

# References for Chapter 13

## Inotropic Agents

Thierry H. LeJemtel, MD

Marc Klapholz, MD

William H. Frishman, MD

1. Warner Stevenson L: Inotropic therapy for heart failure. *N Engl J Med* 339:1848, 1998.
2. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure: *J Am Coll Cardiol* 46: e1, 2005.
  - 2a. Jefferies JL, Towbin JA: Dilated cardiomyopathy. *Lancet* 375: 752, 2010.
  - 2b. Goldhaber JJ, Hamilton MA: Role of inotropic agents in the treatment of heart failure. *Circulation* 121: 1655, 2010.
3. LeJemtel TH, Sonnenblick EH, Frishman WH: Diagnosis and management of heart failure. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart*, 11th ed. New York: McGraw-Hill, 2004:723.
4. Ferguson DW: Digitalis and neurohormonal abnormalities in heart failure and implications for therapy. *Am J Cardiol* 69:24G, 1992.
5. Felker GM, O'Connor CM: Inotropic therapy for heart failure: An evidence-based approach. *Am Heart J* 142:393, 2001.
6. Burger AJ, Elkayam U, Neibaur MT, et al: Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. *Am J Cardiol* 88:35, 2001.
7. Patel MB, Kaplan IV, Patni RN, et al: Sustained improvement in flow mediated vasodilation after short-term administration of dobutamine in patients with severe congestive heart failure. *Circulation* 99:60, 1999.
8. Drazner MH, Solomon MA, Thompson B, Yancy CW: Tailored therapy using dobutamine and nitroglycerin in advanced heart failure. *Am J Cardiol* 84:941, 1999.
9. Withering W: *An Account of the Foxglove, And Some of Its Medical Uses: With Practical Remarks on Dropsy and other Diseases*. London: GGJ and J Robinson, 1785.
10. Fothergill JM: *Digitalis: Its Mode of Action*. London, 1871.
11. Dock W, Tainter ML: The circulatory changes after full therapeutic doses of digitalis, with critical discussion of views on cardiac output. *J Clin Invest* 8:467, 1929.
12. Fisch C: William Withering: An account of the foxglove and some of its medical uses, 1785–1985. *J Am Coll Cardiol* 5:1A, 1985.
13. Gillis RA, Quest JA: The role of the nervous system in the cardiovascular effects of digitalis. *Pharmacol Rev* 31:19, 1980.
14. Rahimtoola SH, Tak T: The use of digitalis in heart failure. *Curr Probl Cardiol* 21:785, 1996.
15. Fozzard HA, Sheets MF: Cellular mechanism of action of cardiac glycosides. *J Am Coll Cardiol* 5:10A, 1985.
16. Charlemagne D: Molecular and cellular level of action of digitalis. *Herz* 18:79, 1993.
17. Scholz H: Inotropic drugs and their mechanisms of action. *J Am Coll Cardiol* 4:389, 1984.
18. Siri FM, Krueger JW, Nordin C, et al: Depressed intracellular calcium transients and contraction in myocytes from hypertrophied and failing guinea pig hearts. *Am J Physiol* 261:H514, 1991.
19. Li P, Park C, Micheletti R, et al: Myocyte performance during evolution of myocardial infarction in rats: Effects of propionyl-L-carnitine. *Am J*

- Physiol* 268:H1702, 1995.
20. Rosen MR: Cellular electrophysiology of digitalis toxicity. *J Am Coll Cardiol* 5:22A, 1985.
  21. Smith TW, Antman EM, Friedman PL, et al: Digitalis glycosides: Mechanisms and manifestations of toxicity. Parts I, II, III. *Prog Cardiovasc Dis* 26:413, 495; 27:21, 1984.
  22. Wantanabe AM: Digitalis and the autonomic nervous system. *J Am Coll Cardiol* 5:35A, 1985.
  23. Newton GE, Tong JH, Schofield AM, et al: Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. *J Am Coll Cardiol* 28:155, 1996.
  24. Wenger T, Butler VP Jr., Haber E, Smith TW: Digoxin-specific antibody treatment of digitalis toxicity. In: Erdmann E, Greeff K, Skou JC, eds. *Update in Cardiac Glycosides 1785–1985*. New York: Springer-Verlag, 1986:377–388.
  25. Braunwald E, Ross J Jr, Sonnenblick EH: *Mechanisms of Contraction of the Normal and Failing Heart*, 2nd ed. Boston: Little, Brown, 1976.
  26. Mason DT, Braunwald E, Karsh RB, Bullock FA: Studies on digitalis. X: Effects of ouabain on forearm vascular resistance and venous tone in normal subjects and in patients with heart failure. *J Clin Invest* 43:532, 1964.
  27. Eberhardt RT, Frishman WH, Landau A, et al: Increased mortality incidence in elderly individuals receiving digoxin therapy: Results of the Bronx Longitudinal Aging Study. *Cardiol Elderly* 3:177, 1995.
  28. Packer M, Gheorghide M, Young JB, et al: Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 329:1, 1993.
  29. Uretsky BF, Young JB, Shahidi FE, et al: Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the PROVED Trial. *J Am Coll Cardiol* 22:955, 1995.
  30. Adams KF Jr, Gheorghide M, Uretsky BF, et al: Clinical predictors of worsening heart failure during withdrawal from digoxin therapy. *Am Heart J* 135:389–397, 1998.
  31. Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539, 1988.
  32. Tauke J, Goldstein S, Gheorghide M: Digoxin for chronic heart failure: A review of the randomized controlled trials with special attention to the PROVED and RADIANCE Trials. *Prog Cardiovasc Dis* 37:49, 1994.
  33. Kraus F, Rudolph C, Rudolph W: Efficacy of digitalis in patients with chronic congestive heart failure and sinus rhythm: An overview of randomized, double-blind, placebo-controlled studies. *Herz* 18:95, 1993.
  34. The Digitalis Investigation Group: The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 336:525, 1997.
  35. Wirth KE: Relevant metabolism of cardiac glycosides. In: Erdmann E, Greeff K, Skou JC, eds. *Update in Cardiac Glycosides, 1785–1985*. New York: Springer-Verlag, 1986:257–262.
  36. Adams KF Jr., Gheorghide M, Uretsky BF, et al: Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 39:946, 2002.
  37. van Veldhuisen DJ: Low-dose digoxin in patients with heart failure: Less toxic and at least as effective? *J Am Coll Cardiol* 39:954, 2002.
  38. Marcus FI: Pharmacokinetic interactions between digoxin and other drugs. *J Am Coll Cardiol* 5:82A, 1985.
  39. Sonnenblick EH, LeJemtel TH: Heart failure: Its progression and its therapy. *Hosp Pract* 28:121, 1993.
  40. Fauchier L, Grimard C, Pierre B, et al: Comparison of beta blocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure. *Am J Cardiol* 103: 248, 2009.
  41. Hauptman PJ, Kelly RA: Digitalis. *Circulation* 99:1265, 1999.
  42. Muller JE, Turi ZG, Stone PH, et al for the MILIS Group: Digoxin therapy and mortality following confirmed or suspected myocardial infarction: experience in the MILIS Study. In: Erdmann E, Greeff JC, Skou JC, eds. *Update in Cardiac Glycosides 1785–1985*. New York: Springer-Verlag, 1986:493.
  43. Ahmed A, Gambassi G, Weaver MT, et al: Effects of discontinuation of digoxin versus continuation at low serum digoxin concentrations in chronic heart failure. *Am J Cardiol* 100: 280, 2007.
  44. Spargias KS, Hall AS, Ball SG: Safety concerns about digoxin after acute myocardial infarction. *Lancet* 354:391, 1999.
  45. Lewis RP: Clinical use of serum digoxin concentrations. *Am J Cardiol* 69:97G, 1992.
  46. Steimer W, Muller C, Eber B: Digoxin assays: Frequent, substantial and potentially dangerous interference by spironoactone, canrenone, and other steroids. *Clin Chem* 48:507, 2002.
  47. Kelley RA, Smith TW: Recognition and treatment of digitalis toxicity. *Am J Cardiol* 69:108G, 1992.
  48. Marcus FI: Digitalis. In: Schlant RC, Alexander RW, eds. *Hurst's The Heart*, 8th ed. New York: McGraw-Hill, 1994:573–588.
  49. Williamson KM, Thrasher KA, Fulton KB, et al:

- Digoxin toxicity. An evaluation in current clinical practice. *Arch Intern Med* 158:2444, 1998.
50. Cardiac glycosides interact with many drugs. *Drugs Ther Perspect* 6(3):11, 1995.
  51. Eddleston M, Rajapakse S, Rajakanthan SJ, et al: Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: A randomised controlled trial. *Lancet* 355:767, 2000.
  52. Marik PE, Fromm L: A case series of hospitalized patients with elevated digoxin levels. *Am J Med* 105:110, 1998.
  53. Benovic JL, Bouvier M, Caron MG, Lefkowitz RJ: Regulation of adenylyl cyclase-coupled  $\beta$ -adrenergic receptors. *Am Rev Cell Biol* 4:405, 1988.
  54. Kelly RB: Storage and release of neurotransmitters. *Cell/Neuron* 72(Suppl. 72):443, 1993.
  55. Hoffman BB, Taylor P: Neurotransmission. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2001:115–153.
  56. Spann JF, Sonnenblick EH, Cooper T, et al: Cardiac norepinephrine stores and the contractile state of the heart. *Circ Res* 19:317, 1966.
  57. Francis GS, Goldsmith SR, Levine TB, et al: The neurohumoral axis in congestive heart failure. *Ann Intern Med* 101:370, 1984.
  58. Insel PA: Adrenergic receptors—evolving concepts and clinical implications. *N Engl J Med* 334:580, 1996.
  59. Movsesian MA: Beta-adrenergic receptor agonists and cyclic nucleotide phosphodiesterase inhibitors: Shifting the focus from inotropy to cyclic adenosine monophosphate *J Am Coll Cardiol* 34:318–324, 1999.
  60. Pagel PS, Haikala H, Pentikainen PJ, et al: Pharmacology of levosimendan: A new myofilament calcium sensitizer. *Cardiovasc Drugs Rev* 14:286, 1996.
  61. Micheletti R, Mattera GG, Rocchetti M, et al: Pharmacological profile of the novel inotropic agent (E,Z)-3-((2-aminoethoxy)imino)androstane-6,17-dione hydrochloride (PST2744). *J Pharm Exp Thera* 303:592, 2002.
  62. Goldberg LI, Rajfer SI: Dopamine receptors: Applications in clinical cardiology. *Circulation* 72:245, 1985.
  63. Leclerc KM, Steele NP, Levy WC: Norepinephrine alters exercise oxygen consumption in heart failure patients. *Med Sci Sports Exerc* 32:2029, 2000.
  64. van de Borne P, Oren R, Somers VK: Dopamine depresses minute ventilation in patients with heart failure. *Circulation* 98:126, 1998.
  65. Elkayam U, Ng TMH, Hatamizadeh P, et al: Renal vasodilatory action of dopamine in patients with heart failure. Magnitude of effect and site of action. *Circulation* 117: 200, 2008.
  66. Hoogenberg K, Smit AJ, Girbes ARJ: Effects of low-dose dopamine on renal and systemic hemodynamics during incremental norepinephrine infusion in healthy volunteers. *Crit Care Med* 26:260, 1998.
  67. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. *Lancet* 356:2139, 2000.
  68. DeBacker D, Biston P, Devriendt J, et al for the SOAP II Investigators: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 362: 779, 2010.
  69. Ruffolo RR Jr.: Review: The pharmacology of dobutamine. *Am J Med Sci* 294:244, 1987.
  70. Sonnenblick EH, Frishman WH, LeJemtel TH: Dobutamine: A new synthetic cardioactive sympathetic amine. *N Engl J Med* 300:17, 1979.
  71. Tisdale JE, Patel R, Webb CR, et al: Electrophysiologic and proarrhythmic effects of intravenous inotropic agents. *Progr Cardiovasc Dis* 38:167, 1995.
  72. Oliva F, Latini R, Politi A, et al for the DICE (Dobutamina nell'Insufficienza Cardiaca Estrema) Investigators: Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial. *Am Heart J* 138:247, 1999.
  73. Silver MA: Intermittent inotropes for advanced heart failure: Inquiring minds want to know. *Am Heart J* 138:191, 1999.
  74. Nanas JN, Kontoyannis DA, Alexopoulos GP, et al: Long-term intermittent dobutamine infusion combined with oral amiodarone improves the survival of patients with severe congestive heart failure. *Chest* 119:1173, 2001.
  75. Parmley WW, Sonnenblick EH: A role for glucagon in cardiac therapy. *Am J Med Sci* 258:224, 1969.
  76. Braunwald E, Sonnenblick EH, Chakrin LW, Schwarz RP Jr., eds. *Milrinone Investigation: A New Inotropic Therapy for Congestive Heart Failure*. New York: Raven Press, 1984.
  77. Grose R, Strain J, Greenberg M, LeJemtel TH: Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. *J Am Coll Cardiol* 7:1107, 1986.
  78. Harris AL, Silver PJ, Lemp BM, Evans DB: The vasorelaxant effects of milrinone and other vasodilators are attenuated by ouabain. *Eur J Pharmacol* 145:133–139, 1988.
  79. Nielsen-Kudsk JE, Aldershvile J: Will calcium sensitizers play a role in the treatment of heart failure? *J Cardiovasc Pharmacol* 26 (Suppl 1):577, 1995.
  80. Packer M, Carver JR, Rodeheffer RJ, et al: Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 325:1468, 1991.

81. Fleming GA, Murray KT, Yu C, et al: Milrinone use is associated with postoperative atrial fibrillation after cardiac surgery. *Circulation* 118: 1619, 2008.
82. Baruch L, Patacsil P, Hameed A, et al: Pharmacodynamic effects of milrinone with and without a bolus loading infusion. *Am Heart J* e6:141, 2000.
83. Givertz MM, Hare JM, Loh E, et al: Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: A rapid test for reversibility of pulmonary hypertension. *J Am Coll Cardiol* 28:1775, 1996.
84. Yano M, Kohno M, Ohkusa T, et al: Effect of milrinone on left ventricular relaxation and Ca<sup>2+</sup> uptake function of cardiac sarcoplasmic reticulum. *Am J Physiol* 279:H1898, 2000.
85. Tanigawa T, Yano M, Kohno M, et al: Mechanism of preserved positive lusitropy by cAMP-dependent drugs in heart failure. *Am J Physiol* 278:H313, 2000.
86. Hatzizacharias A, Makris T, Krespi P, et al: Intermittent milrinone effect on long-term hemodynamic profile in patients with severe congestive heart failure. *Am Heart J* 138:241, 1999.
87. Milfred-LaForest SK, Shubert J, Mendoza B, et al: Tolerability of extended duration intravenous milrinone in patients hospitalized for advanced heart failure and the usefulness of uptitration of oral angiotensin-converting enzyme inhibitors. *Am J Cardiol* 84:894, 1999.
88. Ewy GA: Inotropic infusions for chronic congestive heart failure. Medical miracles or misguided medicinal? *J Am Coll Cardiol* 33:572, 1999.
89. Cesario D, Clark J, Maisel A: Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: A preliminary study. *Am Heart J* 135:121, 1998.
90. Mehra MR, Ventura HO, Kapoor C, et al: Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 80:61, 1997.
91. Canver CC, Chanda J: Milrinone for long-term pharmacologic support of the status of heart transplant candidates. *Ann Thorac Surg* 69:1823, 2000.
92. Cusick DA, Pfeifer PB, Quigg RJ: Effects of intravenous milrinone followed by titration of high-dose oral vasodilator therapy on clinical outcome and rehospitalization rates in patients with severe heart failure. *Am J Cardiol* 82:1060, 1998.
93. Cuffe MS, Califf RM, Adams KF Jr. et al: Short-term intravenous milrinone for acute exacerbation of chronic heart failure. A randomized, controlled trial. *JAMA* 287:1541, 2002.
94. Lowes BD, Higginbotham M, Petrovich L, et al: Low-dose enoximone improves exercise capacity in chronic heart failure. *J Am Coll Cardiol* 36:501, 2000.
95. Shakar SF, Bristow MR: Low-level inotropic stimulation with type III phosphodiesterase inhibitors in patients with advanced symptomatic chronic heart failure receiving  $\beta$ -blocking agents. *Curr Cardiol Rep* 3:224, 2001.
96. Metra M. ESSENTIAL: the Studies of Oral Enoximone Therapy in Advanced Heart Failure. Presented at: European Society of Cardiology Congress; September 5–8, 2005; Stockholm, Sweden: Late Breaking Clinical Trials.
97. Cavaşoglu E, Frishman WH, Klapholz M: Vesnarinone: A new inotropic agent for treating congestive heart failure. *J Card Fail* 1:249, 1995.
98. Matsumori A, Shioi T, Yamada T, et al: Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. *Circulation* 89:955, 1994.
99. OPC 8212 Multicenter Research Group: A placebo-controlled, randomized, double-blind study of OPC 8212 in patients with mild chronic heart failure. *Cardiovasc Drugs Ther* 4:419, 1990.
100. Feldman AM, Bristow MR, Parmley WW, et al for the Vesnarinone Study Group: Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 329:149, 1993.
101. Cohn JN, Goldstein SO, Greenberg BH et al: A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 339:1810, 1998.
102. Sugiyama A, Satoh Y, Hashimoto K: Electropharmacologic effects of a new phosphodiesterase III inhibitor, toborinone (OPC-18790), assessed in an in vivo canine model. *J Cardiovasc Pharmacol* 38:268, 2001.
103. Yu Y, Mizushige K, Ueda T, et al: Effect of olprinone, phosphodiesterase III inhibitor, on cerebral blood flow assessed with technetium-99m-ECD SPECT. *J Cardiovasc Pharmacol* 35:422, 2000.
104. Slawsky MT, Colucci WS, Gottlieb SS, et al: Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. *Circulation* 102:2222, 2001.
105. Kivikko M, Lehtonen L, Colucci WS, et al. Sustained hemodynamic effects of intravenous levosimendan. *Circulation* 2003;107:81-6.
106. Fuhrmann JT, Schmeisser A, Schulze MR, et al: Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 36: 2257, 2008.
107. Russ MA, Prondzinsky R, Christoph A, et al: Hemodynamic improvement following levosimendan

- treatment in patients with acute myocardial infarction and cardiogenic shock. *Crit Care Med* 35: 2732, 2007.
108. Lehtonen L: Levosimendan: A promising agent for the treatment of hospitalized patients with decompensated heart failure. *Curr Cardiol Rep* 2:233, 2000.
  109. Figgitt DP, Gillies PS, Goa KL: Levosimendan. *Drugs* 61:613, 2001.
  110. Folláth F, Hinkka S, Jäger D, et al: Dose-ranging and safety with intravenous levosimendan in low-output heart failure: Experience in three pilot studies and outline of the levosimendan infusion versus dobutamine (LIDO) trial. *Am J Cardiol* 83:211, 1999.
  111. Ukkonen H, Saraste M, Akkila J, et al: Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clin Pharmacol Ther* 68:522, 2000.
  112. Harjola V-P, Peuhkurinen K, Nieminen MS, et al: Oral levosimendan improves cardiac function and hemodynamics in patients with severe congestive heart failure. *Am J Cardiol* 83:4I, 1999.
  113. Nijhawan N, Nicolosi AC, Montgomery MW, et al: Levosimendan enhances cardiac performance after cardiopulmonary bypass: A prospective, randomized placebo-controlled trial. *J Cardiovasc Pharmacol* 34:219, 1999.
  114. Hosenpud JD, for the Oral Levosimendan Study Group: Levosimendan, a novel myofilament calcium sensitizer, allows weaning of parenteral inotropic therapy in patients with severe congestive heart failure. *Am J Cardiol* 83:9I, 1999.
  115. Follath F, Cleland JGF, Just H, et al: Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomised double-blind study. *Lancet* 360:196, 2002.
  116. Moiseyev VS, Pöder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J* 23:1422, 2002.
  117. Lehtonen L, Pöder P: The utility of levosimendan in the treatment of heart failure. *Ann Med* 39: 2, 2007.
  - 117a. REVIVE-II summary data. <http://www.cardiosource.com/pops/trialSum.asp?trialID=1378>; accessed February 17, 2010.
  118. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA* 297:1883, 2007.
  119. Fujimoto S, Matsuda T. Effects of pimobendan, a cardiotonic and vasodilating agent with phosphodiesterase inhibiting properties, on isolated arteries and veins of rats. *J Pharmacol Exp Ther* 1990; 252(3): 1304-11.
  120. Matsui K, Kiyosue T, Wang JC, et al. Effects of pimobendan on the L-type Ca<sup>2+</sup> current and developed tension in guinea-pig ventricular myocytes and papillary muscle: comparison with IBMX, milrinone, and cilostazol. *Cardiovasc Drugs Ther* 13:105, 1999.
  121. Kuriya S, Ohmori S, Hino M, et al. Identification of cytochrome P-450 isoform(s) responsible for the metabolism of pimobendan in human liver microsomes. *Drug Metab Dispos* 28:73, 2000.
  122. Chu KM, Shieh SM, Hu OY. Pharmacokinetics and pharmacodynamics of enantiomers of pimobendan in patients with dilated cardiomyopathy and congestive heart failure after single and repeated oral dosing. *Clin Pharmacol Ther* 57: 610, 1995.
  123. Chu KM, Shieh SM, Hu OY. Pharmacokinetics and pharmacodynamics of enantiomers of pimobendan in patients with dilated cardiomyopathy and congestive heart failure after single and repeated oral dosing. *Clin Pharmacol Ther* 57: 610, 1995.
  124. Hagemeyer F. Calcium sensitization with pimobendan: pharmacology, haemodynamic improvement, and sudden death in patients with chronic congestive heart failure. *Eur Heart J* 14:551, 1993.
  125. Sasayama S, Asanoi H, Kihara Y, et al. Clinical effects of long-term administration of pimobendan in patients with moderate congestive heart failure. *Heart Vessels* 9:113, 1994.
  126. Katz SD, Kubo SH, Jessup M, et al. A multicenter, randomized, double-blind, placebo-controlled trial of pimobendan, a new cardiotonic and vasodilator agent, in patients with severe congestive heart failure. *Am Heart J* 123:95, 1992.
  127. Kubo SH, Gollub S, Bourge R, et al. Beneficial effects of pimobendan on exercise tolerance and quality of life in patients with heart failure: results of a multicenter trial. The Pimobendan Multicenter Research Group. *Circulation* 85:942, 1992.
  128. The Pimobendan in Congestive Heart Failure (PICO) investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 76:223, 1996.
  129. The EPOCH study group. Effects of pimobendan on adverse cardiac events and physical activities in patients with mild to moderate chronic heart failure – The Effects of Pimobendan on Chronic Heart Failure Study (EPOCH Study). *Circ J* 66:149, 2002.
  130. Sasaki T, Kubo T, Komamura K, Nishikimi T. Effects of long-term treatment with pimobendan on neurohormonal factors in patients with non-ischemic chronic moderate heart failure. *J Cardiol* 33:317, 1999.
  131. Iwasaki A, Matsumori A, Yamada T, et al: Pimo-

- bendan inhibits the production of proinflammatory cytokines and gene expression of inducible nitric oxide synthase in a murine model of viral myocarditis. *J Am Coll Cardiol* 33:1400, 1999.
132. Dorigo P, Floreani M, Santostasi G, et al: Pharmacological characterization of a new Ca<sup>2+</sup>sensitizer. *J Pharmacol Exp Ther* 295:994, 2000.
  133. Brixius K, Reicke S, Reuter H, Schwinger RH. Effects of the Ca<sup>2+</sup> sensitizers EMD 57033 and CGP 48506 on myocardial contractility and Ca<sup>2+</sup> transients in human ventricular and atrial myocardium. *Z Kardiol* 91:312,2002
  134. Yang G, Liu L, Xu J, Li T. Effects of MCI-154 on vascular reactivity and its mechanisms after hemorrhagic shock in rats. *J Cardiovasc Pharmacol* 47:751, 2006.
  135. Müller-Ehmsen J, Brixius K, Schwinger RHG: Positive inotropic effects of a novel Na<sup>+</sup>-channel modulator BDF 9198 in human nonfailing and failing myocardium. *J Cardiovasc Pharmacol* 31:684, 1998.
  136. Doggrel S.A.: Effects of BDF 9198 on left ventricular contractility in advanced spontaneously hypertensive rats with heart failure. *J Pharmacy Pharmacol* 54: 1097, 2002.
  137. Satoh N, Sato T, Shimada M, et al. Lusitropic effect of MCC-135 is associated with improvement of sarcoplasmic reticulum function in ventricular muscles of rats with diabetic cardiomyopathy. *J Pharm Exper Ther*298:1161, 2001.
  138. Kawasumi H, Satoh N, Kitada Y: Caldaret, an intracellular Ca<sup>2+</sup> handling modulator, limits infarct size of reperfused canine heart. *J Pharmacol Sci* 103: 222, 2007.
  139. Bär FW, Tzivoni D, Dirksen MT, et al. Results of the first clinical study of adjunctive Caldaret (MCC-135) in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: the randomized multicentre CASTEMI study. *Eur Heart J* 27:2516,2006.
  140. Tzivoni D, Balkin J, Bär FW, et al: Effect of Caldaret on the incidence of severe left ventricular dysfunction in patients with ST-elevation myocardial infarction undergoing primary coronary intervention. *Am J Cardiol* 103; 1,2009.
  141. Shah SJ, Blair JEA, Filippatos GS, et al for the HORIZON-HF Investigators: Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: results from the hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure (HORIZON-HF) trial. *Am Heart J* 157: 1035, 2009.
  142. Micheletti R, Mattera GG, Rocchetti M, et al. Pharmacological profile of the novel inotropic agent (E,Z)-3-((2-aminoethoxy)imino)androstane-6,17-dione hydrochloride (PST2744). *J Pharm Exp Thera* 303:592,2002.
  143. Adamson PB, Vanoli E, Mattera GG, et al. Hemodynamic effects of a new inotropic compound, PST-2744, in dogs with chronic ischemic heart failure. *J Cardiovasc Pharmacol* 42:169,2003.
  144. Gheorghide M, Blair JEA, Filippatos GS, et al. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent. *J Am Coll Cardiol* 51:2276,2008.
  145. McMurray J, Pfeffer MA: New therapeutic options in congestive heart failure, Part II. *Circulation* 105:2223, 2002.
  146. Maurice JP, Hata JA, Shah AS, et al: Enhancement of cardiac function after adenoviral-mediated in vivo intracoronary  $\beta_2$ -adrenergic receptor gene delivery. *J Clin Invest* 104:21, 1999.
  147. Weig H-J, Laugwitz K-L, Moretti A, et al: Enhanced cardiac contractility after gene transfer of V2 vasopressin receptors in vivo by ultrasound-guided injection or transcatheter delivery. *Circulation* 101:1578, 2000.
  148. del Monte F, Harding SE, Schmidt U, et al: Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. *Circulation* 100:2308, 1999.
  149. del Monte F, Williams E, Lebeche D, et al: Improvement in survival and cardiac metabolism after gene transfer of sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase in a rat model of heart failure. *Circulation* 104:1424, 2001.
  150. Sakata S, Lebeche D, Sakata Y, et al: Transcatheter gene transfer of SERCA2a increases coronary blood flow and decreases cardiomyocyte size in a type 2 diabetic rat model. *Am J Physiol Heart Circ Physiol*. 292:H1204,2007.
  151. Sakata S, Lebeche D, Sakata N, et al: Targeted gene transfer increases contractility and decreases oxygen cost of contractility in normal rat hearts. *Am J Physiol Heart Circ Physiol*. 292:H2356,2007.
  152. Sakata S, Lebeche D, Sakata N, et al: Restoration of mechanical and energetic function in failing aortic-banded rat hearts by gene transfer of calcium cycling proteins. *J Mol Cell Cardiol*. 42:852,2007.
  153. Calcium Up-Regulation by Percutaneous Administration of Gene therapy In Cardiac Disease (CUPID Trial) -Presented at American Heart Association Meeting 2008. *J Card Fail* 14:355,2008.
  154. Late Breaking Clinical Trials. *Circulation* 118:2309,2008.
  155. Leri A, Anversa P, Frishman WH: *Cardiovascular Regeneration and Stem Cell Therapy*. UK: Blackwell