group received 2 (CPR2, n=10), 4 (CPR4, n=8), or 6 (CPR6, n=8) minutes of mechanical chest compressions, respectively.

**Results:** Myocardial ATP (nmol/mg·protein) and ATP/ADP ratio in No-VF group was 5.49±1.71 and 0.23±0.12. Myocardial ATP in No-CPR group decreased as duration of VF was prolonged (4.27±1.58 in No-CPR4, 4.13±1.31 in No-CPR6, 3.77±1.42 in No-CPR8, and 3.52±0.90 in No-CPR10, respectively; $p<0.05$ between No-CPR8 and No-CPR10 vs. No-VF group). Myocardial ATP in CPR2 was not different compared to No-VF group.

However, myocardial ATP decreased as CPR time was prolonged than 2 minutes (5.27±1.67 in CPR2, 3.77±1.05 in CPR4, and 3.49±1.08 in CPR6, respectively; $p<0.05$ between CPR4 and CPR6 vs. no-VF group).

Myocardial ATP/ADP ratio in No-CPR group tended to be lower (0.13±0.05 in No-CPR4, 0.15±0.04 in No-CPR6, 0.17±0.06 in No-CPR8, and 0.17±0.05 in No-CPR10, respectively) than No-VF group. Myocardial ATP/ADP ratio in CPR2 increased to the level of No-VF group and tended to decrease as CPR time was prolonged (0.26±0.15 in CPR2, 0.20±0.09 in CPR4, and 0.19±0.03 in CPR6, respectively).

**Conclusion:** Myocardial ATP decreases as duration of ventricular fibrillation is prolonged. Cardiopulmonary resuscitation for 2 minutes after prolonged ventricular fibrillation restores myocardial ATP.

Key words: cardiac arrest, cardiopulmonary resuscitation, ventricular fibrillation, myocardial ATP

# Effect of Cardiopulmonary Resuscitation on Restoration of Myocardial ATP in Prolonged Ventricular Fibrillation

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## Ⅰ. INTRODUCTION

Sudden unexpected cardiac arrest is most commonly due to ventricular fibrillation (VF) in patients with extensive atherosclerotic coronary artery disease[1)]. Immediate and effective treatment of VF is the primary goal of advanced cardiovascular life support (ACLS). For successful ACLS, defibrillation within minutes of collapse is neccessary for patient with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). For victims with witnessed VF arrest, early cardiopulmonary resuscitation (CPR) and rapid defibrillation can significantly increase the chance for survival to hospital discharge[2,3)].

According to the *2010 International Liaison Committee on Resuscitation (ILCOR)* Guidelines for CPR and emergency cardiac care (ECC), performing CPR while a defibrillator is being readied for use is strongly recommended for all patients in cardiac arrest. However, its value of an intentional delay of defibrillation to perform CPR is not clear[4]. One randomized controlled trial (RCT)[5] and one clinical trial[6] including adults with out-of-hospital cardiac arrest not witnessed by emergency medical system (EMS) personnel showed that survival was improved by a period of CPR performed before the first defibrillation shock when the EMS response interval was >4 to 5 minutes. Cobb et al[6] reported that the routine provision of approximately 90 seconds of CPR prior to use of automated external defibrillator (AED) was associated with increased survival when response intervals were 4 minutes or longer. According to the Wik et al[5] research, the patients with VF and ambulance response intervals longer than 5 minutes had better outcomes with CPR first before defibrillation was attempted. On the other hand, two RCTs[7,8] demonstrated no improvement in return of spontaneous circulation (ROSC) or survival to hospital discharge in patients with out-of-hospital cardiac VF/pulseless VT who received CPR from EMS personnel for 1.5 to 3 minutes before defibrillation, regardless of EMS response interval. Simpson et al[9] reported that delaying initial defibrillation to allow a short period of CPR in out-of-hospital cardiac arrest due to VF demonstrated no benefit over immediate defibrillation for survival to hospital discharge irrespective of response time. At this time the benefit of delaying defibrillation to perform CPR before defibrillation is unclear.

In order to function properly the myocardium requires an uninterrupted supply of energy. Energy-requiring processes in the heart are fuelled by vast amounts of adenosine triphosphate (ATP), which is derived from a number of sources including free fatty acids, glucose, lactate, ketone bodies, and glycogen[10]. β-Oxidation of free fatty acids ending up in acetyl-Co A (further metabolized in Kreb's cycle) comprises the main energy source of the myocardium under normoxic conditions[11]. The transport of free fatty acids into the myocyte occurs by saturable carriers as well as by non-saturable diffusion across the plasma membrane (sarcolemma)[12]. Glucose enters the myocyte through active transport while lactate and ketone bodies are transported via an H+ symporter[13]. The complete metabolism of glucose, lactate, and glycogen involves the oxidative decarboxylation of pyruvate by the pyruvate dehydrogenase complex (PDH). Although pyruvate decarboxylation in the heart account for only 3-6% of the flux in the Kreb's cycle *in vivo*, it appears necessary for maintenance of normal activity1[14,15]. Moreover, it was well known that glycolysis is more efficient than β-oxidation in terms of ATP generated per mole O2 consumed[16].

VF prompts myocardial oxygen demands that are comparable to or exceed those of the normally beating heart[17,18]. Thus, when cardiac arrest occurs and coronary blood flow ceases, a severe and progressive energy imbalance develops, causing, within minutes, profound intramyocardial acidosis along with depletion of high-energy nucleotides[19]. These conditions are not favorable for successful defibrillation and that hemodynamic interventions aimed at reversing or ameliorating these myocardial abnormalities may be required before attempting defibrillation.

To this end, establishing a coronary perfusion pressure (CPP) above critical thresholds for successful resuscitation is of primary importance[20,21]. Defibrillation after prolonged untreated VF typically requires multiple electrical shocks, which in and of themselves can cause myocardial injury[22,23]. In addition, interruptions in chest compression, which are required to deliver electrical shocks, also can be detrimental[24]. Thus, delaying the delivery of electrical shocks until more favorable myocardial conditions are restored could reduce injury to the myocardium, potentially minimizing adverse effects on post-resuscitation myocardial function[25].

The data about the depletion and restoration of myocardial ATP during resuscitation is essential to suggest the proper treatment guideline about the optimal timing of defibrillation in prolonged VF arrest. Up to the present, there had been little reports about the depletion pattern or the restoration of myocardial ATP during chest compression after VF/pulseless VT arrest.

The aim of this study is to investigate the effect of CPR on restoration of myocardial high-energy phosphate in prolonged VF. By using murine VF cardiac arrest model, this study was performed to know the pattern of depletion of myocardial ATP along the time after initiation of VF and the changes in myocardial ATP after certain durations of CPR.

# Ⅱ. MATERIALS AND METHODS

## 1. Animal group of experimental design

Experimental procedures and protocols confirmed to institutional guidelines for the care and use of animals in research and were approved by the Wonju College of Medicine, Yonsei University Institutional Animal Care and Use Committee.

Spraque-Dawley rats were block randomized at the end of stabilization as three groups including No-VF, No-CPR, and CPR. No-VF group (n=9) was designed for the measurement of a basal level of myocardial ATP and ADP prior to the induction of VF. No-CPR group was designed for providing myocardial ATP level at various period including 4, 6, 8, or 10 minutes after induction of VF and received no CPR. Then, No-CPR group was consisted of four subgroups including No-CPR4 (n=9), No-CPR6 (n=10), No-CPR8 (n=8), or No-CPR10 (n=10), respectively. CPR group received mechanical chest compressions after 4 minutes of VF. CPR group was composed of three subgroups according to duration of mechanical chest compression comprising 2 (CPR2, n=10), 4 (CPR4, n=8), or 6 (CPR6, n=8) minutes, respectively.

## 2. Animal preparation

Sprague-Dawley rats weighing approximately 330-400 g were fasted overnight except for free access to water.

Animals were anesthetized with Zoletil (tiletamine + zolazeppam, 5 mg/kg, Vicbac, Inc, France) and Rompun (xylazine, 50 mg/kg, Bayer Korea, Inc, Korea) delivered by intramuscular injection. Intubation and ventilation were not performed due to the short experiment time and our intention to exclude the effect of rescue breathing on restoration of myocardial ATP. During procedures, body temperature was maintained between 36.5 to 37.5℃ by an incandescent heating lamp. Arterial blood pressure (BP) was measured with the water-filled blood pressure transducer catheter (MLT1199, AD instruments, Inc, CA, USA) inserted through the left femoral artery. A saline filled PE-50 catheter (0.58 mm ID) was inserted in to the right jugular vein for fluid administration. Blood pressure and needle-probe ECG monitoring data were recorded with a PC-based data acquisition system (PowerLab 4/30, AD instruments, Inc, CA, USA).

## 3. Induction of cardiac arrest

Ventricular fibrillation was induced with an electrical method. Through a catheter inserted in the right jugular vein, a pre-curved guide wire was fed in to the right ventricle for electrical induction of VF. VF was induced by a delivery of a 60-Hz alternating current to the right ventricular endocardium (0.1-0.6 mA) for an uninterrupted interval of 4 minutes. Cardiac arrest was confirmed by VF waveform on the surface ECG and the loss of the arterial trace with a mean arterial pressure of <20 mm Hg (**Figure 1**).

## 4. Experimental protocols

After animal preparation, animals were stabilized for 10 minutes. In No-CPR group, no intervention was done after induction of VF. In CPR group, mechanical chest compressions were begun with a pneumatic chest compressor at a rate of 200 times/min and a compression depth of approximately 50% of the AP chest diameter in these animals. 2, 4, or 6 minutes of mechanical chest compressions was provided to each subgroup, respectively (**Figure 2**). In the phase of pre-arrest and the end of chest compression, blood samples for arterial blood gas (ABG) profiles and serum lactate were obtained. Arterial blood gas profiles and serum lactate were measured by using a portable ABG analyzer (the *i-STAT system*, Abbot, Inc, CA, USA).

## 5. ATP and ADP measurement

Mid-thoracotomy was performed for extracting animal's heart at the end of chest compression. Left ventricular endocardium was sampled by about 1 $mm^3$-sized muscle chip and contained in the Eppendorf-tube. The myocardial sample was kept in the liquid nitrogen, and then myocardial ATP and ADP were measured immediately.

Sampled myocardial tissues were added to 300 $\mu\ell$ of 0.9 N perchloric acid in a sterile microfuge tube. The tube was vortexed and allowed to sit on ice for 5 seconds and repeated for 3 to 4 times, after which it was centrifuged for 5 minutes at 13,000 rpm in a microcentrifuge. A 200 $\mu\ell$ (100 $\mu\ell$ x 2 tubes) aliquot of the supernatant was transferred to a new sterile microfuge tube. The supernatant was then assayed for ATP and ADP by the bioluminescent methods.

These phosphorous substances were measured using luminometer (Synergy 2 SL luminescence microplate reader, BioTek, Inc, NY, USA). All values were standardized by sample protein amounts. The ADP/ATP ratio for judging the cellular energy state was also calculated.

Against the ATP measurement, the ADP assay was performed in two parts. The first step was the irreversible conversion of ATP to AMP with ATP sulfurylase in the presence of molybdate. The complete reaction mixture contained 50 mM Tris-HCL buffer, pH 8.5 (Sigma 80866, USA), 5 mM $MgCl_2$ (Sigma 63042, USA), 10 mM $Na_2MoO_4$ (Sigma M1003, USA), 2.5 mM GMP (Sigma G8377, USA), sample (deproteinized and neutralized extract, 50 ㎕), and 30 ㎕/ml ATP sulfurylase (Sigma A8957, USA) in a total volume of 0.2 ml. The reaction mixture was incubated in a sterile microfuge tube for 20 minutes at 30℃. The tube was spun for 1 minute at 12,000 rpm in a microcentrifuge and then immersed in a boiling water bath for 2.5 minutes to inactivete the sulfurylase. The sample was cooled on ice and again centrifuged in to 0.36 ml water, and residual ATP was measured bioluminometrically. This generally amounted to less than 1% of the original ATP content. On the second step of the assay, ADP was measured following its conversion to ATP by pyruvate kinase. A 100 ㎕ aliquot of the boiled, microfuged reaction mixture from the first step was mixed with 100 ㎕ of a cocktail containing 47 mM Tris-HCL buffer, pH 8 (Sigma 70603, USA), 4.7 mM $MgCl_2$ (Sigma 63042, USA), 38 mM KCL (Sigma 05433, USA), 0.5 mM phosphoenolpyruvate (Sigma P0564, USA), and 0.12 mg/ml pyruvate kinase (Sigma P0294, USA), in a sterile tube. The reaction mixture was incubated for 30 minutes at room temperature, after which 0.8 ml water was added. The ATP produced was then measured bioluminometrically.

ADP was calculated as the difference between the ATP measured following incubation with pyrubate kinase and the residual ATP measured following treatment with sufurylase alone. Duplicate assays of ADP were routinely run.

## 6. Statistical analysis

Demographic profiles, including hemodynamic data and arterial blood gas analysis results, are reported as mean±SD. Comparisons between No-CPR and CPR groups on the values of ATP, ADP, ADP/ATP ratio, serum lactate and ABG results were analyzed through the paired Student's t test. Statistical significance was defined as $p<0.05$. We used SPSS 12.0 programs (SPSS for Window release, SPSS Inc, USA) for all statistical analysis.

# Ⅲ. RESULTS

## 1. Demographic data

72 animals were enrolled in this study. Demographic data including animal weight, heart rate, and mean arterial pressure did showed significant differences in the three groups. Arterial blood gas profiles, including $pO_2$, $pCO_2$, serum bicarbonate, and base excess, were not different significantly between the groups (Table 1).

Table 1. Demographic data

| | No-VF[a] (n=9) | No-CPR (n=37) | CPR (n=26) |
|---|---|---|---|
| Weight, g | 350±10 | 362±33 | 348±31 |
| Heart rate before arrest, bpm[b] | 350±55 | 302±71 | 262±48 |
| MAP[c] before arrest, mm Hg | 115±29 | 111±16 | 98±12 |
| Oxygen profiles | | | |
| pH | 7.30±0.04 | 7.25±0.04 | 7.21±0.07 |
| $PaO_2$, mm Hg | 81±6.4 | 92±13.7 | 85±11.1 |
| $PaCO_2$, mmHg | 47±7.6 | 50±7.6 | 48±9.6 |
| $HCO_3$, mmol/L | 23±2.4 | 22±3.8 | 20±5.0 |
| Base excess, mmol/L | -2.3±2.2 | -4.2±4.2 | -5.1±4.9 |

[a] ventricular fibrillation

[b] beats per minute

[c] mean arterial pressure

## 2. Myocardial ATP

Myocardial ATP of No-CPR group was lower than No-VF group (No-CPR group: 4.27±1.58 nmol/mg·protein in No-CPR4, 4.13±1.31 nmol/mg·protein in No-CPR6, 3.77±1.42 nmol/mg·protein in No-CPR8, and 3.52±0.90 nmol/mg·protein in No-CPR10, respectively; No-VF group: 5.49±1.71 nmol/mg·protein; $p<0.05$ between No-CPR8 and No-CPR10 vs. No-VF group), which suggested that myocardial ATP decrease as VF duration is prolonged. Myocardial ATP of CPR2 was restored to the level of No-VF group, and then decreased as CPR time was prolonged (5.27±1.67 nmol/mg·protein of CPR2, 3.77±1.05 nmol/mg·protein of CPR4, and 3.49±1.08 nmol/mg·protein of CPR6, respectively; $p<0.05$ between CPR4 and CPR6 vs. No-VF group) (**Figure 3**).

Myocardial ATP/ADP ratio of No-CPR group was lower than No-VF group (No-CPR group: 0.13±0.05 of No-CPR4, 0.15±0.04 of No-CPR6, 0.17±0.06 of No-CPR8, and 0.17±0.05 of No-CPR10, respectively; No-VF group: 0.23±0.12; $p<0.05$ between No-CPR4, No-CPR6, No-CPR8 and No-CPR10 vs. No-VF group). Myocardial ATP/ADP ratio of CPR2 increased to the level of No-VF group and then converted to the drop as CPR time was prolonged (0.26±0.15 of CPR2, 0.20±0.09 of CPR4, and 0.19±0.03 of CPR6, respectively) (**Figure 4**).

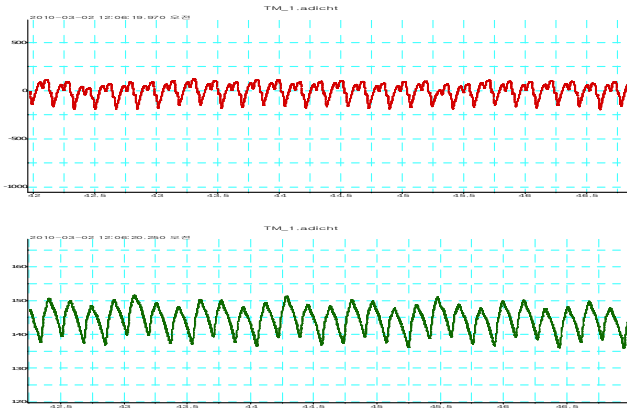
## 3. Oxygen profiles

Myocardial energy restoration in the initial phase of resuscitation did not have an effect on the tissue oxygenation. Serum lactate level did not show the improvement with time during chest compression (**Figure 5**). Oxygen profiles did not differ between No-CPR and CPR groups with comparable time intervals (**Table 2**).

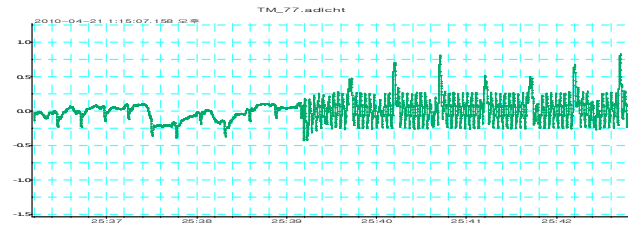
**Table 2. Effect of CPR on oxygen profiles**

| | No-CPR6 (n=10) | CPR2 (n=10) | No-CPR8 (n=8) | CPR4 (n=8) | N0-CPR10 (n=10) | CPR6 (n=8) |
|---|---|---|---|---|---|---|
| Oxygen profiles | | | | | | |
| pH | 6.86±0.17 | 6.75±0.11 | 6.71±0.08 | 6.72±0.11 | 6.66±0.07 | 6.81±0.12 |
| $PaO_2$, mm Hg | 32±15 | 32±16 | 15±7 | 23±9 | 11±8 | 33±11 |
| $PaCO_2$, mm Hg | 107±26 | 117±11 | 125±6 | 129±1 | 125±14 | 108±21 |
| $HCO_3$, mmol/L | 20±3.8 | 18±2.8 | 17±4.8 | 21±4.5 | 13±0.1 | 18±5.7 |
| Base excess, mmol/L | -11.6±5.8 | -15.4±4.0 | -18±6.9 | -12±6.3 | -21±0.1 | -15±7.3 |

A. Pre-arrest



B. VF arrest induction



C1. Arrest, pre-CPR C2. Arrest, CPR

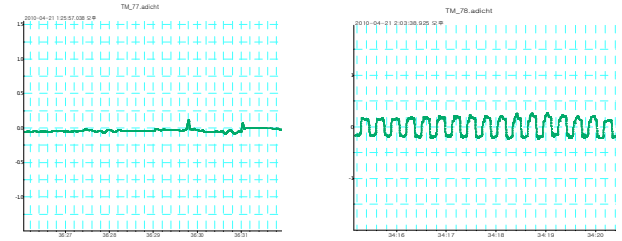


**Figure 1. Illustrative ECG and arterial pressure recordings.** These tracings are from a representative animal during the arrest protocol described in Methods section. A, upper tracing represents ECG and lower tracing represents arterial wave form, prearrest tracing. B, VF induction tracing. C1, Arrest before CPR. Fine VF waveforms are observed. C2, Arrest, CPR. Chest compression artifacts are seen on ECG tracing.

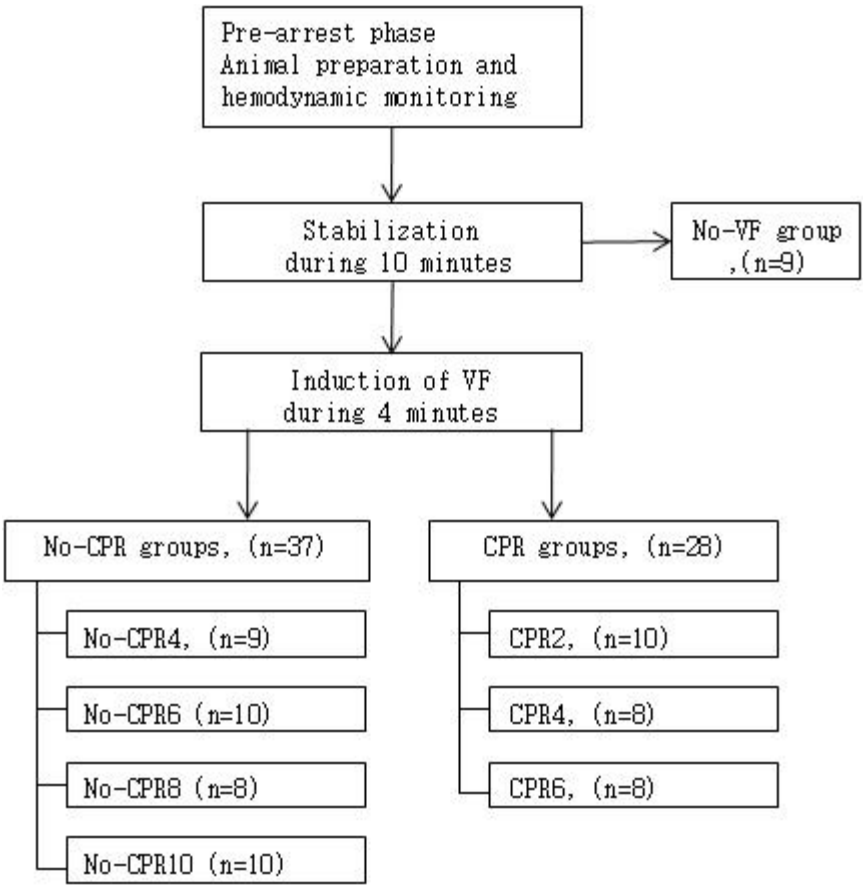



**Figure 2. Experimental protocols.** This diagrams are experimental protocols for No-CPR and CPR groups. No-CPR groups were designed for providing myocardial ATP level at various period including 4, 6, 8, or 10 minutes after induction of VF and received no CPR. CPR groups received mechanical chest compressions after 4 minutes of VF. CPR group was composed of three subgroups according to duration of mechanical chest compression.

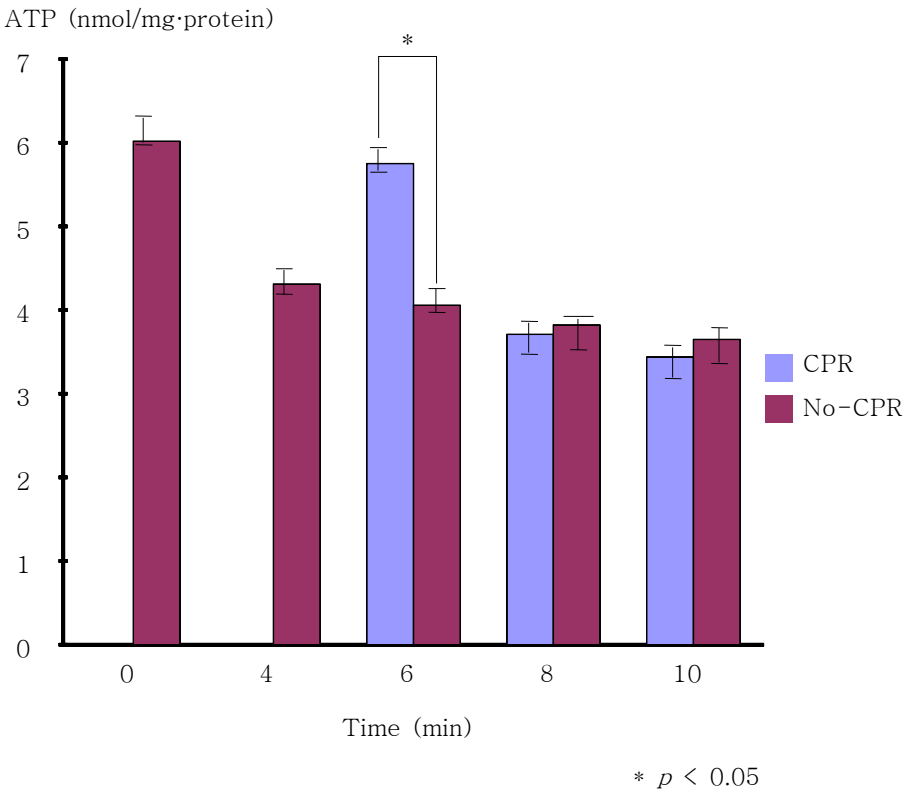
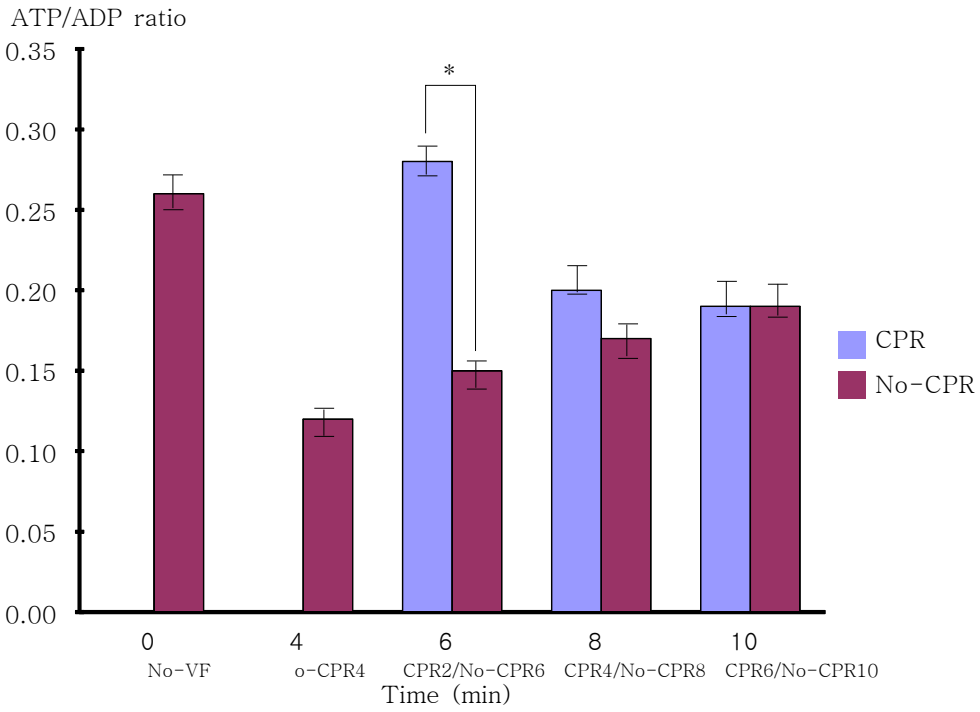



**Figure 3. Effect of CPR on the restoration of myocardial ATP.** Myocardial ATP after 2 min of CPR was restored to baseline level and decreased as CPR time was prolonged (5.27±1.67 after CPR for 2 min, 3.77±1.05 after CPR for 4 min, and 3.49±1.08 after CPR for 6 min, respectively; $p<0.05$ after CPR for 4 min and 6 min vs. No-VF).




* $p < 0.05$

**Figure 4. Effect of CPR on myocardial ATP/ADP ratio.** Myocardial ATP/ADP ratio after 2 min of CPR increased to the level of No-VF group and then converted to the drop as CPR time was prolonged (0.26±0.15 after CPR for 2 min, 0.20±0.09 after CPR for 4 min, and 0.19±0.03 after CPR for 6 min, respectively). VF: ventricular fibrillation

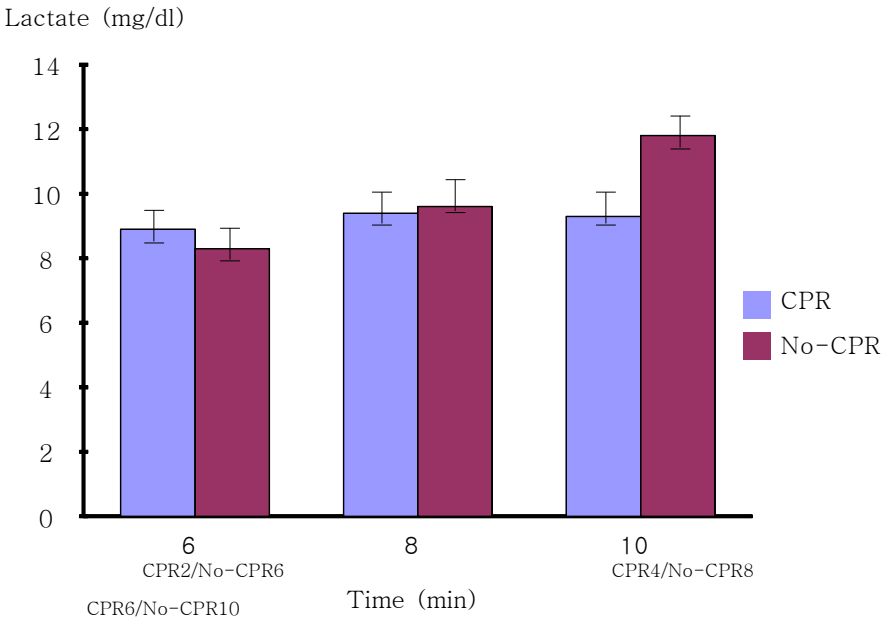



**Figure 5. Effect of CPR on serum lactate.** Serum lactate level tends to increase in No-CPR group while it remains unchanged in CRP group.

# Ⅳ. DISCUSSION

Our data suggests that, during prolonged VF arrest, the myocardial ATP without resuscitation shows gradual depletion compared to myocardial ATP value of normal beating heart. After prolonged VF, two minutes of chest compression helps to restore myocardial energy store. However, a long duration of chest compression over 2 minutes does not have further increase in myocardial ATP level.

ATP production in heart is deprived from a number of sources including free fatty acids, glucose, lactate, ketone bodies, and glycogen. Physiologic heart work is consistent with high ATP turnover and rapid shifts in the amount of workload. This places an enormous pressure on myocardial energy delivery, necessitating intermediary energy buffering systems. The myocyte possesses several such systems out of which the phosphocreatine (PCr) shuttle is the most significant. Creatine synthesized in the liver and kidney is taken up by the myocyte through active transport, phosphorylated to PCr and stored in the cytosol for future use. Upon demand PCr together with ADP is catalysed by creatine kinase to yield ATP and creatine[25].

During inadequate oxygenation there is a rapid shift in cardiac utilization of energy substrates from fatty acids to glucose and subsequent lactate formation[26]. In the myocyte, glucose is supplied either by the extracellular fluid or by mobilization of glycogen. Upon ischemia myocardial contractility and energy expenditure is considerably reduced[27]. Nonetheless, acidosis and a progressive drop in myocardial ATP levels will follow.

In the myocardium, maintained ATP levels are essential not only for the contractile effort but also for the proper function of membrane ion pumps the function of which are essential for sustaining the structural integrity of the cell. Hence, following ischemia and subsequent low levels of ATP, profound ionic changes will occur including depletion of intracellular K+ and Mg2+ and an increase in cytosolic Na+ and Ca2+. The physiologic response to ischemia further includes an increased gene expression of a variety of enzyme systems such as enzymes of glycolysis and glucose transporter proteins, which further influence myocardial energy metabolism[28]. During sustained ischemia (lasting more than 30 minutes) myocyte energy production is seriously compromised, due to a low pH (lactic acidosis, and inorganic phosphate accumulation) and depletion of energy reserves. Membrane instability and mitochondrial swelling will commence making the risk of cell death imminent. Moreover, catecholamine released during ischemia stimulate glycogenolysis and glycolysis thereby influencing substrate availability and thus myocardial metabolism.

Numerous investigators have demonstrated a high correlation between myocardial high-energy phosphate levels at the end of arrest and subsequent myocardial performance. Lowe et al[29] have reported that cell death first occurs in the canine heart when depletion of ATP exceeds 65%. They found that alterations in cell volume regulation, ion distribution, and ultrastructure were reversible if more than 35% of ATP was preserved. In a further study by Schaper and colleagues[30], it was concluded that a very narrow range of ATP values might determine whether irreversible ischemic injury occurred, and that a close correlation existed between the rates of structural, metabolic, and functional deterioration at the end of an ischemic interval.

Several interesting findings are seen in our study. First the depletion of myocardial ATP after a VF induction does not drop to the bottom at the end of experiment. Possible explanation about this result is that myocardial ATP might be restored by energy buffering systems in myocyte. Phosphocreatine shuttle is the most dominant system[15]. Creatine kinase, if it is measured, might show a abrupt decrease with time. Enzymes related to ATP dephosphorylation and phosphorylation, like creatine kinase will be depleted during prolonged VF. Another explanation is an insufficient post-arrest time. However, 10 minutes after cardiac arrest is a sufficient time for entering the metabolic phase. Further study should be required for solving this problem.

Second, during 2 min-duration chest compression, myocardial ATP increases in response to resuscitative effort. This is the most important observation through our investigation. As described previously, a proper level of myocardial ATP is the basic and essential element for maintaining, especially under ischemic condition, functional cardiac contractility. There are lots of reports about the depletion of myocardial ATP during cardiac arrest and the beneficial effect of CPR prior to defibrillation in cases of VF arrest. But there is no report about that myocardial ATP can be restored during resuscitation. However, during prolonged resuscitation period, CPR dose not influence on the restoration of myocardial ATP. The likelihood of successful restoration of spontaneous circulation after electrical countershock appears to be time dependent. The earlier that countershock can be performed, the greater the likelihood that defibrillation will be followed by a spontaneous perfusing rhythm and survival[31].

As the duration of ventricular fibrillation is prolonged and immediate defibrillation is used as first therapy, the likelihood of successful resuscitation decreases due to the increasing occurrence of post-countershock asystole and pulseless electrical activity[32]. Myocardial ATP restoration during initial 2 minutes CPR might relate to the recovery of coronary perfusion pressure. A brief period of chest compression can deliver oxygen and energy substrates and unload the volume-overloaded right ventricle, increasing the likelihood that a perfusing rhythm will return after shock delivery[33].

Third, a serum lactate level and oxygen profiles do not show the improvement corresponding to the restoration of myocardial energy. According to the report of Angelos et al[34], the high flow requirements needed to preserve myocardial high-energy phosphate stores during VF. These flow rates are much greater than the 20 to 25 % of normal flow generated under the most optimal VF cardiac arrest conditions with standard CPR technique[35]. Cardiac output during CPR was only 1/3 compared to the normal value. The coronary perfusion pressure generated by chest compression was around 20 mm Hg and this coronary flow was insufficient to deliver oxygen to myocardium. For this reason, the restoration of myocardial ATP by chest compression was not maintained for a long duration of resuscitation and a tissue oxygenation was not restored promptly.

Limitations in this study include that its predictive value on human physiology remains to be demonstrated and a cellular mechanism of ATP restoration was not presented. However, the rat model appears to be meaningful approach to understand the global ischemia/reperfusion mechanisms such as those pathways suggested in the recently described ‘metabolic phase’of cardiac arrest[36].

Our data can make a contribution to the understanding of the timing of defibrillation and chest compression during prolonged VF cardiac arrest. Also, our study design is basically *in vivo* experiments. The mechanism of cellular events was hard to define at *in vivo* study.

We do not consider the rescue breathing in the experimental design. This is a big difference compared to other animal studies relate to cardiac arrest. However the optimal method for out-of-hospital bystander CPR is controversial[37,38]. There are a lot of animal and human studies about chest-compression-only CPR, or hands only CPR. Berg et al[39] reported that interrupting chest compression for rescue breathing can adversely affect hemodynamics during CPR for VF. Kern et al[40] demonstrated that 6 minutes of chest compressions alone with a clamped endotracheal tube resulted in equivalent 24-hour survival and good neurological outcomes compared with standard CPR. Hallstㅱm et al[41] confirmed that in cases of witnessed sudden cardiac arrest with a non-respiratory cause, CPR by chest compression alone is as good as, and possibly better, than standard CPR by compression plus ventilation. So, by our experimental design, the sole effect of chest compression on the restoration of myocardial ATP can be analyzed. Also our report can be a experimental evidence of Hands-only CPR.

# Ⅴ. CONCLUSION

In an animal model of cardiac arrest with electrically induced, prolonged ventricular fibrillation, myocardial ATP level decreases gradually and external chest compression of two-minutes duration can restore myocardial ATP.

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# 국 문 요 약

## 장시간 지속되는 심실세동모델에서 심폐소생술이 심근 ATP의 회복에 미치는 영향

**배경**: 목격자가 없는 급성심정지 환자의 심정지리듬이 심실세동일때 제세동에 선행하여 짧은 시간동안 흉부압박을 시행하는 것이 환자의 예후를 호전시킨다는 보고가 있다. 그러나 장시간 지속되는 심실세동 환자에게 흉부압박을 시행하는 것이 실제로 심근내의 ATP (adenosine triphosphate)를 회복시킨다는 보고는 아직 없다. 본 연구의 목적은 장시간 지속된 심실세동 동물모델에서 일정 기간 동안의 심폐소생술이 심근 ATP의 회복에 미치는 영향을 확인하기 위하여 수행되었다.

**방법**: 72 마리의 Sparague-Dawley 쥐( 330-400 g, male)가 연구에 사용되었다. 9 마리의 대조군을 대상으로 심실세동을 유도하기 이전의 심근 ATP와 ADP (adenosine diphosphate) 값을 구하였다(No-VF 군). ATP와 ADP의 측정을 위해서 심근내막에서 시료를 채취한 이후, 생체발광법(bioluminescent method)을 사용하여 수치를 구하였다. 나머지 63 마리의 실험동물은 교류전류를 사용하여 심실세동을 유발하였으며, 심실세동을 유발한 후 무작위로 No-CPR 군(n=37)과 CPR 군(n=26)으로 나누었다. No-CPR 군은 심실세동 유도 이후, 4 (n=9), 6 (n=10), 8 (n=8), 또는 10 (n=10) 분이 되었을 때 심근 ATP와 ADP를 측정하였다. CPR 군은 4분간의 심실세동 유도가 끝난 이후 2 (n=10), 4 (n=8), 또는 6 (n=8) 분 동안 흉부압박을 시행한 이후에 심근 ATP와 ADP를 측정하였다.

**결과**: No-VF 군의 심근 ATP (nmol/mg·protein)와 ATP/ADP ratio는 각각 5.49±1.71과 0.23±0.12 였다. 2분간의 심폐소생술을 시행한 그룹의 심근 ATP가 심실세동 유도 이전의 수준으로 회복되었다(CPR2 군: 5.27±1.67, CPR4 군: 3.77±1.05, CPR6 군: 3.49±1.08).

No-CPR 군과 비교하였을 때에 CPR2 군의 ATP 값이 유의하게 상승하였다 (No-CPR4 군: 4.27±1.58, No-CPR6 군: 4.13±1.31, No-CPR8 군: 3.77±1.42, No-CPR10 군; CPR2 군과 No-CPR6 군 사이의 p값은 <0.05 로 유의한 차이를 보였다).

심근 ATP/ADP ratio는 2분간의 심폐소생술을 시행한 군에서 정상 수준으로 회복되었고 시간이 흐름에 따라 소생술의 시행 여부와 상관없이 감소하였다(CPR2 군: 0.26±0.15, CPR4 군: 0.20±0.09, CPR6 군:0.19±0.03). No-CPR 군(No-CPR4 군: 0.13±0.05, No-CPR6 군: 0.15±0.04, No-CPR8 군: 0.17±0.06, No-CPR10 군: 0.17±0.05)과 비교하였을 때 CPR2 군의 ATP/ADP ratio가 유의하게 상승하였다 ($p<0.05$).

**결론**: 심근 ATP는 심실세동 기간이 장기화 될수록 감소한다. 4분간의 심실세동을 유지한 동물에서 2분 동안의 흉부압박을 시행하면 심근 ATP가 정상 수준으로 회복되지만 2분 이상의 흉부압박은 심근 ATP회복에 영향을 주지 않는다.

핵심 되는 말 : cardiac arrest, cardiopulmonary resuscitation, ventricular fibrillation, myocardial ATP