

Non-invasive assessment of cardiac hemodynamics in patients with advanced cancer and with chronic heart failure: a pilot feasibility study

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Abstract

Introduction: Relationships between cardiac pressure and volume have been suggested as markers of cardiac contractility; parameters include stroke work and the maximal rate of pressure rise during isovolumic contraction (dP/dt_{max}). Patients with cancer often display dyspnea and fatigue. These are also frequent symptoms in patients with chronic heart failure (HF). The reasons for similar symptoms in cancer patients are unknown. Using the novel Nexfin Finapres technique, we sought to assess measures of cardiac performance in patients with cancer and compare these values with those from control subjects and patients with chronic HF.

Material and methods: We prospectively studied 98 patients (control $n = 18$, chronic HF $n = 37$, advanced pancreatic or colorectal cancer $n = 43$) and assessed blood pressure (BP), stroke volume (SV), cardiac output (CO), and dP/dt_{max} at rest.

Results: All parameters of interest could be assessed using the Nexfin Finapres technique with SV and CO being significantly higher in patients with cancer than in controls (both $p < 0.05$). The SV was significantly higher in patients with chronic HF than in controls ($p < 0.05$). In patients with cancer, SV correlated with age ($r = -0.45$, $p < 0.01$) and body weight ($r = +0.55$, $p = 0.0001$). In chronic HF, SV declined with increasing age ($r = -0.49$, $p < 0.01$); in control subjects, SV increased with increasing body weight ($r = +0.57$, $p = 0.01$).

Conclusions: Patients with cancer tended to display elevated BP, CO, SV, and dP/dt_{max} as compared to control subjects and patients with HF. These findings may reveal an elevated risk for cardiovascular diseases in this group.

Key words: heart failure, cancer, hemodynamics, cardiac output, stroke volume.

Introduction

Cardiac performance can be described by various cardiac indices. Although heart failure (HF) is much more than mere pump failure but a multifaceted clinical syndrome, it can be described as the worst perturbation of cardiac performance [1-4]. One of the most accepted clinical parameters to describe HF severity is left ventricular ejection fraction (LVEF). Unfortunately, LVEF is also the least specific of all indices of contractility [5] and does not provide much insight into how a patient will develop clinically. An ideal parameter would, from a pathophysiological standpoint, be independent of afterload, preload, heart rate, and the state of remodeling. Relations between cardiac pressure and volume come closest to achieving this [6]. Thus, interesting parameters include stroke work and the maximal rate of pressure rise during isovolumic contraction (dP/dt_{max}) [5], and it would be desirable to measure these parameters non-invasively.

The Finapres method was developed in the late 1970s for continuous and non-invasive assessments of finger arterial pressure. Based on the volume-clamp method by Panez, it allows blood pressure (BP) monitoring throughout the cardiac cycle. The technique has become a widely accepted substitute for invasive intraarterial BP measurements. Recently, the Nexfin™ monitor became available, allowing not only continuous measurements of BP using the volume-clamp technique, but also calculation of cardiac output (CO). The reproducibility of the Nexfin BP assessment has been validated in several patient populations including healthy subjects [7], pregnant women [8], and in patients

undergoing abdominal or orthopedic surgery [9] or surgery with the requirement of cardiopulmonary bypass [10]. The measurement of CO has been validated in the latter group and in critically ill patients on a surgical intensive care unit [11].

In patients with HF, CO is expected to be reduced as a consequence of reductions in stroke volume (SV). The reduction in SV is a result of systolic or diastolic dysfunction. In patients with cancer such hemodynamic parameters have not been intensively investigated thus far. Patients with cancer often display dyspnea and fatigue, which are also frequent symptoms in patients with chronic HF [12]. The exact reasons for such symptoms in cancer are unknown. Some chemotherapy agents, such as anthracyclines, have been shown to be cardiotoxic [13]. However, almost all cancer patients present with such symptoms independent of which agents they are being treated with or even if they are not undergoing chemotherapy.

We aimed to investigate hemodynamic parameters in patients with cancer and compare our findings with those of healthy control subjects and patients with chronic HF. Thus, we prospectively assessed BP, heart rate, CO, SV, and dP/dt_{max} in patients with advanced cancer using the non-invasive Nexfin technique.

Material and methods

Patient recruitment

We prospectively studied 98 subjects in three different cohorts of patients, recruited at the Charité Medical School, Campus Virchow-Klinikum,

Table I. Subjects' clinical characteristics at baseline

Variables	Control (n = 18)	Chronic HF (n = 37)	Cancer (n = 43)	ANOVA Value of p
Age [years]	62.4 ±9.7	64.9 ±9.2	59.1 ±11.2 ⁺	0.05
Sex (% male)	50	83.8 ^{**}	41.9 ⁺⁺⁺	0.0001
Weight [kg]	72.2 ±11.4	85.9 ±22.4 ^{**}	72.4 ±15.3 ⁺⁺	0.002
Body mass index [kg/m ²]	25.2 ±3.2	28.0 ±6.3	24.9 ±3.3 ⁺	0.03
NYHA class	–	2.4 ±0.5	–	
LVEF [%]	60.5 ±5.1	35.0 ±8.1 ^{***}	60.7 ±6.2 ⁺⁺⁺	< 0.0001
Etiology or diagnosis [%]	–	CAD: 67.5 DCM: 32.4	PCA: 23.3 CRC: 76.7	–
Hemoglobin [g/dl]	13.7 ±0.9	13.6 ±1.5	11.7 ±1.5 ^{***,+++}	< 0.0001
Leukocytes [nl ⁻¹]	5.8 ±1.7	7.6 ±1.8 ^{**}	5.7 ±2.0 ⁺⁺⁺	< 0.0001
Platelets [nl ⁻¹]	277 ±95	231 ±90	249 ±92	0.3
Sodium [mmol/l]	141 ±2	140 ±4	140 ±3	0.7
Creatinine [mg/dl]	0.8 ±0.1	1.1 ±0.3 ^{***}	0.8 ±0.2 ⁺⁺⁺	< 0.0001

CAD – coronary artery disease, CRC – colorectal cancer, DCM – dilated cardiomyopathy, LVEF – left ventricular ejection fraction, PCA – pancreatic cancer. *vs. control subjects, +vs. patients with CHF. One symbol – $p < 0.05$, two symbols – $p < 0.01$, three symbols – $p < 0.001$

Berlin, Germany. Thus, we included 37 patients with stable chronic HF, 43 patients with advanced cancer, and 18 healthy subjects of similar age. The subjects' characteristics are provided in Table I, and patients' medication in Table II.

The diagnosis of chronic HF was based on appropriate clinical signs and symptoms according to current guidelines issued by the European Society of Cardiology [14], together with documented objective evidence of left ventricular diastolic or systolic dysfunction. The etiology of HF was coronary artery disease or dilated cardiomyopathy. No patient with chronic HF had signs of peripheral or pulmonary edema or was limited by exertional angina. We excluded patients younger than 18 years of age, with an acute myocardial infarction and those with a history of unstable angina, or stroke within three months prior to being studied. The diagnosis of cancer (pancreatic cancer, $n = 10$, colorectal cancer, $n = 33$) was based on histopathological examination. All patients had advanced cancer stage III or IV, were clinically stable, and received unchanged medication for at least four weeks. All patients with pancreatic cancer were receiving current chemotherapy while in the study, 4 patients gemcitabine only. Six patients were participating in clinical trials to investigate novel chemotherapy regimens, 3 patients a combination of gemcitabine and aflibercept or placebo, 2 patients a combination of gemcitabine with or without sorafenib, and 1 patient a combination of oxaliplatin, folic acid, 5-fluorouracil, and lapatinib. Among patients with colorectal cancer, 29 patients (88%) had undergone surgical tumor resection at the time of examination. A total of 21 patients with colorectal cancer (64%) were receiving current chemotherapy while in the study, 15 of them were receiving 5-fluorouracil, 2 patients capecitabine, 7 irinotecan, 7 oxaliplatin, 8 bevacizumab, 1 cetuximab, 2 panitumumab and 1 mitomycin, according to different regimens. One patient was receiving radiotherapy. In all cohorts we excluded subjects with clinical signs of infection, severe neuro-muscular disease, rheumatoid arthritis, or significant renal dysfunction (serum creatinine > 2.5 mg/dl). The local ethics committee approved the study and all patients gave written informed consent.

Assessment of blood pressure, cardiac output, and left ventricular ejection fraction

We used the Nexfin method (BMEYE B.V., Amsterdam, The Netherlands) to assess BP, heart rate, CO, SV, and dP/dt_{max} . The technique has been described previously [15] and the monitoring system is an approved medical device in Switzerland. It is based on the development of a pulsatile unloading of the finger arterial wall that is picked up by an inflatable cuff with a built-in photoelec-

Table II. Subjects' cardiovascular medication at baseline

Variables	Control ($n = 18$)	Chronic HF ($n = 37$)	Cancer ($n = 43$)
ACE inhibitor or ARB [%]	–	94.6	23.3
β -Blocker [%]	–	97.3	14.0
Aspirin [%]	–	69.4	2.3
Loop diuretic [%]	–	50.0	4.7
Aldosterone antagonist [%]	–	54.1	4.7
Statin [%]	–	73.0	4.7
Warfarin or phenprocoumon [%]	–	29.7	7.0
Digitalis [%]	–	13.9	–

ACE – angiotensin-converting enzyme, ARB – angiotensin receptor blocker

tric plethysmograph. Carbon oxide is calculated during BP measurements. Measurements were performed after at least 15 min of rest in a supine position. The cuff was applied around the patient's middle finger as recommended by the manufacturer. In all subjects, LVEF was assessed using Simpson's technique, biplane.

Statistical analysis

Data are expressed as mean \pm standard deviation. Data were checked for normal distribution before analysis using the Kolmogorov-Smirnov test. Fisher's exact test, analysis of variance (ANOVA) with Fisher's *post hoc* test, and simple regression analysis were used as appropriate. A value of $p < 0.05$ was considered significant. All statistics were performed using StatView 5.0 software for Macintosh (Abacus Concepts, Berkeley, CA).

Results

We studied 18 control subjects, 37 patients with chronic HF, and 43 patients with advanced cancer. The patients' baseline characteristics are provided in Table I. Arterial hypertension was present in 9 (20.9%), and atrial fibrillation in 1 (2.3%) of all cancer patients. No significant difference was detected with regards to age between control subjects and the two patient groups (all $p > 0.05$) but patients with chronic HF were somewhat older than patients with cancer ($p = 0.01$). We detected a significantly higher weight in patients with chronic HF as compared to control subjects and patients with cancer (both $p < 0.01$) as well as a higher body mass index (BMI) than patients with cancer ($p = 0.01$). Patients with chronic HF presented with a significantly lower LVEF than controls or patients with cancer (both $p < 0.0001$). Serum creatinine was significantly higher in patients with chronic HF as compared to either controls or patients with cancer (both $p < 0.001$,

Table III. Data derived using the Nexfin technique

Variables	Control (n = 18)	Chronic HF (n = 37)	Cancer (n = 43)	ANOVA Value of p
BP systolic [mm Hg]	121 ±18	110 ±21	129 ±23	0.0008
BP diastolic [mm Hg]	72 ±12	63 ±12	72 ±10	0.0006
Heart rate [min ⁻¹]	69 ±11	67 ±13	72 ±10	0.1
Cardiac output [l/min]	4.5 ±1.2	4.9 ±1.3	5.5 ±1.2	0.006
Stroke volume [ml]	66 ±13	77 ±21*	78 ±15*	0.05
dP/dt _{max} [mm Hg/s]	724 ±251	667 ±238	852 ±371	0.03

*p < 0.05 vs. control

Table I). We detected significant differences for hemoglobin with significantly lower values among patients with cancer as compared to controls or patients with chronic HF (both $p < 0.0001$). Patients with chronic HF presented with elevated leukocyte counts when compared with both other groups (both $p < 0.01$, Table I).

Data derived from the Nexfin technique included systolic and diastolic BP, heart rate, CO, SV, and dP/dt_{max}. These values are given in Table III. Systolic BP was significantly higher in patients with cancer as compared to patients with chronic HF ($p = 0.0002$). Likewise, diastolic BP was significantly higher in patients with cancer as well as in control subjects compared to patients with chronic HF (both $p < 0.003$, Table III). Cancer patients showed a significantly higher heart rate compared to chronic HF ($p = 0.03$). The CO and SV were significantly higher in cancer patients compared to control subjects (both $p < 0.02$); these values are depicted in Figure 1. Likewise, patients with HF showed higher levels of SV than control subjects ($p = 0.03$). The values for dP/dt_{max} were significantly higher in patients with cancer as compared to patients with chronic HF ($p = 0.008$, Table III).

The SV correlated significantly with age and body weight. These associations are depicted in Figure 2. However, significant negative correlations between SV and age were only present in patients with cancer and in patients with chronic HF. Likewise, we observed significant positive correlations between SV and weight only in patients with cancer and in control subjects. We detected significant correlations between CO and age, weight, and heart rate, although these associations were not evident in all groups of subjects. The CO correlated with age in patients with chronic HF ($r = -0.54$, $p = 0.0006$) and in patients with cancer ($r = -0.49$, $p = 0.0008$), but not in control subjects ($r = -0.24$, $p = 0.33$). The CO correlated with body weight and heart rate only in control subjects (weight: $r = +0.67$, $p = 0.003$; heart rate: $r = +0.50$, $p = 0.03$) and in patients with cancer (weight: $r = +0.34$, $p = 0.03$; heart rate: $r = +0.52$, $p = 0.0003$). A trend towards association between CO and hemoglobin was detected only in control subjects ($r = +0.53$, $p = 0.05$). An overview of these associations is provided in Figure 3.

We detected consistent correlations between dP/dt_{max} and CO in controls ($r = +0.47$, $p = 0.047$), patients with chronic HF ($r = +0.53$, $p = 0.0008$),

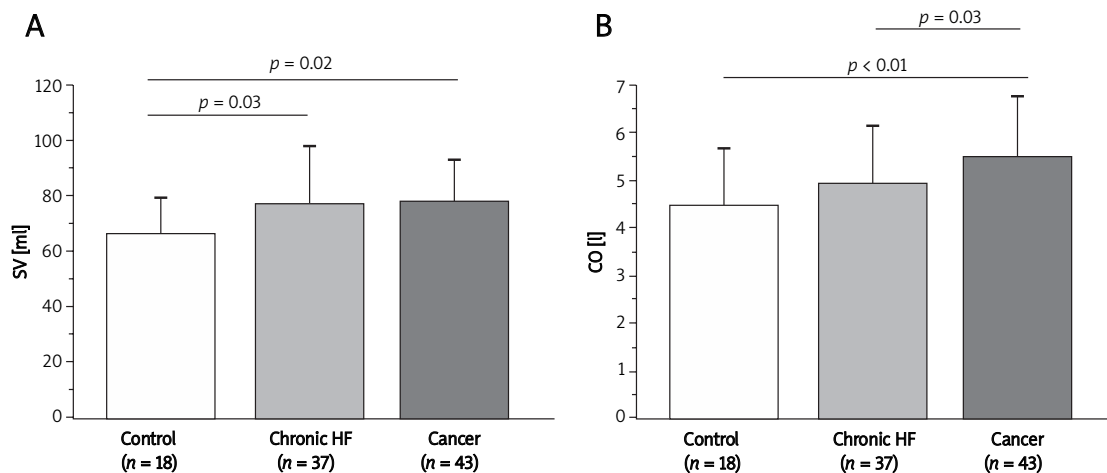


Figure 1. Stroke volume (SV, A) and cardiac output (CO, B) as assessed using the Nexfin technique in the three groups of subjects

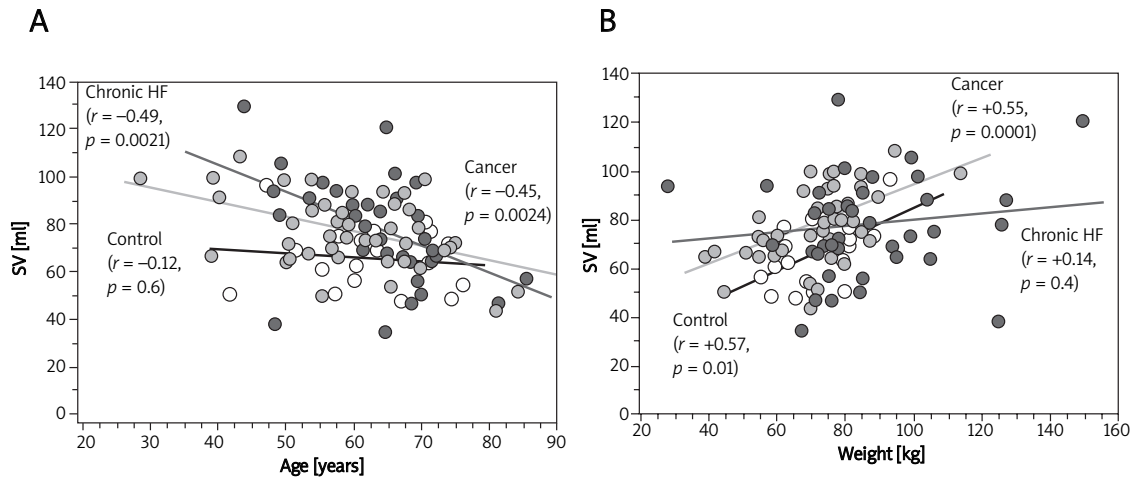


Figure 2. Correlations between stroke volume (SV) and age (A) or weight (B) for control subjects (open circles), patients with chronic heart failure (HF, full dark grey circles), and patients with cancer (full light grey circles)

and in patients with cancer ($r = +0.45, p = 0.003$). Similar associations were found between dP/dt_{max} and SV in these patient groups (control: $r = +0.47, p = 0.0497$; chronic HF: $r = +0.50, p = 0.002$; cancer: $r = +0.39, p = 0.01$). Further, dP/dt_{max} correlated with systolic BP (control: $r = +0.64, p = 0.005$; chronic HF: $r = +0.77, p < 0.0001$; cancer: $r = +0.83, p < 0.0001$). A correlation between dP/dt_{max} and diastolic BP was present only in patients with chronic HF ($r = +0.40, p = 0.02$) and those with cancer ($r = +0.50, p = 0.0006$) but not in controls ($r = +0.41, p = 0.09$). No significant relationship was detected between LVEF and dP/dt_{max} (control: $r = -0.47, p = 0.08$; chronic HF: $r = +0.25, p = 0.15$; cancer: $r = +0.08, p = 0.64$) or between heart rate and dP/dt_{max} (all $p > 0.3$). A correlation between body weight and dP/dt_{max} was evident only in control subjects ($r = +0.53, p = 0.03$).

Discussion

We have shown that patients with cancer present with pronounced higher SV and CO values than control subjects. Patients with HF showed lower LVEF and more severe kidney impairment than control subjects or patients with cancer. Hemoglobin values were lower in patients with cancer as compared to control subjects and patients with chronic HF. Likewise, SV was higher in patients with chronic HF than in control subjects. Major determinants for these variables appear to be age and body weight. Hemoglobin seems to have an influence on CO only in control subjects.

Elevated resting CO and heart rate predispose patients to develop cardiac disorders such as arterial hypertension [16]. In obese subjects, it is well established that not only CO is augmented, but also SV, and left ventricular filling pressure [17]. Indeed, earlier studies had demonstrated that increases in

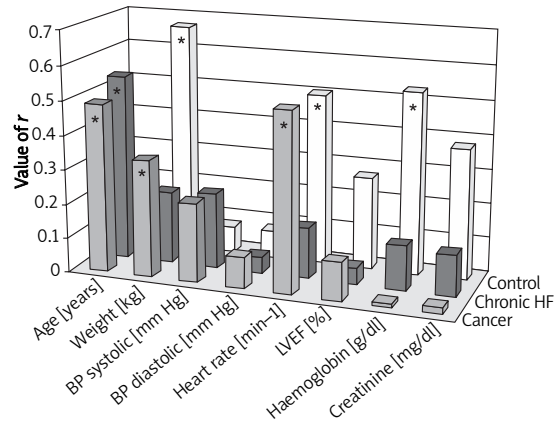


Figure 3. Values of r for simple regression analyses between cardiac output (dependent) and several clinical variables in control subjects (white bars), patients with chronic heart failure (HF, dark grey bars), and patients with cancer (light grey bars) $*p < 0.05$

CO in obese patients are primarily related to higher SV rather than higher heart rate [18]. Increases in CO and SV are necessary to meet the higher-than-usual metabolic requirements in these patients. This is also a likely explanation for increases in both values observed in patients with cancer. Altogether, it appears that patients with cancer tend to have higher values for BP, CO, SV, and also for dP/dt_{max} . This may represent cardiovascular disturbances in this group or at least a higher cardiovascular risk compared to control subjects. The only study that aimed to assess CO in cancer subjects thus far investigated patients with hematological cancer using ultrasound cardiac output monitoring technique. They showed an initial increase in CO after commencement of chemotherapy with a subsequent quick decrease in CO remaining decreased for the rest

of time [19]. These results could be explained by severe cardiotoxicity of anthracyclines [13].

Several determinants of cardiac hemodynamics have been discussed in the literature over the last decades. The CO is known to correlate with several factors including increasing age [20] and obesity [16]. Both CO and heart rate can be reduced by use of, for example, β -blockers. The CO has been shown to be associated with body weight [15, 18]. This was also the case in our study in control subjects and in patients with cancer, but not in patients with chronic HF. This fact might be due to the patient cohort studied that presented with significantly higher body weight than all other groups (Table I); however, it is more likely that the use of β -blockers in patients with chronic HF influenced the presence of this association. Indeed, O'Malley *et al.* [21] assessed the association between CO and body weight in untreated dogs with experimental heart failure and found a strong positive correlation, similar to our findings in controls and in patients with cancer.

A decrease in CO with advancing age has been reported already decades ago [22]. Although this association was not found among our control subjects, it was present in patients with cancer and in those with chronic HF. Although there were no statistical differences with regards to age distribution between patients and controls, the age range of patients with cancer was broader than that of our control subjects (Figure 3). This has to be considered in the interpretation of our results.

For clinicians, the findings for LVEF and creatinine do not come as a surprise. Alterations in leukocyte counts (i.e. increased leukocyte levels in patients with chronic HF) have been described previously and might be explained by an altered distribution of leukocyte subsets [23]. It is interesting to note that in conflict with current literature patients with chronic HF showed a higher SV than control subjects in the present study. This might be due to the patient cohort investigated that presented with significantly higher body weight than all other groups and because all patients were under stable therapy for HF.

A note of caution should be added particularly for the measurement of dP/dt_{max} , because the peripheral assessment with the Nexfin technique does not provide measurements that are identical with invasive measurement. Indeed, in normal subjects dP/dt_{max} should be in the range 1500-2000 mm Hg/s [24]; in our study, the mean value was 724 mm Hg/s (Table III). Thus, comparisons between patient groups such as the one that we did or comparisons before and after therapeutic interventions may be applicable, but the notion of a peripheral measurement should be heeded. Our study has a number of limitations. The number of subjects is small, particular-

ly in the group of control subjects, and the distribution of gender, body weight, and hemoglobin was not well matched between groups as our patients were recruited from typical patients attending the out-patient departments of our hospital. This fact should be considered when looking at the data. In addition, we did not perform serial measurements that would allow the analysis of intra-individual changes and the assessment of test reproducibility. Our echocardiography testing remained preliminary in scope, and we were therefore not able to compare findings from the Nexfin technique with our echo data.

The Nexfin technique is easy to use in clinical routine and in research settings and may provide useful information on cardiac performance. It has been validated using different standard assessments of CO [25-27]. It has recently been suggested that the similarity of clinical signs and symptoms of patients with chronic HF and those with cancer may have a basis in cardiac alterations in the patient with cancer [28]. In other words, exertional dyspnea, fatigue, and body wasting in patients with advanced cancer may partly be a reflection of developing HF. In our study, patients with cancer tended to show elevated values of BP, CO, SV, and dP/dt_{max} , displaying at least a higher cardiovascular risk in this group. Both CO and heart rate can be reduced by use of, for example, β -blockers. Our data suggest that such kind of treatments may have beneficial effects on cardiovascular function in these patients in the long term. These findings warrant further investigation in larger studies.

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