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Cardiovascular Function and Predictors of Exercise Capacity in Patients With Colorectal Cancer

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ABSTRACT

BACKGROUND Patients with colorectal cancer (CRC) often present with dyspnea and fatigue. These are also frequent symptoms in patients with chronic heart failure (CHF).

OBJECTIVES We hypothesized that similar patterns of cardiovascular perturbations are present in CRC and CHF.

METHODS We prospectively studied 50 patients with CRC, 51 patients with CHF, and 51 control subjects. The CRC group was divided into 2 subgroups: patients who underwent chemotherapy ($n = 26$) and chemotherapy-naive patients ($n = 24$). We assessed exercise capacity (spiroergometry), cardiac function (echocardiography), heart rate variability (Holter electrocardiography), body composition (dual-energy x-ray absorptiometry), and blood parameters.

RESULTS Compared with the control arm, the left ventricular ejection fraction (CRC group 59.4%; control group 62.5%) and exercise performance as assessed by peak oxygen consumption (peak VO_2) (CRC group 21.8 ml/kg/min; control group 28.0 ml/kg/min) were significantly reduced in CRC patients (both $p < 0.02$). Markers of heart rate variability were markedly impaired in CRC patients compared with control subjects (all $p < 0.008$). Compared with the control group, the CRC group also showed reduced lean mass in the legs and higher levels of the endothelium-derived C-terminal-pro-endothelin-1 (both $p < 0.02$). Major determinants of cardiovascular function were impaired in chemotherapy-treated patients and in the chemotherapy-naive patients, particularly with regard to exercise capacity, left ventricular ejection fraction, lean mass, and heart rate variability (all $p < 0.05$ vs. control subjects).

CONCLUSIONS Some aspects of cardiovascular function are impaired in patients with CRC. More importantly, our findings were evident independently of whether patients were undergoing chemotherapy. (J Am Coll Cardiol 2014;64:1310–9) © 2014 by the American College of Cardiology Foundation.

More than 1 million new cases of colorectal cancer (CRC) are diagnosed worldwide each year. CRC is the third most common malignancy and the fourth most common cause of cancer mortality worldwide (1). Due to improvements in early detection and cancer treatment, survival rates have increased continuously over the last few decades, leading to a growing interest for maintaining

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optimal health in this group of patients. Although treatment of some cancer- or therapy-related symptoms has improved considerably, there is still no accepted treatment for complaints of fatigue. The exact origin of fatigue in cancer patients is unknown; it may be caused by the disease itself, by its treatment, or it may be a psychological response (2). Fatigue can lead to impaired quality of life, decreased levels of physical activity (detraining), and increased incidences of sick leave (3).

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Understanding the pathophysiology of fatigue may help to develop therapies aimed at improving patients' exercise capacity, and thus, quality of life. Because fatigue is also a frequent observation in patients with chronic heart failure (CHF), comparing CRC and CHF may be clinically worthwhile. Both groups of patients with CRC and CHF present with similar symptoms, such as impaired exercise capacity, dyspnea, or weight loss. Recent data have shown that CHF, once considered a pure hemodynamic problem, is a complex interplay of underlying cardiac injury, chronic neurohormonal stress, immune activation, and metabolic imbalance (4).

We hypothesized that aspects of the well-known pathophysiology of CHF play an important role in understanding the impairment of exercise capacity in patients with CRC, independent of the commencement of chemotherapy. To better understand these mechanisms, we studied body composition, cardiac function, exercise capacity, heart rate variability (HRV), and blood parameters in patients with CRC and compared these with the parameters in control subjects and in patients with CHF.

METHODS

PATIENT RECRUITMENT. We prospectively studied 50 patients with CRC, 51 patients with CHF, and 51 control subjects of similar age. Table 1 lists the patients' clinical characteristics. We recruited CRC patients from the Department of Hematology and Oncology of the Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany, between July 2009 and November 2010. We identified and screened patients with CRC for eligibility by medical chart review of patients scheduled to attend treatment or in treatment of CRC. The primary diagnosis of CRC was on the basis of histological proof from tissue biopsy. Exclusion criteria for patients with CRC were clinical signs of infection, inflammatory disease, chronic obstructive pulmonary disease, clinical signs or symptoms of CHF, significant cardiovascular disease other than hypertension, other cancer diagnosis in the 5 years before recruitment, age <18 years, and an Eastern Cooperative Oncology Group performance status of more than 2. Patients with CHF of similar age to patients with CRC were included when the following criteria were met: symptoms and clinical signs of CHF and documented left ventricular impairment measured by echocardiography (left ventricular ejection fraction [LVEF] ≤45%). All patients were stable and were maintained on their medications for at least 4 weeks before being studied. Control subjects of similar age were recruited from patients' relatives and hospital staff. They were allowed antihypertensive or antidiabetic medication. Table 2 lists the subjects' medications. All cancer patients completed the questionnaire Short Form-36 about their quality of life.

To understand the impact of chemotherapy in the course of CRC, the CRC group was divided into 2 subgroups: the first group included patients who were already being treated (26 patients), and the second group included patients who were just diagnosed with CRC and were not receiving therapy (24 patients). The local ethics committee approved the study, and all subjects provided written informed consent.

BLOOD COLLECTION. Venous blood was collected from an antecubital vein and analyzed immediately. Full blood count, clinical chemistry parameters, and coagulation were analyzed according to local laboratory standard operating procedures. High-sensitivity C-reactive protein (hsCRP) was assessed using particle-enhanced nephelometry BN2 (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany); the lower reference limit was 5 mg/l. Levels of high-sensitivity troponin T (hsTnT) were measured by electrochemiluminescence on a Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany); the lower reference limit was 14 pg/ml. After centrifugation, aliquots were stored at -80°C before analysis.Detection of mid-regional pro-adrenomedulin (MR-proADM), C-terminal pro-endothelin (CT-proET)-1, mid-regional pro-atrial natriuretic peptide (MR-proANP), and the C-terminal portion of pro-vasopressin, copeptin, was performed using novel assays provided by Thermo Fisher/B.R.A.H.M.S GmbH (Hennigsdorf, Germany). The analytical detection limits of these assays are 0.08 nmol/l (5), 0.4 pmol/l (6), 20 pmol/l (7), and 1.7 pmol/l (8), respectively. Due to the lack of material, hsCRP was not measured in control subjects, MR-proADM and MR-proANP were not measured in 8

ABBREVIATIONS AND ACRONYMS

5-FU = 5-fluorouracil

CHF = chronic heart failure

CRC = colorectal cancer

CT-proET = C-terminal pro-endothelin

FEV_1 = forced expiratory volume in 1 second

FVC = forced vital capacity

HF = high frequency

HRV = heart rate variability

hsCRP = high-sensitivity C-reactive protein

hsTnT = high-sensitivity troponin T

LF = low frequency

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

LVM = left ventricular mass

MR-proADM = mid-regional pro-adrenomedulin

MR-proANP = mid-regional pro-atrial natriuretic peptide

SDANN = SD of 5-min mean RR intervals

SDNN = SD of all normal RR intervals

SDNN index = mean of the SD of normal RR intervals every 5 min

VCO_2/VO_2 = respiratory exchange ratio

VE/VCO_2 = ratio of minute ventilation and carbon dioxide output

VLF = very low frequency

VO_2 = oxygen consumption

TABLE 1 Clinical Characteristics of Control Subjects, Patients With CRC, and Patients With CHF

	Control Subjects (n = 51)	Patients With CRC (n = 50)	Patients With CHF (n = 51)	p Value*
Age, yrs	61.3 ± 11.2	59.9 ± 12.0	63.5 ± 10.9	0.26
Male	50.9	40.0†	82.3‡	< 0.001
Body mass index, kg/m^2	24.9 ± 3.3	25.5 ± 5.2§	27.5 ± 5.0‖	0.02
Heart rate, min^{-1}	64.7 ± 12.3	73.0 ± 10.9†‡	64.6 ± 11.2	0.0002
Systolic blood pressure, mm Hg	128.9 ± 17.7	126.1 ± 17.7	118.9 ± 23.0¶	0.03
Diastolic blood pressure, mm Hg	78.8 ± 10.2	76.9 ± 8.5§	72.5 ± 11.5‖	0.007
Hemoglobin, g/dl	14.1 ± 1.1	12.0 ± 1.3†‡	13.4 ± 1.5‖	< 0.001
Leukocytes, nl^{-1}	6.3 ± 1.7	6.0 ± 1.9#	7.2 ± 2.4¶	0.006
Platelets, nl^{-1}	234.8 ± 57.2	266.0 ± 86.6§	230.7 ± 80.2	0.09
Sodium, mmol/l	141.6 ± 2.2	140.5 ± 2.8	141.1 ± 3.8	0.17
Potassium, mmol/l	4.2 ± 0.4	4.0 ± 0.3#	4.3 ± 0.5	0.02
Creatinine, mg/dl	0.9 ± 0.1	0.8 ± 0.2†	1.1 ± 0.3‡	< 0.001
ALT, U/l	25.3 ± 13.1	30.0 ± 39.5	24.9 ± 12.7	0.85
AST, U/l	25.0 (22.0–29.0)	23.0 (20.0–32.0)	26.0 (22.2–33)	0.81
GGT, U/l	25.0 (17.0–30.0)	42.0 (25.0–82.0)‡	43.0 (31.5–67.7)‡	< 0.001
Albumin, g/l	40.3 ± 5.5	36.4 ± 4.4‡	36.7 ± 3.9‡	0.0002

Values are mean ± SD, %, or odds ratio (95% confidence intervals). *Analysis of variance or chi-square p value. †p<0.001 versus patients with CHF. ‡p<0.001 versus control subjects. §p<0.05 versus patients with CHF. ‖p<0.01 versus control subjects. ¶p<0.05 versus control subjects. #p<0.01 versus patients with CHF.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHF = chronic heart failure; CRC = colorectal cancer; GGT = gamma-glutamyl transferase.

control subjects and 3 CHF patients, and CT-proET-1 and copeptin were not measured in the CHF group and 19 control subjects.

CARDIOVASCULAR ASSESSMENTS AND BODY COMPOSITION. All subjects underwent transthoracic 2-dimensional echocardiography using a Vivid S6 ultrasonographic system (GE Healthcare, Waukesha, Wisconsin). LVEF, left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVESV) were calculated using multiplane techniques. If multiplane assessment was impossible, measurements were obtained from monoplane views (<20% of patients). The LVEDV index and the LVESV index were assessed as LVEDV or LVESV divided by body surface area. Left ventricular mass (LVM) was calculated following the recommendations of the American Society of Echocardiography (9). The LVM index was obtained as the ratio of the LVM to body surface area. Due to technical problems, 1 CRC patient did not undergo echocardiography, and LVEF was not measured in 4 control subjects.

A treadmill exercise test was performed according to the Bruce or the modified Naughton protocol, depending on the performance status of each subject. Peak oxygen consumption (peak VO_2) and anaerobic threshold were measured as ml per kilogram body weight per minute; the ratio of minute ventilation and carbon dioxide output (VE/VCO_2 slope) assessed breathing efficiency. Absolute peak VO_2 (ml/min) was used for regression analyses. All patients exercised until limited by symptoms and until the respiratory exchange ratio (VCO_2/VO_2) was ≥1. One control subject, 2 CRC patients, and 4 CHF patients refused to undergo treadmill exercise testing. One control subject, 3 CRC patients, and 11 CHF patients did not reach a VCO_2/VO_2 of 1; therefore, these test results were excluded from the analysis.

Dual-energy X-ray absorptiometry, using a Lunar prodigy model with Lunar "enCore 2002" software (both from GE Healthcare, Waukesha, Wisconsin) assessed body composition. For technical reasons, 1 patient with CRC did not undergo the dual-energy X-ray absorptiometry scanning.

All subjects underwent 24-h electrocardiographic monitoring using a 12- or 3- channel DMS-300 recorder (DMS, Beijing, China). The tapes were subsequently analyzed to measure HRV using validated CardioScan Premier 12 software (version 12.4.0051a, DMS).

NONSPECTRAL ANALYSIS. The mean RR duration (mean of all normal intervals between 2 QRS complexes) from the whole recording was assessed, and the following measures were calculated: SD of all normal RR intervals (SDNN), SD of 5-min mean RR intervals (SDANN), and mean of the SD of normal RR intervals every 5 min (SDNN index) (10).

SPECTRAL ANALYSIS. After determination of the total oscillatory power, spectral analysis allowed identification of very low-frequency (VLF) (0.003 to 0.04 Hz), low-frequency (LF) (0.04 to 0.15 Hz), and high-frequency (HF) (0.15 to 0.40Hz) components. The power within each band was expressed in ms^2. VLF seems to be related to thermoregulation,

TABLE 2 Medication at Study Entry

	Control Subjects (n = 51)	Patients With CRC (n = 50)	Patients With CHF (n = 51)
Aspirin	8	8	78
ACE-I/ARB	12	24	96
Beta-blocker	6	12	94
Spironolactone	0	4	57
Diuretics	6	10	75
Anticoagulants	0	2	43
Lipid-lowering drugs	12	8	29
Antidiabetics	2	6	8
Insulin	0	4	16
Proton pump inhibitors	0	32	31
Opioids	0	8	2
Antidepressants	0	8	10

Values are %.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; other abbreviations as in Table 1.

the renin-angiotensin-aldosterone system, and peripheral vasomotor tone. LF relates to baroreflex activity and is primarily influenced by sympathetic activity. HF corresponds to the respiratory modulation and is vagally mediated (10).

For technical reasons, 1 control subject, 5 CRC patients, and 2 CHF patients did not undergo electrocardiographic Holter monitoring. In the CHF group, 3 patients had atrial fibrillation, and 19 patients had an implanted device, such as a pacemaker (n = 6), an implanted cardioverter-defibrillator (n = 15), or cardiac resynchronization therapy (n = 9). Therefore, they were excluded from this part of the analysis.

STATISTICAL ANALYSIS. Normally distributed data are presented as mean ± SD, and non-normally distributed data are presented as median (25th and 75th percentiles). The Kolmogorov-Smirnov test assessed normal distribution. Unpaired Student's *t*-test, analysis of variance (ANOVA) with Fisher's post-hoc test, chi-square test, and simple regression (using log-transformed data when necessary) were used as appropriate. A p value <0.05 was considered significant in all experiments. Statistical analysis was performed using StatView 5.0 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Among the CRC patients, 47 (86%) had surgical tumor resection, and 26 (52%) presented with metastatic disease at the time of examination. The median time since first diagnosis of CRC was 22.8 months (range 2 to 24 months). Regarding tumor localization, 22 patients (44%) had adenocarcinoma of the rectum, 14 (28%) had adenocarcinoma of the sigmoid colon, 3 (6%) had adenocarcinoma of the ascending colon, 3

TABLE 3 Results of Body Composition Analysis, Treadmill Exercise Test, Holter Electrocardiography and Biomarker Analyses in Control Subjects and in Patients With CRC or CHF

Characteristic	Control Subjects (n = 51)	Patients With CRC (n = 50)	Patients With CHF (n = 51)	p Value*
Body composition, kg				
Entire body				
Lean	51.2 ± 11.8	47.2 ± 9.8†	54.3 ± 11.0	0.005
Fat	21.4 ± 8.0	23.8 ± 11.1	26.2 ± 10.3‡	0.05
Arms				
Lean	5.5 ± 1.8	4.9 ± 1.4†	5.9 ± 1.4	0.007
Fat	1.8 ± 0.7	2.2 ± 1.1	2.4 ± 1.1§	0.03
Legs				
Lean	17.3 ± 4.5	15.2 ± 3.8‡‖	17.2 ± 3.7	0.01
Fat	6.7 ± 2.6	7.7 ± 4.0	7.5 ± 3.7	0.28
Cardiovascular function				
Breath efficiency, VE/VCO_2 slope	28.0 (25.0-30.0)	31.0 (28.0-34.2)§‖	33.0 (29.5-38.5)¶	<0.0001
Anaerobic threshold, ml/kg/min	16.4 ± 4.5	14.5 ± 3.6‡†	11.7 ± 3.0¶	<0.0001
LVEDVI, ml/m^2	41.4 (32.3-56.4)	46.7 (39.8-56.3)#	70.8 (49.7-97.3)¶	<0.0001
LVESVI, ml/m^2	16.4 (10.6-23.0)	19.6 (13.4-25.6)‡#	45.5 (32.8-71.9)¶	<0.0001
LVMI, g/m^2	84.8 (71.8-112.5)	87.5 (70.9-97.6)‖	143.7 (113.6-175.9)§	0.0006
SDNN index, ms	53.0 ± 17.0	41.2 ± 13.0¶	44.7 ± 20.1‡	0.003
VLF, ms^2	2173.7 ± 1308.6	1365.2 ± 792.5¶	1311.4 ± 911.8¶	0.0002
LF, ms^2	691.5 ± 430.0	406.6 ± 292.2¶	356.7 ± 335.0¶	<0.0001
HF, ms^2	126.4 (83.2-246.2)	95.7 (51.3-149.4)§	128.4 (54.8-250.2)	0.03
Biomarkers				
MR-proADM, nmol/l	0.5 ± 0.2	0.6 ± 0.2#	1.0 ± 0.5¶	<0.0001
MR-proANP, pmol/l	95.2 (61.9-122.6)	71.2 (48.4-106.2)‡#	233.2 (126.6-365.8)¶	<0.0001
CT-proET-1, pmol/l	42.7 ± 14.6	55.7 ± 22.7	–	0.005
Copeptin, pmol/l	4.1 (2.9-6.3)	5.7 (3.9-11.1)	–	0.01
hsCRP, mg/l	–	5.4 (1.8-13.4)	2.9 (1.4-4.4)	0.01
hsTnT, pg/ml	5.0 (4.0-5.7)	6.0 (4.0-8.2)#	17 (11-23)¶	<0.001

Values are mean ± SD or odds ratio (95% confidence intervals). *Analysis of variance or chi-square p value. †$p < 0.01$ versus patients with CHF. ‡$p < 0.05$ versus control subjects. §$p < 0.01$ versus control subjects. ‖$p < 0.05$ versus patients with CHF. ¶$p < 0.001$ versus control subjects. #$p < 0.001$ versus patients with CHF.

CT-proET = C-terminal pro-endothelin; HF = high frequency; hsCRP = high-sensitivity C-reactive protein; hsTnT = high-sensitivity troponin T; LF = low frequency; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVMI = left ventricular mass index; MR-proADM = midregional pro-adrenomedulin, MR-proANP = midregional pro-atrial natriuretic peptide; SDNN index = mean of the SD of normal RR intervals every 5 min; VE/VCO_2 = ratio of minute ventilation and carbon dioxide output; VLF = very low frequency.

TABLE 4 Results of Body Composition Analysis, Treadmill Exercise Test, Echocardiography, Holter Electrocardiography and Biomarker Analyses in Chemotherapy-Treated Patients and in Therapy-Naïve Patients

	Control Subjects (n = 51)	Naïve Patients (n = 24)	Chemotherapy Patients (n = 26)	p Value*
Body composition, kg				
Entire body				
Lean	51.2 ± 11.8	45.9 ± 10.6†	48.3 ± 9.0	0.13
Fat	21.4 ± 8.0	24.2 ± 10.9	23.5 ± 11.5	0.44
Arms				
Lean	5.5 ± 1.8	4.6 ± 1.3†	5.1 ± 1.4	0.12
Fat	1.8 ± 0.7	2.2 ± 1.1	2.2 ± 1.2	0.16
Legs				
Lean	17.3 ± 4.5	14.8 ± 3.9†	15.9 ± 3.5	0.05
Fat	6.7 ± 2.6	7.7 ± 3.5	7.8 ± 4.7	0.29
Cardiovascular function				
Peak heart rate, min^{-1}	149.2 ± 18.5	160.7 ± 20.7†‡	142.8 ± 24.2	0.02
Peak VO_2, ml/kg/min	28.0 ± 7.0	23.4 ± 4.3§	20.4 ± 5.6‖	<0.0001
Breath efficiency, VE/VCO_2 slope	28.0 (25.0–30.0)	30.0 (25.5–33.2)‡	33.0 (30.0–38.0)‖	<0.0001
LVEF, %	62.5 ± 5.7	58.9 ± 4.5§	59.9 ± 5.3	0.02
SDNN index, ms	52.9 ± 17	45.0 ± 12.5†	37.2 ± 12.7‖	0.0003
HF, ms^2	126.4 (83.2–246.2)	109.1 (84.0–161.2)‡	68.6 (37.7–121.4)‖	0.0004
Biomarkers				
MR-proADM, nmol/l	0.50 ± 0.22	0.56 ± 0.17¶	0.70 ± 0.28‖	0.003
MR-proANP, pmol/l	95.2 (61.9–122.6)	63.7 (41.2–89.6)§	86.4 (51.6–115.4)	0.03
CT-proET-1, pmol/l	42.7 ± 14.6	49.9 ± 20.8¶	61.1 ± 23.5‖	0.003
Copeptin, pmol/l	4.1 (2.9–6.3)	5.3 (3.5–9.2)	7.3 (4.5–11.9)§	0.02
hsTnT, pg/ml	5.0 (4.0–5.7)	4.0 (2.0–6.5)‡	7.0 (4.0–10.5)§	0.007

Values are mean ± SD or odds ratio (95% confidence intervals). *Analysis of variance or chi-square p value. †$p < 0.05$ versus control subjects. ‡$p < 0.01$ versus patients undergoing chemotherapy. §$p < 0.01$ versus control subjects. ‖$p < 0.001$ versus control subjects. ¶$p < 0.05$ versus patients undergoing chemotherapy.
Peak VO_2 = peak oxygen consumption; other abbreviations as in Table 3.

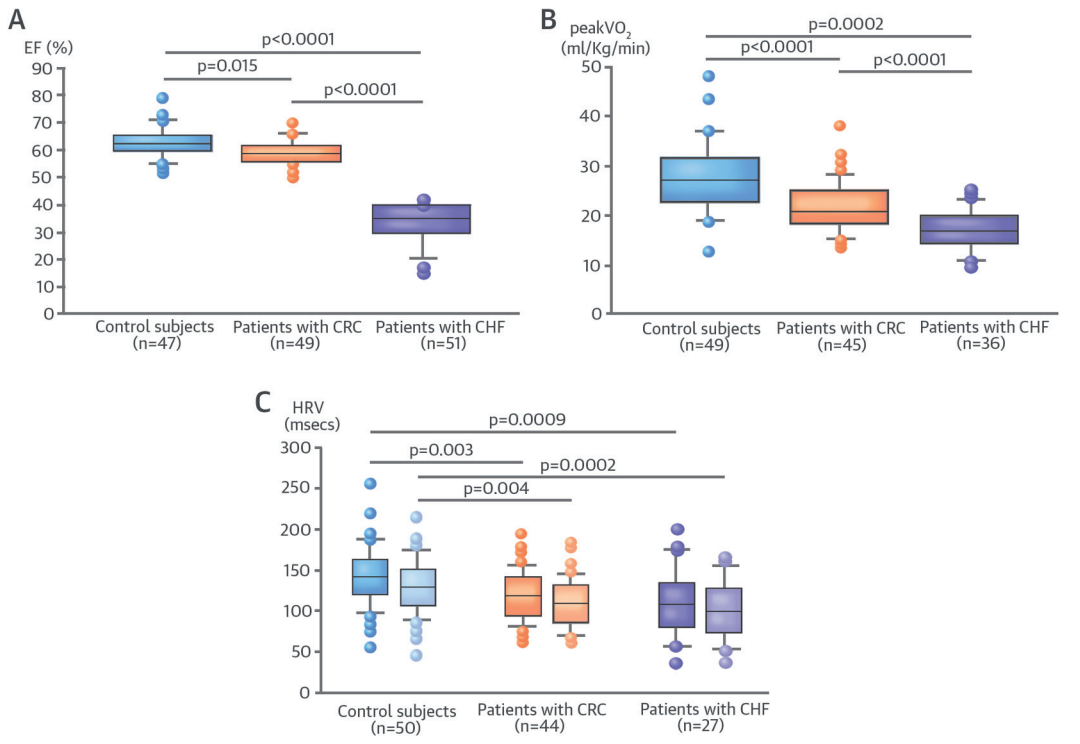
(6%) had adenocarcinoma of the transverse colon, and 8 (16%) had adenocarcinoma in other locations. The patients' median carcinoembryonic antigen level was 3.8 μg/l (1.6 to 15.2 μg/L). A total of 26 CRC patients (52%) received chemotherapy while in the study; 21 of them (81%) received 5-fluorouracil (5-FU), 2 patients received capecitabine (8%), 10 were on irinotecan (38%), 11 received oxaliplatin (42%), 11 were on bevacizumab (42%), 1 was on cetuximab (4%), 3 were on panitumumab (11%), and 1 was on mitomycin (4%), according to different regimens. One patient received radiotherapy.

There were no significant differences in terms of age among the 3 groups of subjects. There were no significant differences with regard to sex, body mass index, and blood pressure between patients with CRC and control subjects (Table 1). Patients with CRC had significantly higher heart rates at test and lower hemoglobin values compared with patients with CHF and control subjects (Table 1). We also found elevated levels of hsCRP in CRC patients compared with CHF patients (Table 1); although 50% of CRC patients were in the normal range (hsCRP >5 mg/l, n = 25). hsTnT was significantly increased in CHF patients only, compared with CRC patients and control subjects; no such elevation was noted in the CRC patients (Table 3). Values of MR-proADM, MR-proANP, CT-proET-1, and copeptin are given in Tables 3 and 4. CT-proET-1 and copeptin were significantly increased in CRC patients compared with control subjects. In the cancer patients, fatigue was reported as "often" in 30%, "sometimes" in 62.5%, and "never" in 7.5%.

No statistical difference was detected between the relatively small subgroups of CRC patients with regard to sex distribution (current chemotherapy: 50%; chemotherapy-naive: 29.2% male; p = 0.13), age (therapy group: 62.2 ± 10.9 years; naive group: 57.3 ± 12.8 years; p = 0.15), body mass index (therapy group: 25.5 ± 4.9 kg/m^2; naive group: 25.4 ± 5.4 kg/m^2; p = 0.93), heart rate (therapy group: 73.5 ± 11.7 beats/min; naive group: 72.3 ± 10.2 beats/min; p = 0.71), systolic blood pressure (therapy group: 129.8 ± 17.1 mm Hg; naive group: 121.8 ± 17.7 mm Hg; p = 0.11), and diastolic blood pressure (therapy group: 78.8 ± 8.5 mm Hg; naive group: 74.8 ± 8.2 mm Hg; p = 0.10). There was borderline significance with regard to hemoglobin levels between the 2 groups (therapy group: 12.3 ± 1.1 g/dl; naive group: 11.6 ± 1.9 g/dl; p = 0.049). CRC patients who underwent chemotherapy had significantly increased values of hsCRP compared with treatment-naive patients (therapy group: 19.5 ± 25.9 mg/l; naive group: 4.8 ± 4.1 mg/l; p = 0.03).

Parameters of lung function as assessed by spirometry did not differ between patients with CRC (forced vital capacity [FVC]: 3.5 ± 0.9 l; forced expiratory volume in 1 s [FEV_1]: 2.7 ± 0.7 l) and control subjects (FVC: 3.9 ± 1.0 l; p = 0.12 and FEV_1: 3.0 ± 0.8 l; p = 0.06), as well as between treatment-naive patients (FVC: 3.5 ± 0.8 l, FEV_1: 2.8 ± 0.6 l) and those who underwent chemotherapy (FVC: 3.6 ± 1.1 l; p = 0.7, and FEV_1: 2.7 ± 0.9 l; p = 0.7).

CARDIOVASCULAR CHARACTERISTICS AND BODY COMPOSITION. Compared with control subjects, LVEF was significantly reduced in CRC patients and in patients with CHF (Central Illustration). The LVESV index was increased in both CHF and CRC patients compared with control subjects (all $p < 0.05$) (Table 3). The LVM index was significantly increased in patients with CHF compared with the other 2 groups (all $p < 0.05$) (Table 3); no such difference was noted between patients with CRC and control subjects. A thickened left ventricular posterior wall was observed in CRC and CHF patients compared with



CENTRAL ILLUSTRATION **Cardiovascular Characteristics**

(A) Cardiac function as assessed by left ventricular ejection fraction (LVEF) in control subjects **(blue bars)**, patients with colorectal cancer (CRC) **(salmon bars)**, and patients with chronic heart failure (CHF) **(purple bars)**. Analysis of variance p value <0.0001. **(B)** Exercise capacity as assessed by spiroergometry in control subjects **(blue bars)**, patients with CRC **(salmon bars)**, and patients with CHF **(purple bars)**. Analysis of variance p value <0.0001. **(C)** Heart rate variability (HRV) as assessed by SD of all normal RR intervals **(darker color boxes)** and SD of 5-min mean RR intervals **(lighter color boxes)** in control subjects **(blue bars)**, patients with CRC **(salmon bars)**, and patients with CHF **(purple bars)**. Analysis of variance p value for SD of all normal RR intervals = 0.001, for SD of 5-min mean RR intervals = 0.0004.

control subjects (CRC group: 10.5 ± 1.8 mm; CHF group: 11.0 ± 2.6 mm; control group: 9.4 ± 2 mm; $p = 0.02$ and $p = 0.0008$, respectively). With regard to diastolic function, no difference was observed between CRC patients and control subjects (E/A [ratio of the peak Doppler velocities of early (E) and late diastolic flow (A) across the mitral valve]: CRC group: 1.0 ± 0.3, control group: 1.0 ± 0.3, $p = 0.8$; E:E′ [ratio of the maximum velocity of early mitral valve inflow to the maximal velocity of the motion of the mitral valve at the lateral annulus]: CRC group: 8.4 ± 2.6, control group: 8.3 ± 3.0; $p = 0.8$). Patients with CHF had a significantly higher E:E′ (mean 12.8 ± 6.2) compared with the other 2 groups (both $p < 0.0001$). Both CRC and CHF patients showed significantly decreased exercise performance as assessed by peak VO_2 compared with control subjects (**Central Illustration**), as well as a significantly impaired breathing efficiency and anaerobic threshold (**Table 3**). Although 86.6% of control subjects showed a normal peak VO_2 adjusted for age, sex, and body weight, this was the case in 44.0% of CRC patients and in 11.8% of CHF patients ($p < 0.0001$). Using simple regression analysis, we found that in CRC patients, peak VO_2 correlated with hemoglobin, lean mass (legs and entire body), maximal heart rate on exercise, VLF, and CT-proET-1 (all $p < 0.05$) (**Table 5**). Patients with CRC who did not receive chemotherapy showed a significantly reduced peak VO_2 and LVEF compared with control subjects (all $p < 0.006$) (**Table 4**).

Most parameters of HRV (e.g., SDNN, SDANN, SDNN index, VLF, and LF) were significantly reduced in CRC patients and CHF patients with CRC compared with control subjects (all $p < 0.04$) (**Central Illustration**, **Table 3**). In patients with CRC, HF was also significantly decreased compared with control subjects. In the CRC group, serum levels of hsCRP correlated with SDNN ($r = -0.44$, $p = 0.003$), SDANN ($r = -0.40$,

TABLE 5 Simple Regression Analyses (With the Respective p Value) With Peak VO_2 (ml/min) Serving as the Dependent Variable in Control Subjects and in Patients With CRC or CHF

	Control Subjects (n = 51)		Patients with CRC (n = 50)		Patients with CHF (n = 51)	
	R	p Value	R	p Value	R	p Value
Age, yrs	−0.55	<0.0001	−0.19	0.20	−0.03	0.87
Body mass index, kg/m^2	0.24	0.09	0.24	0.11	0.52	0.001
hsCRP, mg/l	—	—	−0.09	0.58	−0.05	0.79
Hemoglobin, g/dl	0.29	0.045	0.36	0.01	0.26	0.13
Body composition, kg						
Entire body						
Lean	0.86	<0.0001	0.64	<0.0001	0.48	0.003
Fat	−0.19	0.19	0.08	0.58	0.47	0.003
Legs						
Lean	0.88	<0.0001	0.65	<0.0001	0.60	0.0001
Fat	−0.32	0.024	−0.04	0.77	0.29	0.08
Cardiovascular function						
Maximal heart rate	0.21	0.14	0.38	0.009	0.23	0.18
Breath efficiency, VE/VCO_2	0.16	0.27	−0.46	0.001	−0.45	0.005
LVEF, %	0.002	0.99	−0.26	0.09	0.38	0.02
SDNN index, ms	0.46	0.0009	0.20	0.19	0.22	0.33
VLF, ms^2	0.42	0.003	0.32	0.04	−0.12	0.59
LF, ms^2	0.60	<0.0001	0.16	0.31	0.006	0.98
HF, ms^2	0.35	0.01	0.09	0.56	−0.27	0.23
Biomarkers						
MR-proADM, nmol/l	−0.07	0.68	−0.29	0.05	0.10	0.58
MR-proANP, pmol/l	−0.07	0.65	−0.26	0.09	−0.21	0.25
CT-proET-1, pmol/l	−0.20	0.29	−0.30	0.04	—	—
Copeptin, pmol/l	0.50	0.004	−0.22	0.15	—	—
hsTnT, pg/ml	0.15	0.37	0.03	0.86	0.35	0.04

Abbreviations as in Tables 1 and 3.

p = 0.007), LF (r = −0.33, p = 0.03), and HF (r = −0.41, p = 0.006). Compared with control subjects, therapy-naive patients also had a significantly lower SDNN index, VLF, and LF (all $p < 0.05$) (Table 4). In the treatment group, significant correlations between hsCRP and parameters of HRV, in particular, SDNN (r = 0.57, p = 0.007), SDANN (r = 0.55, p = 0.009), SDNN index (r = −0.47, p = 0.03), and HF (r = −0.47, p = 0.04) were noted. No such relationship was observed in the chemotherapy-naive group.

As shown in Table 3, analysis of body composition showed a significantly decreased lean mass in the legs in CRC patients compared with control subjects and those with CHF. In the subgroup of therapy-naive patients, decreased lean mass in the arms, legs, and entire body were observed compared with control subjects (all $p < 0.05$) (Table 4). As shown in the Online Tables 1 and 2, no material changes were noted in our main variables of interest when CRC patients were analyzed according to subgrouping by local versus metastatic disease or treatment regimens with bevacizumab versus without bevacizumab.

DISCUSSION

Because this was the first prospective study to systematically examine parameters of cardiovascular function in CRC patients, our data demonstrated that CRC patients' exercise capacity is severely impaired compared with their age-matched control subjects. In addition, we found that a mild, but statistically significant, reduction of the LVEF in CRC patients was present, and that all markers of HRV were decreased in these patients. Although the reduction in LVEF appeared to be similar in patients with or without chemotherapy, the reduction in HRV not only reached the level of that in patients with CHF, but it was further reduced by commencement of chemotherapy, a therapeutic step that also led to increases in hsTnT values. This effect was underscored by the lower peak heart rate and lower peak VO_2 during exercise after chemotherapy initiation. Although serum levels of MR-proADM and MR-proANP were similar in patients with CRC and controls subjects, and never reached those of patients with CHF, levels of CT-proET-1 and copeptin were elevated in CRC patients compared with control subjects.

Exercise testing using spiroergometry, and thus peak VO_2 measurement, is viewed as an objective measure of cardiopulmonary exercise capacity. Although not reduced to the level of CHF patients, exercise capacity of CRC patients is severely impaired compared with control subjects, and this effect is independent of chemotherapy. Several of our findings suggested themselves as explanations for these findings: the mild reduction in LVEF, the severe reduction in HRV, the reduction in lean mass in the legs, the reduction in hemoglobin, inflammatory activation, and the progressive endothelial dysfunction, as reflected by elevated levels of CT-proET-1. These effects might also help in understanding the impaired exercise capacity in other clinical entities, such as coronary artery disease (11), CHF with digoxin therapy (12), in elderly patients (13,14), and in patients after heart transplantation (15). These patients present with limited exercise capacity. The assessment of HRV using standard 24-h measurements could also help to understand sympathetic and parasympathetic activity levels. In CRC patients, sympathetic function and parasympathetic function seemed to be decreased to a similar extent. Interestingly, the reduction in parasympathetic tone, as reflected by HF analysis, is more pronounced in CRC than in CHF, whereas sympathetic tone, reflected by LF analysis, is more severely reduced in CHF than in CRC. However, these effects may be easily explained by the use of beta-blockers in patients

with CHF. Studies in patients with essential hypertension, post-infarction patients, and in CHF patients have confirmed that beta-blockers decrease sympathetic fluctuations and increase parasympathetic fluctuations, and thus, are able to restore the sympathetic–parasympathetic balance in cardiovascular disease (16). Interestingly, in our study, the subgroup of chemotherapy-treated patients had a significantly lower HF component compared with therapy-naive patients. The HF corresponded to short-term changes in the heart rate and was an indicator of parasympathetic performance. In therapy-naive patients, HF was in the normal range, similar to control subjects ($p = 0.35$), indicating that impairment of the parasympathetic system occurs in the early stages of therapy. Impairment in sympathetic activity does not seem to be influenced by chemotherapy, because the LF component was reduced to the same extent in the 2 groups. In line with reduced HRV, patients who underwent chemotherapy had a decreased maximal heart rate during exercise testing compared with that of therapy-naive patients. Our study was not designed to provide direct insight into the mechanisms involved in these perturbations; however, the much higher levels of hsCRP in treated patients and the associations between hsCRP and HRV in this group buttressed the view that activation of inflammatory pathways were involved.

In accordance with numerous previous reports, our study revealed overactivity of hsCRP in cancer patients (17,18). Such effects might have secondary consequences on endothelial function, as underlined by increased levels of CT-proET-1, which is a potent vasoconstrictor peptide secreted mainly by endothelial cells (19,20). Therefore, the overactivity of hsCRP might also serve as a proxy for endothelial function (21); these effects were directly associated with exercise capacity in the CRC patients.

Although we found that many parameters of cardiovascular function were impaired in CRC patients, whether or not they were currently treated with chemotherapy, it was reassuring to note that the echocardiographic parameters were hardly affected. In addition, although they did not fulfill the criteria of tachycardia, the CRC patients in our study demonstrated significantly higher heart rates at rest than the patients with CHF or the control subjects. It was already demonstrated that with normal left ventricular systolic function, the first sign of cardiac damage might be tachycardia (22). In our study, we observed more prominent cardiac alterations in patients after commencement of chemotherapy, which aligned with the findings in previous reports. 5-FU is the key drug for chemotherapy of CRC. Cardiotoxicity, which has been recognized in other anticancer agents, has also been reported after 5-FU administration (23), mostly as ischemic cardiomyopathy, but also as cardiac failure (24). Another study showed a reversible and asymptomatic decrease in left ventricular systolic function in patients who received 5-FU; an impairment of diastolic function was also observed (25).

From a clinical standpoint, our findings might help in understanding the impaired exercise capacity of CRC patients. Both CRC and CHF patients are affected by systemic inflammation and endothelial dysfunction. Unlike CHF patients, CRC patients only present with mildly reduced LVEF, whereas reduced exercise capacity and reduced HRV are present in both clinical entities. From a symptomatic standpoint, it might be possible to understand some of the symptomatic similarities between the 2 syndromes. Inflammatory pathways might be involved in the onset of clinical symptoms.

There is ample evidence that inflammation is associated with a number of pathophysiological changes and co-morbidities in patients with CHF, for example, muscle wasting (26) and generally poor outcomes (27). Likewise, the relationship between inflammatory markers and fatigue already has been shown in many studies in advanced cancer patients (28,29). However, the most important clinical determinant of quality of life is the exercise capacity of patients (30–32). HRV also seems to be an important clinical determinant for quality of life. Patients' heart rates appear to be "stiff" and unable to adjust to the requirements of the activities of daily living. Decreased HRV has been shown to worsen multiple clinical symptoms, such as fatigue, nausea, erectile dysfunction, constipation, increased proinflammatory cytokines, and increased risk of sudden death (33–35).

STUDY LIMITATIONS. Although we consider the number of patients in the present study adequate, larger studies should confirm our findings.

CONCLUSIONS

In total, our data showed that exercise capacity in patients with CRC was significantly reduced. This finding was already true in patients before commencement of chemotherapy and was worsened further by this therapy. The reduction in LVEF, HRV, lean mass in the legs, and reduction in hemoglobin, as well as inflammatory activation and progressive endothelial dysfunction all appeared to play a role in this regard. Our data suggested that treatments that tackle these phenomena might have beneficial effects. Such treatments include exercise programs (36,37) and drug classes, such as beta-blockers (38–43)

or angiotensin-converting enzyme inhibitors (44–46). All of these have positive effects on HRV and endothelial function. Additional studies are required to verify such effects.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with CRC often display dyspnea and fatigue due to impaired cardiovascular function independent of chemotherapy.

TRANSLATIONAL OUTLOOK: The efficacy of beta-blockers and angiotensin-converting enzyme inhibitors in conjunction with regular exercise in improving dyspnea and cardiovascular function in patients with CRC should be evaluated in future studies.

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APPENDIX For supplemental tables, please see the online version of this article.