Vascular Pharmacology 52 (2010) 138–141

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Thyroid hormone and chronically unloaded hearts

Kenta Ito [a], Yutaka Kagaya [b,*], Hiroaki Shimokawa [a]

[a] Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[b] Graduate Medical Education Center, Tohoku University Hospital, Sendai, Japan

ARTICLE INFO

Article history:
Received 15 September 2009
Accepted 9 October 2009

Keywords:
Cardiac unloading
Thyroid hormone
Calcium handling

ABSTRACT

The heart is subjected to chronic mechanical unloading during prolonged spaceflight and microgravity. The heart in patients with end-stage heart failure is also unloaded in prolonged duration after left ventricular assist devices (LVAD) are implanted. Heterotopic heart transplantation in rats is an established model of chronic cardiac unloading, and has been used to investigate the effects of chronic cardiac unloading on the heart. Observations that have been found using this experimental model are as follow. Chronic cardiac unloading induces time-dependent depressions of Ca^{2+} handling and myocyte contractility, which are associated with the shift of myosin heavy chain (MHC) isozymes and altered expressions of Ca^{2+} cycling-related proteins. Treatment with the physiological treatment dose of thyroid hormone restores the expression levels of Ca^{2+} cycling-related proteins, Ca^{2+} handling, and contractile function of cardiac myocytes in chronically unloaded hearts. Although future studies are required to determine precise mechanisms of the beneficial effects of thyroid hormone on chronically unloaded hearts, these observations may have clinical implications in the future for chronic cardiac unloading in the space industry as well as in the treatment of patients with end-stage heart failure supported by LVAD.

Contents

1. Introduction

The cardiovascular system is subjected to chronic mechanical unloading during prolonged spaceflight and microgravity (Bungo et al., 1987; Goldstein et al., 1992; Martin et al., 2002). The heart in patients with end-stage heart failure is also unloaded in prolonged duration when left ventricular assist devices (LVAD) are implanted (Hunt and Frazier, 1998; Burkhoff et al., 2006). The effects of left ventricular (LV) pressure overload on gene expression and contractile function of the heart have been extensively studied in animals and humans (Kagaya et al., 1996; Hasenfuss, 1998; Hunter and Chien, 1999; Ito et al., 2000; Faber et al., 2006). However, although it is reported that chronically unloaded hearts replicate fetal gene expressions of cardiac hypertrophy (Depre et al., 1998), little was known about contractile function of the normal hearts subjected to chronic LV unloading (Welsh et al., 2001; Ito et al., 2003). Using heterotopic heart transplantation in rats as an established model of cardiac unloading, we previously demonstrated that chronic cardiac unloading induces time-dependent depressions of myocyte contractility and calcium handling (Ito et al., 2003). We also demonstrated that the treatment with physiological treatment dose of thyroid hormone rescues impaired relaxation and depressed contractile reserve of cardiac myocytes in chronically unloaded hearts (Minatoya et al., 2007). In this article, we review the effects of long-term mechanical unloading on calcium handling and contractile function of cardiac myocytes. We also discuss the beneficial effects of thyroid hormone in such condition and its possible clinical application.

* Corresponding author. Graduate Medical Education Center, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai, 980-8574, Japan. Tel.: +81 22 717 7765, fax: +81 22 717 7143.
E-mail address: kagaya@m.tains.tohoku.ac.jp (Y. Kagaya).

1537-1891/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.vph.2009.10.004

2. Effects of chronic cardiac unloading on contractile performance

The heart is subjected to prolonged mechanical unloading during long-term spaceflight because of microgravity. The heart of patients with end-stage heart failure who are supported by LVAD is also unloaded in prolonged duration. Heterotopic heart transplantation in rats is an established experimental model of cardiac unloading (Ono and Lindsey, 1969). Briefly, the ascending aorta of the donor is anastomosed end-to-side on the abdominal aorta of the recipient, and the pulmonary artery of the donor is anastomosed end-to-side on the inferior vena cava of the recipient. The donor heart is perfused through the coronary arteries. Although the heart beats, the left ventricle is kept unloaded and flaccid. In this experimental model of cardiac unloading, both recipient hearts and transplanted unloaded hearts are perfused with the same arterial blood. The effects of cardiac unloading on systolic and diastolic functions have been investigated in different experimental conditions in terms of the duration of unloading as well as the methods to measure cardiac performance. Welsh et al. (2001) reported that both contraction and relaxation of isolated cardiac myocytes and papillary muscles were intact after 2-week cardiac unloading although the size of cardiac myocytes was significantly reduced due to cardiac atrophy. However, they argued that, in the absence of compensatory increases in contractile performance, reductions in myocyte mass would lead to impaired overall work capacity of the heart. Kolár et al. (1993) investigated the effect of 3-, 14-, and 28-day cardiac unloading on the systolic and diastolic functions using isolated heart preparations with isovolumic contraction. Within 3, 14, and 28 days after cardiac unloading, the mass of transplanted left ventricles was decreased to 84, 54, and 43% compared with the corresponding recipient hearts, respectively. Although the developed pressure, maximum rate of pressure development, and the slope of the systolic stress–strain relation were unaffected in the transplanted atrophic ventricles, the rate of relaxation was significantly decreased.

We investigated the effects of chronic cardiac unloading on both Ca^{2+} handling and contractile performance in rats (Ito et al., 2003). Cardiac unloading and reductions in LV mass were induced by heterotopic heart transplantation to the abdominal aorta in isogenic rats. Native in situ hearts from recipient animals were used as the controls. Contractility and intracellular calcium regulation in LV myocytes were studied at both 2 and 5 weeks after transplantation. Both myocyte relaxation and intracellular calcium decay were slower in 5-week unloaded hearts compared to recipient hearts, but not in 2-week unloaded hearts. Contractile reserve in response to high extracellular calcium was depressed in 5-week unloaded hearts, but not in 2-week unloaded hearts. In addition, LV protein levels of phospholamban (PLB) were increased in 5-week unloaded hearts, but not in 2-week unloaded hearts, while protein levels of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) were not changed. These alterations in protein levels led to the markedly reduced SERCA2a-to-PLB protein ratio, which is a major determinant of cardiac contractile performance and sarcoplasmic reticulum (SR) Ca^{2+}-uptake function (Brittsan and Kranias, 2000), in 5-week unloaded hearts compared with recipient hearts predominantly due to the increase in PLB expression levels. The PLB is phosphorylated at Ser-16 and Thr-17, and inhibits SR Ca^{2+} uptake function of SERCA2a in its unphosphorylated state (Hagemann and Xiao, 2002). We recently reported that chronic cardiac unloading suppresses PLB phosphorylation at both Ser-16 and Thr-17 (Minatoya et al., 2007). Therefore, both the reduced SERCA2a-to-PLB protein ratio and the suppressed PLB phosphorylation may explain the impaired calcium handling in cardiac myocytes isolated from 5-week unloaded hearts (Fig. 1). This notion is strongly supported by the report of Korecky et al. (1986) who found reduced SR Ca^{2+} uptake activity in membrane fractions enriched with SR vesicles in 8-week unloaded hearts compared with corresponding native hearts using the same rat model of cardiac unloading.

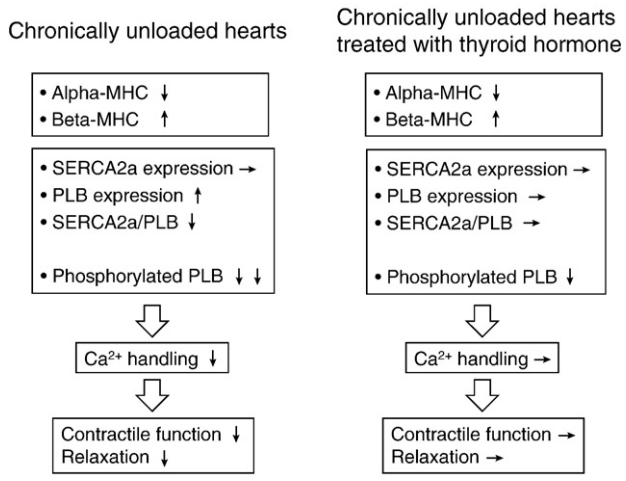

Fig. 1. Alterations in the expression levels of myosin heavy chain (MHC) isoforms and Ca^{2+} cycling-related proteins, Ca^{2+} handling, and contractile function in chronically unloaded hearts with and without the treatment with thyroid hormone: Chronic cardiac unloading is associated with the increased expression levels of beta-MHC and phospholamban (PLB), decreased expression levels of alpha-MHC, and decreased sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a)-to-PLB ratio. Ca^{2+} handling is impaired and contractile function is deteriorated in chronically unloaded hearts without the treatment with thyroid hormone. Treatment with the physiological treatment dose of thyroid hormone normalizes the expression levels of PLB and SERCA2a-to-PLB ratio, but not the MHC isoform shift. Both Ca^{2+} handling and contractile function are normalized in chronically unloaded hearts treated with the physiological treatment dose of thyroid hormone.

We and others also have reported that cardiac unloading induces isoform shift from alpha-myosin heavy chain (MHC) to beta-MHC (Depre et al., 1998; Minatoya et al., 2007). As beta-MHC has slower ATPase activity than alpha-MHC does (Bárány, 1967; Pope et al., 1980), the impaired contractile performance in cardiac myocytes isolated from unloaded donor hearts compared with recipient hearts (Ito et al., 2003; Minatoya et al., 2007) might be explained partially by the isoform shift from alpha-MHC to beta-MHC in chronically unloaded hearts. Taken together, both impaired calcium handling and MHC isoform shift would be, at least in part, the mechanisms for the time-dependent deterioration of contractile performance in chronically unloaded hearts.

The reduced myocyte contractile reserve and depressed SERCA2a-to-PLB protein ratio in chronically unloaded hearts are similarly observed in hypertrophied failing hearts induced by long-term pressure overload (Ito et al., 2000). However, there are differences in the alterations in the expressions of calcium cycling-related proteins between unloaded hearts and hypertrophied failing hearts. Namely, the reduced SERCA2a-to-PLB ratio was mainly due to the increase in PLB protein levels and was not accompanied by a decrease in SERCA2a protein levels in unloaded hearts while both a decrease in SERCA2a protein levels and an increase in PLB protein levels were observed in hypertrophied failing hearts (Hasenfuss, 1998).

We found that the expressions of Ca^{2+} cycling-related proteins and MHC isoforms are altered in hearts with prolonged cardiac unloading, and that the contractile performance is deteriorated. These results implicate that humans that are subjected to extremely prolonged cardiac unloading in space because of microgravity as well as patients with excessive long-term cardiac unloading due to support by LVAD may suffer from a similar unfavorable condition. Echocardiographic studies by others in astronauts before and after spaceflight revealed decreased ejection fraction and increased left ventricular end-systolic volume after the spaceflight in long-duration crewmembers but not in short-duration crewmembers (Martin et al., 2002), although precise mechanisms of the impaired left ventricular performance are not clear. Although LVAD are primarily used as a bridge to cardiac transplantation, successful weaning and removal of LVAD

have frequently been reported (Kumpati et al., 2001; Birks et al., 2004; Wohlschlaeger et al., 2005). It is not uncommon, however, that recurrent cardiac dysfunction results in a re-implantation of LVAD or heart transplantation after successful weaning and removal of LVAD (Helman et al., 2000; Hetzer et al., 2001; Farrar et al., 2002; Dandel et al., 2005). Mechanisms for the recurrent cardiac dysfunction in these patients are not fully understood, neither. Although it is possible that the results of our animal experiments using transplanted unloaded hearts explain partially these findings in the clinical setting, future studies are required to clarify the mechanisms of impaired cardiac performance after prolonged spaceflight as well as those of recurrent cardiac dysfunction after successful weaning and removal of LVAD.

3. Effects of thyroid hormone on chronically unloaded hearts

Alterations in thyroid hormone metabolism accompany various heart diseases such as chronic heart failure and acute myocardial infarction (Klein and Danzi, 2007). Altered thyroid function also leads to the change in vascular resistance, rhythm disturbances of the heart, and impaired lipid metabolism (Klein and Ojamaa, 2001; Dillmann, 2002; Klein and Danzi, 2007). Thyroid hormone is known to improve cardiac contractility by positively regulating SERCA2a and alpha-MHC and by negatively regulating PLB and beta-MHC (Carr and Kranias, 2002). Chang et al. (1997) investigated the effect of thyroid hormone (T4) on hypertrophied hearts induced by long-term pressure overload in rats, and found that T4 improved function of the hypertrophied left ventricle, which was associated with increased concentrations of alpha-MHC and SERCA proteins. Ojamaa et al. (2000) treated rats with thyroid hormone (T3) after acute myocardial infarction induced by coronary artery ligation, and found that the treatment with T3 normalized the mRNA expression levels of alpha-MHC, beta-MHC, and the SERCA2-to-PLB ratio in non-infarcted hypertrophied myocardium. Cardio-protective effects of thyroid hormone have also been demonstrated in a myocardial ischemia and reperfusion model, the mechanisms of which include those similar to ischemic preconditioning (Pantos et al., 2002) and the prevention of apoptosis (Pantos et al., 2009).

As mentioned in the previous chapter, depressed contractile performance induced by chronic cardiac unloading is explained partially at least by impaired calcium handling and MHC isoform shift. Since the past studies demonstrated that thyroid hormone could improve cardiac performance by reversing the impaired expressions of calcium cycling-related proteins and MHC isoform shift in both normal and failing hearts (Chang et al., 1997; Ojamaa et al., 2000; Klein and Ojamaa, 2001; Pantos et al., 2004; Trivieri et al., 2006), we attempted to prevent the LV unloading-induced myocardial dysfunction with pharmacological intervention using thyroid hormone. Cardiac unloading was induced by heterotopic heart transplantation in isogenic rats for 5 weeks, and the animals were treated with vehicle or a low-dose of 3,5,3′-triiodo-L-thyronine (T3; 1.2 μg/day) that does not cause hyperthyroidism using an osmotic pump for the last 3 weeks. In vehicle-treated animals, myocyte relaxation and intracellular calcium decay were slower in unloaded hearts than in recipient hearts. Contractile reserve of myocytes in response to high extracellular calcium was also depressed with impaired augmentation of peak-systolic calcium in unloaded hearts compared with recipient hearts. In contrast, in the T3-treated animals, the slower relaxation, delayed calcium decay, and the depressed contractile reserve in unloaded hearts were all returned to normal levels. SERCA2-to-PLB ratio, which is a major determinant of SR Ca^{2+} ATPase function and cardiac contractile performance, was severely depressed in unloaded hearts in the control group, and was almost completely normalized by the treatment with T3. The normalization of SERCA2-to-PLB ratio by the treatment with T3 was predominantly due to a decrease in the expression of PLB. Moreover, the decreased expression of Ser 16-phosphorylated PLB in unloaded hearts, which elicits the suppression of SERCA2a function, was ameliorated by the treatment with this dose of T3 (Minatoya et al., 2007) (Fig. 1).

The decreased expression of Ser 16-phosphorylated PLB and no change in that of Thr 17-phosphorylated PLB have also been reported by Brixius et al. (2003) in myocardium from patients with dilated cardiomyopathy when compared with non-failing hearts. Furthermore, Zinman et al. (2006) reported that thyroid hormone increased Ser 16-phosphorylation of PLB, which was predominantly induced by cyclic AMP dependent protein kinase A (PKA) in cardiac myocytes. Therefore, it is plausible that the physiological treatment dose of T3 employed in our study increased PKA activity, and maintained Ser 16-phosphorylated state of PLB. In our study, T3 treatment did not affect the isoform profile of MHC protein levels although thyroid hormone is reported to increase the expression of alpha-MHC and to decrease that of beta-MHC (Ojamaa et al., 1992). These data suggest that the dose of T3 employed in our study (1.2 μg/day) was too low to elicit an increase in the proportion of alpha-MHC as compared with the established dose (>2.5 μg/day) that has been demonstrated to alter the MHC isoform profile (Danzi and Klein, 2005). It is also possible that the effect of LV unloading in our experimental condition overcame that of T3 in terms of the alteration in the isoform profile of MHC. Thyroid hormone is also reported to enhance cardiac performance by inducing LV hypertrophy (Degens et al. 2003). However, the treatment with the physiological treatment dose of T3 did not alter the LV weight/body weight ratio in either recipient or unloaded hearts in our study. Therefore, neither MHC isoform shift nor induction of LV hypertrophy explains the beneficial effects of this dose of T3 on unloaded hearts.

The beneficial effects of thyroid hormone on relaxation and contractile reserve in cardiac myocytes from unloaded hearts, therefore, are mainly due to restoration of calcium handling by normalizing the expression of PLB protein and its phosphorylation state. This notion is consistent with the past reports, which demonstrated that the overexpression of PLB impairs myocyte contractility while both the ablation of PLB and increased phosphorylation of PLB accelerate contractile performance (Brittsan and Kranias, 2000; MacLennan and Kranias, 2003; Antoons et al., 2006).

In the model of cardiac unloading using heterotopic heart transplantation, we have not studied the effects of thyroid hormone on the expression of its receptors (Kinugawa et al., 2001; Pantos et al., 2005), or cardio-protective signaling such as anti-apoptotic Akt pathway, heat shock proteins, and protein kinase C (Pantos et al., 2008). Lack of experiments to determine systolic and diastolic function of unloaded whole hearts with and without the treatment with thyroid hormone may be another limitation of our study, and should be investigated in a future study.

Yacoub's group (Barton et al., 2005; Birks et al., 2006) reported that a combined therapy of LVAD support and pharmacotherapy using beta-2 adrenergic agonist clebuterol successfully improved the rate of LVAD removal without the need for a re-implantation of LVAD or heart transplantation. Although precise mechanisms of the beneficial effects of clebuterol are not clear, Tsuneyoshi et al. (2005) demonstrated that clebuterol improved the papillary muscle function of unloaded normal hearts using the same animal models as ours. In this regard, a combined therapy of LVAD and the physiological treatment dose of T3 might also provide a novel strategy to treat patients with end-stage heart failure.

4. Conclusions

Prolonged cardiac unloading is associated with the altered expression levels of Ca^{2+} cycling-related proteins, MHC isoform shift, and deteriorated cardiac performance. The treatment with the physiological treatment dose of thyroid hormone has a potential to restore calcium handling and contractile performance in chronically

unloaded hearts although future studies are required to determine another possible mechanisms of the beneficial effect of thyroid hormone on unloaded hearts. These observations may have clinical implications in the future for chronic cardiac unloading in the space industry as well as in the treatment of patients with end-stage heart failure supported by LVAD.

Acknowledgments

This work was supported in part by the Grants-in-Aid (15590715, 19590801) from the Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

References

Antoons, G., Vangheluwe, P., Volders, P.G., Bito, V., Holemans, P., Ceci, M., Wuytack, F., Caroni, P., Mubagwa, K., Sipido, K.R., 2006. Increased phospholamban phosphorylation limits the force-frequency response in the MLP−/− mouse with heart failure. J. Mol. Cell. Cardiol. 40, 350–360.

Bárány, M., 1967. ATPase activity of myosin correlated with speed of muscle shortening. J. Gen. Physiol. 50, 197–218 Suppl.

Barton, P.J., Felkin, L.E., Birks, E.J., Cullen, M.E., Banner, N.R., Grindle, S., Hall, J.L., Miller, L.W., Yacoub, M.H., 2005. Myocardial insulin-like growth factor-I gene expression during recovery from heart failure after combined left ventricular assist device and clenbuterol therapy. Circulation 112, I46–I50 Suppl.

Birks, E.J., Yacoub, M.H., Banner, N.R., Khaghani, A., 2004. The role of bridge to transplantation: should LVAD patients be transplanted? Curr. Opin. Cardiol. 19, 148–153.

Birks, E.J., Tansley, P.D., Hardy, J., George, R.S., Bowles, C.T., Burke, M., Banner, N.R., Khaghani, A., Yacoub, M.H., 2006. Left ventricular assist device and drug therapy for the reversal of heart failure. N. Engl. J. Med. 355, 1873–1884.

Brittsan, A.G., Kranias, E.G., 2000. Phospholamban and cardiac contractile function. J. Mol. Cell. Cardiol. 32, 2131–2139.

Brixius, K., Wollmer, A., Bölck, B., Mehlhorn, U., Schwinger, R.H., 2003. Ser16-, but not Thr17-phosphorylation of phospholamban influences frequency-dependent force generation in human myocardium. Pflugers Arch. 447, 150–157.

Bungo, M.W., Goldwater, D.J., Popp, R.L., Sandler, H., 1987. Echocardiographic evaluation of space shuttle crew members. J. Appl. Physiol. 62, 278–283.

Burkhoff, D., Klotz, S., Mancini, D.M., 2006. LVAD-induced reverse remodeling: basic and clinical implications for myocardial recovery. J. Card. Fail. 12, 227–239.

Carr, A.N., Kranias, E.G., 2002. Thyroid hormone regulation of calcium cycling proteins. Thyroid 12, 453–457.

Chang, K.C., Figueredo, V.M., Schreur, J.H., Kariya, K., Weiner, M.W., Simpson, P.C., Camacho, S.A., 1997. Thyroid hormone improves function and Ca^{2+} handling in pressure overload hypertrophy. Association with increased sarcoplasmic reticulum Ca^{2+}-ATPase and alpha-myosin heavy chain in rat hearts. J. Clin. Invest. 100, 1742–1749.

Dandel, M., Weng, Y., Siniawski, H., Potapov, E., Lehmkuhl, H.B., Hetzer, R., 2005. Long-term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. Circulation 112, 137–145 Suppl.

Danzi, S., Klein, I., 2005. Posttranscriptional regulation of myosin heavy chain expression in the heart by triiodothyronine. Am. J. Physiol. 288, H455–H460.

Degens, H., Gilde, A.J., Lindhout, M., Willemsen, P.H., Van Der Vusse, G.J., Van Bilsen, M., 2003. Functional and metabolic adaptation of the heart to prolonged thyroid hormone treatment. Am. J. Physiol. Heart Circ. Physiol. 284, H108–115.

Depre, C., Shipley, G.L., Chen, W., Han, Q., Doenst, T., Moore, M.L., Stepkowski, S., Davies, P.J., Taegtmeyer, H., 1998. Unloaded heart in vivo replicates fetal gene expression of cardiac hypertrophy. Nat. Med. 4, 1269–1275.

Dillmann, W.H., 2002. Cellular action of thyroid hormone on the heart. Thyroid 12, 447–452.

Faber, M.J., Agnetti, G., Bezstarosti, K., et al., 2006. Recent developments in proteomics: implications for the study of cardiac hypertrophy and failure. Cell Biochem. Biophys. 44, 11–29.

Farrar, D.J., Holman, W.R., McBride, L.R., Kormos, R.L., Icenogle, T.B., Hendry, P.J., Moore, C.H., Loisance, D.Y., El-Banayosy, A., Frazier, H., 2002. Long-term follow-up of Thoratec ventricular assist device bridge-to-recovery patients successfully removed from support after recovery of ventricular function. J. Heart Lung Transplant. 21, 516–521.

Goldstein, M.A., Edwards, R.J., Schroeter, J.P., 1992. Cardiac morphology after conditions of microgravity during COSMOS 2044. J. Appl. Physiol. 73, 94S–100S.

Hagemann, D., Xiao, R.P., 2002. Dual site phospholamban phosphorylation and its physiological relevance in the heart. Trends Cardiovasc. Med. 12, 51–56.

Hasenfuss, G., 1998. Alterations of calcium-regulatory proteins in heart failure. Cardiovasc. Res. 37, 279–289.

Helman, D.N., Maybaum, S.W., Morales, D.L., Williams, M.R., Beniaminovitz, A., Edwards, N.M., Mancini, D.M., Oz, M.C., 2000. Recurrent remodeling after ventricular assistance: is long-term myocardial recovery attainable? Ann. Thorac. Surg. 70, 1255–1258.

Hetzer, R., Muller, J.H., Weng, Y., Meyer, R., Dandel, M., 2001. Bridging-to-recovery. Ann. Thorac. Surg. 71, S109–S113.

Hunt, S.A., Frazier, O.H., 1998. Mechanical circulatory support and cardiac transplantation. Circulation 97, 2079–2090.

Hunter, J.J., Chien, K.R., 1999. Signaling pathways for cardiac hypertrophy and failure. N. Engl. J. Med. 341, 1276–1283.

Ito, K., Yan, X., Tajima, M., Su, Z., Barry, W.H., Lorell, B.H., 2000. Contractile reserve and intracellular calcium regulation in mouse myocytes from normal and hypertrophied failing hearts. Circ. Res. 87, 588–595.

Ito, K., Nakayama, M., Hasan, F., Yan, X., Schneider, M.D., Lorell, B.H., 2003. Contractile reserve and calcium regulation are depressed in myocytes from chronically unloaded hearts. Circulation 107, 1176–1182.

Kagaya, Y., Hajjar, R.J., Gwathmey, J.K., Barry, W.H., Lorell, B.H., 1996. Long-term angiotensin-converting enzyme inhibition with fosinopril improves depressed responsiveness to Ca^{2+} in myocytes from aortic-banded rats. Circulation 94, 2915–2922.

Kinugawa, K., Yonekura, K., Ribeiro, R.C., Eto, Y., Aoyagi, T., Baxter, J.D., Camacho, S.A., Bristow, M.R., Long, C.S., Simpson, P.C., 2001. Regulation of thyroid hormone receptor isoforms in physiological and pathological cardiac hypertrophy. Circ. Res. 89, 591–598.

Klein, I., Ojamaa, K., 2001. Thyroid hormone and the cardiovascular system. N. Engl. J. Med. 344, 501–509.

Klein, I., Danzi, S., 2007. Thyroid disease and the heart. Circulation 116, 1725–1735.

Korecky, B., Ganguly, P.K., Elimban, V., et al., 1986. Muscle mechanics and Ca^{2+} transport in atrophic heart transplants in rat. Am. J. Physiol. 251, H941–H950.

Kolár, F., MacNaughton, C., Papousek, F., Korecky, B., 1993. Systolic mechanical performance of heterotopically transplanted hearts in rats treated with cyclosporin. Cardiovasc. Res. 27, 1244–1247.

Kumpati, G.S., McCarthy, P.M., Hoercher, K.J., 2001. Left ventricular assist device bridge to recovery: a review of the current status. Ann. Thorac. Surg. 71, S103–S108.

MacLennan, D.H., Kranias, E.G., 2003. Phospholamban: a crucial regulator of cardiac contractility. Nat. Rev. Mol. Cell Biol. 4, 566–577.

Martin, D.S., South, D.A., Wood, M.L., Bungo, M.W., Meck, J.V., 2002. Comparison of echocardiographic changes after short- and long-duration spaceflight. Aviat. Space Environ. Med. 73, 532–536.

Minatoya, Y., Ito, K., Kagaya, Y., Asaumi, Y., Takeda, M., Nakayama, M., Takahashi, J., Iguchi, A., Shirato, K., Shimokawa, H., 2007. Depressed contractile reserve and impaired calcium handling of cardiac myocytes from chronically unloaded hearts are ameliorated with the administration of physiological treatment dose of T3 in rats. Acta. Physiol. (Oxf) 189, 221–231.

Ojamaa, K., Samarel, A.M., Kupfer, J.M., Hong, C., Klein, I., 1992. Thyroid hormone effects on cardiac gene expression independent of cardiac growth and protein synthesis. Am. J. Physiol. 263, E534–E540.

Ojamaa, K., Kenessey, A., Shenoy, R., et al., 2000. Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. Am. J. Physiol. 279, E1319–E1324.

Ono, K., Lindsey, E.S., 1969. Improved technique of heart transplantation in rats. J. Thorac. Cardiovasc. Surg. 57, 225–229.

Pantos, C.I., Malliopoulou, V.A., Mourouzis, I.S., Karamanoli, E.P., Paizis, I.A., Steimberg, N., Varonos, D.D., Cokkinos, D.V., 2002. Long-term thyroxine administration protects the heart in a pattern similar to ischemic preconditioning. Thyroid 12, 325–329.

Pantos, C., Malliopoulou, V., Varonos, D.D., Cokkinos, D.V., 2004. Thyroid hormone and phenotypes of cardioprotection. Basic Res. Cardiol. 99, 101–120.

Pantos, C., Mourouzis, I., Saranteas, T., et al., 2005. Thyroid hormone receptors alpha1 and beta1 are downregulated in the post-infarcted rat heart: consequences on the response to ischaemia-reperfusion. Basic Res. Cardiol. 100, 422–432.

Pantos, C., Mourouzis, I., Xinaris, C., Papadopoulou-Daifoti, Z., Cokkinos, D., 2008. Thyroid hormone and "cardiac metamorphosis": potential therapeutic implications. Pharmacol. Ther. 118, 277–294.

Pantos, C., Mourouzis, I., Saranteas, T., Clavé, G., Ligeret, H., Noack-Fraissignes, P., Renard, P.Y., Massonneau, M., Perimenis, P., Spanou, D., Kostopanagiotou, G., Cokkinos, D.V., 2009. Thyroid hormone improves postischaemic recovery of function while limiting apoptosis: a new therapeutic approach to support hemodynamics in the setting of ischaemia-reperfusion? Basic Res. Cardiol. 104, 69–77.

Pope, B., Hoh, J.F., Weeds, A., 1980. The ATPase activities of rat cardiac myosin isoenzymes. FEBS Lett. 118, 205–208.

Trivieri, M.G., Oudit, G.Y., Sah, R., Kerfant, B.G., Sun, H., Gramolini, A.O., Pan, Y., Wickenden, A.D., Croteau, W., Morreale de Escobar, G., Pekhletski, R., St Germain, D., Maclennan, D.H., Backx, P.H., 2006. Cardiac-specific elevations in thyroid hormone enhance contractility and prevent pressure overload-induced cardiac dysfunction. Proc. Natl. Acad. Sci. U.S.A. 103, 6043–6048.

Tsuneyoshi, H., Oriyanhan, W., Kanemitsu, H., Shiina, R., Nishina, T., Matsuoka, S., Ikeda, T., Komeda, M., 2005. Does the beta2-agonist clenbuterol help to maintain myocardial potential to recover during mechanical unloading? Circulation 112, I51–I56 Suppl.

Welsh, D.C., Dipla, K., McNulty, P.H., Mu, A., Ojamaa, K.M., Klein, I., Houser, S.R., Margulies, K.B., 2001. Preserved contractile function despite atrophic remodeling in unloaded rat hearts. Am. J. Physiol. 281, H1131–H1136.

Wohlschlaeger, J., Schmitz, K.J., Schmid, C., Schmid, K.W., Keul, P., Takeda, A., Weis, S., Levkau, B., Baba, H.A., 2005. Reverse remodeling following insertion of left ventricular assist devices (LVAD): a review of the morphological and molecular changes. Cardiovasc. Res. 68, 376–386.

Zinman, T., Shneyvays, V., Tribulova, N., Manoach, M., Shainberg, A., 2006. Acute, nongenomic effect of thyroid hormones in preventing calcium overload in newborn rat cardiocytes. J. Cell. Physiol. 207, 220–231.