

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

**EXAMINATION OF FACTORS INFLUENCING THE OUTCOME OF
CARDIOPULMONARY RESUSCITATION**

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Dissertation in the branch of health sciences for the attainment of a doctoral (PhD) degree

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The Examination takes place at meeting room of Department of Preventive Medicine Faculty of Public Health, University of Debrecen, at 10:00 AM, July 7, 2022.

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1. INTRODUCTION

1.1. Epidemiology of sudden cardiac death

Sudden cardiac death (SCD) is one of the most frequent cause of death. Sudden cardiac death accounts for 15-20% of total mortality and causes higher mortality rates than colon and prostate cancer. Each year approximately 275000 and 359800 patients suffer out of hospital sudden cardiac death in Europe and in the United States respectively. Approximately one person dies of sudden cardiac death every minute in both continents. Based on a survey, conducted in European countries, sudden cardiac death affects 84 inhabitants in a population of 100000. Despite developing diagnostics and effective preventive methods, the frequency of sudden cardiac death has not changed considerably. The incidence of sudden cardiac death found to be lowest in Cyprus (4 cases per 100000) and highest in the United Kingdom (1536 cases per 100000).

Most of the SCD cases occur outside the hospital. Chances for survival are quite low, spontaneous circulation returns in 10% of the cases. Exact data are currently not available in Hungary; according to certain estimates there may be 25-26 thousand cases annually that is, on average 50-60 cases of death occurs each day. Approximately 3-5% of survivors are discharged from hospital without serious neurological deficit. Thanks to the effective therapies and preventive methods, case numbers of sudden cardiac death have been decreased over the last decades.

Sudden cardiac death is defined as a sudden, unexpected death occurring within an hour of symptom onset or occurring in individuals found dead within 24 hours of being asymptomatic. Victims of sudden cardiac death have a history of congenital or acquired cardiac disease or cardiovascular anomaly identified as probable cause of event during autopsy or noncardiac etiology is not identified during postmortem examination, therefore the cause of death is presumably an arrhythmic event.

1.2. Risk factors of sudden cardiac death

Several different factors have been identified to be associated with sudden cardiac death. Some of the underlying causes are non-modifiable factors, while others are considered modifiable cardiovascular risk factors. Clinicians and scientists still face difficulties in identifying risk

factors in time in patients with high risk of sudden cardiac death, although it can be stated that the number of these risk factors are directly proportional to the total risk of sudden cardiac death.

Knowledge of the risk factors and their timely recognition enable clinicians to treat them and prevent sudden cardiac death.

Age and sex clearly have an effect on the incidence of sudden cardiac death. The risk for SCD increases with age. The incidence is 100/100000 in men in their fifties, while it is 800/100000 in 75-year-olds. It is well-known that the sudden cardiac death is more frequent among men than in women (6.68/100000 vs. 1.4/100000); furthermore, males up to the age of 65 have sevenfold chance for SCD which can be explained by the increased cardiovascular risk in men as well as the favorable protective hormonal status in premenopausal women. After the menopause, the male/female ratio decreases to 2:1, but men still show higher rates of developing SCD. A study conducted by the American Heart Association (AHA) on US citizens found significant difference in the rates of SCD between Afro-Americans and White inhabitants. The incidence of sudden cardiac death was higher in each age group of Afro-American population. The study was included 6451 patients: 3207 Whites, 2910 Afro-Americans and 334 patients belonging to another race. The incidence of sudden cardiac death in patients over 17 years of age was 167/100000/year. Chances for survival of Afro-Americans and Whites were 0.8% (24/2910) and 2.6% (84/3207, $p \leq 0.001$) respectively. Higher survival rates were observed in men and women as well.

Conversely, Latin Americans seem to have lower risk for sudden cardiac death. A study conducted in the US in 1992 was aimed at examining the rates of sudden cardiac death among Afro-American and Latin American inhabitants. The findings revealed that 53% (8194) of the cases of sudden cardiac death in Latin Americans over the age of 25 years old was out of hospital cardiac arrest. Compared to White and Afro-American inhabitants, the rate for sudden cardiac death was proved to be lower among Latin Americans. Annual incidence for sudden cardiac death was 75/100000 among Latin America men, 166/100000 among White men, 209/100000 among Afro-American men, 35/100000 in Latin American women, 74/100000 in White women and 108/100000 in Afro-American women. Afro-American women demonstrated highest rates for death in each age group.

A positive family history increases the chance of sudden cardiac death by 50%. Inherited conditions also constitute important predisposing factors for sudden cardiac death.

Ischemic heart disease is proved to be the underlying factor of 75% of all cases of sudden cardiac death, and myocardial infarction is the commonest cause that is identified in the

background. Factors increasing the rates of sudden cardiac death can be grouped into four main categories: ischemic heart diseases, non-ischemic heart diseases, non-structural heart diseases and non-cardiologic conditions (Table 2).

The rate of ischemic heart disease among adult inhabitants is estimated to be 6.3%, which only in the United States results in 16.5 million inhabitants over 20 years of age. Since 75% of the victims of sudden cardiac death suffer from ischemic heart disease, risk factors for ischemic heart disease indirectly increase the risk of sudden cardiac death. Some of these risk factors are hypertension, hyperlipidemia, diabetes mellitus, smoking and obesity.

1.3. Symptoms of sudden cardiac death

Taking thorough medical history, evaluating risk factors, and performing detailed medical examination are all important in the prevention of sudden cardiac death.

During history taking particular attention should be paid to certain symptoms such as chest pain, dyspnea at rest or on exertion, orthopnea, paroxysmal nocturnal dyspnea, pitting edema and the decrease of functional capacity. Symptoms referring to presence of arrhythmias are also important to recognize, these symptoms may involve palpitation, dizziness, altered mental status and loss of consciousness (syncope). Occurrence of sudden cardiac death, heart failure, sudden infant death syndrome, epilepsy among first degree relatives should also be identified when taking family history. During physical examination special attention should be given to the regularity of heart rhythm, jugular vein distension, blood pressure, presence of heart murmurs and signs of cardiac.

Although, sudden cardiac death is generally not preceded by specific warning signs, a study conducted by Kuller et al. in 1972 reported that 38% of patients develop general weakness, shortness of breath, chest pain and coughing within 24 hours before sudden cardiac death occurs.

2. MECHANISM OF ARRHYTHMIAS CAUSING SUDDEN CARDIAC DEATH

Pathogenesis of sudden cardiac death has not been fully understood; however, malignant arrhythmias are proved to have primary role in the process leading to cardiac arrest. Ventricular fibrillation, one of the commonest arrhythmias during cardiac arrest, observed initially in

approximately 30% of the cases. Development of ventricular fibrillation can be a consequence of structural or functional heart diseases, inherited, or acquired heart diseases, temporary medical conditions, and coexistence of these factors.

Channelopathies listed under inherited primary arrhythmia syndromes, like long and short QT syndromes and Brugada-syndrome (BrS), are important pathogenetic factors. In 70% of long QT syndromes, mutation of one of the potassium channels or L-type calcium channel can be identified. Among the 15 known genes, KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3) are affected in most of the cases, although in many patients the mutation responsible for the syndrome cannot be clarified. Catecholaminergic polymorphic ventricular tachycardia (CPVT) which can progress to ventricular fibrillation, results from the autosomal dominant inherited mutation of the type-2 cardiac ryanodine receptor (RYR2). In the case of Brugada syndrome several gene mutations have been described, which can refer to its polygenic origin. Arrhythmogenic right ventricular dysplasia (ARVD) may also have an effect in arrhythmogenesis and the development of sudden cardiac death. Furthermore, it has been reported that the single nucleotide polymorphisms (SNPs) located in the 21q21 and 2q24.2 loci also contribute to an increased risk for sudden cardiac death.

The electrophysiological substrate underlying the ventricular fibrillation include ectopic automaticity, reentry and triggered activity (due to early and late afterdepolarizations). In the case of ectopic automaticity, it is a ventricular premature beat caused by inherited or acquired ectopic impulse-generating foci that most frequently play a role in triggering VF.

A frequent underlying cause of the unidirectional block serving as the basis of so-called functional reentry mechanism may be the prolongation of the monophasic action potential of the myocyte and the consequential heterogeneity of ventricular repolarization. This process may be facilitated by myocardial ischemia and may trigger an increase in the monophasic AP duration restitution slope as well as changes in the amplitude of AP (electrical alternans).

Triggered activity may also appear because of early (EAD) or delayed afterdepolarization (DAD). EAD is caused by the early reactivation of L-type Ca-channels, a consequence of a decrease in repolarising potassium currents or an increase in the activity of positive currents toward the intracellular space.

Furthermore, changes in action potential duration, oxidative stress, hypokalemia and conditions associated with QT prolongation and heterogeneity may also play a role in the arrhythmogenesis.

In contrast, DAD develops after the repolarization of the myocyte membrane due to intracellular calcium excess or an increased sensitivity of intracellular ryanodine receptors.

3. RECOGNITION OF THE RISK FACTORS FOR SUDDEN CARDIAC DEATH. SPECIAL ISSUES OF TREATMENT AND PREVENTION

3.1. Early recognition of increased risk for sudden cardiac death, risk assessment and prevention.

Sudden cardiac death is not a single disease but the most serious complication of different diseases, therefore sudden cardiac death can effectively be prevented by treating these diseases.

Congenital and acquired heart diseases are common underlying factors which can lead to arrhythmias and then cardiac arrest. Warning signs can be observed in 80% of the cases, which creates the basis for effective prevention. One of the most important elements of the prevention is to identify those patients who have higher chance of developing sudden cardiac death. Importantly, sudden cardiac death may develop in patients who has no history of the currently known risk factors. Recognition of the underlying predisposing structural or functional heart diseases and the early diagnosis of ischemic heart disease as the commonest predisposing factor are also crucial elements of the prevention.

4. RECOGNITION OF SUDDEN CARDIAC DEATH, LEVELS AND POSSIBILITIES OF EMERGENCY CARE

4.1. Factors that affect the outcome of resuscitation

In case of sudden cardiac arrest, early resuscitation might be the only treatment, the most important elements of which is continuous high-quality chest compression interrupted for the shortest possible times (a maximum of a 10-second pause). However, the chances of survival after cardiac arrest are also influenced by other factors. Early detection of circulatory collapse, cardiopulmonary resuscitation started in time and applied efficiently, early defibrillation and effective post-resuscitation care – they all serve to increase the chances of survival and to reduce

complications. The chain of survival which is also known in international recommendations represents those steps that are fundamental for the survival of patients in case of sudden cardiac death.

In accordance with the current international resuscitation guideline, the ratio of chest compression to ventilation in case of adult resuscitation is 30:2.

Previous animal and human studies have shown that the continuous maintenance of coronary perfusion pressure (CPP) during the resuscitation is a vital condition of the return of spontaneous circulation (ROSC). In 1990, Paradis et al. proved that the return of spontaneous circulation was solely achieved in the case of patients with CPPs of 15 mmHg or more. Moreover, it was also demonstrated that perfusion is determined by the quality of chest compressions. In the course of adult cardiopulmonary resuscitation, chest compressions are considered effective when they are carried out continuously (with interruptions not exceeding 10 second) at a rate of 100–120 per minute, with a depth range of 5 -6 cm, and allows full recoil of the chest after each compression. Recoil, i.e. complete relaxation of the chest, plays key role of successful resuscitation and long-term neurological outcome. At this stage, negative intrathoracic pressure develops, which helps the outflow of blood from the venous system to the right atrium, increasing the overall preload of the heart.

4.2. Mechanical chest compression devices

It is well known that the maintenance of quality chest compressions are increasingly difficult as time passes. Providers become fatigued early on and as a result, the compression depth decreases and full recoil is no longer assured, preventing venous return to the heart. In addition, during manual compressions the duration of interruptions between chest compressions becomes longer, which may decrease myocardial perfusion even within a few seconds leading to lower chances of survival. The provision of continuous high-quality manual chest compressions is almost impossible and before the appearance of mechanical devices, meant a great challenge to prehospital emergency care providers. Lately, the most widespread mechanical compression devices are the LUCAS-2 and 3 and the AutoPulse. All of them are capable of providing superior, uninterrupted and hands-free chest compressions, and enable for the providers to perform further necessary interventions. Currently, two major types of mechanical devices are available on the market: LUCAS (Lund University Cardiopulmonary Assist System) and AutoPulse (Load distributing band CPR). LUCAS is a system operating on the basis of a piston principle and also contributes to the active decompression of the chest; a silicone ring is to be

pressed against the patient's chest, which thereafter exercises pressure in a depth of 5-6 cm with a frequency of 100/minute, and promotes the relaxation of the chest wall also. On the contrary, in the case of AutoPulse, a wide bandage is placed across the patient's chest, which thereafter implements pressure on the chest with a frequency of 80/minute, however, does not play a part in the relaxation of the chest. Research findings comparing resuscitations accomplished with the respective devices have not shown any differences in regard to the success of resuscitation. In 2010, animal studies conducted by Liao et al. shown that the coronary and cerebral perfusion pressure was significantly higher in the group resuscitated with the LUCAS mechanical device than in the manual control group. As reported by their results, in the case of LUCAS-CPR the mean coronary perfusion pressure was 20 mmHg and the cerebral perfusion pressure was 65 mmHg in opposition to the manual group in which they measured 17 and 40 mmHg respectively.

Opposed to these observations, relevant studies, such as the CIRC (Wik 2014) , PARAMEDIC (Perkins 2015) , LINC studies (Rubertsson 2014) and the large clinical study carried out by Hallstrom et al. did not find differences between the two methods either in the short-term outcome or in the 30-day survival. Neurological status of patients discharged from hospital was also compared, but obvious benefit regarding mechanical devices was not disclosed.

Wik and Rubertsson did not discovered variance in this respect. At the same time, Hallstrom found less favourable neurological outcome in the mechanical group ($p=0.006$).

The recent resuscitation guideline dedicates a separate part to discuss the use of mechanical chest compression devices. Before the publication of ERC Guidelines 2015, a total of 7582 patients had been assessed in relevant studies. On the basis of these data, the ERC does not recommend the routine out of hospital use of mechanical chest compression devices, however it emphasizes certain circumstances which justify the use of such device. These circumstances include need for resuscitation during transfer and prolonged resuscitation (e.g. hypothermic patients, during coronary intervention). The latter is especially important, since myocardial infarction is considered one of the most frequent underlying condition of sudden cardiac death and can effectively be treated with early coronary intervention. Therefor, searching for reversible causes (4 Hs and 4 Ts: hypoxia, hypothermia, hyper/hypokalemia, hypovolemia, tension pneumothorax, pericardial tamponade, toxins, thromboembolism) systematically during CPR can reveal the underlying cause enabling providers to apply causal therapy. As far as coronary embolism is suspected as an underlying condition, continuous chest compressions provided with mechanical device may contribute to a better outcome, and can help in transferring the patient to the nearest PCI center.

The current guideline published in 2021, still dedicates a separate part to discuss the use of mechanical chest compression devices. At the time, two major studies examined the results of resuscitation carried out by mechanical devices or manual. Koster and et. compared the results of resuscitation performed by AutoPulse device to the manual group in case of 133 patients. Survival rate was higher in the AutoPulse group (18,8% vs. 6,3%, $p=0,03$), however, there was no significant difference in neurological outcome between the groups (16,2% vs. 13,4%). In another study, Gao et al. compared results of resuscitation performed by AutoPulse device as well. There was no difference in survival, injury or neurological outcome. Overall, the results did not make a change in the recommendation of the usage of mechanical devices described in the previous guidelines.

4.3. The importance of defibrillation in the event of sudden cardiac death

The most effective treatments of ventricular fibrillation and pulseless ventricular tachycardia (pVT) are the following: immediate high-quality chest compression and early defibrillation. The latter plays an important part in terminating these arrhythmias. Survival rate by early defibrillation in the event of resuscitation performed by lay people is 37.4 %. The fact that the rate of successful resuscitation falls by 7-10% per minute from the circulatory collapse underlines the necessity of earliest possible electrical treatment. The availability of automated external defibrillators (AED) in public places and broad-scale training for lay persons about the use of the device may increase the current survival rate of 10%.

An improvement in the chance of long-term survival and the least neurological damage were discovered in the case when the initial rhythm recorded on site was ventricular fibrillation. Another significant part of improving the neurological outcome is post-resuscitation care started in time, which constitutes coronary intervention and targeted temperature management (TTM). Derived from the results of the examination of 136 patients, the Hypothermia after Cardiac Arrest Study Group discovered that the application of TTM obviously improved neurological outcome (based on CPC) and decreased mortality. (Hypothermia after Cardiac Arrest Study Group., 2002) Stanger et al. observed 570 patients resuscitated after out-of-hospital sudden cardiac death who were administered TTM therapy in hospital. The patients were divided into two groups based on how many minutes after arrival in hospital TTM was started. The most significant difference between the early (20-81 minutes) and the late (167-319 minutes) groups was in survival. The early group had 1.59 times higher chance for survival

in comparison to the late group, while they had only 1.49 times higher chance for a good neurological outcome, which did not prove evidently significant.

In 2021, Granfeldt et al. contrasted the results of 32 studies between a group of TTM patients and non TTM patients. It was discovered that in the TTM group (n = 2968) neither survival (RR: 1.08; 95% CI: 0.89-1.30) nor neurological outcome (RR: 1.21; 95% CI: 0.91-1.61) did not prove better results in comparison to the normothermic group. Out of the 32 studies, there were 10 cases in the event of which TTM therapy was started already prehospitally, was compared with a prehospital normothermic patient. Hypothermic patients showed no improvement in survival (RR: 1.01; 95% CI: 0.92-1.11) or neurological outcome (RR: 1.0; 95% CI: 0.90-1.11) in comparison to the control group. All of these results increase the possibility that TTM does not enhance the survival potential of the patients, nor does it improve the neurological outcome. On the basis of the abovementioned, Granfeldt and colleagues advised to remove the TTM from the international guideline of post-resuscitation care, which is currently being reviewed.

In case of sudden cardiac arrest caused by Acute Coronary Syndrome (ACS), it is recommended to start primary coronary intervention (PCI) immediately based on the 2021 Resuscitation Guideline.

Kahn et al. had already discovered that early PCI performed on patients who had suffered SCD due to STEMI could help survival with a good neurological outcome. Examining 35 and 190 patients respectively, Nanjaya et al. and Bro-Jeppesen et al. contrasted patients who underwent and others who did not undergo immediate angiography and PCI in hospital, after out-of-hospital sudden death. Both studies showed that early PCI had no significant favourable impact on mortality. On the contrary, Strote et al. discovered by retrospectively analysing the data of 270 patients who had suffered sudden cardiac death that acute PCI (provided that carried out within 6 hours after the emergence of symptoms) ensured significantly better survival than PCI performed beyond 6 hours.

4.4. Drug therapy during resuscitation

In international recommendations, treatment of VF and pVT comprises the administration of epinephrine and amiodarone. In the case of cardiac arrest, the mechanism of action of epinephrine is the consequence to α -adrenergic effect, which increases myocardial blood supply by directing systemic blood flow towards the heart, consequently ensuring the minimum coronary perfusion pressure (CPP) necessary for successful defibrillation. Beyond its

undeniably positive effect in regard to cardiac arrest, its detrimental β adrenergic activity can be assumed as well. By the deterioration of systemic oxygen demand and the increase in myocardial oxygen consumption, it may further aggravate the lack of balance between oxygen supply and demand, that is particularly important in the case of ventricular fibrillation. To eliminate this adverse effect, trials are being conducted under standard resuscitation with the beta-blocker esmolol in RVF. Successful cases have been reported with this agent, but due to the limited number of cases, recommendations in this regard are not yet available.

In a study published in 2007, Bourque et al. summarised the results on the application of β -adrenoceptor antagonists. They presented the findings of animal tests carried out between 1966 and 2006, in the case of which more positive effects – in comparison with epinephrine – of β -adrenoceptor antagonists on myocardial oxygen demand were discovered among others.

Two randomised trials of adrenaline efficacy were performed in 2011 and 2018 for out-of-hospital resuscitations, PACA (n = 534) and PARAMEDIC2 (n = 8014). On the basis of data from a total of 8548 patients, adrenaline was found to significantly increase ROSC (36% vs. 12%) and to have a moderately better survival rate until hospital discharge (3.2% vs. 2%). 4%). The effect of adrenaline was more positive with regard to neurological outcome (2.2% vs. 1.9%) as well, although insignificantly during the first three months. The rate of ROSC was also higher in cases when adrenaline was given in the first phase of care, according to the findings.

According to the recommendations, the other drug recommended to use is amiodarone. Amiodarone is an iodinated benzofuran, which was originally developed for the treatment of angina pectoris. Amiodarone prolongs the action potential duration and increases the refractory period of the atrial and ventricular myocardium, the AV-node and the Purkinje system. Amiodarone, a type III antiarrhythmic drug, has the qualities of all the four groups of antiarrhythmic agents-, blocks the activity of sodium and potassium channels, antagonises the functioning of both alpha- and beta-adrenergic receptors and as a mild calcium antagonist, it also has a blocking effect on the sinoatrial node, and the AV nodal tissue. In the case of VF recurring after three defibrillations, the administration of 300 mg and later 150 mg of amiodarone is recommended. The replacement of the earlier recommended lidocaine by amiodarone occurred on the basis of the findings of two major studies, carried out in 1999 and 2002. In 2016, Laina et al. analysed the findings of 1,663 studies which involved amiodarone and discovered that amiodarone considerably increased short-term survival rate (OR=1.42 p=0.015). Findings concerning the long-term effects of amiodarone primarily affecting the neurological outcome are not straightforward, thus promising in comparison to other antiarrhythmic agents. In 2016, the ROC-ALPS study (n=3026) examined the short and long-

term effects of captisol-based formulation of amiodarone and lidocaine in the case of out-of-hospital cardiac arrests. Both had a better short-term effect compared to the placebo, however, the examination has shown no differences concerning long-term outcome, neurological status and admission from hospital.

5. SCIENTIFIC QUESTION

During daily medical practice, I often meet critically ill patients and participate in treating patients with cardiac arrest. In my opinion, saving the life of a patient who is in the state of clinical death is one of the biggest challenges to face.

Dynamically changing international guidelines, a huge number of open questions regarding the pathomechanism, triggering factors of critical conditions all drew my attention to the topic and strengthen my commitment.

As a PhD student, emergency care specialist and oxyologist working at the National Ambulance Service and the Department of Emergency Medicine at the University of Debrecen my attention has focused on the pathomechanism of sudden cardiac death as well as the factors that may influence the outcome of resuscitation.

In my research I intended to identify such causative factors and underlying conditions of cardiac arrest that may have impact on the effectiveness and result of critical care. Recognition of these factors not only establish the possibility to implement preventive approach in the medical care but may also improve the patients' chances for survival and quality of life.

One of the main objectives of my research was to study the potential clinical benefit and risks associated with the use of mechanical compression devices.

During my research and clinical practice, I paid special attention to the causative factors especially the myocardial ischemia, since I treated several patients who suffered myocardial infarction and suddenly developed cardiac arrest due to myocardial hypoxia and required continuous, high quality cardiopulmonary resuscitation even when being taken to hospital.

6. SCIENTIFIC OBJECTIVES

The following questions were addressed in each topic on the impact of risk factors for sudden cardiac death on survival, short- and long-term outcomes and complications in the case of manual and mechanical resuscitation.

6.1. Impact of risk factors for sudden cardiac death on survival in the case of manual and mechanical resuscitation groups

- a.) What is the relationship between cardiovascular risk factors and the outcome of resuscitation?
- b.) To what extent do known cardiovascular risk factors contribute to sudden cardiac death?
- c.) Is there a difference between manual and mechanical resuscitation in terms of spontaneous return of circulation on site?
- d.) Is there a correlation between lay resuscitation and the outcome of resuscitation?
- e.) Is there a significant difference in long-term neurological outcome between patients who have undergone successful resuscitation manually or with mechanical devices?

6.2. In studying percutaneous coronary intervention during continuous resuscitation, I sought to answer the following questions:

- a.) Can coronary intervention be safely performed during resuscitation with a mechanical chest compression device?
- b.) Do mechanical resuscitations cause different types or more severe injuries than manual chest compressions?

7. RESEARCH OF CARDIOVASCULAR RISK FACTORS DIFFERENTLY AFFECTING THE SURVIVAL OF PATIENTS UNDERGOING RESUSCITATION

7.1. Patients and methods

Our study was conducted by the Department of Emergency Medicine, University of Debrecen, Hungary. Retrospectively analysing the period of 01.10.2010-31.12.2013, we processed the data of 287 patients requiring care for sudden, non-traumatic out-of-hospital death. In the framework of our retrospective and randomised study, we evaluated ambulance service case descriptions, Utstein sheets, acute coronary syndrome sheets recorded during treatment and documents outlining previous illnesses from an electronic hospital database (Medsol). In accordance with the resuscitation method (manual vs. performed with an external chest compression device – Lucas-2), patients were divided into two study groups. The prime

endpoint was on-site restoration of spontaneous circulation (ROSC). We analysed the correlations between the time passed before resuscitation, initial heart rate, the efficiency of non-professional resuscitation and the outcome. Our aim was to determine the neurological status of the patients undergone successful resuscitation when discharged from hospital, as along with the influence of risk factors leading to SCD on the outcome of resuscitation. The study protocol was approved by the Ethics Committee of the University of Debrecen (number of ethics approval: 16871-2016/EKU 0364/16). The statistical analysis was carried out with SPSS for Windows version 24.0. (Armonk, NY: IBM Corp., Released 2016). Variables were defined with descriptive statistics (case number, average, median and quartile). In the case of normal distribution, differences between the variables were compared by 2-sample t-tests; in the case of non-normal distribution, they were compared by using Mann-Whitney tests. Where the variances of the parameters examined were significantly different, Welch correction was applied. We established the correlation between the variables by using Spearman rank test. The Odds ratios were calculated with logistic regression. The borderline of significance was $p < 0.05$. In case of Odds ratios 95%, confidence intervals were determined.

7.2. Results of cardiovascular risk factors and the outcome of resuscitation

By reviewing medical history data from patients registered in the study, we aimed to collect well known risk factors for sudden cardiac death.

We analysed the relationship of the outcome of resuscitation with the risk factors.

In one hundred and sixty-seven cases (87%) hypertension was observed (with RR permanently above 140/90 mmHg depending on earlier documentation). In the event of hypertension, resuscitation failed in 104 cases (62%) and was successful in case of 63 occasions (38%). It was observed that hypertension had a significant correlation with the negative outcome of resuscitation ($p=0.018$; $r=0.143$). In accordance with our calculations, the presence of hypertension poses 1.82-fold risk of unsuccessful resuscitation. There was information available on patients' lipid parameters in 149 cases. Fifty-four percent of patients had hypercholesterolaemia (serum cholesterol > 5.2 mmol/L), while no lipid abnormalities were evaluated in forty-six percent of patients. In the case of higher serum cholesterol, resuscitation failed in 37 cases (46%) and was successful in 33 occasions (54%). Taking into consideration our observations, we discovered that there is no significant correlation between hypercholesterolaemia and the outcome of resuscitation ($p=0.379$; $r=0.024$).

We found information on ventricular hypertrophy (LVH) (interventricular septal and/or posterior wall thickness >12 mm) in 174 cases. Out of these 174 cases, in 151 cases (87%) LVH was present, while in the case of the remaining 23 subjects (13%) this information was not proved. In the event of existing LVH, resuscitation failed in 109 cases (72%). At the same time, it resulted in ROSC in 42 occasions (28%). We found a significant correlation between left ventricular hypertrophy and the unsuccessful resuscitation ($p=0.0009$; $r=0.1995$). Importantly, depending on our calculations, the presence of LVH poses 5.1-fold risk of failed resuscitation. In 193 cases data on body mass index (BMI) were disclosed. In 78 cases (40%) obesity (BMI >25) was observed, while in 115 cases (60%) no pathological overweight was detected. In the event of obesity, circulation did not return in the case of 44 patients (56%), while regarding 34 subjects (44%) resuscitation was successful. Accordingly, no significant correlation could be settled between body weight and the outcome of resuscitation ($p=0.2766$; $r=0.043$).

In 211 cases, information on any previous myocardial infarction was found. In 56 cases (26.5%), previous heart attacks were confirmed. Although, in the case of 155 patients (73.5%) there were no information indicating any earlier myocardial infarction. Regarding post-infarction patients, resuscitation was unsuccessful in 35 (62.5%), and successful in 21 cases (37.5%). Along these lines, no significant correlation was discovered between previous myocardial infarction and the outcome of resuscitation ($p=0.4579$; $r=0.007$).

Sixty-six patients had documented diabetes mellitus (36%), while in 118 cases (64%) there were no recorded data indicating the abovementioned condition. Consequently, no significant correlation has been observed between diabetes mellitus and the success of resuscitation.

Out of 192 patients, there was information on earlier treatment for stroke in 13 cases (7%). Regarding the patients treated for stroke, resuscitation failed in 8 cases (61.5%), while spontaneous circulation returned in the case of five patients (38.5%). Therefore, no significant correlation could be found between earlier stroke and the outcome of resuscitation ($p=0.4399$; $r=0.0104$).

In ninety-three cases, it was recorded that the patients took anticoagulants. Cardiopulmonary resuscitation (CPR) was successful in the case of 45 patients and failed in 48 subjects. On the basis of the abovementioned data, no significant correlation between anticoagulant therapy and successful ROSC could be established ($p=0.8798$; $r=0.0176$).

7.3. Presentation of results in resuscitation groups with manual chest compression and mechanical compression device

In 55 cases, resuscitation was performed using a LUCAS-2 device (19%), while traditional manual chest compression was performed in 232 cases (81%). One hundred and seven cases of resuscitation (37%) appeared to be successful (on-site ROSC, sustained circulation, admission to hospital). Out of the 55 cases of care carried out with the assistance of a mechanical device 26 (46%) were successful. At the same time, spontaneous circulation returned in 83 cases out of 232 (36%) in the manual group. With respect to the patients with successful resuscitation, in 26 cases (23%) a Lucas-2 device was used, while emergency care was performed manually in 83 cases (77%). Despite of the fact that no significant difference was observed between the two groups in relation to a successful outcome, a non-significant tendency implying the efficiency of the Lucas device was observable ($p=0.072$). The mean age of the successfully resuscitated group was 64 ± 13 years, whilst it was significantly higher (65 ± 13 years) in the case of the deceased. This means that a significant positive correlation was confirmed regarding advanced age and unsuccessful resuscitation ($p<0.017$; $r= 0.1246$).

In the case of both men and women, 39% of resuscitations ended with the ROSC. In 72 cases, we managed to acquire information on the length of time elapsed before the resuscitation was started and the time elapsed until the ROSC happened. ROSC returned within 1-15 minutes in 31 cases (43%), out of which the return happened by using a Lucas-device 4 cases (13%), and by manual resuscitation in 27 cases (87%). In the case of 21 subjects (29%), ROSC occurred within 16-30 minutes, with a ratio of 12 manual resuscitations to 9 resuscitations carried out with the assistance of LUCAS (57% and 43% respectively). In the case of eight patients (11%), ROSC was observed within 31-45 minutes, in 5 cases (71%) in the Lucas-2 group and in 3 cases (29%) in the manual group. In six cases (8%) spontaneous circulation returned in 46 – 60 minutes, in 3 cases in both categories (50%-50%). Lastly, with respect to 6 patients (8%), spontaneous circulation returned after resuscitation lasting for more than an hour, in 2 cases (40%) using Lucas-2 and in 4 occasions (60%) during CPR performed manually. Regarding the Lucas group, there was a higher rate of success even in the event of prolonged resuscitation ($p < 0.05$).

Correlation between the first rhythm documented and the success of resuscitation were also analysed. Registration of the first rhythm was available in the case of 127 patients: in 42 cases (33%) asystole, in 52 cases (41%) ventricular fibrillation, in 5 cases (4%) ventricular tachycardia, in 21 cases (16.5%) pulseless electrical activity (PEA) and in 7 cases (5.5%) other

rhythms were defined. With respect to asystole, resuscitation turned out to be successful in 14 cases (33%), 3 of which (21%) occurred with the use of a Lucas-2 device. Respecting the 52 ventricular fibrillation cases, spontaneous circulation returned in the case of 47 subjects (90%), 14 of which (30%) happened by using a mechanical device. In the 21 cases of PEA, emergency care was successful on 13 occasions (62%). In the event of the initial asystole, resuscitation was substantially more effective when using a Lucas device.

Moreover, we desired to observe the percentage of successful resuscitations performed by non-professional providers. We found the documentation of eighty cases which described non-professional resuscitation; on 34 occasions (42.5%) resuscitation was started by an untrained individual, whilst in 46 cases (57.5%) initial care was provided by the ambulance service. Neurological status of patients (based on Cerebral Performance Category - CPC criteria) at the time of release from hospital was also analysed. There was information available on the neurological status of 70 manually resuscitated patients. In twenty cases (28.5%) we awarded 1 score on the CPC scale, in 5 cases (7%) 3 scores, in 4 cases (6%) 4 scores and in 41 cases (58.5%) 5 scores to the neurological status of the patient. We found information in the database on the neurological status of twenty-one patients successfully resuscitated using a Lucas-2 device. In two cases (9.5%) we awarded 1 score to the patients' neurological status, in the case of 1 patient (5%) 4 scores were awarded, and in 18 cases (85.5%) 5 scores were awarded. With regards to the neurological end status, we established two categories: patients in the categories CPC 1-2 scores were classified as "good" and patients with CPC 3-4-5 scores were classified as "bad". In the event of successful resuscitations, neurological end status was better in the case of manually resuscitated group ($p < 0.05$). In one case where resuscitation was performed with a chest compression device, we found a remark about a chest injury in the pathological findings. There was a total of 175 times where it was possible to accurately identify the pathophysiological process led to the sudden cardiac arrest. Thirty-four (19.42%) cases of acute myocardial infarction, 84 cases (48%) of heart failure, 1 case (0.57%) of bronchopneumonia, 14 cases (8%) of respiratory failure, hypoglycaemia in 1 case (0.57%), epileptic seizures in 1 patient (0.57%), cardiogenic shock in 1 case (0.57%), hemorrhagic shock in 4 cases (1.71%), cardiac tamponade and pulmonary embolism in 13 cases (7.42%), primary ventricular fibrillation in 8 cases (4.57%) and ventricular tachycardia in 3 cases (1.71%).

8. CARDIOPULMONARY RESUSCITATION WITH MECHANICAL CHEST COMPRESSION DEVICE DURING PERCUTANEOUS CORONARY INTERVENTION. A CASE REPORT.

8.1. Clinical characteristics of the patient in the study

Sudden cardiac death appears to be the leading cause of death worldwide and myocardial infarction is considered the most frequent underlying condition. Considering that myocardial infarction is the most frequent cause of sudden cardiac death, primary coronary intervention became a core element of the post-resuscitation care in the ERC Guidelines 2015.

Given the contradictory viewpoints on the compression devices, our aim was to represent our results through a middle-aged female patient who suffered sudden cardiac death due to myocardial ischemia, was given mechanical chest compressions as a part of her emergency treatment, and the continuous mechanical circulatory support was maintained until the completion of coronary intervention. Our female patient's exam reports and other relevant documents such as case report from the National Ambulance Service of Hungary, along with the medical documents recorded in the "MedSolution" medical recording system to be used at the University of Debrecen, were collected and then analysed retrospectively. Findings and results were evaluated comprehensively with special regard to the return of spontaneous circulation, long-term survival, neurological outcome and cardiovascular status, and the data collected were contrasted to the information published in the international medical literature. Aiming to compare conventional manual CPR with CPR including mechanical chest compression devices, we presented the odds ratios and associated 95% confidence intervals which could be found in the relevant medical literature.

On 25th November, 2013 an ambulance of a city with own ambulance station, located 18 km away from the Eastern-Hungarian Debrecen, was dispatched to a 44-year-old woman. As reported by the call received at 9:50 a.m., the patient had no spontaneous breathing. It took the ambulance crew 5 minutes from the call to arrive at the scene. The patient seemed unconscious lying on the ground in front of the front door. Outdoor temperature was about 4 degree Celsius (39.2 Fahrenheit). According to the family's report, the patient had no other known diseases than hypertension which was treated with medications.

8.2. Circumstances of sudden cardiac arrest, primary assessment and care

In the morning on the day of the call, the patient complained of chest pain and numbness of her left arm and then suddenly lost her consciousness. Bystander CPR was not attempted, her relatives did not even check her vital signs. After the arrival of the ambulance crew at the scene, primary assessment was started in the course of which the patient showed no signs of life, her pupils were dilated and non-reactive to light. The ambulance crew started performing manual chest compressions immediately (9:56 a.m.) and assessed the heart rhythm. The initial rhythm analysis showed ventricular fibrillation, thus they attempted defibrillation using energy level of 200 J (9:58 a.m.) and continued the resuscitation by strictly adhering to the Adult Life Support cardiac arrest algorithm. At 10:05 a.m., the ambulance crew applied the LUCAS-2 mechanical chest compression device using it in a continuous mode. Considering that the patient was already intubated at that time, ventilation and compression ratio of 30:2 did not need to be maintained, ventilations could be provided without interrupting the chest compressions. Notwithstanding a total of 5 shocks (200-360-360 J), the VF still persisted. However, after the fifth shock, the rhythm changed to P-wave asystole. According to the ALS algorithm, a total of 8 mg of epinephrine (first epinephrine was administered at 10:04 a.m.) and 450 mg (300 mg + 150 mg) of amiodarone were given during the CPR via a peripheral venous catheter (16 G). Taking into consideration the patient's initial complaints told by the family members, acute coronary syndrome was suspected as the underlying condition. Consequently, following 25 minutes of CPR, the team leader contacted the University of Debrecen Institute of Cardiology by phone, where the patient was accepted for admission (10:24 a.m.). When the ambulance left the scene, the CPR including mechanical chest compressions was carried out for 50 minutes. It took approximately 15 minutes for the ambulance to reach the hospital which was located 20 km away. During the transport, the patient received 500 ml of crystalloid solution and 2 g of magnesium sulfate, furthermore 250 mg of dobutamine (3.6 µg/kg/h) and 100 mg of dopamine (8.2 µg/kg/h) were administered in a continuous infusion due to persistent arterial hypotension (60/40 mmHg).

8.3. Primary coronary intervention

The patient was handed over at the hemodynamic laboratory at 11:30 a.m. A catheter was introduced through the right femoral artery and coronary angiography was performed with ongoing mechanical chest compressions due to the lack of spontaneous circulation. The

intervention revealed an 80% stenosis in the middle segment of the left anterior descending artery (LAD) and a distal occlusion of the dominant right coronary artery. Coronary angioplasty was performed on both arteries with stent implantation. Return of spontaneous circulation was achieved after the intervention. The ECG showed a complete atrioventricular block. As a result, intracavitary pacing wire is inserted into the right ventricle through right femoral artery approach which paced the heart effectively resulting in a maintainable spontaneous circulation. The mechanical chest compressions could be discontinued. Total duration of the CPR with mechanical chest compressions was 2 hours and 35 minutes. The patient was still at the hemodynamic laboratory when atrial fibrillation and systolic heart failure developed, since after the angioplasty intra-aortic balloon pump (IABP, ARROW) was inserted and she was moved to the intensive care unit (ICU) with continuous circulatory support.

8.4. Intensive care

At the ICU, targeted temperature management (TTM) was initiated (the core temperature was reduced to 33 °C); in an effort to treat persistent arterial hypotension (BP: 90/70 mmHg), continuous infusion of norepinephrine (60 µg with a rate of 10ml/h) and dobutamine (250 mg with a rate of 6 ml/h) was started. Echocardiography performed at 2:35 p.m. disclosed inferobasal akinesis. At the same time, the remainder of the left ventricle seemed hyperkinetic. The left ventricular ejection fraction was determined to be 60%. No pericardial fluid was detected. No fracture or pulmonary infiltrate were found on the chest x-ray. 3 days later, the catecholamine therapy for circulatory support could be terminated and the IABP was removed. Four days after the first echocardiography, as the pacemaker wire was removed, progressive heart failure appeared requiring another echocardiography which showed circumferential intrapericardial hematoma with a width of 20 mm. The hematoma resulted in cardiac tamponade necessitating urgent surgical repair (600 ml defibrinated blood drained and a hematoma was evacuated, the puncture site recognized at the apical aspect of the right ventricle was then closed with 4-0 prolene suture and 2 silicone tube were left in the pericardial sac). The intervention lasted 30 minutes and lead to a quick improvement in the patients' hemodynamic state, aftereffects of the cardiac tamponade were not detected. On hospital day 4, head CT was performed due to delayed awakening from narcosis. CT head scan showed cerebral edema and a hypodense area in the parasagittal lane within the cerebral hemisphere corresponding to a recent vascular lesion. No signs of midline shift were observed; however, a small amount of blood was detected along the tentorium. As a consequence the risk for imminent herniation

caused by the subarachnoid haemorrhage, the patient was given dehydration with mannitol infusion (100 mg q.i.d. for 7 days). Regardless of hemorrhagic cerebral lesions – taking into account the intracoronary stents– the platelet aggregation inhibitor along with heparin therapy (100 mg of acetylsalicylic acid and 150 mg of clopidogrel/day, sodium heparin 500-950 U/h) proceeded. Aiming to prevent of vasospasm, the neurologist suggested the calcium channel blocker nimodipine as well as abundant hydration, additionally, raised the possibility of bilateral hemispheric dysfunction in the background of altered level of consciousness (coma). As a result of the aforementioned treatment, a slow improvement was observed in the patient's neurological status. On hospital day 7, the patient was successfully extubated and she was capable of following simple commands. On 3rd December, 2013, follow-up CT scan disclosed a hypodense lesion of 4 cm in the area of trigonum. In the parieto-occipital region, a hypodense band was found in the parasagittal plane within the territory of the posterior cerebral artery (PCA). The latter was considered to be an ischemic lesion within the territory of PCA. Some blood density was also recognised along the tentorium. Signs referring to cerebral aneurysm were not found. In comparison to the previous scan, no significant change was disclosed. Neurological consultation was carried out on the same day and found right-sided homonymous hemianopsia, mild right-sided central facial paresis, mild dysphonia, hypotonic limbs and moderate paresis in the proximal muscles of upper extremities. The patient was alert but disoriented in time and place. With the intention of controlling her agitation, she received meprobamate tablets regularly (200 mg in the morning and at noon, 400 mg at night). The dehydration was terminated; she subsequently received 6 g of piracetam daily and 30 mg nimodipine six times a day. Transthoracic echocardiography, performed again on the eighth day of admission, disclosed inferobasal akinesis, whilst the remainder of the left ventricle seemed hyperkinetic. Multiple echocardiographic examinations, which were performed during the hospital course, did not find any significant reduction either in the ejection fraction (determined by Simpson's rule) representing the left ventricular systolic function or in the tricuspid annular plane systolic excursion (TAPSE) describing the right ventricular systolic capacity.

As a result of of temporary febrile state and elevated inflammatory markers (CRP: 152 mg/L, WBC:8,41 G/L) antibiotic (1.2 g of intravenous amoxicillin + clavulanic acid t.i.d.) treatment was also provided from the second day of admission. In view of anemia developed (Hgb dropped from 100 to 86 g/l), the patient was given a total of 5 units B+ RBC transfusion. Gastrointestinal bleeding could not be proven to be the root of the cause, the pericardial and intracranial bleedings were considered responsible for the decrease in hemoglobin levels. The

patient was given 40 mg of intravenous pantoprazole twice a day and 1 g of oral sucralfate three times a day for gastric protection, from the start of the treatment. Mobilisation was implemented successfully and residual symptoms were no longer detectable. As the quality of life of the patients surviving sudden cardiac death is significantly affected by the neurological outcome, our analysis was broadened to cover the results of Cerebral Performance Category scale that is commonly used for assessing the neurological outcome.

8.5. Events after hospital discharge, patient follow-up

Abnormalities disclosed in her lab tests returned to normal levels, thus the patient was discharged home in a good general state of health, after 16 days of inpatient care. She was advised to quit smoking, come to follow-ups regularly and take her medicines (100 mg of acetyl salicylic acid, 75 mg of clopidogrel, 5 mg of bisoprolol, 5 mg of perindopril b.i.d., 10 mg of rosuvastatin, 10 mg of amlodipine and 40 mg of pantoprazole) as prescribed.

Our patients' first follow-up examination occurred one year after being discharged when she complained about a half-year history of atypical chest pain. During echocardiography a I-II degree tricuspid insufficiency was recognised, the left ventricular ejection fraction was 60% and the wall motion abnormality was no longer observable. No atrial fibrillation or other arrhythmia were discovered. Taking into consideration her complaints and past medical history, exercise tolerance test was made. As a result of the exercise, the patient's resting ST depressions became more significant. Re-coronarography, performed on the basis of complaints and positive exercise tolerance test, visualised patent coronary stents and a 75-80% stenosis in the middle right coronary artery. Therefore, angioplasty was performed and a coronary stent (3.5×12 mm REBEL™ stent, inflation pressure: 16 atm) is placed without any complications. Repeated cardiological examination was carried out 2 years later, in January, 2016, when she presented with chest pain and shortness of breath on exertion. However, echocardiography did not show any progression in comparison to the preceding findings, it found an apical and inferobasal wall motion abnormality as well as preserved left ventricular function. Re-coronarography identified a 70% stenosis in the origin of the LAD, however, angioplasty was not performed by reason of an elective gynecological operation. After a coronary angioplasty, dual antiplatelet therapy which carries a greater surgical bleeding risk would have been necessary. Finally, the gynecological operation was performed without any complication, and the coronarography was repeated on 17th June, 2016. The stenosis, which was limited to the

origin of the LAD, did not show any progression, and coronary intervention was therefore not performed.

9. DISCUSSION

9.1. Factors influencing the outcome of resuscitation

The prognosis and long-term outcome of resuscitated patients who survived aborted cardiac death are significantly influenced by comorbidities (ischemic heart disease, hypertension), the extent of potential left ventricular hypertrophy and the mechanism of ventricular arrhythmogenesis. Koldobskiy et al. discovered that kidney failure, immunosuppression and obesity had a negative impact on the outcome of resuscitation. Herlitz et al. analysed the data of 33,453 patients and ascertained that initial rhythm, lay resuscitation and the age of the patient had a certainly significant impact on the outcome of CPR. Frequently, the first and only 'symptom' of myocardial infarction is sudden cardiac death, and SCD appeared to be the reason of the death of almost half of the coronary patients and for roughly 325,000 deaths per year in the United States. Recently, cardiological rehabilitation, favourable influence on the lipid profile and favourable medication along with the management of comorbidities have significantly improved long-term prognosis in the case of SCD with ACS in the background. Refractory VF, which is a relatively uncommon morbidity factor, involves clearly poor outcome. Along with the circumstances influencing long-term prognosis, neurological outcome is the most important for the characterisation of which the CPC (Cerebral Performance Category) scale is the most widespread approach. In our present study, our purpose was to examine the outcome of manual and mechanical device-assisted resuscitation in patients suffering sudden cardiac arrest out of hospital, in addition to the effects of the risk factors leading to sudden cardiac arrest on survival. Derived from the results of our study, heart failure, acute myocardial infarction, pulmonary embolism, and respiratory failure meant the greatest risks in inducing sudden cardiac death in the group of patients under our study.

Advanced age, left ventricular hypertrophy, and hypertension have been discovered to be the most adversely influencing substrates of resuscitation. The initial rhythm detected on the scene also had an impact on the outcome of resuscitation (in case of PEA CPR was unsuccessful more than 30% of cases and the presence of ventricular fibrillation meant a higher chance for return of circulation).

On the basis of our significant observation, left ventricular hypertrophy poses 5.1-fold risk, and, at the same time, the presence of hypertension indicates 1.82-fold risk of unsuccessful resuscitation. Despite of the fact that there was no significant correlation between increased body weight and the outcome of resuscitation, our data indicate that pathogenic factors playing a role in the thickening of the left ventricular wall, including obesity, may indirectly be important underlying factors regarding survival. Interestingly, previous stroke and myocardial infarction did not result in a decrease in the likelihood of success in the population we examined. The estimation of risk factors involved in the development of sudden cardiac death and increasing its chances have been the subject of plenty of researches. The Framingham Heart Study which began in 1948 and is still ongoing today, focuses on this issue. Derived from multiple evaluations of the results compared, it came to light that hypertension, elevated serum cholesterol, left ventricular hypertrophy, obesity, diabetes, smoking, age, and sex contribute to the increased risk of sudden cardiac death. An animal study conducted by Wang et al. in 2016, contrasted the effects of the two most common risk factors, hypertension and left ventricular hypertrophy on resuscitation success, and disclosed no significant differences between hypertension, LVH, and ROSC ($p < 0,001$). The treatment was started by the ambulance service in more than 57% of the cases. Unfortunately, there was no non-professional resuscitation or first aid available in these specific cases. Accordingly, as for the majority of our patients, we can come to the conclusion that a hypoxic and/or anoxic period may have been a considerable risk factor and may have had an essential impact on the outcome of resuscitation. This might be the explanation for the unfavourable trend recognised in the neurological status of the resuscitated. The disappointingly low number of non-professional resuscitations emphasises the importance of teaching basic life support (BLS) and widespread awareness raising about the chance enhancing potential of early care. We highlight that the frequency of traumatic injuries in the course of CPR using mechanical compression devices was not higher in comparison to manual resuscitation, showing the clinical applicability of this method. Importantly, mechanical resuscitation did not lead to a worse outcome compared to the manual method, although chest compression had to be temporarily interrupted while the compression device was placed on the patient.

9.2. Resuscitation carried out by manual and mechanical chest compression device

Sudden cardiac death seems to mean a huge challenge for the health care system, and especially for the emergency medicine profession. Its importance is not only the bad prognostic, but also

the fact that it can affect any people of all ages, it can happen suddenly, without any previous, preliminary sign. Over the last two decades, cardiovascular mortality rates have decreased as a consequence of preventive measures. Nevertheless, cardiovascular diseases continue to take the lives of 17 million people a year all over the world, 25% of which are caused by SCD. Mortality depends on the underlying disease and the causes of sudden cardiac death as well. In preceding examinations, successful resuscitation has seem to fall significantly in the case of confirmation of asystole by an initial heart rhythm analysis. On such occasions, only 10% of patients have been successfully stabilised on the spot moreover up to 2% survived hospital treatment. It has also been verified as a warning sign for the prognosis when the cardiac arrest happened because of pulseless electrical activity (PEA). The key to the improvement of survival is the properly performed cardiopulmonary resuscitation (CPR) described by continuous, high-quality chest compressions and minimised interruptions. Manual chest compressions are known to degrade in quality after a few minutes; accordingly, the quality of resuscitation deteriorates continuously. It was confirmed in previous human and animal studies that the maintenance of continuous coronary perfusion pressure (CPP) during the resuscitation seemed to be an essential condition for the ROSC. In 1990, Paradis et al. showed that the ROSC was achieved only in the case of patients with CPPs of 15 mmHg or more. Moreover, it was also verified that perfusion was determined by the quality of chest compressions. In the course of adult CPR, chest compressions are considered effective when they are performed continuously (without interruptions exceeding 10 seconds) at a rate of 100–120 per minute, with a depth range of 5–6 cm, allowing full recoil of the chest after each compression. It is well known that the maintenance of quality chest compressions are increasingly difficult as time passes. The reason is that providers become fatigued early on and as a result, the compression depth decreases and full recoil is no longer assured, preventing venous return to the heart. Furthermore, during manual compressions, the interruptions between chest compressions become longer, which may decrease myocardial perfusion even in a couple of seconds, leading to lower chances of survival. The provision of continuous high-quality manual chest compressions seemed almost impossible and, before the appearance of mechanical devices, meant a great challenge to prehospital emergency care providers. Lately, the most widespread mechanical compression devices are the LUCAS-2, the LUCAS-3 and the AutoPulse. All of them are capable of providing superior, uninterrupted and hands-free chest compressions, and enable for the providers to perform further necessary interventions. In 2010, animal studies conducted by Liao et al. demonstrated that the coronary and cerebral perfusion pressure was significantly higher in the group resuscitated with the LUCAS mechanical device than in the manual control group.

In accordance with the abovementioned results, the mean coronary perfusion pressure in the case of the LUCAS-CPR was 20 mmHg and the cerebral perfusion pressure was 65 mmHg, contrasted with the manual group, in which they measured 17 and 40 mmHg, respectively. Despite these observations, relevant studies, such as the CIRC (Wik 2014), PARAMEDIC (Perkins 2015), LINC trials (Rubertsson 2014) and the large clinical study conducted by Hallstrom et al. did not discover differences between these two approaches, neither regarding the short-term outcome nor the 30-day survival. The neurological status of patients discharged from hospital was also analysed, however, there was no obvious benefit regarding mechanical devices revealed. In 2016, Bonnes et al. carried out a meta-analysis of multiple previous studies. They examined 20 studies involving a total of 21,363 patients. The mechanical group involved 9,391 patients, while 11,972 patients were in the manual group. Survival to hospital admission was the primary endpoint of the meta-analysis. Regarding the primary endpoint, there was no difference between the four randomised-controlled trials; however, on the basis of twelve non-randomised studies (n=7,751), the survival rate was significantly higher in the mechanical group (OR: 1.42, 95% CI: 1.21–1.67; p<0.001). The secondary endpoint of the meta-analysis involved the ROSC, survival to discharge and neurological status. The results of randomised-controlled trials did not disclose any significant differences considering the ROSC (OR: 1.03; 95% CI: 0.93–1.14). At the same time, the outcomes of non-randomised trials indicated a significant benefit in the mechanical group (OR: 1.74; 95% CI: 1.23–2.45; p=0.002). In a meta-analysis performed in 2018, Wang et al. evaluated the results of 11,771 patients in view of the ROSC. Among 8 studies, only 3 (n=300) discovered an advantage of the mechanical device (Dickinson 1998: 14.3% vs. 0%; RR: 4.13, 95% CI: 0.19–88.71; Lu 2010: 55.3% vs. 37.8%; RR: 1.46; 95% CI: 1.02–2.08; Gao 2016: 44.9% vs. 23.4%; RR: 1.92, 95% CI: 1.15–3.21). Furthermore, 4 studies (n=7,240) did not find any significant differences between the groups. On the contrary, in the CIRC trial (n=4,231), published in 2014, Wik et al. found that the use of a mechanical device was associated with lower chances of the ROSC (RR: 0.88; 95% CI: 0.81–0.97); consequently, they opposed mechanical chest compressions. In their studies, Rubertsson and Hallstrom examined the 24-hour survival between manual and mechanical CPR groups and their results did not show any differences (p<0.99 and p=0.62, respectively). Favourable neurologic status upon discharge from the hospital, characterised by CPC scores 1 and 2, meant an important parameter in the studies. In this respect, Wik and Rubertsson did not discover differences, while Hallstrom found less favourable neurological outcome in the mechanical group (p=0.006). On the basis of the aforementioned meta-analyses, it might be settled that no significant difference in the short-term and long-term survival nor in the

neurological outcome has been experienced between the mechanical and manual groups. It should be taken into consideration that the presented data are rated as evidence of only low or moderate quality in accordance with the widely-used GRADE Working Group guidelines.

In the framework of this study we also addressed to examine the type and occurrence of injuries caused by mechanical compression devices. Smekal et al. analysed the data of 222 patients, out of which 83 patients were given conventional manual compressions, while 139 patients were resuscitated with the assistance of a compression device. Regarding the manual group, 53 (64.6%) costal fractures and 45 (54.2%) sternal fractures were registered. At the same time, in the mechanical group, 108 (78.8%) costal fractures and 81 (58.2%) sternal fractures were documented ($p=0.01$ and $p=0.555$). With regard to further injuries, a total of 59 cases of mediastinal and retrosternal hemorrhages were registered in the mechanical group, whilst in the manual group, injuries of this kind occurred in 27 cases. In 2018, Ondruschka et al. carried out a retrospective analysis of forensic autopsy reports of patients who underwent unsuccessful out-of-hospital or intrahospital resuscitation. They examined data from 614 patients with non-traumatic causes of cardiac arrest. 501 patients were involved in the manual group, while the mechanical group comprised 113 patients. No statistically significant difference was recorded regarding the severity of injuries between the two groups ($p=0.09$), and none of the injuries were fatal. Costal and sternal fractures turned out to be the most frequent in both groups. In accordance with their outstanding observation, advanced age and prolonged resuscitation were associated with a higher incidence of costal and sternal injuries ($p<0.001$). In addition, the autopsy reports also highlighted that hemothorax ($p=0.047$), pneumothorax ($p=0.008$), hemopericardium ($p=0.025$), pulmonary ($p=0.008$) and hepatic injuries ($p=0.001$) were remarkably more frequent in resuscitations carried out with the assistance of a mechanical device. On the basis of the abovementioned findings, it may be concluded that costal fractures, which are considered acceptable along with other injuries, are more common during CPR with mechanical devices. Nevertheless, the results of studies are often partial regarding injuries, which should also be taken into consideration, given that the various procedures (e.g., autopsy, CT, ultrasound, X-ray) for evaluating injuries have a significant impact on the results. The patient's age and duration of resuscitation also have a considerable influence on the incidence of injuries. Resuscitations with mechanical devices are commonly take longer time than manual CPRs, thus prolonged resuscitation efforts may also contribute to the higher incidence of complications. Additionally, deviating from the instructions on the application of the device may also lead to higher rates of injuries. As stated by the studies conducted by Hallstrom, Rubertsson and Wik, the time to first defibrillation was typically 1.5 minutes longer in the

mechanical group. They underlined that the application and deployment process of the device may confuse the providers, increasing the risk of injuries and resulting in a less favourable outcome.

There is no clear guideline of usage of external chest compression devices, there are insufficient evidences. The most recent resuscitation guideline dedicates a separate part for the discussion of the usage of mechanical chest compression devices. On the basis of the abovementioned, the Guideline of European Resuscitation Council published in 2021, already recommends that Lucas and Auto-Pulse appear to be suitable during catheter intervention and after thrombolysis, thus complications are more frequent and the impact on survival remains uncertain. On the basis of our data it can be suggested that chest compression devices can provide effective and safe help to emergency care providers, served as a guarantee of patient survival. Further research of the short- and long-term effects of chest compression devices is warranted.

9.3. Cardiopulmonary resuscitation with mechanical chest compression device during percutaneous coronary intervention. A case report.

The most recent resuscitation guideline dedicates a separate part for the discussion of the usage of mechanical chest compression devices. A total of 7,582 patients had been examined in relevant studies. On the basis of these data, the ERC does not recommend the routine out-of-hospital use of mechanical chest compression devices; however, it points out certain circumstances which justify the use of such devices. These circumstances comprise the need for resuscitation during transfer and prolonged resuscitation (e.g., hypothermic patients, during coronary intervention). The latter is particularly important, given that myocardial infarction is regarded as one of the most frequent underlying conditions of sudden cardiac death and can effectively be treated with early coronary intervention. Accordingly, searching for reversible causes (4 Hs and 4 Ts: hypoxia, hypothermia, hyper/hypokalemia, hypovolemia, tension pneumothorax, pericardial tamponade, toxins, thromboembolism) systematically during CPR can reveal the underlying cause, enabling the application of causal therapy for the providers. Once coronary embolism is suspected as an underlying cause, continuous chest compressions performed with the help of a mechanical device may lead to a better outcome and can help in transferring the patient to the nearest PCI centre. Based on the systematic review of the relevant literature, we come to the conclusion that, in the case of our patient, early coronary intervention appeared as the only chance for survival. The LUCAS mechanical device undoubtedly played a crucial role in the survival by delivering high-quality chest compressions during the transfer

and maintaining adequate coronary and cerebral perfusion, which is verified by the ROSC and the favourable neurological outcome. The mechanical device enabled the performance of coronary intervention with ongoing chest compressions, and the success of the intervention warranted the ROSC and, eventually, the survival of the patient. The maintenance of stable coronary perfusion with mechanical compressions was well-represented by the multiple echocardiographic examinations, which found preserved left ventricular function. Furthermore, the function of the right ventricle, which was predominantly affected by the ischemic insult, did not show signs of a significant decrease either. Our working group did not observe injuries attributable to the mechanical device. Contrasted with the results of preceding studies, our results were more positive regarding the long-term survival and neurological outcome. Based on our experience, when strictly adhering to professional guidelines, mechanical chest compression is considered a safe treatment modality. Results of our and other working groups suggest a need for utilizing further opportunities offered by mechanical compression devices. In order to increase the knowledge on the use of mechanical chest compression devices, further studies are desired.

The demonstrated case can be used as an example for the effective and safe use of a mechanical compression device. On the basis of our outcomes, it can be stated that identifying reversible causes of cardiac arrest is crucial for causal therapy. Our case demonstrates that coronary intervention ensuring the patient's survival can safely be carried out while resuscitation with a mechanical compression device as well. Due to contradictory information in the recent relevant literature, further studies are required to assess the safety and effectiveness of mechanical compression devices.

10. SUMMARY

1. The successful outcome of cardiopulmonary resuscitation is adversely affected by advanced age, hypertension and the presence of left ventricular hypertrophy.
2. In accordance with our results, the presence of left ventricular hypertrophy decreases the risk of successful resuscitation by the factor of 4.8. In accordance with our calculations, the presence of hypertension poses 1.82-fold risk of unsuccessful resuscitation.
3. Obesity does not show a significant association with the outcome of resuscitation, although our results suggest that pathogenic factors involved in left ventricular wall thickening, such as obesity, may be indirect pathogenetic factors regarding survival.

4. On the basis of our examinations, percutaneous coronary intervention can be safely carried out during chest compressions by mechanical chest compression device. Mechanical chest compression device can be used effectively and safely during cardiopulmonary resuscitation with the strict following of professional rules.

11. KEYWORDS

sudden cardiac arrest, cardiopulmonary resuscitation, mechanical chest compression, arrhythmia, ischemic heart disease, risk factors



Registry number: DEENK/113/2022.PL
Subject: PhD Publication List

Candidate: Dóra Ujvárosy
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Ujvárosy, D.**, Borbásné Sebestyén, V., Ötvös, T., Ratku, B., Lőrincz, I., Szűk, T., Csanádi, Z., Berényi, E., Szabó, Z.: Cardiopulmonary Resuscitation With Mechanical Chest Compression Device During Percutaneous Coronary Intervention: a case report.
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IF: 6.05 (2020)
2. **Ujvárosy, D.**, Borbásné Sebestyén, V., Pataki, T., Ötvös, T., Lőrincz, I., Paragh, G., Szabó, Z.: Cardiovascular risk factors differently affect the survival of patients undergoing manual or mechanical resuscitation.
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List of other publications

3. Borbásné Sebestyén, V., Szűcs, G., Páll, D., **Ujvárosy, D.**, Ötvös, T., Csige, I., Pataki, T., Lőrincz, I., Szabó, Z.: Electrocardiographic markers for the prediction of ventricular arrhythmias in patients with systemic sclerosis.
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Orv. Hetil. 153 (50), 1967-1983, 2012.
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