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(54) **METHOD AND APPARATUS FOR
MODULATING CELLULAR METABOLISM
DURING POST-ISCHEMIA OR HEART
FAILURE**

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(76) **Inventors: Joseph M. Pastore**, Minneapolis, MN (US); **Julio C. Spinelli**, Shoreview, MN (US); **Helen L. Reeve**, St. Paul, MN (US); **Jeffrey Ross**, Roseville, MN (US); **Rodney W. Salo**, Fridley, MN (US); **Allan Shuros**, St. Paul, MN (US)

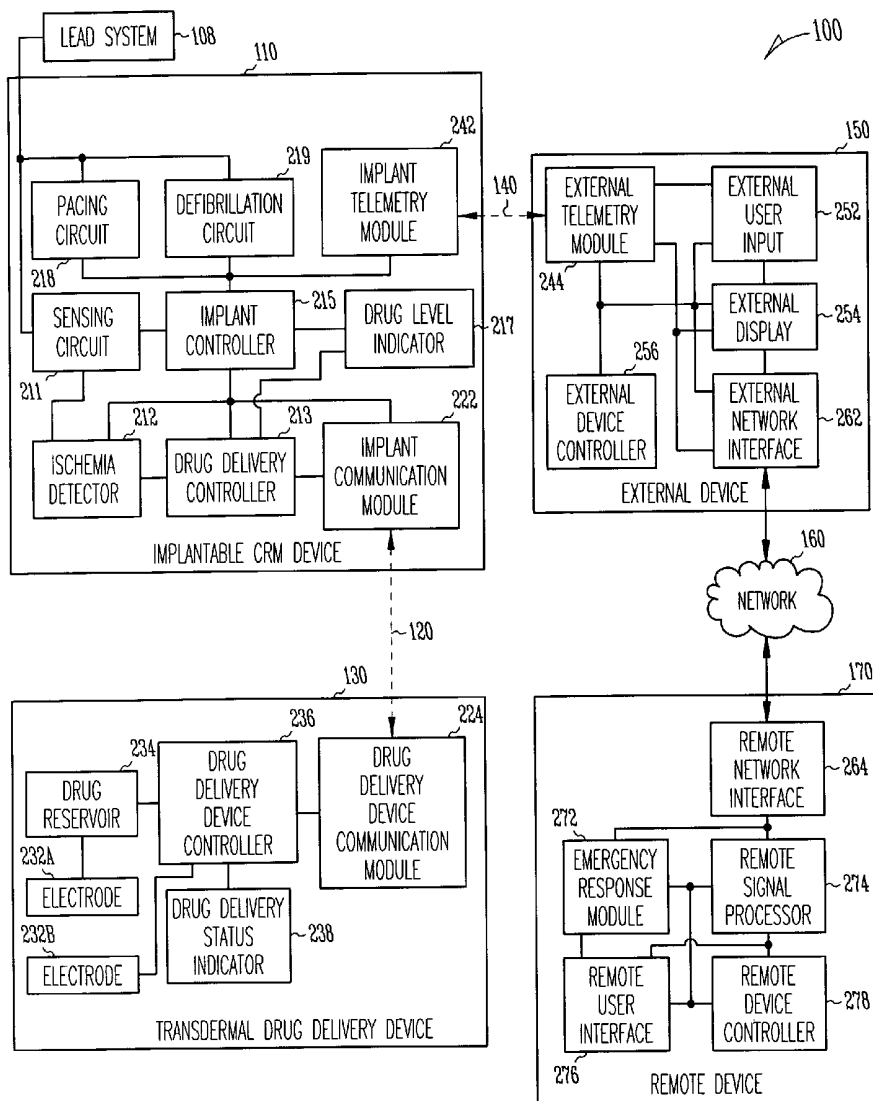
(57) **ABSTRACT**

A drug delivery system detects a cardiac condition indicative of a need for increasing a cardiac metabolic level and, in response, releases a drug into tissue or blood to shift a source of metabolically synthesized energy fueling cardiac contraction from fatty acid to glucose. One example of such a system includes an implantable device detecting an ischemia and a transdermal drug delivery device delivering a drug when an ischemic condition is detected. Another example of such a system includes one or more implantable devices detecting a predefined change in cardiac metabolic level and delivering a drug when the change is detected. Such systems are applied to treat, for example, patients suffering ischemia and/or heart failure and patients having suffered myocardial infarction.

Correspondence Address:
Schwegman, Lundberg, Woessner & Kluth, P.A.
P.O. Box 2938
Minneapolis, MN 55402 (US)

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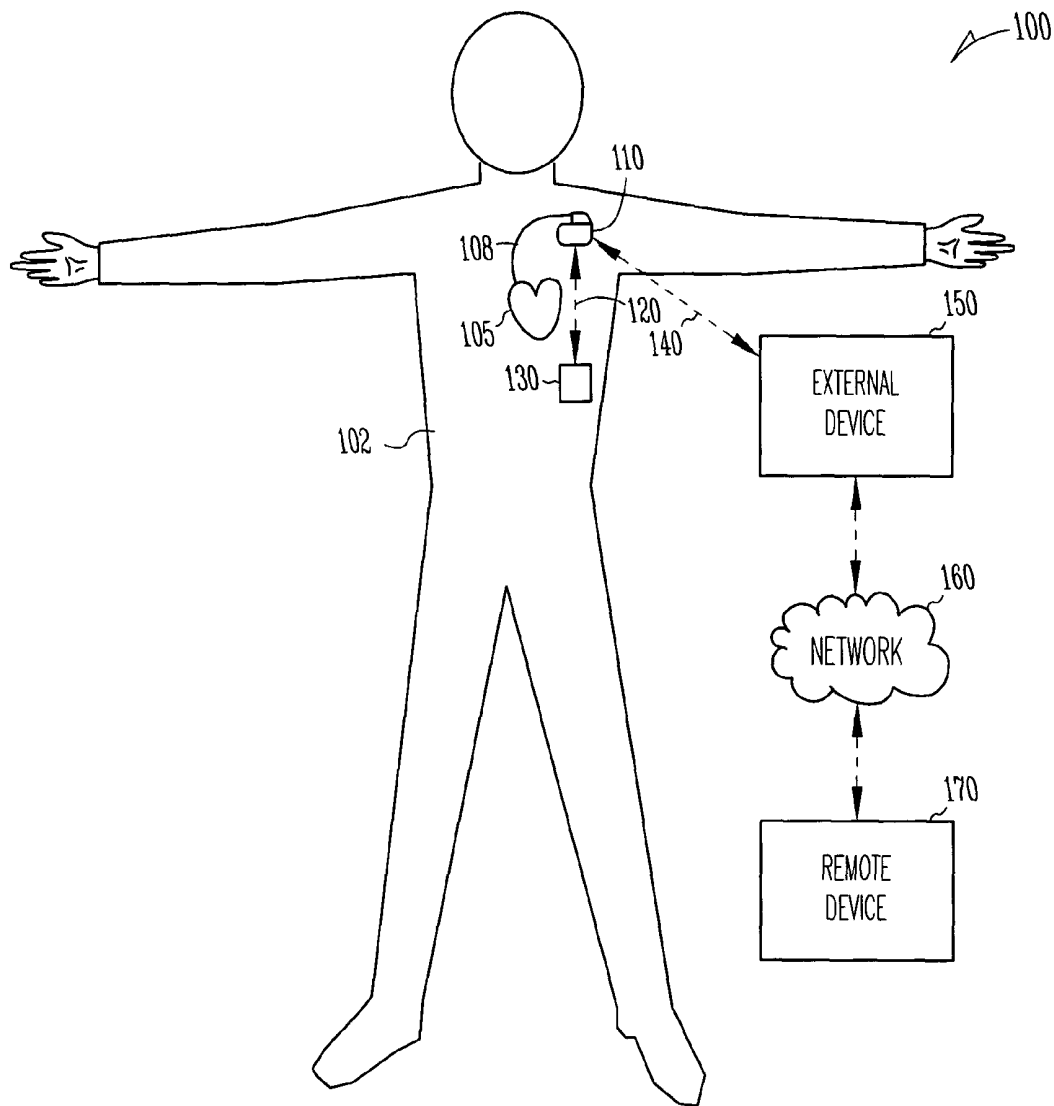


Fig. 1

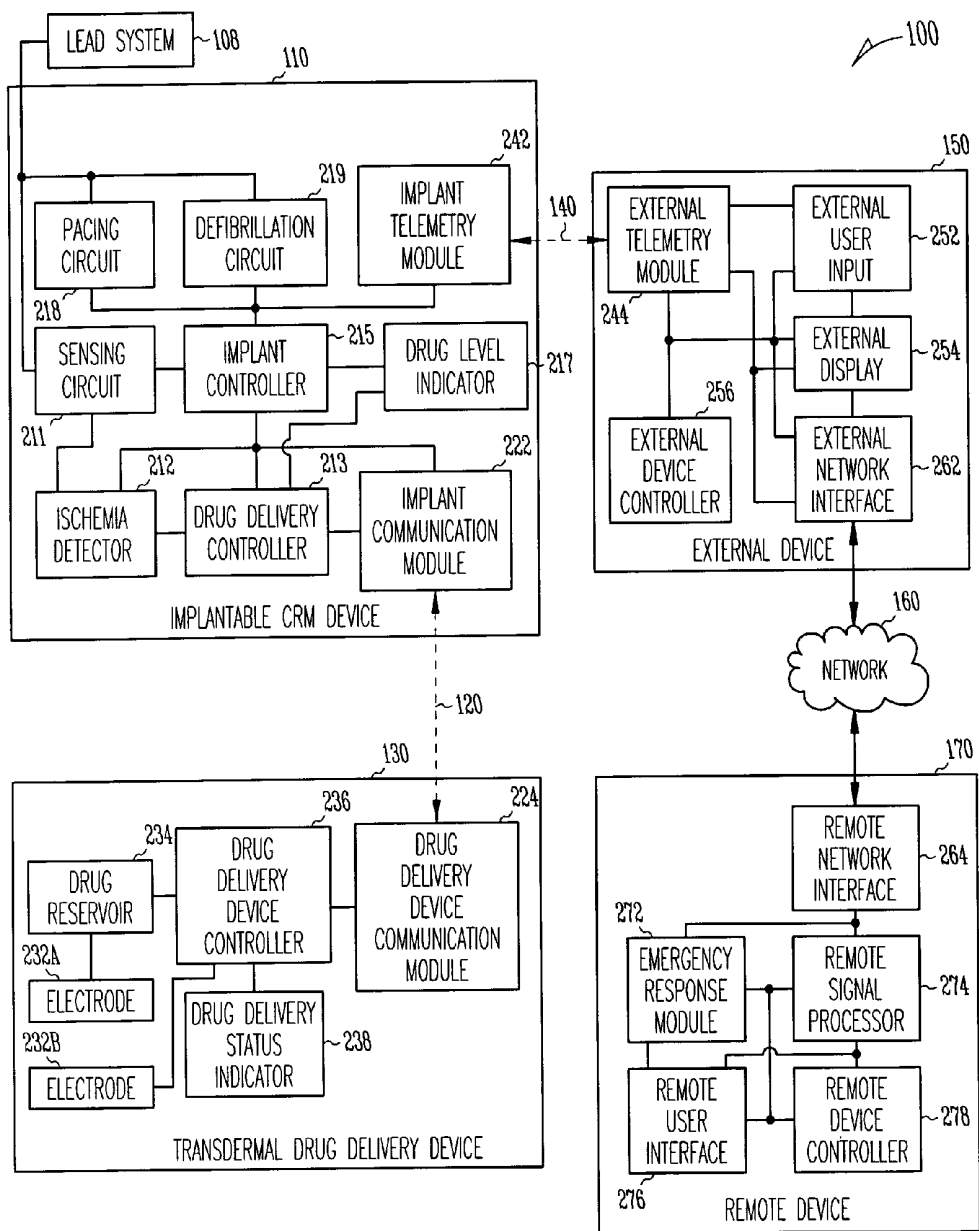


Fig. 2

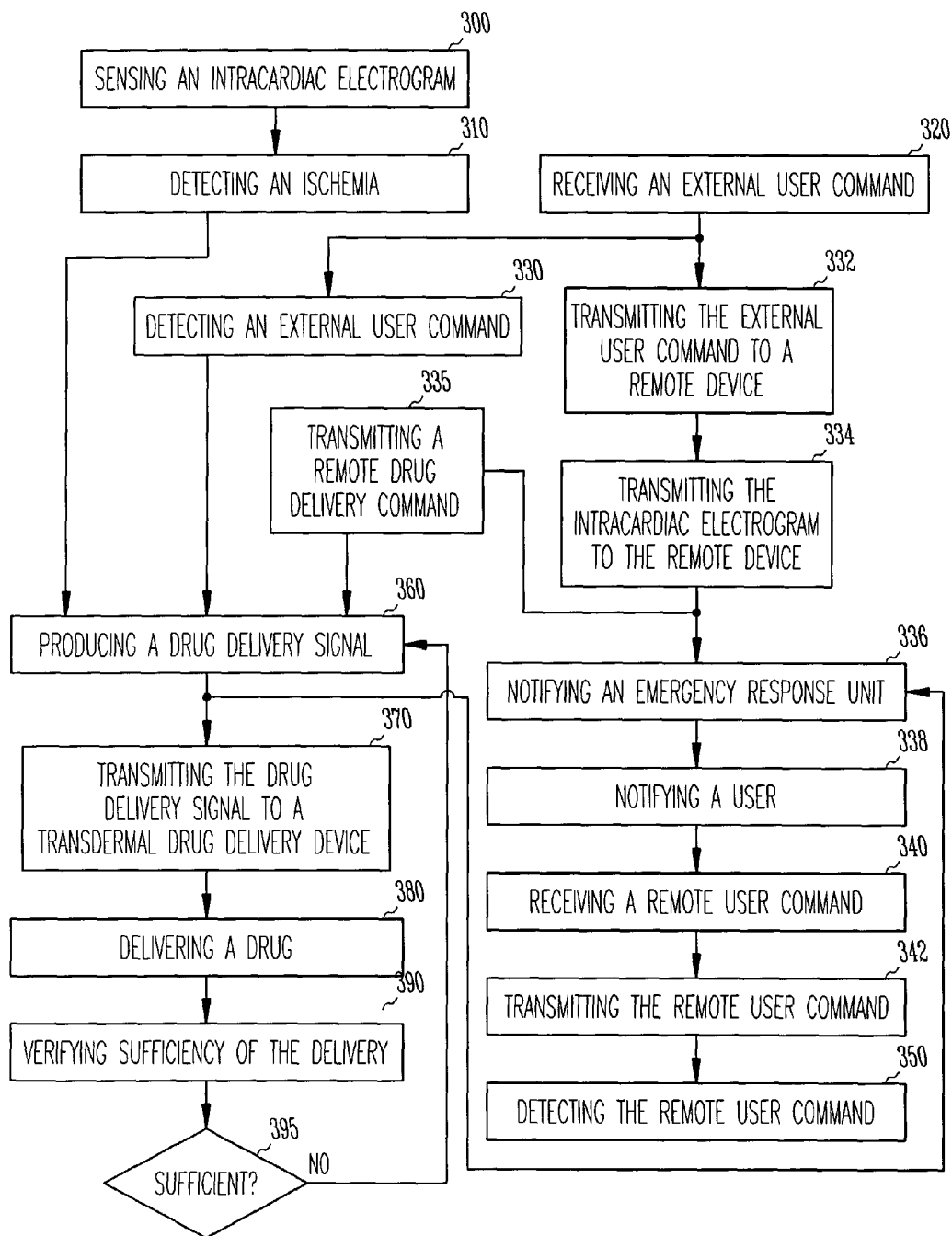


Fig. 3

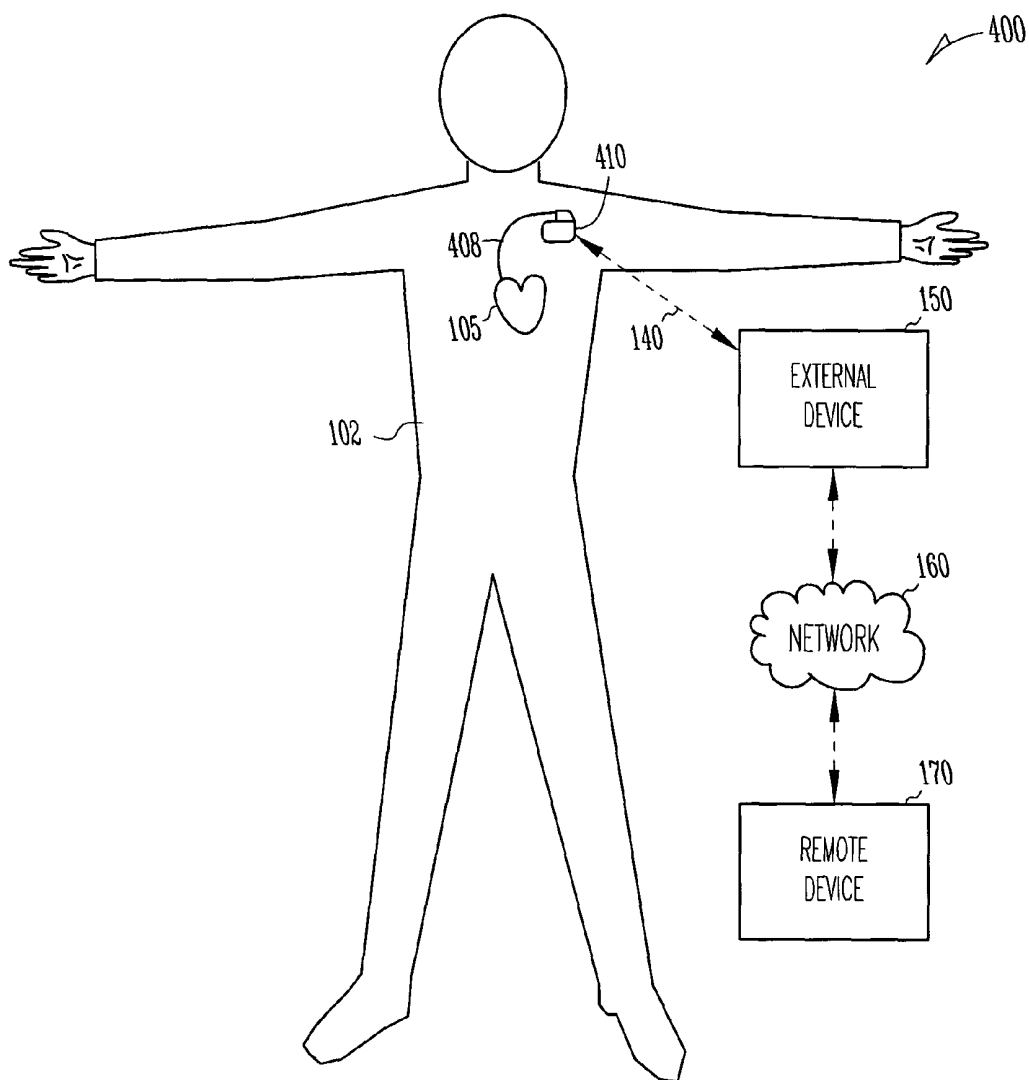


Fig. 4

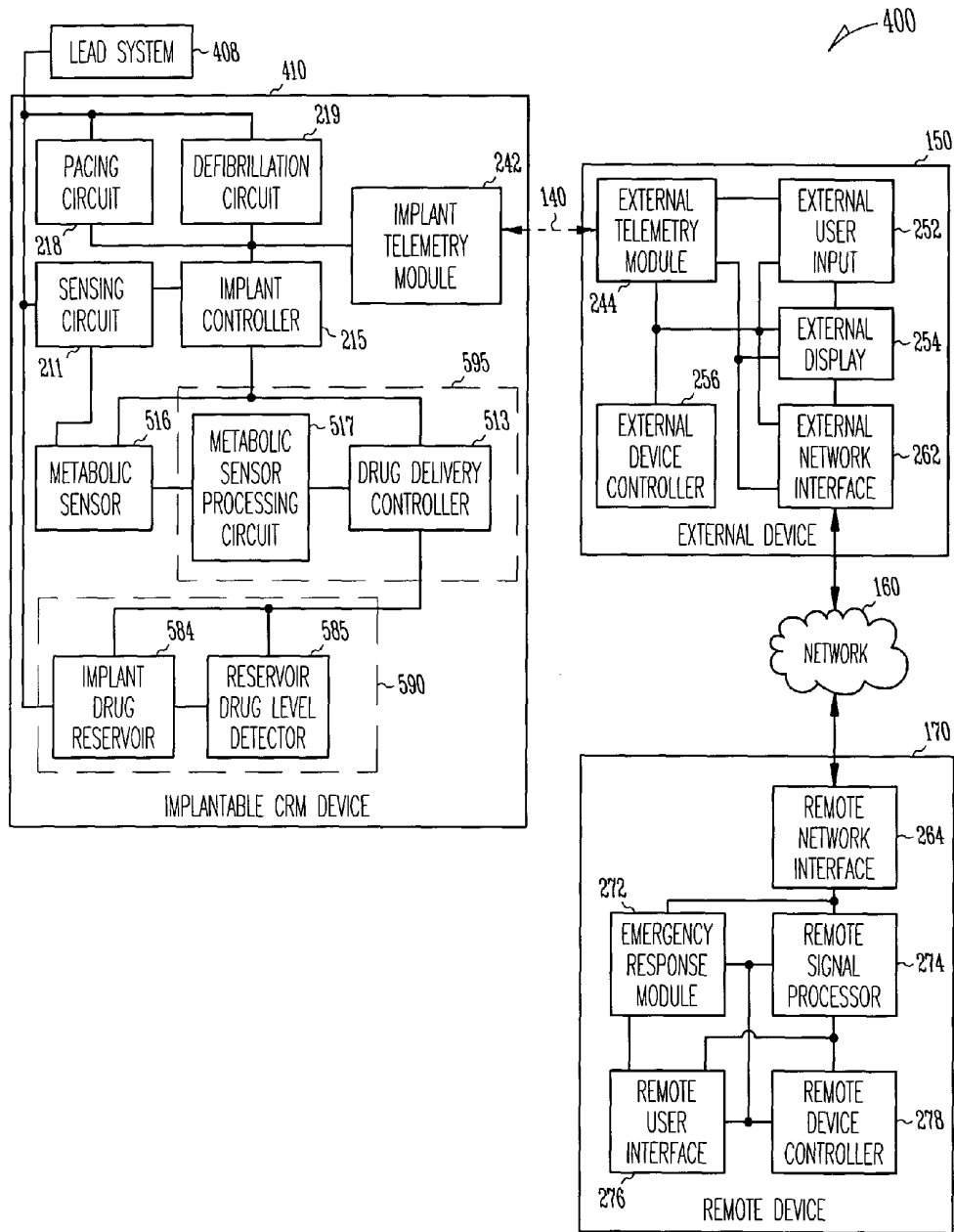


Fig. 5

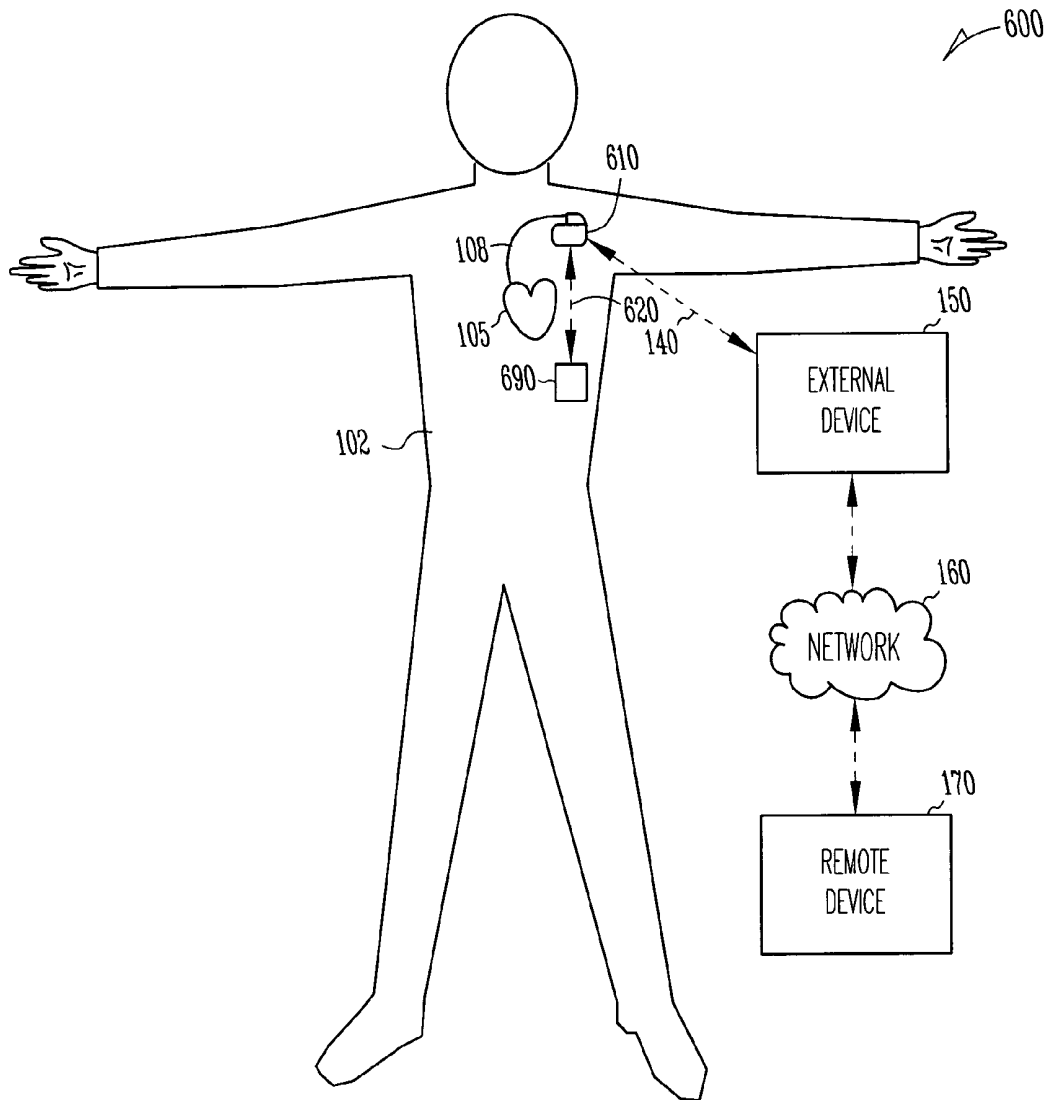


Fig. 6

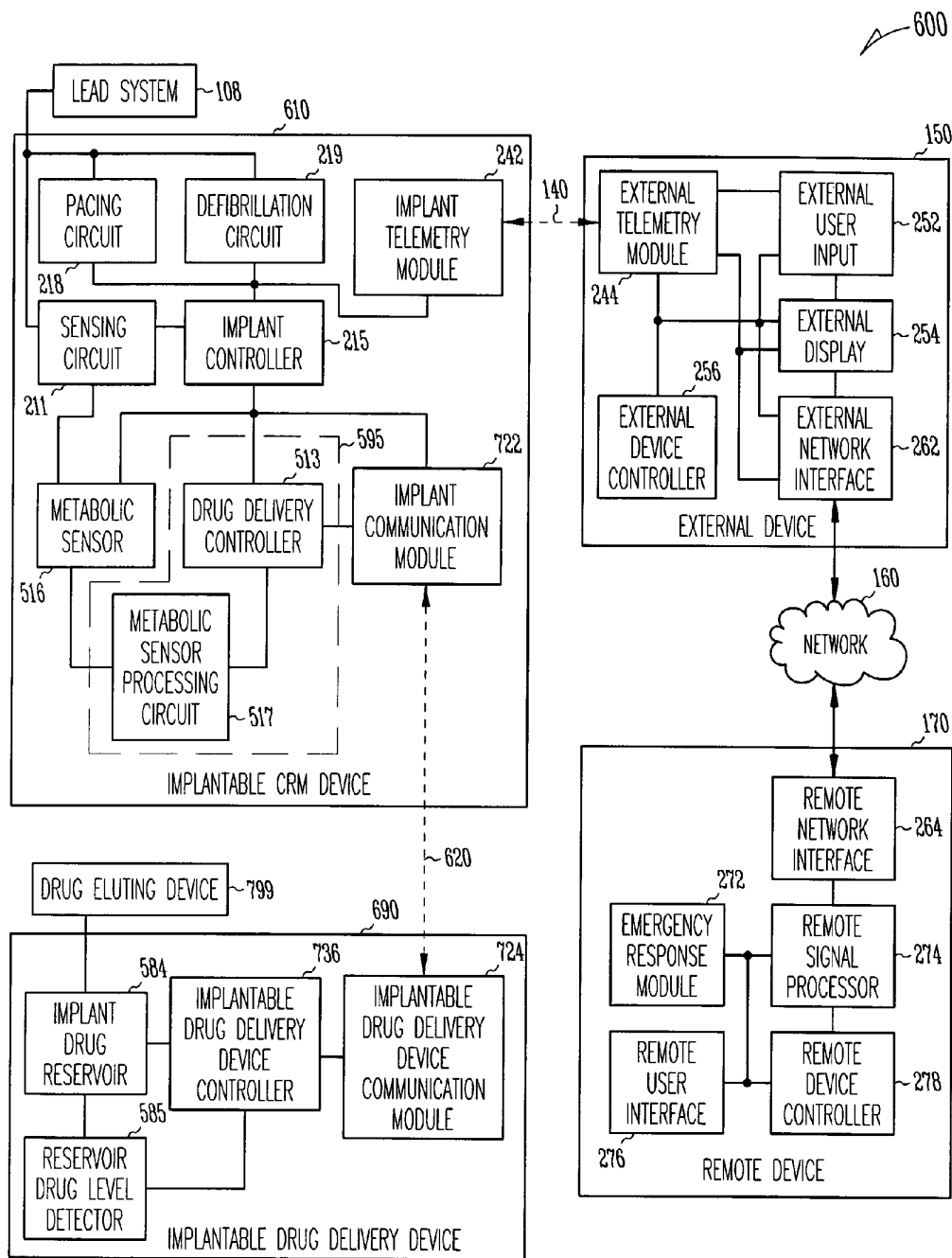


Fig. 7

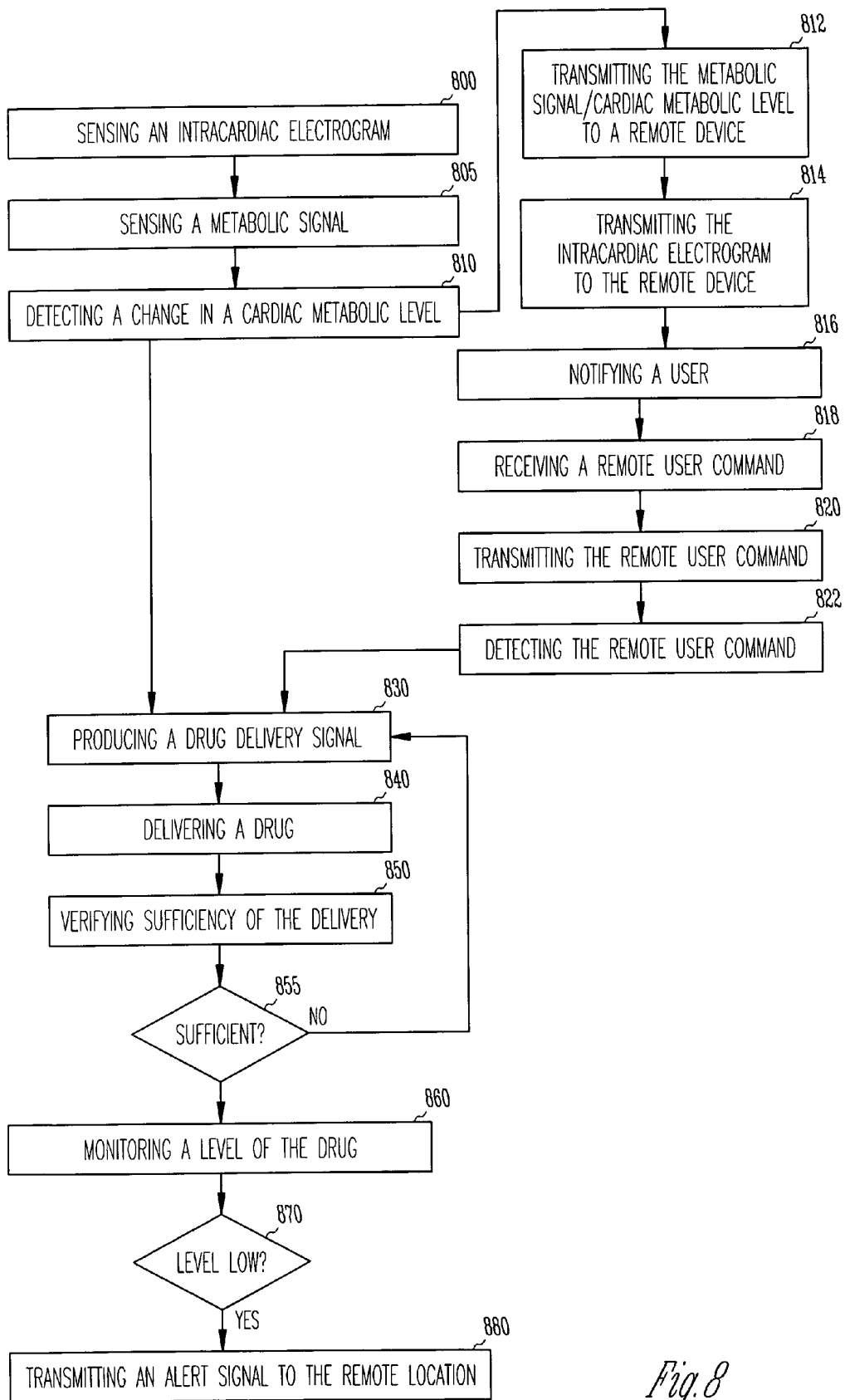


Fig. 8

METHOD AND APPARATUS FOR MODULATING CELLULAR METABOLISM DURING POST-ISCHEMIA OR HEART FAILURE

FIELD OF THE INVENTION

[0001] This document generally relates to cardiac rhythm management systems and particularly, but not by way of limitation, to such systems modulating cardiac cellular metabolism with drug delivery.

BACKGROUND

[0002] A heart is the center of a person's circulatory system. It includes a complex electro-mechanical system performing two major pumping functions. The left portions of the heart, including the left atrium and the left ventricle, draw oxygenated blood from the lungs and pump it to the organs of the body to provide the organs with their metabolic needs for oxygen. The right portions of the heart, including the right atrium and the right ventricle, draw deoxygenated blood from the organs and pump it into the lungs where the blood gets oxygenated. These pumping functions are accomplished by cardiac contractions, i.e., contractions of the myocardium (heart muscles).

[0003] Cardiac cells produce the energy required for the cardiac contractions from free fatty acids and glucose via aerobic metabolism. The energy production from glucose is more oxygen efficient than the energy production from fatty acids. In a normal adult heart, about 60-90% of the energy is produced from fatty acid oxidation. If the heart becomes ischemic, blood flow to the heart is reduced, resulting in insufficient oxygen supplying the aerobic metabolism of cardiac cells. In decompensated heart failure, glucose oxidation becomes the primary source of energy produced by the aerobic metabolism. During ischemia and compensated heart failure, fatty acids are still the primary source of energy, even though it is less oxygen-efficient than glucose. In both situations, the heart fails to maintain the normal rate of metabolism because of the reduced availability of oxygen. This results in a reduction of myocardial contractility, and hence, reduction of the heart's pumping efficiency and thus diminished blood flow.

[0004] Therefore, as a treatment for ischemia and heart failure, as well as related conditions and symptoms, there is a need to increase the rate of metabolism in cardiac cells in response to the reduced availability of oxygen.

SUMMARY

[0005] A drug delivery system detects a cardiac condition indicative of a need for increasing a cardiac metabolic level and, in response, releases a drug into tissue or blood to shift a source of metabolically synthesized energy fueling cardiac contraction from fatty acid to glucose. Such a system is applied to treat, for example, a patient suffering ischemia and/or heart failure or a patient having suffered myocardial infarction.

[0006] In one embodiment, a system includes a transdermal drug delivery device, an implantable cardiac rhythm management (CRM) device, and an external device. The implantable CRM device communicates with the transdermal drug delivery device and includes an ischemia detector, a drug level detector, and a drug delivery controller. The

ischemia detector produces an ischemia indicating signal upon detection of an ischemia. The drug level detector detects a drug concentration in blood and produces an indication of the blood drug concentration. The external device communicates with the implantable CRM device and includes an external user input to receive an external user command. The drug delivery controller of the implantable CRM device controls the transdermal drug delivery device based on at least one of the ischemia indicating signal, the indication of the blood drug concentration, and the external user command.

[0007] In one embodiment, a system includes an implantable metabolic sensor, an implantable processor, and an implantable drug delivery device. The implantable metabolic sensor senses a metabolic signal indicative of a cardiac metabolic level. The implantable processor includes a metabolic sensor processing circuit and a drug delivery controller. The metabolic sensor processing circuit determines the cardiac metabolic level from the metabolic signal. The drug delivery controller produces a drug delivery signal based on the cardiac metabolic level. The implantable drug delivery device communicates with the implantable processor and delivers a drug in response to the drug delivery signal. The implantable drug delivery device includes a drug reservoir storing a drug shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.

[0008] In one embodiment, an implantable CRM device executing an automated ischemia detection algorithm is used to detect an ischemia. The implantable CRM device also detects an external user command directing a drug delivery. The external user command is transmitted from an external device. A drug delivery signal is produced upon a detection of at least one of the ischemia and the external user command. The drug delivery signal is transmitted to a transdermal drug delivery device. In response, a drug is delivered from the transdermal drug delivery device.

[0009] In one embodiment, a metabolic signal is sensed using an implantable sensor. A cardiac metabolic level is determined based on the metabolic signal using an implantable processor. A drug delivery signal is produced based on the cardiac metabolic level. The drug delivery signal is transmitted from the implantable processor to an implantable drug delivery device. In response, the implantable drug delivery device delivers a drug to shift a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.

[0010] This Summary is an overview of some of the teachings of the present application and not intended to be an exclusive or exhaustive treatment of the present subject matter. Further details about the present subject matter are found in the detailed description and appended claims. Other aspects of the invention will be apparent to persons skilled in the art upon reading and understanding the following detailed description and viewing the drawings that form a part thereof, each of which are not to be taken in a limiting sense. The scope of the present invention is defined by the appended claims and their equivalents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] In the drawings, which are not necessarily drawn to scale, like numerals describe similar components throughout the several views. The drawings illustrate generally, by way

of example, but not by way of limitation, various embodiments discussed in the present document. The drawing are for illustrative purposes only and not to scale nor anatomically accurate.

[0012] FIG. 1 is an illustration of an embodiment of a transdermal drug delivery system and portions of an environment in which it is used.

[0013] FIG. 2 is a block diagram showing one embodiment of the circuit of portions of the transdermal drug delivery system such as shown in FIG. 1.

[0014] FIG. 3 is a flow chart illustrating an embodiment of a method for delivering a cardiac metabolism drug using the transdermal drug delivery system such as shown in FIG. 1.

[0015] FIG. 4 is an illustration of an embodiment of an implantable drug delivery system and portions of an environment in which it is used.

[0016] FIG. 5 is a block diagram showing one embodiment of the circuit of portions of the implantable drug delivery system such as shown in FIG. 4.

[0017] FIG. 6 is an illustration of another embodiment of an implantable drug delivery system and portions of an environment in which it is used.

[0018] FIG. 7 is a block diagram showing one embodiment of the circuit of portions of the implantable drug delivery system such as shown in FIG. 6.

[0019] FIG. 8 is a flow chart illustrating an embodiment of a method for delivering a cardiac metabolism drug using one of the implantable drug delivery systems such as shown in FIGS. 4 and 6.

DETAILED DESCRIPTION

[0020] In the following detailed description, reference is made to the accompanying drawings which form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that the embodiments may be combined, or that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the spirit and scope of the present invention. The following detailed description provides examples, and the scope of the present invention is defined by the appended claims and their equivalents.

[0021] It should be noted that references to “an”, “one”, or “various” embodiments in this disclosure are not necessarily to the same embodiment, and such references contemplate more than one embodiment.

[0022] Cardiac contraction is fueled by energy synthesized aerobically by cardiac cells from energy sources including glucose and free fatty acids. In normal adult hearts, the majority of the energy is produced from fatty acid oxidation. However, in certain cardiac disorders, decompensated heart failure for example, glucose becomes the primary energy source for aerobic metabolism. During ischemia and compensated heart failure, fatty acids are still the primary energy source even though fatty acids are less oxygen efficient than glucose. Pharmaceutical agents which shift

metabolism from fatty acid oxidation to glucose oxidation are beneficial in patients with ischemia or heart failure, and, when administered chronically, are beneficial in heart failure or post-myocardial infarction patients. These pharmaceutical agents are generally most effective when administered in response to certain physiological signals and/or events, such as a change in cardiac metabolic level and/or an ischemic event. This is achieved by using a drug delivery system that detects the certain physiological signals and/or events and, in response, delivers one or more pharmaceutical agents that shift cardiac metabolism from fatty acid oxidation to glucose oxidation. The term “pharmaceutical agents,” as used in this document, include agents that are chemical, biochemical, and/or biologic in nature.

[0023] Such a drug delivery system can be employed to deliver pharmaceutical agents to treat acute events, for instance, for relief of angina or heart failure decompensation, or to deliver pharmaceutical agents chronically to treat compensated heart failure or left ventricular dysfunction, or prophylactically to patients having previously suffered myocardial infarction. The pharmaceutical agents act upon cardiac cells to decrease the oxygen requirements to fuel cardiac metabolism by, for example, inhibiting or reducing fatty acid oxidation and/or increasing, enhancing, or stimulating pyruvate, glucose or lactate oxidation, preferably in cardiac cells. By decreasing the oxygen requirement for maintaining a normal or tolerable rate of cardiac metabolism by increasing its oxygen efficiency, the drug delivery system can be employed to minimize necrosis and apoptosis during chronic ischemia or an ischemic event.

[0024] In one embodiment, pharmaceutical agents within the scope of the present subject matter include, but are not limited to, those which shift metabolism from fatty acid oxidation to glucose oxidation, e.g., agents which decrease, inhibit (suppress) or reduce fatty acid oxidation (trimetazidine or ranolazine), and/or increase, enhance or stimulate pyruvate, glucose or lactate oxidation, preferably in cardiac cells. Thus, agents which inhibit lipolysis (nicotinic acid, aka niacin, and beta-adrenergic receptor antagonists), the rate of fatty acid release from fat cells, lower plasma fatty acid concentrations, uptake of fatty acids by the heart, entrance of fatty acids into the mitochondrion, for instance, by inhibiting CPT-1 (carnitine, L-propionylcarnitine, perhexiline, etoxomir, or oxfenicine), or inhibit the levels or activity of acyl-CoA dehydrogenase, e.g., long chain or medium chain acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, or beta-ketothiolase, or enhance the levels or activity of pyruvate dehydrogenase, e.g., dichloroacetate inhibits pyruvate dehydrogenase kinase, and increases cytosolic acetyl-CoA, which inhibits fatty acid oxidation, glucose (insulin) and/or lactate transporters or otherwise alter glucose transport (Akt-1) or stimulates insulin secretion (GLP-1). Acetyl CoA is converted to malonyl CoA, which inhibits carnitine palmitoyltransferase-1 (CPT-1), thereby reducing fatty acid uptake into mitochondria.

[0025] Those agents may be employed alone or in conjunction with other agents such as anti-hypertensive agents, anti-arrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, inotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor block-

ers, or any combination thereof, including but not limited to diuretics such as thiazides, e.g., hydrochlorothiazide, loop diuretics, e.g., furosemide, and potassium-sparing agents, e.g., amiloride, spironolactone and triamterene and hydrochlorothiazide, beta-blockers such as bisoprolol, carvedilol, labetalol and metoprolol, angiotensin-converting enzyme inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, delapril, pentopril, moexipril, spirapril, temocapril, and imidapril, calcium channel blockers, alpha blockers, angiotensin II antagonists, e.g., losartan, statins, e.g., atorvastatin, pitavastatin, and pravastatin, or other lipid lowering agents, moxonidine, dihydropyridines, e.g., amlodipine, class III and IV antiarrhythmics, e.g., amiodarone, azimilide, sotalol, dofetilide, and ubutilide, aspirin, selective non-adrenergic imidazole receptor inhibitors, heбиволol, vasopeptidase inhibitors, e.g., fasidotritat, omapatrilat, samapatrilat, substrates, inhibitors or inducers of cytochrome P450 enzymes, lidocaine, warfarin, oligonucleotides (sense or antisense), natriuretic peptides such as ANP, BNP, NT pro BNP, CNP, and DNP, colforsin daropate hydrochloride (forskolin derivative), antagonists of platelet integrin IIb/IIIa receptors, e.g., abciximab and trofibrant, repletease, P2 receptor antagonists, e.g., ticlopidine and clopidogrel, mibefradil, hirudin, acetylcholinesterase inhibitors, cardiac glycosides, e.g., digoxin and digitoxin, bradykinin, neutral endopeptidase inhibitors, e.g., neprilysin, direct-acting vasodilators, e.g., hydralazine, nitroglycerin, sodium nitroprusside, catecholamines, dobutamine and dopamine, phosphodiesterase inhibitors, e.g., amrinone and milrinone, TNF α , pentoxifylline, growth hormone, cytokine inhibitors, aldosterone receptor antagonists, calcium sensitizers, nesiritide, 3,5-dicodothyropropionic acid, etomoxir, endothelin receptor antagonists, chlor-thiadone, doxazosin, nesiritide, cilostazol, rilmenidine, ticlopidine, dihydropines such as nifedipine and nisoldipine, timolol, propranolol, verapamil, diltiazem, lisinopril, noopept (N-phenylacetyl-L-polyglycine ethylester), cariporide, geldanamycin, radicicol, ibudilast, selective delta (1) agonists such as 2-methyl-4 α -(3-hydroxy-phenyl)-1,2,3,4,4a,5,12,12a-alpha-octahydroquinolino[2,3,3-g]isoquinoline, monophosphoryl lipid A, RC552, adenosine, adenosine receptor agonists, adenosine triphosphate sensitive channel openers, dipyridamole, fibroblast growth factor, atenolol, ezetimibe, lerosimendan, sirolimus, paclitaxil, actinomycin D, dexamethasone, tacrolimus, everolimus, estradiol, quinapril, tranilast, antiopeptin, trapidil, lacidipine, thiazolidinediones, fenofibrate, lacidipine, nebrivolol, nicotinic acid, probucal, rosuvastatin, gemfibrozil, glitazones, indobugen, alpha-tocopherol, dipyridamole, resins, e.g., cholestyramine and colestipol, bezafibrate, or listat, niacin, heparin, e.g., low molecular weight heparins such as dalteparin sodium and nadroparin calcium, bivalirucin, nitroglycerin, nicorandil, denopamine, eptifibatide, xemilofiban, or bofiban, trimetazidine, nicorandil, dalteparin, and isosorbide 5-mononitrate. Additional pharmaceutical agents may be considered based on evidence of their direct or indirect roles in preventing or reducing injury or hemodynamic compromise related to myocardial infarction and/or heart failure. Examples of such pharmaceutical agents include, but are not limited to, L-arginine; nitric oxide (NO); NO derivatives such as nitroxyl anion (HNONO $^-$) and peroxynitrite (ONOO $^-$); iNOS, eNOS, and inhibitors such as nitro-L-

arginine methyl ester; NO donors such as diethylamine (DEA) NO and nitroglycerin (NTG); and interleukins and interleukin inhibitors.

[0026] This document discusses, among other things, drug delivery systems each deliver a drug including one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Specific examples of the one or more pharmaceutical agents include, but are not limited to, all pharmaceutical agents discussed in this document.

[0027] FIG. 1 is an illustration of an embodiment of a transdermal drug delivery system 100 and portions of an environment in which it is used. System 100 includes, among other things, an implantable cardiac rhythm management (CRM) device 110, a transdermal drug delivery device 130, an external device 150, a remote device 170. As shown in FIG. 1, implantable CRM device is implanted in a body 102. Transdermal drug delivery device 130 is attached to the skin surface of body 102 at a site near heart 105. A lead system 108 provides electrical connection between heart 105 and implantable CRM device 110. A communication link 120 allows signal transmission between implantable CRM device 110 and transdermal drug delivery device 130. A telemetry link 140 provides for bidirectional communication between implantable CRM device 110 and external device 150. A network 160 provides for bidirectional communication between external device 150 and remote device 170. System 100 allows a drug delivery to be triggered by any one of implantable CRM device 110, external device 150, and remote device 170. In one embodiment, implantable CRM device 110 triggers a drug delivery upon detecting a predetermined signal or condition. External device 150 triggers a drug delivery upon receiving an external user command from the patient wearing implantable CRM device 110 and transdermal drug delivery device 130 or from another person such as a relative, a friend, or a physician/caregiver. The patient enters the external user command when he or she detects an abnormal condition, such as a chest pain indicative of angina. Another person caring for the patient may also enter the external user command upon a request by the patient or an observation of an abnormal condition. Remote device 170 triggers a drug delivery upon receiving a remote user command from a physician/caregiver, who has been notified of the patient's condition. In other embodiments, external device 150 and/or remote device 170 process signals and/or a condition detected by implantable CRM device 110 to determine whether to trigger a drug delivery.

[0028] In one embodiment, system 100 is used for an acute treatment for relief of angina or heart failure decompensation. In another embodiment, system 100 is used to treat "silent myocardial infarctions" that are not detectable by the patient. A drug delivery is triggered upon detection of ischemia by implantable CRM device 110 and/or upon receiving an external user command from a patient in response to angina.

[0029] FIG. 2 is a block diagram showing one embodiment of the circuit of portions of system 100. Implantable CRM device 110 as shown in FIG. 2 includes pacing and defibrillation capabilities. In addition to drug delivery, examples of therapies delivered by implantable CRM device 110 include, but are not limited to, bradyarrhythmia pacing,

anti-tachyarrhythmia pacing, atrial and/or ventricular cardioversion/defibrillation, cardiac resynchronization therapy, and cardiac remodeling control. However, the pacing and defibrillation capabilities are not necessary for system 100 to perform drug delivery, and hence, are not necessary elements of implantable CRM device 110. In other words, implantable CRM device 110 can be an implantable pacemaker and/or defibrillator with additional functions including control of drug delivery, or it can be a dedicated implantable drug delivery processor or controller.

[0030] In one embodiment, implantable CRM device 110 includes a sensing circuit 211, an ischemia detector 212, a drug delivery controller 213, a drug level indicator 217, a pacing circuit 218, a defibrillation circuit 219, an implant controller 215, an implant communication module 222, and an implant telemetry module 242. Sensing circuit 211 senses an intracardiac electrogram through a lead of lead system 108. Ischemia detector 212 detects an ischemia and produces an ischemia indicating signal when an ischemic condition is detected. In one embodiment, ischemia detector 212 has an input connected to sensing circuit 211 and an ischemia analyzer running an automatic ischemia detection algorithm to detect an ischemic condition from the electrogram. One specific example of an electrogram-based ischemia detector 212 is discussed in Zhu et al., U.S. patent application Ser. No. 09/962,852, entitled "EVOKED RESPONSE SENSING FOR ISCHEMIA DETECTION," filed on Sep. 25, 2001, assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety. In another embodiment, ischemia detector 212 includes an electrical impedance based sensor using a low carrier frequency (e.g. 100 Hz) and an ischemia analyzer running an automatic ischemia detection algorithm to detect an ischemic condition from the electrical impedance signal. Tissue electrical impedance has been shown to increase significantly during ischemia, as discussed in Min, et al. *International Journal of Bioelectromagnetism*, 5(1): 53-56 (2003). Ischemia detector 212 senses low frequency electrical impedance signal between electrodes interposed in the heart, and detects the ischemia as abrupt changes in impedance (such as abrupt increases in value). In yet another embodiment, ischemia detector 212 includes a local heart motion based sensor utilizing an accelerometer located within a lead body positioned on or in the heart and an ischemia analyzer running an automatic ischemia detection algorithm to detect an ischemic condition from the acceleration signal. Ischemia detector 212 detects ischemia as an abrupt decrease in the amplitude of local cardiac accelerations. Upon receiving at least one of the ischemia indicating signal from ischemia detector 212, an external user command from external device 150, and a remote user command from remote device 170, drug delivery controller 213 generates a drug delivery signal. The drug delivery signal is transmitted through communication link 120 to transdermal drug delivery device 130 to trigger a drug delivery. After the drug delivery, drug level indicator 217 measures or estimates a blood drug concentration of the drug delivered to produce an indication of the blood drug concentration. In one embodiment, drug level indicator 217 includes a drug level detector that measures the blood drug concentration. In another embodiment, drug level indicator 217 includes a sensor measuring a physiological parameter indicative of the blood drug concentration. Examples of such a sensor include a respiration sensor and a heart rate detector. If drug level

indicator 217 produces an indication of a blood drug concentration that is below a predetermined minimum level, drug delivery controller 213 produces a drug delivery signal to continue the drug delivery or start another drug delivery. Implant controller 215 provides for overall control and signal processing for implantable CRM device 110. Implant communication module 222 provides for a signal transmission interface allowing implantable CRM device 110 to communicate with transdermal drug delivery device 130, such as to transmit the drug delivery signal, via communication link 120. Implant telemetry module 242 provides for a telemetry interface allowing implantable CRM device 110 to communicate with external device 150 via telemetry link 140.

[0031] Lead system 108 includes one or more pacing leads, defibrillation leads, pacing-defibrillation leads, or any combination of such leads. It allows sensing of electrical signals from heart 105 and/or delivery of pacing pulses and/or defibrillation shocks to heart 105. In one embodiment, lead system 108 includes one or more transvenous leads each having at least one sensing-pacing electrode disposed within heart 105. In one embodiment, lead system 108 includes one or more epicardial leads each having at least one sensing-pacing electrode disposed on heart 105. In one embodiment, lead system 108 includes one or more leads each having at least one sensor such as an accelerometer or a metabolic sensor. In one specific embodiment, lead system 108 includes one or more leads each having a metabolic sensor disposed in a blood pool when the lead is implanted.

[0032] Transdermal drug delivery device 130 includes electrodes 232A-B, drug reservoir 234, drug delivery device controller 236, drug delivery status indicator 238, and drug delivery communication module 224. One specific example of transdermal drug delivery device 130 is discussed in Scheiner et al., U.S. Pat. No. 6,361,522, entitled "DRUG DELIVERY SYSTEM FOR IMPLANTABLE CARDIAC DEVICE," assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety. In one embodiment, transdermal drug delivery device 130 is a skin patch allowing electrically controlled transdermal drug delivery by, for example, iontophoresis, electroporation, electrorepulsion, or electro-osmosis. The skin patch is to be attached on a surface site of body 102 near heart 105. Electrodes 232A and 232B are skin-contact electrodes. Drug reservoir 234 contains the drug, which includes one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Drug delivery status indicator 238 allows the patient and any other person such as a physician/caregiver to monitor, for example, whether the drug is being delivered and/or the amount of the drug remains in drug reservoir 234. Drug delivery device controller 236 controls the overall operation of transdermal drug delivery device 130. In one embodiment, drug delivery device controller 236 generates an electrical potential to cause the drug delivery upon receiving and/or decoding the drug delivery signal. Drug delivery communication module 224 provides for a signal transmission interface allowing transdermal drug delivery device 130 to communicate with implantable CRM device 110, such as to receive the drug delivery signal, via communication link 120.

[0033] Communication link 120 is supported by implant telemetry module 222 and drug delivery communication module 224. It allows communications between implantable CRM device 110 and transdermal drug delivery device 130. In one embodiment, communication link 120 is a telemetry link. In another embodiment, implantable CRM device 110 transmits electrical signals representative of the drug delivery signal into tissue of body 102, to be sensed through electrodes 232A-B and hence received by transdermal drug delivery device 130. In this embodiment, communication link 120 uses body 102 as the conductive medium for conducting electrical signals. One specific example of such a communication link is discussed in Sweeney et al., U.S. patent application Ser. No. 09/740,129, entitled "DRUG DELIVERY SYSTEM FOR IMPLANTABLE MEDICAL DEVICE," filed on Dec. 18, 2000, assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety.

[0034] External device 150 includes an external user input 252, an external display 254, an external device controller 256, an external telemetry module 244, and an external network interface 262. External user input 252 receives the external user command from the patient or another person. In a further embodiment, it also receives other commands or instructions to control the operation of transdermal drug delivery device 130 and/or implantable CRM device 110. External device 150 transmits the external user command to implantable CRM device 110, resulting in a production of the drug delivery signal by drug delivery controller 213. In one embodiment, external device 150 also transmits the external user commands to remote device 170. In response, a remote user command directing a drug delivery may return from remote device 170. External device 150 relays the remote user command to implantable CRM device 110, resulting in a production of the drug delivery signal by drug delivery controller 213. External user input 252 includes a switch. In one embodiment, external user input 252 includes a push button. The patient pushes it, for example, when feeling a chest pain indicative of angina. In another embodiment, external user input 252 includes a voice controlled switch such that the patient may orally order a drug delivery. External telemetry module 244 provides for a telemetry interface allowing external device 150 to communicate with implantable CRM device 110 via telemetry link 140. External network interface 262 provides for a network interface allowing external device 150 to communicate with remote device 170 via network 160.

[0035] Telemetry link 140 is a wireless bidirectional data transmission link supported by implant telemetry module 242 and external telemetry module 244. In one embodiment, telemetry link 140 is an inductive couple formed when two coils—one connected to implant telemetry module 242 and the other connected to external telemetry module 244—are placed near each other. In this embodiment, the patient or another person places external device 150 on body 102 over implantable CRM device 110. In another embodiment, telemetry link 140 is a far-field radio-frequency telemetry link allowing implantable CRM device 110 and external device 252 to communicate over a telemetry range that is at least ten feet.

[0036] Remote device 170 includes an emergency response module 272, a remote signal processor 274, a remote user interface 276, a remote device controller 278,

and a remote network interface 264. By executing one or more predetermined algorithms, remote signal processor 274 processes signals transmitted from external device 150 and signals transmitted from implantable CRM device 110. Emergency response module 272 contacts an emergency response unit, such as by calling 911 (in the United States), in response to an emergency situation as determined by one of implantable CRM device 110, external device 150, and remote device 170. In one embodiment, external device 150 transmits the external user command to remote device 170 as a request for contacting the emergency response unit through emergency response module 272. In another embodiment, remote signal processor 274 analyzes signals acquired by implantable CRM device 110 and transmitted to remote device 170, such as a portion of the electrogram sensed by sensing circuit 211, to determine the need for contacting the emergency response unit. In yet another embodiment, a physician/caregiver observes signals and/or the result of the analysis through remote user interface 276 to determine whether to contact the emergency response unit. Remote user interface 276 allows the physician/caregiver to enter a remote user command to be transmitted to transdermal drug delivery device 130. It also allows physician/caregiver to enter the remote user command to be transmitted to implantable CRM device 110 for a delivery or adjustment of pacing and/or defibrillation therapy. Remote device controller 278 controls the overall operation of remote device 170. In one embodiment, remote device controller 278 generates commands controlling one or more of transdermal drug delivery device 130, implantable CRM device 110, and external device 150 based on the received signals such as the portion of electrogram and the external user command. In one embodiment, remote device controller 278 executes an automatic algorithm to determine whether to issue a drug delivery command or to issue an electrical therapy (pacing and/or defibrillation, including cardiac resynchronization and/or remodeling control) command, such as when a physician/caregiver is not immediately available. Remote network interface 264 provides for an interface allowing communication between remote device 170 and external device 150 via network 160.

[0037] Network 160 provides long distance bidirectional communication between external device 150 and remote device 170. It allows management of multiple implantable devices, such as implantable CRM device 110 and transdermal drug delivery device 130, from a central facility at a remote location. In one embodiment, this allows prompt response by a physician/caregiver at the central facility as demanded by the condition of a patient. In one embodiment, network 160 is based on a wireless communications system. In another embodiment, network 160 is based on a wired communications system. In one embodiment, network 160 utilizes portions of a standard communications system such as the Internet, a telephone system, or a radio frequency telemetry system.

[0038] FIG. 3 is a flow chart illustrating an embodiment of a method for delivering a drug using system 100. In one embodiment, the drug includes the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose, and the method is used as an acute treatment for relief of angina or heart failure decompensation. The method can also be used to treat "silent myocardial infarctions" that are not detectable by the patient.

[0039] Sensing circuit 211 senses at least one electrogram from heart 105 at 300. Ischemia detector 212 detects an ischemia at 310, by executing an automated ischemia detection algorithm. In one embodiment, ischemia detector 212 detects an ischemia by executing an automated ischemia detection algorithm that analyzes the electrogram. When an ischemia is detected, ischemia detector 213 produces an ischemia indicating signal and sends it to drug delivery controller 213.

[0040] External user input 252 receives an external user command at 320. The patient enters the external user command by in response to chest pain indicative of angina. Alternatively, another person, such as a physician/caregiver, an attendant, or a relative, enter the external user command after determining that the patient should receive an immediate drug therapy. After external device 150 transmits the external user command to implantable CRM device 110, drug delivery controller 213 detects the external user command.

[0041] In one embodiment, in addition to transmitting the external user command to implantable CRM device 110, external device 150 transmits the external user command to remote device 170 through network 160 at 332. In one embodiment, remote device 170 also receives signals acquired by implantable CRM device 110, such as the electrogram, and transmits the signals to remote device 170 at 334. In one embodiment, after receiving the external user command and/or analyzing the signals acquired by implantable CRM device 110, remote device 170 notifies an emergency response unit, such as by calling 911 (as in the United States), at 336. In one embodiment, after receiving the external user command and/or analyzing the signals acquired by implantable CRM device 110, remote device 170 automatically produces a remote drug delivery command that is transmitted to implantable CRM device 110 through external device 150 at 335. In one embodiment, after receiving the external user command and/or analyzing the signals acquired by implantable CRM device 110, remote device 170 also notifies a user such as a physician/caregiver at 338. After the user makes a decision, remote device 170 receives a remote user command at 340. The remote user command directs a drug delivery and/or a delivery or adjustment of pacing (including such as cardiac resynchronization and remodeling control) or defibrillation therapy. Remote device 170 transmits the remote to external device 150 through network 160, and external device 150 relays the remote user command to implantable CRM device 110 at 342. Drug delivery controller 213 of implantable CRM device 110 detects the remote user command at 350.

[0042] Drug delivery controller 213 produces a drug delivery signal at 360, upon the detection of at least one of the ischemia, the external user command, the remote drug delivery command, and the remote user command. In one embodiment, the drug delivery signal is also transmitted to remote device 170 for notifying the emergency response unit and/or the user. Implantable CRM device 110 transmits the drug delivery signal to transdermal drug delivery device 130 at 370. In one embodiment, implantable CRM device 110 transmits the drug delivery signal to transdermal drug delivery device 130 via a telemetry link between implantable CRM device 110 and transdermal drug delivery device 130. In another embodiment, implantable CRM device 110 transmits an electrical signal representing the drug delivery signal to transdermal drug delivery device 130 via tissue conduction. In one specific embodiment, implantable CRM device 110

transmits a voltage signal representing the drug delivery signal into tissue of body 102 to be detected by transdermal drug delivery device 130.

[0043] In response to the drug delivery signal, transdermal drug delivery device 130 delivers a drug into tissue at 380. The drug includes one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Then, drug level indicator 217 verifies that a sufficient amount of the drug has been delivered at 390, by detecting a signal indicative of a blood drug concentration. In one embodiment, this includes measuring a blood drug concentration directly. In another embodiment, this includes sensing a respiratory signal or measuring a heart rate. If drug level indicator 217 indicates that the blood drug concentration is below a predetermined level at 395, it produces an insufficiency alert signal and transmits it to drug delivery controller 213. Upon detection of the insufficiency alert signal, drug delivery controller 213 produces an additional drug delivery signal, and steps 360-395 are repeated until the drug level indicator 217 indicates that the blood drug concentration reaches the predetermined level at 395, or until a predetermined maximum dosage is reached.

[0044] FIG. 4 is an illustration of an embodiment of an implantable drug delivery system 400 and portions of an environment in which it is used. System 400 includes an implantable CRM device 410, which includes a drug delivery capability, and a drug eluting lead system 408. Identical numerals appearing in both FIGS. 1 and 4 indicate corresponding system components included in systems 100 and 400 that are structurally substantially identical.

[0045] System 400 allows a drug delivery to be triggered by any one of implantable CRM device 410, external device 150, and remote device 170. In one embodiment, implantable CRM device 410 triggers a drug delivery upon detecting a predetermined signal or condition. External device 150 triggers a drug delivery upon receiving an external user command from the patient wearing implantable CRM device 410 or from another person caring for the patient. Remote device 170 triggers a drug delivery upon receiving a remote user command from a physician/caregiver. In other embodiments, external device 150 and/or remote device 170 process signals and/or condition detected by implantable CRM device 410 to determine whether to trigger a drug delivery.

[0046] In one embodiment, system 400 is used for a chronic treatment for compensated heart failure or left ventricular dysfunction. In another embodiment, system 400 is used for a chronic treatment of patients having suffered myocardial infarction. A drug delivery is triggered upon detection that a change in the cardiac metabolic level exceeds a predetermined threshold. In one embodiment, a drug delivery is triggered upon detection that a change in the BNP level exceeds a predetermined threshold.

[0047] FIG. 5 is a block diagram showing one embodiment of the circuit of portions of system 400. While implantable CRM device 410 as shown in FIG. 5 includes pacing and defibrillation capabilities, such capabilities are not necessary for system 400 to perform drug delivery, and hence, are not necessary elements of implantable CRM device 410. In other words, implantable CRM device 410 can be a pacemaker and/or defibrillator with additional functions including control of drug delivery, or it can be an implantable drug delivery device.

[0048] In one embodiment, to perform the drug delivery function, implantable CRM device 410 includes an implant-

able metabolic sensor **516**, an implantable processor **595** including a metabolic sensor processing circuit **517** and drug delivery controller **513**, and an implantable drug delivery device **590** including an implant drug reservoir **584** and a reservoir drug level detector **585**. In the embodiment shown in **FIG. 5**, implantable processor **595** and implantable drug delivery device **590** are functional modules housed within the same implantable housing. Metabolic sensor **516** senses a metabolic signal indicative of a cardiac metabolic level (rate of metabolism of cardiac cells). Examples of metabolic sensor **516** include a pH sensor, an oxygen pressure (PO_2) sensor, a carbon dioxide pressure (PCO_2) sensor, a glucose sensor, a creatine sensor, a C-creative protein sensor, a creatine kinase sensor, a creatine kinase-MB sensor, and any combination of such sensors. Metabolic sensor processing circuit **517** determines the cardiac metabolic level from the metabolic signal. Drug delivery controller **513** produces a drug delivery signal based on one or more of the cardiac metabolic level, the external user command, and the remote user command. Implant drug reservoir **584** contains the drug including the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Reservoir drug level detector **585** monitors the amount of the drug remaining in implant drug reservoir **584** and produces a drug-level-low alert signal when the amount of the drug is below a predetermined level. The drug-level-low alert signal is transmitted to remote device **170** to inform a physician/caregiver.

[0049] Lead system **408** includes at least one drug eluting lead connected to implant drug reservoir **584**. In one embodiment, the drug eluting lead includes a fluid passageway having one opening at one end of the lead connected to implant drug reservoir **584** and another opening connected to a drug eluting electrode at or near the other end of the lead that is to be disposed in or about heart **105**. The fluid passageway allows fluid communication between implant drug reservoir **584** and the location to which the drug is released. In one embodiment, where implant CRM device **410** has pacing and/or defibrillation capability, lead system **408** includes one or more pacing leads, defibrillation leads, pacing-defibrillation leads, or any combination of such leads. At least one of these leads includes the fluid passageway allowing drug delivery. Thus, lead system **408** allows sensing of electrical signals from heart **105** and/or delivery of pacing pulses and/or defibrillation shocks to heart **105**, as well as delivering drug to heart **105**. In one embodiment, lead system **408** includes an endocardial lead including at least one drug eluting electrode configured to be disposed within one of a coronary sinus and a portion of a great cardiac vein adjacent to the left ventricle of heart **105**. In another embodiment, lead system **408** includes an epicardial lead including at least one drug eluting electrode configured to be attached to a portion of an epicardial wall of heart **105**. In one embodiment, metabolic sensor **516** is built-in or attached to a lead of lead system **408**, such that when the lead is implanted, metabolic sensor **516** is in a blood pool.

[0050] Telemetry link **140**, external device **150**, network **160**, and remote device **170** in system **400** are substantially identical to the identically numbered elements of system **100**, except that the signals acquired by implantable CRM device and transmitted to remote device **170** include the metabolic signal and/or the cardiac metabolic level. Remote device controller **278** of remote device **170** generates commands controlling one or more of implantable CRM device **410**, including metabolic sensor **516**, implantable processor

595, and implantable drug delivery device **590**, and external device **150** based on the received signals and the remote user command.

[0051] **FIG. 6** is an illustration of an embodiment of another implantable drug delivery system **600** and portions of an environment in which it is used. System **600** includes an implantable CRM device **610**, an implantable drug delivery device **690**, and a communication link **620** between the two devices. Identical numerals appearing in both **FIGS. 4 and 6** indicate corresponding system components included in systems **400** and **600** that are structurally substantially identical. In one embodiment, system **600** differs from system **400** by having the implantable drug delivery device physically separate from the implantable CRM device.

[0052] System **600** allows a drug delivery to be triggered by any one of implantable CRM device **610**, external device **150**, and remote device **170**. In one embodiment, implantable CRM device **610** triggers a drug delivery upon detecting a predetermined signal or condition. External device **150** triggers a drug delivery upon receiving an external user command from the patient wearing implantable CRM device **610** and implantable drug delivery device **690** or from another person caring for the patient. Remote device **170** triggers a drug delivery upon receiving a remote user command from a physician/caregiver. In other embodiments, external device **150** and/or remote device **170** process signals and/or condition detected by implantable CRM device **610** to determine whether to trigger a drug delivery.

[0053] In one embodiment, system **600** is used as a chronic treatment for compensated heart failure or left ventricular dysfunction. In another embodiment, system **600** is used as a chronic treatment of patients having suffered myocardial infarction. A drug delivery is triggered upon detection that a change in the cardiac metabolic level exceeds a predetermined threshold.

[0054] **FIG. 7** is a block diagram showing one embodiment of the circuit of portions of system **600**. While implantable CRM device **610** as shown in **FIG. 5** includes pacing and defibrillation capabilities, such capabilities are not necessary for system **600** to perform drug delivery, and hence, are not necessary elements of implantable CRM device **610**. In other words, implantable CRM device **410** can be a pacemaker and/or defibrillator with additional functions including control of drug delivery, or it can be an implantable processor dedicated to control of a separate implantable drug delivery device.

[0055] Implantable CRM device **610** generally retains implantable metabolic sensor **516** and implantable processor **595** of implantable CRM device **410**, where implantable processor **595** includes a metabolic sensor processing circuit **517** and drug delivery controller **513**. Implantable drug delivery device **590** of implantable CRM device **410** is replaced by a separate implantable device, that is, implantable drug delivery device **690**.

[0056] Implantable drug delivery device **690** includes implant drug reservoir **584**, reservoir drug level detector **585**, implantable drug delivery device controller **736**, and implantable drug delivery device communication module **724**. Implantable drug delivery device controller **736** controls the overall operation of implantable drug delivery device **690**. Implantable drug delivery device communication module **724** and an implant communication module **722** of implantable CRM device **610** support communication link **620**. In one embodiment, communication link **620** is a

telemetry link. In another embodiment, implantable CRM device **610** and transdermal drug delivery device **609** each transmit electrical signals into tissue of body **102**, to be received by the other device through electrical conduction using tissue as the medium.

[**0057**] A drug eluting device **799** is connected to implant drug reservoir **584** to allow fluid communication between implant drug reservoir **584** and a body location to which the drug is released. In one embodiment, drug eluting device **799** includes at least one electrode connected to implant drug reservoir **584**. In one specific embodiment, the electrode is disposed in blood to allow the drug to be released to the blood. In another specific embodiment, the electrode is disposed in tissue to allow the drug to be diffused into tissue. In one embodiment, drug eluting device **799** allows electrically controlled drug delivery by, for example, iontophoresis, electroporation, electrorepulsion, or electro-osmosis. In one embodiment, drug eluting device **799** includes a porous polymer that is sensitive to electric field applied on it. The drug is embedded in the polymer. Implantable drug delivery device controller **736** controls the drug delivery by controlling the electric field applied to the polymer. A change in the electric field changes the size of the pores in the polymer and/or the binding affinity of the polymer, resulting in the release of the drug.

[**0058**] Implantable drug delivery device **690** and drug eluting device **799** can be incorporated to another implantable device (other than implantable CRM device **610**). In one embodiment, implantable drug delivery device **690** and drug eluting device **799** are incorporated into or attached onto a coronary stent. In one specific example, the coronary stent is placed near an electrode from which electrical stimuli are delivered, such as a pacing electrode of lead system **108**. The electrical stimuli (e.g., pacing pulses) cause the drug to release from drug eluting device **799**, in response to the changing electric field created by the electrical stimuli.

[**0059**] FIG. 8 is a flow chart illustrating an embodiment of a method for delivering a drug using either system **400** or system **600**. In one embodiment, the drug includes the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose, and the method is used as a chronic treatment of compensated heart failure or left ventricular dysfunction. The method can be applied to treat patients having previously suffered myocardial infarction.

[**0060**] Sensing circuit **211** senses at least one electrogram from heart **105** at **800**. Metabolic sensor **516** senses a metabolic signal at **805**. In one embodiment, metabolic sensor **516** senses one or more of a blood pH level, a blood oxygen pressure (PO_2), a blood carbon dioxide pressure (PCO_2), a blood glucose level, a blood creatine level, a blood C-creative protein level, a blood creatine kinase level, and a blood creatine kinase-MB level. Metabolic sensor processing circuit **517** determines a cardiac metabolic level based on the metabolic signal, and detects a change in the cardiac metabolic level at **810**. In one embodiment, metabolic sensor processing circuit **517** detects the change in the cardiac metabolism when the cardiac metabolic level exceeds a predetermined threshold. When the change in the cardiac metabolism is detected, metabolic sensor processing circuit **517** sends a signal indicative of the change to drug delivery controller **213**.

[**0061**] In one embodiment, implantable CRM device **410** or **610** transmits the metabolic signal and/or the cardiac metabolic level to remote device **170** at **812**. In one embodi-

ment, this transmission is performed upon the detection of the change in the cardiac metabolism. In another embodiment, this transmission is performed in response to a request from remote device **170**. In yet another embodiment, this transmission is performed on a predetermined schedule, such as on a periodic basis or when the patient is sleeping. In one embodiment, implantable CRM device **410** or **610** transmits additional acquired signals, such as a portion of the electrogram, to remote device **170** at **814**. In one embodiment, after receiving the metabolic signal, the cardiac metabolic level, and/or the additional signals, remote device **170** notifies a user such as a physician/caregiver at **816**. After the user makes a decision based on the signals received, remote device **170** receives a remote user command at **818**. The remote user command directs a drug delivery and/or a delivery or adjustment of pacing or defibrillation therapy. Remote device **170** transmits the remote to external device **150** through network **160**, and external device **150** relays the remote user command to implantable CRM device **410** or **610** at **820**. Drug delivery controller **513** of implantable CRM device **410** or **610** detects the remote user command at **822**.

[**0062**] Drug delivery controller **513** produces a drug delivery signal at **830**, upon the detection of at least one of the changes in the cardiac metabolic level and the remote user command. In one embodiment with system **600**, implantable CRM device **610** transmits the drug delivery signal to implantable drug delivery device **690** via telemetry or electrical conduction of the tissue intervening implantable CRM device **610** and implantable drug delivery device **690**. In response to the drug delivery signal, implantable CRM device **410** or implantable drug delivery device **690** delivers the drug into tissue at **840**. In one embodiment, this includes delivering the drug through a drug eluting lead, such as the drug eluting endocardial lead or the drug eluting epicardial lead. In another embodiment, this includes delivering the drug through a drug eluting stent. The drug includes the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Then, implantable CRM device **410** or **610** verifies that a sufficient amount of the drug has been delivered at **850**, by monitoring the cardiac metabolic level after the drug delivery. If the cardiac metabolic level is below a predetermined threshold at **855**, drug delivery controller **513** produces an additional drug delivery signal, and steps **830-855** are repeated until the cardiac metabolic level reaches the predetermined level at **855**.

[**0063**] Reservoir drug level detector **585** monitors the level of the drug remaining in implant drug reservoir **584** at **860**. If reservoir drug level detector **585** determines that the level is below a predetermined low threshold at **870**, it produces a drug-level-low alert signal. The drug-level-low alert signal is transmitted to remote device **170** at **880**. Subsequently, remote device **170** notifies a physician/caregiver.

[**0064**] It is to be understood that the above detailed description is intended to be illustrative, and not restrictive. For example, transdermal drug delivery device **130** can substitute for implantable drug delivery device **690**. Although the present therapy is described in the example of cardiac therapy, it is understood that many other applications are possible. Systems **100**, **400**, and **600** may be generally applied in drug delivery controlled by a condition detected or a signal sensed from a person. Other embodiments, including any possible permutation of the system components discussed in this document, will be apparent to those

of skill in the art upon reading and understanding the above description. The scope of the invention should, therefore, be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A system, comprising:
 - a transdermal drug delivery device;
 - an implantable cardiac rhythm management (CRM) device communicatively coupled to the transdermal drug delivery device, the implantable CRM device including:
 - an ischemia detector producing an ischemia indicating signal;
 - a drug level detector producing an indication of a blood drug concentration; and
 - a drug delivery controller coupled to the ischemia detector and the drug level indicator; and
 - an external device communicatively coupled to the implantable CRM device, the external device including an external user input receiving an external user command,

wherein the drug delivery controller controls the transdermal drug delivery device based on at least one of the ischemia indicating signal, the indication of the blood drug concentration, and the external user command.
2. The system of claim 1, wherein the implantable CRM device comprises a sensing circuit to sense at least one electrogram.
3. The system of claim 2, wherein the ischemia detector comprises an input coupled to the sensing circuit and an ischemia analyzer to produce the ischemia indicating signal based on an analysis of the at least one electrogram.
4. The system of claim 1, wherein the ischemia detector comprises:
 - an impedance sensor to sense an electrical impedance signal; and
 - an ischemia analyzer to produce the ischemia indicating signal based on an analysis of the electrical impedance signal.
5. The system of claim 1, wherein the ischemia detector comprises:
 - an accelerometer to sense an acceleration signal; and
 - an ischemia analyzer to produce the ischemia indicating signal based on an analysis of the acceleration signal.
6. The system of claim 1, further comprising:
 - a remote device receiving signals including at least one of the external user command and the at least one electrogram; and
 - a network coupled between the external device and the remote device to provide for bidirectional communication between the external device and the remote device.
7. The system of claim 6, wherein the remote device comprises an emergency response module adapted to contact an emergency response unit in response to the external user command.

8. The system of claim 6, wherein the remote device comprises a remote signal processor to process the received signals using at least one predetermined algorithm.

9. The system of claim 8, wherein the remote device further comprises a remote user interface providing for monitoring of the processed received signals and entry of remote user commands.

10. The system of claim 9, wherein the remote device further comprises a remote device controller generating commands controlling one or more of the transdermal drug delivery device, the implantable CRM device, and the external device based on the received signals and the remote user commands.

11. The system of claim 1, wherein the drug level indicator comprises a blood drug level detector to measure the blood drug concentration.

12. The system of claim 1, wherein the drug level indicator comprises a respiratory sensor to sense a respiratory signal as the indication of the blood drug concentration.

13. The system of claim 1, wherein the drug level indicator comprises a heart rate detector to determine a heart rate as the indication of the blood drug concentration.

14. The system of claim 1, wherein the transdermal drug delivery device comprises a drug reservoir containing one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.

15. The system of claim 14, wherein transdermal drug delivery device further comprises at least one skin contact electrode for transdermal drug delivery.

16. The system of claim 14, wherein the one or more pharmaceutical agents comprise one or more of agents decreasing, inhibiting, and/or reducing fatty acid oxidation and agents increasing, enhancing, and/or stimulating pyruvate, glucose, and/or lactate oxidation.

17. The system of claim 16, wherein the one or more pharmaceutical agents further comprise one or more of anti-hypertensive agents, anti-arrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, ionotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers.

18. A system, comprising:

- an implantable metabolic sensor to sense a metabolic signal indicative of a cardiac metabolic level;

- an implantable processor coupled to the implantable metabolic sensor, the implantable processor including:

- a metabolic sensor processing circuit to determine the cardiac metabolic level from the metabolic signal; and

- a drug delivery controller producing a drug delivery signal based on the cardiac metabolic level; and

- an implantable drug delivery device communicatively coupled to the implantable processor, to delivery a drug based on the drug delivery signal, the implantable drug delivery device including a drug reservoir storing a drug shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.

19. The system of claim 18, further comprising:
- a remote device receiving signals including at least one of the metabolic signal and the cardiac metabolic level; and
 - a network coupled between the external device and the remote device to provide for bidirectional communication between the external device and the remote device.
20. The system of claim 19, wherein the remote device comprises a remote signal processor to process the received signals using at least one predetermined algorithm.
21. The system of claim 20, wherein the remote device further comprises a remote user interface providing for monitoring of the processed received signals and entry of remote user commands.
22. The system of claim 21, wherein the remote device further comprises a remote device controller generating commands controlling one or more of the implantable metabolic sensor, the implantable processor, the implantable drug delivery device based on the received signals and the remote user commands.
23. The system of claim 18, wherein the implantable metabolic sensor comprises a pH sensor.
24. The system of claim 18, wherein the implantable metabolic sensor comprises an oxygen pressure (PO₂) sensor.
25. The system of claim 18, wherein the implantable metabolic sensor comprises a carbon dioxide pressure (PCO₂) sensor.
26. The system of claim 18, wherein the implantable metabolic sensor comprises a glucose sensor.
27. The system of claim 18, wherein the implantable metabolic sensor comprises a creatine sensor.
28. The system of claim 18, wherein the implantable metabolic sensor comprises a C-creative protein sensor.
29. The system of claim 18, wherein the implantable metabolic sensor comprises a creatine kinase sensor.
30. The system of claim 18, wherein the implantable metabolic sensor comprises a creatine kinase-MB sensor.
31. The system of claim 18, wherein the implantable drug delivery device comprises a reservoir drug level detector, coupled to the drug reservoir, to produce a drug-level-low alert signal indicative of a low reservoir drug level.
32. The system of claim 18, further comprises a drug-eluting stent coupled to the implantable drug delivery device, wherein the implantable drug delivery device is communicatively coupled to the implantable processor.
33. The system of claim 18, wherein the implantable processor and the implantable drug delivery device are housed within a single implantable housing.
34. The system of claim 33, further comprises a drug eluting endocardial lead coupled to the implantable drug delivery device, the drug eluting endocardial lead including at least one drug eluting electrode configured to be disposed within one of a coronary sinus and a portion of a great cardiac vein adjacent to a left ventricle.
35. The system of claim 33, further comprises a drug eluting epicardial lead coupled to the implantable drug delivery device, the drug eluting epicardial lead including at least one drug eluting electrode configured to be attached to a portion of an epicardial wall.
36. The system of claim 18, wherein the drug comprises one or more of agents decreasing, inhibiting, and/or reducing fatty acid oxidation and agents increasing, enhancing, and/or stimulating pyruvate, glucose, and/or lactate oxidation.
37. The system of claim 36, wherein the one or more pharmaceutical agents further comprises one or more of anti-hypertensive agents, anti-arrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, inotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers.
38. A method, comprising:
- detecting an ischemia using an implantable cardiac rhythm management (CRM) device executing an automated ischemia detection algorithm;
 - detecting an external user command directing a drug delivery, the external user command transmitted to the implantable CRM device from an external device;
 - producing a drug delivery signal upon the detection of at least one of the ischemia and the external user command;
 - transmitting the drug delivery signal to a transdermal drug delivery device; and
 - delivering a drug from the transdermal drug delivery device.
39. The method of claim 38, wherein detecting the ischemia comprises:
- sensing at least one electrogram; and
 - detecting the ischemia by using an automated algorithm analyzing the electrogram.
40. The method of claim 38, wherein detecting the ischemia comprises:
- sensing an electrical impedance signal; and
 - detecting the ischemia by using an automated algorithm analyzing the electrical impedance signal for abrupt changes in electrical impedance.
41. The method of claim 38, wherein detecting the ischemia comprises:
- sensing an acceleration signal indicative of a heart motion; and
 - detecting the ischemia by using an automated algorithm analyzing the acceleration signal for abrupt decreases in amplitude.
42. The method of claim 38, further comprising:
- receiving the external user command by the external device; and
 - transmitting the external user command from the external device to a remote device through a network connecting the external device and the remote device.
43. The method of claim 42, further comprising notifying an emergency response unit upon reception of the external user command by the remote device.
44. The method of claim 42, further comprising transmitting at least a portion of the at least one electrogram from the external device to a remote device through a network connecting the external device and the remote device.

- 45.** The method of claim 44, further comprising:
 notifying a remote user;
 receiving a remote user command directing the drug delivery at the remote device;
 transmitting the remote user command from the remote device to the external device through the network;
 transmitting the remote user command from the external device to the implantable CRM device; and
 detecting the remote user command transmitted from the external device to the implantable CRM device.
- 46.** The method of claim 45, wherein producing the drug delivery signal comprises producing a drug delivery signal upon the detection of at least one of the ischemia, the external user command, and the remote user command.
- 47.** The method of claim 38, wherein transmitting the drug delivery signal to the transdermal drug delivery device comprises transmitting through a telemetry link between the implantable CRM device and the transdermal drug delivery device.
- 48.** The method of claim 38, wherein transmitting the drug delivery signal to the transdermal drug delivery device comprises transmitting a voltage signal representing the drug delivery signal via tissue conduction.
- 49.** The method of claim 38, wherein delivering the drug comprises delivering one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.
- 50.** The method of claim 49, wherein delivering the drug comprises releasing one or more of agents decreasing, inhibiting, and/or reducing fatty acid oxidation and agents increasing, enhancing, and/or stimulating pyruvate, glucose, and/or lactate oxidation.
- 51.** The method of claim 50, wherein delivering the drug further comprises releasing one or more of anti-hypertensive agents, anti-dysrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, inotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers.
- 52.** The method of claim 38, further comprising verifying whether a sufficient amount of the drug has been delivered.
- 53.** The method of claim 52, wherein verifying whether the sufficient amount of the drug has been delivered comprises detecting a signal indicative of a concentration of the drug in blood.
- 54.** The method of claim 53, wherein detecting the signal indicative of a concentration of the drug in blood comprises at least one of:
 measuring a blood drug concentration;
 sensing a respiratory signal; and
 measuring a heart rate.
- 55.** The method of claim 54, further comprises:
 producing an insufficiency alert signal if the concentration of the of the drug in blood is below a predetermined level;
 transmitting the insufficiency alert signal from the transdermal drug delivery device to the implantable CRM device;
 detecting the insufficiency alert signal transmitted from the transdermal drug delivery device to the implantable CRM device; and
 wherein producing the drug delivery signal comprises producing a drug delivery signal upon the detection at least one of the ischemia, the external user command, and the insufficiency alert signal.
- 56.** A method, comprising:
 sensing a metabolic signal using an implantable sensor;
 determining a cardiac metabolic level based on the metabolic signal using an implantable processor connected to the implantable sensor;
 producing a drug delivery signal based on the cardiac metabolic level; and
 delivering a drug from an implantable drug delivery device, upon receipt of the drug delivery signal, to shift a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.
- 57.** The method of claim 56, further comprising:
 determining whether the cardiac metabolic level exceeds a predetermined threshold level; and
 producing a drug delivery signal when the cardiac metabolic level exceeds a predetermined threshold level.
- 58.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood pH level.
- 59.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood oxygen pressure (PO₂).
- 60.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood carbon dioxide pressure (PCO₂).
- 61.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood glucose level.
- 62.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood creatine level.
- 63.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood C-creative protein level.
- 64.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood creatine kinase level.
- 65.** The method of claim 56, wherein sensing the metabolic signal comprises sensing a blood creatine kinase-MB level.
- 66.** The method of claim 56, further comprising transmitting at least one of the metabolic signal and the cardiac metabolic level to a remote device though a network.
- 67.** The method of claim 66, further comprising:
 sensing at least one electrogram from the heart; and
 transmitting at least a portion of the at least one electrogram to the remote device through the network.
- 68.** The method of claim 67, further comprising:
 notifying a user by using the remote device;
 receiving a remote user command directing the drug delivery at the remote device;
 transmitting the remote user command from the remote device to the implantable processor through the network; and

detecting the remote user command transmitted from the external device to the implantable processor,

wherein producing the drug delivery signal comprises producing the drug delivery signal based on at least one of the cardiac metabolic level and the remote user command.

69. The method of claim 68, further comprising:

monitoring a level of the drug stored in the drug delivery device; and

transmitting an drug-level-low alert signal to the remote device when the level of the drug stored in the drug delivery device is below a predetermined minimum level.

70. The method of claim 56, wherein transmitting the drug delivery signal comprises transmitting the drug delivery signal through a telemetry link between the implantable processor and the drug delivery device.

71. The method of claim 56, wherein transmitting the drug delivery signal comprises transmitting the drug delivery signal via electrical conduction through tissue intervening the implantable processor and the drug delivery device.

72. The method of claim 56, wherein delivering the drug from the implantable drug delivery device comprises delivering the drug through a drug eluting stent.

73. The method of claim 56, wherein delivering the drug from the implantable drug delivery device comprises delivering the drug through a lead having an endocardial drug eluting electrode.

74. The method of claim 56, wherein delivering the drug from the implantable drug delivery device comprises delivering the drug through a lead having an epicardial drug eluting lead.

75. The method of claim 56, wherein delivering the drug comprises releasing one or more of agents decreasing, inhibiting, and/or reducing fatty acid oxidation and agents increasing, enhancing, and/or stimulating pyruvate, glucose, and/or lactate oxidation.

76. The method of claim 75, wherein delivering the drug further comprises releasing one or more of anti-hypertensive agents, anti-dysrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, inotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers.

77. The method of claim 56, further comprising verifying whether a sufficient amount of the drug has been delivered.

78. The method of claim 77, wherein verifying whether a sufficient amount of the drug has been delivered comprises:

sensing a response metabolic signal using the implantable sensor;

determining a response cardiac metabolic level based on the response metabolic signal using the implantable processor connected to the implantable sensor; and

determining whether the sufficient amount of the drug has been delivered by determining whether the response cardiac metabolic level is below a predetermined threshold.

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专利名称(译)	用于在缺血后或心力衰竭期间调节细胞代谢的方法和装置		
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[标]申请(专利权)人(译)	PASTORE JOSEPH中号 SPINELLI JULIOÇ REEVE HELEN大号 罗斯杰夫瑞 SALO RODNEYW SHUROS ALLAN		
申请(专利权)人(译)	PASTORE约瑟夫M. SPINELLI JULIO C. REEVE HELEN L. 罗斯杰夫瑞 SALO RODNEY W. SHUROS ALLAN		
当前申请(专利权)人(译)	心脏起搏器 , INC.		
[标]发明人	PASTORE JOSEPH M SPINELLI JULIO C REEVE HELEN L ROSS JEFFREY SALO RODNEY W SHUROS ALLAN		
发明人	PASTORE, JOSEPH M. SPINELLI, JULIO C. REEVE, HELEN L. ROSS, JEFFREY SALO, RODNEY W. SHUROS, ALLAN		
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摘要(译)

药物递送系统检测指示需要增加心脏代谢水平的心脏状况，并且作为响应，将药物释放到组织或血液中以将促进心脏收缩的代谢合成能量源从脂肪酸转移到葡萄糖。这种系统的一个实例包括检测缺血的可植入装置和当检测到缺血状况时递送药物的透皮药物递送装置。这种系统的另一个例子包括一个或多个可植入装置，其检测心脏代谢水平的预定变化并在检测到变化时输送药物。这种系统用于治疗例如患有局部缺血和/或心力衰竭的患者和患有心肌梗塞的患者。

