ON THE CAUSES OF VENTRICULAR ARRHYTHMIA, ITS TREATMENT AND OUTCOME

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"When the heart is diseased, its work is imperfectly performed: the vessels proceeding from the heart become inactive, so that you cannot feel them....if the heart trembles, has little power and sinks, the disease is advanced and death is near." Ebers Papyrus 1500 BC

To Anne and Stefan

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ABSTRACT

Background: Ventricular arrhythmia is the most common aetiology of sudden cardiac death. Death can sometimes be prevented by the implantation of a defibrillator (ICD). When an out-of-hospital cardiac arrest (OHCA) has occurred some circumstances characterize those who survive. Medication used to treat disease is not always harmless.
Methods: The population in the Swedish Cardiac Arrest Register was used to characterize the survivors, and for the recently added drugs, before an OHCA, used together with the Swedish Prescribed Drug Register. The outcome of all consecutive acute myocardial infarction patients during 21 month time at Sahlgrenska University Hospital was investigated to determine if a simple echocardiographic criterion could identify the patients that would die of arrhythmia during two years after the myocardial infarction. Thirty patients with an implanted defibrillator were tested with Transcutaneous Electrical Nerve Stimulation (TENS) to determine the risk of electrical interference with the ICD.
Results: The echocardiographic criterion of an ejection fraction ≤30% alone, found only three of the patients who died of presumed arrhythmia and only one of them would have been implanted with an ICD in clinical practice. Six patients who died of presumed arrhythmia had a better ejection fraction. The TENS interfered with 16/30 ICDs. Among survivors of OHCA 20% were from the group found in a non-shockable rhythm and the majority was not reached by the ambulance within five minutes. Recently added drugs before OHCA were most often prescribed for infectious, respiratory and neuro-psychological diseases. 16.2% of the OCHA victims had recently claimed a drug from the" qtdrugs.org" lists
.Conclusion: Better criteria or combinations are needed to identify the patients that would benefit from an ICD on a primary prevention indication after myocardial infarction. The TENS device cannot be recommended to be used simultaneously with an ICD and protocols for testing other implantable devices to be used together with an ICD are warranted. New drugs frequently claimed before OHCA should be further investigated and the OHCA victims found in non-shockable rhythm need more attention. The delay-time for ambulance arrival to the OHCA victim is long.

Keywords: Cardiac arrest, ICD, ventricular arrhythmia
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Sammanfattning på svenska

Kammararytmi, dess orsaker, behandling och resultat

Kammararytmi kan vara ett livshotande tillstånd. Det finns flera typer av kammararytmier. Farligast är kammarflimmer som obehandlat leder till döden. Det är den vanligaste rytmen vid hjärtstopp. Vid kammarflimmer är hjärtats elektriska aktivitet mycket snabb och oregelbunden, hjärtat kan inte längre pumpa runt blod utan blodcirkulationen upphör. För att komma igång igen måste hjärtat defibrilleras, vilket betyder att det behöver en elektrisk stöt för att komma igång igen. Den elektriska aktiviteten blir då ”nollställd” och den normala impulsbildningen kan ta över igen.

Andra kammararytmier är monomorf kammararytmi och polymorf kammararytmi. I den förstnämnda ser alla EKG komplex ungefär likadana ut och rytmen är regelbunden men mycket snabb ca 150 till 220 slag per minut men kan ibland vara långsammare eller ändå snabbare. En polymorf kammararytmi har oregelbunden rytm och olikstora EKG komplex. Om kammararytmierna varar längre än 30 sekunder eller kräver åtgärd dessförinnan kallas de långvariga. En speciell sorts kammararytmi kallas ” Torsades de Pointes ”. Den har fått sitt namn av att den EKG-mässigt vrider sig runt sin egen axel vilket ger den ett spolformat utseende. Den kan ibland gå över av sig själv men kan också övergå i kammarflimmer.

Sjukdomar i hjärtat kan ge upphov till kammararytmier t.ex. vid akut hjärtinfarkt. Även efter genomgången hjärtinfarkt finns risk för kammararytmier och risken är högre om hjärtats pumpkraft blivit nedsatt. För att avgöra vilka som hade störst risk för kammararytmi efter hjärtinfarkt och som kunde ha nytta av en inopererad defibrillator(ICD) har flera studier gjorts. En känd studie visade att om hjärtats pumpkraft var till räckligt nedsatt så hade man större möjlighet att överleva om man fick en ICD. I studie I undersöktes alla patienter som vårdades för akut hjärtinfarkt på Sahlgrenskas hjärtavdelningar under 21 månader och sedan följdes dessa under två år. Denna studie visade att ett mått på hjärtats pumpförmåga inte var så användbart som ensamt mått i klinisk praxis. Vi behöver fortfarande andra undersökningsmetoder för att kunna avgöra vilka som har bäst nytta av en ICD.

Innan patienten kommer till sjukhus kan han/hon drabbas av plötsligt hjärtstopp. Detta kan orsakas av hjärtsjukdom, lungsjukdom och drunkning för att bara nämn tre av de nio kategorier som registreras i Det Svenska Hjärtstoppsregistret. Vid hjärtstopp kan hjärtrytmen antingen vara kammarflimmer eller mycket snabb kammarrytm, med upphörd cirkulation. Det är då viktigt med snabb defibrillering. Det finns också en annan variant av hjärtstopp då hjärtat inte slår alls eller den elektriska aktiviteten är ganska normal men pumpförmågan har upphört. Då hjälper det inte med defibrillering utan annan behandling behövs. I studie II undersöktes de patienter som överlevde ett hjärtstopp i en månad eller längre. Det visade sig då att överlevarna i ungefär 20 %

kom från gruppen som inte hade en defibrillerbar rytm, och att de flesta, som hade en defibrillerbar rytm inte hade kunnat bli defibrillerade inom 5 minuter. Det betyder att man bör undersöka mer om hur patienten med icke defibrillerbar rytm skall behandlas då fler överlever än man tidigare trodde. Att gruppen, som hade en defibrillerbar rytm men inte kunde defibrilleras tidigt var större än man trott, kan bero på att ambulansen nu kommer fram senare till händelseplatsen än tidigare.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Presumed arrhythmic death in consecutive survivors of acute myocardial infarction--implications for primary implantable cardioverter defibrillator implantation
Holmgren CM, Nyström BM, Karlsson TK, Herlitz JD, Edvardsson NG.
Coron Artery Dis. 2009 Mar;20(2):155-62

II. Analysis of initial rhythm, witnessed status and delay to treatment among survivors of out-of-hospital cardiac arrest in Sweden
Holmgren C, Bergfeldt L, Edvardsson N, Karlsson T, Lindqvist J, Silfverstolpe J, Svensson L, Herlitz J.
Heart. 2010 Nov;96(22):1826-30. Epub 2010 Oct 3.

III. Risk of interference from transcutaneous electrical nerve stimulation on the sensing function of implantable defibrillators
Holmgren C, Carlsson T, Mannheimer C, Edvardsson N.
Pacing Clin Electrophysiol. 2008 Feb;31(2):151-8.

IV. Recent changes in medication in out-of-hospital cardiac arrest victims
Holmgren C, Abdon NJ, Bergfeldt L, Edvardsson N, Herlitz J, Svensson L, Åstrand B

In manuscript

CONTENT

ABBREVIATIONS

AMI	Acute myocardial infarction
ARP	Absolute refractory period
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ATC	International Anatomical Therapeutical Chemical
ATP	Anti tachycardia pacing
AV	Atrio-ventricular
CABG	Coronary artery by-bass grafting
CaMKII	Ca/Calmodulin Kinase II
CPC	Cerebral performance categories
CPR	Cardio pulmonary resuscitation
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
DAD	Delayed After Depolarisations
EAD	Early After Depolarisations
EF	Ejection fraction
EMS	Emergency Medical Services
GP	General Practitioner
HCM	Hypertrophic cardiomyopathy
HOCM	Hypertrophic cardiomyopathy with outflow tract obstruction
HRT	Heart rate turbulence
HRV	Heart rate variability
ICaL	L-type calcium channel
ICD	Implantable cardioverter defibrillator

IK_{atp}	ATP-dependent potassium channel
IK_{to}	Transient outward potassium channel
IK_{r}	Rapid potassium rectifier
mM	Millie molar
NCX	Sodium Calcium Exchanger
OHCA	Out-of-Hospital Cardiac Arrest
PCI	Percutaneous coronary intervention
PIN	Personal identification number
QALY	Quality-adjusted life-year
RRP	Relative refractory period
RVOT	Right Ventricular Outflow Tract
RyR	Ryanodine receptor
SCD	Sudden Cardiac Death
SCS	Spinal Cord Stimulation
SD	Sudden death
SERCA	Sarcoplasmatic Ca-ATP-ase
STEMI	ST elevation myocardial infarction
TdP	Torsade de pointes
TENS	Transcutaneous nerve stimulation
VF	Ventricular fibrillation
VOO	Ventricular pacing without sensing
VPC	Premature ventricular contractions
VT	Ventricular tachycardia
VVI	Ventricular pacing and sensing with inhibition if sensed events

BACKGROUND

Basic electrophysiology and arrhythmic mechanisms

Basic electrophysiology

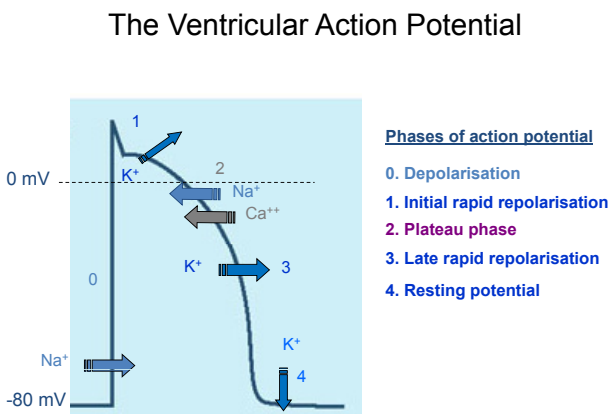
The cardiomyocyte is a specialized cell. Some of the cardiomyocytes have an intrinsic property of initiating electrical impulses, the sinus node, the atrio-ventricular (AV) node and the His-Purkinje system. Those are the cells that constitute the conduction system. Under normal circumstances the impulse is generated in the sinus node, propagating through the atrial myocardium to the atrio-ventricular (AV) node, down through the His-bundle to the Purkinje fibres thereby making the contractions of the heart appropriate by first filling the heart with blood from the veins and atria, and thereafter contracting the chambers pumping the blood to the pulmonary artery and to the aorta. The influence of the sympathetic nervous system will increase the rate of impulses and, under the influence of the parasympathetic nervous system, the rate will slow down.

The myocyte cell membrane acts as a capacitor. Current is borne by the electrically charged ions through channels, exchangers and pumps in the cell membrane. The membrane potential reflects the charge distribution. The membrane potential is determined by the electrochemical forces, i.e. the electrical force consisting of the ions striving for electrical balance between the cations and the anions and the osmotic force striving to eliminate the concentration gradient. The intracellular concentration of potassium is around 150 mM/l and the extracellular about 5mM/l. The resting potential is about -85mV near the equilibrium of potassium. This is because the cell membrane is more permeable to potassium than to other ions.

The action potential

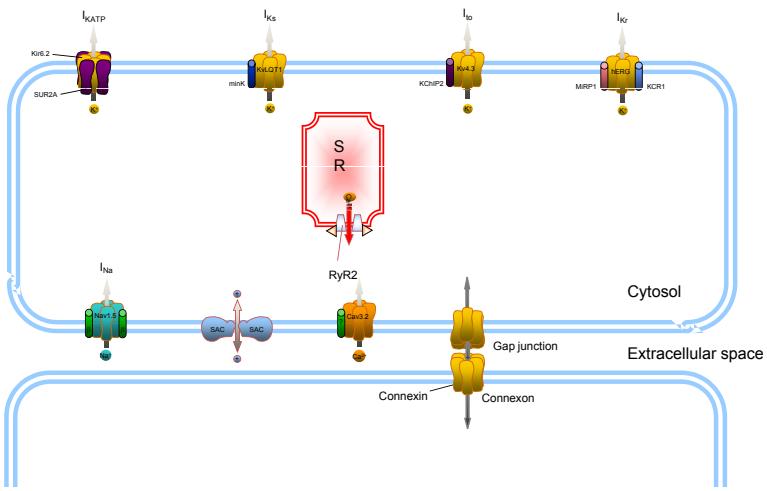
When the membrane potential reaches the threshold potential, the action potential will occur. The permeability to sodium will increase dramatically as the sodium channels open and the membrane potential will strive towards the equilibrium potential of sodium that is positive. This depolarization corresponds to the upstroke in the action potential and is called phase 0 and lasts for a few milliseconds. As the positive level is reached, the permeability to potassium will again increase, and the first channel to open is the IK_{to},which is dominant in phase 1. In the second phase (the plateau) the calcium channels that transport calcium into the cell and the potassium channels IK_s and IK_r that transport potassium out of the cell will be dominant. In phase 3, the repolarization continues and the IK_r is the most dominant until the resting membrane potential is again reached and the fourth phase starts. During phases two and three there is a

considerable contribution of Na^+-K^+- ATPase, which actively transports sodium out of the cell and potassium into the cell. In the same phases, the electrogenic Na^+ -Ca^{++} exchanger (NCX) is activated according to the concentrations of calcium and sodium inside the cell.



The action potential

The sarcoplasmatic reticulum is the storage of calcium in the cell. The discharge of calcium and its re-uptake is necessary for the electric-contraction coupling that makes the cell contract. Calcium will be released from the sarcoplasmatic reticulum through the Ryanodine receptor (RyR) as a response to the calcium flux into the cell via the L-type Ca channel during the plateau phase of AP and the re-uptake is mostly through the Sarcoplasmatic Ca-ATP-ase (SERCA) ≈ (70%), while approximately 30% of the cytosolic calcium leaves the cell via the NCX.



Cell membrane with a selection of ion channels

Refractory periods

During the initial phases of the action potential (80-85% of the duration) the cell will be refractory for other depolarizing impulses. The first period is called the absolute refractory period (ARP) and the second the relative refractory period (RRP). As repolarization continues, the cell will require less and less depolarizing current to be able to depolarize again.

Mechanisms of malignant arrhythmias are commonly divided into three groups:
re-entry, increased automaticity and triggered activity.

Re-entry

An area of slow conduction and unidirectional block in one of the alternative pathways are prerequisites for re-entry and dispersion of refractoriness that might promote re-entry.

Re-entry mechanisms

Single circuit re-entry occurs when an impulse is propagating around a physiological or functional obstacle with longer refractory period on the one side than the other, leading to a one-way entrance block in a single circuit. An impulse may reach an injured area, e.g. in the border zone between normal and scar tissue after a myocardial infarction, where the propagation will be slow. Another part of the tissue beyond this area has already been depolarized from another direction and will then be refractory when the first impulse arrives. An entrance block is here created. The impulse will take another direction and, when it reaches the tissue formerly depolarized, it will find it repolarized and possible to depolarize again. A re-entry circuit is then created.

Figure of eight re-entry occurs when two waves propagate in different circles, one clockwise and the other counter-clockwise, sharing a common pathway with slower conduction abilities. [1]

Reflection waves emerge when the current passes through a part of the tissue that cannot be depolarized itself but is able to transmit the current. When the slowly conducted impulse reaches the end of that particular tissue and the junction to a tissue with different electrical properties, reflection might occur at this junction. Very slow antegrade conduction allowing recovery of the tissue just behind the impulse/wavefront is a prerequisite. At the tissue junction, antegrade conduction block might occur or impulse conduction continues, depending on the source-sink relationship. The importance lies in the return of the reflected wavefront to the proximal tissue where a VPC might emerge.[2]

The phase 2 re-entry mainly occurs when inhomogeneities of the myocardial wall give

rise to different shapes in the action potential configuration in different layers, the endocardium, the midmyocardial cells and the epicardial cells. This mechanism has been proposed to initiate the VT/VF in the Brugada syndrome and VPC from the right ventricular outflow tract**.** This mechanism has also been a candidate for the initiation of ischemic VF by causing early R-on-T VPC.[3-5]

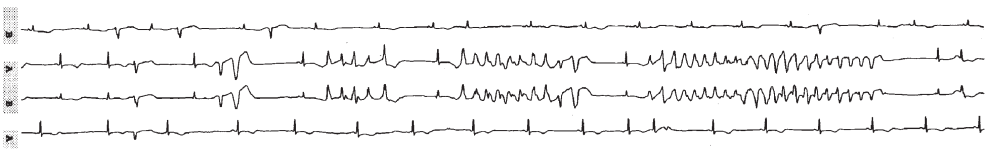
Increased automaticity

The coupling interval between two consecutive beats shortens by an increase of the diastolic slope between normal action potentials of cells with pacemaker properties such as in the sinus node and the Purkinje fibres. Diastolic potentials can sometimes reach the threshold potential in the diastolic interval under the influence of catecholamines and other agents. Cells without pacemaker properties during normal conditions may acquire these properties under pathologic conditions. This is a common mechanism of reperfusion arrhythmias following thrombolysis and PCI. These arrhythmias are often slower than the re-entrance VT.

Triggered activity

These are basically of two different kinds, Early After Depolarizations (EAD) and Delayed After Depolarizations (DAD). The EADs emerge in slow rhythms with prolonged action potentials and the DADs are favoured by fast rhythms.

EADs occur in the action potentials late in phase 2 or in phase 3. In phase 3, the calcium channel, CaL, has recovered from its inactivated state and is conductive of Ca again. Small amounts of calcium will be attenuated in the cytosol although larger amounts will activate the ryanodine (RyR) receptor and cause an efflux of Ca^{2+} ions from the sarcoplasmatic reticulum. One example of this mechanism is the torsade de pointes (TdP) VT seen in the LQT syndromes. TdP can also appear when certain drugs block the IK_r for anti-arrhythmic or other purposes (the pro-arrhythmic mechanism).The ECG characteristics are the turning of the axis and apparent differences in amplitude giving it a fusiform appearance.



Torsade de pointes (TdP) in a woman using sotalol and recently added diuretics

DADs occur in phase 4 in the action potential. When the calcium concentration in cytosol is sufficiently high, a calcium wave will start and spread along the cell and through the gap junctions to the neighbouring cells. This high calcium concentration will activate the Sodium Calcium Exchanger (NCX) to extrude calcium out of the cell and im-

port sodium in a 1:3 mode, raising the concentration of sodium inside the cell and making the inside more positively charged. Calcium is discharged from the sarcoplasmatic reticulum through the ryanodine (RyR) receptor. In catecholaminergic polymorphic ventricular tachycardia (CPVT) with mutations in the RyR receptors, the calcium leaks out through the receptor increasing the Ca concentration in the nearby cytosol and a spreading calcium wave will start. The excess of calcium can also be mediated by a late Na current that will shift the NCX to a reversed mode, raising the calcium concentration.
The regulation of Ca handling is also dependent on cell structure through the T tubuli. Those tubuli are absent in pacemaker cells but seem to be necessary in working myocardium. Their role seems to be to synchronize the action potential and the contraction. [6, 7]

Clinical classification of malignant arrhythmias

According to Myerburg et al. [8] ventricular arrhythmias are commonly divided into premature ventricular contractions (VPC) and ventricular tachyarrhythmias (VT), the latter including ventricular fibrillation (VF).

Monomorphic and polymorphic tachycardias can also be sustained or non-sustained, meaning that a sustained tachycardia will last for at least 30 seconds or, before that, result in a significant drop in blood pressure. The definition of VT varies in the literature from three to six consecutive beats.
Monomorphic ventricular tachycardia is defined as all consecutive beats having the same QRS morphology and a reasonably similar cycle length.
Polymorphic ventricular tachycardia has a variation in QRS morphology and cycle length.
A special kind of polymorphic ventricular tachycardia is torsade de pointes.

Ventricular fibrillation is defined by its mechanical features. Ventricular fibrillation is pulse less and polymorphic ventricular arrhythmia produces at least a weak pulse.
There is a relationship between the tachycardias from VPC to VT. The VPC can be harmless without conditioning factors while for VT to occur there must be triggering events.
Conditioning factors can be myocardial infarction, myocardial hypertrophy, electrical abnormalities, infiltration and inflammation and fibrosis in the myocardium. [8]

The influence of ischemia

There are different conditioning factors according to time after the myocardial infarction: the first minutes after the ischemia, the period of acute infarction, the healing period and the chronic state. [8]

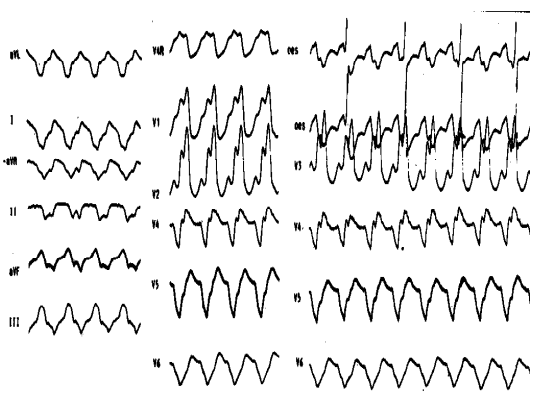
Activation of the ATP-dependent potassium channel (IK_{atp}) will occur when the concentration of ATP is lower than normal, as during ischemic conditions. An outward potassium current will occur and will hyperpolarize the membrane. This influence will be seen preferably in the epicardial tissue, facilitating re-entry by dispersion of refractoriness.

During ischemic conditions there will be an accumulation of extra cellular potassium, activation of the sympathetic nervous system and an increase of reactive oxygen species from the collapsed mitochondrial membranes.

The ischemic cells will depolarize. This is possibly caused by the accumulation of sodium inside the cell together with an effect of Na^+-H^+ exchanger. This accumulation of sodium will reverse the NCX and cause calcium intrusion.
The influence of the transient outward potassium channel (IK_{to}) current is unevenly distributed. In the ischemic myocardium it possibly mediates the loss of the action potential dome in an inhomogeneous way, facilitating the risk of ventricular extra systoles and possible re-entry.

Reperfusion arrhythmias

Reperfusion arrhythmias may occur when the blood flow is restored or improved in a previously ischemic area. The risk of serious reperfusion arrhythmias will increase if the transient ischemia has lasted up to 20 minutes. After longer ischemic periods, accelerated ventricular rhythms and VPC with an automatic origin are more common. Transient occlusions are more prone to initiate polymorphic VT and VF but the treatment with thrombolysis and PCI will favour accelerated ventricular rhythms. The mechanisms of triggered activity and focal re-entry will be facilitated in the reperfused regions. Hypertrophied cells seem to be more vulnerable to triggered activities, and regional hypertrophy is seen in healed myocardial infarction.



Monomorphic VT from the left ventricle

Heart failure

The hallmarks of heart failure are myocyte hypertrophy and fibrosis formation leading to decreased contractility in parallel with electrical remodelling.[9]
The genetic message is altered from a normal adult response to a previous mode altering the expression of gene products. [10] One factor involved in the remodelling process is endothelin, which promotes remodelling and fibrosis formation.[6, 7] Viable myocardium is mixed with fibrosis, facilitating re-entry tachycardia.

The T tubuli will decrease, possibly impairing the synchronization of calcium handling as the T tubuli are supposed to organize the L-type Ca^{2+} channel to the RyR receptors in a functional unit (the couplon). The sarcoplasmatic Ca-ATP-ase (SERCA) receptors are down-regulated, impairing the calcium re-uptake to the sarcoplasmatic reticulum. The increased intracellular concentration of sodium will reverse the NCX so that Ca^{2+} will be transmitted into the cell in exchange for the excess of Na^{+}. In the failing heart, this process will be facilitated by the up-regulation of the NCX. The disorganized Ca-handling will facilitate after depolarizations which can be arrhythmogenic. [6, 7] Under basal conditions the Ca/Calmodulin Kinase II CaMKII is inactive. It will be activated by longer action potentials and facilitate calcium influx by increasing the open mode of the L-type Ca^{2+} channel. A CaMKII excess contributes to cardiomyopathy and heart failure with action potential prolongation. It can contribute to hypertrophy and arrhythmias.[11]

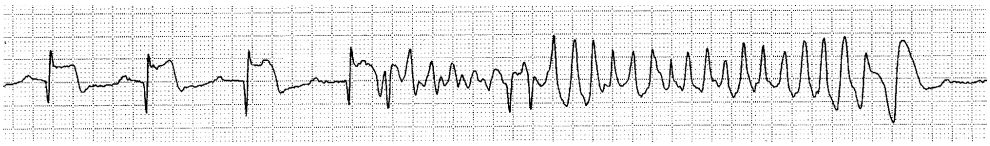
Elecrolyte disturbances

Electrolyte disturbances are commonly seen. The most common disturbance is hypokalemia as an effect of impaired intake and/or the use of diuretics or of diarrhoea. Although some drugs are known to decrease the efficacy of the rapid potassium rectifier (IK_r), their adverse effect will increase in the hypokalemic state, increasing the risk of a prolonged QT interval as a consequence of ADP prolongation. Early afterdepolarizations (EADs), increasing the risk of torsade de pointes (TdP) might occur. The delayed rectifier current will decrease, resulting in delayed repolarization and a longer relative refractory period. The Na^{+}-K^{+} pump will be suppressed and the intracellular calcium concentration will rise, possibly by the reversal of NCX. Those alterations will increase excitability and the risk of ectopies. Conduction will be slower as depolarization will begin in partly repolarized fibres. The hypokalemia affects the tissue in an inhomogenous way as the ADP plateau shortens in the ventricular myocytes but prolongs in the conduction fibres, increasing dispersion. It also increases automaticity by increasing diastolic depolarization. Re-entry will be facilitated by the increased dispersion and the slowing of conduction. The risk of ventricular fibrillation will increase in the normal and even more in the ischemic heart. [12] Hypokalemia has been found in up to 50% of patients rescued from VF causing Out-of-Hospital Cardiac Arrest, [13] although this was attributed to the arrhythmia and resuscitation and not playing a role in initiating

the arrhythmia.
Hyperkalemia is less frequent and is most often seen accompanying decreased renal function. The ADP plateau will shorten preferentially in the Purkinje fibres, decreasing the dispersion. In experimental ischemia the rise in potassium will shorten the refractory period and increase the risk of ventricular fibrillation. The failing myocardium is more vulnerable to ischemic threats and the potassium concentration rises to higher values, thereby increasing the risk of malignant arrhythmias in the failing heart[12] as well as to decreasing conduction velocity.

The combination of hyperkalemia and hypocalcemia is even more dangerous as it has a cumulative effect. As a therapeutic agent, the supply of calcium will diminish the risk of ventricular fibrillation.

Magnesium acts as a cofactor in enzymatic reactions. It can block the L-type calcium channel (ICaL) and modify several potassium currents. Magnesium acts on the Na-K ATP ase function. As a therapeutic agent it can contribute to inhibiting TdP in the setting of a prolonged QT interval.[12]



Rhythm strip of polymorphic VT in acute myocardial infarction

Cardiac arrest

Epidemiology

Sudden death (SD), sudden cardiac death (SCD) and out-of-hospital cardiac arrest (OHCA) are major problems for society. SD is commonly defined as death in one hour after the onset of symptoms or, in unwitnessed cases, in 24 hours since the victim had been seen alive. The incidence of SCD varies according to the different definitions and is estimated to affect 180,000 to >450,000 individuals annually in the US.[14] In official US statistics, the incidence of sudden cardiac arrest in the US is about 295,000.[15]

The aetiology of SD can be arrhythmia, pulmonary embolism, aortic aneurysm and cerebral haemorrhage among others. SCD is a proportion of SD cases in which the aetiology is presumed to be cardiovascular.
Of SCDs, structural coronary artery disease accounts for approximately 80% of the cases, cardiomyopathy (dilated and hypertrophic) for 10-15%, and other causes 5% in Western populations[16].

In younger people, a recent study conducted in Denmark among individuals aged 1-35 years reported an incidence rate of 1.9 to 2.8 per 100,000 person-years of SCD. [17]
In a recent study done in Finland of 2661 SCD victims that focused on non-ischemic causes of SCD, 21.8% were judged to be non-ischemic. Fibrotic cardiomyopathy was the most common in patients younger than 40 years of age and alcoholic cardiomyopathy the most common between 40 and 59 years of age[18].

The incidence of SD in the community and in the post-myocardial infarction population was assessed in Olmsted County, Minnesota, US, and has the highest incidence the first 30 days after a MI [19], thereafter declining to about 1.2% a year. These figures are in line with what was found in the Valiant study where 14,609 patients with left ventricular dysfunction and/or heart failure after MI were studied. [20] The Framingham heart study in 363 cases of initial MI [21] showed a cumulative age and gender adjusted five-year incidence of SD of 8.3% for Q wave and 1.4 % for non-Q wave infarctions. The largest numbers of people affected are those without known risk factors, while the people at high risk are fewer and account for a smaller amount of the total number of SCD.[22] The incidence of SCD is declining in the US population according to a comparison between 1979-1987 and 1997-2005 [19]. The incidence of SCD is also declining in Europe[23] and among younger Australians.[24]
The Swedish Cardiac Arrest Register includes cardiac arrests of all aetiologies, since 1990, where an attempt to resuscitate has been performed.
It is estimated that in Sweden about 5000 persons each year experience a cardiac arrest outside of hospital and have been objects of cardiopulmonary resuscitation (CPR).[25]
The incidence of VT/VF as the initial rhythm of cardiac arrest has decreased.[26]

In addition to coronary artery disease, many factors may contribute to the increased risk of malignant arrhythmias. [10, 27]
Genetic disposition plays a role and cause different heart diseases such as arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy with (HOCM) and without (HCM) outflow tract obstruction, [28] Brugada syndrome, congenital long QT syndromes, short QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT)[29] .

Prophylaxis

The incidence of ischemic heart disease is declining[23] in the Western world although it is still an escalating problem in developing countries. [30, 31] In the Western world, efforts have been made to stop smoking, to increase physical activity and to eat healthier food, which have probably contributed to lowering the figures and more can be done.
Primary prevention should focus on risk individuals, including those with a possibly inherited risk as relatives of patients with known arrhythmogenic heart diseases such as HCM and LQTS. There are also reports of a higher incidence of SD in relatives of other SD cases even without any known disease. [32] A screening of relatives of patients with dilated cardiomyopathy [33] resulted in the identification of subjects at risk. Screening of athletes is still debated.[34] For the monogenetic arrhythmic diseases, we now have the possibility of genetic testing [35]in close relatives, making it possible to reduce the risk before the disease will clinically appear, i.e. beta-blockers in the treatment of LQT1. Screening for risk factors could lead to an optimization of important conditions, e.g. diabetes, hyperlipidemia and hypertension. The rigorous control of new drugs before they are launched on the market is also important for minimizing the risk of potentially fatal proarrhythmic events.

Pathophysiology

OHCA can be the result of different causes. In the Swedish Cardiac Arrest Register, the ambulance crew divides supposed reasons for cardiac arrest into nine groups. Those groups are cardiac disease, respiratory disease, trauma, suffocation, drowning, intoxication, suicide, sudden infant death syndrome and other reasons.
Cardiac ischemic events are the most common aetiology of SD and cardiac arrest. Among cardiac causes of OHCA are ischemic heart disease with myocardial infarction, heart failure, electrolyte disturbances and arrhythmias. There is a growing awareness of the risk that drugs alone and in combinations or under certain conditions may increase the risk of malignant arrhythmias. The mechanisms may vary, but excessive prolongation of the QT interval by a direct effect on ion currents or on enzymatic levels or causing electrolyte imbalance are most probable.[36] There is a genetic disposition in SD, increasing the risk 1.8 times if one parent has been affected and even more if both parents have died of SD. [32] For antiarrhythmic agents, excess mortality in the treatment group vs. placebo was shown in the CAST[37] study (encainide and flecainide)

and the SWORD[38] study (d-sotalol).

Survival and the survivors

In European countries, about 10% survived an OHCA with all kinds of rhythms on the first ECG recording and about 20% when the initial rhythm was VF.[39] In the United States, the survival rate was 8% for any rhythm and 18% for VF. [40] In Sweden, 24% were brought alive to hospital, of whom 44% survived one month in 2010. [25] Thus, survival to one month was 10%.

Triggering factors

Among triggering factors, a novel ischemic event, concomitant use of QT-prolonging drugs[36] and even environmental factors such as air pollution [41] can be mentioned. There is a diurnal rhythm in sudden death and in myocardial infarction, with the highest incidence in the morning hours, [42-44] although this is not seen in HCM.[45]

Table 1
Triggering events for ventricular arrhythmias

Acute ischemia
Reperfusion
Haemodynamic fluctuations
Hypoxemia
Acidosis
Electrolyte disturbances
Sympathetic and parasympathetic changes
Proarrhythmic substances
Toxic agents

Treatment - the chain of survival

Treatment of cardiac arrest follows the guidelines of CPR that were recently updated in 2011. [25] The chain of survival has four links: early recognition and call for help, early basic life support, early defibrillation and post resuscitation care. Factors of importance to the outcome are bystander witnessed event or not, time to ambulance arrival, initial rhythm and time to defibrillation. [46] The first link in the chain implies the recognition of a cardiac arrest and the ability of bystanders to call for help. The second link implies that bystanders know how to start basic CPR, which may be learned at school or at work. This education must be provided to a large number of people, since the majority of OHCA events occur in individuals who may not be regarded to be at increased risk. Many OHCAs occur at home and most victims are males, meaning that special attention should be given to their spouses who commonly are the first to recognize the event.

[47] The third link in the chain, early defibrillation, will be provided by first responders that can be organized in different ways. Public defibrillators can be placed in public buildings such as sports arenas and airports. Much effort must be put into the easiness to use these devices and to find them in an emergency situation. [48-50] The emergency responders should be organized in such a way that as little time as possible will pass from the call for help until the arrival of the rescue team. The patient should have access to the fourth link as soon as possible, although this can often not be accomplished until the arrival at the emergency department. This link includes efforts to preserve brain function, e.g. post-resuscitation cooling. In the case of an acute ischemic event, preparations for acute PCI may be appropriate. The ambulance crew should have the proper education to handle malignant arrhythmias during the transport.
There is a positive relationship between a short delay time of ambulance arrival and subsequent survival.[51] The delay time can partly be overcome by educating relatives, first-line responders such as policemen and the general population.

Treatment of malignant ventricular arrhythmias

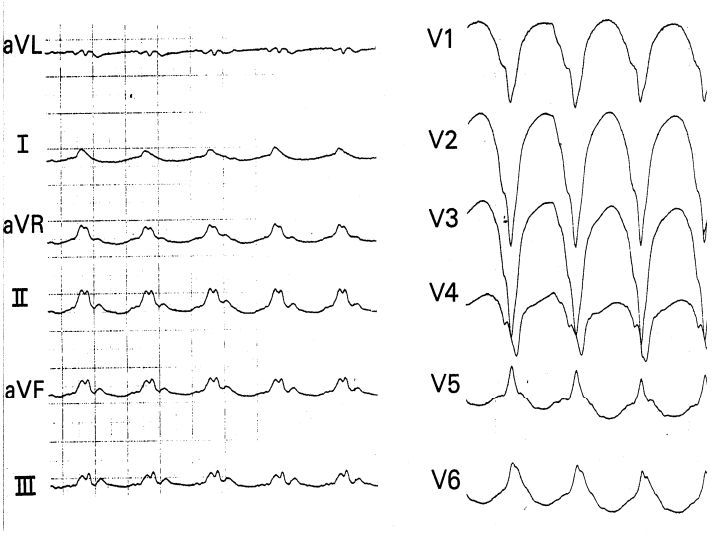
Pharmacological treatment

The goal of pharmacological treatment is rhythm control and prevention of recurrences. However, available agents for treatment of malignant arrhythmias have been proven to decrease the number of VTs and subsequent implantable cardioverter defibrillator (ICD) treatments, although they cannot reduce the risk of death. [52]
Among pharmaceuticals known to reduce the incidence of SCD are beta-blockers, which seem to be particularly effective in electrical instability, e.g. in reducing the risk of VF in the post-infarction period.[53]
In the case of recurrent VT, which is more substrate dependent, agents such as amiodarone are an alternative, perhaps in combination with beta-blockers. Class I antiarrhythmics are no longer recommended in these patients and have in randomized, controlled studies been found to cause excess mortality [37]. The use of beta-blockers to decrease the risk of malignant arrhythmias in LQT 1 and 2 syndromes is well known although the effect in LQT 3 is not well documented. Beta-blockers can also in part suppress the risk in of malignant arrhythmias in CPVT. [29] In HCM beta-blockers are standard treatment. The optimal treatment in a survivor of malignant ventricular arrhythmia is often a combination of an ICD and one or more pharmaceuticals.

Ablation

Idiopathic, i.e. non-ischemic, VTs from the Right Ventricular Outflow Tract (RVOT) and from the fascicles usually have distinct mapable arrhythmia mechanisms that can be found and ablated with good long-term effect and without ICD back-up.
Monomorphic ventricular tachycardias in ischemic patients most often occur in a more

or less developed substrate and can also be candidates for ablation, especially with the aim to reduce the number of appropriate shocks of an implanted ICD.
There have recently also been some reports of ablating the initiating VPC in VF initiated from the right ventricle or the Purkinje fibres. The ablation has been successful when targeting the initiating premature beets originating from the fascicles and RVOT. The initiating VPC could be preceded by potentials from the Purkinje network that could be mapped and ablated. [39-41]



Monomorphic VT from the Right Ventricle in an ARVC patient

ICD implantation

The implantable cardioverter defibrillator (ICD) is a device that has the properties of pacing and defibrillation. Via electrodes usually transvenously placed in the heart, it responds to the patient's rhythm and its disorders. With regard to its programming the device can deliver shock therapy and anti tachycardia pacing (ATP) at certain levels of ventricular rate that are detected by the device. The ATP (if programmed to be on) delivers ¨overdrive¨ pacing to the ventricle, after sensing and reconfirming the intrinsic rhythm. The shock function delivers defibrillations of the heart if the registered and reconfirmed rhythm and/or rate reach the programmed level. Different levels of ATP and shock therapies and combinations are programmable. Nowadays all ICDs have conventional pacing opportunities.

ICD use for secondary prevention is documented in three major studies, the AVID [54], CASH [55]and CIDS [56]. There is also a meta-analysis that pooled the original data from these studies supporting the benefit of ICD in secondary prevention.[57] The latter showed a 28% risk reduction for all cause mortality and a 50% reduction of arrhythmic death with ICD although the AVID and CIDS studies that were included had

higher rates of beta-blockers in the ICD arm.
The use of ICDs for primary prevention has been documented in major studies in recent decades, i.e. MADIT,[58] MUSTT[59] and MADIT II.[60] The latter study raised the possibility of using a simple criterion such as ejection fraction ≤ 30% as the selection criterion for implanting an ICD in the post myocardial infarction patients. The benefit of ICD implantation in ischemic and non-ischemic patients with low EF for primary prevention has been shown to be superior to anti-arrhythmic therapy. [52] The appropriate timing of ICD implantation has been a matter of discussion. Although the risk of arrhythmic death is higher in the first period after myocardial infarction [19, 20], ICD implantation early in the post myocardial infarction period has not been proven effective [61], [62]. The risk of SCD seems to have attenuated in the early, post infarction period in patients receiving beta-blocker. [53] A recent meta-analysis found that data are not conclusive for an all cause mortality benefit in elderly patients for primary prevention as elderly persons are more likely to die of concomitant diseases.[63] Current guidelines for ICD implantation are published by AHA, ACC and ESC. [64, 65]

Implantable Cardioverter Defibrillator (ICD)

Remaining challenges with ICD treatment

Problems with ICD treatment are inappropriate shocks, and peri-operative complications such as haematomas, and infections. Supraventricular arrhythmias, e.g. atrial fibrillation, can result in anti-tachy-pacing (ATP) and so called inappropriate shocks from the ICD because of a high ventricular rate. The ATP is not painful for the patient but leads to pacing in the ventricle at faster rates than the intrinsic rhythm, which may accelerate the ventricular rhythm. The shock therapy is usually unpleasant and/or painful for the patient when given for a supraventricular arrhythmia as the patient is usually conscious. Oversensing, which means that the device sensing algorithm interprets other signals than ventricular beats as R waves, could be the result of lead malfunction, T wave

oversensing and electromagnetic interference.
The T wave oversensing can lead to double count of the ventricular rate, triggering the ICD to respond. Sometimes these problems can be overcome by reprogramming or the lead has to be repositioned. If the cause of oversense is lead malfunction, the lead usually has to be replaced or the set-screw corrected. Problems with magnetic fields may occur. Strong magnetic fields could reset the read switch that can turn off the ATP and shock functions as the signals will not be interpreted. Other devices could interfere with the ICD, especially pacemakers, but they are now seldom used together with the ICD as the latter has full pacemaker capabilities [66]. More common is interference with other devices such as the transcutaneous nerve stimulator (TENS). There is also a possible risk in other devices used to treat other diseases such as epilepsy [67] and Parkinson disease. [68]

Transcutaneous electrical Nerve Stimulation (TENS)

The TENS device is used to decrease long-term pain in different parts of the body. The effects are documented in e.g. [69]. The TENS also has a documented effect on anginal pain [70-73]. The effect is thought to be mediated by gate control of the painful impulses. [74] Patients can use the TENS device by themselves after instruction given by a physician or a physiotherapist. Most TENS stimulators deliver low (1-10 Hz) and high frequency (40-120Hz) through the skin giving a not uncomfortable sensation at the painful body areas.

AIMS

1 To determine whether MADIT II criteria are useful in the clinical setting. What will be the result of using a simple criterion as ejection fraction ≤ 30% to decide whether or not an ICD should be implanted on a primary prevention basis?

2 To characterize the survivors of OHCA in relation to the initial rhythm, gender, bystander witnessed status, time to defibrillation and cerebral performance according to initial rhythm.

3 By means of a standardized test protocol, to assess the risk of potentially dangerous interference between the TENS and the ICD devices.

4 To study which recently added medications that are more common in cardiac arrest victims at the time of OHCA than one year before.

PATIENTS AND METHODS

Paper I: Presumed arrhythmic death in consecutive survivors of acute myocardial infarction – implications for primary implantable cardioverter defibrillator implantation

This was a single-centre observational study comprising all patients admitted to the CCUs of a Swedish university hospital. The patients were screened every Monday to Friday between June 2001 and February 2003 (21 months). Patients who were admitted on weekends were screened on the following Monday. All patients (none excluded) who fulfilled the criteria of a diagnosis of AMI were consecutively added to a log list and followed for two years or until death. In all, 583 consecutive patients, 405 men and 178 women, were diagnosed as having myocardial infarction. All patients' records were read initially and all medication, vital status, heart rhythm and diagnosis of heart failure were obtained from the patients' hospital records and general practitioner (GP) records when two years had passed from the initial event. Of the 532 patients who survived the first 30 days, 461 (87%) underwent an echocardiogram before discharge. One patient, who survived 30 days, was lost to follow-up because of emigration. The remaining 460 patients were followed for two years or until they died.

Paper II: Analysis of initial rhythm, witnessed status and delay to treatment among survivors of out-of-hospital cardiac arrest in Sweden

The Swedish Cardiac Arrest Registry was started in1990 and covers about 70% of OHCA patients in Sweden, which now has 9.1 million inhabitants and covers an area of 450 300 square kilometres, large parts of which are sparsely inhabited. Most of the population live in cities or towns. The registry is a collaboration between the Federation of Leaders in Swedish Ambulance and Emergency Services and the Swedish Resuscitation Council. All patients entered into the registry between 1992 and 2007 in whom cardiopulmonary resuscitation (CPR) was attempted and who survived for at least one month were included in the study. During the entire study period, 43,982 patients were entered in the study. Information about vital status after one month was available in 99%. Among these patients, 2,432 (6%) survived to one month and constitute the study cohort.

Paper III: Risk of Interference from Transcutaneous Electrical Nerve Stimulation on the Sensing Function of Implantable Defibrillators

Thirty patients were included after having signed an informed consent form. The group included two women and 28 men aged 37–81 years, with a mean age of 64 years. The patients had received their ICD because of ventricular tachycardia (VT; 20), ventricular fibrillation (VF; 7), VT and VF, and for primary prevention. We used a standardized test protocol. The noise reversion mode, if available, was programmed to VOO 50 (ventricular pacing without sensing, at 50 bpm) if available, and the mode during the test was VVI 50 (ventricular pacing and sensing with inhibition if sensed events, at 50 bpm). The patients had to have an adequate intrinsic rhythm for safety reasons. The patients were positioned in a resting supine position. We placed Transcutaneus Electrical Nerve Stimulation (TENS) electrodes at the hips and at the mamilla level at two energy levels, and at the highest comfortable stimulation level. All but one patient had sinus rhythm; the other patient had atrial flutter. The ICDs had to have been implanted at least two months before the investigation. The ICDs were manufactured by St. Jude Medical (Sylmar, CA, USA; 10), Guidant/Boston Scientific Corp. (St. Paul, MN,USA; 10), or Medtronic (Minneapolis, MN, USA;10).The effects of TENS on the electrocardiogram lead II, intracardiac electrograms and the ICD marker channels were analyzed.

Paper IV: Recent changes in medication in out-of-hospital cardiac arrest victims

Data from the web based Swedish Cardiac Arrest Register were matched with corresponding data from The Swedish Prescribed Drug Register.
Study cohort: The study cohort consisted of 7243 OHCA cases. The Cardiac Arrest Register in Sweden has been web-based since November 2007 and contains the unique 10-digit personal identification number (PIN) of all registered OHCA victims. It now covers all Emergency Medical Services (EMS) organizations in Sweden. This study included all patients entered into the web-based register from November 2007 through January 2011. The register includes patients with cardiac arrest in whom a resuscitation attempt was performed. According to the presumed cause of OHCA, as judged by the EMS team, the event was classified as being due to any of the following nine reasons: cardiac disease, respiratory disease, trauma, suffocation, drowning, intoxication, suicide, sudden infant death syndrome or others. In our analysis we paid specific attention to cardiac aetiology.
Prescribed and claimed pharmaceuticals: All OHCA cases in the register were matched with the Swedish Prescribed Drug Register which contains information on all claimed prescriptions delivered from Swedish pharmacies since 1999 and which since 2005 also contains information on the unique 10-digit (PIN). A case-crossover design was used and the drugs claimed at Swedish pharmacies during a six-month period immediately before the OHCA were compared with the claimed prescriptions 18-12 months before the event in the individual OHCA cases, thereby assessing which drugs had been added and which had been withdrawn. Different levels of the International Anatomical Thera-

peutical Chemical (ATC) codes were used. The main groups were first analyzed, and then the 4-digit code identifying groups of substances and finally the 7-digit code that identifies single drugs. The ¨qtlist¨ from the ¨qtdrugs.org" [75] was used to compare individual drugs on the list to all drugs used.

The OHCA patients were divided into four groups. Group1 consisted of the patients who claimed at least one drug (n=5122) in the period immediately before the OHCA that was not claimed in the period 18-12 months before. The second group (group 2), (n=690) consisted of the patients who had at least one drug withdrawn in the six-month period before the OHCA compared with the 18-12-month period. The third group (group 3) (n=495) consisted of the patients who had claimed the same drugs in both periods and the fourth group (group 4) (n=936) of patients who had not claimed any drugs in either period.

STATISTICAL METHODS

The Kaplan-Meier method was used in paper I for estimation of survival and cumulative mortality. The log-rank test was used to test for univariate associations between baseline variables and mortality. The Cox proportional hazard model was used to calculate hazard ratios (with corresponding confidence intervals) and for multivariate analyses (i.e. age adjustments and identification of independent predictors of mortality).
In all papers, Fischer's exact test and Mann-Whitney U test were used for group comparisons of proportions and continuous/ordered variables, respectively.
All tests are two-tailed and p-values below 0.05 in papers I, III and IV and below 0.01 in paper II were considered statistically significant.
All statistical analyses were performed using SAS for Windows version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Paper I: Presumed arrhythmic death in consecutive survivors of acute myocardial infarction – implications for primary implantable cardioverter defibrillator implantation

All 583 patients who had been diagnosed with myocardial infarction were followed for two years or until they died. Their mean age was 68.8±11.9 years (range 27–94years). Fifty-one patients (8.7%) died during the first 30 days after admission and, of these, 14 survived the first seven days. Of these 51 patients, an echocardiogram was performed in 29. Their mean EF was 39±10%.
Of the 532 patients who survived the first 30 days, 461 (87%) underwent an echocardiogram before discharge. Of the 471 patients whose EF was measured and who survived the first week, ten died a presumed arrhythmic death. Between one week and 30 days, ten patients died, one of them of presumed arrhythmic aetiology. Of the remaining 461 patients, one was lost to follow-up. Thirty-four patients (7.4%) had an EF ≤ 30%. Of them, ten patients would not have been candidates for ICD implantation because of high age and/or severe co-morbidity. Of the remaining 24, one died of presumed arrhythmia and could therefore, theoretically, have been saved by an ICD. Four hundred and twenty-seven patients had an EF ≥ 30% and of them six died a presumed arrhythmic death.

Paper II: Analysis of initial rhythm, witnessed status and delay to treatment among survivors of out-of-hospital cardiac arrest in Sweden

We found that 80% of the survivors had a shockable rhythm and the rest a non-shockable rhythm. Most survivors belonged to the bystander witnessed group and one-third was crew witnessed. The majority of the survivors had to wait ≥ five minutes until ambulance arrival from cardiac arrest if witnessed or call for ambulance if not witnessed.

Those who were bystander witnessed and had a shockable rhythm were defibrillated later than five minutes after collapse in most cases.
Among survivors, estimated cerebral function (according to cerebral performance categories score) was better among patients who had a shockable rhythm as compared with those who had a non-shockable rhythm.

Among all survivors, 28% were women and 27% of them were found in a non-shockable rhythm as compared with 18% among men ($p<0.0001$).
Approximately 80 % of survivors had a cardiac aetiology, while the most common non-cardiac aetiologies were in order of frequency: pulmonary disease, drug overdose and drowning. Slightly more than one-third had a cardiac arrest at home, and nearly half of the survivors received bystander CPR. The proportion of survivors with a cardiac aetiology was higher among men, whereas the proportion of survivors with a cardiac arrest at home was higher among women. Finally, the proportion of survivors who had received bystander CPR was higher among men.

Paper III: Risk of interference from transcutaneous electrical nerve stimulation on the sensing function of implantable defibrillators

Disturbance from the TENS device on the sensing function of the ICD was seen at all stimulation attempts. Interference between the systems was seen in 16 patients. In eight patients (27%) the interference was interpretation as VT/VF and in14 patients as ventricular extra beats. Other kinds of interactions were seen in five patients (16%). Interference was more often seen with integrated bipolar than dedicated bipolar leads (14/19, 73.7% vs. 2/11, 18.2%). Interference was more commonly detected at the mamilla level than at the hip level, (16/30, 53% vs. 7/30, 23%) and at 80Hz stimulation vs. 2Hz at each level, 15/30, 50%, vs. 14/30, 47% at the mamilla level and 6/30, 20%, vs. 5/30, 17%, at the hip level.

Paper IV: Recent changes in medication in out-of-hospital cardiac arrest victims

The association between prescription of new medication and various demographic and clinical characteristics was studied.

The study cohort consisted of 7243 OHCA cases. A minority of the cases, 2324 (~30%), were women. The patients in group 4, i.e. those in whom no drugs were prescribed, were significantly younger, 54±21 vs. 70±16 years for the patients in groups 1-3; $p<0.001$. Out of the entire cohort, 5122 had new prescriptions, where 3211 (65%) of them were categorized as having a cardiac aetiology, compared with 349 (73%) of 474 with unaltered prescriptions, 468 (71%) of 659 with at least one drug withdrawn and 483 (54%) of 893 with no drugs at all. The patients with drugs (groups 1-3) were more often women, 34% of all with drugs compared to 20% of those without drugs, $p<0.0001$, and they were less likely to live after one month, 7.2%, as compared to 13.9% among those with no drugs, $p<0.0001$.

The most common claimed prescriptions of a new medication

According to the ATC codes, 1118 (15%) of all OHCA victims had claimed a new prescription of drugs used for infectious diseases, followed by 813 (11%) of drugs for respiratory diseases and 797 (11%) drugs used for diseases in the nervous system, during the six months immediately preceding the OHCA.

According to the 4-digit ATC code, 799 (11%) had claimed different kinds of penicillins, 744 (10%) light analgesics, 579 (8%) opioids and 568 (8%) loop diuretics.

The most frequent single drugs, when using all ATC codes of individual drugs, were paracetamol claimed by 744 (10%), furosemide 567(8%), and omeprazole 554(8%).

When restricting the search for individual drugs from the ¨qtdrugs.org" list, [75] the most common were ciprofloxacin 247 (3.4%), citalopram 156 (2.1%) and terbutaline 152 (2.1%). Of all OHCA cases, 1176 (16.2%) had a new claimed prescription of drugs on the QT list.
Rhythm control drugs with class III mode of action were not commonly initiated, i.e. sotalol 10 (0.1%) and amiodarone 19 (0.3%).

In summary, new claimed prescriptions during the six-month period before the OHCA were most often not for cardiac disease. However, diuretics and drugs with suspected or known QT-prolonging effects were not uncommon and could, especially together, be a potentially arrhythmogenic combination.

DISCUSSION

Many people die suddenly, most of them from malignant arrhythmias due to coronary artery disease. It is challenging to identify candidates for sudden arrhythmic death before an event has occurred and to quickly reach and treat those who suffer an out-of-hospital cardiac arrest. Added to these problems are the imperfections of available treatments.

Since before the millennium shift, we have used the knowledge from secondary prevention studies about the benefit of ICD in the population that has already experienced a malignant arrhythmia. This led to the trials to find out whether this strategy may also be beneficial for primary prevention. The first studies MUSTT[59] and MADIT[58] showed that high-risk post myocardial infarction patients could benefit from ICD treatment, but the group was restricted to patients with EF <35-40% who had had non-sustained VT and where anti-arrhythmics could not suppress the arrhythmia in electrophysiological studies. As the ICD studies showed a benefit and the necessity of electrophysiological studies had been questioned, the next important study was the MADIT II study that used a single criterion, EF≤ 30, as the inclusion criterion. There was uncertainty about the number of patients that would be eligible and there were discussions about the MADIT II population, as the patients were recruited long after the myocardial infarction and revascularization. The patients were recruited on average five years after the myocardial infarction. [76] This led us to conduct our study of patients in common clinical practice. We found that only one of our 471 patients who had an ECHO performed in a CCU at a University Hospital during a period of almost two years would have been found and could have benefited from an ICD implantation if this had been the only criterion used. In our study we could not find that the simple EF ≤30% criterion reliably predicted which patients would later die of arrhythmia. Thirty-four patients that survived one month had an EF of ≤30%; ten of them would not have been eligible because of severe concomitant diseases and very high age and only one of the resting 24 died of presumed arrhythmia that might have been prevented by an ICD. Of the patients with better EF, six died an arrhythmic death. A recent meta-analysis of primary prevention studies shows benefit, both for ischemic patients and dilated cardiomyopathy patients,[77] although this has been questioned by others. [78] The data are not very conclusive for elderly patients that have a greater risk of dying of concomitant diseases. There is also an ongoing debate as to whether these trials are applicable in the modern patient, who will be revascularized early and be treated with a beta-blocker. [53, 79] The treatments used in our population were early revascularization with thrombolysis, PCI and coronary artery by-bass grafting (CABG), and 97% of our patients received beta-blockers. There have been efforst to find risk scores that would select the most suitable patients for ICD implantation showing a U-formed curve in benefit, meaning that the severely diseased patients will not benefit because they have a high mortality rate for other reasons, e.g. heart failure, and that the healthiest patients perhaps not benefit since they have a high survival rate even without an ICD. [80] In our study we found that a simple criterion such as an ejection fraction of ≤30% did not select the patients that would have benefited from an ICD in our population. Better algorithms to find the patients that will benefit from ICD implantation are highly warranted.

How should patients be selected for primary prevention in the future?

Different strategies could be explored to address this in the future: one is to identify those patients who will not benefit from ICD implantation. A thorough work-up should be performed to find patients with other diseases that it is possible to cure and arrange for their follow-up. When malignant conditions are found that can not be cured that will shorten the patient's life to less than a year, an ICD should not be implanted. There are also other risk factors, such as severe heart failure and renal impairment that will likely bring the patient's life to an end and make the ICD implantation less beneficial. Efforts should be made to keep complications to the implantation, e.g. infections, at a minimum. DINAMIT[61] and IRIS[62] were two primary prevention studies that did not show any all cause mortality benefit of ICD implantation early post infarction although there was a reduction in arrhythmic mortality. There can be different reasons for this finding. In the DINAMIT study, patients that fulfilled the MADIT I criteria with non-sustained VT were not included, and the other criterion, heart rate variability (HRV), has been shown simply to be a predictor of cardiac death and is not as reliable for sudden arrhythmic death. The risk of right ventricular pacing inducing or worsening heart failure is shown in the DAVID study [81] as just one example. This risk could be minimized by sophisticated programming and newer devices. With the introduction of cardiac resynchronization therapy with and without ICD, the Companion study[82] showed a reduction in all cause mortality with CRT alone of 23.9% and CRT-D of 43.4%, and the Care HF study[83] showed an all cause mortality rate of 30% with medical therapy and, with the addition of CRT, an all cause mortality of 20%; a new opportunity for patients with low EF emerged. The former study showed a reduction in mortality with ICD back-up and the latter a mortality reduction even without ICD. In recent years, new studies have come that might increase the number of CRT indications.[84]

Another direction to follow is to better characterize the patient with better EF that will have a high risk of dying an arrhythmic death after myocardial infarction. Patients with non-sustained and sustained ventricular arrhythmias are at risk. Patients with non-sustained VT and EF≤35-40% will benefit from ICD, as shown in MADIT I[58] and MUSTT.[59] Patients with sustained VT 48 hours or more after an MI will be implanted as a secondary prevention. But how should we find the others?

All kinds of arrhythmias are a marker of electrical instability and are more common in heart failure. Myocardial hypertrophy without reduced ventricular performance can increase the risk and is possible to measure. Various non-invasive measures have been proposed but usually lack adequate positive predictive value for arrhythmic death even if they find patients that will die of cardiac reasons. Most non-invasive measurements are markers of the existence of an arrhythmia substrate that could predispose for VT and/or cardiac death, e.g. because of heart failure. They usually do not predict VF. In the Carisma and Refine studies [85, 86], heart rate turbulence (HRT) has recently been shown

to predict arrhythmic death in the post myocardial infarction population with a low EF. We still do not have good instruments for finding the patient with a better EF that will be at high risk for arrhythmic death. As many of the non-invasive tests have a high negative predictive value, there could be value in conducting at least a few of them before discharge. If all of them turn out negative, it is not inappropriate to assume that the risk is low, although this must be proven in prospective studies. The HRV has been used in the DINAMIT [61] study as an additional variable to define the high risk patients. In that study there was no benefit of ICD implantation in all cause mortality. The various non-invasive test instruments have a low positive predictive value for arrhythmic death in individual patients, especially in patients with preserved myocardial function. To find them, we need new instruments.

Strengths and weaknesses of our study

Our cohort was consecutive patients at a CCU unit at a University Hospital in Sweden. There is a possibility that patients that are older and have more concomitant diseases will not be referred to such a facility.

A weakness of our study is that we did not have the possibility to assess the EF at one month as this was an observational study that reflects the common practice at that time. We included all patients, but no ECHO was performed in 13% of the one-month survivors. This reflects the clinical practice at that time. There is also a possibility that the mode of death could have been misclassified in a few cases, as almost none of the patients were monitored at the moment of death.

The strength is that we conducted a study in all everyday clinical patients, who are those for whom we have to make the decisions. We lost only one patient to follow-up.

Can we extrapolate our results to other communities?

In our observational study we followed the patients admitted and ECHO measurements were made before discharge. This is the clinical dilemma, as some patients will recover their myocardial function and will have a lesser risk, but even among these patients there will be a substantial portion with arrhythmic risk. In our study we found the ECHO finding during the hospitalization to be a good predictor of death. Better prognostic instruments should be available as we know that the risk of dying is higher for SCD and of heart failure in the first period after the myocardial infarction. [79] In the MADIT II [60] study, patients were enrolled after at least one month, making it a selected population. We investigated what will be the result in common practice, as the decision to implant usually has to be made during the early post infarction period. It is possible to assume that similar populations treated with early revascularization and beta-blockers, ACE-inhibitors and statins will have a similar outcome.

The survivors

When an OHCA has occurred, all links in the chain of survival are equally important. The EMS personnel must reach the victims in a short time after the event. This delay could be shortened if the population is educated to rapidly call the EMS in the case of chest pain and if ambulances are located in the country in such a way that the patients can be reached in a reasonable time. This is not always possible in our sparsely inhabited country. Lives can be saved by training relatives and laymen in basic CPR, and educating first-line responders such as fire-fighters in the use of AEDs offers further possibilities. The proportion of patients found in a shockable rhythm as the initial rhythm has declined through the years, even though this trend has flattened out in Sweden in the last years.[87] This trend is not seen in the survivors, where around 20% had a non-shockable rhythm at their first ECG. Efforts should also be made in research in how to best handle those cases that may perhaps have been somewhat overlooked owing to the emphasis placed on the shockable cases, which usually have a better prognosis. [88]

Why is it important to study the survivors of OHCA?

Similar studies have not been done before. Who are the survivors? With this type of retrospective analysis we could show that a relatively large proportion of survivors is recruited from the group of OHCA patients that has an expected low chance of survival. Thus 20% of the survivors were found in non-shockable rhythm, and more survivors were from the group with longer delays in the ambulance response than for the shorter delays, probably because most OCHA victims will be reached later. This has also raised the importance of how to best manage the victims found in a non-shockable rhythm as they have a poorer outcome in terms of the CPC score.

Aspects of the OHCA population

The study included all registered patients who had suffered an OHCA and had been subjects of resuscitation attempts and is thus representative of OHCA patients found early after the event. However, circadian rhythms differ, and there is a possibility that patients who die during their sleep are not recognised until morning and the time to resuscitate has passed. Patients who die suddenly and in whom no attempt is made to resuscitate are not included in the register. Furthermore, we have learned from validation that about 30% of patients suffering from OHCA and in whom CPR was attempted are not reported to the register at the time of the OHCA for unknown reasons.

Can we extrapolate our data to other communities?

It is possible to partially extrapolate our data to other communities in the Western world, but EMS systems vary between countries and there are differences in EMS response times as well as access to AEDs in various communities. [89, 90] Even the fourth

link, i.e. post resuscitation care, most likely differs between communities. Survival to discharge has been reported to vary considerably between regions in Sweden among patients who were brought to hospital alive.[87]

Do we find more male than female survivors?

In earlier studies [91] the proportion of women vs. men who were admitted to hospital alive after OHCA was higher, although the difference in survival rate after one month was not significant. We found that, among all the survivors, 28% were women, 27% of whom were found in a non-shockable rhythm compared with 18% of men. In our study we found an almost equal proportion of female survivors as the proportion of female OHCA victims. Proportionally, more female survivors were found in a non-shockable rhythm compared to men. We also know that women less often experience VF than men, the reason for which might be the higher incidence of ischemic heart disease among men at the same age and/or a difference in arrhythmia mechanisms.[91-93] In conclusion, female survivors are found in a non-shockable rhythm in 27 % of the cases while male survivors, were found in a non-shockable rhythm in18 % of the cases. Female survivors had a lesser proportion of cardiac etiology, were more often found at home and received bystander CPR to a lesser extent, compared to men.

Do survivors of a shockable rhythm have better cerebral function?

Patients with a shockable rhythm have signs of better cerebral function according to the CPC score. One contributing factor might be that these patients had a shorter delay to the start of treatment. Another contributing factor might be that they were less severely diseased and that patients found in non-shockable rhythm could be in end-stage disease. The CPC score is easy to interpret although it has not been validated, and an inter observer variability is reported by [94].
The CPC score was measured one month after OHCA. If repeated a few months later, there is a possibility that results had differed owing to a further improvement in cerebral function.[95]

Inappropriate ICD treatment

A problem with ICDs is the risk of inappropriate shocks. The risk is increased among the patients with atrial fibrillation, known or unknown, with a high ventricular rate reaching the rate level of ventricular tachycardia or VF programmed to the ICD. Inappropriate shocks that are initiated by oversensing and lead problems are not uncommon. Another problem is the interference with other devices, some of them used for the treatment of angina pectoris and long term pain such as the TENS. Angina is a common problem in ICD recipients although refractory angina is not very common. We tested 30 ICDs, ten from each of our manufacturers at that time. We found interference with

the proper ICD function in 16/30 of the patients and therefore do not recommend that the two devices should be used together. The interference could have resulted in inappropriate ICD shocks or reversing to noise mode with an inhibition to sense normal and abnormal ventricular beats. The risks were higher at the mamilla position (nearer the leads), with integrated bipolar leads and with higher stimulation frequencies (80Hz vs.2Hz), as the former will likely be interpreted as VT/VF and the latter as VPC. Oversensing can also inhibit normal pacing, making the patient dizzy, and can lead to syncope. Another problem of oversensing is reversion to noise mode, which in some ICDs inhibits it from ventricular sensing. A malignant arrhythmia will then be undetected during that time period. We also found undersensing in one case. Instead, with proper precautions, Spinal Cord Stimulation (SCS) can be used, which has been proven effective in ischemic conditions. [96, 97]
There are devices used for treatment of e.g. epilepsy, Parkinson's disease, incontinence and diaphragmal paralysis that at least theoretically have the possibility to interfere with ICDs. [67] [68] The problem with the interference is primarily the risk of oversensing which makes the ICD misinterpret the signals as ventricular beats. Misinterpretation of these signals could result in inappropriate shocks and missed detection of arrhythmias, and can be lethal. [98] There can also be interference from other electrical devices such as radio transmitters and electrical welders. Interference with Magnet Resonance Imaging is known but not within the scope of these thesis.

Future implications

Interference between different devices has a further implication. The use of two different devices is contraindicated in different recommendations. Patients in need of investigations and other device treatments may perhaps not be investigated or implanted because of a fear of interactions. Recent studies report that the risk of interference can be overcome and recommend practical protocols. As we have shown in our study, the risk is lower with dedicated bipolar leads than integrated bipolar leads and at a longer distance from the device and leads.[99-102] The risk in TENS to ICD patients is too high to recommend their concomitant use at this time.

Was our study cohort representative?

Our study cohort included equal numbers of ICDs of all manufacturers that were used in our hospital at that time. There are also other brands on the market that were not used in our region at the time. We do not have knowledge of the behavior of these devices. Neither can we say anything about differences between manufacturers. Some of the devices had dedicated bipolar leads and others had an overrepresentation of integrated bipolar leads.
Our study included only 30 individuals. The tests were not performed in a randomized manner, and each patient had been implanted on their clinical indication. There was an unequal distribution between leads and devices as some manufacturers were over rep-

resented in terms of dedicated bipolar leads. There were only two women in our study and, in a further study, the weight of the patient should be annotated, as adipose tissue could theoretically have isolating properties. Our study was small but our findings are consistent that make them worth attention.

Is it possible to eliminate these types of inferences in the future?

By developing better sensing algorithms in ICDs, it could be possible to decrease this problem. The risks seem to be smaller when dedicated bipolar leads are used, and there seems to be a lesser risk the longer the distance to the electrode. It is also of importance that, when electrical devices are developed, the possibility of other devices for simultaneous use for other concomitant diseases in the same patient is regarded. More and more devices are developed and have to co-operate with each other. In the case of angina pectoris the use of spinal cord stimulation (SCS) seems to be safer. The possible additional benefit of reducing the risk of VT in acute ischemia has been investigated in experimental studies.[96]

Is it possible to prove an association between the use of a drug and the risk of OHCA?

An association between a drug and SD is difficult to prove as the most probable reason for the use of drugs is the disease itself. It is likely that the disease killed the patient, however, we know from randomized studies such as CAST [37] that certain drugs, such as encainide and flecainide, are associated with an increase in the risk of death after myocardial infarction. There are OHCA of different aetiologies in the Cardiac Arrest Register. [25] The risks of e.g. anti-depressants could be different in the group of probable cardiac aetiology vs. suicide by means of drug intoxication. In (paper IV) we evaluated all types of OHCA, regardless of aetiology. Different aetiology groups will be assessed in a future study. What can be found is an association between certain drugs and certain adverse outcomes. We also have the possibility to link to other databases to find out more about the patient's disease. Although the patients claimed the prescribed drugs, we do not know whether they in fact used them. Other drugs not recently added are not shown. What we did was to investigate changes in medication before OHCA to find associations.

What are the weaknesses and the strengths of the case cross-over design?

The strength in the study is that the patient is his or her own control, which makes it possible to control differences between patients, such as genetic differences and differences in lifestyle and the socio-economic situation. There could have been a change in

some patients, however e.g. patients could have stopped smoking, become a widower, lost his or her occupation etc.
The cohort is also one year older in the second period. If a case-control study had been made, even with a large group of controls, not as many variables could have been controlled. In a case-control study, we can know the precise amount of claimed drugs of different kinds but would not know which of them were new. It is reasonable to believe that the condition of the patient has changed in some way when a new drug is added. In a review from the Swedish pharmacovigilance database, which is a register of adverse events where drugs are involved, it was found that, of drugs supposed to be involved in TdP, 38% of the adverse events were recorded during the first month after initiation. [103] Choosing to look at new drugs, we had the possibility to find pharmaceuticals that were added before the OHCA.
We recently found added drugs used for infectious disease in 15%, for respiratory disease in 11% and drugs used for diseases in the nervous system in 11% of the OHCA patients. In the pharmacovigilance [103] study, the most frequently reported drugs were sotalol, digoxin and citalopram.

Is the patient population of the Swedish Cardiac Arrest Register representative?

The register now contains all ambulance organizations in Sweden, although this has grown successively. While all cardiac arrests where an attempt has been made to resuscitate should be included, the register is not complete. We have retrospectively found that about 30% of the patients are not reported to the register at the time of the cardiac arrest. We are currently evaluating the way in which these patients differ from the patients who were included in the register directly. What we can say is that we have shown which drugs were most commonly added before an OHCA. We cannot say that they were commonly added before death since death can occur e.g. in hospitals and since the victims could be found in such a condition that CPR is not started.

The clinical relevance of these data could be defined as hypothesis generating. This is the first study in which we linked the Prescribed Drug Register and the Swedish Cardiac Arrest Register. Using our findings here, we can in further studies also link to the Patient Register to find out more about the individuals that suffered an OHCA.
We cannot say that these drugs contributed to the event, although a precaution could be noted and new studies initiated. Drugs that are commonly added before OHCA could be a warning sign and, if possible, other alternatives should be used.

Does the Prescribed Drug Register reflect the use of drugs?

All drugs claimed at Swedish pharmacies are registered with the 10-digit personal identification number (PIN) of the customer. Drugs sold over the counter are not registered.

In Sweden, most drugs need a prescription although it is possible to buy small amounts of e.g. light analgesics, cough remedies, ranitidine, anti-allergics and vitamins and herbal remedies without prescription, even in common food stores. As the patient usually has to pay at least some of the cost, it is likely that there was at least an intention to use the drugs, although we do not know about the compliance.

Can our data be extrapolated to other parts of the world?

Our data can not automatically be extrapolated to other parts of the world. In the Swedish Cardiac Arrest Register and the Prescribed Drug Register, there is no note about a person's race and/or ethnic origin, and most people in Sweden are Caucasian. There has been an immigration of people of other origins to Sweden in recent decades. We cannot say that the results would be similar in other populations. The availability of drugs differs between countries. Similar studies should be performed in other populations and other cultures, if possible. We found in the drug group comparison that the most frequently added drugs were antibiotics, even though there is a somewhat restrictive use of antibiotics in Sweden compared to other countries.

Was our way of dividing drugs appropriate?

The international ATC codes can be used in different ways. We did not want to exclude any drugs in our study so that we could have the possibility to assess all recently made changes in drug use before the OHCA. This is a way to explore an unknown field and make it possible to discover all the drugs that were used in some way before the OHCA. If we had limited the search to certain drugs, unknown, eventual harmful effects would not have been discovered. The most frequently claimed drugs during the six months prior to the OHCA, but not during a six-month period one year before, were antibiotics, which tell us that patients that get new antibiotics may perhaps have a higher risk of OHCA either owing to the infectious disease or to the drug treatment or both.

The nature of infectious disease makes the likelihood of treatment appearing for the first time higher than treatment of chronic disease such as diabetes. When we looked at the individual drug level with the 7-digit code, it was possible to assess the recently added drugs with a known or unknown potential to harm. Individual drugs from the list to be avoided by people with known or suspected LQTS (list 4) were not common but the accumulated addition of drugs from that list was found to be around 16% of the individual OHCA patients.

There are four different lists in the "qtdrugs.org" database:[75] 1 "Drugs with risk of TdP"; 2 "Drugs with possible risk of TdP"; 3 "Drugs with conditional risk of TdP"; and 4 "Drugs to be avoided by patients with known or suspected LQTS". The percentages of recently claimed new prescriptions of drugs on the different lists were 1.5%, 3.6%, 10% and 20%, respectively. The difference between 16% of the patients and 20% of the new prescriptions probably reflects the concomitant use of more than one such drug, or that such drugs could have been added one after another in the last six-month period, e.g. a period of erythromycin followed by an addition of sotalol.

The patients with recently claimed new drugs were older, were more often women, had an OHCA of presumed cardiac aetiology and had a lower survival rate to one month compared with OHCA patients without drugs. This might indicate that these patients had a more advanced disease. It is also reasonable to expect more medication in patients with cardiac disease than for instance when the OHCA was caused by drowning or suffocation.

CONCLUSION

This thesis has shown the difficulties in finding a simple criterion to evaluate which post myocardial infarction patients should receive an ICD implant to prevent sudden cardiac death. As has been suggested, the ECHO criterion of EF ≤ 30% does not find the patients that will die of arrhythmia, when used in the clinical setting at a University Hospital in Sweden. Survivors of OHCA were found not only among patients with a shockable rhythm when CPR was started, and not only among the ones who could be reached by the EMS staff within five minutes.

Twenty per cent of those who survived were found in non-shockable rhythm and, of those in a shockable rhythm, only a minority was defibrillated within five minutes. More attention should be given to the best treatment of the patients found in a non-shockable rhythm.

There are still some unresolved problems after the implantation of an ICD. The problems of oversensing and inappropriate shocks are well known. Here the TENS device was tested together with the ICD. Slightly more than half of the ICDs were disturbed and interpreted the signals as VT, VF, VPC or noise. Those misinterpretations could result in inappropriate shocks, inhibited pacing and inhibited therapy when necessary. Our recommendation is not to use these devices together.

When investigating drugs recently claimed by OHCA victims, drugs used to cure infectious diseases, respiratory diseases and neuropsychological diseases were the most common. Furosemide, citalopram and proton-pump inhibitors were claimed by a considerable number of the OHCA victims. Drugs appearing on any of the" qtdrugs.org" lists were added by 16.2% of the OHCA victims, although the frequencies of single drugs were low. Our results imply the need of further investigations in the recent medication of OHCA victims

FURTHER IMPLICATIONS

It was shown in this thesis that the ECHO criterion of EF≤30% was not good enough to be used as single criterion for selecting patients who will die of presumed arrhythmia in the nearest two years and who would benefit from ICD implantation. Better criteria or combinations must be found. About 20% of the survivors come from the OHCA group found in a non-shockable rhythm. More research on the optimal treatment of this group is warranted. The interference between different implantable devices is of concern; both because of the risk of interference between them, making their function inappropriate, and because of the fear of interactions would withhold adequate treatment of patients. Protocols and guidelines for their simultaneous use should be established. Finally, some drugs are more often added before OHCA. Their role should be further investigated with a focus on safety.

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