

THE COLD PRESSOR TEST DURING RADIONUCLIDE VENTRICULOGRAPHY: A FEASIBILITY STUDY IN CANCER PATIENTS

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To monitor the use of cardiotoxic drugs, adequate assessment of myocardial function is required. Although serial radionuclide left ventricular ejection fraction (EF) studies allow a simple and rapid assessment of the myocardial function without risk or discomfort to the patient, they appear not to be sensitive enough. Determination of the EF during cold application may be more sensitive. In this study we tested the feasibility of the cold pressor test (CPT) in relation to EF determination in 23 cancer patients. Only minor side effects were recorded. The response of heart rate to cold was similar to the response reported in healthy volunteers and patients with coronary artery disease. In selected cases EF determination during CPT appeared to be more sensitive than EF at rest. EF_{CPT} may be an attractive alternative for $EF_{exercise}$ in cancer patients who cannot perform enough exercise to stress cardiac function adequately, but for a more definite conclusion a prospective comparative study is required.

Key words: Radionuclide angiography, Cold pressor test, Cancer patients, Ejection fraction, Cardiotoxicity.

INTRODUCTION

The need for evaluation of myocardial function in patients receiving cardiotoxic drugs has become increasingly important. Non-invasive techniques such as radionuclide angiography (RNA) determining the left ventricular ejection fraction (EF),¹ should be preferred. EF appears to allow identification of patients at risk for developing congestive heart failure.² The use of exercise stress during RNA seems to be even more sensitive in predicting cardiotoxicity at early stages.^{3,4} However, the performance status of cancer patients often does not permit adequate exercise. In patients with coronary artery disease (CAD) and congestive cardiomyopathy (CM) the cold pressor test (CPT) was found to be a useful alternative stimulant compared to dynamic and isometric exercise in the assessment

of myocardial function.^{5,6} The present study investigated the feasibility of peripheral cold exposure as a cardiac stress test during determination of the EF by RNA in cancer patients.

MATERIALS AND METHODS

A total of 50 RNA-EF determinations at rest (EF_{rest}) followed by determinations during CPT (EF_{CPT}) were performed in 23 patients, 12 males and 11 females, aged 34-72 years. None of them was known to have ischemic cardiac disease. Among others, they were all treated with doxorubicin (DX) and/or mitomycin C (MMC). Diagnosis included breast cancer (7), gastric cancer (4), prostatic cancer (3), adenocarcinoma of unknown primary (3), cervical cancer (2) and miscellaneous (4).

Performance score ranged from WHO 0-3, with a median of 1. Three patients had previous mediastinal radiotherapy (dose 40-50 Gy) and doxorubicin treatment (cumulative dose 250-500 mg m⁻²). The number of studies ranged from 1 to 6 per patient.

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Eighteen patients were studied at least twice. Gated bloodpool scintigraphy at rest using Tc99M was performed 15 min after i.v. administration of stanous chloride (Technescan Pyp®, Mallinckrodt). A Picker Dyna 4 gamma camera, fitted with a high resolution collimator, placed in approximately 40 degrees LAO position over the supine patient and interfaced to a PDP 11/34 computer, running under Gamma 11 software (Digital Equipment Company), was used. Counts of 6×10^6 were collected. The patient was requested to hold the hand for 2½ min in a bath of ice-water with a temperature of 3–5°C. Thirty seconds after immersion of the hand into ice-water, data collection for the CPT-study was initiated and during the 2 min data were collected with simultaneous ECG registration. After data acquisition both studies were framed into a sequence of images representing the average cardiac cycle. The rest study was framed into 28 frames, the CPT-study into 16 frames in order to obtain a sufficient number of counts. For each study the ejection fraction was obtained by manually drawing a global region of interest around the left ventricle. Selection of end-diastolic (ED) and end-systolic (ES) frames depended on the frame with respectively maximum and minimum counts in the global region. Thereafter, the left ventricle outline was redrawn in each of these frames. Also a background region was drawn, usually lateral to the free wall, to correct ED and ES counts.

The EF was then calculated from $EF = (EDC - ESC) / (EDC - BCG)$ where EDC = end-diastolic counts, ESC = end-systolic counts and BCG = background corrected counts. EF studies were always performed at least 4 days following administration of chemotherapy.

RESULTS

Two patients experienced pain, one of them refused a second CPT. All other patients experienced tolerable cramps in the hand applied in ice-water. Acceleration of the heart rate was recorded during 20 CPTs, while the heart rate was stable in 22 and dropped in 8. Every change occurred within 30 sec and lasted 2–3 min. Ventricular extrasystoles were observed in one patient. All EF_{rest} values were in the normal range. During CPT the EF rose in 11 instances, remained unchanged in 8 and dropped in 31 (Fig. 1). Out of this last group 9 times (18%) in 6 different patients the EF decreased more than 7%, which has been suggested to be a pathological response to cold application.^{5,6} The only 3 patients who had received previous mediasti-

nal radiotherapy in combination with DX treatment, showed abnormal decreases in EF_{CPT} in a total of 4 sessions. Five other abnormal decreases of EF_{CPT} occurred during treatment with MMC (2 instances) and DX + MMC (3 instances). One of these cases was a 72-year-old male treated with 5-FU, DX and MMC for advanced gastric cancer. Initial EF studies were unremarkable (Table 1). The next two studies revealed a diminished EF_{rest} , but still within normal ranges. However, the EF_{CPT} became abnormal. Shortly after the third study the patient developed left ventricular failure (after a cumulative dose of 150 mg m^{-2} DX and 30 mg m^{-2} MMC).

He was treated successfully with diuretics and digitalis and recovered completely, even with normalization of the EF_{CPT} . In this patient the progressive drop of EF_{CPT} appears to have been predictive for reversible myocardial damage, while EF_{rest} was not.

DISCUSSION

In the present study the CPT appeared to be a feasible test in cancer patients, even for those with a poor performance score. The general side effect was a tolerable cramp, with only one patient (5%)

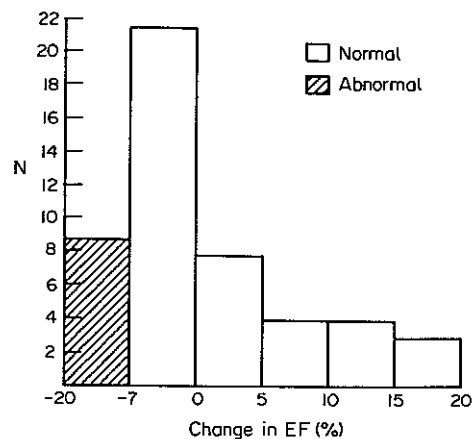


Fig. 1. Changes in ejection fraction values induced by cold application. An increase in EF, or a decrease of less than 7% is considered a normal response. N = number of studies.

Table 1. Ejection fractions in the case reported

Sequence of studies	Ejection fraction (%) / Heart rate (BPM)				
	1	2	3	4	5
Rest	69/71	54/69	57/80	61/87	59/80
CPT	68/71	50/65	49/64	44/85	68/75

refusing a second CPT because of intolerable pain.

Non-invasive techniques suitable for serial study of myocardial function are needed in cancer patients receiving potential cardiotoxic drugs and for the screening of newly-developed anthracycline analogs. Application of such techniques may allow identification of patients at risk for development of congestive heart failure (CHF), as well as those in whom beneficial high-dose chemotherapy may be continued without adverse effect. ECG, chest films and PEP/LVET ratio¹¹ were found to be of only very limited value for this purpose. However, determination of EF_{rest} by RNA has been shown to have practical value,¹ but appears not to be sensitive enough.⁸

In healthy volunteers dynamic exercise causes a significant increase of EF ($EF_{exercise}$).^{3,6,9,10} A decrease of $EF_{exercise}$ was found to reflect abnormality in CAD- as well as DX-treated patients.^{3,4,9} $EF_{exercise}$ detected a higher frequency of often subclinical DX-cardiotoxicity than previously suspected^{3,4} and appears to be more sensitive in predicting deterioration of LV function.

The latter observation agrees with that of Burns *et al.*¹¹ in patients who received mediastinal radiotherapy 7–20 years prior to determination of cardiac function. They found 57% abnormal $EF_{exercise}$ in 21 asymptomatic patients. This percentage far exceeds previous reported radiation cardiotoxicity.^{12,13} Maybe this also accounts for our observation that EF_{CPT} was abnormal in 3 patients previously treated by mediastinal radiotherapy.

Many patients with CAD as well as cancer patients cannot perform enough exercise to stress cardiac function adequately because of poor physical condition and hence deterioration of cardiac function may not always be detected by $EF_{exercise}$. For this reason the CPT has been advocated as an alternative in CAD patients.^{5,6}

The CP was first applied by Hines in 1932 in studies on hypertensive patients.¹⁴ The heart rate is known to rise during CPT in hypertensive and CAD patients.^{5,15,16} while it rose or remained unchanged in healthy volunteers.^{6,16,17} The individual response to CPT was found to be consistent. In the present study, the heart rate also rose in most instances or remained unchanged. The maximal effect of the stimulus is achieved after 60 sec and lasts several minutes on continuous cooling.^{5,18} Adaptation to continuous peripheral cold exposure has not been observed within 2 min.^{5,15,19} For this reason we started collecting counts 30 sec after the initiation of cold application, in order to acquire an acceptable number of counts during the maximal effect of the stimulus.

The EF_{CPT} has been determined by roentgen angiography as well as by RNA.^{5,6,17} Normally during CPT, EF remains unchanged or rises without utilisation of diastolic volume reserves⁵ probably due to augmentation of myocardial contractility. A decrease of > 7% has been found to reflect abnormal myocardial function.^{5,6} In a comparative study in CAD patients Manyari *et al.*⁶ found EF_{CPT} not to be as sensitive as $EF_{exercise}$, but they suggested CPT as a useful alternative in subjects in whom adequate exercise cannot be accomplished, confirming the results of Wainwright *et al.*⁵ If similar criteria for an abnormal reaction to cold had been used, then maybe Drymond *et al.*²⁰ would have drawn the same conclusion. In some of our patients EF_{CPT} was found to change the interpretation of cardiac performance, compared to EF_{rest} .

Although the number of patients is too small to permit definite conclusions, and a high percentage of cardiotoxicity was not to be expected based on the selection of our patients, most of whom only received a low cumulative dose of DX, the results of this study support the previous data in CAD patients^{5,6,17} and suggest that EF_{CPT} is more sensitive for prediction of cardiotoxicity in cancer patients than EF_{rest} .

However, we should also keep in mind that some investigators found EF_{CPT} less useful in CAD patients.^{21,22}

In conclusion there are indications that determination of the EF_{CPT} might be an attractive alternative for $EF_{exercise}$ to evaluate cardiac performance.

CPT will be feasible in cancer patients receiving conventional cardiotoxic antineoplastic agents, and patients participating in clinical research with analogs of such agents. To allow more definite conclusions on the sensitivity of the EF_{CPT} , larger studies in patients receiving high cumulative doses of DX will be needed. Finally, a prospective comparison of EF_{CPT} and $EF_{exercise}$ is warranted.

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