Journal of Cachexia, Sarcopenia and Muscle (2015)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12093

Concurrent depletion of skeletal muscle, fat, and left ventricular mass in patients with cirrhosis of the liver

Evidence for cardiac atrophy has now been demonstrated multiple times in animal models of cancer cachexia[1]; however, prospective clinical studies to detect an active process of cardiac atrophy in patients with cachexia have not yet been undertaken. Nevertheless if this were to occur, it would be expected that in patients with diseases associated with cachexia, a very low cardiac mass would coincide with the presence of severe skeletal muscle depletion (i.e. *sarcopenia*) as well as depletion of the fat mass. To test this conjecture, we evaluated left ventricular mass (LVM) determined by echocardiography and body composition [skeletal muscle (SM) and total adipose tissue (TAT)] by computed tomography (CT) cross-sectional images at the level of the third lumbar vertebra,[2] in a population of patients with liver cirrhosis, 50% of whom had concurrent hepatocellular carcinoma ($n = 100$). These patients were candidates for liver transplantation and had routine evaluations with echocardiography and CT, from which LVM and body composition can be derived. Cirrhotic patients are at risk for weight loss and sarcopenia, which associate with mortality.[2,3] Cross-sectional areas of SM and TAT were used to calculate estimated total body fat free mass (FFM) and fat mass (FM), respectively.[4] All parameters (SM, TAT, FFM, FM) were normalized for stature (divided by

Table 1 Distribution of left ventricular mass index and cachexia characteristics

	Left ventricular mass indexed by height^2		
	Low LVMI[a] ($n = 17$)	Average LVMI[b] ($n = 66$)	High LVMI[c] ($n = 17$)
Age (y) (95% CI)	57.5 ± 8.5; (53.1–61.8)	58.0 ± 9.0; (55.7–60.2)	56.7 ± 6.5; (53.4–60.0)
Male (%)	10 (58.8)	43 (65.2)	12 (70.6)
BMI (kg/m^2) (95% CI)	24.2 ± 5.2; (21.6–26.9)	27.0 ± 5.4; (25.7–28.4)	25.7 ± 7.1; (22.1–29.4)
LVM (g) (95% CI)	95.8 ± 16.5*** (87.3–104.3)	164.9 ± 25.8 (158.6–171.3)	221.7 ± 36.0$^{\times\times\times}$ (203.3–240.2)
LVMI (g/m^2) (95% CI)	33.4 ± 7.2*** (29.7–37.1)	57.7 ± 7.3 (55.8–59.5)	77.7 ± 10.7$^{\times\times\times}$ (72.2–83.2)
LVM indexed by BSA (g/m^2) (95% CI)	52.3 ± 11.7*** (46.3–58.3)	87.3 ± 11.7 (84.4–90.1)	119.8 ± 13.1$^{\times\times\times}$ (113.1–126.5)
Normal diastolic function *n* (%)	8 (47.1)	35 (53.0)	9 (52.9)
Hypertension (%)	1 (5.9)	8 (12.3)	2 (11.8)
Diabetes mellitus (%)	3 (17.6)	11 (16.7)	2 (11.8)
CT-defined SMI (cm^2/m^2) (95% CI)	42.7 ± 7.5***; (38.9–46.6)	51.5 ± 8.2; (49.5–53.5)	49.3 ± 10.7; (43.9–54.9)
Men, Women	♂44.7 ± 5.5*** ♀39.9 ± 9.3***	♂54.2 ± 7.1 ♀46.4 ± 7.7	♂51.3 ± 8.8 ♀44.8 ± 14.4
CT-defined TATI (cm^2/m^2) (95% CI)	69.5 ± 61.1 (38.1–100.9)	107.8 ± 70.1 (90.5–125.0)	113.9 ± 71.8 (77.0–150.8)
Estimated FFMI (kg/m^2) (95% CI)	14.8 ± 2.3*** (13.6–16)	17.5 ± 2.4 (16.9–18.1)	16.8 ± 3.2 (15.2–18.5)
Estimated FMI (kg/m^2) (95% CI)	6.4 ± 2.7 (4.9–7.7)	8.1 ± 3.0; (7.3–8.7)	8.3 ± 3.0; (6.7–9.8)
Sarcopenia[d] (%)	12 (70.6)**	18 (27.3)	9 (52.9) $^{\times}$
Fat depletion[e] (%)	12 (70.6)	29 (43.9)	8 (47.1)
Creatinine (μmol/L) (95% CI)	138.4 ± 155.1 (55.7–221.0)	85.2 ± 36.4 (76.3–94.2)	91.1 ± 38.4 (71.3–110.8)
Bilirubin (μmol/L) (95% CI)	152.0 ± 233.4 (27.5–276.3)	118.8 ± 223.3 (63.9–173.7)	134.3 ± 154.5(54.9–213.8)
Albumin (g/L) (95% CI)	35.1 ± 6.0; (31.9–38.2)	34.2 ± 5.7; (32.8–35.6)	35.2 ± 9.4; (30.3–40.0)
Hepatocellular carcinoma *n* (%)	9 (52.5)	31 (47.0)	10 (58.8)
Hepatitis C virus (aetiology) *n* (%)	7 (41.2)	36 (54.5)	8 (47.1)

[a]Low LVMI; > 1 SD below of gender-specific mean value of LVMI.
[b]Average LVMI; within ±1 SD of gender-specific mean value of LVMI.
[c]High LVMI; >1 SD above gender-specific mean value of LVMI.
[d]Sarcopenia, skeletal muscle depletion based on CT findings as described previously[2].
[e]Fat depletion, TATI< gender-specific median value of TATI. BMI, body mass index; BSA, body surface area; CT, computed tomography; FFMI, fat free mass indexed by height^2; FMI, fat mass indexed by height^2; LVMI, left ventricular mass indexed by height^2; SMI, skeletal muscle indexed by height^2; TATI, total adipose tissue indexed by height^2.
Values (quantitative and qualitative) of Low LVMI group vs. Average LVMI group:
***$p < 0.001$.
**$p < 0.01$.
Values of High LVMI group vs. Average LVMI group:
$^{\times\times\times}p < 0.001$.
$^{\times}p < 0.05$.

height in m^2). Patients were categorized based on LVM/height^2 (LVMI): Low LVMI (>1 SD below gender-specific mean value, $n = 17$), Average LVMI (within ±1 SD of gender-specific mean value, $n = 66$), and High LVMI (>1 SD above gender-specific mean value, $n = 17$) (*Table* 1).

As patients were candidates for a major surgery (liver transplantation), all of them presented with normal left ventricular ejection fraction (>50%), and none showed any echocardiographic evidence of myocardial infarction or severe valvular disease. Mean age, gender distribution, diastolic dysfunction, main aetiology of cirrhosis, serum creatinine, albumin, and bilirubin, and prevalence of HCC were not different among the three groups (Low, Average, and High LVMI) (*Table* 1). Low LVMI group included individuals with absolute LVM ranging from 57 to 124 g (♂) and 88–112 g (♀). Overall *sarcopenia*[2] was more prevalent in patients with Low LVMI compared to the patients with Average LVMI (70.6% vs. 27.3%; HR = 6.4; 95% CI, 1.9–20.7; $p = 0.002$). Five (29%) patients in the Low LVMI group were extremely sarcopenic (SMI $<39\,cm^2/m^2$ ♂ and SMI $<34\,cm^2/m^2$ ♀, while only two (3%) of patients with Average LVMI group were extremely sarcopenic ($p = 0.003$, Fisher's Exact Test). Fat depletion (TAT index <gender-specific median value) tended to be more prevalent in patients with Low LVMI (70.6%) vs. the Average LVMI (43.9%) ($p = 0.08$). Collectively, these data suggest concurrent depletion of SM, TAT, and LV mass.

The High LVMI group deserves separate consideration. As expected for a group of polymorbid elderly patients, this population with cirrhosis includes some individuals with evidence of cardiac hypertrophy. The High LVMI group appeared to show some manifestations of cardiac cachexia. Overall sarcopenia was more prevalent in patients with High LVMI vs. Average LVMI (52.9% vs. 27.3%; HR = 3.0; 95% CI, 1.1–8.9; $p = 0.04$). Four (23.5%) patients in the High LVMI group were extremely sarcopenic (SMI $<39\,cm^2/m^2$ ♂ and SMI $<34\,cm^2/m^2$ ♀). Over the entire population there was a weak correlation between LV mass and CT-defined SM area ($r = 0.37$; $p < 0.001$), and this was not surprising given that patients with the largest hearts could be of high or average muscularity, sarcopenic, or indeed extremely sarcopenic. Also, TAT correlated weakly with LV mass ($r = 0.26$; $p = 0.009$). Both these relationships were weaker than those reported in the general population ($r = 0.5$ for lean body mass and $r = 0.6$ for fat)[5,6] perhaps because chronic catabolic disease results in additional variation in organ mass not present in healthy individuals. We recently discussed that in human patients with chronic hypercatabolic diseases both atrophied and hypertrophied hearts could be significantly associated with severe muscle depletion.[1] The association between muscle and fat depletion and both extreme ends of cardiac remodelling (atrophy and hypertrophy) in diseases associated with cachexia need to be tested in larger scale studies with specific focus on related underlying mechanisms.

Acknowledgements

SMRKB is supported by Alberta Innovates Health Solutions Graduate Studentship award and also Izaak Walton Killam Memorial Scholarship. The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia, and Muscle (von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia, and Muscle. J Cachexia Sarcopenia Muscle 2010; 1:7–8).

Conflicts of interest

SMRKB, HB, SG, AML and VEB declare that they have no conflict of interest.

Seyyed Mohammad Reza Kazemi-Bajestani
Department of Oncology, Division of Palliative Care Medicine, University of Alberta, Edmonton, AB, Canada

Harald Becher
Department of Medicine, Division of Cardiology, University of Alberta, Edmonton, AB, Canada

Sunita Ghosh
Department of Medical Oncology, Cross Cancer Institute, Edmonton, AB, Canada

Aldo J. Montano-Loza
Division of Gastroenterology and Liver Unit, University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada

Vickie E Baracos
Department of Oncology, Division of Palliative Care Medicine, University of Alberta, Edmonton, AB, Canada
vbaracos@ualberta.ca

References

1. Kazemi-Bajestani SM, Becher H, Fassbender K, Chu Q, Baracos VE. Concurrent evolution of cancer cachexia and heart failure: bilateral effects exist. *J Cachexia Sarcopenia Muscle* 2014;**5**:95–104.
2. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, *et al.* Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012;**10**:166–173.
3. Montano-Loza AJ. New concepts in liver cirrhosis: clinical significance of sarcopenia in cirrhotic patients. *Minerva Gastroenterol Dietol* 2013;**59**:173–186.
4. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;**33**:997–1006.

5. Andren B, Lind L, Larsson K, Hedenstierna G, Ljunghall S, Lithell H. The influence of body composition on left ventricular mass and other echocardiographic and Doppler measurements in 70-year-old males. *Clin Physiol* 1995;**15**:425–433.
6. Rider OJ, Francis JM, Ali MK, Byrne J, Clarke K, Neubauer S, *et al.* Determinants of left ventricular mass in obesity; a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2009;**11**:9.

DOI: 10.1002/jcsm.12093