CLINICAL STUDY

Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association?

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Abstract

Objective: This study investigated whether changes in thyroid hormone (TH) in plasma are associated with the recovery of cardiac function in patients with acute myocardial infarction (AMI). Previous experimental studies have provided evidence of potential implication of TH signaling in post-ischemic recovery of cardiac function.

Methods: A total of 47 patients with AMI and early reperfusion therapy were included in this study. Myocardial injury was analyzed by peak creatinine kinase–MB (CKMB) and cardiac function was assessed by echocardiographic left ventricular ejection fraction (LVEF%). Recovery of function (Δ EF%) was estimated as the difference of LVEF% between 48 h and 6 months (6 mo) after AMI. Total triiodothyronine (T_3), thyroxine (T_4), and TSH were measured in plasma at different time points (24 h, 48 h, 5 d, and 6 mo). **Results:** A significant correlation between LVEF% and T_3 ($r=0.5$, $P=0.0004$) was found early after AMI (48 h), whereas no correlation was observed between CKMB and T_3 ($r=-0.04$, $P=0.81$). A strong correlation was found between Δ EF% and total T_3 ($r=0.64$, $P=10^{-6}$) at 6 mo after AMI. Furthermore, multivariate regression analysis revealed that T_3 at 6 mo ($r=0.64$, $r^2=0.41$, $P=10^{-6}$) was an independent determinant of Δ EF%.

Conclusion: Changes in T_3 levels in plasma are closely correlated with the early and late recovery of cardiac function after AMI. T_3 levels at 6 mo appear to be an independent predictor of late functional recovery.

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Introduction

Acute and chronic illnesses can cause changes in thyroid hormone (TH) profile, a condition known as 'non-thyroidal illness syndrome' (1–3). This syndrome affects nearly 70% of patients hospitalized with diseases of various etiologies (4). The physiological significance of this response is not fully understood, and there is a long-lasting dilemma whether this abnormality needs correction (1, 2).

Low triiodothyronine (T_3) state is common in severe chronic heart failure (5), acute myocardial infarction (AMI) (6–8), and cardiac surgery (9). Furthermore, changes in TH in plasma are linked to high mortality both in patients with heart failure (5) and those with AMI (8), indicating potential implication of TH signaling in the post-ischemic cardiac recovery. Interestingly, this hypothesis has recently been addressed in experimental models of ischemia–reperfusion and myocardial infarction in animals and accumulating evidence reveals that TH is critical for the response of the myocardium to ischemic stress and TH may possess

cytoprotective properties that are 'silent' in healthy tissue, manifesting only during stress (10–13).

Based on this evidence, this study investigated whether changes in TH in plasma are associated with early and late recovery of cardiac function in patients with AMI. This issue has not been previously addressed and may be of clinical relevance. AMI results in loss of cardiac function due to tissue necrosis, reperfusion injury, and cardiac remodeling, causing significant morbidity and mortality with a high risk (30–75%) of developing heart failure despite modern reperfusion and pharmacological therapy (14–17).

Methods

Patients and measurements

A total of 47 patients (61.7% male, mean age 62.3 ± 10.2 years) admitted to the emergency cardiac care and diagnosed with ST elevation AMI (STEMI) were included in this study. AMI diagnosis and treatment was based on the guidelines of the European Society of

Cardiology 2008 (18). All patients with AMI underwent coronary angiography and primary percutaneous coronary intervention (PCI) within 120 min after first medical contact.

Of the 67 patients in total, 12 had a history of coronary artery disease (CAD), thyroid dysfunction (based on medical history and treatment), amiodarone treatment, clinical evidence of sepsis, cachexia, or other severe systemic disease (e.g. cancer, autoimmune disease, and chronic renal disease) were not included in the study. Furthermore, eight patients with acute pulmonary edema, stent thrombosis, new AMI, death, or need for coronary artery bypass graft surgery (CABG) during the 6-month follow-up period were also excluded. Thus, of the 67 patients with STEMI that were initially selected, 47 patients were analyzed.

All patients had standard laboratory tests according to acute coronary syndrome protocol and subjected to echocardiographic evaluation within 48 h from admission and 6 months (6 mo) later. At hospital discharge, all patients were given standard therapeutic treatment that remained unchanged during the following 6 mo.

The local ethics review committee approved the study and the investigation conformed to the principles of the Declaration of Helsinki. All the enrolled patients signed an informed consent.

Measurement of myocardial injury

Myocardial injury was measured from peak value of CKMB after serial measurements of CKMB on admission and at 6, 12, 24, and 48 h. CKMB normal values were <25 U/l. Diagnosis of AMI was also based on qualitative troponin assessment.

Measurement of left ventricular ejection fraction

Left ventricular ejection fraction (LVEF) was measured with transthoracic echocardiography (General Electric Vigment Ultrasound System, with a 3.5 MHz transducer, Pollards Wood, Chalfont St. Giles, UK) according to the guidelines set by the American Society of Echocardiography. Left ventricular end-diastolic diameter (mm), left ventricular end-systolic diameter (mm), and fractional shortening were also determined. Patients were divided into two groups according to the change of LVEF (Δ EF%) between 6 mo and 48 h after AMI. The analysis of the distribution of Δ EF% values showed a median value of 5.0, a mean value of 5.7, and a s.d. of 5.5. Thus, on the basis of this analysis, patients were divided into two groups: group A (Δ EF% < 5%) and group B (Δ EF% $\geq$ 5%).

Measurement of TH in plasma

Changes in TH profile were assessed in all patients at 24 h, 48 h, 5 d, and 6 mo after myocardial infarction.

Blood samples were collected from an antecubital vein, and after centrifugation, serum was collected and total T₃ and thyroxine (T₄) were determined using a Hitachi Modular E170 Chemistry Analyzer, whereas TSH was measured using ADVIA Centaur Immunoassay System (Siemens, Athens, Greece). The reference intervals for our laboratory were as follows: T₃, 1.2–2.5 nmol/l; T₄, 66–181 nmol/l; and TSH, 0.40–4.2 μ U/ml.

Statistical analysis

Continuous variables are expressed as mean $\pm$ s.d., whereas categorical variables are expressed as numbers or percentages. Potential correlations between continuous variables were evaluated by Pearson's product-moment (Pearson r) or by Spearman's rank correlation coefficient (Spearman r) as appropriate. Independent sample t -test or non-parametric Mann–Whitney U test (for continuous variables) and χ^2 test (for dichotomized variables) were used to assess differences in parameters between groups. All tests were two-sided. A P value < 0.05 was considered statistically significant. Continuous variables (T₃, T₄, TSH, and creatinine) and dichotomized variables (gender, Killip class) were entered in the linear multiple logistic regression model using a

Table 1 Patients, baseline characteristics.

Characteristics	Values n (%)
Gender (male/female)	29 (61.7)/18 (38.3)
Age (years; mean $\pm$ s.d.)	62.3 $\pm$ 10.2
Smoking	41 (87.2)
Diabetes	14 (29.8)
Family history of CAD	32 (68.1)
Hypertension	40 (85.1)
Dyslipidemia	36 (76.6)
Infarct location	
Anterior	13 (27.7)
Lateral	5 (10.6)
Posterior	7 (14.9)
Anterolateral	22 (46.8)
Culprit vessel	
LAD	35 (74.5)
LCX	6 (12.8)
RCA	6 (12.8)
Number of diseased vessels	
1 Vessel	22 (46.8)
2 Vessel	23 (48.9)
3 Vessel	2 (4.3)
Pharmacological therapy* (%)	
Anti-platelets	100
β -Blockers	97.9
ACEIs	100
Statins	100
Aldosterone antagonists	43
Diuretics	46.8
Nitrates	12.8

*therapy from discharge to 6 mo. CAD, coronary artery disease; LAD, left anterior descending artery; LCX, circumflex artery; RCA, right coronary artery; ACEIs, angiotensin converting enzyme inhibitors.

Table 2 Functional and laboratory data, early (during hospital stay) and late, after AMI.

	After AMI			
	Early		Late	
	At 24 h	At 48 h	At 5 days	At 6 months
Functional data				
LVEF (%)		41.4 ± 9.4		47.2 ± 11.7
LVFS (%)		28 ± 7.9		32 ± 8.5
LVEDD (mm)		49.5 ± 5.3		52.8 ± 5.2
LVESD (mm)		35.5 ± 5.5		36.1 ± 6.4
Laboratory data				
Hct (%)	41.7 ± 3.8			41.1 ± 3.9
Creatinine (mg/dl)	0.99 ± 0.28			1.08 ± 0.3
LDL (mg/dl)	149 ± 40			128 ± 31
HDL (mg/dl)	41.9 ± 10.6			45 ± 11
T ₃ (nmol/l)	1.2 ± 0.23	1.28 ± 0.24	1.38 ± 0.25	1.51 ± 0.39
T ₄ (nmol/l)	92.1 ± 19.3	94.4 ± 16.9	93.3 ± 23.6	98.9 ± 24
TSH (μIU/l)	1.93 ± 1.6	2.1 ± 2.0	2.4 ± 2.7	2.2 ± 2.1

AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LDL, low density lipoprotein; HDL, high density lipoprotein.

stepwise method to identify potential independent determinants of EF% change (Δ EF%). Statistical analysis was performed using statistical software package (SPSS 17.0, IBM SPSS Chicago, IL, USA).

Results

Patients' baseline characteristics

Patients' baseline characteristics are shown in Table 1. All patients were subjected to optimal reperfusion strategy consisting of primary PCI. Post-intervention medical therapy was maximal according to current recommendations including β -blockers, angiotensin converting enzyme inhibitors, statins, and anti-platelet therapy. Aldosterone antagonists were administered in patients with EF% <40% whereas diuretics were administered depending on the symptoms and clinical evaluation. A small percentage of patients (12.8%) were on nitrate treatment (Table 1). Functional and standard laboratory data of all patients early and late after AMI are shown in Table 2.

TH and early functional recovery

Total T₃ levels in plasma at 48 h were found to be significantly correlated to EF% at 48 h ($r=0.50$, $P=0.0004$; Fig. 1A), although no correlation was shown between T₃ levels and the peak value of CKMB ($r=-0.04$, $P=0.81$; Fig. 1B).

No significant correlations between EF% at 48 h and T₄ or TSH at 48 h were observed.

TH and late functional recovery

Total T₃ levels in plasma at 6 mo were found to be significantly correlated to EF% at 6 mo ($r=0.68$, $P=2 \times 10^{-7}$). A significant correlation also existed between EF% at 6 mo and T₃ at 24 h ($r=0.53$, $P=10^{-4}$), T₃ at 48 h ($r=0.59$, $P=10^{-5}$), and T₃ at 5 d ($r=0.71$, $P=2 \times 10^{-7}$).

Total T₃ levels in plasma at 6 mo were found to be significantly correlated to Δ EF% ($r=0.64$, $P=10^{-6}$). Δ EF% was not found to correlate with T₃ at 24 h ($r=0.25$, $P=0.09$) but significantly correlated with T₃ at 48 h ($r=0.4$, $P=0.006$) and T₃ at 5 d ($r=0.53$, $P=10^{-4}$).

No significant correlations between EF% (at 6 mo) or Δ EF% and T₄ or TSH at any time point were observed.

Pattern of TH recovery in plasma and late recovery of cardiac function

A differential profile of TH recovery was observed between patients with Δ EF% $\geq 5\%$ and those with

Figure 1 Scatterplots showing correlation between (A) EF% at 48 h and T₃ at 48 h and (B) peak CKMB and T₃ at 48 h. A significant correlation exists only between EF% at 48 h and T₃ at 48 h.

Table 3 Group characteristics. Data are presented as percent (%)

	Group A (<i>n</i> =22; ΔEF% <5%)	Group B (<i>n</i> =25; ΔEF% ≥5%)	P value
Age (years; mean ± s.d.)	64.6±9.9	60.3±10.4	0.16
Gender (male/female)	45.5/54.5	76/24	0.032
Smoking	86.4	88	0.87
Family history of CAD	63.6	72	0.54
Diabetes	31.8	28	0.78
Hypertension	80.8	89.7	0.35
Dyslipidemia	81.8	88	0.55
Culprit vessel (LAD/ LCX/RCA)	86.3/4.6/9.1	64/20/16	0.18
No. of diseased vessels (1/2/3; mean±s.d.)	36.4/63.6/0	56/36/8	0.10
Peak CKMB (U/l)	332±253	220±256	0.14
Killip class (I/II/III)	22.7/40.9/36.3	48/48/4	0.014

P<0.05 is presented in boldface.

ΔEF% <5% (groups B and A respectively). Similarities and differences regarding the characteristics of both groups are shown in Tables 3 and 4.

T₃ levels were found to be low in most of the patients at 24 h from admission and were significantly different between the two groups at 24 h (1.12±0.05 in group A versus 1.27±0.05 in group B, *P*<0.05). In addition, T₃ levels at 48 h, 5 d, and 6 mo were significantly lower in group A compared with group B (1.16±0.04, 1.23±0.04, and 1.23±0.04 vs 1.37±0.05, 1.51±0.05, and 1.77±0.07, respectively, *P*<0.05). Thus, T₃ levels remained nearly unchanged from baseline values measured at 24 h in group A, whereas in group B, T₃ levels progressively restored to normal values after 6 mo (Fig. 2A).

T₄ levels were not significantly different between the two groups during the acute phase of myocardial infarction. In fact, T₄ levels at 24 h, 48 h, and 5 d were 87.9±5.0, 89.7±4, and 91.3±4.3 in group A versus 95.8±2.8, 98.6±2.8, and 95.1±5.3 in group B, respectively, *P*>0.05. At 6 mo, T₄ levels were

significantly lower in group A compared with group B (89.4±4.6 vs 107.2±4.7, *P*<0.05; Fig. 2B).

TSH levels were not significantly different between the two groups during the acute phase of myocardial infarction. In fact, TSH levels at 24 h, 48 h, and 5 d were 2.2±0.4, 2.6±0.6, and 3.0±0.84 in group A versus 1.6±0.2, 1.7±0.14, and 1.8±0.15 in group B, respectively, *P*>0.05. At 6 mo, TSH levels were significantly higher in group A compared with group B (2.9±0.55 vs 1.46±0.16, *P*<0.05; Fig. 2C).

Determinants of late cardiac recovery after AMI

A linear multiple logistic regression model with a stepwise method was used to identify potential independent determinants of EF% change (ΔEF%). Thus, total T₃ at 6 mo, gender and high-density lipoprotein (HDL) at early phase were found to be independent determinants of ΔEF% (Table 5). The variables, which were entered into the statistical model and found not to be independent predictors of ΔEF%, included age, smoking, family history of CAD, diabetes, hypertension, dyslipidemia, Killip score, culprit vessel, number of diseased vessels, peak CKMB, THs (T₃ 24 h, T₄ 24 h, TSH 24 h, T₃ 48 h, T₄ 48 h, TSH 48 h, T₃ 5 d, T₄ 5 d, TSH 5 d, T₄ 6 mo, and TSH 6 mo), Hct, low-density lipoprotein (LDL), and creatinine early after AMI and Hct, LDL, HDL, and creatinine late after AMI. The regression equation, which predicted recovery of EF% according to T₃ values at 6 mo for male, was as follows: ΔEF% = -12.8 + (9.2 × (T₃ at 6 mo)) + (0.15 × HDL) with ΔEF% to be lesser by 4.3% in female group for any given value of T₃ and HDL (Fig. 3).

Discussion

Although it has been long recognized that changes in TH profile occur in patients with AMI, the physiological significance of this response has not been extensively

Table 4 Functional and laboratory data, early (during hospital stay) and late (6 mo), after AMI. Data are presented as percent (%) or mean±s.d.

	Early after AMI			Late after AMI		
	Group A	Group B	<i>P</i>	Group A	Group B	<i>P</i>
LVEF (%)	38.1±8.3	44.4±10.2	0.022	39.3±8.2	54.0±9.8	2×10⁻⁶
LVFS%	24.5±7.7	31.6±6.6	0.002	27.2±7.0	35.8±7.7	0.0003
LVEDD (mm)	49.9±5.5	49.2±5.3	0.63	54.2±5.9	51.6±4.2	0.09
LVESD (mm)	37.6±5.7	33.6±4.6	0.011	39.4±5.8	33.2±5.4	0.0004
Hct (%)	41.0±4.3	42.3±3.4	0.25	39.9±4.0	42.2±3.5	0.04
Creatinine (mg/dl)	1.07±0.36	0.92±0.17	0.07	1.22±0.36	0.95±0.18	0.001
LDL (mg/dl)	148±38	150±43	0.91	126±22	130±38	0.68
HDL (mg/dl)	43.1±10.7	40.9±10.7	0.47	45.4±9.2	44.3±12.7	0.72

LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LDL, low-density lipoprotein; HDL, high-density lipoprotein. *P*<0.05 is presented in boldface.

Figure 2 Time course analysis of T₃ (A), T₄ (B), and TSH (C) after myocardial infarction in patients with poor recovery of function (group A, ΔEF% < 5%) and patients with better recovery of function (group B, ΔEF% ≥ 5%). A different pattern of T₃ recovery is observed between the two groups. **P* < 0.05 versus group A.

explored (6–8). Thus, this study provides some evidence showing a potential link of changes in TH in plasma to early and late functional recovery in patients with AMI.

Patients with AMI and early reperfusion therapy were included in this study. Myocardial injury was estimated by peak CKMB and cardiac function was assessed by

echocardiographic LVEF (LVEF%). LVEF% seems to be a suitable indicator of cardiac performance and thus it has been used in several studies for the assessment of functional recovery after myocardial infarction, testing the efficacy of applied treatments and as a marker of prognosis (19–21). Changes in TH profile were assessed by measuring T₃, T₄, and TSH in plasma at different time points after AMI. In particular, total T₃ has previously been shown to be correlated to functional status and an index of the disease outcome (5, 8, 22).

TH and early functional recovery

Early after myocardial infarction, cardiac function is compromised due to ischemic injury and also to reperfusion injury in the case of early reperfusion therapies (23). During the acute event, a number of changes in the neurohormonal and inflammatory systems occur with potential physiological consequences. Decrease in TH levels is a frequent observation and is considered as an energy adaptation to acute stress, which may lead to cardioprotection. However, TH can control contractile function via the regulation of contractile proteins, calcium handling, and ion channels (24). Thus, TH changes early after AMI may affect cardiac function with potential hemodynamic consequences. This issue, although of clinical relevance, has not been previously addressed. However, in this study, we provide some evidence showing that T₃ levels in plasma early after AMI were strongly correlated with LVEF, whereas no correlation was seen with T₄ and TSH. These data probably indicate that TH may be implicated in post-ischemic functional recovery. Several lines of evidence support this assumption. T₃ and not T₄ treatment at reperfusion was shown to improve post-ischemic recovery of function while limiting apoptosis in experimental models of ischemia–reperfusion (25). This response was contrary to detrimental effect caused by dobutamine, which is often used to improve post-ischemic hemodynamics (26). Furthermore, T₃ cardioprotection was shown to be mediated via the suppression of the pro-apoptotic p38MAPK signaling pathway and be TRα1 receptor dependent (13, 25). More importantly, in accordance with this experimental evidence, T₃ treatment resulted in marked increase of post-surgery cardiac function in patients undergoing cardiac bypass operations (27, 28).

Table 5 Multivariate linear regression analysis revealed that T₃ at 6 mo and gender and high-density lipoprotein (HDL) at early phase were independent predictors of myocardial function recovery (ΔEF%) after acute myocardial infarction.

Independent variables	<i>r</i>	<i>r</i> ²	<i>P</i> value
T ₃	0.64	0.41	0.000001
T ₃ +gender	0.71	0.50	0.006
T ₃ +gender+HDL	0.76	0.58	0.01

Figure 3 Scatterplot showing a strong correlation between $\Delta\text{EF}\%$ and T_3 at 6 mo in both females and males. Regression equation that estimates recovery of function is as follows: $\Delta\text{EF}\% = -12.8 + (9.2 \times (T_3 \text{ at 6 mo})) + (0.15 \times \text{HDL})$ with $\Delta\text{EF}\%$ to be lesser by 4.3% in female group for any given value of T_3 at 6 mo and HDL at early phase.

TH and late functional recovery

Non-ischemic viable myocardium after myocardial infarction undergoes a series of structural and functional changes, known as cardiac remodeling (15). Thus, nearly half of the patients with AMI show small or absence of left ventricular functional recovery at 6 mo, despite early reperfusion treatments and intense anti-remodeling treatments (20). According to these data, nearly half of our patients showed $<5\%$ difference in the recovery of LVEF ($\Delta\text{EF}\%$). Interestingly, time course analysis of TH changes in plasma revealed poor recovery of T_3 levels in this group of patients, indicating a potential association of T_3 to cardiac function late after AMI. In fact, further analysis revealed that T_3 levels at 6 mo were an independent predictor of $\Delta\text{EF}\%$. In addition, $\Delta\text{EF}\%$ was strongly correlated to 6 mo T_3 levels in plasma.

The potential implication of TH in post-ischemic recovery of function has been recently demonstrated in animal and cell-based models. Thus, induction of myocardial infarction in animals resulted in a series of changes in TH signaling including alterations in T_3 tissue levels, enzyme type 3 deiodinase activity, and in the expression of TH receptors all resulting in changes in T_3 -dependent transcription activity (12, 29, 30). Interestingly, $\text{TR}\alpha 1$ receptor, which is predominantly expressed in the myocardium and regulates important structural and functional genes, was shown to be an important component of the growth kinase signaling pathways that are activated early after AMI and promote pathological growth (29, 31). In accordance with this evidence, induction of hypothyroidism resulted in exacerbation of cardiac remodeling (32, 33), whereas TH treatment improved post-ischemic cardiac hemodynamics in animal models of myocardial infarction

(10, 34–38). Here, it should be noted that low T_3 levels have also been associated with worse neurological outcome and T_3 appears to be a predictor of functional improvement in acute ischemic stroke (39). This is in accordance with recent experimental evidence showing the reparative effect of TH after neuronal injury (40).

Limitations of the study

To our knowledge, this study is the first to show potential association of early and late recovery of function in patients with AMI. However, this study has not included a large number of patients, which would allow the investigation of possible association of TH with mortality after AMI. Interestingly, this issue has been addressed by a previous study (8). Furthermore, assessment of cardiac function was performed with echocardiography, which does not allow accurate measurement of specific indices of cardiac remodeling. Finally, the patients included in this study were urgently admitted to the hospital so that TH disorders were excluded on the basis of the medical history and treatment, but silent thyroid dysfunction cannot be excluded.

In conclusion, changes in T_3 levels in plasma are closely correlated with the early and late recovery of cardiac function after AMI. T_3 levels at 6 mo appear to be an independent predictor of late functional recovery.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Bello G, Ceacchisciuc I, Silva S & Antonelli M. The role of thyroid dysfunction in the critically ill: a review of the literature. *Minerva Anestesiologica* 2010 **76** 919–928.
- 2 De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 151–164. (doi:10.1210/jc.84.1.151)
- 3 Warner MH & Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. *Journal of Endocrinology* 2010 **205** 1–13. (doi:10.1677/JOE-09-0412)
- 4 Bermudez F, Surks MI & Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. *Journal of Clinical Endocrinology and Metabolism* 1975 **41** 27–40. (doi:10.1210/jcem-41-1-27)
- 5 Pingitore A, Landi P, Taddei MC, Ripoli A, L'abbate A & Iervasi G. Triiodothyronine levels for risk stratification of patients with chronic heart failure. *American Journal of Medicine* 2005 **118** 132–136. (doi:10.1016/j.amjmed.2004.07.052)

- 6 Eber B, Schumacher M, Langsteger W, Zweiker R, Fruhwald FM, Pokan R, Gasser R, Eber O & Klein W. Changes in thyroid hormone parameters after acute myocardial infarction. *Cardiology* 1995 **86** 152–156. (doi:10.1159/000176862)
- 7 Franklyn JA, Gammage MD, Ramsden DB & Sheppard MC. Thyroid status in patients after acute myocardial infarction. *Clinical Science* 1984 **67** 585–590.
- 8 Friberg L, Werner S, Eggertsen G & Ahnve S. Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina? *Archives of Internal Medicine* 2002 **162** 1388–1394. (doi:10.1001/archinte.162.12.1388)
- 9 Cerillo AG, Storti S, Clerico A & Iervasi G. Thyroid function and cardiac surgery: what should we measure, and when? *Annals of Thoracic Surgery* 2010 **89** 1010–1011 (author reply 1011–1012). (doi:10.1016/j.athoracsur.2009.08.046)
- 10 Kalofoutis C, Mourouzis I, Galanopoulos G, Dimopoulos A, Perimenis P, Spanou D, Cokkinos DV, Singh J & Pantos C. Thyroid hormone can favorably remodel the diabetic myocardium after acute myocardial infarction. *Molecular and Cellular Biochemistry* 2010 **345** 161–169. (doi:10.1007/s11010-010-0569-4)
- 11 Pantos C, Mourouzis I & Cokkinos DV. Rebuilding the post-infarcted myocardium by activating 'physiologic' hypertrophic signaling pathways: the thyroid hormone paradigm. *Heart Failure Reviews* 2010 **15** 143–154. (doi:10.1007/s10741-008-9111-0)
- 12 Pantos C, Mourouzis I & Cokkinos DV. New insights into the role of thyroid hormone in cardiac remodeling: time to reconsider? *Heart Failure Reviews* 2011 **16** 79–96. (doi:10.1007/s10741-010-9185-3)
- 13 Pantos C, Mourouzis I, Saranteas T, Brozou V, Galanopoulos G, Kostopanagiotou G & Cokkinos D. Acute T₃ treatment protects the heart against ischemia–reperfusion injury via TRalpha1 receptor. *Molecular and Cellular Biochemistry* 2011 In Press. (doi:10.1007/s11010-011-0791-8)
- 14 Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC & Mcalister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *Journal of the American College of Cardiology* 2009 **53** 13–20. (doi:10.1016/j.jacc.2008.08.067)
- 15 Gajarsa JJ & Kloner RA. Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. *Heart Failure Reviews* 2011 **16** 13–21. (doi:10.1007/s10741-010-9181-7)
- 16 Shafazand M, Rosengren A, Lappas G, Swedberg K & Schaufelberger M. Decreasing trends in the incidence of heart failure after acute myocardial infarction from 1993–2004: a study of 175 216 patients with a first acute myocardial infarction in Sweden. *European Journal of Heart Failure* 2011 **13** 135–141. (doi:10.1093/eurjhf/hfq205)
- 17 Weir RA, McMurray JJ & Velazquez EJ. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. *American Journal of Cardiology* 2006 **97** 13F–25F. (doi:10.1016/j.amjcard.2006.03.005)
- 18 Van De Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F & Weis M. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *European Heart Journal* 2008 **29** 2909–2945. (doi:10.1093/eurheartj/ehn526)
- 19 Holper EM, Blair J, Selzer F, Detre KM, Jacobs AK, Williams DO, Vlachos H, Wilensky RL, Coady P & Faxon DP. The impact of ejection fraction on outcomes after percutaneous coronary intervention in patients with congestive heart failure: an analysis of the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry and Dynamic Registry. *American Heart Journal* 2006 **151** 69–75. (doi:10.1016/j.ahj.2005.03.053)
- 20 Ndrepepa G, Mehilli J, Martinoff S, Schwaiger M, Schomig A & Kastrati A. Evolution of left ventricular ejection fraction and its relationship to infarct size after acute myocardial infarction. *Journal of the American College of Cardiology* 2007 **50** 149–156. (doi:10.1016/j.jacc.2007.03.034)
- 21 Parodi G, Memisha G, Carrabba N, Signorini U, Migliorini A, Cerisano G & Antonucci D. Prevalence, predictors, time course, and long-term clinical implications of left ventricular functional recovery after mechanical reperfusion for acute myocardial infarction. *American Journal of Cardiology* 2007 **100** 1718–1722. (doi:10.1016/j.amjcard.2007.07.022)
- 22 Pantos C, Dritsas A, Mourouzis I, Dimopoulos A, Karatasakis G, Athanassopoulos G, Mavrogeni S, Manginas A & Cokkinos DV. Thyroid hormone is a critical determinant of myocardial performance in patients with heart failure: potential therapeutic implications. *European Journal of Endocrinology* 2007 **157** 515–520. (doi:10.1530/EJE-07-0318)
- 23 Pantos C, Mourouzis I & Cokkinos DV. Myocardial ischemia: basic concepts. In *Myocardial Ischemia: From Mechanisms to Therapeutic Potentials*, pp 11–77. Eds DV Cokkinos, C Pantos, G Heusch & H Taegtmeier, New York: Springer, 2006.
- 24 Pantos C, Mourouzis I, Xinaris C, Papadopoulou-Daifoti Z & Cokkinos D. Thyroid hormone and "cardiac metamorphosis": potential therapeutic implications. *Pharmacology and Therapeutics* 2008 **118** 277–294. (doi:10.1016/j.pharmthera.2008.02.011)
- 25 Pantos C, Mourouzis I, Saranteas T, Clave G, Ligeret H, Noack-Fraissignes P, Renard PY, Massonneau M, Perimenis P, Spanou D, Kostopanagiotou G & Cokkinos DV. Thyroid hormone improves postischemic recovery of function while limiting apoptosis: a new therapeutic approach to support hemodynamics in the setting of ischemia–reperfusion? *Basic Research in Cardiology* 2009 **104** 69–77. (doi:10.1007/s00395-008-0758-4)
- 26 Pantos C, Mourouzis I, Tzeis S, Moraitis P, Malliopolou V, Cokkinos DD, Carageorgiou H, Varonos D & Cokkinos D. Dobutamine administration exacerbates postischemic myocardial dysfunction in isolated rat hearts: an effect reversed by thyroxine pretreatment. *European Journal of Pharmacology* 2003 **460** 155–161. (doi:10.1016/S0014-2999(02)02927-8)
- 27 Kaptein EM, Sanchez A, Beale E & Chan LS. Clinical review: thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review and synthesis. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4526–4534. (doi:10.1210/jc.2010-1052)
- 28 Ranasinghe AM, Quinn DW, Pagano D, Edwards N, Farouqi M, Graham TR, Keogh BE, Mascaro J, Riddington DW, Rooney SJ, Townend JN, Wilson IC & Bonser RS. Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. *Circulation* 2006 **114** 1245–1250. (doi:10.1161/CIRCULATIONAHA.105.000786)
- 29 Pantos C, Mourouzis I, Galanopoulos G, Gavra M, Perimenis P, Spanou D & Cokkinos DV. Thyroid hormone receptor alpha1 downregulation in postischemic heart failure progression: the potential role of tissue hypothyroidism. *Hormone and Metabolic Research* 2010 **42** 718–724. (doi:10.1055/s-0030-1255035)
- 30 Pol CJ, Muller A, Zuidwijk MJ, Van Deel ED, Kaptein E, Saba A, Marchini M, Zucchi R, Visser TJ, Paulus WJ, Duncker DJ & Simonides WS. Left-ventricular remodeling after myocardial infarction is associated with a cardiomyocyte-specific hypothyroid condition. *Endocrinology* 2010 **152** 669–679. (doi:10.1210/en.2010-0431)
- 31 Pantos C, Xinaris C, Mourouzis I, Perimenis P, Politi E, Spanou D & Cokkinos DV. Thyroid hormone receptor alpha 1: a switch to cardiac cell "metamorphosis"? *Journal of Physiology and Pharmacology* 2008 **59** 253–269.
- 32 Chen YF, Redetzke RA, Said S, Beyer AJ & Gerdes AM. Changes in left ventricular function and remodeling after myocardial infarction in hypothyroid rats. *American Journal of Physiology. Heart and Circulatory Physiology* 2010 **298** H259–H262. (doi:10.1152/ajpheart.00755.2009)

- 33 Pantos C, Mourouzis I, Tsagoulis N, Markakis K, Galanopoulos G, Roukounakis N, Perimenis P, Liappas A & Cokkinos DV. Thyroid hormone at supra-physiological dose optimizes cardiac geometry and improves cardiac function in rats with old myocardial infarction. *Journal of Physiology and Pharmacology* 2009 **60** 49–56.
- 34 Chen YF, Kobayashi S, Chen J, Redetzke RA, Said S, Liang Q & Gerdes AM. Short term triiodo-L-thyronine treatment inhibits cardiac myocyte apoptosis in border area after myocardial infarction in rats. *Journal of Molecular and Cellular Cardiology* 2008 **44** 180–187. (doi:10.1016/j.yjmcc.2007.09.009)
- 35 Forini F, Lionetti V, Ardehali H, Pucci A, Cecchetti F, Ghanefar M, Nicolini G, Ichikawa Y, Nannipieri M, Recchia FA & Iervasi G. Early long-term L-T₃ replacement rescues mitochondria and prevents ischemic cardiac remodeling in rats. *Journal of Cellular and Molecular Medicine* 2010 **15** 514–524. (doi:10.1111/j.1582-4934.2010.01014.x)
- 36 Henderson KK, Danzi S, Paul JT, Leya G, Klein I & Samarel AM. Physiological replacement of T₃ improves left ventricular function in an animal model of myocardial infarction-induced congestive heart failure. *Circulation. Heart Failure* 2009 **2** 243–252. (doi:10.1161/CIRCHEARTFAILURE.108.810747)
- 37 Pantos C, Mourouzis I, Markakis K, Dimopoulos A, Xinaris C, Kokkinos AD, Panagiotou M & Cokkinos DV. Thyroid hormone attenuates cardiac remodeling and improves hemodynamics early after acute myocardial infarction in rats. *European Journal of Cardio-Thoracic Surgery* 2007 **32** 333–339. (doi:10.1016/j.ejcts.2007.05.004)
- 38 Pantos C, Mourouzis I, Markakis K, Tsagoulis N, Panagiotou M & Cokkinos DV. Long term thyroid hormone administration reshapes left ventricular chamber and improves cardiac function after myocardial infarction in rats. *Basic Research in Cardiology* 2008 **103** 308–318. (doi:10.1007/s00395-008-0697-0)
- 39 Zhang Y & Meyer MA. Clinical analysis on alteration of thyroid hormones in the serum of patients with acute ischemic stroke. *Stroke Research and Treatment* 2010 **2010** pii: 290678. (doi:10.4061/2010/290678)
- 40 Shulga A, Blaesse A, Kysenius K, Huttunen HJ, Tanhuanpaa K, Saarma M & Rivera C. Thyroxin regulates BDNF expression to promote survival of injured neurons. *Molecular and Cellular Neurosciences* 2009 **42** 408–418. (doi:10.1016/j.mcn.2009.09.002)

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