METHOD AND APPARATUS FOR CARDIAC RESUSCITATION

VENTILATION

CIRCULATORY SUPPORT

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METHOD AND APPARATUS FOR CARDIAC RESUSCITATION

The present invention relates generally to the field of cardiac resuscitation and, in particular, to a method for restoring cardiac activity after a prolonged period of asystole or near-asystole by delivering a combination of circulatory assistance and a series of depolarizing cardiac stimulation pulses.

Sudden cardiac death (SCD) takes the lives of an estimated 400,000 to 450,000 people in the United States each year, and the incidence of SCD among young adults is increasing. SCD is typically caused by an arrhythmia or coronary artery disease. Because of the unexpected nature of SCD, it is difficult to prevent and remains the attributed cause of a high proportion of cardiac-related deaths.

Ventricular tachycardia (VT) or ventricular fibrillation (VF) often precede SCD. Defibrillation shocks delivered within the first minute of fibrillation onset can be highly effective in preventing death and restoring normal heart rhythm. Patients diagnosed with a propensity for arrhythmias can benefit from implantable cardioverter defibrillators, which provide life-saving electrical stimulation therapies quickly after the onset of an arrhythmia.

However, a patient’s risk for SCD is often unknown prior to the first arrhythmia episode, which, unless treated quickly, is often fatal. The chance of successful resuscitation from cardiac arrest using cardiopulmonary resuscitation (CPR) alone is very low. As few as 1-2% of patients treated with CPR in a hospital are discharged. CPR alone will generally not convert VF to sinus rhythm, but even if external defibrillation shocks are delivered to terminate VF, the result is often asystole or pulseless electrical activity (PEA), also referred to as electro-mechanical dissociation (EMD). The success rate of delivering defibrillation shocks decreases dramatically over the first two to three minutes following the onset of VF. See August 2003 Annals of Emergency Medicine Volume 42 at pages 242-250 entitled, “Optimal Defibrillation Response Intervals for Maximum Out-of-hospital Cardiac Arrest Survival Rates,” by V. DeMaio et al. The likelihood of an emergency responder arriving on the scene within four minutes is small and so the probability of a successful resuscitation using existing techniques is low. The probability of emergency responders arriving on scene within fifteen minutes is good.
Thus, new cardiac resuscitation techniques that allow successful reversion to sinus rhythm after prolonged VF, fine VF, or asystole are needed.

A consequence of VF that limits the rate of successful resuscitation using current methods is the hypoxia that results from impaired perfusion during VF. During normal cardiac function, contraction of myocardial fibers occurs when calcium enters the cell via calcium channels (L-type channels). Calcium enters the cell when the cell membrane is depolarized by a passing action potential to cause an increase in permeability to calcium via the L-type channels. Calcium entering the cell causes additional release of calcium from the sarcoplasmic reticulum (SR) through ryanodine channels into the sarcoplasm. This “calcium-induced calcium release” increases the sarcoplasma calcium concentration, allowing the calcium to interact with the myofilaments to cause mechanical cycling of the myofilaments and sarcomere shortening.

Calcium is sequestered back into the SR via intracellular calcium pumps, which requires the cellular fuel adenosine triphosphate (ATP) to operate and are known as “sarcoplasmic or endoplasmic reticulum calcium ATPases” (or “SERCA”). Myofilament cycling, in particular during the relaxation phase, also requires ATP. Thus both of these operations are affected by hypoxia because oxygen is required for the production of ATP. During fibrillation, poor perfusion of the heart leads to hypoxia and a lack of ATP available for cellular functions. When a VF, asystolic, or near-asystolic episode persists for several minutes, the hypoxic state becomes severe and is a limiting factor in preventing external defibrillation attempts from being successful.

However, other mechanisms may play an important role. The ryanodine calcium channels, which normally release calcium from the SR during calcium-induced calcium release, are “leaky,” i.e., some calcium is released from the SR in the absence of the calcium-induced calcium release mechanism. Normally, SR calcium stores are replenished during each cardiac cycle via calcium entering the cell through the L-type channels and by the SR reuptake of calcium from the sarcoplasma via SERCA. In the absence of a regular sequence of action potentials, the SR calcium stores may be reduced as calcium is leaked out of the SR and is removed from the cell by sodium-calcium ion channels which maintain the cell’s normal resting potential. As a result, this “leaked” calcium is not available to contribute to sarcomere shortening upon the next action potential.
In the past, this SR calcium leak was considered trivial, however, recent work suggests that this calcium leak can be substantial. If so, one can theorize that during fibrillation, cardiac function becomes increasingly compromised by at least two mechanisms. First, hypoxia due to insufficient myocardial perfusion from the effective loss of circulation reduces the ATP available for myofilament cycling and SR calcium uptake via SERCA. Second, SR calcium depletion due to calcium leaking becomes significant due to a lack of sufficient cellular depolarization and SERCA activity to replenish SR calcium stores thereby reducing calcium available for myofilament cycling. Thus, cumulative ATP loss and SR calcium depletion may both contribute to an exacerbation of loss of function during the first three to five minutes following cardiac arrest, precluding successful resuscitation using currently known techniques.

Defibrillation alone may restore a heart beat when the SR calcium stores have not been substantially depleted, which theoretically corresponds to the maximum three to five minute time course in which defibrillation can be effective. A single high-voltage defibrillation shock may act to depolarize a large myocardial mass to allow an influx in calcium, which in turn creates a cycle of calcium handling which is able to regenerate the normal cardiac cycling process if ATP reserves are not yet depleted. If, however, SR calcium stores are substantially depleted, defibrillation alone may not be sufficient to restore SR calcium losses without the contribution of extra-cellular calcium influx through L-type channels that occurs only with repeated cellular depolarization. If hypoxia has set in, ATP is unavailable for myofilament cycling and SERCA. A number of recent publications have emphasized the importance of CPR administered before shock delivery. It has been reported that one minute of CPR delivered before shock delivery when fibrillation has been present for longer than four minutes resulted in better survival than immediate defibrillation.

Even when CPR has been administered, however, individual defibrillation shocks typically do not restore sinus rhythm after a prolonged fibrillation or asystolic episode. A single depolarizing shock may not be adequate in restoring the cellular cycling of calcium handling because the calcium influx occurring during a single depolarization may be insufficient to restore normal SR calcium concentration. Early works in the development of transcutaneous defibrillation therapies reported that a series of shocks was more effective than a single, more energetic, shock. In one study, a series of shocks were
uniformly successful if the initial shock failed to defibrillate completely. A series of depolarizations may be necessary to restore normal SR calcium concentration through the additive effect of a sequence of depolarizations making intracellular calcium available for SR sequestration.

Despite the early observations in defibrillation studies, later work largely focused on single shock defibrillation as currently implemented in implantable defibrillation devices. Single shock defibrillation requires less energy than a series of shocks and is thus more feasible to implement in implantable devices. Ultimately, single shock defibrillation has proven effective in the scenario of fibrillation detection within seconds of onset by arrhythmia detection algorithms available in implantable devices.

The use of multiple pulses during treatments of cardiac arrhythmias has been proposed in several patents. A method of reducing the likelihood of onset of pulseless electrical activity (PEA) after defibrillation in a subject afflicted with a fibrillating heart including a first treatment waveform insufficient to defibrillate the heart and a second treatment waveform that defibrillates the heart is generally disclosed in U.S. Pat. Appl. Publication No. 2002/0161407 to Walcott et al. A system and method for delivering multiple closely spaced defibrillation pulses to a heart is generally disclosed in U.S. Pat. No. 5,620,464, issued to Kroll, et al., which reduces the overall size of the main energy delivery capacitor for pulse delivery. A process to apply an electrical pretreatment to a fibrillating heart that begins the process of organizing the action of the chaotically contracting myocardial cells, so that the defibrillating waveform applied after the pretreatment can accomplish its task with less energy than would otherwise be required is generally disclosed in U.S. Pat. No. 5,314,448 issued to Kroll et al. In U.S. Pat. No. 6,314,319 issued to Kroll, et al., an electrical method of stimulating cardiac cells causing contraction to force hemodynamic output during fibrillation, hemodynamically compromising tachycardia, or asystole is generally disclosed in a method referred to as "Electrical Cardiac Output Forcing."

A method for treating the heart to restore blood flow where electromechanical dissociation occurs after termination of a ventricular tachyarrhythmia of ventricular fibrillation including identifying electromechanical disassociation after termination of a ventricular tachyarrhythmia or a fibrillation and providing electrical therapy, the therapy comprising a series of packets of electrical pulses is generally disclosed in PCT
Publication No. WO 00/66222, issued to Rosborough and Deno. The series of pulse packets is delivered after ventricular tachyarrhythmia or fibrillation is terminated and electromechanical dissociation is detected.

There remains a need, however, to address the problem of cardiac resuscitation after a prolonged episode of ventricular fibrillation or asystole, after which the severity of hypoxia plays an important role in limiting the success of electrical stimulation based methods for defibrillating the heart. In the scenario of prolonged fibrillation or asystole, e.g., greater than one or two minutes, the inventors of the present invention propose that both hypoxia and progressive SR calcium loss contribute to the lower success rate of single-shock defibrillation. In order to improve the success of cardiac resuscitation, resuscitative methods must therefore address hypoxia and intracellular calcium loss. Resuscitative methods are needed, therefore, that include mechanisms for alleviating hypoxia for making ATP available for ATP-dependent calcium pumps to allow normalization of SR calcium stores because the repetitive delivery of electrical stimulation are believed to make more calcium available to the pumps.

The present invention is directed toward providing a system and method for performing cardiac resuscitation, in particular after a prolonged episode of VF, fine VF or asystole. The present invention is achieved in a system and method that include the provision of circulatory assistance, which may be in the form of manual or automatically delivered CPR or other perfusion or hemodynamic assistance, and inducing a series of cardiac depolarizations after a period of circulatory assistance. In one embodiment, the series of cardiac depolarizations are induced by electrical stimulation pulses delivered at a pulse energy that depolarizes a mass of myocardial cells. The pulse series may therefore contain pulses of relatively low energy, such as the energy normally associated with cardiac pacing pulses, referred to herein as “pacing-class pulses,” and/or pulses of relatively high energy normally associated with defibrillation shocks, referred to herein as “defibrillation-class pulses.” The series of cardiac stimulation pulses may be delivered at a regular or varying rate and regular or varying amplitude for an interval of time or number of pulses. In one embodiment, the series of stimulation pulses is concluded with a high-voltage defibrillation shock at a specified interval following the last stimulation pulse of the series.
Apparatus for delivering the electrical stimulation portion of the resuscitation therapy may be embodied as an external stimulation device and associated set of electrodes for delivering cardiac stimulation pulses transcutaneously, percutaneously, or esophagally. Alternatively, apparatus for delivering cardiac stimulation pulses may be embodied as an implantable cardiac stimulation device and electrode system capable of delivering cardiac stimulation pulses via intracardiac electrodes, epicardial electrodes, or subcutaneously or sub-muscularly placed electrodes. In a programmable, implantable device the resuscitation method provided by the present invention may be included in a selectable menu of arrhythmia therapies.

In other embodiments, the cardiac stimulation device further includes cardiac stimulation therapies provided for improving cardiac output following cardiac resuscitation. In one embodiment, the cardiac stimulation device includes the provision of extra systolic stimulation pulses delivered to achieve the mechanical benefits of post-extra systolic potentiation.

In yet other embodiments, a physiological sensor, capable of generating a signal related to the delivery of circulatory support, is included in the system. The sensor may be provided as a sensor of blood oxygen saturation (SaO2) or a surrogate therefore such as lactate or hydrogen peroxide, pH or other metabolic parameter that directly or indirectly indicates the degree of hypoxia. In alternative embodiments, the sensor may be provided as a mechanical sensor that generates a signal related to the presence of circulatory support such as a blood pressure sensor, accelerometer or a mechanical sensor sensitive to chest compressions delivered during CPR. The sensor signal may be used by an implantable stimulation device for automatically detecting the presence and duration of circulatory assistance for use in determining the appropriate time for initiating the electrical stimulation portion of the resuscitation therapy.

Figure 1 is a schematic diagram of a method for delivering a cardiac resuscitation therapy after a prolonged episode of VF, near asystole or asystole.

Figure 2 is a functional block diagram of one embodiment of an external stimulation device, which may be used in delivering the cardiac resuscitation therapy.
Figure 3 is an illustration of an implantable cardiac stimulation device and associated cardiac lead deployed in a patient's heart, which may be used in delivering the cardiac resuscitation therapy.

Figure 4 is a functional block diagram of the implantable cardiac stimulation device of Figure 3.

Figure 5 is a functional block diagram of an implantable cardiac stimulation device that includes a sensor used for determining when the electrical stimulation portion of the resuscitation therapy should be initiated.

Figure 6 is a timing diagram of one method for delivering cardiac resuscitation according to the methods of the present invention.

Figure 7 is a timing diagram depicting the events occurring during an alternative method for delivering cardiac resuscitation according to the present invention.

Figure 8 is a timing diagram of a method for performing cardiac resuscitation according to the present invention that includes the delivery of extra systolic stimulation for improving hemodynamic function after successfully resuscitating the heart.

Figure 9 is a timing diagram illustrating a method for delivering cardiac resuscitation that includes delivering both pacing class and defibrillation class pulses.

Figure 10 is a timing diagram illustrating an alternative method for performing cardiac resuscitation according to the present invention.

Figure 11 is a graph of experimental results obtained from an isolated myocyte preparation.

Figure 1 is a schematic diagram of a method for delivering a cardiac resuscitation therapy after a prolonged episode of VF, fine VF, or asystole. As used herein, VF refers to coarse VF which appears on an ECG as relatively high amplitude fibrillation waves which are typically readily observable on ECG monitoring equipment; “fine VF” refers to the presence of relatively low amplitude fibrillation waves which may not be observable on some ECG monitoring equipment. The term “asystole” as used herein refers to the complete absence of electrical activity and activity that is sometimes referred to as “bradycardia asystole” wherein electrical activity may be present but at a very low rate of about 10 depolarizations per minute or less.
The method includes delivering circulatory assistance 52, which may be in the form of external chest compressions as used in CPR. Preferably, the patient 50 is provided with circulatory assistance 52 to prevent or alleviate hypoxia during a prolonged episode of VF, fine VF or asystole. By preventing or alleviating hypoxia, it is believed that ATP will be made available for SERCA as well as other cellular functions. In addition, maintaining perfusion of the brain is of particular importance during the prolonged VF, fine VF, or asystole in order to avoid irreversible cerebral damage upon successful cardiac resuscitation.

Chest compressions may be delivered manually by an emergency responder or automatically using automated resuscitative equipment. If the patient 50 is not breathing spontaneously, ventilatory support may also be required. Ventilation 54 may be delivered manually, according to known CPR techniques, or with the use of a ventilator. Depending on the location of the patient, equipment available at the site, and the skill of the emergency responders, the type of ventilation 54 and circulatory assistance 52 applied may vary. For example, in a hospital or emergency room setting the patient may be placed on a ventilator and receive manual or automated chest compressions. In a surgical setting, direct heart massage may be provided for circulatory assist or another type of circulatory assist mechanism may be in place such as an intra-aortic balloon pump or extra-corporeal membrane oxygenation (ECMO). In an out-of-hospital setting, manual CPR may be the only circulatory assist available.

The resuscitation method further includes the delivery of cardiac stimulation pulses using a stimulation device 56, which, in the embodiment shown in Figure 1 is an external electrical stimulation device. Device 56 delivers cardiac electrical stimulation pulses via an associated set of leads 58 and electrodes 60. Electrodes 60 may be provided as cutaneous electrodes, typically placed on the torso and generally in the thoracic area, for transcutaneous cardiac stimulation. The depicted positions of electrodes 60 are merely exemplary and alternate locations of electrodes 60 may be used for delivering cardiac stimulating pulses. Electrodes 60 may alternatively be adapted for percutaneous or esophageal placement for stimulating the heart. For intra-operative cardiac resuscitation applications, electrodes 60 may take the form of epicardial electrodes that may be placed directly on the surface of the heart. Other types of electrodes known for invasively or non-
invasively applying cardiac electrical stimulation may be utilized for delivering cardiac
stimulation pulses in practicing the present invention.

Device 56 includes an interface 64 for coupling leads 58 to pulse generating output
circuitry 62. Output circuitry 62 may include high-voltage output circuitry for delivering
high-voltage, defibrillation-class, shocking pulses and/or low-voltage output circuitry for
delivering low-voltage, pacing-class pulses. High-energy output circuitry for use in an
external defibrillator is generally disclosed in U.S. Pat. No. 5,824,017 issued to Sullivan et
al., incorporated herein by reference in its entirety. Device 56 may be a battery powered
device and may alternatively or additionally include DC input with appropriate electrical
shielding to allow connection to a wall socket.

In a basic embodiment, the rate, pulse energy, pulse shape and other features of the
electrical stimulation pulses delivered by device 56 are fixed and delivered by output
circuitry 62 upon enabling or empowering device 56 via the user interface 66. In
alternative embodiments, parameters controlling the delivery of a cardiac electrical
stimulation pulse series may be set by an emergency responder via a user interface 66
coupled to output circuitry 62. Various output parameters including, but not limited to,
pulse energy, pulse amplitude, pulse width, pulse rate, and/or duration of the pulse series
may be set by an emergency responder using the user interface 66.

Figure 2 is a functional block diagram of one embodiment of the cardiac
stimulation device of Figure 1. In this embodiment, the stimulation device 56 is an
external stimulation device that includes sensing circuitry 70 for monitoring the patient’s
ECG. Sensing circuitry 70 is coupled to lead interface 64 for receiving ECG signals from
electrodes 60. The ECG may be visually displayed on display 68 for viewing by the
emergency responder and/or used by external stimulation device 56 for detecting the
presence of cardiac activity and classifying the heart rhythm. Such information may be
used by device 56 for selecting stimulation pulse parameters and controlling the time that
a depolarizing stimulation pulse series is initiated. Device 56 may be provided with
asystole detection capabilities as generally disclosed in U.S. Pat. No. 6,304,773 issued to
Taylor et al., incorporated herein by reference in its entirety. Other rhythm detection and
classification algorithms known for use in cardiac stimulation or monitoring devices may
be implemented for detecting and classifying the heart activity and in recommending
and/or automatically selecting a resuscitation therapy based on the detection of prolonged VF, fine VF, or asystole.

Display 68 may include visual or audio signals correlating to electrical activity of the heart. During or after the delivery of a series of depolarizing stimuli, the depolarizations, intrinsic or evoked, are expected to be initially accompanied by mechanically weak contractions, which will grow in strength with subsequent depolarizations. Hemodynamic benefit may be provided by synchronizing chest or heart compressions with the weak heartbeats. As such, a depolarization sensed by sense circuit 70 may cause display 68, under the control of microprocessor 72, to generate a signal perceivable by an emergency responder, which may be an acoustic, tactile and/or visual signal, indicating the occurrence of a cardiac depolarization or other triggering event for the delivery of manual CPR. An emergency responder may then deliver chest or heart compressions, or another form of generally pulsatile circulatory assistance, synchronized to the depolarizations so as to enhance the cardiac output of the weak mechanical contraction.

External stimulation device 56 is shown in Figure 2 as a microprocessor-controlled device wherein cardiac stimulation functions may be controlled by microprocessor 72. However, it is recognized that device 56 may be provided as other types of pulse generating devices that are not microprocessor-based, for example devices that utilize a platform of dedicated digital or analog circuitry. User interface 66 may allow entry of patient-related data such as time of VF/asystole episode onset and/or duration of CPR or other circulatory assistance. Such data may be used by device 56, in conjunction with the currently sensed cardiac activity, in automatically selecting or recommending when and what type of electrical pulse series should be delivered.

In alternative embodiments, a cardiac stimulation device used in delivering the electrical stimulation portion of cardiac resuscitation according to the present invention may be provided as an implantable electrical stimulation device. Figure 3 is an illustration of an implantable cardiac stimulation device 210 and associated cardiac lead 216 deployed in a patient’s heart 208. Stimulation device 210 includes a connector block 212 for receiving the proximal end of one or more cardiac leads deployed in operative relation to a patient’s heart 208. In Figure 3, a right ventricular lead 216 is used for positioning electrodes for sensing cardiac activity and delivering cardiac stimulation pulses which may
include relatively low-energy, pacing-class pulses and/or high-energy cardioversion/defibrillation-class shock pulses. For these purposes, right ventricular (RV) lead 216 is equipped with a ring electrode 224, a tip electrode 226, optionally mounted retractably within an electrode head 228, an RV coil electrode 220, and a superior vena cava (SVC) coil electrode 230, each of which are connected to an insulated conductor contained within the body of lead 216. The proximal end of the insulated conductors are coupled to corresponding connector terminals carried by lead connector 217 at the proximal end of lead 216 for providing electrical connection to the device 210.

The electrodes 224 and 226 may be used as a bipolar pair for sensing cardiac activity or delivering low-energy stimulation pulses, commonly referred to as a “tip-to-ring” configuration, or individually in a unipolar configuration with the device housing 211 serving as the indifferent electrode, commonly referred to as the “can” or “case” electrode. The device housing 211 may also serve as a subcutaneous electrode in combination with one or both of the coil electrodes 220 or 230 for delivering high-energy stimulation pulses to the atria or ventricles.

The depicted positions of the RV lead 216 and electrodes 224, 226, 220 and 240 shown in Figure 3 in or about the right heart chambers are approximate and merely exemplary. Furthermore, it is recognized that alternative leads having other combinations of tip, ring, canister-based, and/or coil electrodes provided for stimulating or sensing at particular sites in one or more heart chambers may be used in conjunction with the present invention. While a particular implantable cardiac stimulation device and lead system is illustrated in Figure 3, methodologies included in the present invention may be applied in single chamber, dual chamber, or multi-chamber systems which include unipolar, bipolar or multipolar leads positioned endocardially, epicardially or within the coronary sinus.

The present invention may alternatively be implemented in a system that does not employ leads for deploying electrodes within or on the heart. For example, a device implanted subcutaneously or sub-muscularly in an operative location relative to the heart, such as in the left or right pectoral regions, could use non-intracardiac lead based methods for electrical sensing to detect cardiac activity and for delivering electrical stimulation. Such systems may employ subcutaneous or submuscular electrodes incorporated in or on the device housing.
Figure 4 is a functional block diagram of the implantable cardiac stimulation device of Figure 3. Device 210 includes a microprocessor 250, pacing output circuitry 252, cardioversion/defibrillation output circuitry 254, and stimulation timing and control circuitry 256 which are linked by control/data bus 258. In accordance with the present invention, device 210 delivers the depolarizing stimulation portion of the cardiac resuscitation therapy. A series of depolarizing electrical stimulation pulses may be delivered by pacing output circuitry 252 and/or cardioversion/defibrillation output circuitry 254 under the control of stimulation timing and control circuitry 256. Device 210 is equipped with terminals 260, 262, 264 and 266 for electrical connection to electrodes placed in operative relation to the heart. Terminals 260 and 262 may be coupled to low-voltage pacing/sensing electrode for delivering relatively low-voltage, pacing-class pulses within the pulse series. Terminals 264 and 266 may be coupled to high-voltage electrodes for delivering relatively high-voltage, defibrillation-class pulses within the pulse series. Parameters controlling the delivery of the pulse series may be programmed or stored in memory associated with microprocessor 250 and communicated to stimulation timing and control 256 via data bus 258.

Device 210 may additionally be capable of sensing cardiac activity and delivering pacing, cardioversion, defibrillation and/or other cardiac stimulation therapies according to methods known in the art. General sensing, pacing and defibrillation function may be provided according to the description provided in U.S. Pat. No. 5,117,824 issued to Keimel, incorporated herein by reference in its entirety.

Typically, electrical signals from terminals 260 and 262 are provided to sensing circuitry 280 on input lines 270 and 272. Terminals 260 and 262 provide electrical connection to a sensing electrode pair, e.g. a bipolar tip-to-ring pair, which may be the same electrode pair used for delivering pacing-class stimulation pulses, and therefore terminals 260 and 262 may be additionally coupled to pacing output circuitry 252, as shown in Figure 4. In response to the detection of a cardiac signal, e.g. a P-wave or an R-wave, the sensing circuitry 280 provides a logic signal on output line 274 to stimulation timing and control circuitry 256, which serves to reset an escape interval used to control the timing of stimulation pulse delivery. Intervals between sensed events may be used for detection and classifying the heart rhythm.
According to general pacing operations, if timing and control circuitry 256 does not receive a signal on output line 352 for a predetermined period of time corresponding to the escape interval set for controlling the timing of cardiac stimulation pulses, the timing and control circuitry 256 will trigger the generation of a pacing pulse by pacing output circuit 252. A disable signal on line 276 prevents sensing of the pacing pulse by default sensing circuitry 280. The gain of sensing circuitry 280 is also controlled by timing and control 256 on signal line 278.

Terminals 264 and 266 provide electrical connection to a high-energy stimulation electrode configuration, which will generally includes at least one coil electrode paired with another coil electrode and/or the device housing. Terminals 264 and 266 are coupled to cardioversion/defibrillation output circuitry 254 and used for delivering high-energy, cardioversion/defibrillation-class pulses.

In response to the detection tachycardia, an anti-tachycardia pacing therapy may be delivered if desired by loading a regimen from microprocessor 250 into timing and control circuitry 256 according to the type of tachycardia detected. In the event that higher voltage cardioversion or defibrillation shock pulses are required, microprocessor 250 activates the cardioversion and defibrillation output circuitry 254. Timing of the delivery of the defibrillation or cardioversion pulse is controlled by timing and control circuitry 256.

Any ventricular cardioversion or defibrillation pulse control circuitry known for use in implantable cardioverter/defibrillators may be usable in conjunction with the present invention. In the illustrated device, delivery of cardioversion or defibrillation pulses is accomplished by cardioversion/defibrillation output circuit 254, under control of timing/control circuitry 256 via control bus 258. Output circuit 254 determines the shock pulse waveform, e.g. whether a monophasic, biphasic or multiphasic pulse is delivered, which electrodes are involved in delivery of the pulse, the pulse shape and tilt, pulse energy, etc.

In modern implantable cardioverter defibrillators (ICDs), the particular therapies are programmed into the device ahead of time by the physician, and a menu of therapies is typically provided. For example, on initial detection of tachycardia, an anti-tachycardia pacing therapy may be selected. On redetection of tachycardia, a more aggressive anti-tachycardia pacing therapy may be scheduled. If repeated attempts at anti-tachycardia...
pacings therapies fail, a higher-level cardioversion pulse therapy may be selected thereafter. As in the case of currently available ICDs, the amplitude of the defibrillation shock may be incremented in response to failure of an initial shock or shocks to terminate fibrillation.

Sustained VF, fine VF or asystole may persist or develop when defibrillation shock therapies fail to convert VF to sinus rhythm using the single-shock defibrillation approach within the first one to two minutes after VF detection. Cardiac resuscitation therapies according to the present invention may be programmed to be initiated after an interval of unsuccessfully treated VF or upon detection of fine VF or asystole following attempted defibrillation therapies. The cardiac resuscitation therapy provided by the present invention may therefore be included in a programmable menu of arrhythmia therapies.

The resuscitative therapy includes the delivery of a series of stimulation pulses delivered either before hypoxia has become severe or after circulatory assistance has been provided to reverse hypoxia. The stimulation pulse series, which may include relatively low energy, pacing-class pulses and/or high-energy defibrillation-class pulses, is delivered by the pacing output circuitry 252 and/or the cardioversion/defibrillation output circuitry 254 under the control of timing and control circuit 256. Parameters controlling the pulse series may be programmable and may include, but are not limited to, the type of pulses included in the series (pacing class or defibrillation class), pulse amplitude, pulse width, pulse shape, pulse rate, and time duration of the pulse series or the total number of pulses. These parameters are applied by timing and control circuitry 256 according to data received from microprocessor 250 on data bus 258.

Device 210 may further include a cardiac event indicator 284, which includes circuitry for generating a signal, such as a visual, tactile, and/or audible signal (such as a beep or a tone), to indicate to an emergency responder the occurrence of a heart beat. As noted previously, during or after the delivery of a series of depolarizing stimuli, the depolarizations, intrinsic or evoked, are expected to be accompanied initially by mechanically weak contractions, which will grow in strength with subsequent depolarizations. Hemodynamic benefit may be provided by synchronizing chest or heart compressions with the weak heartbeats. As such, a depolarization sensed by sense circuit 280 or a depolarizing pulse delivered by pace output circuitry 252 or cardioversion/defibrillation output 254 may cause event indicator 284, under the control of
microprocessor 72, to generate a signal perceivable by an emergency responder, indicating the occurrence of a cardiac event.

Generation of such signals may be automatically or manually enabled after the stimulating pulse series is initiated such that an emergency responder may deliver chest or heart compressions, or another form of pulsatile circulatory assistance, synchronized to the cardiac event so as to enhance the cardiac output produced by the weak mechanical contraction during and/or after the series of pulses. The generation of cardiac event indicator signals may be disabled automatically after a predetermined interval of time during which normal cardiac function is expected to be restored and/or manually disabled at any time by the emergency responder using an external programming device.

Alleviating hypoxia via circulatory assistance prior to delivering the series of depolarizing stimuli is important in preparing the myocytes to benefit from the stimulation portion of the resuscitation therapy. As such, a sensor capable of generating a signal indicative of the delivery of circulatory assistance or for detecting blood oxygen levels may be included in an implantable device provided for practicing the present invention. By detecting the delivery and duration of circulatory assistance and/or the level of or change in blood oxygen saturation, the implantable device can determine when initiation of the stimulation portion of the resuscitation therapy is appropriate.

Figure 5 is a functional block diagram of an implantable cardiac electrical stimulation device that includes a sensor used for determining when the stimulation portion of the resuscitation therapy should be initiated. Sensor 290 may be included within and/or on the housing of the implantable device 210 or may be located external to device 210 but implanted within the body of the patient. Sensor 290 is connected to sensor processing circuitry 292 for receiving and processing signals generated by sensor 290.

Sensor 290 may be embodied as an oxygen sensor used for detecting blood oxygen saturation levels to indicate the relative level of hypoxia. In this embodiment, sensor 290 may be positioned on a lead and deployed in an intra-cardiac or intra-arterial location. Such a lead may further include cardiac stimulation or sensing electrodes and be coupled to device 210 via the connector block.

A signal that is correlated to blood oxygen saturation levels may be conditioned and processed by sensor processing circuitry 292. The resulting oxygen saturation data is
provide to microprocessor 250 for use in determining if the measured oxygen saturation level indicates a reversal of hypoxia during a prolonged episode of VF, fine VF or asystole as is expected after CPR or other circulatory assistance has been delivered for a period of time, e.g. about one minute or more. Upon detection an oxygen saturation level that is increased by a specified amount over a previous, hypoxic oxygen saturation level or upon detection of an oxygen saturation greater than a specified minimum level, the stimulation portion of the resuscitation therapy may be initiated by device 210.

In alternative embodiments, sensor 290 may be provided as a mechanical sensor capable of generating a signal indicating the presence of circulatory assistance. In one embodiment, sensor 290 may be embodied as a pressure sensor capable of detecting the increase in blood pressure created during CPR or other circulatory assistance delivery. In another embodiment, sensor 290 may be embodied as an accelerometer or piezoelectric sensor capable of generating a signal corresponding to the application of chest compressions delivered during manual or automated CPR. The output of a mechanical sensor is provided to sensor processing circuitry 292 for signal conditioning and processing such that data relating to the mechanical effects of circulatory assistance can be provided to microprocessor 250. Microprocessor 250 may initiate the stimulation portion of the resuscitation therapy after detecting circulatory assistance for a sustained interval of time, e.g., after about one minute.

Figure 6 is a timing diagram of one method for delivering cardiac resuscitation according to the methods of the present invention. An ECG signal initially shows essentially no cardiac activity during a prolonged episode of asystole 100. The resuscitation methods may be administered following a prolonged episode of VF, fine VF, or asystole. An emergency responder begins to deliver CPR or another form of circulatory support at 102 to alleviate hypoxia. If medical-grade oxygen is available, ventilation of medical-grade oxygen will more quickly reverse hypoxic conditions. CPR or other circulatory assistance is delivered for a period of time 104 prior to initiating the stimulation portion of the resuscitation therapy. Current cardiac resuscitation techniques generally emphasize administration of defibrillation shocks as quickly as possible following cardiac arrest. However, in order to achieve a successful response to the stimulation portion of the resuscitation method, it is expected that ATP must be available for powering calcium-handling functions such as SERCA. Therefore, CPR or another
form of circulatory support is provided for an interval of time to alleviate myocyte hypoxia and make ATP available to the myocytes for calcium handling functions. An appropriate interval of time for delivering circulatory support may be on the order of one minute, but may be longer or shorter depending on the severity of the hypoxia and the duration of the VF, fine VF or asystolic episode. The duration of circulatory assistance may be a nominal interval of time, such as one minute, or be based on sensing blood oxygen levels or another physiological indicator of hypoxia such as pH.

After an interval of circulatory assistance 104, the stimulation portion of the resuscitation therapy is administered by delivering a series of stimulation pulses 106. The stimulation pulses may be delivered by an external device or an implantable device, such as the devices described in conjunction with Figures 1 through 5 above. The stimulation pulses may be relatively low-voltage, electrical pacing-class pulses that are of high enough energy to cause depolarization of a mass of myocardial cells. The pulses may alternatively be high-energy electrical shocking pulses. The pulses are delivered at a predetermined pulse rate, for example a rate of on the order of 1 Hz. The pulses are delivered for an interval of time 108, for example on the order of a minute or longer. Without intending to limit the present invention to any particular theory, it is presently believed that a series of depolarizing pulses is needed to restore normal SR calcium concentrations by the influx of calcium during successive cellular depolarizations and sequestration of that calcium by the aerobic function of the calcium pumps.

After the pulse series 106 is delivered, the cardiac activity is monitored to verify successful restoration of normal sinus rhythm 112. In some cases, a prolonged condition of asystole or fine VF may be reverted to VF rather than sinus rhythm. Figure 7 is a timing diagram depicting the events occurring during an alternative method for delivering cardiac resuscitation according to the present invention. In this example, a series of low-voltage pulses 106 delivered after a period of circulatory support 102 is terminated by a defibrillation pulse 120, which may follow the last of pulses 106 by a predetermined time interval 118. The defibrillation pulse 120 is provided in order to convert VF 116 to sinus rhythm 122 when the prolonged asystole or fine VF 100 is converted to VF 116 by the pulse series 106.

It is further recognized that an implantable or external stimulation device may deliver bradycardia pacing to maintain a desired heart rate once normal electromechanical
association is regained after a successful resuscitation therapy but the intrinsic rate remains bradycardic.

While the interval of circulatory assistance 102 is shown to end prior to the onset of the pulse series 106 in Figures 6 and 7, it is contemplated that circulatory assistance may be delivered continuously during the depolarizing stimulation delivery if the circulatory assistance does not interfere with stimulation delivery and the pulse series is not composed of high-voltage electrical stimulation pulses that would impose risk to an emergency-responder delivering CPR or other circulatory assistance. It is further contemplated that intervals of circulatory assistance may be interspersed with intervals of stimulation pulses.

A form of circulatory assistance may additionally be continued or restarted after the series of stimulation pulses is completed to support post-resuscitation hemodynamic recovery. In some embodiments, cardiac stimulation therapies aimed at improving cardiac hemodynamic performance may be delivered by the stimulation device after the pulse series in order to increase cardiac output. Such stimulation therapies may include, but are not limited to, cardiac resynchronization therapy and/or extra systolic stimulation. Figure 8 is a timing diagram of a method for performing cardiac resuscitation according to the present invention that includes the delivery of extra systolic stimulation for improving hemodynamic function after successfully resuscitating the heart.

A prolonged VF or asystolic episode 100 is first treated with CPR 102 or other circulatory assistance for alleviating hypoxia. The circulatory assistance is followed by a series of depolarizing stimulation pulses 106, presently believed to alleviate SR calcium loss. After completing the series of pulses 106 and verifying that sinus rhythm 112 is restored, or electro-mechanical association is restored and the heart rate is maintained by bradycardia pacing, extra-systolic stimulation 140 is delivered to enhance cardiac pumping function by achieving a post-extra systolic potentiation effect. Aspects and benefits of extra-systolic stimulation for achieving the mechanical benefits of post-extra systolic potentiation are described in PCT Patent Publication WO 03/020364 to Deno, et al., incorporated herein by reference in its entirety.

Extra systolic stimulation 140 may be applied by delivering an extra systolic stimulation pulse 136 following ventricular events (VE) 134, which may be sensed R-waves or ventricular pacing pulses. Extra systolic stimulation pulses 140 may be
delivered with every paced or intrinsic cardiac cycle or less frequently, e.g., at some ratio of the intrinsic or paced heart rate. In the example of Figure 8, an extra systolic (ES) stimulation pulse 136 is delivered after every other R-wave 130 sensed as a ventricular event (VE) 134 in order to induce an extra systolic depolarization 132. Additional details regarding the control of extra systolic stimulation pulse delivery are provided in non-provisional U.S. patent application no 10/ XXX,XXX (Att No P-11214.00) to Burnes et al., and non-provisional U.S. patent application no 10/ XXX,XXX (Att No P-11252.00) to Burnes, et al., both of which are incorporated herein by reference in their entirety.

The pulse series 106 shown in Figures 6, 7 and 8 is shown to be consisting of pulses of fixed pulse amplitude delivered at a constant rate. It is recognized that a pulse series may consist of pulses of different or varying pulse energies or amplitudes and may be delivered at different or varying rates within a pulse series. A series of pulses delivered with the intention of restoring normal SR calcium levels and myocyte calcium handling may be tailored in order to provide the most effective restoration of normal cardiac activity, which may depend in part on the initial cardiac activity present when the resuscitation methods are begun and/or the cardiac activity present during or after the interval of circulatory support and an initial pulse series.

In one embodiment, the cardiac stimulation device monitors for a return of VF during resuscitation procedures and alters the stimulation portion of the resuscitation therapy if VF is detected. Figure 9 is a timing diagram illustrating a method for delivering cardiac resuscitation that includes delivering both pacing-class and defibrillation-class pulses. After the pulse series 106 is initiated, the asystolic episode 100 is converted to VF at 142. Upon detecting VF, a high-energy shocking pulse is delivered in place of a low-energy pulse in the pulse series. A number of high-energy shock pulses 146 may replace the low-energy pulses in the pulse series, or all remaining pulses in the pulse series may be delivered as high-energy shocking pulses to convert and prevent VF. Alternatively, or additionally, a pulse series may include a sequence of varying rate pulses 148. A sequence of varying rate pulses 148 may be delivered at a high rate that is gradually reduced to a slower rate in an attempt to convert or prevent VF from resuming during or after the pulse series.
In the example of Figure 9, circulatory assistance 102 is provided for an interval of time 104 prior to the onset of the stimulation pulse series 106 and continues during administration of the pulse series until the high-voltage defibrillation-class pulses 146 are delivered in response to VF 142 detection. Upon terminating VF, low-energy pulses 148 are delivered, and circulatory assistance is resumed at 103.

Figure 10 is a timing diagram illustrating an alternative method for performing cardiac resuscitation according to the present invention. The fibrillation waves of a sustained VF or fine VF episode may contribute to the depletion of intracellular calcium since these waves, though mechanically ineffective, still require energy. The outcome of a defibrillation shock delivered late after VF or fine VF onset may be asystole. However, this conversion to asystole may be advantageous in reducing ATP losses due to the generation of fibrillation waves. Therefore, in Figure 10, a prolonged episode of VF 152, which may be coarse or fine VF, may first be treated with a defibrillation shock 154 to convert the VF to asystole 156. Upon inducing asystole 156, an interval of circulatory assistance 102 is delivered followed by a series of depolarizing pulses 106 as described previously in conjunction with Figure 6.

Figure 11 is a graph of experimental results obtained from an isolated myocyte preparation. A continuously-perfused, isolated guinea pig myocyte was stimulated using 1Hz supra-threshold pulses until reaching a steady-state mechanical response. Stimulation was discontinued for intervals of 1, 2.5, 5, 10, 15 and 20 minutes after which 1 Hz stimulation was resumed. The results of the 20-minute quiescent period experiment are shown in the graph of Figure 1. Sarcomere length is plotted over time. Baseline steady-state shortening 10 was established during 1Hz stimulation followed by a 20-minute quiescent period at 12. Upon re-initiating 1 Hz stimulation at 14, sarcomere shortening was initially impaired but recovered to the baseline steady-state response at 16 over the course of approximately one minute of sustained 1 Hz stimulation. Thus, in the presence of adequate oxygenation, recovery of normal myocyte shortening is attainable even after 20 minutes of no activity.

Of note, is that significant mechanical impairment is present after 20 minutes of no depolarizations despite adequate oxygenation. Thus, hypoxia may not be the only cause of electromechanical dissociation (EMD) that occurs after sustained fibrillation or asystole. Results for shorter quiescent periods of 5 minutes or more were similar to the results
shown in Figure 1 in that myocyte shortening was reduced to approximately 10 percent of baseline shortening after the quiescent period, and full recovery of baseline shortening was achieved after approximately one minute of sustained 1 Hz stimulation. Mechanical impairment was lesser and recovery toward baseline shortening occurred more quickly following quiescent times of less than five minutes. These results support the theory that SR calcium losses increase with an increased period of inactivity due to calcium leaking and that a sustained series of depolarizations is required in order to replenish calcium stores. These results further support the need for resuscitative methods that reverse both hypoxia and SR calcium loss.

Of course, the present invention may be readily implemented as instructions stored on a computer readable medium and execute under computer control in an implantable or external medical device. The computer readable medium includes magnetic, optical and other storage medium now known or later developed in all forms such as random-access, read-only, serial-access and dynamic and erasable versions thereof (e.g., RAM, ROM, SAM, DRAM, EPROM, EEPROM and the like).

Thus, a cardiac resuscitation method has been described that addresses the need for resuscitating the heart after a prolonged episode of VF, fine VF, or asystole. The methods and apparatus described herein for practicing the invention have been described according to specific embodiments. These embodiments are intended to be exemplary, not limiting, with regard to the following claims.
CLAIMS

1. A method of resuscitating a heart during an episode of ventricular fibrillation, a fine ventricular fibrillation, or a sustained asystole, comprising:
   delivering circulatory support for an interval of time appropriate for alleviating a myocardial hypoxia condition of a heart; and
   delivering a series of therapeutic electrical pulses capable of depolarizing at least a portion of a myocardium of the heart.

2. A method according to claim 1, wherein said delivering step comprises at least one of:
   manually delivering cardiopulmonary resuscitation, delivering extracorporeal oxygenation circulatory support via an apparatus coupled to a patient, activating an implantable ventricular assist device fluidly coupled to a portion of vasculature of the patient,
   activating an automated cardiopulmonary resuscitation apparatus coupled to the patient.

3. A method according to claim 2, wherein said step of manually delivering cardiopulmonary resuscitation further comprises:
   initiating chest compressions by a signal

4. A method according to claim 3, wherein said signal comprises at least a one of: an audible signal, a tactile signal, a visual signal.

5. A method according to claim 4, wherein a periodic manual compression initiation signal is provided wirelessly from an implantable pulse generator to an external device and said external device conveys said signal to a person attempting to manually resuscitate a patient.

6. A method according to claim 1, wherein said series of therapeutic electrical pulses comprise pacing-class pulses.
7. A method according to claim 6, wherein some of said pacing-class pulses have at least a one common characteristic, said common characteristic comprising: a pulse width characteristic, a polarity characteristic, a pulse energy, a pulse amplitude.

8. A method according to claim 1, wherein said series of therapeutic electrical pulses are conducted through at least a one of the following electrodes: an intracardiac electrode, an epicardial electrode, a subcutaneously electrode, a sub-muscular electrode.

9. A method according to claim 1, wherein said method is invoked by at least one of the following: a clinician operating a telemetric programming device, a detection of a potentially lethal arrhythmia, a mechanical sensor, a detection of an arrhythmia by an external defibrillator, detection of an unsuccessful prior defibrillation attempt, a relatively low heart rate, a relatively low cardiac output condition, a relatively low saturated oxygen condition.

10. A method according to claim 9, wherein said mechanical sensor comprises at least a one of: an accelerometer adapted to be coupled to sense cardiac activity, a pressure sensor adapted to be coupled to sense cardiac activity, an impedance-based sensor adapted to be coupled to sense cardiac activity.

11. A method according to claim 1, further comprising: displaying one or more parameters related to the delivery of circulatory support or related to the delivery of the series of therapeutic electrical pulses.

12. A method of resuscitating a heart, comprising: providing cardiopulmonary resuscitation to a patient; and applying a series of electrical pulses capable of depolarizing at least a portion of a myocardium of the patient.

13. An apparatus for resuscitating a heart during ventricular fibrillation, fine ventricular fibrillation, or sustained asystole, comprising:
means for delivering circulatory support for an interval of time appropriate for alleviating a myocardial hypoxia condition of a heart; and means for delivering a series of therapeutic electrical pulses capable of depolarizing at least a portion of a myocardium of the heart.

14. An apparatus for resuscitating a heart following unsuccessful high-voltage defibrillation therapy delivered as a result of a ventricular fibrillation condition, a fine ventricular fibrillation condition, or a sustained asystole condition, comprising: means for delivering circulatory support for an interval of time to alleviate a myocardial hypoxia condition of at least a portion of a heart; means for delivering a series of therapeutic electrical pulses capable of depolarizing at least a portion of a myocardium of the heart.

15. A computer readable medium for performing a method of resuscitating a heart, comprising:
instructions for delivering circulatory support for an interval of time appropriate for alleviating a myocardial hypoxia condition of a heart, and instructions for delivering a series of therapeutic electrical pulses capable of depolarizing at least a portion of a myocardium of the heart.
FIG. 1
FIG. 2
FIG. 10
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61N1/362 A61N1/39 A61H31/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61N A61H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO–Internal, WPI Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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☐ Further documents are listed in the continuation of box C.  ■ Patent family members are listed in annex.

* Special categories of cited documents:

*A* document defining the general state of the art which is not considered to be of particular relevance

**E** earlier document but published on or after the International filing date

*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

**O** document referring to an oral disclosure, use, exhibition or other means

**P** document published prior to the International filing date but later than the priority date claimed

* T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search:

16 December 2004

Date of mailing of the international search report:

27/12/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2940, Tx. 31 651 epo nl Fax (+31-70) 340-3016

Authorized officer

Wetzig, T
**INTERNATIONAL SEARCH REPORT**

**Box II**  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 1–12 because they relate to subject matter not required to be searched by this Authority, namely:

   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2.  Claims Nos.; because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.; because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

**Box III**  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.;

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.;

**Remark on Protest**

- The additional search fees were accompanied by the applicant’s protest.
- No protest accompanied the payment of additional search fees.
**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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