Robert Pasold, BSc

Development of a waveform to reduce the energy consumption of the electrical signal for automated external defibrillation

MASTER'S THESIS

to achieve the university degree of

Diplom-Ingenieur

Master's degree programme: Biomedical Engineering

submitted to

Graz University of Technology

Supervisor

Ass.Prof. Dipl.-Ing. Dr.techn., Theresa Margarethe Rienmüller

Institute of Health Care Engineering

Graz, October 2019

EIDESSTATTLICHE ERKLÄRUNG

AFFIDAVIT

Ich erkläre an Eides statt, dass ich die vorliegende Arbeit selbstständig verfasst, andere als die angegebenen Quellen/Hilfsmittel nicht benutzt, und die den benutzten Quellen wörtlich und inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. Das in TUGRAZonline hochgeladene Textdokument ist mit der vorliegenden Masterarbeit/Diplomarbeit/Dissertation identisch.

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly indicated all material which has been quoted either literally or by content from the sources used. The text document uploaded to TUGRAZonline is identical to the present master‘s thesis/diploma thesis/doctoral dissertation.

18.10.2019

Datum / Date

Unterschrift / Signature

Acknowledgement

This work started as a cooperation-project between the institute of Health Care Engineering of the university of technology Graz and a start-up company called "Liimtec". In the course of working on development of a project called “Pocketdefi“ under the control of Jasper Ettema, I was required to dive into this very interesting topic. I´m very grateful, that I was included in his very enthusiastic and motivated team, working hard on a very good idea to save life.
Thanks to him and his entire team and special thanks to Jürgen Rack, an idea-spreading, young engineer, as I have never seen someone more committed than him. Thank you Jürgen for your support.

A sincere thanks to the very good collaboration with Univ.-Prof. Dipl.-Ing. Dr.techn. Christian Baumgartner, Assoc.Prof. Dipl.-Ing. Dr.techn. Jörg Schröttner and special thanks to my direct supervisor Ass.Prof. Dipl.-Ing. Dr.techn. Theresa Rienmüller for her advices and warmly support.

I feel indebted to thank also the Author Max E. Valentinuzzi for his book “Cardiac Fibrillation – Defibrillation”. This book is outstanding in explaining the complexity of this topic.

My final acknowledgements I want to address to my family, which gave me so much support and strength. Words can not express how much I love them.

Graz, 18.10.2019

Robert Pasold

KURZFASSUNG / ABSTRACT

Titel: Entwicklung einer Wellenform zur Reduzierung des Energieverbrauchs des elektrischen Signals für die automatische externe Defibrillation

Zusammenfassung: Das Design einer Wellenform steht in einem komplexen Zusammenhang mit vielen technischen und physiologischen Parametern, die in dieser Arbeit erklärt werden sollen. Ein umfassender Überblick zeigt Aspekte auf, die berücksichtigt werden müssen, um eine optimale Wellenform zu entwickeln. Es kann gezeigt werden, dass Zellzeitkonstanten und mittlerer Strom wichtige Referenzwerte für die Anpassung externer Signale sind und sich zur Simulation, Bewertung und zum Vergleich der Wirksamkeit von Wellenformen eignen. Im Gegensatz dazu ist Energie nicht aussagekräftig. Eine zweiphasige Wellenform mit kapazitiver Entladung scheint überlegen zu sein. Optimal angepasst an die Elektrophysiologie lässt sich Wirksamkeit vorhersagen und der Energieverbrauch reduzieren, was einen schnellen Einsatz am Patienten gewährleistet.

Schlüsselwörter: Myocardium; Schock; Effizienz; Zellzeitkonstante; Elektrophysiologie

Title: Development of a waveform to reduce the energy consumption of the electrical signal for automated external defibrillation

Conclusion: The design of a waveform is in a complex relationship with many technical and physiological parameters, this work tries to explain. A comprehensive review shows aspects that have to be considered to develop an optimal waveshape. It can be shown that cell time constants and average current are important references for the adaption of external signals and usable to simulate, evaluate and compare the efficacy of waveforms. In opposite, energy can not be seen appropriate for comparisons. A biphasic, capacitive discharge waveform seems to be the superior to optimize electrophysiologic adaptions. This pattern shows predictive efficacy and reduces the energy consumption to provide mobility for minimized time to treatment.

Key words: Myocardium; Shock; Efficiency; Cell-time-constant; Electrophysiology

TABLE OF CONTENTS

1 INTRODUCTION 9

1.1 General situation of SCAs and the importance of AED-application 9
1.2 Energy - why less is more?? 10
1.3 Waveforms 13
1.3.1 Monophasic waveforms 13
1.3.1.1 Monophasic damped sine waveform (MDS) 14
1.3.1.2 Monophasic truncated exponential waveform (MTE) 14
1.3.2 Biphasic waveforms 15
1.3.2.1 Biphasic truncated exponential (BTE) 16
1.3.2.2 Rectilinear biphasic waveform (RBW or RLB) 17
1.3.2.3 Pulsed biphasic waveform (PBW) 18
1.3.2.4 Lossless constant current pulse (LLCC) 19
1.3.3 Triphasic waveforms 20
1.3.4 Multiphasic waveforms 20
1.4 Normative Aspects 21
1.5 Why AEDs should be more portable 23
1.6 Research question 24
1.7 General traget 25

2 BASIC PROBLEMS 25

2.1 Risk-benefit-principle 25
2.2 Human body as a black box – parameters with influence on defibrillation 26
2.2.1 Internal aspects with influence on defibrillation 28
2.2.2 External aspects with influence on defibrillation 28
2.3 Cellular electrophysiology 30
2.3.1 Layers forming the transthoracic impedance (TTI) 30
2.3.2 Which types of cells are affected 31
2.3.3 How those cells interact 31
2.3.4 Cardiac conducting system 31
2.5.4.1 Sinoatrial (SA) node 32
2.5.4.2 Atrioventricular (AV) node 33
2.5.4.3 His bundle & bundle branches 33
2.5.4.4 Purkinje fibers 33
2.5.4.5 Cardiomyocytes 33
2.5.5 Ion channels 33
2.5.6 Potential creation 34
2.5.6.1 Transmembrane potential (TMP) 34
2.5.6.2 Resting potential 35
2.5.6.3 Threshold potential 35
2.5.6.4 Action potential 36
2.5.7 Conduction of action potential 37
2.5.8 Pathophysiology 37
2.5.9 Electrophysiological aspects with relevance for external discharge 38
2.5.9.1 Time aspects with relevance for defibrillation 39
2.5.9.2 Rheobase and chronaxie 40
2.5.9.3 Membrane potential optimization 41
2.5.9.4 Boundaries of the RC model 42
2.5.10 Electrophysiologic effects of high electric field strength 42

2.4 Waveform efficency comparison 44

3 METHODS 47

3.1 Research – systematic review 47
3.1.1 Manual search 48
3.1.2 Automated search 48
3.1.2.1 Database Selection 48
3.1.2.2 Developing Automated Search 49
3.2 Waveform efficacy determination 50

4 RESULTS 52

4.1 Technical parameters with relevance 52
4.1.1 Impedance 53
4.1.2 Voltage 53
4.1.3 Current 53
4.2 Waveform 55
4.2.1 Waveform – duration 55
4.2.2 Waveform – response of impedance 55
4.2.3 Waveform – phase number and ratio 56
4.2.4 Waveform – shape 56
4.3 Suspected mechanisms 57
4.3.1 Charge banking and charge burping 57
4.3.2 Frequency concentration 57
4.3.3 Stimulus strength and duration 58

5 DISCUSSION 58

6 CONCLUSION 61

7 REFERENCES 62

8 APPENDIX 65

GLOSSARY

AC	Alternating current
APD	Action potential duration (also: refractory period)
ALS	Advanced life support
ACLS	Advanced cardiovascular life support
AED	Automated external defibrillator
AHA	American heart association
ATP	Antitachycardia pacing
AV Block	Atrioventricular Conduction Block
AV node	Atrioventricular node
Biowave	Multiphasic waveform – Schiller patented
BE	Balanced biphasic exponential waveform
BHF	Balanced high frequency chopped biphasic exponential (also PBW)
BLS	Basic life support
BTE	Biphasic truncated exponential
CENELEC	European Committee for Electrotechnical Standardization
CI	Cardiac Index
CI	Confidence interval
CPR	Cardiopulmonary resuscitation.
DC	Direct current
DS	(Monophasic) damped sinusoid waveform (also MDS)
DFT	Defibrillation threshold
ECG	Electrocardiogram
ECPR	Extracorporal CPR
ED 50	Effective dose – 50% probability of defibrillation success
EMS	Emergency medical service
ERP	Effective refractory period
FDA	Food and drug administration
HCN-channel	Hyperpolarization-activated cyclic nucleotide-gated channel
ICD	Implantable cardioverter defibrillator
LLCC	Lossless consatant current pulses
MDD	Medical Device Directive
MDS	Monophasic damped sinusoid waveform
MTE	Monophasic truncated exponential waveform

MI	Myocardial infarction
NSR	Normal sinus rhythm
OHCA	Out-of-hospital cardiac arrest
PAD	Public Access Defibrillator
Pads	Self adhesive electrodes
Paddels	paddled electrodes
PAS	Patient analysis system
PEA	Pulseless electric activity
PBW	Pulsed biphasic waveforms
pVT	pulseless ventricular tachycardia
Q	Phase-ratio (e.g. Q1/Q2)
QRS complex	pattern of the derived electrical activity of the heart
RBW	Rectiliniear biphasic waveform (also RLB)
RCB	Randomized controlled trial
RE	Reserve of efficacy
RLB	Rectiliniear biphasic waveform (also RBW)
RMP	Resting Membrane Potential
RMS	Root mean square
ROC	Residual operating channel (also ligand operating channel)
ROSC	Return of spontaneous circulation
SA node	Sinoatrial node
SAS	Shock Advisory System ™ - Physio Control patented
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SR	Sarcoplasmic reticulum
ST-segement	Segment of QRSsignal drived from ECG
TMP	Transmembrane potential
TTI	Transthoracic impedance
VF	Ventricular fibrillation.
VOC	Voltage operating channel (1^{st} gating mechanism)
VT	Ventricular tachycardia
Z	Figure of merit from Mc Neymar

FORMULAS

$Q_1 / Q_2 = 3$	Recommended waveform phase ratio between phase 1 and phase 2	(1)
$\eta C = W / W_{C0}$	Ratio of energy oft the capacitor W_{C0} utilized	(2)
$1\text{-}e^{-1}$	Voltage drop of capacitive discharge	(3)
$I(\tau) = I_{\mathrm{Rheobase}} \cdot (1 + \frac{\tau_{\mathrm{Chronaxie}}}{\tau})$	Koening equation based on Weiss-Lapique law with I(τ) current depending on the duration of the pulse	(4)
$W = U^2 \times \tau / TTI$	Energy = Voltage² x Duration / Transthoracic impedance	(5)
$I_{RMS} = U_{RMS} / TTI$	Root mean square (RMS) current	(6)
$U_{RMS} = U_{max} \times TTI \times F / (Phase\ 1 + 2) \times (1 - e^{(-F / (TTI \times F))})$	RMS voltage	(7)

SYMBOLS

I_f	funny current [A]
Q	Phaseratio [%]
t	Time since start of discharge [ms]
T	Total refractory time [ms]
V	Conduction speed [m/s]
k_f	Ratio between delivered energy W and a reference energy
W	Energy [VAs or J]
W_{C0}	Capacitor energy [J]
T_{on}	signal activate durance [µs]
T_{off}	signal pause durance [µs]
τ_s	shock system time constant [ms]
τ_m	cell membrane time constant [ms]
T_r	period of time to return from max. transmembrane potential to initial [ms]
V_m	transmembrane potential [mV]
Z	figure of merit

1 INTRODUCTION

1.1 General situation of SCAs and the importance of AED-application

SCA is the abbreviation for sudden cardiac arrest. It describes spontaneous death caused by cardiovascular collapse within one hour after first symptoms. Often the reasons are already existing heart diseases. First symptoms like chest pain can be indicators of cardiac arrhythmias or ventricular tachycardia until persons lose consciousness and have finally cardiac arrest.[1]

Scenarios of SCA are:
- cardiac dysrhythmia
- atrial fibrillation (AF)
- atrial flutter
- ventricular fibrillation (VF)
- pulseless ventricular tachycardia (pVT)

in which the percentage of ventricular tachycardia (VT) causing cardiac arrest is reported to be over 40 %.[2]

The purpose of Basic Life Support (BLS) with Automated External Defibrillators (AEDs) is to analyse, if there is a shockable rhythm like VF or VT and to instruct first responders with recommended steps like activating an electric shock. Non-shockable rhythms are pulseless electrical arrhythmia (PEA) and asystole. In these cases AEDs give instructions for starting cardiopulmonary resuscitation (CPR) with further analyzation-intervals.

Defibrillation or electric countershock is applied in emergency situations of atrial flutter, atrial tachycardia or ventricular tachycardia. It is very important to treat these arrhythmias as fast as possible. Early CPR and performed defibrillation within 3-5 minutes after onset of abnormal heart rhythm can set survival rates to 50-75 %.[3] There

[1] [1]
[2] [2, p. 1273]
[3] [2, p. 1273]

is a big urge to treat fibrillation this fast because survival chances decrease for patients approximately 7-10 % per minute delay of shock application by AED.[4]
The decrease of survival chances can be reduced on 3-4 % per minute if bystander CPR and immediate call of Emergency Medical Service (EMS) is provided.[5]

The European Resuscitation Council (ERC) meets every 5 years to discuss new findings for Basic (BLS) and Advanced Life Support (ALS). In the last published Guidelines from 2015, they address to healthcare providers that treatment of VF and pVT needs efficient coordination between CPR and shock delivery. The physiological background is that a persistent VF of more than a few minutes depletes the myocardium of oxygen and metabolic substrates. Even brief periods of chest compressions provide myocardium-supply again and increase the chance of a successful defibrillation.[6] Time aspects are also underlined. Even a few seconds between chest compression, shock delivery and resuming compressions (Peri-shock-pause) can determine shock success.[7]

1.2 Energy - why less is more??

Norms and guidelines describe limits for specific defibrillation-energy with preinstalled settings for children and adults.[8] The EN 60601-2-4 recommends a range of selectable energy between 360 J[9] and 150 J and a weakening for paediatric use. They define a safe energy dose of 2 J/kg for patients < 10 kg.[10] The ERC Guidelines for resuscitation recommends an energy-dose of 4 J/kg for children up to 8 years or patients being lighter than 25 kg[11] at initial and all other shocks. Furthermore they report that there are successful defibrillations documented with up to 9 J/kg with negligible side effects.[12] An only optionally offered children dose reduction mode provides the emission of 50 to 75 J.[13] Paediatric pads with smaller size should regulate this energy-dose for higher

[4] [2, p. 1273]
[5] [3]
[6] [4, p. 109]
[7] [4, p. 109]
[8] [5, p. 218]
[9] [6, p. 28]
[10] [6, p. 65]
[11] [7, p. 8]
[12] [5, p. 220]
[13] [5, p. 220]

secureness.[14] Those efforts already suggest that high energies are not only a guarantee of successful defibrillation – they are also a risk. In connection with energy there are different waveform patterns. Mainly they can be divided into monophasic, biphasic and multiphasic signals. A second way of classification distinguishes between capacitive discharge waveforms and waveforms created by generators.

An excurse to the historical development shows that traditional high-energy shock sequences of 200-360 J have not been evidence-based on results of randomized clinical trials. Prospective studies supporting the use of this high energy or showing values for step-up energy delivery do not exist.[15] In 1982 Weaver et al. proved that 175 J monophasic damped sine (MDS) waveform defibrillate as good as the 320 J pendant without the negative appearance of AV blocks.[16] Six years later Kerber et al. demonstrated the decline of successful defibrillation rates proportional to increasing peak currents over 41 A for MDS-shocking.[17] The Journal for Cardiovascular Electrophysiology reports already in 1997 that lower energies reduce post shock cardiac dysfunction.[18] As a conclusion, the energy level of a single shock should be kept as low as possible.[19] Revolutionary impact brought the development of an impedance-compensating biphasic waveform. This led to first considerations, if lower energy levels may be more appropriate.[20] Step by step, waveform-design came along with findings about parameters and this knowledge about parameters influenced the waveform-shape again. At every time the area of conflict to terminate arrhythmias but also reduce post shock cardiac dysfunction was present. Electric countershocks should influence a critical mass of myocardium by a sufficient electrical energy to erase all wavefront-activities of VF and provide restoration of spontaneous synchronized electrical activity, creating a rhythmic organized pulse again.[21] Basically the success of conversion is defined by two criteria. Fist, fibrillation is defined as successful after absence of VF for at least 5 seconds post shock.[22] Second, effectivity takes also into consideration that no harmful side effects occur. The shock-energy is seen ideal, if the signal achieves defibrillation while causing the minimum of myocardial damage.[23] Each observable ST-

[14] [5, p. 10]
[15] [8, p. 1380]
[16] [8, p. 1380]
[17] [8, p. 1380]
[18] [8, p. 1374]
[19] [9, p. 1050]
[20] [8, p. 1380]
[21] [4, p. 115]
[22] [10, p. 17]
[23] [4, p. 115]

segment shift in the QRS-complex derived by ECG is a meaningful indicator for deviant signal guidance caused by myocardial damage. ERC Guidelines of 2010 and 2015 have the same recommendations for energy levels in biphasic shocking with at least initial 150 J and 150-360 J for subsequent defibrillations. Manufacturers should concretize their recommended energy steps.[24] Still, a trend to lower energies is observable.

A second goal for efficient, successful defibrillation in addition to conversion of arrhythmias with least energy is a small number of shocks. Conversion success declines with repeated defibrillations at the same energy. An optimal chosen energy level can reduce the number of repetitive shocking and comprehensibly avoid further myocardial damage.[25] A study from 2007 compares fixed lower doses and escalating high energy to see which approach provides a better outcome for patients receiving more than one shock. This comparison reveals no significant difference in return of spontaneous circulation (ROSC).[26] For the aspect of repetitive shocking the Emergency Cardiovascular Care (ECC) Guidelines from 2015 refer to data of AEDs, administering a high peak current at 150 Joule biphasic fixed energy to stop initial persistent or recurrent VF with high conversion rate.[27] They say, the number of shock has to be kept as small as possible.

Additional to the energy and the number of shocks it is also known that the waveform is relevant for a positive outcome. Lower energy biphasic waveforms are associated with less post-shock ST segment shifts than high-energy monophasic shocks. Biphasic waveforms achieve a high conversion rate for the first shock, which is good, but at the same time this makes it more difficult to define energy-requirements for further shocking, if necessary.[28] It is shown in a nonrandomized trial with biphasic truncated exponential (BTE) waveform, that there is a decline in shock success with repeated shocks. Reports of another observational study determine termination-rates for 120 J rectilinear biphasic (RLB) waveform at 87,8 % for initial VF conversion and 86,4 % if VF is persistent.[29]

[24] [5, p. 116]
[25] [4, p. 115]
[26] [10, p. 17]
[27] [10, p. 17]
[28] [10, p. 17]
[29] [10, pp. 17-18]

Walcott, Killingsworth published in 2002 that multiple BTE countershocks at lower energy levels of only 100-200 J had success terminating VF.[30] But ERC Guidelines from 2015 recommend that an initial biphasic energy dose for cardioversion of atrial fibrillation should be 150 J. Providers are advised to increase the dose in a stepwise fashion if the initial shock fails.[31] It is recognizable that guidelines try to define doses of energy as low as possible to reduce post shock cardiac dysfunction[32] but also have to point out that it is better to reach ROSC by the first shock than to defibrillate more than one time.

1.3 Waveforms

Waveforms represent the temporal pattern of the emitted electrical pulse in Volt or Ampere.[33] The shape describes the time, potential or current and polarity. The polarity shows the direction, in which the electrical pulse is delivered between electrodes.[34] The area under the curve represents the energy distributed in Joule (1 J = 1 VAs). The general classification distinguishes monophasic, biphasic and multiphasic signals produced by generator or capacitive discharge.

In the very beginning experimental alternating current (AC) defibrillators sent 100 V sine waves in 0,25-1 second through the chest wall. Even at this time the urge of portability led to DC defibrillators with perceivable more effective shocking.[35]

1.3.1 Monophasic waveforms

After these first efforts, two monophasic waveform-developments came up (Fig. 1). They are called monophasic damped sinusoidal (MDS) and monophasic truncated exponential (MTE) pulses.[36] The defibrillation protocol requires 3 stacked shocks with

[30] [11, p. 359]
[31] [10, p. 47]
[32] [8, p. 1374]
[33] [12, p. 247]
[34] [13, p. 2]
[35] [14, p. 404]
[36] [14, p. 404]

200 J, 200-360 J, 360 J followed by triplets of 360 J.[37] Shocks are performed without impedance adjustment[38] by occurring amperage of 30-40 A.[39]

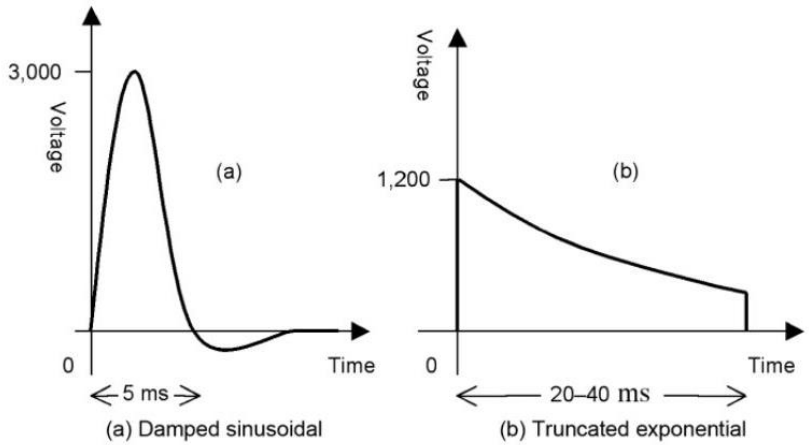

Figure 1: Monophasic Defibrillation Waveforms[40]

1.3.1.1 Monophasic damped sine waveform (MDS)

The monophasic damped sinusoidal (MDS) waveform (Fig. 1 a) has a parabolic ascent to 3000 Volts and immediate decline into negative area to fulfil. A slight counter curve within a total pulse time of 5 ms follows. The current decrease to zero is gradually.[41] An out-of-hospital study from Weaver et al. demonstrated in 1982, that a 175 J monophasic damped sine (MDS) waveform has the same conversion rate like a 320 J MDS shock, eliminating negative side effects of increased post shock AV blocks.[42]

1.3.1.2 Monophasic truncated exponential waveform (MTE)

Monophasic truncated exponential (MTE) waveform (Fig. 1 b) immediately starts at 1200 V, sloping slowly to about 400 V, within total pulse duration of 20-40 ms. The current decreases to zero instantaneously.[43] There is no peer-reviewed literature data to support its effectiveness. However, this waveform was widely implemented in manual and automated external defibrillation.[44] The American Heart Association recommended a shock protocol with 200 J for the initial shock, 200-300 J for the second and 360 J in

[37] [15, p. 56]
[38] [8, p. 1381]
[39] [16, p. 12]
[40] [14]
[41] [7, p. 6]
[42] [8, p. 1380]
[43] [7, p. 6]

third attempt.[45] Behr et al. shows efficacy data of MTE below MDS, but could not attest significant difference between both waveforms in resumption of an organized rhythm or survival of patients.[46] A review of high energy defibrillation studies shows a first shock conversion rate of 63 % and an all-shock conversion rate with an average of 58 %.[47]

1.3.2 Biphasic waveforms

Valentinuzzi reports that in the early times FDA approved the usability for both, monophasic and biphasic procedures. The reason was that observations of monophasic waveforms with increasing energy had better conversion-rates for patients with high chest impedance than biphasic truncated pulses.[48] Conversely Jones and Jones found out that the prolonged pulse duration is a disadvantage of the long MTE pulse. Waveform durations longer than 20 ms can cause refibrillations.[49] Younger research eventually proved superiority of biphasic pulses by lower requirements on energy.[50]
Finally ECC Guidelines renewed their treatment-advice in 2005. SCA with VF or pVT should be treated with single biphasic shocks instead of 3 stacked monophasic shocks followed by CPR by a much better first shock conversion success.[51]

For biphasic discharge, less energy is required.[52] Later experimental and clinical trials left no doubt that biphasic waveforms are more effective than monophasic shocks.[53] They perform in a range between 150-200 J by first sending energy in one direction through the myocardium and repeat shocking in the opposite direction immediately after. These low-energy impedance-compensating biphasic waveforms proved high VF conversion rates in out-of-hospital cardiac arrest.[54] They work with impedance-adjustment, delivering 15-20 A by maximum 2000 V.[55] In comparison to MDS pulses with 350 J and 5000 peak volts, biphasic truncated pulses only have a standard setup with 150 J and 1700 peak volts.[56] To achieve the impedance-compensation, the first

[44] [8, p. 1380]
[45] [7, p. 6]
[46] [17]
[47] [8, p. 1380]
[48] [18, p. 181]
[49] [19]
[50] [18, p. 181]
[51] [20, 25]
[52] [18, p. 181]
[53] [9, p. 1047]
[54] [8, p. 1373]
[55] [16, p. 12]
[56] [18, p. 181]

phase tilt and the relative phase duration is adjusted by a maximum shock duration of 20 ms to avoid refibrillations.[57]

There are three different waveform-designs with significant different morphology. In use for external defibrillation there are biphasic truncated exponential (BTE) (Fig. 2 A), rectilinear biphasic (RBW) (Fig. 2 B) and pulsed biphasic (PBW) waveforms (Fig. 2 C) .[58]

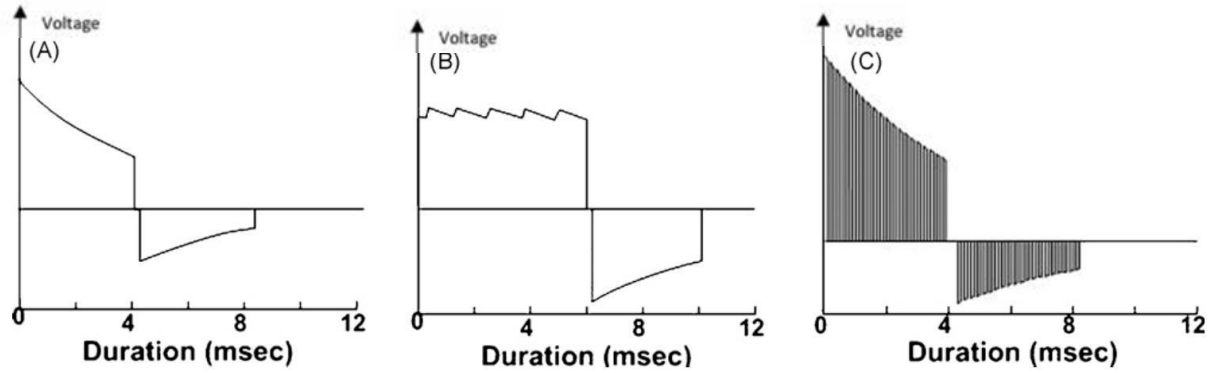

Figure 2: Biphasic Defibrillation Waveforms – (A) biphasic truncated exponential (BTE), (B) rectilinear biphasic waveform (RBW) and (C) pulsed biphasic waveform (PBW) [59]

1.3.2.1 Biphasic truncated exponential (BTE)

The biphasic truncated exponential (BTE) waveform is originally developed for intracorporal use but it turned out that this pulse-delivery is also useful for external defibrillation. It is even superior to monophasic shocking because lower energy requirements reduce post-shock dysfunction.[60] The earliest capacitive-discharge waveforms are not truncated. Without truncation, voltage approaches zero asymptotically. That means, the potential drops far beneath the so called defibrillation threshold (DFT). DFT defines the minimum-level of energy to stimulate myocardial cells.[61] Effectiveness of truncation for transthoracic defibrillation was intensively

[57] [7, p. 6]
[58] [9, p. 1047]
[59] [9, p. 1048]
[60] [8, p. 1374]
[61] {Kroll #19D}

examined.[62] As a result, research work shows that the BTE waveforms are also safe and effective in external defibrillation and finally this waveform-design was adapted from various vendors for external defibrillators.[63]

The BTE pulse (Fig. 2 A) starts at 1790 V. The capacitive discharge of this waveform creates an asymptotic approach for the first phase. The truncation to regulate durations of the first and second phase is automatically adjusted within the first 2 ms of the discharge. This real time measurement provides impedance-compensation. For the second phase polarity switches to negative to repeat the slightly decreasing asymptotic signal on lower voltage. The total pulse duration can vary between 5 and 20 ms.[64] 150 J impedance-compensating BTE waveforms show a high conversion rate at VF-episodes despite a very wide range of impedance. This waveform maintains high efficacy without the need of step-up energy levels or high-energy shocks.[65]

1.3.2.2 Rectilinear biphasic waveform (RBW or RLB)

The RBW or also called RLB waveform is specially developed for external defibrillation. High and variable patient impedance levels are taken into consideration. There is a successful verification of efficacy in multicenter, prospective, randomized, transthoracic defibrillator animal and clinical trials. RBW waveforms showed superior efficacy to monophasic damped sine waveforms and monophasic truncated waveforms to terminate VF and AF. Compared with BTE the same success of converting AF is displayed.[66] As ECC Guidelines recommend 150 to 200 J for BTE, they specify 120 J or greater for RLB based on first shock conversion results of 85-88 % by randomized controlled trial (RCT) and cohort studies, although they have only low-quality evidence. Low evidence means that there is a downgrade by imprecision and risk of bias. [67]

The pulse of the rectilinear biphasic (RLB) waveform (Fig. 2 B) belongs to the family of constant current pulses. It shows initially a ramp with minimal rising voltage level within the first milliseconds and returning to initial level of within 2 ms. This procedure is repeated 5 times. The result is a sawtooth pattern, interrupted after 6 ms, to change polarity to negative. The voltage-level in opposite direction starts with a peak again and

[62] {Kroll #19D}
[63] [9, p. 1047]
[64] [8, p. 1374]
[65] [8, p. 1378]
[66] [9, p. 1047]
[67] [21, 87–88]

decreases slightly over 4 ms in one line. The resulting total pulse time is 10 ms. Impedance compensation is given by the almost constant current.[68]

1.3.2.3 Pulsed biphasic waveform (PBW)

The high frequency chopped or pulsed biphasic waveform (PBW) (Fig. 3 C) has almost the same pattern like BTE concerning two phase current-flow in opposite direction and total pulse duration. Just in detail (Fig. 3) it is possible to see that these signals are chopping-modulated in high frequency of 5 kHz with 50 % “duty cycle”[69] and slightly higher peak voltage in comparison to the previous biphasic pulses.[70] The interrupted character with active and inactive segments reduces the area under the curve, representing the energy, by almost 50 % and also leads to a lower average current.

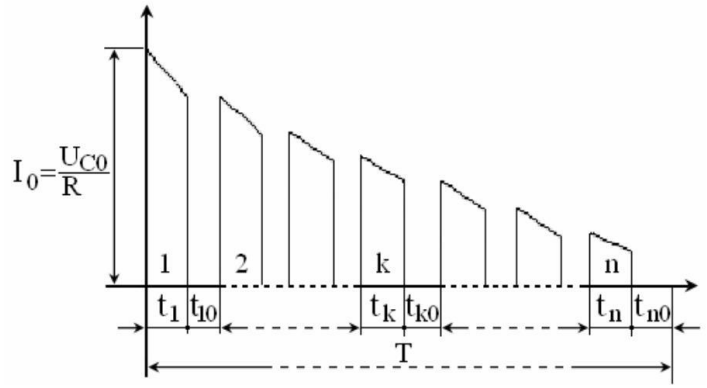

Figure 3: Patient current during the positive phase of PBW in detail[71]

Studies attested clinical effectiveness for all mentioned biphasic waveforms. Differences can be seen in the impedancecompensation technique. PBW increases the duty cycle of high frequency active pulses after measuring a high pathway impedance. Nonetheless a potentially higher peak current at the same energy like BTW and RBW can be noticed.[72]

The waveform multipulse biowave (Fig. 4) is patented and registered from Schiller. The black marking on every signal-bar indicates the average current of this waveform.

[68] [9, p. 1048]
[69] {Krasteva 2001 #39D: 68}
[70] [14, p. 405]
[71] [22, p. 51]
[72] [9, p. 1047]

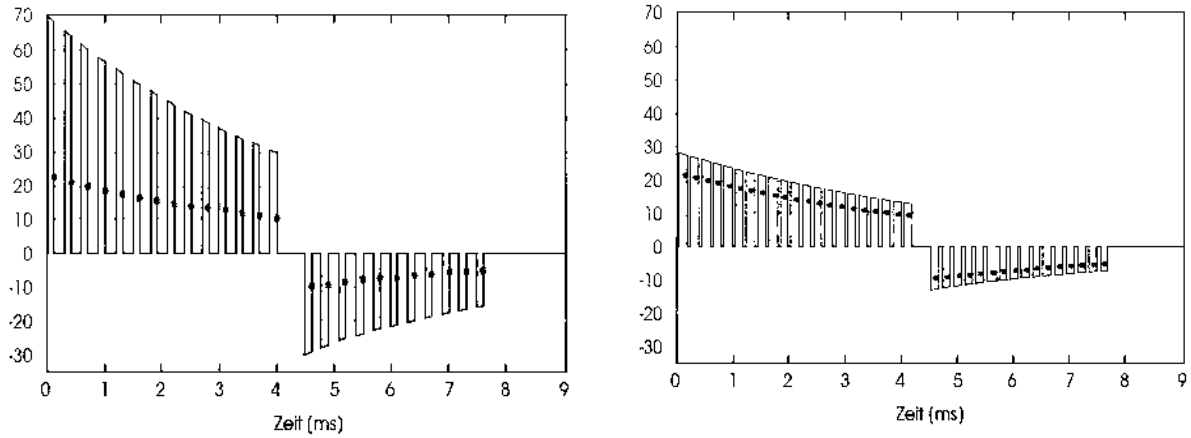

Figure 4: Patients impedance 40 Ohm (left side) and Patients impedance 100 Ohm (right side)

1.3.2.4 Lossless constant current pulse (LLCC)

Lossless constant current (LLCC) pulses are described in the patent US 2006/0004415 A1 - Defibrillator with improved output stage.[73] This waveform consists of a positive and a negative phase. The constant current leads to a rectangular shape of both phases without any explicitly named details. Only the quantity of electricity of first and second phase is defined as ratio $Q_1 / Q_2 = 3$.[74]

Recommended waveform phase ratio: $Q_1 / Q_2 = 3$ (with Q as phase duration in ms) (1)

In comparison to RBW the the relation between delivered energy and capacitor-energy, initially loaded (ηC-index), is favorable. The LLCC-pulse shows an optimal performance at inter-electrode transthoracic impedances smaller than 80 Ohm.[75]

But the realization of this pulse is technically complicated. The defibrillator has to handle strong electromagnetic influences, a complex current control and a big inductive coil creating the constant current amplitude. This is inappropriate for AEDs that should be small and portable.[76]

[73] [23]
[74] [22, p. 50]
[75] [22, p. 45]
[76] [22, p. 45]

1.3.3 Triphasic waveforms

The patent US4637397 A US 06/739,133 - Triphasic wave defibrillation from 1987 describes the character of triphasic pulses, emphasising that magnitude and pulse durations are optimized for defibrillation efficacy.[77] Voltage, polarity and time are predeterminate from each phase to the next with the first phase titled “the conditioning pulse”.[78] Second phase is in opposite polarity to the previous with the declaration “correcting pulse”.[79] And the third phase is named “healing pulse” with change in polarity again.[80] This waveform design has no (single) capacitive discharge character because voltage levels do not necessarily decline over time. Conditioning pulses can follow with time and voltage magnitude even higher than the first phase. Since the findings of dangerous refibrillations after more than 20 ms were not yet given in 1987, phase durations of up to 50 ms are supposed.[81]

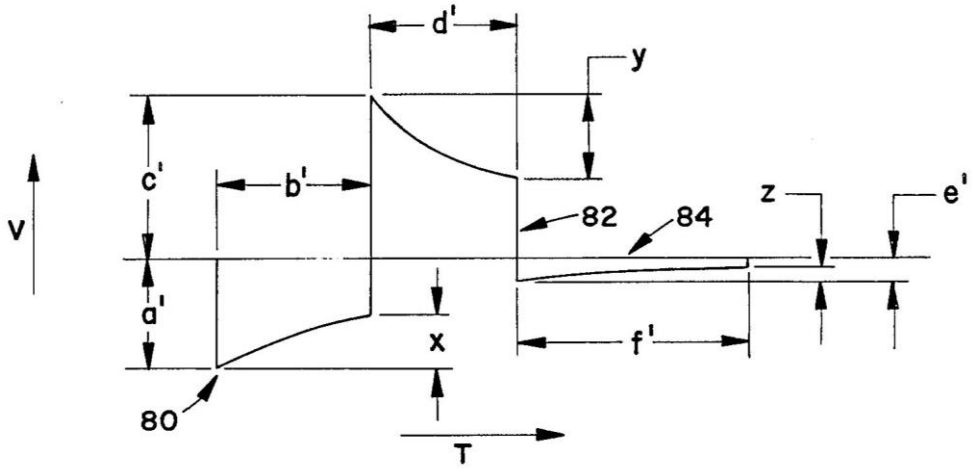

Figure 5: Triphasic waveform in detail[82]

1.3.4 Multiphasic waveforms

Actually multiphasic shock applications are older than biphasic waveforms. Oscillating capacitive discharge waveforms had been already used in the former USSR.[83]

The patent US 6493580 B1 Cansell and Daskalov presents suggestions to modulate two ore more phases in opposite polarity with cutting and chopping of each phase into

[77] [24, p. 1]
[78] [24, p. 5]
[79] [24, p. 5]
[80] [24, p. 5]
[81] [24, p. 5]
[82] [24]

rectangular pulses. (Fig. 6) He points out, that it is possible to adjust the delivered dose of energy by varying the cutting and chopping pattern.[84]

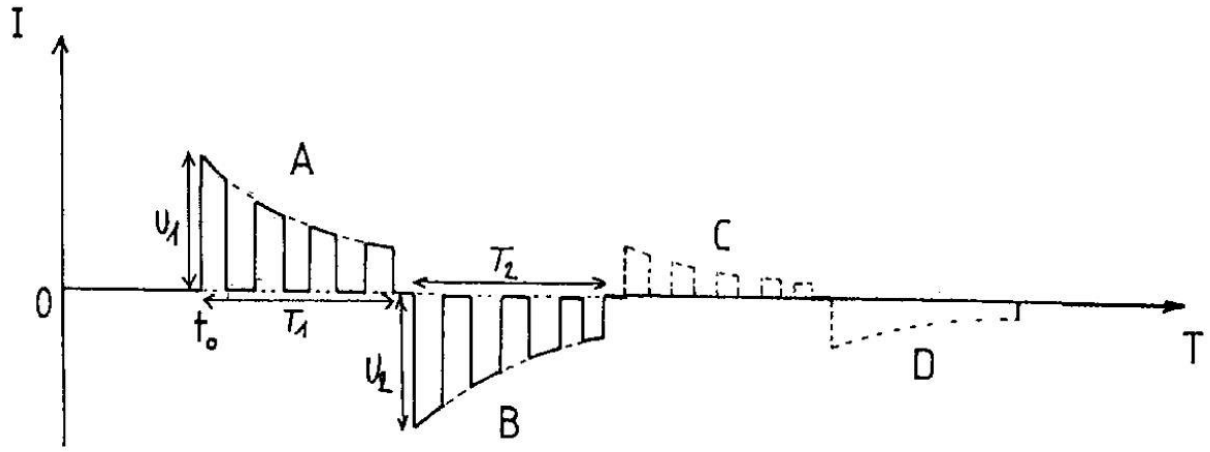

Figure 6: Multiphasic chopped waveform[85]

1.4 Normative Aspects

Normative hierarchy for defibrillation-technology starts with legal regulations. In Europe, the legislation creates EU-directives with takeover-commitment for national law. At national level the MPG (Medizinproduktegesetz) enables the ministry of Austria to enact regulations with intervals of 4 years to change them. Most relevant for the present topic is the content of IEC 60601-2-4:2010 Medical Electrical Equipment, Part 2-4: Particular requirements for the safety of cardiac defibrillators. The European Committee for Electrotechnical Standardization (CENELEC) accepts this version without changes. The European edition of this standard is published in 2011 from International Electronic Commission (IEC) - The primary international standard for external defibrillators. The Austrian edition is called: OEV_OENORM_EN_60601-2-4_2012_06 Medizinische elektrische Geräte. Teil 2-4: Besondere Festlegungen für die Sicherheit einschließlich der wesentlichen Leistungsmerkmale von Defibrillatoren.

Going through all passages of OEV_OENORM_EN_60601-2-4_2012_06 reveals the following relevant requirements for safety and performance for defibrillators. At the time when the first edition was published damped sinusoidal waveforms were state of the art. The delivered energy increases proportional to patients impedances between 25 and

[83] {Albert Cansell 2002 #51I: 8}
[84] [25, p. 8]
[85] [25]

175 Ohm. The present version of 2012 requires exact reports of dependence between delivered energy and occurring impedance. Now actually delivered energies have to follow the expected energy (par value) with a deviation of maximum +/- 3 J or +/- 15 % for the existing impedance.[86] Intentional transgressions are forbidden. On account of the aspect that high initial energy can cause irreversible damage on myocardial tissue, additional prevention strategies are introduced to avoid unwanted overdoses. But certainty about the right dose of energy, that is necessary for conversion but still low enough to prevent damage, is still subject of further research.[87] 360 J is stated as the upper limit for automated external defibrillation. Further the output voltage must not excelerate 5000 Volts for 175 Ohm.[88] The technical description has to contain diagrams with the relationship between time and current or voltage of the waveform with simulation of the load resistance for 25, 50, 75, 100, 125, 150 and 175 Ohm for the maximum power output and all pre-set protocols of the defibrillator. Additionally a accuracy certificate is required for the energy applied at 50 Ohm and finally (if applicable) a limit has to be defined for a stoppage of delivering energy, if the patients impedance value is too high.[89]

Unless it is very unlikely that children need defibrillation, AEDs should have an adapter, weakening the energy-dose in child-mode. A value of 2 J/kg is suggested to be safe.[90]

Electrodes are the interface between device and patient. Also at this point children (< 10 kg) should have individual electrodes in terms of surface and placement.[91]

The impedance of self-adhesive pads can be higher than handled electrodes. This is ok as long as the share of impedance is smaller than 6 %.[92] Further discussed points are material, construction, placement and function-combinations of electrodes. The main goal is a good electrical conductance. Characteristics about adhesion, set-up time and reactions to sweat or other temperature influences should be insured by the supplier.[93]

To provide quick and reliable performance, there are time requirements on charging for AEDs frequently used and rarely used. Charging times from starting, after program-changes and for recharge of fully discharged energy storages are defined.[94]

[86] [6, 60,61]
[87] [6, p. 62]
[88] [6, p. 28]
[89] [6, p. 18]
[90] [6, p. 65]
[91] [6, p. 44]
[92] [6, p. 66]
[93] [6, 44,45]
[94] [6, 33,34]

Power supply is also differentiated by the frequency of use. The battery capacity has to guarantee 20 discharges at highest energy-level with slightly varying requirements of cycle times and pauses in between shock series.[95] The EN_60601-2-4_2012 mentions that AEDs perform in a range of energy starting with 150 J[96] but it is also emphasized right at the beginning that waveform technology is under constant observation and shows rapid developments regarding waveform design and efficacy. The choice of one particular waveform with preferential shape, energy, efficacy and safety is explicitly excluded to be a thematic subject of this norm.[97]

The protection class for AEDs is defined in accordance to EN 61140. Electrodes for defibrillation belong to protection class CF.

Guidance on regulation of medical devices by Medical Device Directive (MDD) 93/42/EWG were replaced by law. Now the Medical Device Regulation (MDR) from 2017 is in charge with new classifications of medical devices into risk classes. Defibrillators are active medical devices and belong to class III with high hazard potential.

Legal basics mainly derive their requirements from the European Resuscitation Council (ERC) – Guidelines for Resuscitation or from the American Heart Association (AHA) publishing Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) Guidelines. These comprehensive reports about basic and advanced life support are updated every 5 years.

1.5 Why AEDs should be more portable

AEDs are designed for laypeople without or only minimal guiding.[98] Their application is an important element of Basic Life Support (BLS). In the ERC Guidelines 2015 every bystander is encouraged to use an AED as early as possible for cardiopulmonary resuscitation (CPR) to provide immediate help after witnessing a collapse and save time until Emergency Medical Service (EMS) arrives.[99] The time to treatment has a high impact on the positive outcome for patients in sudden cardiac arrest (SCA) scenarios.[100] The American Heart Association (AHA) already introduced “public access defibrillation”

[95] [6, 36,37]
[96] [6, p. 65]
[97] [6, p. 9]
[98] [5, p. 10]
[99] [8, pp. 1373-1374]
[100] [5, p. 3]

with extended distribution of AEDs for nonmedical, basically trained persons like security guards or risk groups.[101]

As already mentioned, defibrillation after 3-5 minutes can increase survival rates to 50-70 %. The logical consequence must be that first responder find AEDs as close and fast as possible to save time.[102] The ERC Guidelines claim that the ful potential of AEDs is not reached as long as they are only situated on public places although the majority of 60-80 % of all SCAs occurs at home. Though the statistical share of found VF is higher in public area, the majority of emergency calls comes from private homes.[103]

The development of waveform design shows that affect size, weight and costs for batteries could be revised. High energy monophasic stimulation[104] was replaced by low energy biphasic truncated exponential (BTE) waveforms.[105] Yet there is no final consensus how to predict and deliver the ideal energy-dose for efficacy and minimized risk. EN 60601 avoids to recommend any waveform at all[106] and ECC Guidelines from 2015 refuse to name any biphasic waveform or energy level superior.[107]

But a reduction of energy-consumption could improve weight, costs, battery needs and mobility and at least time to treatment related to the outcome of patients.

1.6 Research question

State of the art, three different designs – biphasic truncated exponential (BTE), rectilinear biphasic (RLB) and pulsed biphasic waveforms (PBW) are in use, but a clear efficiency-comparison between manufacturers is difficult. Adjustments by impedance compensation and different peak currents at the same energy setting occur between the different devices.[108] Additionally, the high conversion rate of first shocks makes it even harder to study energy requirements for a second or subsequent shock.[109]

For automated external defibrillators, the evidence summary of ECC Guidelines only confirms that high peak currents at 150 J biphasic fixed energy are able to convert initial

[101] [26, p. 1677]
[102] [5, p. 46]
[103] [5, p. 72]
[104] [8, p. 1374]
[105] [8, p. 1374]
[106] [6, p. 9]
[107] [10, p. 17]
[108] [10, p. 17]
[109] [10, p. 17]

persistent or recurrent VF with a high success rate.[110] But is there a pulse form that enables a successful automated external defibrillation with minimized energy? This necessitates to define which parameters have impact, how is it possible to do an objective waveform comparison and which electrophysiological effects are useful for new waveform-technology.

As it is seen unlikely to find ways to improve biphasic waveforms with asymptotic pattern, leading authors of this topic like Kroll and Swerdlow recommend to rethink efficient waveform design.[111]

1.7 General traget

The aim is a comprehensive review to clarify the relevance and limits of parameters to provide a successful external defibrillation with lowest energy-consumption. Energy is technically related to battery-size and charging time. The conclusion of this work should be helpful to create technical solutions with better performance, higher mobility and lower costs.

2 BASIC PROBLEMS

2.1 Risk-benefit-principle

Development and design of biomedical devices mostly faces two aspects: on one side, there are therapeutic benefits on the other side risks for patients and staff.[112] For AED-application there is an urge of fast, successful conversion of arrhythmias to save myocardial tissue and in further consequence life. To quantify risk and benefit, a “safety factor” can be calculated as a ratio between the potential of producing post-shock damage and the voltage producing cellular excitation.[113] But this calculation is not complete because statistics show that the survival chances depend on early defibrillation too. The likelihood of successful resuscitation is 50-75 % if basic life support is performed within 3-5 minutes after onset of a shockable rhythm.[114] In addition

[110] [10, p. 17]
[111] [12, p. 247]
[112] [14, p. 20]
[113] [24, p. 5]
[114] [2, p. 1273]

to that, studies show that the number of shocks has an impact of survival-chances of a patient. That means voltage, time-to-treatment and the possible number of shock repetitions, all have to be included for risk-benefit-considerations. In conclusion, it is possible to argue that less energy carries the risk of repetitive shocking and other reports say that only one shock is better than subsequent[115] but high energy doses might damage heart muscle cells the same way as ischemia could do. That means Injuries of myocardial tissue occur with or without a certain application of energy. The only factor that remains without contradiction is time. So this should be the curtail factor that can decide for or against application.

As long as manufacturers come to technical limits, they will more likely use higher energy doses that may risk minor injuries of the patients myocardium and body by shunting effects or burnings of the skin surface by attachment-problems, instead of using low energy applications that might defibrillate gentle for myocardial tissue but not fast and effective enough to trigger the defibrillation threshold which may lead to death in last consequence. If there is a waveform providing sufficient success in conversion with small requirements of energy, this will allow lower limits in size, weight and costs of components and accumulators providing higher mobility. Portability enables an increase of AED device density and higher chances for immediate help [116]. Until this moment, AEDs are distributed in urban space and public institutions with short distance to go if help is required. But most SCAs happen in domestic area[117] and the potential of first responder help is not exploit as long as AEDs are not as small as mobile phones to put them in the pocket. For a risk-benefit-analysis it is possible to argue that smaller, mobile gadgets shorten the time of application and increase the chance of survival by 7-10% every minute.[118]

2.2 Human body as a black box – parameters with influence on defibrillation

Defibrillation only works in specific cases of arrhythmia. The “American Heart Association Task Force on Automatic External Defibrillation” defines three groups: shockable rhythm, non shockable rhythms where defibrillation has no impact and as a third group intermediate rhythms, where it is not possible to clarify if benefits are

[115] [4, p. 115]
[116] [8, p. 1374]
[117] [5, p. 72]
[118] [2, p. 1273]

superior to the risks of shock delivery.[119] A table is attached (Appendix A1) with all types of arrhythmia classified in the mentioned rhythm categories.[120]

Next to the type of arrhythmia, there are patient-specific requirements with impact on the performance of ICD and AED devices. The principles of defibrillation threshold (DFT) and concept of dose are valid for both application-types. Defibrillation threshold is characterized as minimum magnitude with 50 % chance to trigger a conversion[121] and the electric dose represents a value with 90 % probability of success at least damage to the heart.[122] A lot of important knowledge for automated external defibrillation comes from ICD-technology. The meanwhile commonly used BTE waveform was yet standard ICD-technology in 1997[123] and replaced high-energy monophasic waveforms in external defibrillation. A big advantage of this low energy pulse form was seen in the possibility to deal with variations in patients transthoracic impedance (TTI).[124] Kerber et al. explains that a shock in high-impedance patients has a decreased success by inadequate current delivery in monophasic damped sine waveforms without impedance-adjustment.[125] Physiological factors that influence transthoracic impedance are weight of the patient, chest width and ventilation phase.[126] Without pre-selection unappropriate energies are delivered.[127] While MDS technology assumed patient impedances of only 50 Ohm, realistic values for adults are between 70 and 80 Ohm. But research shows that BTE waveforms have superior shock success unaffected by variations in patient impedance. This is challenging the previous conclusion and questions the dominant role of current. Impedance might only be relevant for MDS or high-energy waveforms in general. For BTE or low-energy waveforms, the role of current might be secondary.[128] This problem shows very well, how crucial the waveform-selection is and how many factors determine successful defibrillation.[129]

[119] [26, p. 1679]
[120] [26, p. 1684]
[121] [18, p. 28]
[122] [18, p. 40]
[123] [8, p. 1374]
[124] [8, p. 1374]
[125] [8, p. 1381]
[126] [27, p. 63]
[127] [3, p. 19]
[128] [8, p. 1381]
[129] [8, p. 1381]

2.2.1 Internal aspects with influence on defibrillation

Defibrillation can be significantly affected by the underlying cardiac substrate. Resuscitation- independently there may be different heart sizes, premedication, implanted ICD-electrodes or scar tissue that may have influence on defibrillation success.[130] Depletion of metabolic or oxygen supply occurs dependant on the time to treatment [131] and ischemia changes the heart-conduction system in every possible manner, causing reentry tachycardia or inhibit sinus-signal transduction. Furthermore, waveforms can interfere differently with pharmacologic resuscitation efforts using e.g. Lidocaine or Amiodarone.[132] Poole et al. measured much higher requirements of energy in monophasic animal trials after medication with those drugs, whereas there was the opposite effect with slightly less energy required for truncated biphasic waveforms.[133]

The shock intensity must be great enough to reach a certain proportion of cells to stop enough unorganized electrical pulse-circuits to avoid that fibrillation is reinitiated. This proportion is called critical defibrillatory mass. It is defined as the minimum number of ventricular fibers converted to stop fibrillation.[134] Since ICD-electrodes are in immediate contact to the myocardium, it can be easily verified which dose of energy reaches a critical mass of myocardium and it is even possible to define the precise moment, where energy of one phase does not longer cause sufficient stimulation. This is not possible to say for external defibrillation on account of following influential aspects.

2.2.2 External aspects with influence on defibrillation

Pads or paddles, how electrodes are called in external defibrillation, are placed on the outside of the body. Since they create the interface between AED and human body, there are many factors that can affect the conductivity of the countershock. Application can be by handled paddles or self-adhesive pads with almost equal performance.[135]
Even though the material of self adhesive pads creates a slightly higher impedance, the adhesive character provides better usability.[136] Further, the pad position is one more

[130] [8, p. 1375]
[131] [4, p. 109]
[132] [28]
[133] [8, p. 1381]
[134] [18, p. 47]
[135] [29, p. 209]
[136] [6, p. 66]

factor, that has impact on transthoracic impedance.[137] Various pad positions are described and evaluated. First position for self-adhesive electrodes is in sub-clavicular/sub-axillar position also called antero-lateral or antero-apical and a second one is antero-posterior.[138] Figure 7 illustrates both attachment-possibilities.

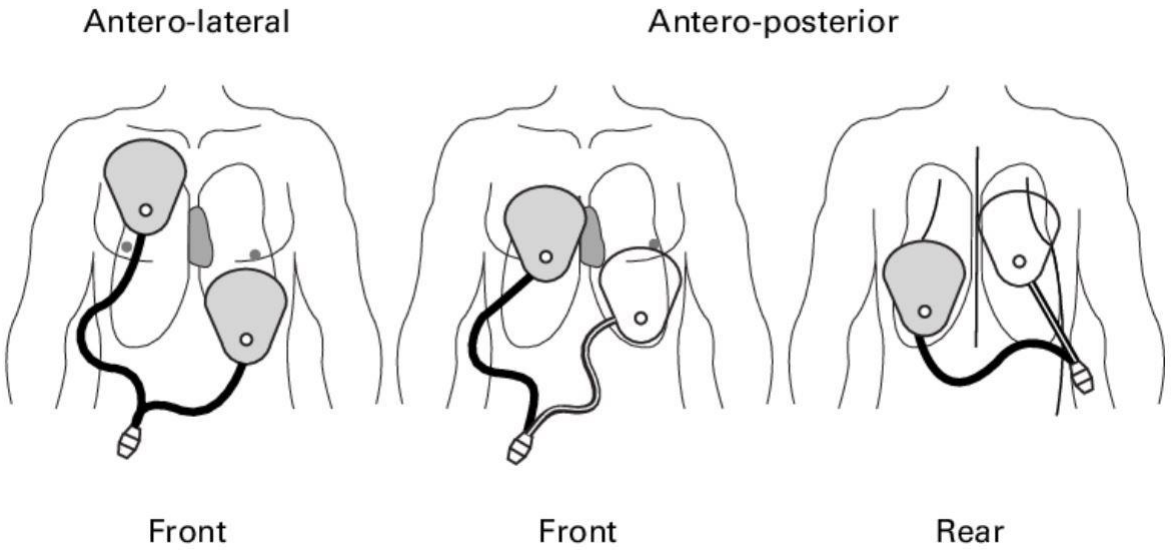

Figure 7: Electrode position 1: antero-lateral = pad/paddle at ventricular apex–right infraclavicular area; Electrode position 2: antero-posterior = pad/paddle at right sternal body at the third intercostal space–angle of the left scapula.[139]

Although antero-posterior position is reported to be superior with a significantly lower TTI mean[140], ECC Guidelines give instructions to place one pad electrode on the upper-right sternal border and the second one lateral to the left nipple[141], which corresponds to antero-lateral position. Meanwhile position one or two, the distance between both electrodes has to be minded. Pads, attached too close, may cause shunting-effects. This means that electricity finds an easier way of floating besides myocardium – maybe even on the skin-surface. For children, the anterior-posterior position is recommended.[142] The contact-field determines the optimal energy-disposal to the body and admission back to second electrode. Humidity or sweat can influence conductivity. Reduced skin contact (e.g. by hair) may cause burnings because readjustments of pad size lead to higher currents. There is a normal temperature-rise of

[137] [30]
[138] [30]
[139] [31]
[140] [30]
[141] [7]
[142] [6, p. 44]

2,5 °C for optimal attachment. 50 % contact area causes a 8 °C higher skin temperature and a contact area of only 10 % leads to increase of 77 °C which is definitely harmful.[143] For optimal contact, pad size has an influence on the delivered energy-dose because bigger pads cause smaller impedance. The size (surface) differs between children and adults. Too large pads may have an inadequate attachment.[144] The contact area of each electrode should be at least 50 cm² for adults and 15 cm² for children to perform external defibrillation.[145] The sum of electrodes contact area should be at least 150 cm² for adults[146] 45 cm² in paediatric use (< 10 kg).[147] Too small electrode-diameters can cause heart muscle necrosis. Paediatric pads on adults or big children lead to undesirable high transthoracic impedances.[148] The chest width determines the possible position of the pads but also the distance to the heart. In out-of-hospital cardiac arrest ventilation phase has no relevance but physiological diversity is certainly a matter for transthoracic impedance.

2.3 Cellular electrophysiology

Cellular electrophysiology is a very important field to understand limitations like time for processes. Better understanding can help to find hidden possibilities to prevent injuries or reduce energy-consumptions. Physiological- and pathophysiological structures, ways of signal transduction and ion channel process-models must be taken into consideration to understand and avoid or use cellular effects. Starting at the surface of the human body, every point of this chapter goes deeper into detail.

2.3.1 Layers forming the transthoracic impedance (TTI)

Dealing with external defibrillation, electrodes are not directly connected with the tissue which is actually intended to be affected. The interface is the skin surface. The skin is also the first layer of many, creating the transthoracic impedance (TTI). Resistance of the first layer can vary a lot by humidity, hair or pad-attachment. TTI values also differ depending on the electrode-position. The TTI range for sub-clavicular/ sub-axillar position with self-adhesive electrodes is between 58 and 152 Ohm. Antero-posterior

[143] [16, p. 20]
[144] [29, p. 209]
[145] [16, p. 22]
[146] [29, p. 209]
[147] [6, p. 44]
[148] [29, p. 209]

position has a slightly lower TTI range of 55 Ohm to 149 Ohm[149] Trials with low-energy impedance-compensating biphasic waveforms even measured patient-resistance values between 36 and 171 Ohm.[150] Further layers in the thorax are created by the chest with pleura and rips, double layered pericardium and finally the heart wall with a three-layer-structure of epicardium, endocardium and myocardium.

2.3.2 Which types of cells are affected

Going over to the heart muscle, the so called myocardium is divided into two types of cells. The first type are pacemaker cells forming the sinoatrial (SA) node. They are the protagonists to initiate electrical pulses which are conducted through pathways of the heart. The second type are myocardial cells or also called cardiomyocytes. They are divided in atrial and ventricular cells and consist of myofibrils having long chains of sarcomeres. Shortening and lengthening of fibers creates a coordinated movement for pumping blood. Additionally, the heart is surrounded by autonomic nerves which can influence the beat rate and strength of contraction.[151]

2.3.3 How those cells interact

The communication and transport between adjacent cells works by paracrine hormones, connexons – creating gap-junctions, called nexus and electric coupling which permits the transfer of excitations from muscle.[152]

2.3.4 Cardiac conducting system

The cardiac conduction system describes the way and speed of an electrical signal through the heart muscle and can be derived and pictured by an electrocardiogram (ECG) (Fig.8).

[149] [30]
[150] [8, p. 1378]
[151] [3, p. 11]
[152] [32]

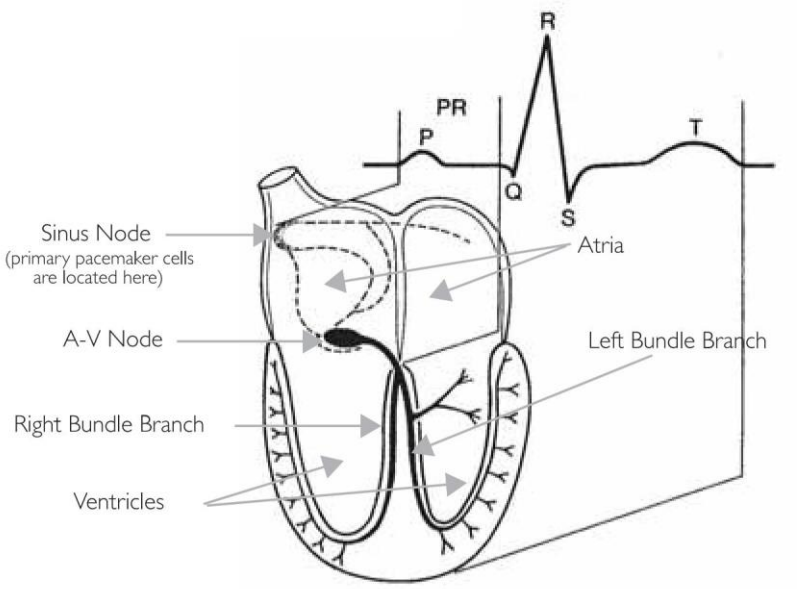

Figure 8: Relation between the anatomy of the cardiac conduction system and the ECG derivation[153]

2.5.4.1 Sinoatrial (SA) node

The electrical pulse conduction starts at the sinoatrial (SA) node. Atrial depolarization can be derived as p-wave in ECG (Figure 6). The sinus node consists of pacemaker cells without the ability to contract. Instead their function is the auto-rhythmic creation and conduction of action potentials. The myocardial cells are connected by gap junctions forming channels for ion flow in which the sinoatrial node has a special electric coupling by HCN-ion channels. HCN stands for hyperpolarization-activated cyclic nucleotide-gated action channel. The current through this channels has the subscript I_f for the “funny” behaviour of being activated by hyperpolarization instead of depolarization. Principally hyperpolarization is the opposite of depolarization, causing a more negative charge in the range of normal diastolic membrane potential. HCN channels are mainly open for sodium-ions (Na^+) floating into the cell and potassium-ions (K^+) floating outward during negative membrane potential.[154] The sodium current is suspected to have a special pacemaker role. But there is also a second model in debate to regulate the heartrate mainly. This theory promotes that calcium-oscillations from Na^+ / Ca^{2+} exchangers create the firing of rhythmic pulses.[155]

[153] [3, p. 11]
[154] [33, p. 237]
[155] [33, p. 237]

2.5.4.2 Atrioventricular (AV) node

In second stage the atrioventricular (AV) node is able to do an electric filtering and slows down the arriving sinus signal to avoid atrial tachyarrhythmia and provide that ventricles have a sustainable filling with blood before the action potential reaches the contractile myocytes.

2.5.4.3 His bundle & bundle branches

His bundle & bundle branches are specialized pathways for rapid conduction of the action potential. Right bundle branches depolarize the right ventricle, left bundle branches depolarize the left ventricle plus interventricular septum.[156]

2.5.4.4 Purkinje fibers

The wavefront of action potentials reaches to the inner ventricular myocardium (endocardium) via millions of small so called Purkinje fibers. This network carries the signal to the walls of the ventricles, stimulating the cardiac muscle cells (cardiomyocytes).

2.5.4.5 Cardiomyocytes

Cardiomyocytes or also cardiac myocytes are divided in the already explained pacemaker cells and secondly contractile cells. The contraction follows an triggering by the action potential of adjacent cells or possibly by defibrillation. Also here, adjacent cells are connected by gap junctions inside the phospho-lipid double layer, forming membrane channels with many different regulating mechanisms to provide cell-to-cell signal transmission. Voltage gated channels in membranes of cardiomyocytes are mainly involved in the highly organized electrical signal creation and signal conduction as a depolarizing wave through all areas of the heart.[157]

2.5.5 Ion channels

Ion channels are membrane-bound proteins that basically maintain the transmembrane potential (TMP) between inside and outside of the cell.[158] Different channels are classified by their gating mechanisms. The two most relevant regulating molecular actors are voltage-operated-channels (VOC) and ligand- or residual-operated-channels

[156] [32]
[157] [34, p. 1317]

(ROC).[159] Chemical or electrical stimuli can lead to conformational changes that open or close them.[160] Dependant on selectivity, voltage and time course, channels permit access and stop after 1-2 ms by conformational changes again. After the opening period, channels are unresponsive for a certain recovery time until the resting confirmation is regained.[161]

2.5.6 Potential creation

A potential can be created electrochemical if cells have a concentration gradient between the inside and the outside of the membrane (chemical gradient) and secondly electrical by the difference in charge between both sides of the membrane.[162] Ion pumps transport sodium and calcium out and potassium in. Once created a gradient, the activity of ion channels is driven by the tendency of ions to move in opposite direction of ions with the same charge and towards equilibrium potential.[163]

2.5.6.1 Transmembrane potential (TMP)

The charge of the voltage potential becomes more positive by positive ions floating in and more negative, if positive ions move outside. The gradient is, as mentioned, maintained by pumps but can also climb by external voltage application. The plot (Figure 9) shows the electric quantities across the membrane represented by the base-line or x-axis and adjacent intracellular and extracellular charge density regions in red and blue. The electric field strength is coloured magenta and the electrostatic potential pale green. The green arrow from bulk-to-bulk voltage indicates the transmembrane potential.[164]

[158] [32]
[159] [32]
[160] [35]
[161] [35]
[162] [32]
[163] [35]
[164] [36]

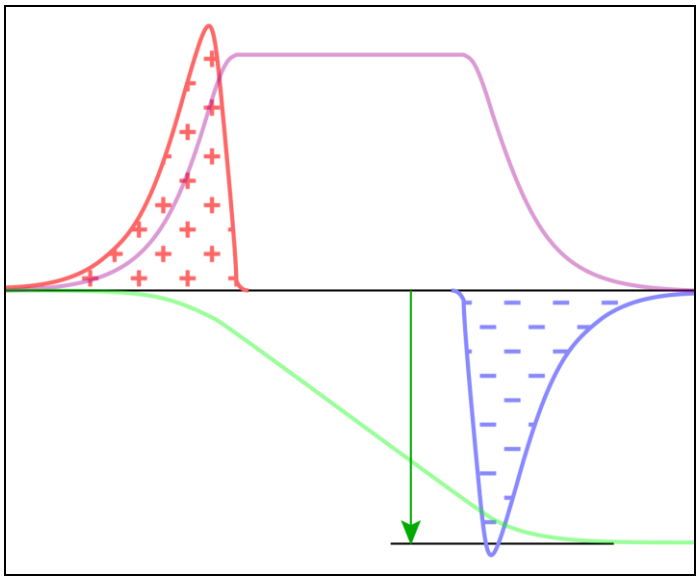

Figure 9: Electric charge density inside (blue) and outside (red) of a heart muscle cell at resting potential[165]

2.5.6.2 Resting potential

At resting state the membrane potential of the cell is negative with more potassium inside and a higher amount of sodium and calcium outside. Heart muscle cells with occurring arrhythmia show other potentials than normal cells. In this case the value for resting potential or also called diastolic membrane potential of myocardial tissue has to be assumed to be near – 60 mV instead of approximately – 90 mV. The reason is an increase of extracellular potassium.[166]

2.5.6.3 Threshold potential

The threshold potential represents the critical value of membrane voltage during depolarization that generates the action potential. The difference between resting potential of unexcited cells and threshold potential of unexcited cells defines the stimulus required to reach the action potential threshold. For external conversion-efforts this stimulus can be created by a defibrillating current which has to reach responding cells in resting phase.[167]

[165] [36]
[166] [24, p. 5]
[167] [18, p. 51]

2.5.6.4 Action potential

The action potential can be explained as the brief reversal of the polarity within one thousandth of a second between the inside and the outside of the cell provided by voltage gated channels.[168] It corresponds to the QRS-sequence derived by ECG (Fig. 8).[169] Different tissue of the myocardium show different action potential-characteristics (Fig. 10).

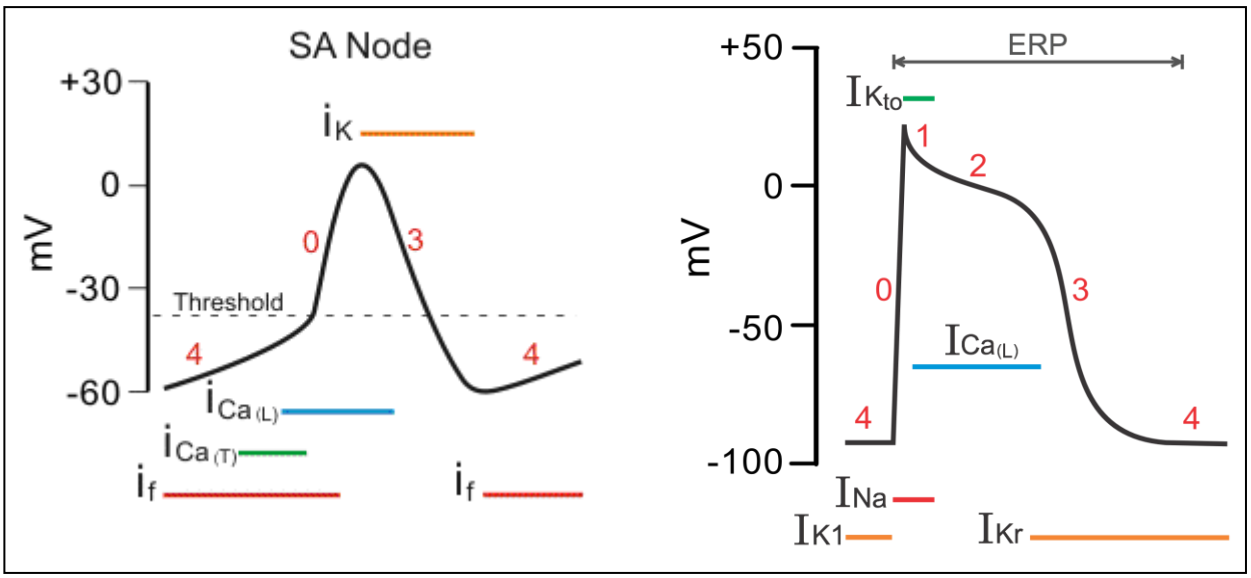

Figure 10: Action potential of sinoatrial cells (left) and ventricular heart muscle cells (right)[170]

The action potential of pacemaker cells from sinoatrial node (Fig. 10, left side) is characterized by the spontaneous generation and the slow response with Ca^{2+} influx. Significant is the unstable resting potential (phase 4) degraded by so called “funny currents” I_f of sodium, initiating depolarization (phase 0) and completely repolarization (phase 3), back to – 60 mV. Next to calcium, potassium-ion-movements are involved to create action potential. They always become restored by several ionic pumps.

The threshold value which has to be reached to fire action potential lays between a value of – 40 mV and – 30 mV. But first a progressive opening of T-type Ca^{2+} channels at – 50 mV and L-type Ca^{2+} channels at – 40 mV is necessary to reach the so called pacemaker potential.[171]

[168] [37]
[169] [35]
[170] [38]
[171] [38]

The action potential-characteristic in atrial and ventricular heart muscle cells is almost similar (Fig. 10, right side). But in comparison with pacemaker cells, there is a different set of ion channels, calcium storage by sarcoplasmic reticulum (SR) and myofibrils performing contractility. The stimulation comes from neighbouring myocytes – starting at resting potential (phase 4) and returning to – 90 mV again after upstroke by rapid depolarization (phase 0), early rapid polarization (phase 1), plateau phase (phase 2), final rapid repolarization (phase 3). In this type of cells a threshold of – 70 mV has to be triggered, to initiate action potential with a depolarization-upstroke from fast Na + and Ca^{2+} influx until 10 mV overshoot. Contrary there is a large outward current of potassium ions. [172]

Once triggered, the depolarizing inward and outward currents can not be interrupted. The voltage operating channels do not react on external voltage changes during this time. The calcium pump can only be inhibited by the regulatory protein phospholamban.[173] Other steps are driven by ion-channel gating regulated according to the occurring voltage.

2.5.7 Conduction of action potential

Since the cardiac conducting system is already described and the spontaneous generation of action potential in pacemaker cells is explained, the propagation of action potential in between contractile cells is the final point of interest. As already mentioned, atrial or ventricular cells are usually stimulated by their neighbours. This is called electric coupling. The interface is created by gap junctions. When cells depolarize, there is a overflow of Ca^{2+} and Na^{+} from inside of the cell through the gap junctions to adjacent cells and brings the resting potential up to the voltage level of the threshold potential at – 70 mV, where a new action potential can start over.

2.5.8 Pathophysiology

Fibrillations can be briefly described as unorganized stimuli in high number of recurrent loops causing rapid contractions, observable in atria and ventricles. It is possible to classify arrhythmia by the QRS-complex, the heart rate or its regularity.[174] Two

[172] [38]
[173] [35]
[174] [10, p. 45]

classification lists are attached in the appendix (Tab. 2 and Tab. 3). However, more important are reasons and mechanisms behind fibrillation to derive strategies to treat pathologic heart rhythms. Fibrillation can arise out of pathological tissue changes like edges from myocardial infarction. An other possible reason is a disease that changes the speed of the stimulus transmission or refractory time. A third cause can be an external electric shocks.[175] In direct consequence ventricular extrasystoles appear with very short coupling intervals of R waves, interrupting T-waves. This is called “R-on-T phenomenon” leading to fibrillation.[176] These fibrillation persist, if a second circumstance is fulfilled, the so called “reentry phenomenon” with circus movement progressing the stimulus as long as responsive heart muscle cells are available.[177] Based on the refractory time and the conduction speed, the size of the heart is a determinant factor for stimulation loops to persist. Wavefronts can only continue, if they arrive at cell bonds with finished refractory period. A second aspect is the constitution of the heart. Different studies found out that an ischemic heart requires much higher energy for a successful conversion. It is supposed that a changed stimulus transmission speed and shorter refractory times may support reentry loops.[178]

2.5.9 Electrophysiological aspects with relevance for external discharge

Electric countershocks try to block re-entry loops. The stimulation of ventricular cells in resting potential should bring them to refractory phase at the moment, when reentry loops propagate. To be successful, a “critical mass of myocardium” has to be depolarized simultaneously.[179] If these depolarized cells from fibrillation and defibrillation recover together at the same time, a reorganized rhythm can be introduced by pacemaker cells from SA node right after.[180]

Observations in trials with small animals show, that reentry loops end spontaneously, if there is not enough tissue for a certain length of the loop.[181] The total loop length hast to be bigger than the product out of refractory time (T) and conduction speed (v). Both factors can be affected by certain influences. T can be shortened by medication or hypothermia of the patient and v is slowed down by muscular hypertrophy.[182] This

[175] [39, p. 221]
[176] [40]
[177] [41]
[178] [39, p. 221]
[179] [3, p. 13]
[180] [39, p. 221]
[181] [18, p. 48]
[182] [39, p. 221]

means that the reentry mechanism can be weakened by drug application and purposeful undercooling of the patient and that the mechanism is weakened of own accord as soon as the heart is running out of metabolism supply. This may not be helpful to treat occurring fibrillation but has big meaning for the outcome after conversion.

2.5.9.1 Time aspects with relevance for defibrillation

As just mentioned, the refractory period (tau, τ) has a big meaning for defibrillation. It is also called the action potential duration (APD) and describes the time, where a heart muscle cell is incapable to respond to stimuli. The absolute refractory period (T) lasts about 250 ms until ventricular cells can respond to a new stimulus. Within this time the plateau phase takes about 200 ms and calcium is released from sarcoplasmic reticulum in the last 100 ms of the plateau to provide muscle contraction.[183] The refractory period allows the muscle to relax and protects him from summation or tetanus.[184] The also mentioned speed of the wave front (v) is 0,4 up to 1 m/s. The time since the discharge has begun is indexed as t. In addition to t, there are two more technical time parameter in connection to capacitive discharge waveforms with relevance. First, the shock system time constant (τ_s) and second the cell membrane time constant (τ_m). The shock system time constant quantifies the time of the voltage decrease during discharge, involving transthoracic pathway resistance and the given capacitance of the defibrillator.[185] The time constant of cell membrane (τ_m) has a predictive character because adaptions to cardiac phase durations show a higher effectiveness[186] The time specification for this cell time constant varies between 2 and 5 ms in literature.[187]
Krasteva et al. (2000) claims that there is no convenient method available to measure this tau.[188] Ignoring voltage and time dependant aspects, a simulation of the heart with help of a resistor-capacitor (RC) model can provide an estimation of τm.[189] Mowrey also refers to the membrane time constant and explains how to determine this value. A calculation is possible by the shock-induced membrane potential (ΔV_m) received from the RC network. The voltage of the membrane response curve can be determined by

[183] [42]
[184] [42]
[185] [12, p. 249]
[186] [12, p. 248]
[187] {Krasteva 2001 #39D: 68}
[188] [43, p. 210]
[189] [12, p. 250]

measurements at the beginning and the end oft shock.[190] ΔV_m and τ_m are in a inversely relation. This makes it possible to determine τ_m as usable value to optimize and validating the efficiency of waveforms.[191] Tau helps to find the ideal time until the capacitive discharge should be interrupted to change polarity and immediately resume with the second phase of electric discharge. This procedure is designated as cutting or chopping.

An additional rule for cutting and chapping is mentioned from Cansell and Daskalov. They say that the chopping frequency should be at least 4 times greater than the frequency of polarity changes without further explanation.[192] The times of signal activation T_{on} and signal pause T_{off} are extremely short. In case of Schiller biowave T_{on} = 100 µs and T_{off} = 150 µs. This is too fast for cells to notice any changes.

Assuming that the first phase is modulated perfect, the main task of the second phase is “burping” (set potential at zero) of delivered charges, that could lead to unwanted refibrillations. Therefor the second phase has to be in a good ratio to phase 1.[193] The so called “phase duration ratio” should be < 1 under the condition that the shock system time constant (τ_S) is bigger than the time constant of the cell membrane (τ_M) and the ratio should be > 1 when τ_M exceeds τ_S.[194]

Krasteva et al introduces the index T_r as period of time to return from maximum transmembrane potential (V_m) to initial level. They call T_r the main parameter in waveform efficacy comparison and argue that an inadequate trailing part duration is seen as major factor for failure defibrillation by refibrillations. [195]

2.5.9.2 Rheobase and chronaxie

Rheobase describes the minimal electric current to trigger an action potential in muscle tissue with long-term persistent stimulation.[196] Chronaxie comes from the Greek word *chronos what* means time and axia which means value and describes the minimum duration for an electric current at a voltage two times the rheobase to cause an excitation in muscle tissue. [197] In a strength-duration curve (Fig. 11) the rheobase is the

[190] {Mowrey 2009 #101D}
[191] [44]
[192] {Albert Cansell 2002 #51I: 8}
[193] {Swerdlow 1996 #20D}
[194] {Swerdlow 1996 #20D: 2278–2284}
[195] {Krasteva 2001 #39D: 68}
[196] {Miller 2003 #103D}
[197] {Miller 2003 #103D}

point, where voltage decrease causes no more decrease in threshold or duration and chronaxie is plotted as pulse width for double voltage of rheobase.

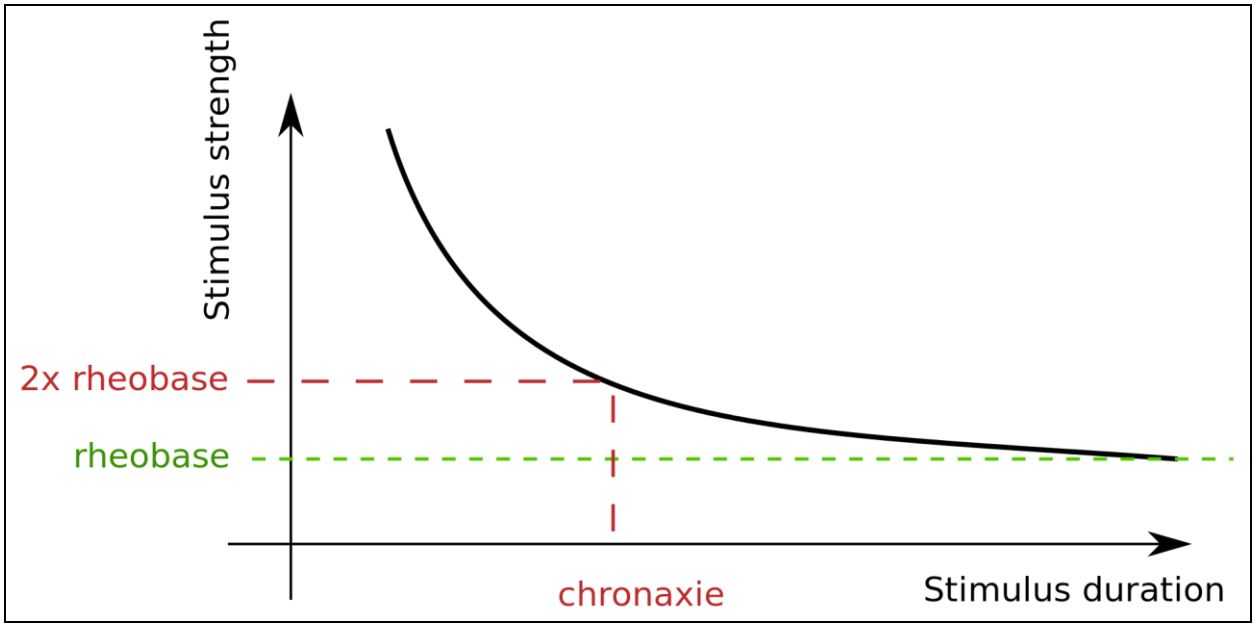

Figure 11: Rheobase and chronaxie in strength duration curve[198]

These values are necessary to define the relationship between current level and pulse duration for muscle cell excitations.

2.5.9.3 Membrane potential optimization

Calcium (Ca^{2+}) is one of two ions that are profoundly involved in signal processing. Ca^{2+} is meaningful for the coupling of electrical excitations, triggering the threshold potential and for the plateau phase of the action potential where a “calcium-induced calcium release” can cause fiber contraction.[199]

Potassium (K^{+}) is the other ion. It is involved in signal processing. K-ions provide the diastolic membrane potential and regulate the degree of excitability.[200]

It is known that more K^{+} outside makes defibrillation easier because lower voltages are required for depolarization.

Bradley and Salil (2003) show that diastolic threshold first decreases and later increases by rising extracellular potassium concentration. This leads to considerations

[198] {Sav vas 30.09.2019 #105}
[199] {Valentinuzzi 2011 #13D: 50, 51}
[200] [18, 50, 51]

to avoid making additional excitations and focus on breaking excitations. Make and break phenomena a described in relation to ICD technology. This is the reason that papers use anode and cathode for description. The anode make is the primary mechanism of excitation during diastole and anode break is the mechanism during the refractory period.[201]

2.5.9.4 Boundaries of the RC model

The cardiac cell model, represented by a RC circuit, can simulate the heart cell characteristic driven by membrane potentials. Predictions of this model are practically verified in animal and human trials and it is useful to get values like the shock-introduced membrane potential to derive τ_m for an efficacy determination.[202] On the other side, it is important to mention that there are also some limitations, this model has. The passive RC model can not simulate the membrane response at the plateau phase of the action potential.[203] It is not possible to simulate tissue heterogenicity and to include the behaviour of active ionic currents.[204] In addition to that there are no experience yet, if the RC model can represent break excitation effects too.[205]

2.5.10 Electrophysiologic effects of high electric field strength

Since monophasic waveforms with high-energy had their debut in transthoracic defibrillation, current came into focus of investigations. 1979 Gold et al. documented animal studies with decreasing shock success while current accelerated over 50 A. 1988 Kerber et al. found out that defibrillation success is related to increasing peak currents beyond 41 A for MDS-shocking,[206] so peak current showed a high impact for monophasic defibrillation efficacy. These animal findings and clinical results can be explained by two effects which appear in the myocardium, if high electric field strength occurs.

First there is electroporation causing prolonged unexcitability, and on the other side the risk of new impulse formations.[207] Electroporation makes holes into the cell membrane.

[201] [45, p. 1351]
[202] {Kroll #19D: 250}
[203] {Zhou 1995 #106D}
[204] {Kroll #19D: 250}
[205] {Kroll #19D: 250}
[206] [8, p. 1380]
[207] [8, p. 1380]

These pores permitting the influx of calcium and potassium into the cell with the result that earlier generated afterdepolarizations have a spontaneous electrical activity. In places of delayed conduction, excessive prolongation of refractoriness can appear. This delay holds the danger for reentry. One single effect or the combination of both mechanisms can threaten the successful defibrillation or give refibrillation a chance.[208] Later on effects of biphasic waveforms were investigated. Their efficacy is unaffected by patient impedance.[209] BTE-shocks showed less harmful effects on hemodynamic performance and myocardial oxidative metabolism in animal trials.[210] Also here the consequences of unnecessarily high energy delivery and multiple shocking is analysed.[211] Low energy biphasic pulses produce less cell membrane damage, detectable by ECG ST-segment-shifts. In relation to the level of shock energy, membrane effects of cell wall electroporation or direct membrane depressant occur[212] and post shock there are free ascorbyl radical formations.[213]

High-energy countershocks also cause the cellular effect of mitochondrial dysfunction.[214] Again, each single effect or the combination, produced by high-energy application, leads to bradyarrhythmia and a myocardial depression.[215] Further abnormalities and their persistence related to the energy-dose are: impairment in left ventricular contractility and relaxation, left ventricular end-diastolic pressure increase, cardiac index (CI) decline and systemic lactate level rise. This shows that despite of defibrillation success the energy-strength has an inverse effect on survival.[216]

Facing that a single application of an electric countershock may cause many primary and secondary effects by current or energy, it is easily comprehensible, that subsequent shocks (not talking about subsequent phases) affect cells even more. The risk rises especially because of measurements that show a decline of transthoracic impedance. But this is much more a technical appearance caused by temperature rise and not a electrophysiological effect listed in table 1.

[208] [8, p. 1380]
[209] [8, p. 1381]
[210] [8, p. 1381]
[211] [8, p. 1381]
[212] [8, p. 1381]
[213] [8, p. 1381]
[214] [8, p. 1381]
[215] [8, p. 1381]
[216] [8, p. 1381]

Table 1: Primary and secondary electrophysiological effects of high electric field strength at the heart muscle

ME	Membrane-effect
CE	Cell-effect

Secondary effects:	Prolonged unexitability	New impulse formation / reentry	Brady-arrhythmia	Myocardial depression	Left ventricular contractility and relaxation impairment	Left ventricular end diastolic pressure rise	Cardiac index decline	Systemic lactate level rise	ST-segment depression
Primary effects by:									
Current (monophasic shocks)									
Electroporation	ME								
Spontaneous depolarization		CE							
Primary effects by:									
Energy (biphasic shocks)									
Cell wall electroporation			ME						
Membrane depressant			ME						
Free ascorbyl radical formations			ME						
Mitochondrial dysfunction				CE					
Primary effects by:									
Multiple shocking									
Ischemia			CE	CE	CE	CE	CE	CE	CE

Studies with cardiac mapping demonstrated, that the stimulation of mycardium arrives 100-500 ms after the defibrillation pulse is delivered.[217] From the emitted energy only 15% may arrive at the heart muscle. This must be a enought to create a wavefront. Too small values beneath chronaxy are highly suspected to cause refibrillations.

2.4 Waveform efficency comparison

A comprehensive research on waveform efficiency leads to several findings. First, as already mentioned at the beginning, monophasic high-energy shock applications with

[217] [8, p. 1375]

step-up protocols are not evidence based by clinical trials.[218] Further, literature often describes waveforms in combination with energy values but rarely refers to the role of voltage or current during defibrillatory discharge, although it is much more complex to say which is the most adequate parameter to describe the nature of a waveform.[219] Finally researchers use different approaches in their studies to compare waveforms. It is necessary to explain them briefly to argue which methods are chosen here.

The AHA publishes methods for electrophysiology laboratory to demonstrate equivalence or superiority of new waveforms drawn up by the Task Force on Automated External Defibrillation (Subcommittee on AED Safety and Efficacy)[220] This approach is considered for practical testing.
The statistical interpretation states, that the equivalence in efficacy of a new waveform is given, if the upper limit of the 90 % two sided confidence interval (CI), representing the difference between the two temporal patterns, and if the new pulse is smaller than 10 %, which permits a 5% chance to approve the waveform despite this pulse is >10 % less effective.[221] The superiority of a new waveform can be attested, if the upper limit of the 90 % two sided confidence interval, representing the difference between approved and new pulse, is smaller 0 %. In this case the new pulse is superior to the approved one. Superiority is also given, if the efficacy of the approved pattern equals 90 %, and the hypothesized new pulse efficacy is 95 %.[222]

Based on already collected data, two methods are commonly used to compare different defibrillation waveforms: fixed efficacy and fixed energy.[223]

a) The fixed efficacy approach varies the shock strength until it is possible to estimate the strength to obtain a fixed efficacy. Afterwards the 50 % efficacious strength is defined as ED50.[224]
b) The fixed energy approach, analyses the same shock strength many times until an estimate of the efficacy can be made.[225]

[218] [8, p. 1380]
[219] [18, p. 64]
[220] [8, p. 1374]
[221] [26, p. 1681]
[222] [26, p. 1681]
[223] [46, p. 362]
[224] [46, p. 362]
[225] [46, p. 362]

McNeymar is a statistically powerful paired tests which allows to compare the efficacies of waveforms using Z as figure of merit with positive and negative range. Z-values <0,0 indicate improved efficacy, Z-values > 0,0 show reduced efficacy.[226]

A comparison of multiphasic waveforms is proposed to be based on recordings of transthoracic impedance (TTI), determination of delivered energy, peak current and ST segment shifts before and after shocking in relation to calculated defibrillation thresholds (DFT) in each shock [227]

DFT_{50} and DFT_{80} should be references representing 50 % and 80 % probability of success. As DFT corresponds to current and energy, these two values are compared after drawing a dose-response curve for each pulseform which was tested.[228]

Two former indices should help to find differences in efficiency between RBW, PBW and CCLL by comparison. First k_f should be calculated by the ratio between delivered energy W and a reference energy W_0 with a rectangular pulse of the same duration and voltage drop. Secondly ηC should show, how many energy oft the capacitor W_{C0} was utilized therefore.[229]

$$\eta C = W / W_{C0} \qquad (2)$$

The last approach is based on stimulus strength-duration. The strength and duration of a stimulus should determine ability to excite. The approach refers to the strength-duration curve, which was already introduced to explain rheobase and chronaxie and is reported as highly predictive for a pacing stimulus The model intends to derive pedictions of succes from the remaining charge of the second phase. As a basic assumption impedance has to remain contsant during defibrillation. The intergral of voltage and the average current are proportional in a certain range and the duration is defined as the time between the first change in voltage and the last change in voltage (pauses included, or total stimulus duration) or as the time that current was actually delivered. (pauses excluded).[230]

[226] [46, p. 362]
[227] [9, p. 1049]
[228] [9, p. 1048]
[229] [22, p. 45]
[230] {MALKIN 2002 #18D: 362}

3 METHODS

Outgoing from the research-question: Which pulseform is optimal for a successful automated external defibrillation with minimized energy? – a comprehensive search for clinical data is intended to show already accomplished research and limitations.

3.1 Research – systematic review

Systematic reviews or meta analysis are valuable tools for tracking down strong scientific evidence and answer research questions.[231] While metanalysis tries to find evidence on statistical ways focusing on numbers how often topics in scientific literature are republished or cited, the more appropriate tool here is the application of a systematic review to answer which energy reduction potential for external defibrillation exists. The advantage of a systematic review is the more critical focus on the content of articles and books.

“Developing a Comprehensive Search Strategy for Evidence Based Systematic Reviews” by DeLuca, Mullins, Lyles[232] gives a good guideline, how to collect papers carefully and make this work reproducible. To find all information, it is necessary to do a comprehensive search with manual and automated search components. Focusing on low energy, high efficacy shocking with automated external defibrillation technology, this topic has three defined key domains:

- Automated External Defibrillation
- Waveform design for defibrillation
- Cellular electrophysiology of heart muscle cells

A lot of physiological basic knowledge comes from ICD-technology. To avoid too much misleading articles about internal cardiac defibrillation, articles referring to cellular electrophysiology are accepted, but articles dealing with ICD-specifications and hardware are excluded.

Though this topic has a lot of aspects to take into consideration, it is helpful to formulate a main research question for answering, and visualize all detailed questions in a mind

[231] [47, p. 4]
[232] [47]

map to keep an overview of things to clarify. The formulated central research-question is: Which pulseform is optimal for a successful automated external defibrillation with minimal energy? The created mind map is attached in the appendix (Fig. 16) (A 3).

3.1.1 Manual search

Manual searching can complement automated searching[233] but it also helps to prepare automated searching. Starting point for manual searching in this work are guidelines from ERC (2010, 2015) and ECC (2015) published by the American Heart Association. Those guidelines bring up further normative aspects and papers from the reference list, but searching by references does not work for long, because these references in papers only lead to older papers. So it is also necessary to look for key authors of this topic, journals plus patents from creators.

The manual search provided a list of 65 titles. With the help of Citavi-software it was possible to organise cites, write down the main information, make tags and assign each cite to the referring chapter of this thesis. Inspired by MEDDEV the relevance of each paper was evaluated. Based on index terms, collected by citing, it was possible to derive keywords. They should help to find further relevant papers. From the first 65 papers, 275 tags were derived. Checking them for relation between each other and relevance can narrow down the list. In this case 59 main keywords with related keywords, truncation, proximity and phrases remained.

3.1.2 Automated search

3.1.2.1 Database Selection

To search through the about 14.000 published biomedical journals available, it is recommended to use electronic databases because no database offers all available citations so multiple databases should be searched through.[234] Here the primary chosen database is MEDLINE. It is the most common electronic database in health care[235] provided from NCBI with public access for research over PubMed. Parallel used databases are Thieme, Springer and ScienceDirect which is provided by Elsevier.

[233] [47, p. 6]
[234] [47, p. 6]
[235] [47, p. 7]

3.1.2.2 Developing Automated Search

It is important to identify medical subject headings (MeSHs). Therefore all citations are analyzed to create a list of MeSH terms. Examination of the subject indexing helped to identify relevant terms and expand the search.[236]

Ongoing from the list of 59 Keywords, evaluation of potential MeSH terms on the MeSH Browser of the National Library of Medicine was conducted. This Browser is linked to MEDELINE. Some searching for Keywords was without entries or results had no relevance for this work. All 9341 hits had to be checked. 80 hits had relevance and sometimes led to important related terms. Finally there were 120 possible MeSH terms listed with (if available) scope note, entry term, related term and previous indexing.
In the next step this terms had to be associated to the 3 key domains. Here it was possible that on keyword was listed in two domains.
Scope notes are useful definitions on the one hand but they also help to check the relevance of subject headings. Related terms are also checked to broaden the search or narrow it down.
Finally the list of MeSH terms for AED was reduced from 50 to 39. The domain cellular electrophysiology stayed almost unmodified with 64 MeSHs and third key domain waveform grew from 16 to 52 terms because there were not many hits in the MeSH-Browser but a lot of related terms from the previous keyword-collection had to be included to find relevant articles concerning waveform design in other databases besides MEDELINE.

So the three lists were adapted with terms that had no result in the MeSH Browser but were definitely important in other databases to find relevant papers for this work.

MEDELINE is the only chosen databases that allows refining by so called subheadings. This is helpful, if MeSH terms are still too general to find relevant papers. For other databases refining only works by truncation and proximity techniques.

Narrowing down the search was possible by specific keyword phrases (i.e. first shock, first phase) and finally automated search could be prepared by Boolean operators that combine terms within one domain (“OR”) or create cross referencing (“AND”) between

different domains. For conducting automated an manual search, all citations received a note of year and database and were assigned by an unique batch-number to enable examination of each database by year.
Checking for citation-duplicates narrows down the results from MEDLINE, Thieme, Springer and ScienceDirect.

3.2 Waveform efficacy determination

The second part of the methods emerges from knowledge collected by systematic collection of relevant papers. A qualitative analysis of defibrillation reports requires peer reviewed publications that fulfil the following criteria:

i. Cases of emergency medical service (EMS) response to out-of-hospital SCAs
ii. Distinction between first shock and all defibrillation efficacy
iii. Information about waveform type in combination with which energy level
iv. Sample size of minimum 20 patients.

Excluding-criteria are:

i. Mixed, inseparable application in-hospital and out-of-hospital
ii. Mixed application of different waveforms.[237]

Meanwhile there is the goal to find the best waveform with least energy consumption, energy is seen as the parameter that provides a handy application but not as most adequate parameter to compare waveforms to reach this aim. So efficacy determinations focuses on voltage, current and time aspects.

There are several approaches to predict defibrillation success by RC network simulation. The simulation of the cell membrane helps to find out, how pulses can be optimized.[238]
The calculation of the cell membrane time constant (τ_m) allows predictions for optimal waveform efficiency. It is also usable to determine the phase duration ratio (between phase 2 and phase 1). This value is expected be ≤ 1 for a good phase ratio.

[236] [29,[30, p. [237] [8, p. 1379]
[237] [8, p. 1379]
[238] {Kroll #19D: 250}

Further, the RC model helps to determine if the second phase is in adequate length to guarantee a optimized efficiency.[239]

The optimal phase-duration ratio depends on the defibrillation system time constant (τ_S).[240] It is the time required for a voltage drop to 1-e^{-1}. (3)

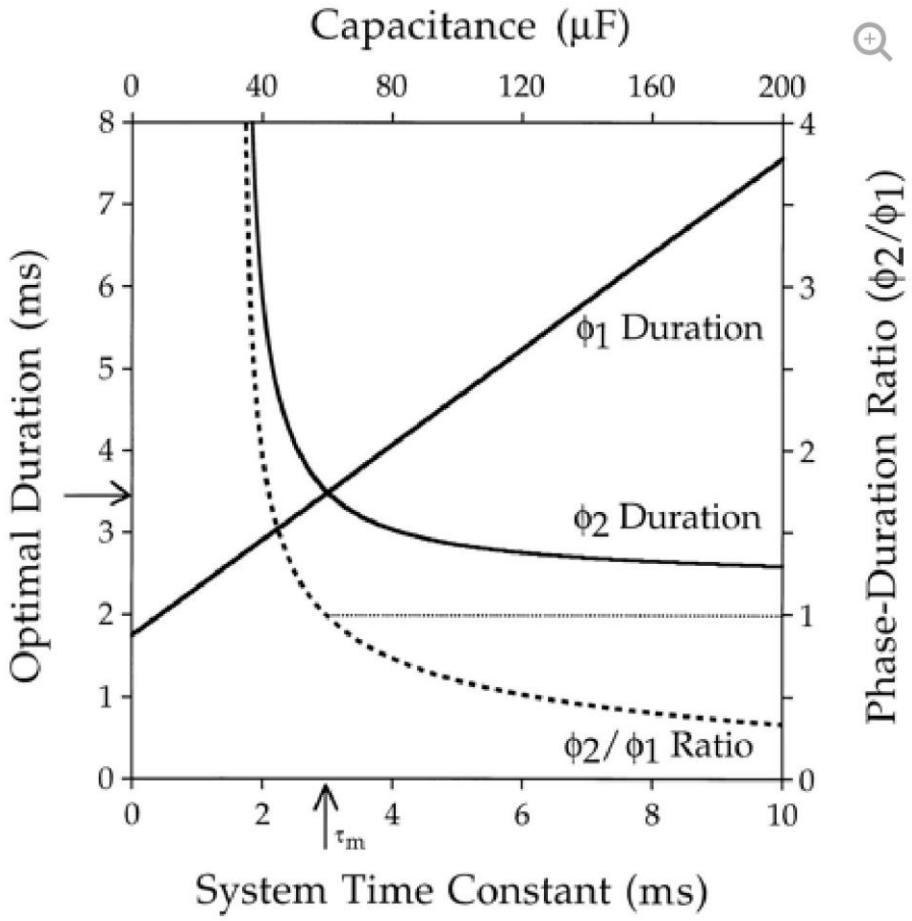

Figure 12: phase duration determination by cell time constants[241]

A second way to determine waveform efficacy uses the average current in combination with the strength-duration curve (Fig. 11).

$$I(\tau) = I_{\text{Rheobase}} \cdot (1 + \frac{\tau_{\text{Chronaxie}}}{\tau}) \quad (4)$$

Koening equation based on Weiss-Lapique law[242]

[239] {Swerdlow 1996 #20D}
[240] {Swerdlow 1996 #20D: 2278–2284}
[241] {Swerdlow 1996 #20: 2281}
[242] {Schönegg #59}

This equation by Koning is in equivalence to the Weiss-Lapique stimulation law with assumed rheobase, chronaxie and duration allows a calculation of the average current.

For efficacy-comparisons of different waveforms, some basic determinations should be done and the RC model can be helpful again to predict the difference in defibrillation success. Additionally, the reserve of energy (RE) can be calculated in advance. This term is defined as maximum energy available devided by the average treshold energy for successful defibrillation.[243]

A general impedance value should be defined and the initial capacitive voltage has to be selected for all waveforms to deliver the same dose of energy and receive comparable current and voltage results. Criteria of comparison can be the differences in mean current, occurring resistance, ST-segment shifts and most important, the number of transient rhythm and conductance disturbances after the shock.[244]

4 RESULTS

Brief statements to every variable of defibrillation should now clarify how big their impact is, which possibilities are good to evaluate efficacy of a single waveform and how it might be possible to do an objective waveform comparison between different waveforms.
The actual defibrillation occurs 100 to 500 ms after an external shock is delivered. A sample calculation with 2000 V and 30 A for 0,5 seconds delivering 300 J shows that only 5 to 15 % of the energy emitted, reaches the heart.[245]

4.1 Technical parameters with relevance

Outstanding is the factor of time to treatment. The earlier SCAs are treated, the less ischemia is in progress and the better the heart muscle can perform impulse conduction. But it is important to analyse and rank the relevance of many parameters affecting external defibrillation. Low efficiency of a shock is as worse as harming energy overdoses because every unsuccessful defibrillation is a waste of time. Especially pre-shock pauses get underlined by ERC Guidelines from 2015 as time that has to be kept

[243] {Krasteva 2001 #39D: 69}
[244] {Krasteva 2001 #39I: 71}

to an absolute minimum.[246] The shock protocol can be an issue for harmful delays in resuming CPR. Monophasic shocks lead to a 37 seconds delay by rhythm analysis until first post shock compression begins while biphasic first shock efficacy of over 90 % allows to start immediately with CPR instead of analysing, if additional shocks should be given.[247]

4.1.1 Impedance

Assuming that time-to-shock issues are kept ideal, many research work on electric counter-shocks puts energy and waveform into focus. But primarily it must be verified, how effective energy-delivery works.[248] Since transthoracic impedance influences the intracardiac current, the electrode interface is one of the significant determinants for defibrillation success.[249] With slightly lower resistance-results, antero-posterior self-adhesive pad position is favourable.[250]

4.1.2 Voltage

Voltage has a big importance in electrophysiological procedures because cellular interactions are based on ion flow and many ion channels are voltage gated. So external voltage is a critical parameter and has big impact for effective conversion. It is possible to describe the electrical field interacting with the myocardium as spatial derivate of potential.[251]

4.1.3 Current

Current is suspected to be the best parameter to compare waveforms. Although voltage and energy-level are also descriptors of waveform design, current is actually the critical parameter for defibrillation.[252] The peak current is the highest current occurring over the course of a shock but depending on the impedance also a risk factor for myocardial

[245] [39, p. 222]
[246] [4, p. 113]
[247] [25,[26, p. 209][3]
9][3]
[249] [30]
[250] [30]
[251] [12, p. 248]
[252] [3, p. 15]

damage.[253] So, it is important to pay attention to the body weight and the patients´ impedance to make sure that the wanted amount of energy is delivered.[254] To formulate this in the manner of cause and effect: The delivered energy causes, dependent on patients constitution, a certain peak current. With an increasing peak current, the probability of a conversion increases.[255] At a certain point, there comes an energy-level, where efficacy has no more improvement.[256] This shows that current is in direct relation to concepts of defibrillation threshold and electric dose and has influence on membrane behaviour.[257] The determination of the right dose is a crucial point. Without a direct interface to the myocardium, AEDs can only assume the membrane potential. The difference of membrane potential of fibers remaining unexcited (in resting potential) during fibrillation and the threshold potential would determine the ideal current to overcom the defibrillation threshold – keeping in mind that this stimulus must be present at the ventricles after passing all layers in between.[258] A simulation of current-behaviour dependent on different body impedance values is attached in the appendix (A 7).

Calculation of the root mean square current (I_{RMS})

$$I_{RMS} = U_{RMS} / TTI \quad (6)$$

is based on the root mean square volteage (U_{RMS}) devided by the measured or assumed resistance (TTI)

$$U_{RMS} = U_{max} \times TTI \times F / (Phase\ 1 + 2) \times (1 - e^{(-F / (TTI \times F))}) \quad (7)$$

The average current is a very interesting point. The value can be calculated with help of the Weiss-Lapiqe equation with assumptions of chronaxie and rheobase derived from strength-duration curve.[259]

Since average current affects the myocardium over the time of the shock, this value can be used as determinant of defibrillation efficacy.[260]

[253] [13, p. 28]
[254] [18, p. 39]
[255] [3, p. 22]
[256] [3, p. 22]
[257] [18, p. 39]
[258] [18, p. 51]
[259] {Schönegg #59}
[260] [13, p. 28]

4.2 Waveform

Basically the energy-level appropriate for one certain waveform can be inappropriate for another one.[261]

Efficacy increased with every step of waveform-development from monophasic to biphasic but the responsible mechanisms of these improvement are hard to find. There is not yet an approved method to construct or predict the optimal defibrillation waveform absolutely accurately.[262]

The basic understanding of interaction between physiological and technological parameters is very important. In the center there is the stimulus. As a single pulse, it is defined by amplitude and duration. The rising and falling times are negligible for cardiac processes because the time-range of electric parameters is much smaller than durations in cardiac cells. They operate between 10 and 500 ms. Electrical signals are perceived rectangular from cardiomyocytes. A train of rectangular pulses leads to other relevant descriptors. First, the frequency of repetitions in pulses per second or minute. Second the on-off-ratio with numbers between 0 and 1. They are calculated by the time current is applied in relation to the repetition period. And the last descriptor is the overall duration including the total number of pulses.[263]

4.2.1 Waveform – duration

As ICD trials show, adaptions to the cardiac cell membrane time constant (τ_m) improves effectiveness. For transthoracic applications pulse response ensues with slightly time shift and is depending on cell time constant, cellular, intracellular, ionic and tissue properties.[264]

4.2.2 Waveform – response of impedance

The transthoracic resistance changes during defibrillation. Actually it is expected that this impedance rises with subsequent phases but the opposite thing happens due to

[261] [3, p. 25]
[262] [46, p. 366]
[263] [18, p. 28]
[264] [12, p. 248]

nonlinearity of low voltage pulses.[265] Impedance compensation can reduce waveform durations to optimize the signal. High-impedances can lead to physiologically active currents for up to 40 ms without triggering the threshold. Impedance compensation should guarantee maximum duration of not more than 20 msec.[266]

4.2.3 Waveform – phase number and ratio

Basically there is a reported decline in shock success with subsequent phases. Phase ratio for biphasic or multiphasic shocks is specified in % of the waveform duration. The phase percentage receives attention for defibrillation success predictions.

There should be at least two pulses whereby the first discharge should cause as many voltage changes in membrane as possible and the second shock should remove the charges of the first shock back to zero potential.[267] Excess charges are a risk for refibrillations, their elimination is also called charge-burping.[268]

But not only the number, furthermore there should be a certain ratio between these (at least) two phases. The so called “phase duration ratio” has to be < 1 under the condition that the shock system time constant (τ_s) is bigger than the time constant of the cell membrane (τ_m) and the ratio should be >1 when (τ_m) exceeds (τ_s).[269]

Although some authors claim that there is no need to think about more than two phases since a deep electrophysiologic manipulation is already done within the first two phases, ERC Guidelines from 2010 see potential in triphasic or quadriphasic waveforms since trials with animals imply that multiphasic waveforms work with low-energy and cause low post-shock myocardial dysfunction. However, those findings only base on short time VF conversion studies. Validation studies in human research are missing and comparison with biphasic results are not available. Also no device with multiphasic protocol is available on the market.[270]

4.2.4 Waveform – shape

Interesting proposals for modifications of the waveform shape are described in connection with triphasic wave defibrillation. First, polarity changes can reactivate fast

[265] [43, p. 210]
[266] [8, p. 1381]
[267] {Kroll #19D: 247}
[268] {Cansell 2002 #45I: 223}
[269] {Swerdlow 1996 #20D: 2278–2284}

excitation channels of the membrane. This leads to a lower defibrillation threshold providing a reduced energy consumption.[271] As a second recommendation, the tail of subsequent pulses should always undershoot the initial phase. This provides less myocardial damage.[272] Finally there is a conclusion that modifications between squared and round pulse formations have no impact for safety and efficacy.[273]

4.3 Suspected mechanisms

Since many improvements in waveform-efficacy are not explained yet, there are suspected mechanism. The 3 most promising hypotheses concerning waveform sensitivity of defibrillation are examined in combination with 126 different waveform-patterns.[274]

4.3.1 Charge banking and charge burping

Delivered charge contains the processes of charge burping and charge banking. Predictions of waveform-efficacy would be possible, if the remaining charge at the end of the pulse influences efficacy. This observation only works for very short time constants (Tau < 2 ms) which is far below physiological typical time constants. The common range is 0.5 to 4 ms. In these limits, there is no predictable minimum charge in RC-model membranes. Further research has to clarify in this context, if cardiac tissue has a different physiologic situation.

4.3.2 Frequency concentration

Frequency concentration is the second aspect, suspected to allow predictions on waveform-efficacy. Most efficient waveforms seem to be between 40 and 160 Hz. Waveforms have to be converted by Fourier transformation to examine the frequency-domain divided into peak frequency representing the frequency with maximum power, median frequency (half power), normalized power at peak frequency (the power at peak frequency divided by total power of the waveform) and to extract the percentage of total

[270] [48, p. 551]
[271] {Janice L. Jones, Ronald E. Jones #54D: 5}
[272] {Janice L. Jones, Ronald E. Jones #54D: 5}
[273] {Janice L. Jones, Ronald E. Jones #54D: 5}
[274] [46, p. 366]

power measured between 40 and 160 Hz.[275] Only from normalized power at the peak frequency, it is possible to derive significant information about efficacy.

4.3.3 Stimulus strength and duration

Delivered strength and duration determines excitement. In order to do this determination, the drawn strength-duration-curve might be highly predictive for a pacing stimulus, but also here the meaningfulness concerning efficacy of a waveform is limited. While strength is defined as the peak current of the waveform, efficacy can be predicted for maximum strength, minimum strength and maximum of the total value but not for total charge. Duration is defined as either complete pulse from onset to offset including breaks or the pulse time excluding breaks for polarity-changes. The only valuable result, derived in testing duration with parabolic fit, was that the minimal conversion is at 11 ms. Reaching all fibers should be the ideal situation but a percentage of total ventricular mass that has to be converted is not clearly determined yet. The range of reported values goes from 28 % to 78 %.[276]

5 DISCUSSION

There is no certain method to develop an optimal waveform for electric countershocks since these many parameters make each conversion individual.

To draw a conclusion out of physiological aspects with influence on defibrillation, cellular effects in electric fields and influential parameters, compiled in the chapter of results, there have to be made some constraints.

First of all, shock energy is the most often occurring performance metric in defibrillation-studies.[277] Also this thesis started with energy as central parameter. But shock strength is not suited for a determination of effectiveness.[278] Assuming energy as the main-aspect, it would be enough to connect 4 small 9 V batteries in a row to apply a sufficient shock of 170 J by calculating:

$$\text{Energy} = \text{Voltage}^2 \times \text{Duration} / \text{Transthoracic impedance} \quad (5)$$

[275] [46, p. 362]
[276] [18, p. 48]
[277] [12, p. 248]
[278] [12, p. 248]

(170 J = 36 V x 36 V x 10 ms / 75 Ω). But this is not possible since voltage, peak and average current shows significant impact. And the usage of energy as reference leads to big difficulties to compare data. It is much better to design waveforms by physiological and technical parameters.

Physiological parameters try to use the cell-characteristics of membrane potentials to reorganize the interaction of myocardial cells, whereas technical parameters have to manage that the delivered energy reaches a critical mass in a therapeutical dose. Often there is no clear separation. Considerations in physiological terms without electronic constraints might be helpful to overthink strategies.[279]

But one big constraint that has to made is the method of waveform generation. Capacitive discharge is the only system for portable solutions at the moment. Other waveform-types need big generators or self-oscillating RLC-circuits. Although patterns like rectangular, sawtooth pulses with rising edge, rounded signals with decay or exponential rising pulses proved superiority to capacitive discharge patterns, technical limits in size make them impracticable.

Based on the pattern, calculations of strength duration curve with тm are useful for waveform optimizing and efficacy prediction. For technical waveform considerations, the average current should be calculated.

In last stage after these parameter are involved to create a good waveform shape, energy comes into charge because the energy stored by capacitor is a determinant of the defibrillator-size .This means that energy remains the final parameter to choose one waveform. Time to treatment has a bigger impact on the patient´s outcome than all minor waveform-optimizations.

Two is the minimum number of shock phases due to the mechanism of charge burping that prevents immediate refibrillations.

Multiphasic waveforms remain an option that needs further research.

All considerations about conversion of a critical mass of myocardium assume that electrophysiological behaviour of fibers is normal during fibrillation.[280]

Valentinuzzi reports that next to several physiological pre-circumstances a successful shock needs to bring enough cells to refractory period.[281] This is the essence of so many research that has been done on defibrillation. But since guidelines state that efficiency of biphasic waveform development is at the edge and rethinking of the whole

[279] [12, p. 250]
[280] [18, p. 51]
[281] [18, p. 51]

research might be necessary, it would be the most radical approach to focus on keeping cells in refractory period until a critical mass of them is collected to resume with a synchronized activity? Waiting for cells and hold them back to perform refibrillations instead of forcing them to refractory period by defibrillation might have a much lower energy consumption. Make and break phenomena might be an interesting topic to do further research. Since one whole cell cycle has a duration of about 5 ms, it would be necessary to wait until the critical mass of cells comes to refractory period and hold first cells of this 78% in refractory state until the threshold is reached to let them resume a synchronized activity.

6 CONCLUSION

In general, external defibrillation stands for electricity, guided through the thorax, affecting a critical mass of myocardium, terminating a chaotic activity of the heart's electrical system, while preventing refibrillations and cardiac injury - may it be shock induced or in a result of undersupply. Due to the complication that external defibrillation has to deliver the life saving energy without direct contact. The quality of shock is divided in effectiveness and harmlessness of the shock.

Electrical parameters like phase duration, voltage, current and physiological aspects like cell time constant, membrane potentials or conductance as well as side influences like pad position, electrode contact, transthoracic impedance forming a complex interaction of cause and effect.

The superiority of one defibrillation waveform is very hard to prove due to the high amount of variables. To decide for one pulse curve, it is important to see the effectivity for the first shock, subsequent shocks, the risk of refibrillation and the post shock effects to evaluate the outcome for patients. Additionally it should be possible to realize the signal with small and light hardware to provide ubiquitous access to AED devices.

Since average current is unveiled as parameter that is predictive for defibrillation success and useful for comparison of waveform efficacy, the title of this work does not lose its relevance because energy remains the outstanding parameter for technical implementations. High frequency chopped capacitive discharge waveforms shows a recommendable performance by its average current and the low energy consumption that allows faster performance between shocks with smaller capacitors. As a bonus aspect, it reduces the battery-size what makes devices maybe cheaper, affordable and is still conform to the requirements of EN 60601-2-4:2011 – 201.101 on charging-time.[282]

May this work help to dive rapidly into this complex topic to investigate new findings, place them into ratio to the explained mechanism and draw new conclusions to clearly define limits that are needed from manufacturers to find technical solutions.

[282] [6, 36,37]

7 REFERENCES

[1] L. S. Lilly and M. E. Mendelsohn, *Braunwald's heart disease: Q66 Review and assessment*. Philadelphia, PA: Elsevier, 2019.

[2] A. C. Scholten, J. G. van Manen, van der Worp, Wim E., M. J. IJzerman, and C. J.M. Doggen, “Early cardiopulmonary resuscitation and use of Automated External Defibrillators by laypersons in out-of-hospital cardiac arrest using an SMS alert service: Q11,” *Resuscitation*, vol. 82, no. 10, pp. 1273–1278, 2011.

[3] Phillips, “Manual Phillips FR3 - Details inkl Literatur: Q12,”

[4] J. Soar *et al.,* “European Resuscitation Council Guidelines for Resuscitation 2015 - Section 3 - Adult advanced life support: Q02,” *Resuscitation*, vol. 95, pp. 100–147, 2015.

[5] Monsieurs, Nolan, Bossaert, Ed., *ERC Guidelines for Resuscitation 2015 - Leitlinien Kompakt (deutsch): Q01*. Section 2: Adult basic life support and automated external defibrillation, 1st ed.

[6] *OEV_OENORM_EN_60601-2-4_2012_06*.

[7] American Heart Association, *Part 4: The Automated External Defibrillator: Q63*. Key Link in the Chain of Survival. [Online] Available: https://ahajournals.org/doi/full/10.1161/circ.102.suppl_1.i-60. Accessed on: Sep. 16 2019.

[8] J. E. POOLE *et al.,* “Low-Energy Impedance-Compensating Biphasic Waveforms Terminate Ventricular Fibrillation at High Rates in Victims of Out-of-Hospital Cardiac Arrest: Q15,” *J Cardiovasc Electrophysiol*, vol. 8, no. 12, pp. 1373–1385, 1997.

[9] Y. Li *et al.,* “Comparison of efficacy of pulsed biphasic waveform and rectilinear biphasic waveform in a short ventricular fibrillation pig model: Q04,” *Resuscitation*, vol. 80, no. 9, pp. 1047–1051, 2009.

[10] American Heart Association, “ECC Guidelines 2015 part-7-adult-advanced-cardiovascular-life-support: Q03,”

[11] G. P. Walcott, C. R. Killingsworth, W. M. Smith, and R. E. Ideker, “Biphasic waveform external defibrillation thresholds for spontaneous ventricular fibrillation secondary to acute ischemia: Q14,” *Journal of the American College of Cardiology*, vol. 39, no. 2, pp. 359–365, 2002.

[12] M. W. Kroll and C. D. Swerdlow, “Optimizing defibrillation waveforms for ICDs: Q20,” pp. 247–263.

[13] Hector Rich, “Different Waveforms, Different Results Understanding the Differences Between Biphasic Technologies: Q76,” 2015.

[14] A.Y.K. Chan, *BIOMEDICAL DEVICE TECHNOLOGY: Q68 Principles and Design*: Charles C. Thomas, publisher, Limited, 2016.

[15] M. D. P.K. Verma, *Principles and Practice of Critical Care: Q69*: B.I. Publications Pvt. Limited, 2006.

[16] Schröttner Jörg, Neubauer Robert, “V4_Medizinische Gerätetechnik.pdf: Q09,”

[17] J. C. Behr, L. L. Hartley, D. K. York, D. D. Brown, and R. E. Kerber, “Truncated exponential versus damped sinusoidal waveform shocks for transthoracic defibrillation: Q70,” (eng), *The American journal of cardiology*, vol. 78, no. 11, pp. 1242–1245, 1996.

[18] M. E. Valentinuzzi, *Cardiac Finrillation-Defibrillation, Clinical and Engineering Aspects: Q13*. S.181-184. Singapore, Hackensack, N.J: World Scientific Pub. Co, 2011.

[19] J. L. Jones and R. E. Jones, “Postshock arrhythmias--a possible cause of unsuccessful defibrillation: Q79,” (eng), *Critical care medicine*, vol. 8, no. 3, pp. 167–171, 1980.

[20] The American Heart Association, “ECC Guidelines 2015 part-2-evidence-evaluation-and-management-of-conflicts-of-interest: Q10,”

[21] American Heart Association, Ed., *Part 4: Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Q62*, 2015.

[22] Dotsinsky, I., Krasteva, V.T., Kostov, J., Mudrov, T., “Is there an Optimal Shape of the Defibrillation Shock: Constant Current vs. Pulsed Biphasic Waveforms?: Q36,” *INT. J . BIO AUTOMATION*, no. 17(1), pp. 45–56, 2013.

[23] Heinz Bucher, “Defibrillator with improved output stage,” US 2006/0004415 A1, Jan 5, 2006.
[24] Janice L. Jones, Ronald E. Jones, “Triphasic wave defibrillation,” US4637397 A US 06/739,133, Jan 20, 1987.
[25] I. D. Albert Cansell, “Impulses or a series of impulses for defibrillation and device to generate them,” US6493580 B1 US 09/492,348, Dec 10, 2002.
[26] R. E. Kerber *et al.,* “Automatic external defibrillators for public access defibrillation: Q71 Recommendations for specifying and reporting arrhythmia analysis algorithm performance, incorporating new waveforms, and enhancing safety. A statement for health professionals from the American Heart Association Task Force on Automatic External Defibrillation, Subcommittee on AED Safety and Efficacy,” (eng), *Circulation*, vol. 95, no. 6, pp. 1677–1682, 1997.
[27] R. D. White, T. H. Blackwell, J. K. Russell, D. E. Snyder, and D. B. Jorgenson, “Transthoracic impedance does not affect defibrillation, resuscitation or survival in patients with out-of-hospital cardiac arrest treated with a non-escalating biphasic waveform defibrillator: Q06,” *Resuscitation*, vol. 64, no. 1, pp. 63–69, 2005.
[28] Tyler Cascade, “1 Sudden Cardiac Death, Prehospital Amiodarone Administration and Defibrillation Waveforms: Q75,” March 2002.
[29] J. M. Field, A.C.E. Physicians, and A. H. Association, *The Textbook of Emergency Cardiovascular Care and CPR: Q72*: Wolters Kluwer/Lippincott Williams & Wilkins, 2009.
[30] V. Krasteva, M. Matveev, N. Mudrov, and R. Prokopova, “Transthoracic impedance study with large self-adhesive electrodes in two conventional positions for defibrillation: Q56,” (eng), *Physiological measurement*, vol. 27, no. 10, pp. 1009–1022, 2006.
[31] G. L. Botto, A. Politi, W. Bonini, T. Broffoni, and R. Bonatti, “External cardioversion of atrial fibrillation: Q74 Role of paddle position on technical efficacy and energy requirements,” (eng), *Heart (British Cardiac Society)*, vol. 82, no. 6, pp. 726–730, 1999.
[32] Ikonnikov and Yelle, *Physiology of cardiac conduction and contractility: Q77*. McMaster Pathophysiology Review. [Online] Available: http://www.pathophys.org/physiology-of-cardiac-conduction-and-contractility/#Cardiac_conducting_system. Accessed on: Sep. 24 2019.
[33] H. P. L arsson, “How is the heart rate regulated in the sinoatrial node? Another piece to the puzzle: Q55,” (eng), *The Journal of general physiology*, vol. 136, no. 3, pp. 237–241, 2010.
[34] E. Balse *et al.,* “Dynamic of ion channel expression at the plasma membrane of cardiomyocytes: Q58,” (eng), *Physiological reviews*, vol. 92, no. 3, pp. 1317–1358, 2012.
[35] *Cardiac Action Potential - an overview | ScienceDirect Topics: Q87.* [Online] Available: https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiac-action-potential. Accessed on: Oct. 11 2019.
[36] Rainald62, *Membrane electric profile: Q57*.
[37] LibreTexts.org, *10.5E: The Action Potential and Propagation: Q84.* [Online] Available: https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Book%3A_Anatomy_and_Physiology_(Boundless)/10%3A_Overview_of_the_Nervous_System/10.5%3A_Neurophysiology/10.5E%3A_The_Action_Potential_and_Propagation. Accessed on: Oct. 07 2019.
[38] P. Richard E. Klabunde, *Cardiovascular Physiology Concepts: Q88*.
[39] A. Cansell, “Die Zukunft der elektrischen Defibrillation des Herzens - The Future of Electric Defibrillation: Q37,” (ger), *Biomed. Technik*, vol. 47, no. 47 // 9-10, pp. 219–233, 2002.
[40] F. Oksuz *et al.,* “The classical "R-on-T" phenomenon: Q89,” (eng), *Indian heart journal*, vol. 67, no. 4, pp. 392–394, 2015.
[41] K. A. Gimbel, “The reentry phenomenon: Q90 A common cardiac event,” (eng), *Chest*, vol. 63, no. 1, pp. 1–2, 1973.
[42] Alila Medical Media, “Cardiac Action Potential, Animation.: Q92 Cardiac action potential in pacemaker cells and contractile myocytes, electrophysiology of a heartbeat.,” Jan. 24 2017.
[43] Krasteva, Cansell, Daskalov, V. Krasteva, I. Iliev, A. Cansell, and I. Daskalov, “Automatic adjustment of biphasic pulse duration in transthoracic defibrillation: Q40,” (eng), *Annals of Emergency Medicine*, vol. September/Oktober 2000 // Volume 24, no. 5, pp. 210–214, 2000.

[44] K. A. Mowrey, I. R. Efimov, and Y. Cheng, “Membrane time constant during internal defibrillation strength shocks in intact heart: Q93 Effects of Na+ and Ca2+ channel blockers,” (eng), *Journal of cardiovascular electrophysiology*, vol. 20, no. 1, pp. 85–92, 2009.
[45] B. J. Roth and S. G. Patel, “Effects of elevated extracellular potassium ion concentration on anodal excitation of cardiac tissue: Q91,” (eng), *J Cardiovasc Electrophysiol*, vol. 14, no. 12, pp. 1351–1355, 2003.
[46] R. A. MALKIN, “Large Sample Test of Defibrillation Waveform Sensitivity: Q19,” *J Cardiovasc Electrophysiol*, vol. 13, no. 4, pp. 361–370, 2002.
[47] J. B. DeLuca *et al., Eds., Developing a Comprehensive Search Strategy for Evidence Based Systematic Reviews: Q67*, 2008.
[48] C. D. Deakin, J. P. Nolan, K. Sunde, and R. W. Koster, Eds., *ERC Guidelines 2010 - 03 - Automatisierte externe Defibrillatoren, Defibrillation, Kardioversion und Schrittmachertherapie.: Q28*, 2010.

8 APPENDIX

Appendix A 1

Table 2: Tachycardias classified in rhythm categories[283]

Types of arrhythmia classified in rhythm categories	
A	***Shockable rhythms*** (require high sensitivity of arrhythmia analysis algorithms in the absence of artifacts):
	Coarse VF (peak-to-peak amplitude >200 µV [AAMI DF39] or other criteria specified in detail by manufacturer)
	Rapid VT (criteria specified in detail by manufacturer) (The task force did not specify a minimum rate above which VT should be shocked, because tolerance for VT varies widely among patients. Each manufacturer should specify criteria for VT used in its algorithm.)
B	***Nonshockable rhythms*** (require high specificity of arrhythmia analysis algorithms):
	Normal sinus rhythm
	Supraventricular tachycardia (includes sinus tachycardia, bundle branch block, WPW syndrome)
	Sinus bradycardia
	Premature ventricular contractions
	Atrial fibrillation, with or without bundle branch block
	Atrial flutter
	Second- or third-degree heart block
	Idioventricular rhythms
	Asystole—for safety and according to AHA Guidelines for CPR and ECC. (Manufacturer should specify amplitud criteria separating fine VF and asystole.)
C	***Intermediate rhythms*** (report sensitivity or specificity of arrhythmia analysis algorithms):
	Low-amplitude, low-frequency (fine) VF (ie, does not meet definitions of coarse VF above)
	Other VT (ie, does not meet criteria for VT in the shockable rhythms category above)

VF indicates ventricular fibrillation; AAMI, Association for the Advancement of Medical Instrumentation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

[283] [26, p. 1684]

Appendix A 2

Table 3: Tachycarias classified by QRS complex[284]

Types of Tachyarrhythmia classified by appearance of the QRS complex	
A	**Narrow–QRS-complex (SVT) tachycardias (QRS <0.12 second), in order of frequency**
	Sinus tachycardia
	Atrial fibrillation
	Atrial flutter
	AV nodal reentry
B	**Accessory pathway–mediated tachycardia**
	Atrial tachycardia (including automatic and reentry forms)
	Multifocal atrial tachycardia (MAT)
	Junctional tachycardia (rare in adults)
C	**Wide–QRS-complex tachycardias (QRS > 0.12 second)**
	Ventricular tachycardia (VT)
	ventricular fibrillation (VF)
	SVT with aberrancy
	Pre-excited tachycardias (Wolff-Parkinson-White [WPW] syndrome)
	Ventricular paced rhythms
Irregular narrow-complex tachycardias are likely atrial fibrillation or MAT; occasionally atrial flutter is irregular.	

[284] [10, pp. 45-46]

Appendix A 3

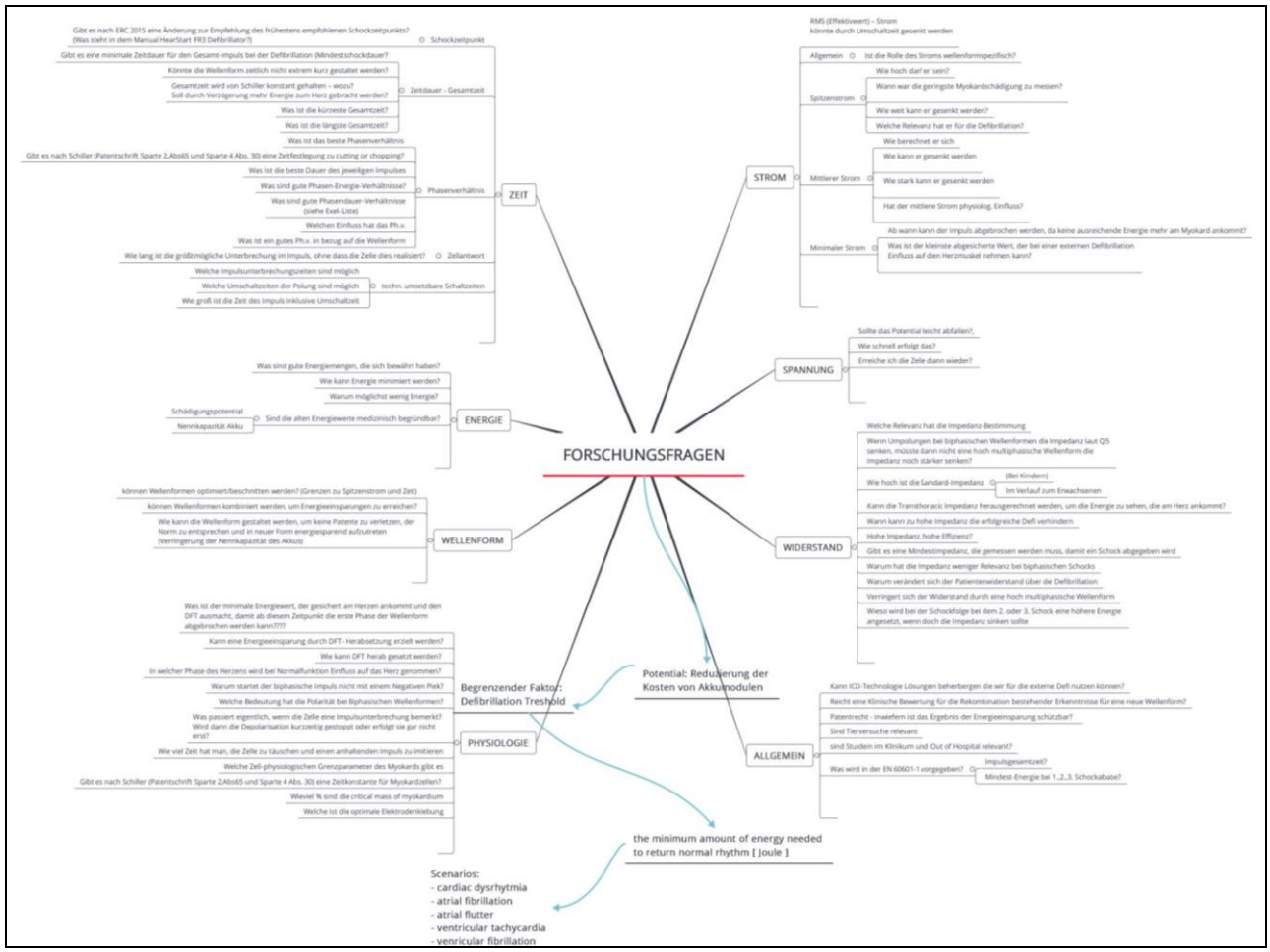

Figure 13: Mindmap - Research questions

Appendix A 4

Table 4: MeSH- Terms AED

	MeSH- term	Related terms, truncation, proximity and phrases
1	Antitachcardia Pacing	Cardiac Pacing, Artifical
2	Automated External Defibrillator	AED; AEDs; Automated External Defibrillation; External Defibrillators
3	Basic Life Support	BLS; Basic cardiac life support
4	Biventricular Pacemaker	Cardiac Pacing, Artifical;
5	Call-to-shock time	Time to treatment
6	Cardiac Pacing	Cardiac Pacing, Artificial ; Cardiac Pacemaker, Artifical;
7	Cardiac Resynchronization Therapy Device	Cardiac Resynchronization Therapy Devices
8	Cardiopulmonary Resuscitation	CPR
9	Charge-banking	
10	Charge-burping	
11	Corresponding Current	
12	Defibrillation Effectiveness;	
13	Defibrillation Percent Success Curve	Predict defibrillation success; successful defibrillation
14	Defibrillation	atrial defibrillation; ventricular defibrillation;; single path defibrillation; dual path defibrillation;
15	Defibrillation Waveform Description	Defibrillationskurvenform-Technologie
16	Efficient Average Current	
17	Electric Countershock	Cardiac Electroversion; Cardioversion; Defibrillation, Electric; Electrical Cardioversion; Electroversion Therapy; Electroversion, Cardiac; Therapy, Electroversion
18	Electric Stimulation	Stimulation, Electric
19	Emergency Medicine	Medicine, Emergency; Emergencies
20	First Shock	optimal timing of shock
21	Internal Cardioverter Defibrillator	ICD; Internal Cardiac Defibrillaton ; Implantable Defibrillators; Internal Defibrillators
22	Out of hospital cardiac arrest	OHCA; Out-of-hospital Heart Arrest
23	Pad Position	Electrode Position, Paddels Position; chest width; Anode, Cathode; Placement; application pressure; hair; Adhesives; Microelectrodes; surface; contact
24	Peak Current	Electrode position; chest width; Pad position; pads; Placement; application pressure; hair; Adhesives; Microelectrodes; surface; contact
25	Peri-shock-pause	Pre-shock-pause; Post-shock-pause
26	Refibrillation	
27	Reserve of Efficacy	RE
28	Return of spontaneous circulation	ROSC
29	Second Shock	

30	Shock Delivery	Charge-delivery; Delivered Charge
31	Shock-Energy	Shock intensity
32	Shock Distribution	
33	Shunting Effect	transient conductance
34	Single Shock	minimum shock duration
35	Sudden Cardiac Arrest	SCA; Heart attac; Victims of SCA
36	Three Stacked Shock Sequence	
37	Time To Treatment	Delayed Treatment; Door-to-Treatment Time; Time-to-Treatment ; Treatment Delay
38	Trailing Part	Trailing edge
	Transthoracic Impedance	Impedance, Transthoracic ; Resistance; tissue resistance; Impedance Adjustment, Impedance Adaption

Appendix A 5

Table 5: MeSh- Terms Cellular Electrophysiology

	MeSH- term	**Related terms, truncation, proximity and phrases**
1	Action Potentials	Spike Potentials
2	Alternate Ion Channel Concept	
3	Arrhythmia, cardiac	Arrhythmia; Arrythmia; Cardiac Arrhythmia; Cardiac Arrhythmias; Cardiac Dysrhythmia
4	Atrial Fibrillation	AF; Auricular Fibrillation; Familial Atrial Fibrillation; Paroxysmal Atrial Fibrillation; Persistent Atrial Fibrillation
5	Atrial Remodeling	Atrium Remodeling; Cardiac Remodeling, Atrial; Electrical Remodeling; Myocardial Remodeling, Atrial
6	Atrio-Biventricular Pacing	Cardiac Pacing, Artifical;
7	Biventricular Pacing	Cardiac Pacing, Artifical;
8	Cardiac Cell Time Constant	Tau
9	Cardiac Cell Model	
10	Cardiac Dysfunction	
11	Cardiac Electrophysiology	
12	Cardiac Mapping	Time to treatment
13	Cardiac Resynchrinization Therapy	Cardiac Resynchronization; Cardiac Resynchronization Pacing Therapy; Resynchronization Pacing Therapy, Cardiac
14	Cardiography, Impedance	Impedance Cardiography; Impedance Plethysmography, Transthoracic; Impedance, Transthoracic; Plethysmography, Impedance, Transthoracic; Plethysmography, Transthoracic Impedance;

		Transthoracic Impedance Plethysmography
15	Cell Communication	
16	Cell Time Constant	
17	Cellular Effects	
18	Chronaxy	Chronaxie
19	Defibrillationthreshold	DFT; Defibrillation Threshold
20	Delayed Rectifier Potassium Channels	Delayed Rectifying Potassium Channels
21	Electrical Conductivity Heart	Conductivity, Electric; Electric Conductivity, Heart
22	Electric Stimulation Heart	Stimulation, Electric; Electrical Stimulation, Heart
23	Electrophysiology Heart	cellular electrophysiology; electrophysiologic effects; electrophysiology lab; electrophysiologic techniques; electrophysiological phenomena;
24	Emergency Medicine	Medicine, Emergency; Emergencies
25	Funny Channels	
26	Galvanic Skin Response	Electric Conductance, Skin; Electrodermal Response; Reflex, Psychogalvanic; Skin Electric Conductance
27	Heart Conduction System	
28	Hyperpolarization-activated Cyclic Nucleotide-gated Channels	HCN Pacemaker Channels; HCN1 Channel; HCN2 Channel; HCN2 Potassium Channel; HCN3 Channel; HCN4 Channel; Hyperpolarization Activated Cyclic Nucleotide-Gated Potassium Channel 2; Hyperpolarization Cyclic-Nucleotide Gated Cation Channel 1; Hyperpolarization Cyclic-Nucleotide Gated Cation Channel 3; Hyperpolarization Cyclic-Nucleotide Gated Cation Channel 4; Hyperpolarization Cyclic-Nucleotide Gated Ion Channels; Hyperpolarization-Activated Cation Channel; I(h) Cation Channels; I(h) Channels; Ih Cation Channels; Potassium-Sodium Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel 2
29	Ion Channels	Ion Channel; Ionic Channel; Ionic Channels; Membrane Channel; Membrane Channels
30	Ion Channel Gating	
31	Intermediate-conductance Calcium-activated Potassium Channels	FIK Channel; Fibroblast Intermediate Conductance Potassium Channel; IK Potassium Channels; Potassium Channels, Intermediate-Conductance Calcium-Activated

32	Large-Conductance Calcium-Activated Potassium Channels	BK Channels; Big K Channels; Maxi-K Channels; MaxiK Channels
33	Membrane Potentials	Resting Membrane Potential Resting Potentials Transmembrane Electrical Potential Difference Transmembrane Potential Difference Transmembrane Potentials
34	Models, Cardiovascular	Cardiovascular Models
35	Myoblasts, Cardiac	
36	Myocetes, Cardiac	Cardiomyocytes; Muscle Cells, Cardiac; Muscle Cells, Heart
37	Myocardial Contraction	Heart Contractility; Inotropism, Cardiac
38	Myocardial Damage	
39	Myocardial Infarction	
40	Myocardial Ischemia	Heart Disease, Ischemic; Ischemia, Myocardial; Ischemic Heart Disease
41	Myocardial Stimulants	
42	Myocardial Stunning	Hibernation, Myocardial; Myocardial Hibernation; Stunned Myocardium
43	Myocardium	Cardiac Muscle; Muscle, Cardiac; Muscle, Heart; Myocardia
44	Myofibrils	
45	Non-ST Elevated Myocardial Infarction	NSTEMI; Non-ST-Elevation Myocardial Infarction
46	Potassium Channels, Voltage-gated	Kv Potassium Channels; Potassium Channel, Voltage-Gated; Voltage-Gated K+ Channels; Voltage-Gated Potassium Channel; Voltage-Gated Potassium Channels
47	Prepulse Facilitation	
48	Prepulse Inhibition	
49	Reflex, Startle	
50	Refractory Periode	
51	Resting Potentials	
52	Signal Transduction	
53	Small-Conductance Calcium-Activated Potassium Channels	SK Potassium Channels
54	ST Elevation Myocardial Infarction	ST Elevated Myocardial Infarction; ST Segment Elevation Myocardial Infarction; STEMI
55	Stimulus Duration	Stimulus Duration squared
56	Stimulus Strength	Stimulus Strength Duration
57	Tachycardia, Ventricular	VT; Ventricular Tachycardia

58	Threshold Potential	
59	Tissue Resistance	
60	Transmembrane Potential Difference	Transmembrane Voltage
61	Transient Conductance	Conductance, Transient; Electric Conductivity
62	Ventricular Fibrillation	VF; VF episode; recurrent VF;
63	Ventricular Remodeling	Cardiac Remodeling, Ventricular; Left Ventricle Remodeling; Left Ventricular Remodeling; Myocardial Remodeling, Ventricular; Ventricle Remodeling
64	Voltage-gated Sodium Channels	Sodium Channels, Voltage-Gated

Appendix A 6

Table 6: MeSh- Terms Waveform

	MeSH- term	**Related terms, truncation, proximity and phrases**
1	Biphasic	biphasic waveform;
2	Biphasic Truncated Exponential	BTE, biphasic; BTE, ICD; BTE, impedance adjusting; BTE, impedance compensating;
3	Charge Banking	charge-banking
4	Charge Burping	charge-burping
5	chopped waveform	chopping
6	Cell Time Constant	Tau
7	Cell-transmembrane voltage time-course	
8	Delivered Charge	
9	Dose of Energy	Intensity
10	Electric Countershock	
11	Energy Level	Energylevel
12	Escalating Energy	
13	First Shock	First Phase
14	Frequency concentration	
15	Fixed Energy	
16	High Energies, Monophasic	
17	Low Energies, Biphasic	low energies, biphasic, BTE
18	minimal firstshock energy level	
19	minimum shock duration	
20	Monophasic	Monophasic Waveform
21	Monophasic Damped Sine	MDS
22	Multiphasic	Multiphasic Waveform
23	optimal waveform energy	
24	Parabolic Fit	
25	Peri-shock-phase	
26	Phase Duration	Shock Duration

27	Phase Number	Shock Number
28	Phase Ratio	
29	Postshockpause	
30	Präschockpause	
31	Pulsed Biphasic	PBW, pulsed biphasic;
32	Pulsed Radiofrequency Treatment	
33	pulsed waveform	
34	Rectiliniear Biphasic	RBW, biphasic; RLB,rectiliniear biphasic
35	Reserve of Efficacy	RE
36	Second Shock	Second Phase
37	seperating pause	
38	Shock Delivery	Shock Distribution
39	Shock Efficacy	
40	Shock Energy	
41	Shock Synchrinization;	optimal timing of shock delivery;;
42	Single Shock	First Shock; First Phase
43	step-up energy levels	
44	Stimulus	Stimulus-Strength-Duration
45	Strength	Stimulus-Strength-Duration
46	three stacked shock sequence	Third Phase; Third Shock
47	total duration	
48	Trailing Part	
49	ventilation phase	
50	Waveform	waveforms
51	waveform design	
52	waveform efficacy	

Appendix A 7

								Phase ratio	
Resistance	Phase 1	Phase 2	Energy	Current max.	Voltage max.	Capacity	switch	Prop. phase 1	Prop. Phase 2
Ω	ms	Ms	J	A	U	µF	ms	%	%
25,00	4,90	4,80	240,00	100,00	0,00	77,00	0,40	51	49
50,00	5,20	4,80	240,00	48,00	0,00			52	48
75,00	5,40	4,00	240,00	34,00	0,00			57	43
100,00	6,00	3,30	240,00	24,00	0,00			65	35
125,00	6,00	3,10	240,00	20,00	0,00			66	34
150,00	6,00	3,10	240,00	19,00	0,00			66	34
175,00	6,00	3,10	240,00	14,00	0,00			66	34

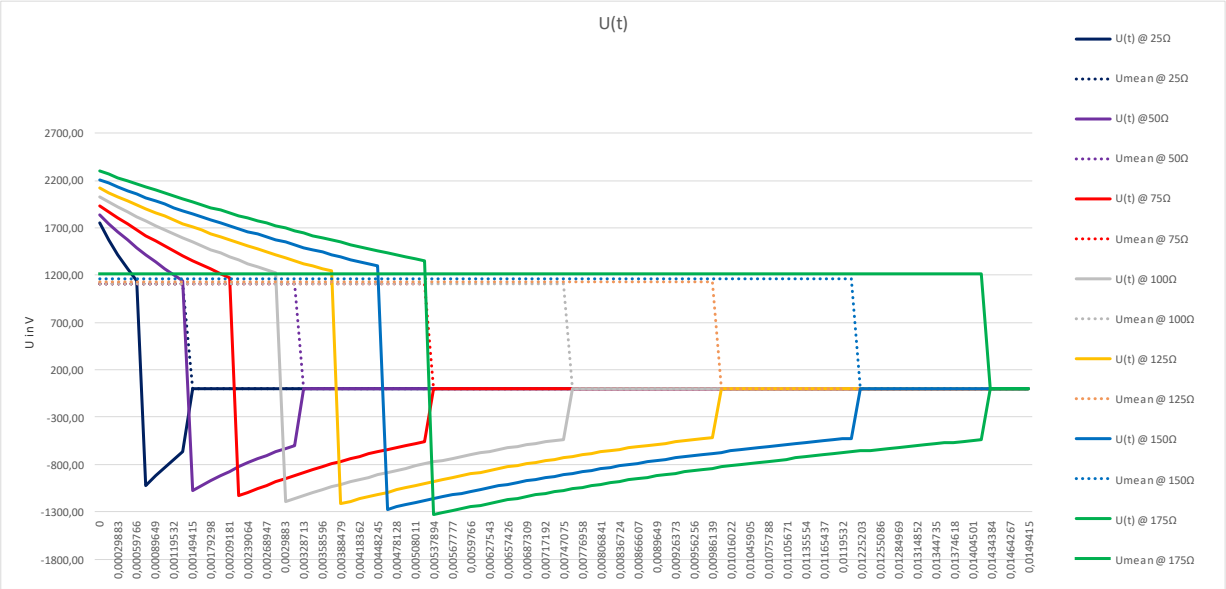

Figure 14: Voltage simulation for different impedances

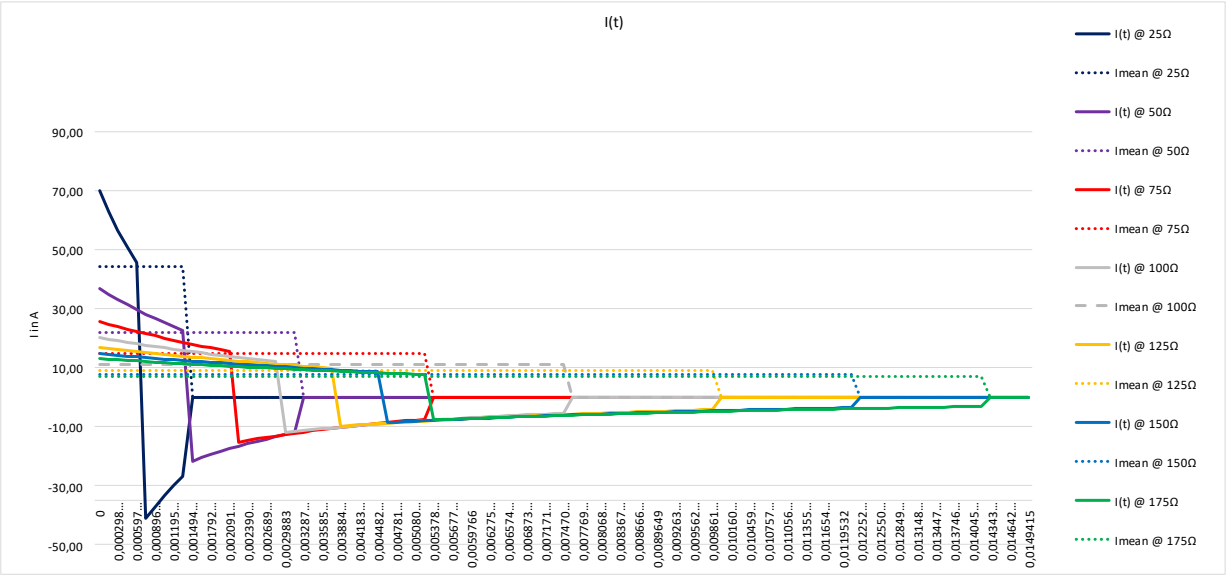

Figure 15: current simulation for differen impedances