JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 13, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.07.948

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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Manuscript received March 31, 2014; revised manuscript received July 19, 2014, accepted July 22, 2014.

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