# Effect of intrathoracic pressure on diastolic function of the heart during cardiopulmonary resuscitation in an animal model of cardiac arrest

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This certifies that the dissertation of Gu Hyun Kang is approved.

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# 감사의 글

먼저 전공의 과정, 석사 과정과 박사 과정까지 부족한 저를 응급의학 전문의, 석사, 박사로 이끌어 주시고 지도해주신 황성오 교수님께 진심으로 감사드립니다. 교수님의 지도와 살피심으로 이 논문이 나오게 되었습니다. 처음 수련병원에서 시작할 때 교수님이 가르치면서 배운다고 하신 말씀에 힘을 얻어 여기까지 왔지만, 이번 과정을 통해 아직 많이 해야겠다는 것을 다시 확인하였습니다. 교수님의 가르침을 기억하고 항상 배우겠습니다.

학위 끝나는 과정까지 바쁘신 중에도 심사위원으로 저에게 많은 관심과 격려를 주신 오중환, 공인덕, 이강현, 유명수 교수님께도 깊은 감사를 전합니다.

어려운 여건에서 힘들게 동물실험을 같이 하고 도움을 주신 육현과 이윤석 선생님을 비롯한 원주세브란스 응급의학과 의국 선생님에게 감사의 말씀을 전합니다. 의국을 떠나고 오랜만에 잠시나마 후배 의국분들과 실험을 하고 시간을 같이 한 것은 저에게 커다란 추억으로 남을 것입니다.

통계과정을 많이 도와준 김원희 교수님과 실험과 논문으로 과와 센터 일을 많이 도와주신 장용수, 최현영 교수님과 한림대 강남성심 응급의학 의국들에게도 감사의 말씀을 전합니다.

나를 항상 응원해주고 논문 작성동안 많은 응원을 해준 아내 안지연과 딸 강은용, 그리고 아버지, 어머니, 장인어른, 장모님에게도 깊은 감사와 사랑을 전합니다.

이 논문이 있기까지 다 나열하지 못했지만 많은 분들의 도움을 받았습니다. 진심으로 감사드립니다.

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강구현

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## ABSTRACT

# Effect of intrathoracic pressure on diastolic function of the heart during cardiopulmonary resuscitation in an animal model of cardiac arrest

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**Background and Purpose:** : The mechanism controlling blood flow during standard cardiopulmonary resuscitation (CPR) remains controversial. The two most likely explanations at present for generation of blood flow by external chest compression are the thoracic pump and cardiac pump theories. However, diastolic phase of the heart during CPR has never been investigated. Cardiac arrest is not associated with the occurrence of either active diastolic relaxations or cardiac value mechanisms that prevent retrograde blood flow and atrial contraction during ventricular diastole. Investigation of the diastolic filling mechanism during cardiac arrest is important for understanding one of the determinants of cardiac performance. The aim of this study was to investigate the effect of changes in intrathoracic pressure (ITP) on diastolic function of the heart during CPR in a swine model of cardiac arrest.

**Subjects and Methods:** : Twelve domestic male pigs weighing 39.6±8.4 kg were acquired from a single-source breeder for use in this study. The animals were fasted overnight with only access to water. After anesthesia,

the right carotid vein, right carotid artery, and both femoral arteries were cannulated with an introducer sheath. Micromanometer-tipped catheters for measuring hemodynamic data were inserted through the sheaths. Carotid blood flow was measured at the left carotid artery with an ultrasonic flow measurement system. Chest tubes were inserted into both thoracic cavities to manipulate and measure the intrathoracic pressure. After 2 minutes of ventricular fibrillation induced by AC current to the right ventricle, the animals received a total of 12 minutes of standard manual cardiopulmonary resuscitation (CPR) comprising two 6-minute courses of CPR consisting of chest tube opening (CTO) for 3 minutes and chest tube closure (CTC) for 3 minutes. A sequence of CPR with CTO or CTC was performed alternatively, according to the randomization schedule. Chest compressors were rotated every 2 minutes.

Pressures were measured from the aorta, left ventricle (LV), right ventricle (RV), and right atrium (RA). Carotid blood flow (CBF) and end-tidal carbon dioxide concentration (EtCO2) were also measured. Coronary perfusion pressure (CPP), maximal and minimal dp/dt, and slopes of dp/dt of the ventricles were calculated.

**Statistical analysis:** Normality tests were conducted on the results. A paired t-test or a Wilcoxon test, as appropriate, was used to compare outcomes of CTO and CTC.

**Results:** Ten animals were included in the final analysis. Maximal dp/dt and upslope dp/dt of the RV and LV were higher during CPR than during spontaneous circulation ($p<0.001$). Minimal dp/dt and downslope dp/dt of the RV and LV were lower during CPR than during spontaneous circulation ($p<0.001$). Maximal dp/dt, upslope dp/dt, minimal dp/dt, and downslope dp/dt of the RV and LV, CBF, CPP, and EtCO2 did not differ

between CPR with CTC and CPR with CTO.

**Conclusion:** Intrathoracic pressure did not affect diastolic filling of the heart during CPR in an animal model of cardiac arrest.

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**Key Words**: Cardiopulmonary Resuscitation, diastole, cardiac arrest, external chest compression, basic life support

# I. Introduction

Closed-chest cardiopulmonary resuscitation (CPR), first introduced in 1960 (1, 2), is now used worldwide. It is documented as effective in cardiac arrest patients, even though the blood flow generated during cardiac arrest by standard CPR is only 17% to 27% of the normal cardiac output (3-5). More than 60 years have passed since the introduction of the technique for CPR, but the mechanism of blood flow still remains to be established (6).

Sudden cardiac arrest is not a rare clinical problem and has a very high mortality. Even within a well-organized, rapidly responding system and with public education, the community survival rates remain low. The International Liaison Committee on Resuscitation (ILCOR) has recommended 'high quality CPR' with emphasis on "push hard and fast, chest recoil, switching compressor every 2 minutes" and avoiding hyperventilation. Chest compression during CPR has been the main focus in recent resuscitation guidelines (7, 8). Chest compression depth and frequency, and switching the compressor every 2 minutes, may be associated with the systolic phase in which blood flows from heart to arteries. Chest recoil during chest compression may be associated with the diastolic phase of CPR, which makes blood flow from the veins to the heart (9). The mechanism of blood flow during standard CPR remains controversial, with the thoracic pump (10-21) and cardiac pump (22-28) theories currently considered the most likely mechanisms for generating

blood flow by external chest compression.

Criley et al. reported that eight patients undergoing coronary angiography were successfully resuscitated from ventricular fibrillation (VF), and three of these patients remained conscious and alert for 24 to 39 seconds after VF by coughing every one to three seconds and coughing could increase intrathoracic pressure (ITP) and maintain a cardiac output (10). Niemann et al. confirmed the cough CPR mechanism through an animal experiment and reported that the CPR "thoracic pump" can sustain systemic perfusion during CPR (15). The thoracic pump model suggests that chest compressions during CPR increase intra-thoracic and aortic pressure, causing blood to flow from the intrathorax to the extrathoracic vascular compartment (17). External chest compression could therefore generate blood flow by phasic changes in ITP without direct compression of the heart (12). The thoracic pump hypothesis proposed that external chest compression produced an elevation of ITP that is transmitted equally to all cardiac chambers and intrathoracic vascular structures. This elevated intravascular pressure is transmitted from the intrathoracic to extrathoracic arteries, but not to extrathoracic veins. The unequal transmission of pressure from the arterial to the venous system then generates a pressure gradient for extrathoracic blood flow.

Several features intrinsic to the anatomical structure of the veins and arteries permit this uneven transmission of elevated ITP. During chest compression, the more rigid arteries at the thoracic inlet resist collapse from the high ITP, whereas the thin walled veins tend to collapse. At the same time, the venous valves in the superior vena cava prevent the

transmission of the increased ITP to the extrathoracic jugular vein. The venous compliance is much greater in the extrathoracic than in the intrathoracic arterial system, so blood flow can be accommodated in the venous system with a much lower rise in venous pressure. The difference in pressure between the intrathoracic arteries and extrathoracic veins causes blood to move from the intrathoracic space into the extrathoracic vascular system.

The thoracic pump model is supported by arterial and venous pressure tracings that demonstrate simultaneous peaks in venous and arterial pressures during chest compressions (18). Echocardiographic studies during CPR in humans demonstrated that the aortic and mitral valves are open and that no reduction occurs in the left ventricular dimensions during chest compression. These findings would support the notion that the heart serves as a conduit, rather than being responsible for pumping blood (13, 14, 20). Haas et al. reported that a cardiac arrest patient with a postoperative complication of cardiac tamponade detected by a thoracoabdominal CT-scan was successfully resuscitated with CPR over 15 min. This observation suggests that the thoracic pump mechanism may have been the predominant mechanism of forward blood flow in the case of a pericardial tamponade (21).

The cardiac pump theory holds that blood flow during the closed chest compression is assumed to result from direct compression of the heart between the sternum and vertebral column. The ventricles play the role of pumps that cause blood flow to the blood vessels (1). If this hypothesis is correct, blood flow and cardiac dynamics during chest compression would

be similar to the normal cardiac cycle. During chest compression (the systole phase), the ventricle would be compressed and the atrioventricular valves would close due to the ventricular-atrial pressure gradient. Blood flow would be driven from the ventricle to the vessels. During chest relaxation (the diastole phase), ventricular pressure would fall below atrial pressure and atrioventricular valve would be opened and ventricular filling would occur. Feneley et al. demonstrated that high impulse chest compressions produced mitral valve closure, no antegrade mitral valve flow, and left ventricular deformation; they suggested a cardiac pump mechanism of antegrade blood flow during CPR (27).

Evidence was demonstrated for direct cardiac compression as the mechanism accounting for effective forward blood flow during CPR and for the persistence of valve function, chamber compression, and pressure gradients during chest compression, in an animal study by echocardiography (28) and in a human study by transesophageal echocardiography (29). Deshmukh et al. demonstrated that both the mitral and the tricuspid valves opened during compression diastole and closed during compression systole, with a reduction observed in the left ventricular area during compression systole in the animal study (28). Other studies reported mitral valve opening during cardiac release, reduction of ventricular cavity size with compression, and atrioventricular regurgitation, in support of the cardiac pump theory of CPR in humans (22, 24, 29). Hwang et al. demonstrated a deformation of the aorta at the maximal compression site and an increase in the cross-sectional area of the proximal aorta, again suggesting a cardiac pump mechanism in humans

(26). Kim et al. demonstrated a retrograde flow to the left atrium and forward blood flow onto the aorta by left ventricular contrast echocardiography during the compression phase during CPR, when the direction of contrast flow was assessed using transesophageal echocardiography in the left ventricle (LV). This finding suggests that an extrinsic compression of the left ventricle by external chest compressions (cardiac pump) is a dominant mechanism for generating blood flow during standard CPR in humans (25). Recent data revealed that the cardiac pump mechanism caused antegrade blood flow during chest compression in humans. However, the actual mechanism of chest compression during CPR in humans remains controversial (18).

The cardiac cycle is composed of electrical, mechanical, and valvular events. The diastole is divided into isovolumic relaxation, early ventricular filling, diastasis, and atrial systole. Isovolumic relaxation is the period between aortic valve closure and mitral valve opening, during which the ventricular volume remains constant and the ventricular pressure rapidly declines (30-32). The initial magnitude of the pressure gradient between the chambers is determined by the rate and extent of the ventricular pressure decline and the atrial pressure resulting from the opening of the atrioventricular valve (33). The increase in ventricular volume observed during early ventricular filling occurs while ventricular pressure decreases. The ventricular pressure decreases to a subatmospheric level if blood flow across the mitral valve is completely obstructed (34, 35). The ventricle will continue to fill through this “diastolic suction” mechanism, even if the atrium pressure is zero (36, 37).

During cardiac arrest and CPR, hemodynamics is compromised by a poor chest compression technique that incorporates inadequate chest compressions and incomplete chest recoil (5, 38, 39). Cardiac and coronary perfusion increases in animals and humans during CPR due to augmentation of negative ITP during the decompression phase (40-43). A higher ITP reduces cardiac filling, increases intracranial pressures, and results in a decrease in cerebral and coronary perfusion pressure (CPP), which reduces the likelihood of survival (44). ITP has been related to positive pressure ventilation and incomplete chest wall recoil (38). Regardless of the actual chest compression mechanism (i.e., the cardiac or thoracic pump mechanism), ITP can play a substantial role in generating blood flow by affecting the diastolic phase during CPR.

In cardiac arrest, neither active diastolic relaxation nor the cardiac value mechanism (that prevents retrograde blood flow and atrial contraction during the ventricular diastole) occurs. The variables of ventricular filling during cardiac arrest are thought to include the negative pressure generated by thoracic recoil, inertia from ventricular compliance, and the venothoracic pressure difference between extrathoracic and intrathoracic vascular compartments. Investigation of the diastolic filling mechanism during cardiac arrest is therefore important for understanding the hemodynamics during cardiac arrest and CPR. The aim of the present study was to investigate the effect of changes in intrathoracic pressure (ITP) on diastolic function of the heart during CPR in a swine model of cardiac arrest.

# II. Materials and methods

## 1. Animals and ethics

Twelve domestic male pigs weighing 39.6±8.4 kg from a single-source breeder were used in this study. Experimental procedures and protocols conformed to the institutional guidelines for the care and use of animals in research and were approved by the Institutional Animal Care and Use Committee of Wonju College of Medicine, Yonsei University (YWC-140408).

## 2. Animal preparation

The animals were fasted overnight but allowed free access to water. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and maintained by ear vein injection of ketamine (30 mg/kg). Body temperature was maintained between 36.5 and 37.5 ○C during the procedures, using an incandescent heat lamp and electric heat pad. After anesthesia, the pigs were positioned prone and endotracheal intubation was conducted with a cuffed endotracheal tube. Intubation was confirmed by endotracheal end-tidal carbon dioxide concentration (EtCO2) (CO2SMO, Phillips Respironics, PA, USA). After intubation, the pigs were positioned supine. Animals were ventilated with room air via a volume controlled

ventilator (MDS Matrix 3000, Orchard Park, NY, USA) during preparation. The tidal volume was set at 10 mL/kg and ventilation rate at 18 breaths per minute. Electrocardiography (ECG lead II) and EtCO2 were monitored continuously.

Under aseptic conditions, the right femoral artery was cannulated with an introducer sheath (7.5 Fr, Arrow International Inc., Reading, PA, USA) using the Seldinger method, and the aortic blood pressures were continuously recorded with a micromanometer-tipped catheter (5 Fr., Millar Instruments, Inc., TX, USA) introduced into the femoral artery. After right cervical dissection, the right carotid artery was cannulated with an introducer sheath (7.5 Fr) using the Seldinger method, and the left ventricular pressures were continuously recorded with a micromanometer-tipped catheter (5 Fr., Millar Instruments, Inc., TX, USA) introduced into the right carotid artery.

Two introducer sheaths were placed in the right external jugular vein: one recorded the RA and RV pressure via a micromanometer-tipped catheter (6 Fr., Millar Instruments, Inc., TX, USA), while the other provided an insertion route for a pacing catheter (5 Fr, bipolar lead, Arrow International Inc., Reading, PA, USA) and then for infusion of saline and epinephrine. After left cervical dissection, the left carotid artery was surgically exposed and an ultrasonic flow probe (T106, Transonic Systems Inc., Ithaca, NY) was placed around it to quantify blood flow. If the left carotid artery cannulation failed, femoral artery cannulation was attempted for measurement of left ventricular pressures. Once the catheters were in place, a heparin bolus (100 unit/kg, I.V.) was administered to prevent

thrombosis.

Chest tubes (16 Fr) were inserted in both mid-lateral thoracic walls. A micromanometer-tipped catheter (5 Fr) was inserted into the thoracic space via the left chest tube to record the ITP. The chest tubes were clamped with a curved hemostat without teeth when chest tube closure was needed during the experiment (Figure 1).

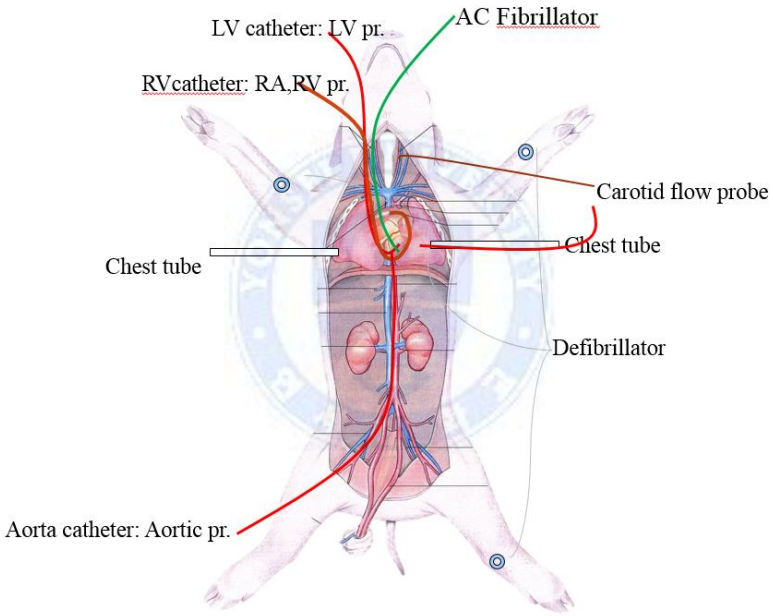


Figure 1. Animal preparation including catheterizations, monitoring, and insertion of chest tubes

LV: left ventricle, RV: right ventricle, RA: right atrium, Pr.: pressure, AC: alternative current

## 3. Experimental protocol

The pigs were randomized into two groups using a sealed envelope randomization before induction of cardiac arrest. After 2 minutes of ventricular fibrillation induced by AC current to the right ventricle, the animals received a total of 12 minutes of standard manual cardiopulmonary resuscitation (CPR) comprising two 6-minute courses of CPR consisting of chest tube opening (CTO) for 3 minutes and chest tube closure (CTC) for 3 minutes. A sequence of CPR with CTO or CTC was performed alternatively, according to the randomization schedule. Chest compressors were rotated every 2 minutes.

## 4. Induction of ventricular fibrillation

After baseline data were collected, a pacing catheter was positioned in the RV. VF was induced by delivering electrical current at 60 Hz to the endocardium and confirmed by the ECG waveform and a decline in aortic pressure. Once VF was induced, the endotracheal tube was disconnected from the ventilator and the pigs were observed for 2 minutes without any procedure or treatment.

## 5. Cardiopulmonary resuscitation

Chest compressions were performed by experienced medical persons who had passed the American Heart Association (AHA) Basic Life Support (BLS) provider course. These chest compressors were blinded to the study design. Two chest compressors performed chest compressions every 2 minutes according to BLS guidelines. According to BLS guidelines, compression and ventilation ratio was 30:2 and the compressors were switched every 2 minutes. Chest compression was performed with a depth of 5 cm and at a rate of 100/min. Positive pressure ventilations every 30 chest compressions were delivered with a resuscitator bag (silicone resuscitator 870040, Laerdal Medical, Stavanger, Norway). Chest compression and ventilation sequences were repeated as four sequences over 12 minutes. In CTO, both chest tubes were left open for the first 3 minutes and closed for the next 3 minutes. In CTC, both chest tubes were closed during the first 3 minutes and opened for the next 3 minutes. Each sequence was repeated twice, for a total of 12 minutes of CPR (Figure 2).

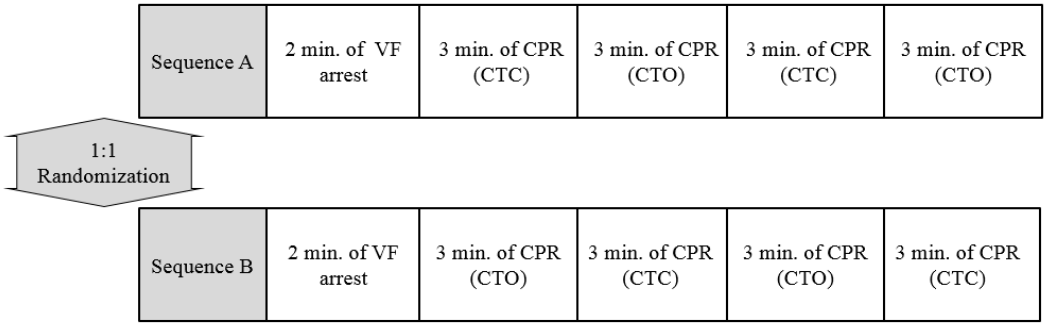


Figure 2. Experimental protocol: randomization and sequence of CPR

VF: ventricular fibrillation, CPR: cardiopulmonary resuscitation, CTO: CPR with chest tube opening, CTC: CPR with chest tube closure

## 6. Data Measurements

Data were digitized with a digital recording system (Powerlab, AD Instruments, CO, USA). All parameters (aortic systolic, diastolic, RV, right atrium (RA), left ventricular, left pleural pressures, carotid blood flow, and EtCO2) were continuously recorded and analyzed at baseline. CPP during CPR was calculated as the difference between aortic pressure and RA pressure in the end-diastolic phase using an electronic subtraction unit (Figure 3).

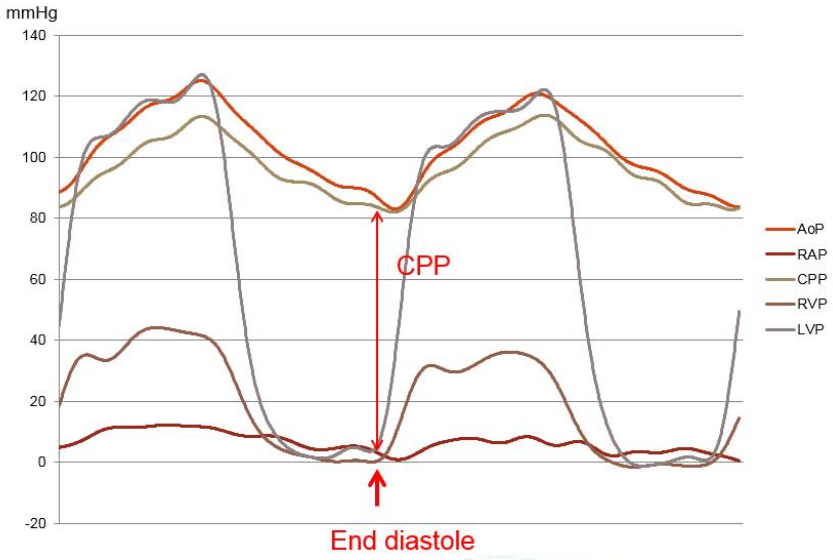


Figure 3. Measurement of coronary perfusion pressure

CPP: Carotid perfusion pressure, AoP: Aortic pressure. RAP: Right atrial pressure, RVP: Right ventricular pressure, LVP: Left ventricular pressure

After 2 minute of untreated VF, chest compressions were started by an experienced medical person and all parameters were continuously recorded and analyzed during chest compression (Figure 4).

The dp/dts of LV and RV (maximum, minimum, upslope, downslope) were calculated with a digital record system program. End diastole was pointed at the end of LV diastole.

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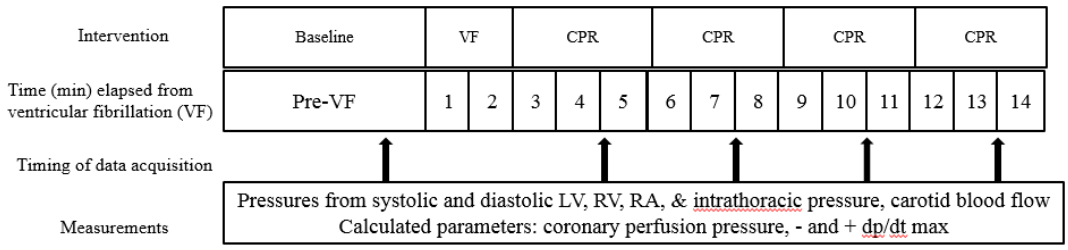


Figure 4. Measurement of hemodynamic parameters during the spontaneous circulation and cardiopulmonary resuscitation

VF: Ventricular fibrillation, CPR: Cardiopulmonary resuscitation, RA: Right atrium, RV: Right ventricle, LV: Left ventricle

## 3. Statistical analysis

Continuous variables were presented as mean±SD. Student's t-test was used to compare continuous variables between the two groups. Categorical variables were reported as counts and percentages. Primary and secondary outcomes were binary, and the paired t-test or Wilcoxon test, as appropriate, was used to compare outcomes in CTO and CTC. A value of $P<0.05$ was considered significant. Analyses were carried out using SPSS V.11.0 software (IBM Corp., Chicago, IL, USA). Any differences were regarded as significant if p-values were less than 0.05.

# III. Results

## 1. Demographic characteristics of animals

Twelve animals were initially included in the study, but two animals suffered VF during preparation, so ten animals were included in the final analysis. Mean body weights and chest circumferences were 39±8 kg and 69±6 cm. No differences were noted in demographic characteristics between the CTC and CTO groups (Table 1).

Table 1. Demographic data of animals.

| Variables | Value (n=10) |
|---|---|
| Bodyweight (Kg) | 39±8 |
| Chest circumference (cm) | 69±6 |
| Rectal temperature (℃) | 38±1 |
| Oxygen saturation (%) | 98±1 |

All variables are given as mean±SEM.

## 2. Comparison of parameters between spontaneous circulation and cardiopulmonary resuscitation.

Significant differences were noted between baseline (during spontaneous circulation) and CPR in terms of systolic hemodynamic parameters, such as aortic systolic pressure (baseline: 122±6 mmHg vs CPR: 124±162 mmHg, p=0.004), left ventricular systolic pressure (baseline: 104±23 mmHg vs CPR: 169±78 mmHg, p<0.001), right ventricular systolic pressure (baseline: 22±14 mmHg vs CPR: 171±90 mmHg, p<0.001), and right atrial systolic pressure (baseline: 3±3 mmHg vs CPR: 162±91 mmHg, p<0.001). Significant differences were also observed between baseline (during spontaneous circulation) and CPR in terms of diastolic hemodynamic parameters, such as aortic diastolic pressure (baseline: 86±9 mmHg vs CPR: 9±8 mmHg, p<0.001), left ventricular diastolic pressure (baseline: 5±5 mmHg vs CPR: 8±7 mmHg, p<0.001), right ventricular diastolic pressure (baseline: 7±16 mmHg vs CPR: 12±6 mmHg, p<0.001), and right atrial diastolic pressure baseline: 3±1 mmHg vs CPR: 11±6 mmHg, p<0.001) (Table 2).

Table 2. Comparison of systolic and diastolic parameters between baseline (during spontaneous circulation) and cardiopulmonary resuscitation.

| Parameter (mmHg) | Baseline (n=10) | CPR (n=10) | p-value |
|---|---|---|---|
| Aortic pressure, systolic | 122±6 | 124±161 | 0.004 |
| Aortic pressure, diastolic | 86±9 | 9±8 | <0.001 |
| LV pressure, systolic | 104±22 | 168±77 | <0.001 |
| LV pressure, diastolic | 5±5 | 8±7 | <0.001 |
| RV pressure, systolic | 22±14 | 171±90 | <0.001 |
| RV pressure, diastolic | 7±16 | 12±6 | <0.001 |
| RA pressure, systolic | 3±3 | 162±91 | <0.001 |
| RA pressure, diastolic | 3±1 | 11 ± 6 | <0.001 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

CPR: cardiopulmonary resuscitation, RA: Right atrium, RV: Right ventricle, LV: Left ventricle

Significant differences were observed between baseline (during spontaneous circulation) and CPR for the maximal dp/dt of the LV (baseline: 492±270 mmHg/sec vs. CPR: 687±558 mmHg/sec, p<0.001), minimal dp/dt of the LV (baseline: -452±169 mmHg/sec vs. CPR: -611±325 mmHg/sec, p<0.001), dp/dt of the LV upslope (baseline: 3609±1250 mmHg/sec2 vs. CPR: 2614±1307 mmHg/sec2, p<0.001), and dp/dt of the LV downslope (baseline: -2858±3204 mmHg/sec2 vs CPR: -6243±3407 mmHg/sec2, p<0.001). Significant differences were also observed between

baseline (during spontaneous circulation) and CPR in terms of maximal dp/dt of the RV (baseline: 159±87 mmHg/sec vs CPR: 698±595 mmHg/sec, $p<0.001$), maximal dp/dt of the RV (baseline: -138±48 mmHg/sec vs CPR: -603±382 mmHg/sec, $p<0.001$), dp/dt of the RV upslope (baseline: 863±434 mmHg/sec2 vs CPR: 2631±1656 mmHg/sec2, $p<0.001$), and dp/dt of the RV downslope (baseline: -1068±521 mmHg/sec2 vs CPR: -6241±4117 mmHg/sec2, $p<0.001$) (Table 3).

Table 3. Comparison of dp/dt of the left ventricle and right ventricle between during spontaneous circulation (baseline) and during CPR

| Parameter | Baseline (n=10) | CPR (n=10) | p-value |
|---|---|---|---|
| dp/dt RV max. (mmHg/sec) | 159±87 | 698±595 | < 0.001 |
| dp/dt RV min. (mmHg/sec) | -138±48 | -603±382 | < 0.001 |
| dp/dt RV upslope ($mmHg/sec^2$) | 863±434 | 2631±1656 | < 0.001 |
| dp/dt RV downslope ($mmHg/sec^2$) | -1068±521 | -6241±4117 | < 0.001 |
| dp/dt LV max. (mmHg/sec) | 492±270 | 687±558 | < 0.001 |
| dp/dt LV min. (mmHg/sec) | -452±169 | -611±325 | < 0.001 |
| dp/dt LV upslope ($mmHg/sec^2$) | 3608±1686 | 2614±1307 | < 0.001 |
| dp/dt LV downslope ($mmHg/sec^2$) | -2858±1457 | -6243±3407 | < 0.001 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

CPR: cardiopulmonary resuscitation, RA: Right atrium, RV: Right ventricle, LV: Left ventricle, Max.: Maximum, Min.: Minimum

## 3. Comparison of hemodynamic parameters between CPR with chest tube opening and CPR with chest tube closure

### 3.1. Systolic parameters

No significant differences were observed in systolic hemodynamic parameters, including aortic systolic pressure (CTO: 104±52 mmHg vs CTC: 124±161 mmHg, p=0.895), left ventricular systolic pressure (CTO: 162±74 mmHg vs CTC: 168±77 mmHg, p=0.324), right ventricular systolic pressure (CTO: 158±85 mmHg vs CTC: 171±90 mmHg, p=0.032), and right atrial systolic pressure (CTO: 151±83 mmHg vs CTC: 162±91 mmHg, p=0.097) (Table 4).

### 3.2. Diastolic parameters

No significant differences were noted in diastolic hemodynamic parameters, including aortic diastolic pressure (CTO: 11±8 mmHg vs CTC: 9±8 mmHg, p=0.02), left ventricular diastolic pressure (CTO: 9±7 mmHg vs CTC: 8±7 mmHg, p=0.229), right ventricular diastolic pressure (CTO: 29±133 mmHg vs CTC: 12±6 mmHg, p=0.0808), and right atrial diastolic pressure (CTO: 12±6 mmHg vs CTC: 11 ± 6 mmHg, p=0.333) (Table 4).

Table 4. Comparison of systolic and diastolic parameters between CPR with chest tube opening and CPR with chest tube closure.

| Parameter (mmHg) | Baseline | CTO (n=10) | CTC (n=10) | p-value |
|---|---|---|---|---|
| Aortic pressure, systolic | 122±6 | 104±52 | 124±161 | 0.895 |
| Aortic pressure, diastolic | 86±9 | 11±8 | 9±8 | 0.020 |
| LV pressure, systolic | 104±22 | 162±71 | 168±77 | 0.324 |
| LV pressure, diastolic | 5±5 | 9±7 | 8±7 | 0.229 |
| RV pressure, systolic | 22±14 | 158±85 | 171±90 | 0.032 |
| RV pressure, diastolic | 7±16 | 29±133 | 12±6 | 0.808 |
| RA pressure, systolic | 3±3 | 151±83 | 162±91 | 0.097 |
| RA pressure, diastolic | 3±1 | 12±6 | 11±6 | 0.333 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

CTO: CPR with chest tube opening, CTC: CPR with chest tube closure, RA: Right atrium, RV: Right ventricle, LV: Left ventricle

### 3.3. dp/dt of left ventricle and right ventricle

No significant differences were observed in the maximal dp/dt of LV (CTO: 674±508 mmHg/sec vs CTC: 687±558 mmHg/sec, p=0.808), maximal dp/dt of LV (CTO: -615±316 mmHg/sec vs CTC: -611±325 mmHg/sec, p=0.965), dp/dt of LV upslope (CTO: 2634±1250 mmHg/sec2 vs CTC: 2614±1307 mmHg/sec2, p=0.947), and dp/dt of LV downslope (CTO: -6111±3204 mmHg/sec2 vs CTC: -6243±3407 mmHg/sec2, p=0.389).

No significant differences were observed in the maximal dp/dt of RV (CTO: 659±545 mmHg/sec vs CTC: 698±595 mmHg/sec, p=0.162), maximal dp/dt of RV (CTO: -582±370 mmHg/sec vs CTC: -603±382 mmHg/sec, p=0.313), dp/dt of RV upslope (CTO: 2600±1656 mmHg/sec2 vs CTC: 2631±1656 mmHg/sec2, p=0.757), and dp/dt of RV downslope (CTO: -5793±3807 mmHg/sec2 vs CTC: -6241±4117 mmHg/sec2, p=0.044) (Table 5).

Table 5. Comparison of dp/dt of left ventricle and right ventricle between CPR with chest tube opening and CPR with chest tube closure.

| Parameter | Baseline | CTO (n=10) | CTC (n=10) | p-value |
|---|---|---|---|---|
| dp/dt RV max. (mmHg/sec) | 159±87 | 659±545 | 698±595 | 0.162 |
| dp/dt RV min. (mmHg/sec) | -138±48 | -582±370 | -603±382 | 0.313 |
| dp/dt RV upslope ($mmHg/sec^2$) | 863±434 | 2600±1656 | 2631±1656 | 0.757 |
| dp/dt RV downslope ($mmHg/sec^2$) | -1068±521 | -5793±3807 | -6241±4117 | 0.044 |
| dp/dt LV max. (mmHg/sec) | 492±270 | 674±508 | 687±558 | 0.808 |
| dp/dt LV min. (mmHg/sec) | -452±169 | -615±316 | -611±325 | 0.965 |
| dp/dt LV upslope ($mmHg/sec^2$) | 3608±1686 | 2634±1250 | 2614±1307 | 0.947 |
| dp/dt LV downslope ($mmHg/sec^2$) | -2858±1457 | -6111±3204 | -6243±3407 | 0.389 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

CTO: CPR with chest tube opening, CTC: CPR with chest tube closure, RA: Right atrium, RV: Right ventricle, LV: Left ventricle, Max.: Maximum, Min.: Minimum

### 3.4. Intrathoracic pressure

The ITP mean was significantly lower during spontaneous circulation than during CTC or CTO (p=0.003), but no significant differences were noted in the ITP maximum (p=0.531), ITP minimum (p=0.003), and ITP gradient (p=0.135) (Table 6).

Table 6. Comparison of intrathoracic pressure between CPR with chest tube opening and CPR with chest tube closure.

| Parameter | Baseline | CTO (n=10) | CTC (n=10) | p-value |
|---|---|---|---|---|
| ITP max. (mmHg) | 0±3 | 10±13 | 16±23 | 0.531 |
| ITP min. (mmHg) | -13±7 | -13±7 | -8±6 | 0.857 |
| ITP mean (mmHg) | -5±3 | 0±5 | 0±4 | 0.003 |
| ITP gradient (mmHg) | 11±8 | 11±8 | 24±26 | 0.15 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

ITP: Intrathoracic pressure, CTO: CPR with chest tube opening, CTC: CPR with chest tube closure, RA: Right atrium, RV: Right ventricle, LV: Left ventricle, Max.: Maximum, Min.: Minimum

### 3.5. Coronary blood flow, end-tidal carbon dioxide concentration, coronary perfusion pressure

No significant differences were noted in coronary blood flow (p=0.056), EtCO2 (p=0.022), and CPP (p=0.005) between CTO and CTC (Table 7).

Table 7. Comparison of coronary blood flow, end-tidal carbon dioxide concentration, coronary perfusion pressure between CPR with chest tube opening and CPR with chest tube closure.

| Parameter | Baseline | CTO (n=10) | CTC (n=10) | p-value |
|---|---|---|---|---|
| $EtCO_2$ (mmHg) | 25±14 | 36±8 | 32±10 | 0.022 |
| CBF (ml/min) | 111±132 | 151±133 | 129±106 | 0.056 |
| CPP (mmHg) | 89±7 | 12±7 | 10±6 | 0.005 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

$EtCO_2$: End-tidal carbon dioxide concentration, CBF: Coronary blood flow, CPP: Coronary perfusion pressure, CTO: CPR with chest tube opening, CTC: CPR with chest tube closure

## 4. Comparison of parameters between chest compressors

To exclude the effect of inter-compressor variability, we compared the parameters of CTO and CTC according to compressor. No significant differences were evident between the CTC and CTO groups in terms of systolic and diastolic parameters (aortic diastolic pressure, left ventricular diastolic pressure, right ventricular diastolic pressure, right atrial diastolic pressure), dp/dt of LV and RV ( maximum, minimum, upslope, downslope), coronary blood flow, EtCO2, and CPP (Tables 8 and 9).

Table 8. Parameters during CPR by chest compressor 1.

| Parameter | CTO (n=10) | CTC (n=10) | p-value |
|---|---|---|---|
| Aortic pressure, systolic (mmHg) | 104.8±53.5 | 116.6±69.5 | 0.572 |
| Aortic pressure, diastolic (mmHg) | 11.4±7.6 | 8.7±8.9 | 0.106 |
| LV pressure, systolic (mmHg) | 164.0±69.8 | 182.5±72.8 | 0.558 |
| LV pressure, diastolic (mmHg) | 10.5±7.8 | 8.6±6.9 | 0.102 |
| RV pressure, systolic (mmHg) | 157±83.7 | 183.9±89.8 | 0.075 |
| RV pressure, diastolic (mmHg) | 12.4±6.6 | 12.3±7.8 | 0.813 |
| RA pressure, systolic (mmHg) | 149±79.7 | 174±87.1 | 0.086 |
| RA pressure, diastolic (mmHg) | 12.3±6.2 | 10.7±6.8 | 0.658 |
| dp/dt RV max. (mmHg/sec) | 641.3±500.1 | 746.7±580.7 | 0.544 |
| dp/dt RV min. (mmHg/sec) | -570.9±354.0 | -657.0±397.4 | 0.781 |
| dp/dt RV upslope (mmHg/sec$^2$) | 2684.4±1658.7 | 2886.3±1753.3 | 0.393 |
| dp/dt RV downslope (mmHg/sec$^2$) | -5692.0±3724.4 | -6825.5±4187.5 | 0.229 |
| dp/dt LV max. (mmHg/sec) | 664.3±464.2 | 751.0±532.9 | 0.813 |
| dp/dt LV min. (mmHg/sec) | -626.4±305.8 | -681.0±321.0 | 0.453 |
| dp/dt LV upslope (mmHg/sec$^2$) | 2762.0±1310.7 | 2944.3±1297.3 | 0.165 |

| | | | |
|---|---|---|---|
| dp/dt LV downslope (mmHg/sec$^2$) | -6171.2±3256.5 | -6905.4±3334.5 | 0.829 |
| ITP max. (mmHg) | 12.4±11.6 | 16.7±22.5 | 0.586 |
| ITP min. (mmHg) | -6.2±5.9 | -9.3±6.6 | 0.141 |
| ITP mean (mmHg) | 0.8±6.6 | -0.2±4.8 | 0.975 |
| ITP gradient (mmHg) | 18.6±9.0 | 26.0±25.0 | 0.441 |
| $EtCO_2$ (mmHg) | 37.1±8.6 | 33.5±9.8 | 0.014 |
| CPP (mmHg) | -4.4±21.5 | -10.9±20.3 | 0.072 |
| CBF (ml/min) | 154.9±129.1 | 139.1±114.2 | 0.033 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

$EtCO_2$: End-tidal carbon dioxide concentration, CBF: Coronary blood flow, CPP: Coronary perfusion pressure, CTO: CPR with chest tube opening, CTC: CPR with chest tube closure, RA: Right atrium, RV: Right ventricle, LV: Left ventricle, ITP: Intrathoracic pressure, Max.: Maximum, Min.: Minimum

Table 9. Parameters during CPR by chest compressor 2.

| Parameter | CTO (n=10) | CTC (n=10) | p-value |
|---|---|---|---|
| Aortic pressure, systolic (mmHg) | 103±54 | 132±220 | 0.360 |
| Aortic pressure, diastolic (mmHg) | 10±8 | 9±9 | 0.125 |
| LV pressure, systolic (mmHg) | 161±74 | 154±80 | 0.491 |
| LV pressure, diastolic (mmHg) | 9±6 | 8±7 | 0.975 |
| RV pressure, systolic (mmHg) | 159±88 | 158±91 | 0.147 |
| RV pressure, diastolic (mmHg) | 47±8 | 12±5 | 0.237 |
| RA pressure, systolic (mmHg) | 153±87 | 149±96 | 0.441 |
| RA pressure, diastolic (mmHg) | 12±7 | 11±7 | 0.120 |
| dp/dt RV max. (mmHg/sec) | 677±596 | 650±616 | 0.206 |
| dp/dt RV min. (mmHg/sec) | -593±391 | -550±365 | 0.206 |
| dp/dt RV upslope ($mmHg/sec^2$) | 2515±1677 | 2376±1541 | 0.245 |
| dp/dt RV downslope ($mmHg/sec^2$) | -5894±3950 | -5657±4032 | 0.056 |
| dp/dt LV max. (mmHg/sec) | 685±556 | 624±584 | 0.600 |
| dp/dt LV min. (mmHg/sec) | -603±332 | -542±319 | 0.465 |
| dp/dt LV upslope ($mmHg/sec^2$) | 2507±1196 | 2507±1196 | 0.206 |

| | | | |
|---|---|---|---|
| dp/dt LV downslope (mmHg/sec$^2$) | -6051±32.6 | -6051±3206 | 0.271 |
| ITP max. (mmHg) | 14±13 | 17±23 | 0.704 |
| ITP min. (mmHg) | -5±5 | -7±6 | 0.047 |
| ITP mean (mmHg) | 1±6 | 1±5 | 0.517 |
| ITP gradient (mmHg) | 20±11 | 25±26 | 0.349 |
| $EtCO_2$ (mmHg) | 35±8 | 32±1 | 0.483 |
| CPP (mmHg) | 12±7 | 10±7 | 0.033 |
| CBF (ml/min) | 148±140 | 120±99 | 0.734 |

All variables are given as mean±SEM. Baseline indicates measurements before induction of cardiac arrest.

$EtCO_2$: End-tidal carbon dioxide concentration, CBF: Coronary blood flow, CPP: Coronary perfusion pressure, CTO: CPR with chest tube opening, CTC: CPR with chest tube closure, RA: Right atrium, RV: Right ventricle, LV: Left ventricle, ITP: Intrathoracic pressure, Max.: Maximum, Min.: Minimum

# IV. Discussion

Significant differences were noted in systolic and diastolic hemodynamic parameters, including pressures of the LV, RV, RA, and aorta, during spontaneous circulation and CPR. The RV and RA pressures exceeded LV pressures during chest compression. The maximal and minimal dp/dt and the dp/dt slopes of both ventricles differed between spontaneous circulation and CPR. The maximal dp/dt and upslope of dp/dt were higher during CPR than during spontaneous circulation and the pressure of the RV exceeded the pressure of the LV. This finding indicates that a higher compression force is exerted on the RV even though both ventricles are subjected to chest compressions during CPR. The lower minimal dp/dt and downslope of dp/dt during CPR than during spontaneous circulation, suggested a lower compliance of both ventricles during cardiac arrest and CPR than during spontaneous circulation. To our knowledge, this is the first study to investigate the diastolic function of the ventricle during CPR. The swine cardiac arrest study by Berg et al. demonstrated substantial early changes in the right ventricular volume that did not result in smaller left ventricular volumes (45). The volume change in the early phase of cardiac arrest may be the cause of the high-pressure RV change. If data on the heart volume were available, detailed information could possibly be obtained on the mechanism of how blood flows during chest compression. More study is need on the volume and changes in heart pressures during chest compression in cardiac arrest.

The pulmonary circulation is an important determinant of the RV afterload. The pulmonary vascular bed is a highly compliant, low-pressure, low-resistance system. In normal pulmonary circulation, the RV performs at approximately one-fourth the rate of the LV. The RV has a higher compliance than the LV in the normal status (46). The pulmonary vessels constrict in response to hypoxia (the Euler-Liljestrand reflex) (47). Hypoxia continues after cardiac arrest, thereby affecting the pulmonary vascular resistance and the RV afterload. Another mechanism increases the RV pressure. Compared to the LV, which has thick walls to resist the compression pressure, the RV may experience greater pressure during chest compression because of its thinner walls.

In the present study, chest tubes were inserted to manipulate the ITP and to investigate the effect of changes in ITP on diastolic function during CPR. Our hypothesis was that if the chest tube was opened, the intrapleural pressure would equal atmospheric pressure and ITP would be removed, which could affect the diastolic phase of the cardiac arrested heart. In contrast, if the chest tube was closed, ITP may react with the diastolic phase, similar to the mechanism of normal heart arrest. No changes were observed in the dp/dt values of the LV and RV during the ITP change. The dp/dt variables were maximum, minimum, upslope, and downslope. The maximal dp/dt and upslope dp/dt were generated by the systolic phase, which increased the pressure by chest compression. The maximal dp/dt downslope occurred in the diastolic phase, which decreased the pressure by chest decompression. No significant differences were observed in diastolic hemodynamic parameters, including aortic diastolic

pressure, left ventricular diastolic, right ventricular diastolic pressure, and right atrial diastolic pressure.

The dp/dt of the RV and LV was measured to evaluate the change in cardiac chamber pressure in detail. The mean dp/dt of RV and LV changes in pressure over time, where the maximal dp/dt and upslope dp/dt represent the pressure change occurring during the systolic phase, which is usually a positive pressure, while the maximal dp/dt of and downslope dp/dt represent the pressure change during the diastolic phase, which is usually a negative pressure. No significant differences were noted in the maximal dp/dt of LV, the LV dp/dt downslope, the maximal dp/dt of RV, and the dp/dt of RV downslope. No significant differences were evident in carotid blood flow, EtCO2 and CPP. These results showed that changes in ITP do not make a difference in the diastolic phase of the arrested heart.

In the normal heart, the diastolic phase is constructed of the LV recoil force (active diastolic relaxation), the cardiac valve mechanism, and atrial kick. In cardiac arrest, neither active diastolic relaxation during cardiac arrest nor the cardiac valve mechanism (which prevents retrograde blood flow and atrial contraction during the ventricular diastole) were evident. Thus, the systolic and diastolic functions of the ventricle were not affected by thoracic pressure changes. Other mechanisms may create a diastolic phase in arrest heart. The variables of ventricular filling during cardiac arrest were supposed to be negative pressure generated by thoracic recoil force, inertia from ventricular compliance and venothoracic pressure difference between extrathoracic and intrathoracic vascular compartments. Inertia is the resistance of any physical object to any change in its state

of motion, including changes to its speed and direction. It is the tendency of an object to keep moving in a straight line at constant velocity. It is used to describe the motion of objects and how they are affected by applied forces. Inertia of the ventricle or thoracic wall which drive force to natural position may affect the diastolic function of the arrested heart. Further study is needed on the inertia of the heart in arrest.

Limitations

The limitations of this study includes an insufficient number of animals, the accuracy of ITP measurement, and the possibility of differences between the two chest compressors. Our study protocol involved switching from CTC to CTO or from CTO to CTC every 3 minutes in one animal and randomizing the CTO and CTC to minimize the variables resulting from the lack of sufficient study animals. Through this method, we were able to gather more data and improve on the different variables affecting individual animal and CPR time factors. The two chest compressors were switched every 2 minutes and chest tube clamping was conducted every 3 minutes to reduce the bias between the chest compressors. A micromanometer-tipped catheter was inserted in the pleural cavity via a chest tube to measure ITP. These data may not exactly match the ITP measured in the lung. A micromanometer-tipped catheter was located in the pleural space, which would represent the intrapleural pressure. Possibilities also existed for malposition of the micromanometer-tipped catheter and bending or moving of the chest tube during chest compression.

# V. Conclusion

Intrathoracic pressure did not affect on diastolic phase during CPR in an animal model of cardiac arrest.

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# ABSTRACT IN KOREAN

## 심정지 동물모델에서 흉강내압이 심폐소생술 이완기에 미치는 영향


**서론**

심폐소생술에서 가슴압박이 혈류를 유발하는 기전은 명확하게 규명되지 않았다. 알려진 혈액순환기전은 심장이 직접 압박되어 혈류가 유발된다는 심장펌프이론과 흉부를 압박할 때 흉강 내압과 외압의 차이에 의하여 혈류가 유발된다는 흉강펌프이론이다. 이러한 이론들은 심장 압박기에 대한 이론으로 심폐소생술 중 심정지 심장에서 정맥환류 기전에 대한 연구는 없다. 가슴압박에 의해 혈류가 발생하려면 압박기에 심장이 압박되어야 할 뿐 아니라, 이완기에 심장으로 혈액충만이 발생해야 한다. 심정지 상태에서는 심장의 능동적 이완이 없어서 심장의 이완기 충만은 다른 요소에 의해 영향을 받을 것으로 추정된다. 이 연구는 심폐소생술 중 흉관 삽관으로 심장의 이완기 충만에 영향을 줄 수 있는 흉강내압의 영향을 제거할 수 있는 동물 모델을 사용하여 심폐소생술 중의 흉강내압이 심장의 이완기 기전에 미치는 효과를 알아보기 위하여 수행되었다.

**연구방법**

몸무게 35-50kg의 동물실험용 돼지 10마리를 12시간 이상 금식 후 마취하고, 기관삽관과 인공호흡을 하였다. 우측 목정맥, 좌측 목동맥, 양측 넙다리동맥을

박리한 후 천자하여 혈역학적 측정기구를 삽입하였다. 양측 가슴에 흉관을 삽입하고 흉강내 압력을 측정하였다. 우심실 도자에 교류를 통과시켜 심실세동을 유발하였고 2분간 심실세동을 유지하였다. 심정지를 유발 2분 후부터 미국심장협회 기본소생술 과정을 이수한 2인이 번갈아 가면서 30:2의 비율로 가슴압박과 인공호흡을 시행하였다. 가슴압박 시행자들은 동물개체에 대한 실험정보는 받지 못했다. 흉강 내압을 변화시키기 위해 흉관을 개방(CPR with chest tube opening: CTO) 또는 폐쇄(CPR with chest tube closure: CTC)하였다. 흉관 개방과 폐쇄는 각 3분간 유지하였으며, 2회 반복(총 12분)하였다. 흉관 개방과 폐쇄의 순서는 실험순서 홀수개체는 폐쇄-개방의 순서, 짝수개체는 개방-폐쇄의 순서로 하였다. 우심방과 우심실, 좌심실, 대동맥 압력을 측정하였고, 경동맥혈류, 호기말 이산화탄소압을 측정하였다. 측정된 우심실과 좌심실의 압력으로 우심실과 좌심실의 dp/dt(maximum, minimum, upslope, downslope)를 산출하였고, 대동맥압과 우심방압으로 관상동맥관류압을 계산하였다.

**통계**

통계학적 방법은 자료의 정규성을 검증하였고, 두 군의 비교는 비모수 검정(Willcoxon singed ranks test)을 시행하였다. 가슴압박자에 의한 영향을 분석하기 위해 압박자간 CTO와 CTC간의 변수를 비모수검정으로 비교하였다.

**결과**

12마리의 수컷 돼지가 실험에 사용되었으며, 실험준비 중 심실세동이 발생한 2마리를 제외한 10마리가 분석대상이 되었다. 좌심실과 우심실의 최대 dp/dt와 upslope of dp/dt는 정상 순환 동안보다 심폐소생술 동안 더 높았고 ($p<0.001$), 최소 dp/dt와 downslope of dp/dt는 정상 순환 동안보다 심폐소생

술 동안 더 낮았다($p<0.001$). 심폐소생술 중 흉관 개방 상태와 흉관 폐쇄 상태 사이에 좌심실과 우심실의 최대 dp/dt와 upslope of dp/dt, 최소 dp/dt와 downslope of dp/dt, 경동맥 혈류, 관상동맥관류압은 차이가 없었다.

**결론**

심폐소생술 중 흉강내압의 변화는 좌심실의 이완기 기능에 영향을 주지 않는다.

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핵심 단어: 심정지, 심폐소생술, 이완기 기능, 흉강 내압, 흉부압박, 기본소생술