

Muscle wasting after coronary artery bypass graft surgery: impact on post-operative clinical status and effect of exercise-based rehabilitation

Peer-reviewed author version

HANSEN, Dominique; BOUJEMAA, Hajar; VERBOVEN, Kenneth; HENDRIKX, Marc; RUMMENS, Jean-Luc; FREDERIX, Ines; OP 'T EIJNDE, Bert & DENDALE, Paul (2020) Muscle wasting after coronary artery bypass graft surgery: impact on post-operative clinical status and effect of exercise-based rehabilitation. In: *Acta cardiologica*, 75 (5), p. 406-410.

DOI: 10.1080/00015385.2019.1598035

Handle: <http://hdl.handle.net/1942/28020>

# Muscle wasting after coronary artery bypass graft surgery: impact on post-operative clinical status and effect of exercise-based rehabilitation

Dominique Hansen, PhD, FESC<sup>a,b</sup>; Hajar Boujemaa, BSc<sup>a</sup>; Kenneth Verboven, MSc<sup>a</sup>; Marc Hendrikx, MD, PhD<sup>a,c</sup>; Jean-Luc Rummens, MD<sup>a,d</sup>; Ines Frederix, MD<sup>a,b,e</sup>; Bert O. Eijnde, PhD<sup>a</sup>, Paul Dendale, MD, PhD, FESC<sup>a,b</sup>

<sup>a</sup>REVAL – Rehabilitation Research Center, BIOMED - Biomedical Research Center, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

<sup>b</sup> Heart Center Hasselt, Jessa Hospital, Hasselt, Belgium

<sup>c</sup>Department of Cardiothoracic Surgery, Jessa Hospital, Hasselt, Belgium

<sup>d</sup>University Biobank Limburg, Hasselt, Belgium

<sup>e</sup>Faculty of Medicine and Health Sciences, Antwerp University, Antwerp, Belgium

Sources of funding: none.

Word count: 1263

Study registration number: NCT01333839

Address correspondence:

Dominique Hansen, PhD, FESC

Hasselt University, Faculty of Medicine and Life Sciences

Agoralaan, Building A, 3590 Diepenbeek, Belgium

dominique.hansen@uhasselt.be

Tel 0032(0)11 294978

Fax 0032(0)11 269329

**Abstract**

**Background:** Coronary artery bypass graft (CABG) surgery is known to induce significant muscle wasting. It remains to be investigated whether muscle wasting after CABG surgery relates to a worse clinical status at entry of rehabilitation and exercise-based rehabilitation remediates such muscle wasting.

**Design:** Prospective observational study.

**Methods:** In 21 males, changes in lean tissue mass (LTM) after CABG surgery were assessed and during a 12-week endurance exercise-based rehabilitation intervention. Changes in blood parameters and cardiopulmonary exercise capacity were assessed, and relations with changes in LTM were analyzed.

**Results:** LTM decreased by  $-1.9 \pm 2.5$  kg ( $p < 0.05$ ) within 3 weeks after CABG surgery: greater LTM loss related to a lower ventilatory threshold at entry of rehabilitation ( $r = 0.58-0.61$ ,  $p < 0.05$ ). LTM was fully restored ( $+2.1 \pm 2.4$  kg,  $p < 0.05$ ) during rehabilitation.

**Conclusion:** In males, CABG-induced LTM reduction was associated with a worse aerobic exercise tolerance at entry of rehabilitation, but this LTM reduction was fully remediated by endurance exercise-based rehabilitation.

Abstract word count: 152

Keywords: coronary bypass surgery, lean tissue mass, rehabilitation

## **Introduction**

After coronary artery bypass graft (CABG) surgery significant muscle wasting is observed (1-3). Although sarcopenia is related to elevated morbidity in heart failure patients (4), it remains unidentified whether patients with significant muscle wasting after CABG surgery are in need of modified intervention, and whether endurance exercise-based rehabilitation can fully remediate such muscle wasting. The aim of this study was, for the first time, to explore the impact of amount of muscle wasting after CABG surgery on clinical status at entry of rehabilitation and whether such muscle wasting is fully remediated by endurance exercise-based rehabilitation.

## **Methods**

### *Population*

This study was approved by the local medical ethical committee (Nr. B24320109465, Jessa Hospital, Hasselt, Belgium), adhered to the Helsinki declaration and all subjects signed an informed consent. Subjects with pulmonary, neurologic, oncologic and/or nephrologic disease, metal implants or previous CABG or valve surgery were excluded prior to study. Patients with previous percutaneous coronary intervention or myocardial infarction, but without heart failure, were allowed to participate in this study. The study sample size (n=30) was based on previous studies assessing the impact of CABG surgery on lean tissue mass (LTM) (2,3) and impact of rehabilitation (5). After inviting 119 eligible Caucasian candidates admitted to the hospital for elective CABG surgery, 30 subjects agreed to participate in this prospective observational cohort study (Supplementary Figure 1). Due to post-operative complications or failure to complete the rehabilitation program, nine subjects were lost during follow-up.

### *Measurements*

Before surgery, at entry of rehabilitation (18±1 days after surgery), after 7 and 12 weeks of rehabilitation body composition was assessed by whole-body dual x-ray absorptiometry (Lunar DPXL, Wisconsin, USA) (1). In addition, cardiopulmonary exercise capacity was assessed by ergospirometry (Jaeger CPX Masterscreen, see Table 1 for parameters) on bike with a 1-minute incremental work stage protocol until exhaustion (RER>1.10) (1). Fasting (07.00-09.00AM) whole-blood, plasma and serum samples were assessed at entry and after 7 and 12 weeks of rehabilitation by state-of-the-art methods in a clinical laboratory (see Table 1 for parameters) (1). Primary outcome measure in this study was lean tissue mass. Secondary outcome measures physical fitness and blood parameters.

### *Rehabilitation*

The rehabilitation intervention (see Table 1 for exercise modalities) involved endurance exercise

training for three times/week at an intensity between the first and second ventilatory threshold (heart rate monitored), for a period of 12 weeks. Every session patients executed 15 minutes of walking, 20 minutes of cycling and 10 minutes of arm cranking.

### **Statistical analysis**

Statistical analyses were executed by SPSS v.24.0 (SPSS Inc., Chicago, USA). Data are presented as mean $\pm$ SD and median (interquartile range). Changes in parameters were analyzed by Wilcoxon signed ranks tests (data were not normally distributed according to Shapiro-Wilk test), in which Bonferroni corrections for multiple comparisons were applied. Relationships between parameters were analyzed by univariate Spearman correlations corrected for age, weight and height. Statistical significance was set at  $P < 0.05$  (2-tailed).

### **Results**

#### *Impact of CABG surgery and rehabilitation on secondary outcomes*

After CABG surgery significant decrease were observed in BMI, blood total, LDL and HDL cholesterol, and triglyceride concentrations, and increments in blood growth hormone concentrations ( $P < 0.05$ ). During rehabilitation significant increments in exercise tolerance and blood HDL cholesterol concentrations were observed ( $P < 0.05$ , Table 1). Whole-body fat mass decreased after CABG surgery ( $-1.3 \pm 0.4$  kg,  $P < 0.05$ ) and further during rehabilitation ( $-2.2 \pm 1.0$  kg,  $P < 0.05$ ) (Figure 1).

#### *Impact of CABG surgery and rehabilitation on Lean tissue mass*

Lean tissue mass decreased by  $-1.9 \pm 2.5$  kg after CABG surgery ( $P < 0.05$ ) (Figure 1), followed by significant increments and full restoration ( $+2.1 \pm 2.4$  kg,  $P < 0.05$ ) during rehabilitation (Figure 1).

#### *Relations between Lean tissue mass reductions after CABG surgery and clinical status at entry of rehabilitation*

Significant correlations ( $p < 0.05$ ) were found between decrease in lean tissue mass after CABG surgery and first ventilatory threshold during exercise testing at entry of rehabilitation ( $r = 0.59-0.61$ ,  $P < 0.05$ ) (Table 2, Supplementary Figure 2).

## Discussion

The major findings of this study were that in males 1. Greater lean tissue mass reduction after CABG was related to a lower first ventilatory threshold during exercise testing at entry of rehabilitation, and 2. Such lean tissue mass reduction was fully restored during endurance exercise-based rehabilitation. In line with a previous study showing that muscle wasting after CABG surgery was associated with decreased vitality (3), we further noticed that greater lean tissue mass reduction after CABG surgery related to a lower first ventilatory threshold during exercise testing ( $r=0.58-0.61$ ,  $P<0.05$ ) at entry of rehabilitation. Moreover, a possible etiology of muscle mass change could not be explained by measured parameters in this study. Our data may thus indicate that patients with greater lean tissue mass reduction after CABG surgery may experience greater physical limitations to exercise, despite equal peak oxygen uptake. Regardless that there was no relation between training modalities and changes in lean tissue mass during rehabilitation, these patients may require adaptations in training modalities, such as initiating exercise intervention at a lower exercise intensity, or at least monitoring of perceived exertion. It remains to be addressed whether these patients are in need of additional strength training exercises as well, because the impact of such modification in exercise intervention on ventilatory threshold, specifically in CABG patients, remains uncertain (6).

Endurance exercise-based rehabilitation for 12 weeks led to a full restoration of lean tissue mass after CABG surgery. This positive effect was already noticed after seven weeks of intervention. In previous studies, increments in lean tissue mass have been observed in patients after CABG surgery when following exercise intervention (5), but our data also indicate, for the first time, that the amount of lean tissue mass gain is sufficient to fully compensate for the post-operative lean tissue mass loss. It thus follows that endurance exercise training only may be sufficient to remediate lean tissue mass loss after CABG surgery.

This study was limited by the examination of males only and the smaller sample size.

## References

1. Hansen D, Linsen L, Verboven K, et al. Magnitude of muscle wasting early after on-pump coronary artery bypass graft surgery and exploration of aetiology. *Exp Physiol* 2015; 100: 818-828.
2. Miller LE, Pierson LM, Pierson ME, et al. Changes in bone mineral and body composition following coronary artery bypass grafting in men. *Am J Cardiol* 2007; 99: 585-587.
3. van Venrooij LM, Verberne HJ, de Vos R, et al. Postoperative loss of skeletal muscle mass. Complications and quality of life in patients undergoing cardiac surgery. *Nutrition* 2012; 28: 40-45.
4. Fulster S, Tacke M, Sandek A, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013; 34: 512-519.
5. Nishitani M, Shimada K, Masaki M, et al. Effect of cardiac rehabilitation on muscle mass, muscle strength, and exercise tolerance in diabetic patients after coronary artery bypass grafting. *J Cardiol* 2013; 61: 216-221.
6. Hansen D, Dendale P, van Loon LJC, et al. The effects of training modalities on clinical benefits of exercise intervention in cardiovascular disease risk patients or type 2 diabetes mellitus. *Sports Med* 2010; 40: 921-940.

**Author contribution**

DH and PD conceived and designed the study. DH and KV acquired the data. DH and HB analyzed and interpreted the data. DH, HB, KV, MH, JLR, IF, BOE and PD drafted the manuscript. DH, HB, KV, MH, JLR, IF, BOE and PD critically revised the manuscript for important intellectual content. DH, BOE and PD supervised the study. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

**Acknowledgements**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



## Tables and Figures

**Table 1** Impact of CABG surgery and rehabilitation on secondary outcomes

	Preoperative		Entry of rehabilitation		7 weeks of rehabilitation		12 weeks of rehabilitation	
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
<b>Subject Characteristics</b>								
Age	64.3 ± 9	65 (10)	--	--	--	--	--	--
Sex (n=male)	21	--	--	--	--	--	--	--
Body mass index (kg/m <sup>2</sup> )	<b>28.1 ± 4.1*</b>	<b>27.47 (4.84)*</b>	27.42 ± 4.3	26.61 (3.19)	27.47 ± 4.5	26.59 (3.81)	27.42 ± 4.7	26.97 (5.06)
<b>Rehabilitation intervention</b>								
Days (n)	--	--	--	--	22.5 ± 4.5 <sup>#</sup>	22 (3)	38.2 ± 5	38 (4)
Duration session (min)	--	--	--	--	40.5 ± 1.6 <sup>#</sup>	40 (0.0)	43.7 ± 2.3	45 (0.0)
Intensity (% of W peak)	--	--	<b>33.6 ± 8.5<sup>#</sup></b>	33.3 (9.36)	52.4 ± 10.4	48.6 (10.75)	59.3 ± 12.5	60 (11.68)
<b>Exercise capacity</b>								
Cycling power output (W)	--	--	<b>118 ± 27<sup>#</sup></b>	<b>120 (38)<sup>#</sup></b>	144 ± 33	150 (44)	155 ± 46	157 (40)
Oxygen uptake (mL/min)	--	--	<b>1522 ± 284<sup>#</sup></b>	<b>1507 (407)<sup>#</sup></b>	1869 ± 371	1795 (302)	1941 ± 458	1916 (530)
First ventilatory threshold (mL/min)	--	--	<b>962 ± 48<sup>#</sup></b>	<b>860 (300)<sup>#</sup></b>	1184 ± 53	1175 (450)	1257 ± 69	1100 (500)
Second ventilatory threshold (mL/min)	--	--	<b>1233 ± 59<sup>#</sup></b>	<b>1162 (360)<sup>#</sup></b>	1472 ± 71	1408 (504)	1494 ± 87	1438 (759)
Heart rate (beats/min)	--	--	<b>109 ± 14<sup>#</sup></b>	<b>109 (20)<sup>#</sup></b>	125 ± 15	124 (47)	127 ± 18	129 (24)
Respiratory gas exchange ratio (RER)	--	--	1.16 ± 0.11	1.18 (0.15)	1.15 ± 0.09	1.16 (0.13)	1.16 ± 0.11	1.20 (0.14)
Test duration (sec)	--	--	370 ± 119	363 (128)	405 ± 78	405 (126)	408 ± 97	420 (110)
<b>Blood parameters</b>								
Total cholesterol (mg/dl)	<b>155 ± 39*</b>	<b>145 (63)*</b>	132 ± 28	127 (36)	135 ± 22	131 (26)	138 ± 19	138 (32)
LDL cholesterol (mg/dl)	<b>84 ± 27*</b>	<b>80 (21)*</b>	72 ± 23	67 (24)	72 ± 18	72 (17)	71 ± 13	70 (23)
HDL cholesterol (mg/dl)	<b>40 ± 12*</b>	<b>36 (10)*</b>	<b>36 ± 9<sup>#</sup></b>	<b>35 (9)<sup>#</sup></b>	41 ± 10	41 (6)	44 ± 9	44 (7)
Triglyceride (mg/dl)	<b>158 ± 95*</b>	<b>125 (153)*</b>	117 ± 54	94 (72)	103 ± 39	103 (39)	116 ± 84	92 (46)
Glucose (mmol/l)	6.1 ± 2.3	5.7 (1.44)	6.2 ± 1.4	5.7 (1.28)	6.3 ± 1.8	5.8 (0.93)	6.2 ± 1.9	5.7 (1.17)
C-peptide (ng/ml)	2 ± 1	2.03 (1.2)	1.9 ± 0.8	1.91 (1.12)	1.7 ± 0.7	1.73 (0.68)	1.8 ± 0.7	1.77 (0.54)
Insulin (mU/l)	11.1 ± 6.3	10.6 (7.5)	11.8 ± 8.7	10.2 (9.4)	12.7 ± 7.5	12.3 (6.9)	11.5 ± 7.4	9.8 (4.5)
HOMA-IR index	3.2 ± 2.4	2.6 (2.37)	3.7 ± 4.2	3.1 (2.43)	4.1 ± 4.6	3.3 (2.49)	3.7 ± 4.6	2.7 (1.87)
C-Reactive protein (mg/dl)	0.51 ± 0.8	0.15 (0.26)	1.02 ± 1.9	0.50 (0.65)	0.54 ± 0.9	0.20 (0.41)	0.22 ± 0.2	0.15 (0.07)
Glycated hemoglobin (mmol/mol)	6.02 ± 0.7	5.8 (0.4)	5.69 ± 0.6	5.5 (0.4)	5.93 ± 0.7	5.8 (0.33)	6.12 ± 0.7	5.9 (0.4)
Cortisol (total; µg/dl)	18.9 ± 4.9	17.7 (5.3)	17.4 ± 5.4	16.7 (8.60)	18.2 ± 4.1	18.2 (5.5)	18.4 ± 3.7	18.5 (6.3)
Testosterone (total; ng/ml)	3.9 ± 1.7	3.9 (2.5)	3.7 ± 1.8	3.1 (1.4)	3.9 ± 1.4	3.8 (1.1)	4 ± 1.1	3.9 (1.1)
Sex hormone-binding globulin (nmol/l)	45 ± 17	44.92 (22)	43 ± 16	39 (22)	43 ± 18	39 (13)	42 ± 16	39.1 (18)
Insulin-like growth factor-1 (µg/l)	143 ± 40	143 (32)	151 ± 51	150 (103)	149 ± 39	149 (61)	138 ± 49	138 (77)
Growth hormone (µg/l)	<b>0.18 ± 0.1*</b>	<b>0.18 (0.08)*</b>	0.84 ± 0.88	0.70 (0.47)	0.48 ± 0.51	0.42 (0.35)	0.52 ± 0.57	0.26 (0.34)
Free androgen index (%)	32 ± 14	32 (16.5)	32 ± 17	27.5 (13.8)	33 ± 7	33.1 (5.5)	36 ± 9	35.8 (2.3)
Cortisol-to-testosterone ratio	5.5 ± 2.8	4.93 (2.31)	5.8 ± 2.7	5.96 (3.88)	5.2 ± 2.1	4.92 (2.0)	4.9 ± 1.6	4.95 (3.09)

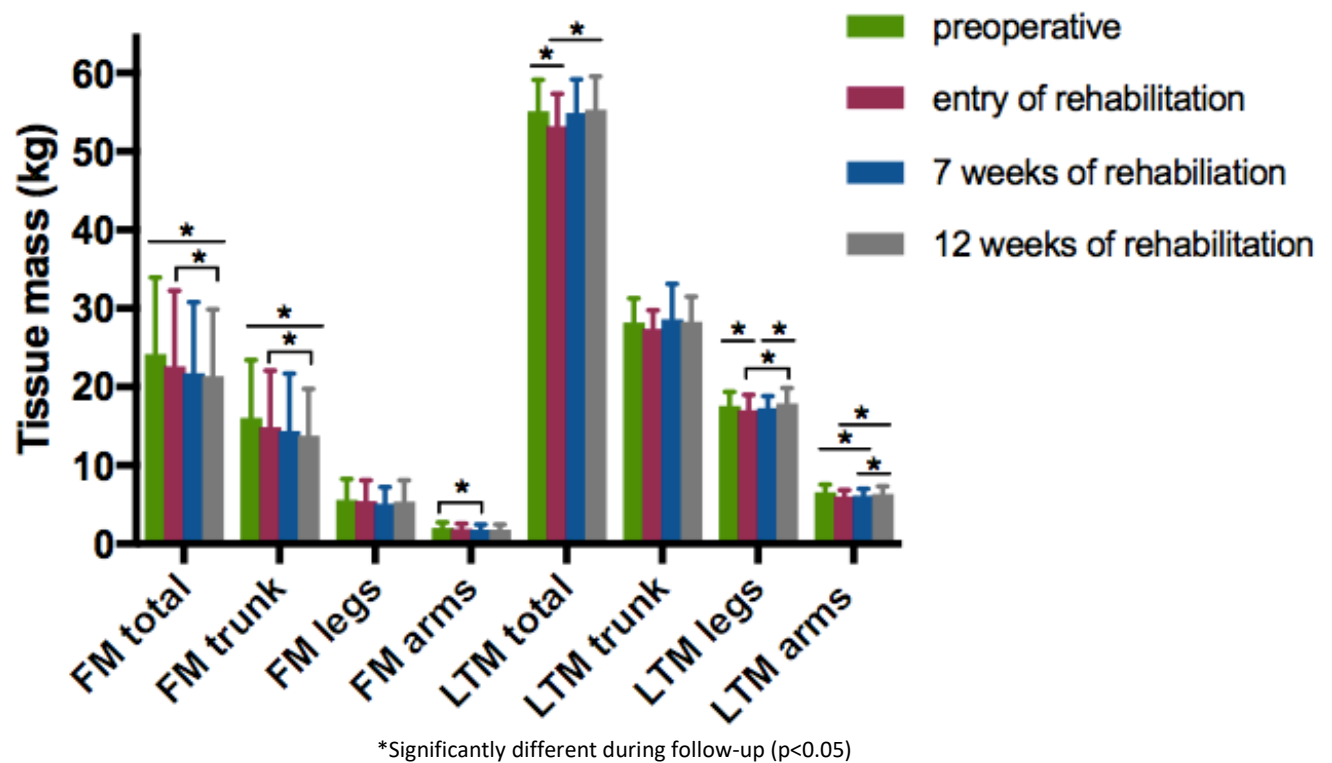
IQR, inter quartile range; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance. \*Significant difference between preoperative parameters compared with entry of rehabilitation (start rehabilitation) (P<0.05). <sup>#</sup>Significant difference between entry and end of rehabilitation (P<0.05). Data are presented as mean±SD. First ventilatory threshold was determined by V-slope method, second ventilatory threshold was determined by VE/VCO<sub>2</sub> slope method.

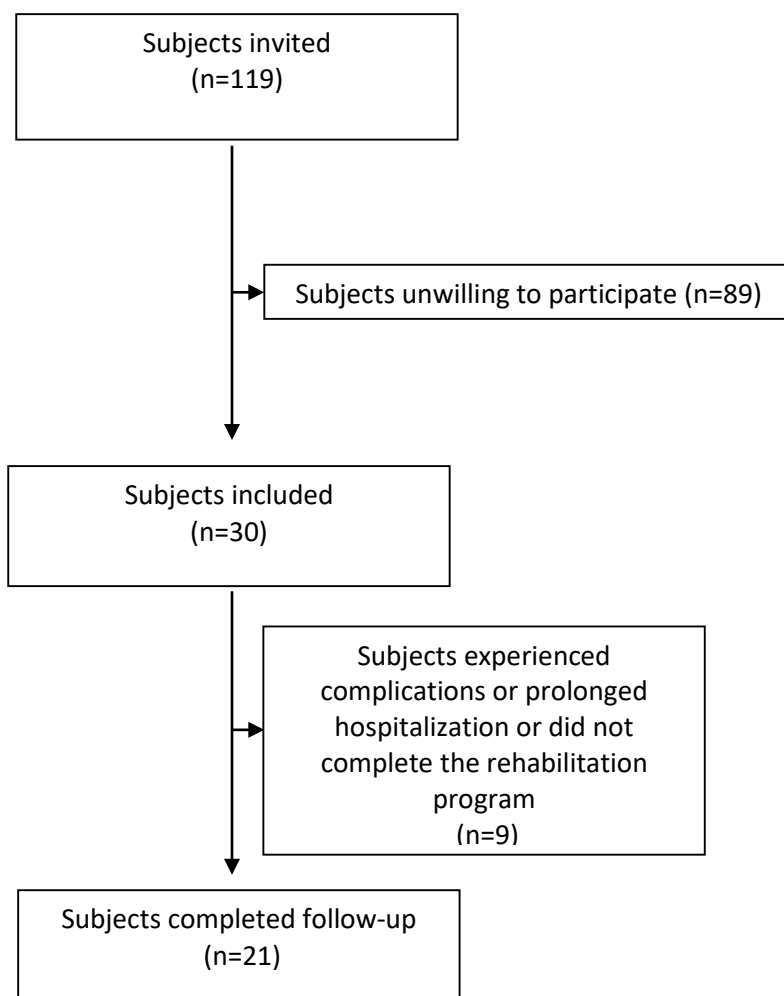
**Table 2** Relations between change in LTM after CABG surgery and clinical status at entry of rehabilitation

	Correlation coefficient (r) total change in LTM (kg)	Correlation coefficient (r) relative change in LTM (%)
<b>Exercise capacity</b>		
Cycling power output (Wmax)	0.19	0.21
Cycling power output (% predicted)	0.31	0.32
Oxygen uptake (mL/min)	0.28	0.29
Oxygen uptake (% predicted)	0.34	0.35
First ventilatory threshold (ml/min)	<b>0.59*</b>	<b>0.61*</b>
Second ventilatory threshold (ml/min)	0.43	0.44
<b>Blood parameters</b>		
Total cholesterol (mg/dl)	-0.22	-0.26
LDL cholesterol (mg/dl)	-0.27	-0.30
HDL cholesterol (mg/dl)	0.17	0.16
Triglyceride (mg/dl)	-0.13	-0.15
Glucose (mmol/l)	0.07	0.10
C-peptide (ng/ml)	-0.38	-0.40
Insulin (mU/l)	-0.34	-0.34
HOMA-IR index	-0.27	-0.27
C-Reactive protein (mg/dl)	0.42	0.42
Glycated hemoglobin (mmol/mol)	-0.25	-0.22
Cortisol (total; µg/dl)	-0.30	-0.31
Testosterone (total; ng/ml)	-0.17	-0.18
Sex hormone-binding globulin (nmol/l)	-0.01	-0.02
Insulin-like growth factor-1 (µg/l)	-0.16	-0.18
Growth hormone (µg/l)	-0.14	-0.14
Free androgen index (%)	-0.30	-0.26
Cortisol-to-testosterone ratio	0.01	0.02

LTM, lean tissue mass; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance. \*Significant correlation ( $P < 0.05$ ). Correlations were corrected for age, body height and weight.

**Figure 1** Change in fat mass (FM) and lean tissue mass (LTM) after CABG surgery and during rehabilitation



**Supplementary Figure 1** Study flowchart

**Supplementary Figure 2** Relation between changes in lean tissue mass after CABG surgery and first ventilatory threshold during exercise testing at entry of rehabilitation

