CHAPTER 10.2

Troponin I, Troponin T, and Creatine Kinase-MB mass in patients with the carcinoid syndrome with and without heart failure.

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Carcinoid heart disease is a well known complication of longstanding carcinoid syndrome. It is characterized by the presence of "carcinoid plaques" on the mural endocardium (1). The carcinoid plaques are composed of smooth muscle cells, embedded in a stroma of acid mucopolysaccharides and collagen. In the plaques the elastine fibre content is decreased, the basal membrane of the endocardium is thickened and sometimes duplicated (2). Carcinoid plaques are predominantly found in the right heart (1), leading to pulmonary and tricuspid valve abnormalities. With echocardiography tricuspid valve regurgitation is found in 56% of patients with a carcinoid syndrome (3). A correlation of echocardiographic abnormalities with (high) serotonin secretion by the carcinoid tumour has been described (3). Heart failure was a cause of death in 41% of 63 midgut carcinoid patients (4). In patients with a carcinoid syndrome, median survival was significantly reduced by the presence of cardiac involvement (5).

Serotonin is a potent vasoconstrictor (6) and can lead to diminished myocardial blood flow (7). Plaque formation itself possibly affects the underlying myocardium. Furthermore, distention of the right heart, resulting from valve abnormalities, could lead to myocardial damage. Troponin I, troponin T, and the creatine kinase (CK) MB isoenzyme are released into the circulation after myocardial damage. Troponin I was reported to be a parameter with higher sensitivity and specificity than the conventional marker CKMB-mass for the detection of minor ischemic myocardial injury (8). Moreover, troponin I and troponin T are markers for risk stratification in patients with acute coronary syndromes. Furthermore, in chronic, non-ischemic cardiac conditions, such as idiopathic dilated cardiomyopathy, increased troponin T concentrations were found to correlate with a short term unfavourable prognosis (9), and cardiac troponin T has been reported to be progressively released in advancing stages of heart failure (10).

We, therefore, we analysed troponin I, troponin T, and CKMB-mass to detect myocardial damage in patients with carcinoid syndrome, who are exposed to increased concentrations of circulating serotonin. The outcomes of the troponin I, troponin T and CKMB-mass measurements were compared between the patients with and without heart failure, and between echocardiographic subgroups.

We investigated 20 consecutive patients (9 men, 11 women) with histologically confirmed midgut carcinoid tumours, and a clinical carcinoid syndrome. The median age was 57.5 years (range 43-74 years). In all 20 patients systemic carcinoid symptoms had been present for 9-154 months (median 72 months) and all had metastatic carcinoid disease. A standardized questionnaire was used for assessment of cardiovascular symptoms. Ten of the 20 patients had symptoms of heart failure (dyspnea (n=4), ankle edema (n=4), orthopnea (n=1) and nycturia (n=5)); 6 of these patients were classified as New York Heart Association class II, and 4 as class III heart failure. None of the patients had a history of precordial pain and electrocardiography revealed no signs of myocardial ischemia in any of the patients. Echocardiography was performed using a two-dimensional technique with color flow imaging. All echocardiographic investigations were interpreted by one experienced cardiologist. The patients were divided into three groups, according to the echocardiographic results. Group I consisted of patients with a normal echocardiogram. Patients were placed in group II if they met one of the following criteria: tricuspid regurgitation, right atrial enlargement, or inferior caval vein collapsing to < 50% of maximal

diameter during inspiration. Patients in group III fulfilled two or three of these criteria. Echocardiography was normal in six patients (group I). In eight patients slight abnormalities were detected (group II), and five patients showed overt carcinoid heart disease (group III). In one patient, transthoracic echocardiography was not feasible.

Urinary 5-hydroxyindoleacetic acid concentrations were determined in ether extracts by HPLC with fluorometric detection and expressed in mmol/mol urinary creatinine (11). All 20 patients showed an increased excretion of urinary 5- hydroxyindoleacetic acid (median 16.5 mmol/mol creatinine, upper limit of reference range, 3.8 mmol/mol creatinine).

Troponin I was measured with an AxSYM(TM) analyser (Abbott Diagnostic Division). Troponin T and CKMB mass analyses were performed using an Elecsys 2010(TM) analyser (Roche). Troponin T was measured with both second and third generation troponin T reagents. In the third-generation procedure, the calibrators are of human origin, leading to more accurate results (12). The cut-off values were 2.0 µg/L for troponin I, 0.1 µg/L for troponin T, and 5.0 µg/L for CKMB mass.

The results of the troponin I and troponin T measurements for all carcinoid patients were below the detection limits of the AxSYM (<0.2 µg/L) as well as the Elecsys 2010 (<0.01 µg/L) analyzers. The CKMB mass concentrations (0.3 - 2.4 µg/L) were also within the reference limits. The 10 patients with clinical heart failure and the 5 patients with overt carcinoid heart disease on echocardiography (group III) also showed no detectable troponin I and troponin T concentrations. In these subsets of patients CKMB-mass ranged from 0.7 to 1.3 µg/L.

From these findings we conclude that patients with carcinoid syndrome have no detectable signs of myocardial damage, if the new and sensitive markers are used. Even patients with *(a)* prolonged exposure to high serotonin levels, *(b)* clinically observable heart failure, and *(c)* echocardiographic evidence of carcinoid heart disease, show no detectable troponin I and troponin T concentrations. This might be explained by the following. In carcinoid syndrome, there is right ventricular failure attributable to the involvement of the pulmonary and tricuspidal valve, whereas the myocardium itself is not primarily involved. Furthermore, the mass of the right ventricle is small compared with the left ventricle. Therefore, myocardial damage may be too small to lead to increases in troponin concentrations in the general circulation.

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