Carcinoid Heart Disease

The Role of Urinary 5-Hydroxyindoleacetic Acid Excretion and Plasma Levels of Atrial Natriuretic Peptide, Transforming Growth Factor-β and Fibroblast Growth Factor

Johanna M. Zuetenhorst, M.D.[1]
Johannes M. G. M. Bonfrer, M.D., Ph.D.[2]
Catharina M. Korse[2]
Rob Bakker, M.D.[3]
Harm van Tinteren, MSc.[4]
Babs G. Taal, M.D., Ph.D.[1]

[1] Department of Gastroenterology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

[2] Department of Clinical Chemistry, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

[3] Department of Cardiology, Slotervaart Hospital, Amsterdam, The Netherlands.

[4] Department of Statistics, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

Address for reprints: Johanna M. Zuetenhorst, M.D., Department of Gastroenterology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; Fax: (011) 31-20-5122572; E-mail: j.zuetenhorst@nki.nl

Received September 9, 2002; revision received October 28, 2002; accepted November 6, 2002.

BACKGROUND. Serotonin excretion plays a role in the development of carcinoid heart disease (CHD), but the exact pathogenesis is not known. In the current study, the authors evaluated 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion, as well as plasma levels of transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and atrial natriuretic peptide (ANP) in patients with and without CHD determined by ultrasound examination.

METHODS. Urine and plasma samples were obtained for 37 patients and cardiac ultrasound was performed during follow-up in 1999 and 2000. Median 5-HIAA excretion was calculated for the period between diagnosis and ultrasound examination. CHD was defined as the thickening of the tricuspid valve with additional III–IV/IV tricuspid valve regurgitation.

RESULTS. CHD was found in 9 of 37 patients (24%). No significant differences were found for age, gender, presence, and duration of liver metastases. All CHD patients had symptoms of the carcinoid syndrome compared with 71% of the non-CHD patients ($P = 0.159$). Median 5-HIAA excretion was significantly higher in the CHD group compared with the non-CHD group: 576 μmol/24 hours versus 233 μmol/24 hours ($P = 0.02$). No difference in TGF-β and FGF plasma levels was observed between both groups ($P = 0.139$ and $P = 0.985$, respectively), nor was there a correlation with morphology of the tricuspid valve or degree of dilatation of the right atrium/ventricle. However, the CHD group had higher median ANP levels than the non-CHD group: 48 ng/L and 25 ng/L, respectively ($P = 0.026$).

CONCLUSIONS. High levels of 5-HIAA excretion and plasma ANP were found to be associated with CHD. No significant relation with TGF-β or FGF was been found.
***Cancer* 2003;97:1609–15.** © *2003 American Cancer Society.*
DOI 10.1002/cncr.11226

KEYWORDS: carcinoid heart disease (CHD), fibrosis, serotonin, 5-hydroxyindoleacetic acid (5-HIAA), atrial natriuretic peptide (ANP).

Carcinoid tumors are neuroendocrine tumors (NET) that derive mostly from the midgut. Patients often present with liver metastases, which lead to the characteristic carcinoid syndrome with diarrhea and flushes caused by overproduction of serotonin. Carcinoid heart disease (CHD) occurs in 20–70% of the patients with metastatic carcinoid tumors.[1–4] In many patients, the cause of death is attributed directly to cardiac disease.[5] Serotonin plays a key role in the development of CHD, but to our knowledge the exact pathogenesis has not yet been elucidated. In several studies, urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion, which is indicative of the amount of serotonin production, was significantly higher in patients with CHD than in patients without the disease.[2–4] Although the sensitivity of elevated serotonin levels for heart valve lesions is almost 100%, the specificity

is much lower.[6] Therefore, it is likely that other factors are associated with CHD. In experimental studies, the development of fibrosis is related to transforming growth factor-β (TGF-β).[7,8] In addition, fibroblast growth factor (FGF) has been reported to be related to pulmonary and renal fibrosis.[9] For patients with carcinoid disease with fibrosis of the heart valves, there currently are no reports regarding the association between CHD and the presence of TGF-β and FGF. Atrial natriuretic peptide (ANP) has been shown to be a diagnostic and prognostic marker in patients with heart failure of any origin.[10,11] In carcinoid patients, ANP may also be a marker for CHD[12] as CHD eventually leads to heart failure.

In the current study, we compared urinary 5-HIAA excretion and the plasma levels of ANP, TGF-β, and FGF in patients with and without CHD to investigate the relation between hormonal activity and markers of fibrosis. We compared these values in patients with severe cardial abnormalities as an expression of late valvular damage with patients with moderate valvular changes. We regarded the latter group as having earlier damage.

MATERIALS AND METHODS

Cardiac ultrasound studies were performed for 37 consecutive carcinoid patients (19 women and 18 men) who visited the outpatient department of The Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital in 1999 and 2000 for follow-up. An NET diagnosis was confirmed by histology for 34 patients. Fine-needle aspiration biopsy led to the diagnosis in two patients. One patient refused a biopsy and the diagnosis was based on strongly elevated 5-HIAA excretion. The mean age of the patients was 61 years (range, 34–77 years). The median interval between the diagnosis of metastatic carcinoid disease and the cardiac investigation plus laboratory testing was 28 months (range, 2–121 months).

Cardiac Ultrasound Imaging

Two-dimensional echocardiography with continuous wave Doppler and color flow Doppler studies were performed using standard techniques (Hewlett Packard [Corvallis, OR] Sonos 5500 or Sonos 2000 with 2.0/2.5 MHz probes). The echocardiographic parameters analyzed were valve morphology (normal or thickened), valve mobility (normal, mildly, moderately, severely diminished, fixed), valve regurgitation (none, I–IV/IV), valvular stenosis, and atrial/ventricular dimensions. Our criterion for CHD was a thickened tricuspid valve with additional III/IV or IV/IV tricuspid valve regurgitation. We also applied a modified scoring system introduced by Westberg et al.[4] and expressed CHD as an index. This index is calculated as a summation of structural tricuspid valve abnormalities (0: no abnormalities; 1: mild thickening; 2: moderate thickening; 3: severe thickening; and 4: severe thickening and retraction) and tricuspid valve regurgitation (0: no regurgitation; 1: mild regurgitation; 2: moderate; 3: severe; and 4: extreme). A high cutoff point (index ≥ 4) is indicative of morphologic fibrosis of the valve as well as functional disturbance comparable to the strict definition we used and was considered as severe (and most likely late) valvular damage. A lower cutoff point (index 2–4) is applied to detect minor heart disease and is comprised of either a moderate morphologic defect or a moderate functional abnormality as an early expression of CHD.

Laboratory Techniques

Urinary 5-HIAA excretion and serum levels of ANP, TGF-β, and FGF were determined at the same time as the cardiac investigation. Twenty-four-hour urine samples were collected routinely and evaluated qualitatively for 5-HIAA using a high-performance liquid chromatography assay (normal, < 40 μmol/24 hours). Median urinary 5-HIAA excretion and areas under the curve (AUC) were calculated for the period between diagnosis and cardiac ultrasound examination. Serum levels of TGF-β and FGF were determined by immunoassays provided by R&D systems (Minneapolis, MN: TGF-β normal, < 3.2 μg/L; FGF normal, < 6.9 ng/L). ANP was measured in plasma samples using an immunoradiometric assay (IRMA) assay manufactured by CIS Bio International (Gif-sur-Yvette, France: normal value < 43 ng/L).

Histology

Histology was classified as low-grade (< 10 mitoses/2 mm^2 without necrosis) and high-grade NET (> 10 mitoses/2 mm^2 and/or necrosis) according to the revised classification of Capella et al.[13]

Statistical Analysis

Comparisons between the CHD and the non-CHD group were made by the Mann–Whitney *U* test or the Kruskal–Wallis test in case of a continuous variable. Dichotomous variables were evaluated by the Fisher exact test.

RESULTS

In this study, 9 of 37 patients (24%) met our criteria for CHD (i.e., they had tricuspid valve lesions combined with regurgitation) (Table 1). Additional pulmonary valve pathology was detected in 5 of these CHD patients, but the inspection was difficult and insufficient in 23 patients. Seventeen patients had mild regurgita-

TABLE 1
Echocardiographic Findings in Carcinoid Patients (n = 37) According to the Presence of Heart Disease

Heart disease	Without carcinoid heart disease (n = 28) (%)	With carcinoid heart disease (n = 9) (%)[a]
Tricuspid valve		
Thickened	1 (4)	9 (100)
Normal	27 (96)	0 (0)
Pulmonary valve		
Thickened	0 (0)	5 (56)
Normal	9 (32)	0 (0)
Not visible[b]	19 (68)	4 (44)
Tricuspid regurgitation		
None	11 (39)	0 (0)
I/IV	9 (32)	0 (0)
II/IV	8 (29)	0 (0)
III/IV	0 (0)	2 (22)
IV/IV	0 (0)	7 (78)
Right atrium		
Normal	23 (81)	0 (0)
Mildly dilatated	3 (11)	1 (11)
Moderately dilatated	1 (4)	1 (11)
Severely dilatated	1 (4)	7 (78)
Right ventricle		
Normal	26 (93)	1 (11)
Mildly dilatated	2 (7)	2 (23)
Moderately dilatated	0 (0)	3 (33)
Severely dilatated	0 (0)	3 (33)

[a] Defined as thickening of the tricuspid valve with additional III/IV or IV/IV tricuspid valve regurgitation.
[b] The pulmonary valve could not be visualized properly.

tion without tricuspid valve thickening and were included in the non-CHD group. Severe dilatation of the right atrium was present in seven of nine patients with CHD and in one patient without valvular lesions. Severe dilatation of the right ventricle was found less frequently (three patients) (Table 1). Valvular lesions of the left ventricle (aortic or mitral valve regurgitation Grade III/IV or IV/IV IV/IV) were only present in two CHD patients, both with severe dilatation of the right atrium and ventricle.

Liver metastases were manifest in all but three patients. The three patients without liver metastases all had a normal ultrasound of the heart. No significant differences between the CHD and non-CHD group were noted with respect to age, gender, and the presence and duration of liver metastases (Table 2). Although the median time between initial diagnosis and ultrasound examination as a measure of carcinoid disease duration was longer in the CHD group (40 months) compared with the non-CHD group (22 months), this finding was not statistically significant ($P = 0.178$). All CHD patients were found to have the carcinoid syndrome (flushes, diarrhea, or wheezing) compared with 71% of the non-CHD patients ($P = 0.159$). CHD was not present in 4 patients (11%) with a foregut tumor localization. There were no significant differences in the distribution of the primary tumor between the CHD and the non-CHD group (Table 2). Histology was scored as low grade in 28 patients and high grade in 6 patients. None of the 6 patients with high-grade tumors met the criteria for CHD, in contrast to 8 of 28 (29%) in the low-grade group. However, these differences failed to reach statistical significance ($P = 0.297$; Table 2).

A total of 33 of 37 patients were treated with somatostatin analoga, 22 at the time of laboratory tests. Pharmacologic doses of meta-iodobenzylguanidine (MIBG) were administered to 20 patients, 2 of them during sample collection. Ten patients received a combination with radioactive-labeled MIBG,[14] all but 1 at least 3 months before blood collection. Fourteen patients were treated with interferon, 4 during the collecting time. There were no significant differences with regard to these treatment modalities between the CHD and the non-CHD group. Median urinary 5-HIAA excretion between diagnosis and cardiac ultrasound examination was significantly ($P = 0.02$) higher in the CHD group (576 μmol/24 hours) compared with the non-CHD group (233 μmol/24 hours; Fig. 1). The calculated AUC of the 5-HIAA excretion during the complete disease period underscored the difference between both groups ($P < 0.001$). Serum TGF-β was elevated (> 3.2 μg/L) in all 37 patients and ranged from 3.4–24.0 μg/L. The median level in the CHD group was 13.2 μg/L compared with 15.6 μg/L in the non-CHD group ($P = 0.139$). The level of FGF was elevated (> 6.9 ng/L) in only 4 of 37 patients. Three of these four cases did not meet our criteria for CHD. No significant differences for the level of FGF in the CHD group compared with the non-CHD group were found (median, 3.6 vs. 3.5 ng/L; $P = 0.985$; Table 3). Between low-grade and high-grade tumors, no significant difference was found for the plasma levels of TGF-β and FGF ($P = 0.85$ and $P = 0.76$, respectively). The level of ANP was significantly higher in the CHD group (48 ng/L) compared with the non-CHD group (25 ng/L [$P = 0.026$]; Fig. 2). The degree of right atrium dilatation was associated with high levels of ANP, although this was not statistically significant ($P = 0.15$).

Survival (Fig. 3) was significantly ($P = 0.026$) longer for the patients in the non-CHD group (median, 23 months) compared with the CHD patients (13 months), who died within 2 years. In the non-CHD group, 68% of the patients were long-term survivors.

We also employed a scoring system that included the severity of the morphologic and functional abnormalities of the tricuspid valve.[4] Using a cutoff value of

TABLE 2
Clinical Characteristics in Carcinoid Patients According to the Presence of Heart Disease

Clinical characteristics	Total group (n = 37)	Without carcinoid heart disease (n = 28)	With carcinoid heart disease[a] (n = 9)	P value
Mean age (yrs) at cardiac ultrasound (range)	61 (34–77)	61 (34–76)	60 (44–77)	0.589
Gender				1.000
Male	18 (49%)	14 (50%)	4 (45%)	
Female	19 (51%)	14 (50%)	5 (55%)	
Median duration (mos) of carcinoid disease at echocardiogram (range)	28 (2–121)	22 (2–121)	40 (9–85)	0.178
Liver metastases	34 (92%)	25 (74%)	9 (100%)	0.562
Median duration (mos) of liver metastases (range)	26 (2–96)	21 (2–96)	40 (9–85)	0.111
Symptoms of carcinoid syndrome				0.159
Yes	29 (78%)	20 (71%)	9 (100%)	
No	8 (22%)	8 (29%)	0 (0%)	
Primary tumor				0.166
Foregut	4 (11%)	4 (14%)	0 (0%)	
Midgut	16 (43%)	13 (47%)	3 (33%)	
Hindgut	1 (3%)	0 (0%)	1 (10%)	
Unknown	16 (43%)	11 (39%)	5 (57%)	
Pathology				
Low-grade NET	28 (76%)	20 (71%)	8 (89%)	0.297
High-grade NET	6 (16%)	6 (22%)	0 (0%)	
Cytologic punction	2 (5%)	2 (7%)	0 (0%)	
No histology	1 (3%)	0 (0%)	1 (11%)	

NET: neuroendocrine tumor.
[a] Defined as thickening of the tricuspid valve with additional III/IV or IV/IV tricuspid valve regurgitation.

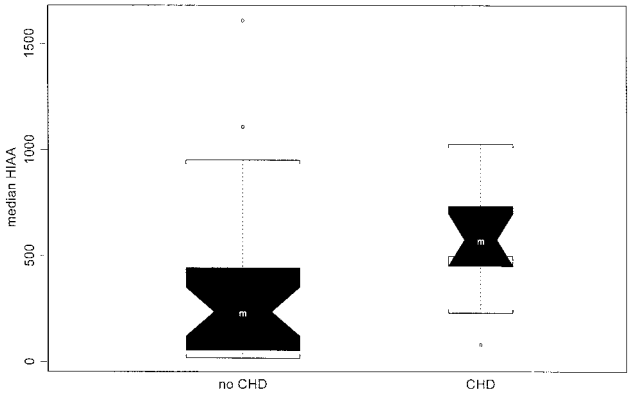

FIGURE 1. The box plots show the median value (m) with 95% confidence intervals (notches of the box), as well as lower and upper quartiles (box). The width of the boxes is proportional to the number of patients in each group. Whiskers show values within 1.5 times the interquartile range. Values beyond the whiskers are considered to be outliers (o). Median urinary 5-hydroxyindoleacetic acid excretion between diagnosis of carcinoid disease and cardiac ultrasound examination.

≥ 4 to detect severe heart disease resulted in 10 of 37 patients with CHD (Table 3). Only one additional CHD patient was defined. Subsequently, we divided our patients into three groups: severe, moderate, or no CHD. A cutoff value of 2–4 to detect early (moderate) valvular damage found 8 of 37 patients. Nine of 37 patients had an index > 4 and were considered to have late (severe) valvular damage.

It did not appear to make a difference whether our patients were divided into two or three subgroups according to a scoring system or whether they were divided on strict definition. The 5-HIAA excretion remained significantly associated with heart disease, whereas the markers of fibrosis still were not significant.

DISCUSSION

Thickening of the right heart valves caused by formation of fibrotic plaques eventually followed by regurgitation is a characteristic feature of CHD. In the current series of 37 patients, the incidence of CHD is 24%, which is rather low compared with the reported 20–70% incidence in patients with metastatic carcinoid tumors.[1–4] This most likely is because of the strict criteria we used for CHD in our patient population. Another explanation may be the extensive treatment focused on reducing the excretion of serotonin given to our patient group. To our knowledge, the pathogenesis of carcinoid heart lesions has not yet been elucidated fully, but serotonin plays an important role.

TABLE 3
Urinary 5-HIAA Excretion and Markers of Fibrosis in CHD Using Various Definitions

Characteristics	CHD criteria: thickened TV and additional TV regurgitation III/IV or IV/IV	Index score: moderate (2–4), severe (> 4), no CHD (< 2)[a]	Index score: ≥ 4[a]
Ultrasound findings (no. of patients) (%)			
CHD	9 (24%)		10 (27%)
Moderate		8 (22%)	
Severe		9 (24%)	
No CHD	28 (76%)	20 (54%)	27 (73%)
Median 5-HIAA ($n < 40$ μmol/24 hr) (range)			
CHD	576 (87–1028)		576 (87–1028)
Moderate		239 (17–502)	
Severe		576 (87–1028)	
No CHD	233 (17–1616)	233 (21–1616)	233 (17–1616)
P value	0.02	0.032	0.031
Median TGF-β ($n < 3.2$ μg/L) (range)			
CHD	13.2 (8.7–17.0)		13.2 (8.7–17.0)
Moderate		14.5 (6.5–17.9)	
Severe		13.2 (8.7–17.0)	
No CHD	15.6 (3.4–24.0)	17.8 (3.4–24.0)	15.6 (3.4–24.0)
P value	0.139	0.141	0.139
Median FGF ($n < 6.9$ ng/L) (range)	3.6 (1.0–9.8)		3.6 (1.0–9.8)
CHD			
Moderate		4.1 (1.0–12.0)	
Severe		3.6 (1.0–9.8)	
No CHD	3.5 (1.0–12.0)	3.6 (1.0–8.0)	3.5 (1.0–12.0)
P value	0.985	0.985	0.900
Median ANP ($n < 43$ ng/L) (range)	48 (16–89)		48 (16–89)
CHD			
Moderate		26 (12–37)	
Severe		48 (16–89)	
No CHD	25 (10–57)	22 (10–57)	25 (10–57)
P value	0.026	0.085	0.026

5-HIAA: 5-hydroxyindoleacetic acid; CHD: carcinoid heart disease; TV: tricuspid valve.

[a] The score index is a summation of structural tricuspid valve abnormalities (0: no abnormalities; 1: mild thickening; 2: moderate thickening; 3: severe thickening; and 4: severe thickening and retraction) and tricuspid valve regurgitation (0: no regurgitation; 1: mild regurgitation; 2: moderate; 3: severe; and 4: extreme).

This is supported by the finding of similar valve lesions in patients using appetite suppressants, such as fenfluramine or dexfenfluramine, and antimigraine drugs such as ergotamin and methysergide, which all act via the serotonin pathway.[15–17] We found a significant correlation between CHD and elevated urinary 5-HIAA excretion, which is indicative of serotonin production. This is comparable to findings reported in the literature.[2–4] No significant difference was found for 5-HIAA excretion between non-CHD patients and patients with moderate valvular lesions. However, non-CHD patients reported in literature have significantly lower serotonin release, but these levels still are elevated.[3,4,18] Apart from using median values of the urinary 5-HIAA excretion, we also estimated the serotonin load over the years by calculating the AUC for the period between diagnosis and ultrasound examina-

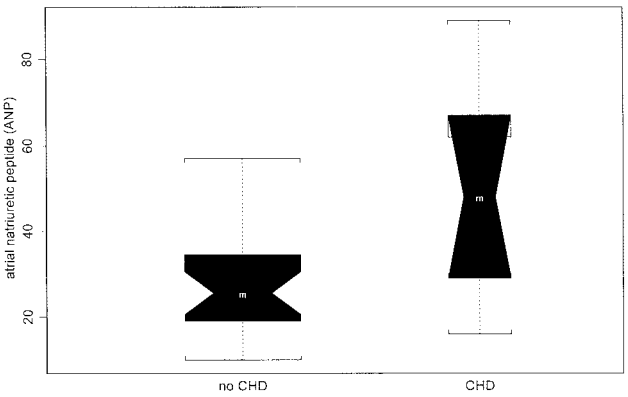

FIGURE 2. Median atrial natriuretic peptide levels in patients with and without carcinoid heart disease.

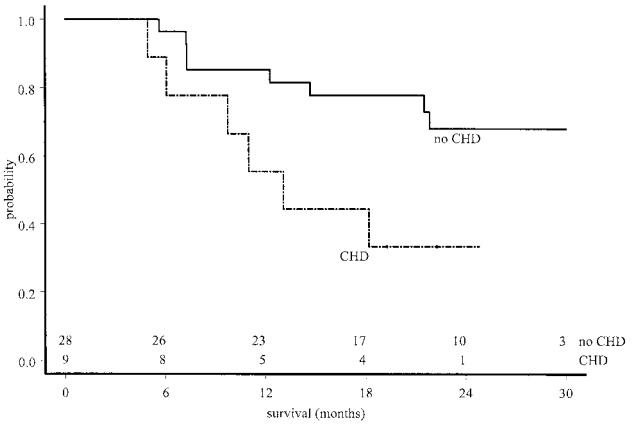

FIGURE 3. Survival of patients with and without carcinoid heart disease.

tion. The effect of 5-HIAA excretion was even more significant using the AUC calculation. This supports the theory that not only a high serotonin level, but also the duration of exposure to serotonin is important in the development of CHD.

Transforming growth factor-β affects the growth and differentiation of cells and stimulates fibroblasts to produce extracellular matrix components. Expression of TGF-β was found in a pancreatic carcinoid tumor cell line, as well as in freshly excised midgut tumors from six carcinoid patients.[8] An interesting finding in this respect is an increased expression of TGF-β in fibrotic plaques on the heart valves reported in tissue specimens obtained from nine CHD patients undergoing valve replacement surgery.[7] It suggests a role for TGF-β in the development of CHD. FGF belongs to a family of polypeptide growth factors. They stimulate angiogenesis and formation of granulation tissue, thus facilitating wound healing. In nonmalignant conditions, such as pulmonary and renal fibrosis, a relation between TGF-β and FGF was reported and suggested that there might be a role for FGF as well.[9,19,20] Analysis of tissue samples of normal gastrointestinal mucosa of 7 subjects and of 41 endocrine tumors of the gut revealed a positive relation between expression of FGF and the amount of fibrous stroma in the tumors, suggesting an involvement of FGF in the proliferation and activation of fibroblasts.[21]

A literature survey did not reveal prior reports about plasma levels of FGF and TGF-β related to CHD. Therefore, we tested for the first time whether increased plasma levels played a role in the development of changes of the tricuspid valve in CHD patients. In our study, the plasma TGF-β level was elevated in all patients, but no relation was found between thickening and regurgitation of the tricuspid valve. The plasma levels of FGF were elevated in only 4 patients (11%). In contrast to what might be expected, a cardiac ultrasonography was normal in 3 of them. We hypothesized that FGF and TGF-β help to initiate the process of fibrosis before clinical symptoms or valvular lesions are detected or that they are only of importance in the early phase of valvular damage. In addition to our strict criteria for CHD, we also applied a score system to detect moderate (early) and late (severe) valvular damage. This subdivision also failed to detect a significant association of elevated levels of FGF and TGF-β with heart valve fibrosis, but the numbers are too small for a definite conclusion. Another explanation might be that the level of TGF-β and FGF in the systemic circulation is not an adequate reflection of the local level and effect of these markers of fibrosis. Transforming growth factor-β is secreted by different cells in a latent form. This pro-TGF-β does not appear to bind to its receptor until it is activated by proteolytic cleavage. Increased production of TGF-β is only biologically significant if activation also occurs.[22] In our samples, we determined the active form of TGF-β, which was elevated in all patients. Although a relation between increased levels of TGF-β and different fibrotic diseases has been described,[22] we could not demonstrate this for our CHD patients.

Cardiac natriuretic peptide hormones (e.g., ANP) are synthesized and secreted by the heart into the right atrium. They play a key role in volume homeostasis and are highly activated during heart failure. Two recent reports[10,11] showed that ANP and fragments of ANP can be used as powerful diagnostic and prognostic markers in patients with heart failure due to myocardial infarction or cardiomyopathy. In 50 carcinoid patients, ANP levels were reported to be significantly higher in patients with the most severe right ventricular failure, whereas the levels remained in the normal range among patients without cardiac failure.[12] Plasma ANP levels, as a reflection of heart failure, were significantly higher in our CHD group. There was also a tendency toward an association between the degree of right atrium dilatation and ANP. As might be expected, survival was significantly shorter in the CHD patients, who died within 2 years, compared with the non-CHD patients, who had a 3-year survival rate of 68%.[5,18] The median survival period was 13 months in the CHD group and 23 months in the non-CHD group.

In the current study, CHD was found in 24% of the carcinoid patients in our series. Atrial natriuretic peptide was a useful marker of heart failure. A clear role for markers of fibrosis, such as plasma TGF-β and FGF, in the development of heart disease was not demonstrated. Urinary 5-HIAA excretion as a marker of serotonin production appears to be related to the

development of CHD. Because survival is poor in patients with CHD, treatment should be focused on reducing elevated levels of hormonal excretion. This can be realized by a combination of different treatment modalities such as octreotide analoga, unlabeled or radioactive MIBG, and interferon. Even in the absence of severe symptoms of the carcinoid syndrome, it is highly recommended that serotonin levels be reduced.

REFERENCES

1. Tornebrandt K, Eskilsson J, Nobin A. Heart involvement in metastatic carcinoid disease. *Clin Cardiol.* 1986;9:13–19.
2. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation.* 1988;77:264–269.
3. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. *Circulation.* 1995;92:790–795.
4. Westberg G, Wangberg B, Ahlman H, Bergh CH, Beckman-Suurkula M, Caidahl K. Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome. *Br J Surg.* 2001;88:865–872.
5. Ross EM, Roberts WC. The carcinoid syndrome: comparison of 21 necropsy subjects with carcinoid heart disease to 15 necropsy subjects without carcinoid heart disease. *Am J Med.* 1985;79:339–354.
6. Bajetta E, Ferrari L, Martinetti A, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. *Cancer.* 1999;86:858–865.
7. Waltenberger J, Lundin L, Oberg K, et al. Involvement of transforming growth factor-beta in the formation of fibrotic lesions in carcinoid heart disease. *Am J Pathol.* 1993;142:71–78.
8. Beauchamp RD, Coffey RJ Jr., Lyons RM, Perkett EA, Townsend CM Jr., Moses HL. Human carcinoid cell production of paracrine growth factors that can stimulate fibroblast and endothelial cell growth. *Cancer Res.* 1991;51:5253–5260.
9. Li CM, Khosla J, Hoyle P, Sannes PL. Transforming growth factor-beta(1) modifies fibroblast growth factor-2 production in type II cells. *Chest.* 2001;120:60S–61S.
10. Hammerer-Lercher A, Puschendorf B, Mair J. Cardiac natriuretic peptides: new laboratory parameters in heart failure patients. *Clin Lab.* 2001;47:265–277.
11. Cappellin E, Gatti R, Spinella P, et al. Plasma atrial natriuretic peptide (ANP) fragments proANP (1-30) and proANP (31-67) measurements in chronic heart failure: a useful index for heart transplantation? *Clin Chim Acta.* 2001;310:49–52.
12. Lundin L, Oberg K, Landelius J, Hansson HE, Wilander E, Theodorsson E. Plasma atrial natriuretic peptide in carcinoid heart disease. *Am J Cardiol.* 1989;63:969–972.
13. Capella C, Heitz PU, Hofler H, Solcia E, Kloppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch.* 1995;425:547–560.
14. Taal BG, Hoefnagel CA, Valdes Olmos RA, Boot H, Beijnen JH. Palliative effect of metaiodobenzylguanidine in metastatic carcinoid tumors. *J Clin Oncol.* 1996;14:1829–1838.
15. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med.* 1997;337:581–588.
16. Wee CC, Phillips RS, Aurigemma G, et al. Risk for valvular heart disease among users of fenfluramine and dexfenfluramine who underwent echocardiography before use of medication. *Ann Intern Med.* 1998;129:870–874.
17. Hendrikx M, Van Dorpe J, Flameng W, Daenen W. Aortic and mitral valve disease induced by ergotamine therapy for migraine: a case report and review of the literature. *J Heart Valve Dis.* 1996;5:235–237.
18. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation.* 1993;87:1188–1196.
19. Strutz F, Zeisberg M, Renziehausen A, et al. TGF-beta 1 induces proliferation in human renal fibroblasts via induction of basic fibroblast growth factor (FGF-2). *Kidney Int.* 2001;59:579–592.
20. Kadono T, Kikuchi K, Kubo M, Fujimoto M, Tamaki K. Serum concentrations of basic fibroblast growth factor in collagen diseases. *J Am Acad Dermatol.* 1996;35:392–397.
21. La Rosa S, Chiaravalli AM, Capella C, Uccella S, Sessa F. Immunohistochemical localization of acidic fibroblast growth factor in normal human enterochromaffin cells and related gastrointestinal tumours. *Virchows Arch.* 1997;430:117–124.
22. Oppenheim JJ, Feldmann M. Cytokine reference, vol. 1. London: Academic Press, 2001.