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

4,299,220 A	11/1981	Dorman	128/260
4,470,987 A	9/1984	Wurtman et al.	424/259
4,544,371 A	10/1985	Dormandy, Jr. et al.	604/891
4,556,063 A	12/1985	Thompson et al.	128/419 PT

(Continued)

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FOREIGN PATENT DOCUMENTS

EP 0054138 6/1982

(Continued)

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OTHER PUBLICATIONS

Arnaud, Claire, et al., "iNOS is a mediator of the heat stress-induced preconditioning against myocardial infarction in vivo in the rat", *Cardiovascular Research*, 58, (2003), pp. 118-125.

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(Continued)

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(57) **ABSTRACT**

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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.

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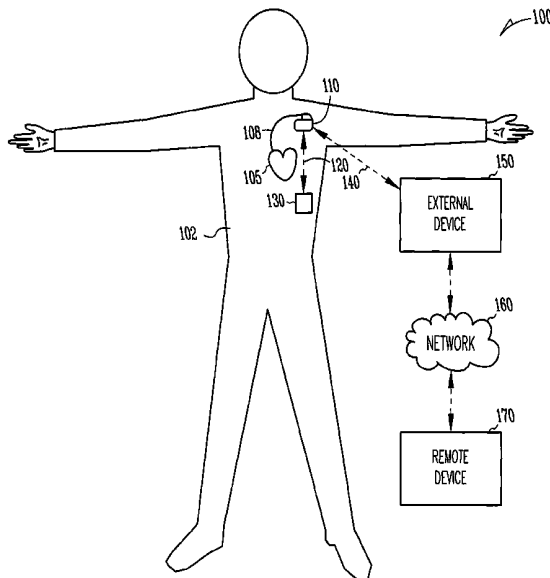
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,692,027 A	9/1972	Ellinwood, Jr.	128/260
4,003,379 A	1/1977	Ellinwood, Jr.	128/260
4,137,908 A	2/1979	Degonde et al.	
4,146,029 A *	3/1979	Ellinwood, Jr.	604/891.1
4,281,664 A	8/1981	Duggan	128/696

43 Claims, 8 Drawing Sheets



U.S. PATENT DOCUMENTS										
4,559,946	A	12/1985	Mower	128/419	D	5,662,689	A	9/1997	Elsberry et al.	607/5
4,561,443	A	12/1985	Hogrefe et al.			5,676,686	A	10/1997	Jensen et al.	607/9
4,674,518	A	6/1987	Salo	128/695		5,683,424	A	11/1997	Brown et al.	607/5
4,686,987	A	8/1987	Salo et al.	128/419	PG	5,690,682	A	11/1997	Buscemi et al.	607/3
4,693,253	A	9/1987	Adams	128/419	D	5,693,075	A	12/1997	Plicchi et al.	607/17
4,871,351	A	10/1989	Feingold	604/66		5,703,125	A	12/1997	Bovy et al.	128/637
4,880,005	A	11/1989	Pless et al.	128/419	PG	5,713,934	A	2/1998	Leckrone	
4,897,987	A	2/1990	Spalla	56/16.7		5,720,770	A	2/1998	Nappholz et al.	607/30
4,904,472	A	2/1990	Belardinelli et al.	514/263		5,730,125	A	3/1998	Prutchi et al.	128/637
4,924,875	A	5/1990	Chamoun	600/509		5,733,313	A	3/1998	Barreras et al.	607/33
4,930,075	A	5/1990	Kortas	364/413.06		5,759,199	A	6/1998	Snell et al.	
4,944,299	A	7/1990	Silvian	128/419	PG	5,782,879	A	7/1998	Rosborough et al.	607/6
4,980,379	A	12/1990	Belardinelli et al.	514/821		5,792,204	A	8/1998	Snell	
4,987,897	A	1/1991	Funke	128/419	PG	5,800,498	A	9/1998	Obino et al.	607/123
5,002,052	A	3/1991	Haluska	607/4		5,807,306	A	9/1998	Shapland et al.	
5,014,698	A	5/1991	Cohen	128/419		5,814,089	A	9/1998	Stokes et al.	607/32
5,040,533	A	8/1991	Fearnot	128/419	PG	5,817,131	A	10/1998	Elsberry et al.	607/5
5,041,107	A	8/1991	Heil, Jr.	604/891.1		5,833,603	A	11/1998	Kovacs et al.	600/317
5,042,497	A	8/1991	Shapland	600/509		5,836,935	A	11/1998	Ashton et al.	604/891.1
5,058,581	A	10/1991	Silvian	128/419	PG	5,893,881	A	4/1999	Elsberry et al.	607/5
5,087,243	A	2/1992	Avitall	604/20		5,899,928	A	5/1999	Sholder et al.	607/27
5,113,869	A	5/1992	Nappholz et al.	128/696		5,906,633	A	5/1999	Mouchawar et al.	607/5
5,127,404	A	7/1992	Wyborny et al.	128/419	P	5,919,210	A	7/1999	Lurie et al.	607/3
5,135,004	A	8/1992	Adams et al.	128/696		5,925,066	A	7/1999	Kroll et al.	607/3
5,137,019	A	8/1992	Pederson et al.	128/419		5,949,659	A	9/1999	Lesche	363/16
5,184,614	A	2/1993	Collins et al.	128/419	PG	5,957,957	A	9/1999	Sheldon	607/17
5,190,035	A	3/1993	Salo et al.	128/419		5,967,986	A	10/1999	Cimochowski et al.	600/454
5,199,428	A	4/1993	Obel et al.	128/419	C	5,978,705	A	11/1999	KenKnight et al.	607/5
5,215,083	A	6/1993	Drane et al.	128/419	D	5,991,668	A	11/1999	Leinders et al.	607/125
5,220,917	A	6/1993	Cammilli et al.	128/419	D	6,016,443	A	1/2000	Ekwall et al.	
5,269,301	A	12/1993	Cohen	607/6		6,016,447	A	1/2000	Juran et al.	607/27
5,282,836	A	2/1994	Kreyenhagen et al.	607/4		6,016,448	A	1/2000	Busacker et al.	607/29
5,284,136	A	2/1994	Hauck et al.	607/24		6,021,350	A	2/2000	Mathson	607/17
5,305,745	A	4/1994	Zacouto	600/324		6,022,322	A	2/2000	Prutchi	600/506
5,334,222	A	8/1994	Salo et al.	607/17		6,066,094	A	5/2000	Ben-Haim	
5,342,408	A	8/1994	deCoriolis et al.	607/32		6,076,015	A	6/2000	Hartley et al.	607/20
5,347,241	A	9/1994	Panaretos et al.			6,104,949	A	8/2000	Pitts Crick et al.	
5,353,800	A	10/1994	Pohndorf et al.	128/673		6,112,116	A	8/2000	Fischell et al.	
5,354,264	A	10/1994	Bae et al.			6,112,117	A	8/2000	KenKnight et al.	607/5
5,354,317	A	10/1994	Alt	607/19		6,115,636	A	9/2000	Ryan	607/60
5,366,485	A	11/1994	Kroll et al.	607/5		6,117,296	A	9/2000	Thomson	
5,368,028	A	11/1994	Palti	128/635		6,128,526	A	10/2000	Stadler et al.	600/517
5,391,190	A	2/1995	Pederson et al.	607/23		6,140,740	A	10/2000	Porat et al.	310/322
5,404,877	A	4/1995	Nolan et al.	128/671		6,141,588	A	10/2000	Cox et al.	607/9
5,405,362	A	4/1995	Kramer et al.	607/5		6,154,672	A	11/2000	Pendekanti et al.	607/5
5,416,695	A	5/1995	Stutman et al.	364/413.02		6,154,675	A	11/2000	Juran et al.	607/29
5,417,717	A	5/1995	Salo et al.	607/18		6,155,267	A	12/2000	Nelson	128/899
5,431,682	A	7/1995	Hedberg	607/5		6,161,042	A	12/2000	Hartley et al.	607/20
5,456,692	A	10/1995	Smith, Jr. et al.	607/31		6,168,801	B1	1/2001	Heil, Jr. et al.	424/426
5,460,605	A	10/1995	Tuttle et al.	604/67		6,184,030	B1	2/2001	Katoot et al.	
5,487,752	A	1/1996	Salo et al.	607/17		6,198,394	B1	3/2001	Jacobsen et al.	340/573.1
5,496,360	A	3/1996	Hoffmann et al.	607/120		6,200,265	B1	3/2001	Walsh et al.	600/300
5,499,971	A	3/1996	Shapland et al.	604/53		6,203,495	B1	3/2001	Bardy	600/301
5,531,768	A	7/1996	Alferness	607/6		6,206,914	B1	3/2001	Soykan et al.	623/1.42
5,540,728	A	7/1996	Shelton et al.	607/23		6,212,434	B1	4/2001	Scheiner et al.	607/123
5,545,186	A	8/1996	Olson et al.	607/14		6,213,942	B1	4/2001	Flach et al.	600/300
5,551,953	A	9/1996	Lattin et al.	604/20		6,221,011	B1	4/2001	Bardy	600/300
5,556,421	A	9/1996	Prutchi et al.	607/36		6,231,516	B1	5/2001	Keilman et al.	600/485
5,558,632	A	9/1996	Lloyd et al.			6,237,398	B1	5/2001	Porat et al.	73/54.09
5,562,711	A	10/1996	Yerich et al.	607/17		6,238,367	B1	5/2001	Christiansen et al.	
5,562,713	A	10/1996	Silvian	607/32		6,251,125	B1	6/2001	KenKnight et al.	607/5
5,579,876	A	12/1996	Adrian et al.	188/322.17		6,254,573	B1	7/2001	Haim et al.	604/157
5,584,868	A	12/1996	Salo et al.	607/17		6,256,233	B1	7/2001	Glass	365/189.05
5,586,556	A	12/1996	Spivey et al.	600/510		6,256,541	B1	7/2001	Heil et al.	607/123
5,591,215	A	1/1997	Greenhut et al.	607/14		6,261,230	B1	7/2001	Bardy	600/300
5,603,331	A	2/1997	Heemels et al.	128/696		6,264,606	B1	7/2001	Ekwall et al.	
5,607,418	A	3/1997	Arzbaecher	604/891.1		6,266,554	B1	7/2001	Hsu et al.	600/515
5,607,463	A	3/1997	Schwartz et al.	623/1.44		6,270,457	B1	8/2001	Bardy	600/300
5,609,613	A	3/1997	Woodson et al.			6,272,377	B1	8/2001	Sweeney et al.	600/515
5,632,766	A	5/1997	Hsu et al.	607/5		6,277,072	B1	8/2001	Bardy	600/300
5,634,899	A	6/1997	Shapland et al.	604/51		6,277,078	B1	8/2001	Porat et al.	600/486
						6,278,894	B1	8/2001	Salo et al.	600/547
						6,280,380	B1	8/2001	Bardy	600/300

6,285,909 B1 9/2001 Sweeney et al. 607/32
 6,298,267 B1 10/2001 Rosborough et al. 607/6
 6,298,269 B1 10/2001 Sweeney 607/28
 6,298,272 B1 10/2001 Peterfeso et al. 607/120
 6,309,370 B1 10/2001 Haim et al. 604/66
 6,312,378 B1 11/2001 Bardy 600/300
 6,321,122 B1 11/2001 Scheiner et al. 607/122
 6,331,160 B1 12/2001 Bardy 600/300
 6,336,903 B1 1/2002 Bardy 600/508
 6,358,202 B1 3/2002 Arent 600/300
 6,358,203 B2 3/2002 Bardy 600/300
 6,361,522 B1 3/2002 Scheiner et al. 604/67
 6,361,780 B1 3/2002 Ley et al. 424/400
 6,363,281 B1 3/2002 Zhu et al. 607/28
 6,368,284 B1 4/2002 Bardy 600/508
 6,370,424 B1 4/2002 Prutchi 600/547
 6,388,043 B1 5/2002 Langer et al.
 6,398,728 B1 6/2002 Bardy 600/300
 6,400,982 B2 6/2002 Sweeney et al. 600/515
 6,411,840 B1 6/2002 Bardy 600/513
 6,411,844 B1 6/2002 Kroll et al. 607/5
 6,415,183 B1 7/2002 Scheiner et al. 607/42
 6,424,847 B1 7/2002 Mastrototaro et al. 600/316
 6,438,419 B1 8/2002 Callaway et al. 607/5
 6,440,066 B1 8/2002 Bardy 600/300
 6,442,413 B1 8/2002 Silver 600/345
 6,443,949 B2 9/2002 Altman 606/41
 6,453,195 B1 9/2002 Thompson 607/3
 6,459,917 B1 10/2002 Gowda et al. 600/345
 6,459,929 B1 10/2002 Hopper et al. 600/513
 6,468,263 B1 10/2002 Fischell et al. 604/890.1
 6,473,640 B1 10/2002 Erlebacher 600/547
 6,478,737 B2 11/2002 Bardy 600/301
 6,501,983 B1 12/2002 Natarajan et al. 600/517
 6,511,477 B2 1/2003 Altman et al. 606/41
 6,518,245 B1 2/2003 Anderson et al. 514/14
 6,539,256 B1 3/2003 KenKnight et al. 607/5
 6,571,125 B2 5/2003 Thompson
 6,604,000 B2 8/2003 Lu 607/17
 6,628,985 B2 9/2003 Sweeney et al. 600/510
 6,689,117 B2 2/2004 Sweeney et al. 604/503
 6,693,133 B1* 2/2004 Lopaschuk et al. 514/557
 6,766,195 B1 7/2004 Bornzin et al.
 6,802,811 B1* 10/2004 Slepian 600/309
 6,824,561 B2* 11/2004 Soykan et al. 623/1.42
 6,969,382 B2 11/2005 Richter
 6,976,982 B2 12/2005 Santini, Jr. et al.
 7,039,462 B2 5/2006 Pastore et al.
 7,072,711 B2 7/2006 Girouard et al.
 7,089,055 B2 8/2006 Cates et al.
 7,201,733 B2 4/2007 Scheiner et al.
 2001/0000802 A1 5/2001 Soykan et al. 623/1.13
 2001/0051787 A1 12/2001 Haller et al.
 2002/0026228 A1 2/2002 Schauerte 607/122
 2002/0031827 A1 3/2002 Kanno et al. 435/446
 2002/0035346 A1 3/2002 Reynolds et al.
 2002/0045809 A1 4/2002 Ben-Haim
 2002/0087116 A1 7/2002 Hartlaub
 2002/0099302 A1 7/2002 Bardy
 2002/0099328 A1 7/2002 Scheiner et al.
 2002/0107553 A1 8/2002 Hill et al.
 2002/0120306 A1 8/2002 Zhu et al.
 2002/0124855 A1 9/2002 Chachques 128/898
 2002/0161410 A1 10/2002 Kramer et al.
 2002/0169485 A1 11/2002 Pless et al.
 2003/0004403 A1 1/2003 Drinan et al. 600/301
 2003/0036773 A1 2/2003 Whitehurst et al.
 2003/0045805 A1 3/2003 Sheldon et al.
 2003/0060854 A1 3/2003 Zhu 607/25
 2003/0069606 A1 4/2003 Girouard et al. 607/3
 2003/0138415 A1 7/2003 Shepard
 2003/0167081 A1 9/2003 Zhu et al.
 2004/0002739 A1 1/2004 Cates et al. 607/6

2004/0059391 A1 3/2004 Sweeney et al. 607/27
 2004/0093034 A1 5/2004 Girouard et al. 607/3
 2005/0137626 A1 6/2005 Pastore et al.
 2005/0192637 A1 9/2005 Girouard et al.
 2005/0283197 A1 12/2005 Daum et al.
 2005/0288721 A1 12/2005 Girouard et al.
 2006/0015146 A1 1/2006 Girouard et al.
 2006/0247686 A1 11/2006 Girouard et al.

FOREIGN PATENT DOCUMENTS

EP 0347708 A1 12/1989
 EP 0467695 A2 1/1992
 EP 0545628 A2 6/1993
 EP 0550343 A1 7/1993
 EP 0550344 A1 7/1993
 EP 0620420 10/1994
 EP 0674916 A2 10/1995
 EP 1050265 11/2000
 EP 1070516 A2 1/2001
 WO WO-93/20888 A1 10/1993
 WO WO-96/32984 A1 10/1996
 WO WO-97/06854 A1 2/1997
 WO WO-97/25098 A1 7/1997
 WO WO-97/33513 9/1997
 WO WO-9834537 A1 8/1998
 WO WO-00/04947 A2 2/2000
 WO WO-0007497 A1 2/2000
 WO WO-01/08748 A1 2/2001
 WO WO-01/30436 A2 5/2001

OTHER PUBLICATIONS

Bralet, J, et al., "Vasopeptidase inhibitors: an emerging class cardiovascular drugs", *Trends Pharmacol Sci.*, 22(3), (Mar. 2001), 106-9.
 Brunner, Friedrich, et al., "Attenuation of myocardial ischemia/reperfusion injury in mice with myocyte-specific overexpression of endothelial nitric oxide synthase", *Cardiovascular Research*, 57, (2003), pp. 55-62.
 Burns, Brent E., "Fabrication Technology for a Chronic In-Vivo Pressure Sensor", *1984 International Electron Devices Meeting Technical Digest*, (1984), pp. 210-212.
 Carr, William N., et al., "Integrated Pressure Sensor With Remote Power Source and Remote Readout", *The 8th International Conference on Solid-State Sensors and Actuators and Eurosensors IX, Digest of Technical Papers*, Stockholm, Sweden, (Jun. 25-29, 1995), pp. 624-627.
 Chau, Hin-Leung, et al., "An Ultraminiature Solid-State Pressure Sensor for a Cardiovascular Catheter", *IEEE Transactions on Electron Devices*, (Dec. 1988), pp. 2355-2362.
 Colonna, P, "Myocardial infarction and left ventricular remodeling: results of the CEDIM trial. Carnitine Ecocardiografia Digitalizzata Infarto Miocardico.", *Am Heart J.*, (Feb. 2000, 139(2 Pt 3)), pp. S124-S130.
 Ferdinandy, Peter, et al., "Nitric oxide, superoxide, and peroxynitrite in myocardial ischaemia-reperfusion injury and preconditioning", *British Journal of Pharmacology*, 138(4), (2003), pp. 532-543.
 Fogel, Ulrich, et al., "Myoglobin: A scavenger of bioactive NO", *PNAS*, 98(2), (Jan. 16, 2001), pp. 735-740.
 Gewaltig, Michael T., et al., "Vasoprotection by nitric oxide: mechanisms and therapeutic potential", *Cardiovascular Research*, 55, (Feb. 14, 2002), pp. 250-260.
 Hada, Yoshiyuki, et al., "Pulsus alternans determined by biventricular simultaneous systolic time intervals", *Circulation*, vol. 65, No. 3, (Mar. 1982), pp. 617-626.
 Lee, Y. C., et al., "Pulsus alternans in patients with congestive cardiomyopathy", *Circulation*, vol. 65, No. 7, (Jun. 1982), pp. 1533-1534.
 Lehman, J, et al., "Gene regulatory mechanisms governing energy metabolism during cardiac hypertrophic growth", *Heart Fail Rev.*, (Apr. 2000), pp. 175-185.

- Levin, L., "Researchers present findings at European cardiology conference", *Advisory Board Daily Briefing*, 8. *Clinical Outlook*, (Sep. 2002), 8 pages [see pp. 5,6].
- Li, Qianghong, et al., "Gene Therapy With Inducible Nitric Oxide Synthase Protects Against Myocardial Infarction via a Cyclooxygenase-2-Dependent Mechanism", *Circulation Research*, 92, (2003), pp. 741-748.
- Lopaschuk, G., "Metabolic abnormalities in the diabetic heart", *Heart Fail Rev.*, (Apr. 2002), pp. 149-159.
- Lovett, Eric G., "Technique for Discriminating Between Coordinated and Uncoordinated Cardiac Rhythms", U.S. Appl. No. 10/435,487, filed May 9, 2003, SLWK Docket No. 279.255US2, assigned to Cardiac Pacemakers, Inc., (May 9, 2003), pp. 36 pgs.
- Luepker, R., "Transthoracic Electrical Impedance: Quantitative Evaluation of a Non-Invasive Measure of Thoracic Fluid Volume", *American Heart Journal*, 85(1), (Jan. 1973), pp. 83-93.
- Mai, J., "Enhanced Rate Response Algorithm for Orthostatic Compensation Pacing", *Pacing Clin. Electrophysiol. (PACE) Abstracts*, 23 (Pt 2), (Apr. 2000), p. 722.
- Min, Mart, et al., "Electrical Impedance and Cardiac Monitoring-Technology, Potential and Applications", *International Journal of Bioelectromagnetism*, 5, (2003), pp. 53-56.
- Ostadal, Petr, et al., "The effect of early treatment by cerivastatin on the serum level of C-reactive protein, interleukin-6, and interleukin-8 in patients with unstable angina and non-Q-wave myocardial infarction", *Molecular and Cellular Biochemistry*, 246, (2003), pp. 45-50.
- Paolucci, Nazareno, et al., "Positive inotropic and lusitropic effects of HNO/NO- in failing hearts: Independence from beta-adrenergic signaling", *PNAS*, vol. 100, No. 9, (Apr. 29, 2003), pp. 5537-5542.
- Pastore, Joseph M., "Method And Apparatus For Modulating Cellular Metabolism During Post-Ischemia Or Heart Failure", U.S. Appl. No. 10/645,823, filed Aug. 21, 2003, 46 pages.
- Rizos, I., "Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration", *Am Heart J.*, 139(2 Pt 3), (Feb. 2000), pp. S120-S123.
- Rosborough, John P., et al., "Electrical Therapy for Pulseless Electrical Activity", *NASPE*, 23(4), Part II, Abstract, (Apr. 2000), p. 591.
- Sabbah, H, et al., "Partial fatty acid oxidation inhibitors: a potentially new class of drugs for heart failure", *Eur J Heart Fail.*, 4(1), (Jan. 2002), pp. 3-6.
- Salloum, Fadi, et al., "Sildenafil Induces Delayed Preconditioning Through Inducible Nitric Oxide Synthase-Dependent Pathway in Mouse Heart", *Circulation Research*, 92, (Apr. 4, 2003), pp. 595-597.
- Schaefer, Saul, et al., "Clinical and hemodynamic characteristics of patients with inducible pulsus alternans", *American Heart Journal*, vol. 115, No. 6, (Jun. 1988), pp. 1251-1257.
- Smith, Damon, et al., "Influence of the Aortic Component of the Second Heart Sound on Left Ventricular Maximal Negative dP/dt in the Dog", *Am. J. Cardiol.*, 55: 205, (1985), pp. 205-209.
- Spiegel, Egbert, "A CMOS Sensor and Signal Conversion Chip for Monitoring Arterial Blood Pressure and Temperature", *IEEE International Solid-State Circuits Conference.*, (Feb. 20, 1992), pp. 126-127.
- Stanley, W, et al., "Energy metabolism in the normal and failing heart: potential for therapeutic interventions", *Heart Fail Rev.*, (Apr. 2002), pp. 115-130.
- Stanley, W, "Partial fatty acid oxidation inhibitors for stable angina", *Expert Opin Investig Drugs*, 11(5), (May 2002), pp. 615-629.
- Suematsu, Yoshihiro, et al., "L-Arginine given after ischaemic preconditioning can enhance cardioprotection in isolated rat hearts", *European Journal of Cardio-thoracic Surgery*, 19, (2001), pp. 873-879.
- Sweeney, Robert J., et al., "Drug Delivery System for Implantable Medical Device", U.S. Appl. No. 10/743,507, filed Dec. 22, 2003, pp. 17.
- Woldbaek, Per R., et al., "Increased cardiac IL-18 mRNA, pro-IL-18 and plasma IL-18 after myocardial infarction in the mouse; a potential role in cardiac dysfunction", *Cardiovascular Research*, 59, (2003), pp. 122-131.
- Wolff, A, et al., "Metabolic approaches to the treatment of ischemic heart disease: the clinicians' perspective", *Heart Fail Rev.*, (Apr. 2002), pp. 187-203.
- Wolfrum, Sebastian, et al., "Acute Reduction of Myocardial Infarct Size By a Hydroxymethyl Glutaryl Coenzyme A Reductase Inhibitor Is Mediated By Endothelial Nitric Oxide Synthase", *J. Cardiovas Pharmacol*, vol. 41, No. 3, (Mar. 2003), pp. 474-480.
- Wunderlich, Carsten, et al., "Acute Inhibition of Myoglobin Impairs Contractility and Energy State of iNOS-Overexpressing Hearts", *Circulation Research*, 92, (2003), pp. 1352-1358.
- Wynn, R, "Cardiovascular drugs and dental considerations", *Cardiovascular drugs and dental considerations. J Calif Dent Assoc.*, 28(7), (Jul. 2000), pp. 9-26.
- Ziaie, Babak, et al., "A Single-Channel Implantable Microstimulator for Functional Neuromuscular Stimulation", *IEEE Transactions on Biomedical Engineering*, 44, (Oct. 1997), pp. 909-920.

* cited by examiner

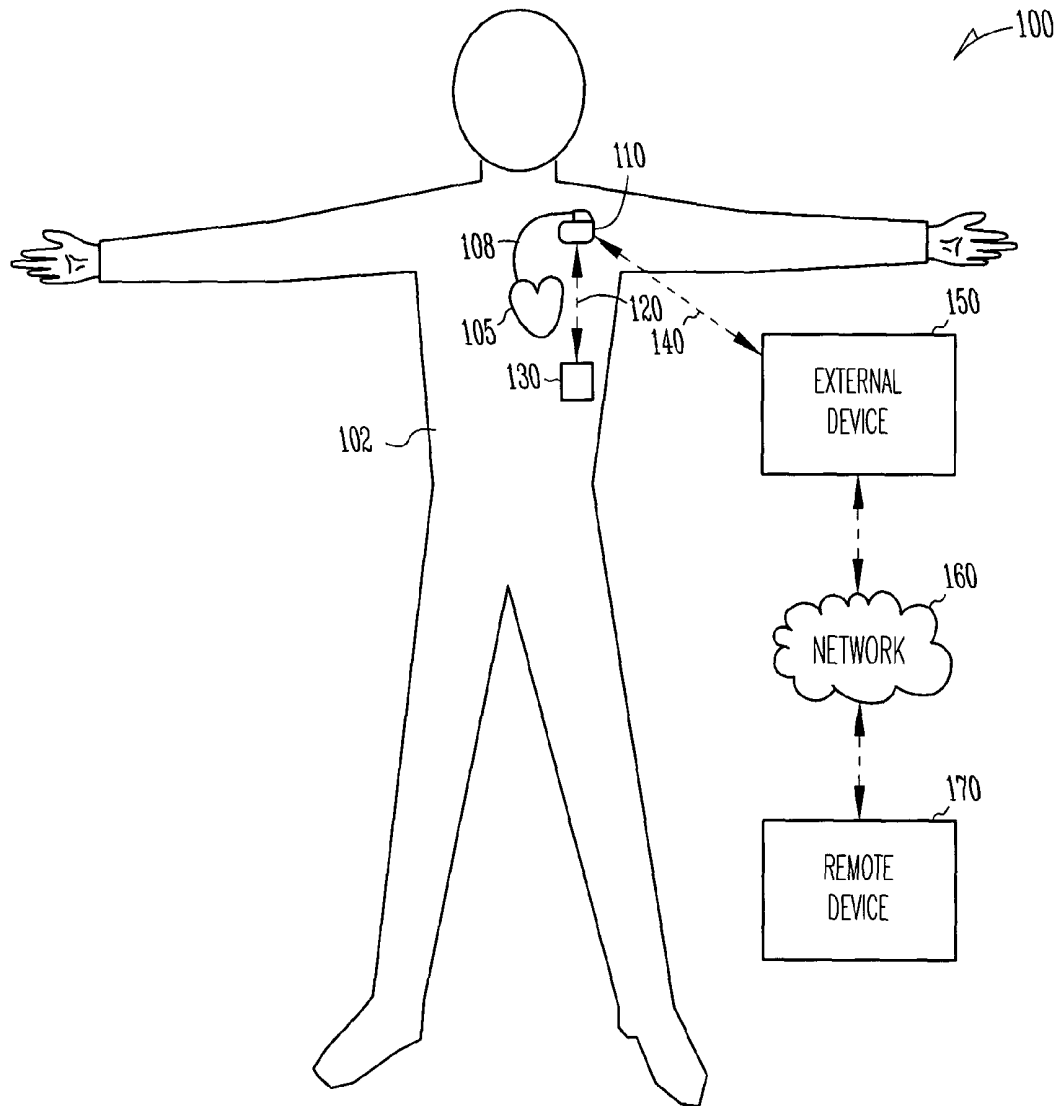


Fig. 1

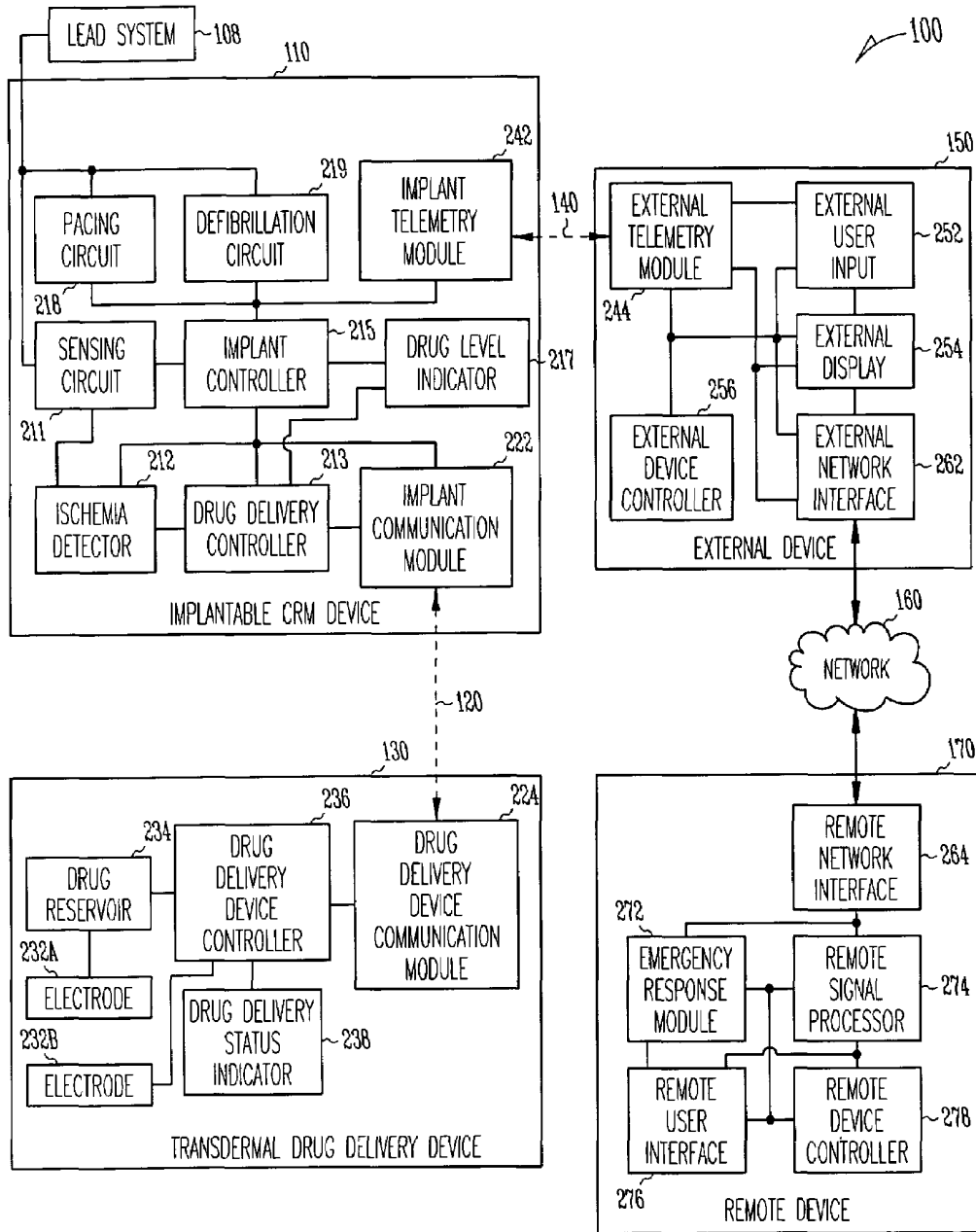


Fig. 2

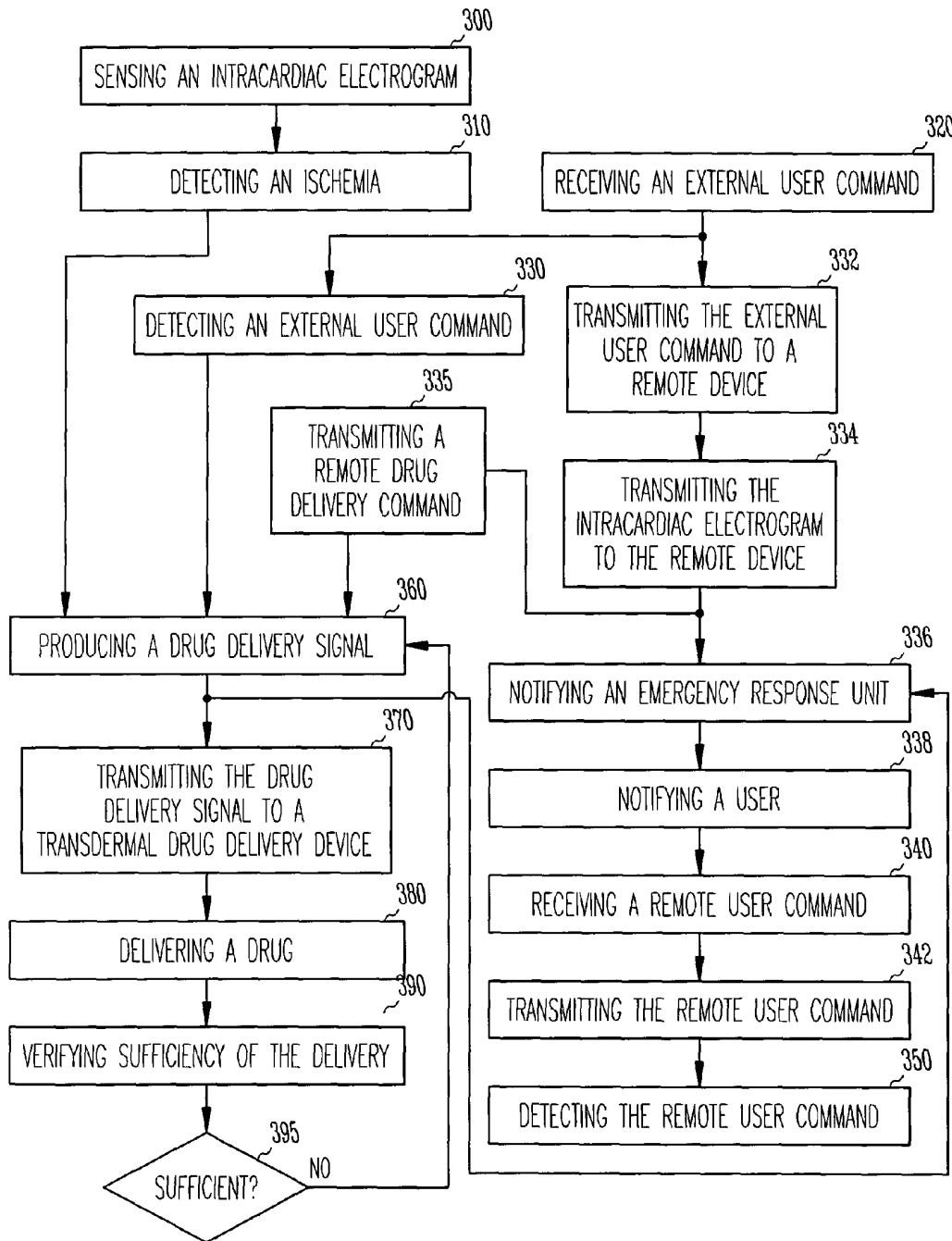


Fig. 3

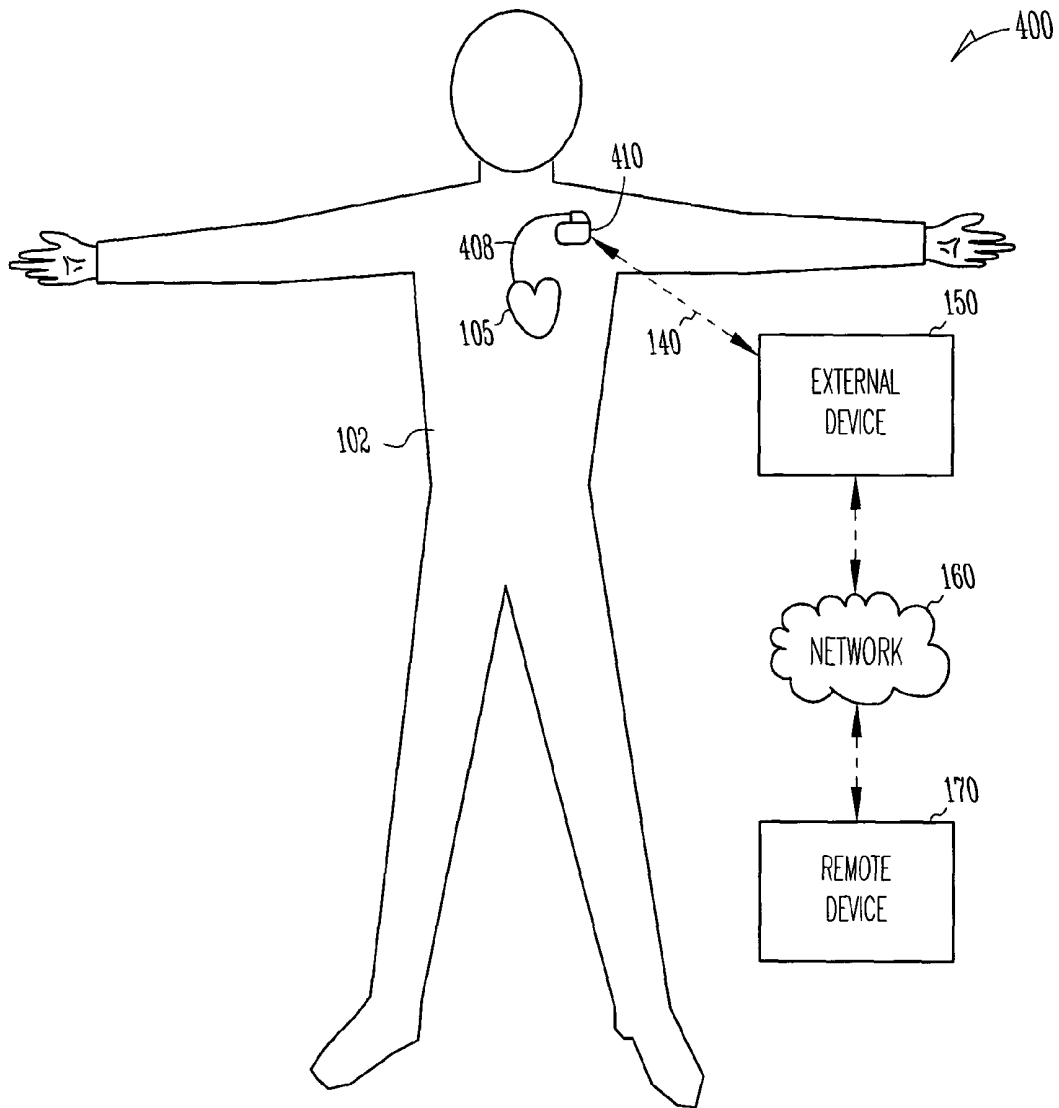


Fig. 4

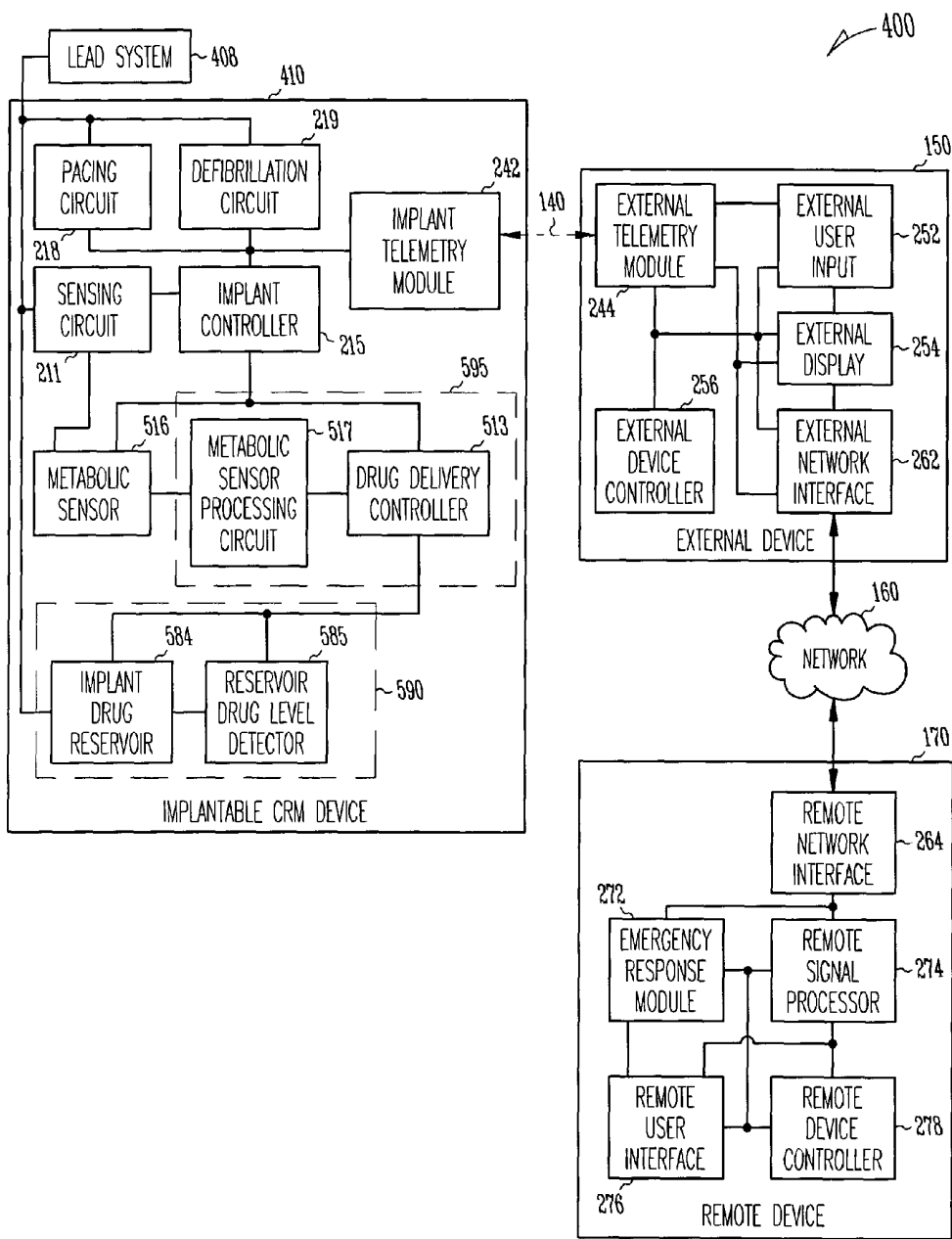


Fig. 5

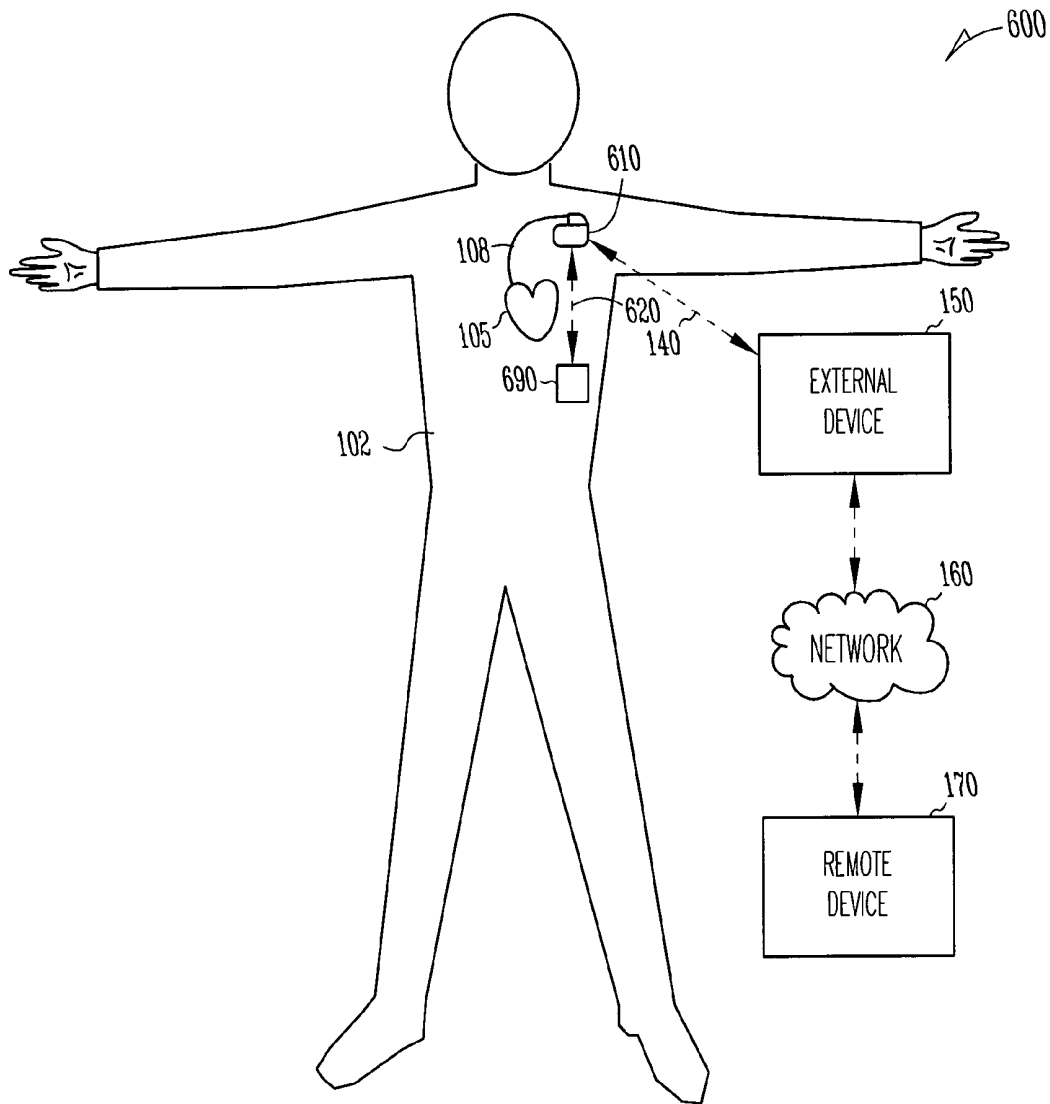


Fig. 6

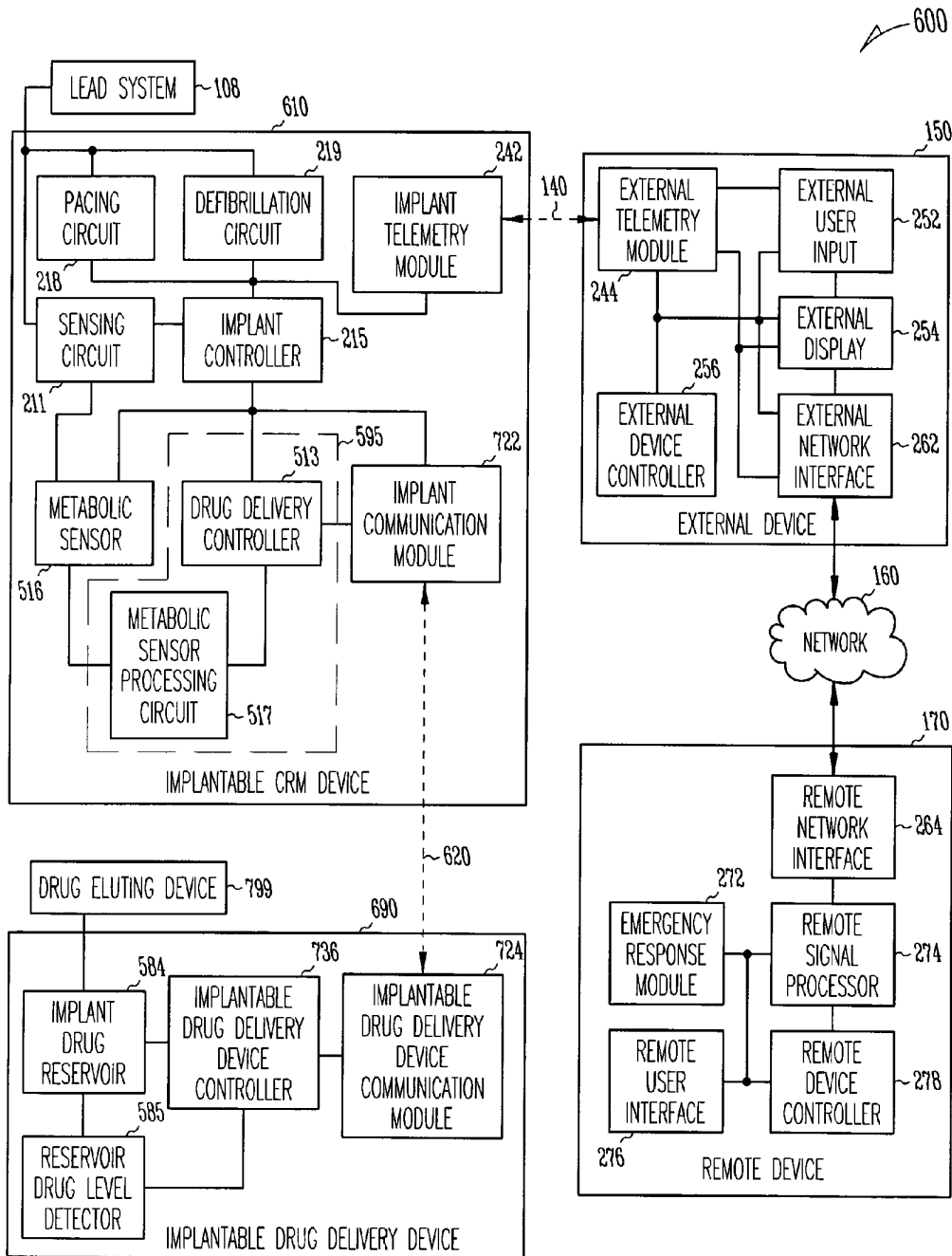


Fig. 7

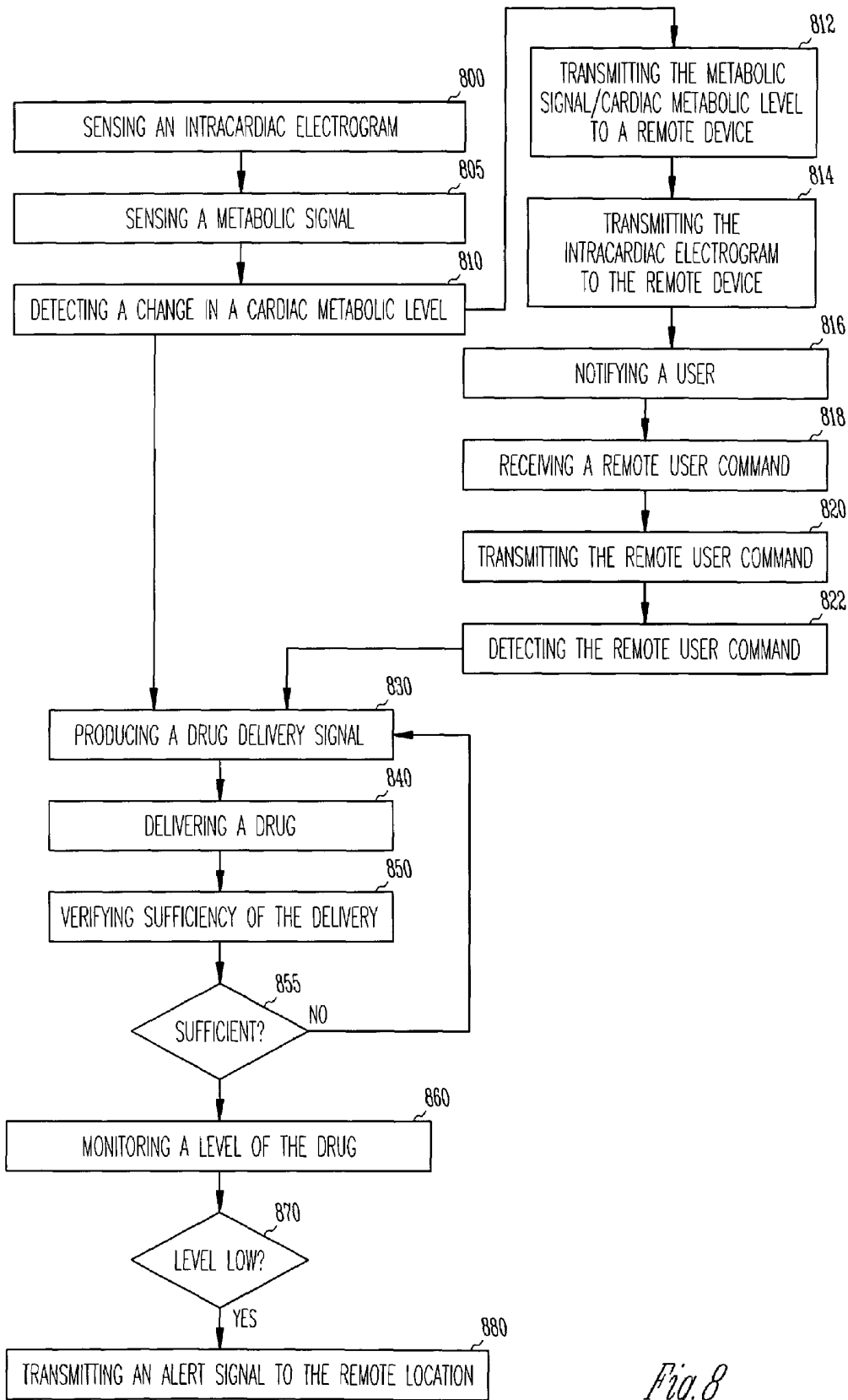


Fig. 8

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

FIELD OF THE INVENTION

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

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).

Cardiac cells produces 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.

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

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.

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 concen-

tration 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.

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.

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.

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.

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

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.

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

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.

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.

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

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.

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

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.

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

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.

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.

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.

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.

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.

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 blockers, 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 imidazoline receptor inhibitors, heбивolol, 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 tirofiban, reteplase, 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, 10 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-dicodithyropionic acid, etomoxir, endothelin receptor antagonists, chlor- 15 thiadone, doxazosin, nesiritide, cilostazol, rilmenidine, ticlopidine, dihydropyridines such as nifedipine and nisoldipine, timolol, propranolol, verapamil, diltiazem, lisinopril, noopept (N-phenylacetyl-L-polyglycine ethylester), cariporide, geldanamycin, radicicol, ibudilast, selective delta (1) 20 agonists such as 2-methyl-4 α -alpha-(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, 25 atenolol, ezetimibe, lerostimendan, sirolimus, paclitaxil, actinomycin D, dexamethasone, tacrolimus, everolimus, estradiol, quinapril, tranilast, antiopeptin, trapidil, lacidipine, thiazolidinediones, fenofibrate, lacidipine, nebrivolol, nicotinic acid, probucal, rosuvastatin, gemfibrozil, glitazones, 30 indobufen, alpha-tocopherol, dipyridamole, resins, e.g., cholestyramine and colestipol, bezafibrate, orlistat, niacin, heparin, e.g., low molecular weight heparins such as dalteparin sodium and nadroparin calcium, bivalirucin, nitroglycerin, nicorandil, denopamine, eftifibatide, xemilofiban, or 35 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. 40 Examples of such pharmaceutical agents include, but are not limited to, L-arginine; nitric oxide (NO); NO derivatives such as nitroxyl anion (HNONO⁻) and peroxyxynitrite (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.

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.

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 65 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 5 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.

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.

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.

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**.

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.

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**.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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 the drug delivery signal 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.

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.

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.

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.

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.

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.

In one embodiment, to perform the drug delivery function, implantable CRM device 410 includes an implantable 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 (PO₂) sensor, a carbon dioxide pressure (PCO₂) 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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 (PO₂), a blood carbon dioxide pressure (PCO₂), 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**.

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 embodiment, 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**.

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**.

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.

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:

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 to produce a drug delivery signal based on the cardiac metabolic level; and

an implantable drug delivery device, communicatively coupled to the implantable processor, to deliver 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.

2. The system of claim 1, 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.

3. The system of claim 2, wherein the remote device comprises a remote signal processor to process the received signals using at least one predetermined algorithm.

4. The system of claim 3, wherein the remote device further comprises a remote user interface providing for monitoring of the processed received signals and entry of remote user commands.

5. The system of claim 4, 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.

6. The system of claim 1, wherein the implantable metabolic sensor comprises a pH sensor.

7. The system of claim 1, wherein the implantable metabolic sensor comprises an oxygen pressure (PO₂) sensor.

8. The system of claim 1, wherein the implantable metabolic sensor comprises a carbon dioxide pressure (PCO₂) sensor.

9. The system of claim 1, wherein the implantable metabolic sensor comprises a glucose sensor.

10. The system of claim 1, wherein the implantable metabolic sensor comprises a creatine sensor.

11. The system of claim 1, wherein the implantable metabolic sensor comprises a C-creative protein sensor.

12. The system of claim 1, wherein the implantable metabolic sensor comprises a creatine kinase sensor.

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13. The system of claim 1, wherein the implantable metabolic sensor comprises a creatine kinase-MB sensor.

14. The system of claim 1, 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.

15. The system of claim 1, further comprises a drug-eluting stent coupled to the implantable drug delivery device.

16. The system of claim 1, wherein the implantable processor and the implantable drug delivery device are housed within a single implantable housing.

17. The system of claim 16, 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.

18. The system of claim 16, 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.

19. The system of claim 1, 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.

20. The system of claim 19, 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.

21. 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.

22. The method of claim 21, 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.

23. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood pH level.

24. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood oxygen pressure (PO₂).

25. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood carbon dioxide pressure (PCO₂).

26. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood glucose level.

27. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood creatine level.

28. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood C-creative protein level.

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29. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood creatine kinase level.

30. The method of claim 21, wherein sensing the metabolic signal comprises sensing a blood creatine kinase-MB level.

31. The method of claim 21, further comprising transmitting at least one of the metabolic signal and the cardiac metabolic level to a remote device through a network.

32. The method of claim 31, 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.

33. The method of claim 32, 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.

34. The method of claim 33, 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.

35. The method of claim 21, 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.

36. The method of claim 21, 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.

37. The method of claim 21, wherein delivering the drug from the implantable drug delivery device comprises delivering the drug through a drug eluting stent.

38. The method of claim 21, wherein delivering the drug from the implantable drug delivery device comprises delivering the drug through a lead having an endocardial drug eluting electrode.

39. The method of claim 21, wherein delivering the drug from the implantable drug delivery device comprises delivering the drug through a lead having an epicardial drug eluting lead.

40. The method of claim 21, 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.

41. The method of claim 40, 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.

42. The method of claim 21, further comprising verifying whether a sufficient amount of the drug has been delivered.

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43. The method of claim 42, 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

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

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,320,675 B2
APPLICATION NO. : 10/645823
DATED : January 22, 2008
INVENTOR(S) : Pastore et al.

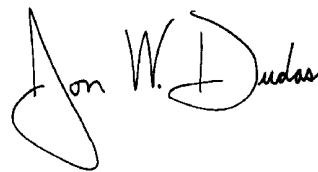
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 18, line 52, in Claim 39, delete "lead." and insert -- electrode. --, therefor.

Signed and Sealed this

Twentieth Day of May, 2008

A handwritten signature in black ink that reads "Jon W. Dudas". The signature is written in a cursive style with a large, stylized initial "J".

JON W. DUDAS
Director of the United States Patent and Trademark Office

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		
公开(公告)号	US7320675	公开(公告)日	2008-01-22
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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		
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CPC分类号	A61B5/0031 A61B5/14546 A61B5/4839 A61M5/1723 A61N1/3627 A61B5/1107 A61B5/14532 A61M5/14244 A61M5/14276 A61M2205/3523		
其他公开文献	US20050043675A1		
外部链接	Espacenet USPTO		

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。

