

ORIGINAL ARTICLE

Factors Associated with Progression of Carcinoid Heart Disease

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ABSTRACT

BACKGROUND

By releasing vasoactive substances into the circulation, carcinoid tumors can cause right-sided valvular heart disease. Factors associated with the progression of carcinoid heart disease are poorly understood. We conducted a retrospective study to identify such factors.

METHODS

Our sample included 71 patients with the carcinoid syndrome who underwent serial echocardiographic studies performed more than one year apart and 32 patients referred directly for surgical intervention after an initial echocardiographic evaluation. A score for carcinoid heart disease was determined on the basis of an assessment of valvular anatomy and function and the function of the right ventricle. An increase of more than 25 percent in the score between studies was considered suggestive of disease progression. Tumor progression was assessed on the basis of abdominal computed tomographic scans and changes in the level of urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.

RESULTS

Of the patients with serial echocardiographic studies, 25 (35 percent) had an increase of more than 25 percent in the cardiac score. As compared with patients whose score changed by 25 percent or less, these patients had higher urinary peak 5-HIAA levels (median, 265 mg per 24 hours [interquartile range, 209 to 593] vs. 189 mg per 24 hours [interquartile range, 75 to 286]; $P=0.004$) and were more likely to have biochemical progression (10 of 25 patients vs. 9 of 46, $P=0.05$) and to have received chemotherapy (13 of 25 vs. 10 of 46, $P=0.009$). Logistic-regression analysis showed that a higher peak urinary 5-HIAA level and previous chemotherapy were predictors of an increase in the cardiac score that exceeded 25 percent (odds ratio for each increase in 5-HIAA of 25 mg per 24 hours, 1.08 [95 percent confidence interval, 1.03 to 1.13]; $P=0.009$); odds ratio associated with chemotherapy, 3.65 [95 percent confidence interval, 1.74 to 7.48]; $P=0.001$).

CONCLUSIONS

Serotonin is related to the progression of carcinoid heart disease, and the risk of progressive heart disease is higher in patients who receive chemotherapy than in those who do not.

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CARCINOID TUMORS ARE UNCOMMON, with an incidence of 1 to 2 per 100,000 people in the United States.¹ The tumors arise from enterochromaffin cells typically located in the gastrointestinal tract or lungs. At the time of diagnosis, 20 to 30 percent of patients have disseminated disease and the carcinoid syndrome, characterized by cutaneous vasomotor flushing, secretory diarrhea, and bronchospasm.^{1,2}

The carcinoid syndrome is caused by the tumor's release of serotonin and other vasoactive substances. Once released, serotonin is metabolized by monoamine oxidases in the liver, lungs, and brain to 5-hydroxyindoleacetic acid (5-HIAA). When vasoactive substances are released from hepatic metastases, the right heart is exposed to high levels of these substances. The exposure is believed to result in endocardial damage, leading to thickening, retraction, and fixation of the right heart valves, valvular dysfunction, and eventually, right heart failure.³⁻⁶ Although serotonin levels are higher in patients with carcinoid tumors who have heart disease than in those without cardiac involvement,³⁻⁶ it is unclear what factors are involved in the progression of the cardiac lesions. Right ventricular failure remains a major cause of morbidity and death in patients with carcinoid heart disease. Knowledge of the mechanisms involved in the progression of the cardiac lesions might lead to the development of treatments that attenuate the process.

We conducted a retrospective study to identify factors associated with the progression of valvular dysfunction in patients with the carcinoid syndrome. We evaluated patients with metastatic carcinoid disease who had undergone serial echocardiographic studies and patients referred directly for surgical intervention after an initial echocardiographic evaluation.

METHODS

SELECTION OF PATIENTS

Between 1980 and 2001, 273 patients with histologically verified carcinoid tumors and the carcinoid syndrome were referred for echocardiographic evaluation at the Mayo Clinic, in Rochester, Minnesota. Echocardiography was clinically indicated because of symptoms or physical findings indicative of valvular heart disease or as part of the preoperative assessment before partial hepatectomy was performed. A total of 170 patients were excluded from

the study because only one echocardiographic study had been performed at our institution (123 patients) or because the interval between serial echocardiographic studies was less than one year (47 patients). Seventy-one patients with at least two echocardiograms obtained more than 12 months apart, without intervening valve surgery, and 32 patients referred for valve replacement after the initial echocardiogram were included in this retrospective study. If multiple echocardiographic studies were performed, the first study performed more than one year after the base-line study was used for the analysis. One patient in the surgical group had taken a selective serotonin-reuptake inhibitor; none of the patients had taken fenfluramine, phentermine, ergotamine, or pergolide. The first echocardiographic evaluation performed at our institution served as the base line. The study was approved by the institutional review board, and all patients provided written informed consent.

ECHOCARDIOGRAPHIC STUDIES

We assessed right ventricular size, systolic function, and the valvular anatomy of the right heart semiquantitatively. For the anatomy of the tricuspid and pulmonary valves, we used a four-point scale based on leaflet motion, thickness, and retraction of the valve (with 0 denoting normal, 1 thickened with reduced mobility, 2 thickened with severe immobility, and 3 thickened and fixed). In cases in which the pulmonary valve was not visualized despite satisfactory visualization of the right ventricular outflow tract, a score of 3 was assigned. We assessed tricuspid-valve regurgitation semiquantitatively on a scale from 0 (minimal or no regurgitation) to 3 (marked regurgitation) on the basis of visual interpretation and the ratio of the maximal jet area to the right atrial area.^{7,8} Pulmonary-valve regurgitation was graded semiquantitatively on a scale from 0 (minimal or no regurgitation) to 3 (marked regurgitation) according to the width and size of the regurgitant jet, as determined by color Doppler studies.

Right ventricular size and systolic function were scored on a scale from 0 (normal) to 3 (severely enlarged or impaired). We used Doppler recordings to assign scores for the presence (1) or absence (0) of diastolic forward flow in the pulmonary artery and systolic flow reversal in hepatic veins.⁹ On the basis of continuous-wave Doppler recordings, tricuspid inflow, the peak regurgitant velocity, pressure half-time, and mean inflow gradient were measured. Re-

cordings of right ventricular outflow were used to measure the peak velocity and mean gradient across the pulmonary valve.

Echocardiograms were analyzed off-line by one of us, who was unaware of the clinical data. In addition, 20 of the electrocardiograms were randomly selected for analysis by a second observer. In 12 studies, the two sets of assigned scores were concordant; in 6, there was a discrepancy of 1 point, and in 2 a discrepancy of 2 points. In six of eight cases in which there was disagreement, it involved the grading of pulmonary-valve regurgitation.

SEVERITY OF CARCINOID HEART DISEASE

The severity of carcinoid heart disease was estimated at both echocardiographic evaluations as the sum of the scores for tricuspid-valve anatomy and regurgitation, systolic flow reversal in hepatic veins, right ventricular size and function, pulmonary-valve anatomy and regurgitation, and diastolic forward flow in the pulmonary artery. The score was reported as the percentage of points possible (maximum, 20 points). Patients with an increase of more than 25 percent in the score (equivalent to an increase of more than five points) from base line to follow-up were considered to have clinically important progression of carcinoid heart disease. This cutoff point corresponded to twice the highest level of interobserver disagreement.

ABDOMINAL IMAGING AND BIOCHEMICAL TESTS

We assessed changes in the tumor burden with the use of serial contrast-enhanced computed tomographic studies of the abdomen. All follow-up studies were compared with previous studies by experienced radiologists to determine whether the disease had progressed (as evidenced by new or enlarged metastases, or both) or regressed (as evidenced by the disappearance or shrinking of metastases, or both).

Multiple 24-hour urine samples from all patients were quantitatively analyzed for 5-HIAA. For the patients with serial echocardiograms, the urinary 5-HIAA level at the time of the first echocardiographic study, the level at the time of the follow-up echocardiographic study, and the highest level during this interval were recorded. Biochemical progression was recorded if the 5-HIAA level had increased by more than 25 percent, and biochemical regression was recorded if the level had decreased by more than 50 percent.^{10,11} In the group of pa-

tients referred for surgery, the 5-HIAA level at the time of echocardiographic study and the highest value before surgery were recorded.

STATISTICAL ANALYSIS

Continuous data are reported as medians with interquartile ranges, unless otherwise specified. Rank-sum tests were used for comparisons of continuous variables; for paired comparisons, the Wilcoxon test was used. Categorical variables were compared with use of the chi-square test or Fisher's exact test, as appropriate. We performed multivariate logistic-regression analysis, with a significance level of 0.05 as the criterion for including and retaining variables in the model, to identify independent predictors of an increase in the cardiac score that exceeded 25 percent.

RESULTS

Clinical characteristics of the patients, 5-HIAA levels, and details of management of the carcinoid syndrome at base line are shown in Table 1. Among the 71 patients with serial echocardiograms, biochemical regression was noted in 18 patients and progression in 19 at follow-up; there was no marked change during follow-up in the other 34 patients. On the basis of abdominal imaging, progression of the tumor mass was reported in 21 patients, regression in 6, and no marked change in 44.

VALVULAR LESIONS

Figure 1, an echocardiogram from one of the patients in the study, shows the typical echocardiographic appearance of advanced carcinoid heart disease. Of the 32 patients referred for surgical intervention, 31 (97 percent) had right-sided valvular involvement, including severe tricuspid-valve regurgitation in all 31 and severe pulmonary-valve regurgitation in 23 (72 percent). One patient with ovarian carcinoid had isolated left-sided involvement.

Among the 71 patients with serial echocardiographic studies, both studies were normal in 21 patients. In the other 50 patients, carcinoid heart disease was present at base line or developed during follow-up; the echocardiographic characteristics of these patients are shown in Table 2. Carcinoid heart disease developed in 15 patients with normal base-line studies. Among these 15 patients, the median increase in the cardiac score was 32 percent (range, 15 to 75 percent). All 15 of these patients

Table 1. Clinical Characteristics of the Patients.*

Variable	Patients with Serial Echocardiograms		Patients Referred for Surgery (N=32)
	No CHD at Base Line (N=36)	CHD at Base Line (N=35)	
Age at diagnosis of the carcinoid syndrome — yr			
Median	57	56	59
Interquartile range	48–66	45–67	43–63
Female sex — no. (%)	12 (33)	12 (34)	9 (28)
Interval between diagnosis and base-line study — yr			
Median	1.8	1.0	2.1
Interquartile range	0.1–7.0	0.1–4.4	0.2–6.1
Primary site of tumor — no. (%)			
Foregut	2 (6)	1 (3)	0
Midgut	29 (81)	28 (80)	27 (84)
Unknown	5 (14)	6 (17)	5 (16)
Metastasis at base line — no. (%)			
Hepatic	33 (92)	32 (91)	31 (97)
Pulmonary	3 (8)	4 (11)	3 (9)
Retroperitoneal	4 (11)	9 (26)	5 (16)
Other	8 (22)	5 (14)	4 (12)
Urinary 5-HIAA — mg/24 hr			
At base line			
Median	110	209	206
Interquartile range	49–177	79–306†	168–305‡
At follow-up			
Median	112	101	—
Interquartile range	28–187	52–231	—
Highest value			
Median	197	249	219
Interquartile range	73–264	149–403	159–362
NYHA class II, III, or IV			
Base line	3 (8)	18 (51)§	30 (94)¶
Follow-up	10 (28)	27 (77)§	—
Treatment at base line			
Somatostatin analogue — no. (%)	17 (47)	22 (63)	29 (91)§
Duration of somatostatin treatment — mo			
Median	1	5	6
Interquartile range	0–9	0–14	2–16
Hepatic-artery embolization — no. (%)	6 (17)	15 (43)	11 (34)
Hepatic-artery ligation — no. (%)	12 (33)	13 (37)	6 (19)
Chemotherapy — no. (%)	10 (28)	13 (37)	15 (47)

* CHD denotes carcinoid heart disease, 5-HIAA 5-hydroxyindoleacetic acid, and NYHA New York Heart Association.
 † P=0.02 for the comparison with patients who did not have carcinoid heart disease at base line.
 ‡ P=0.001 for the comparison with patients who did not have carcinoid heart disease at base line.
 § P<0.001 for the comparison with patients who did not have carcinoid heart disease at base line.
 ¶ P<0.001 for both comparisons.
 || P=0.008 for the comparison with patients who had carcinoid heart disease at base line.

had thickening and reduced mobility of the tricuspid leaflet, resulting in tricuspid regurgitation at follow-up; 8 also had pulmonary-valve involvement.

Of the 35 patients with carcinoid heart disease at base line, 17 had an increase of at least 1 point in

the scores for both tricuspid-valve anatomy and regurgitation; in 18 patients, the score remained unchanged. None of the patients had an improvement in either score. Fourteen patients had a worsening of pulmonary-valve anatomy and regurgitation. In

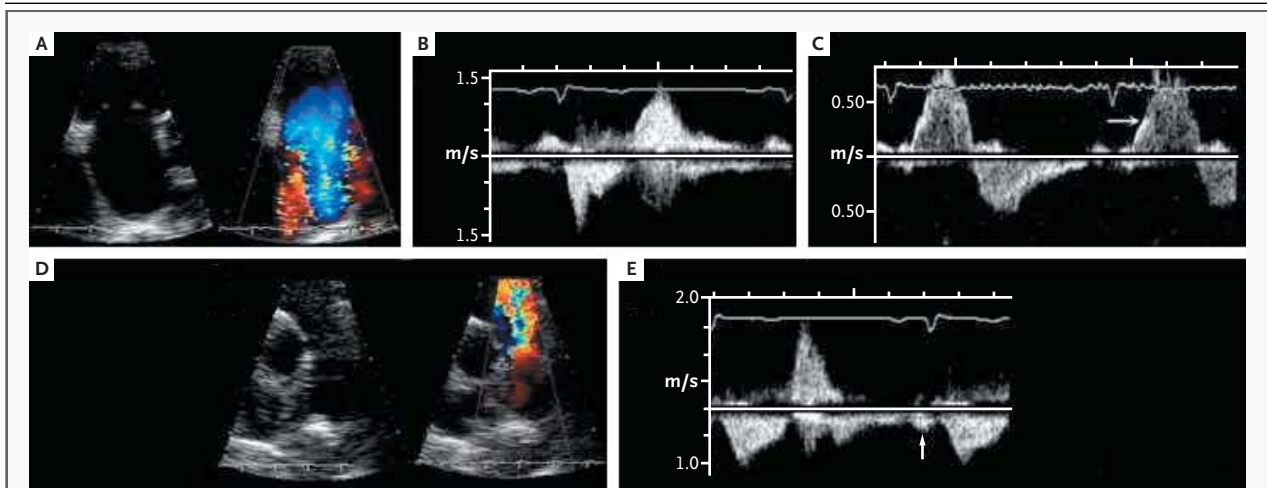


Figure 1. Typical Echocardiographic Appearance of Advanced Carcinoid Heart Disease.

A two-dimensional color-flow echocardiogram (parasternal short axis) shows thickened and retracted tricuspid-valve leaflets with poor coaptation, leading to severe regurgitation (Panel A). A continuous-wave Doppler study of the tricuspid valve shows a dagger-shaped regurgitant flow profile and increased inflow velocity due to severe regurgitation (Panel B). A pulsed-wave Doppler study of the hepatic vein shows marked systolic flow reversal (arrow), indicating severe tricuspid-valve regurgitation (Panel C). A two-dimensional color-flow echocardiogram (parasternal short axis) shows carcinoid involvement of the pulmonary valve, which is poorly visualized because of retraction of cusps leading to severe regurgitation (Panel D). A continuous-wave Doppler study of the right ventricular outflow tract shows rapid deceleration of the regurgitant signal resulting from rapid equalization of right ventricular and pulmonary arterial pressures (Panel E). Diastolic forward flow in the pulmonary artery (arrow) is due to a rapid rise in right ventricular diastolic pressure.

three patients, pulmonary-valve anatomy was graded 1 point lower on follow-up, and in two, this was accompanied by improvement in the score for pulmonary regurgitation. Right ventricular enlargement and deterioration of systolic function occurred in 18 patients, right ventricular enlargement alone in 6, and a decrease in systolic function in 1. In two patients, right- as well as left-sided valvular involvement was present at base line and follow-up; both patients had a patent foramen ovale. In these 35 patients, the median change in the cardiac score was 20 percent (range, -9 to 65 percent).

The cardiac score increased by more than 25 percent in 25 patients; 9 of these patients had no carcinoid heart disease at base line, and 16 had pre-existing carcinoid heart disease. Representative echocardiograms from a patient with preexisting disease are shown in Figure 2.

RELATION BETWEEN CLINICAL VARIABLES AND THE CARDIAC SCORE

Figure 3 shows the highest level of urinary 5-HIAA excretion in the group of patients with base-line and follow-up echocardiographic studies, according to the change in the cardiac score, and in the group

of patients referred directly for cardiac surgery. Table 3 shows the relation between clinical variables and the change in the cardiac score. Among the patients with an increase of 25 percent or less in the cardiac score, the follow-up study was performed after a median of 1.9 years (interquartile range, 1.3 to 3.1) and among those with an increase of more than 25 percent, the follow-up study was performed after a median of 2.3 years (interquartile range, 1.2 to 3.2; $P=0.95$). Seventeen patients (68 percent) had an increase of more than 25 percent in the score despite base-line treatment with somatostatin analogues. Among nine patients with no evidence of carcinoid heart disease at base line and an increase in the cardiac score of more than 25 percent, six received base-line treatment with somatostatin.

The median change in the cardiac score did not differ significantly between patients who were treated with somatostatin analogues (15 percent [interquartile range, 0 to 40]) and those who were not (8 percent [interquartile range, 0 to 29], $P=0.18$), or between patients who underwent dearterialization (12 percent [interquartile range, 0 to 40]) and those who did not (2 percent [interquartile range, 0 to 38], $P=0.88$). However, the change in the cardi-

Table 2. Echocardiographic Findings in Patients with Carcinoid Heart Disease.

Variable	Development of Heart Disease during Follow-up (N=15)			Heart Disease Present at Base Line (N=35)		
	Base Line	Follow-up	P Value	Base Line	Follow-up	P Value
Moderate or severe right ventricular systolic dysfunction — no. (%)	0	5 (33)	0.05	4 (11)	20 (57)	<0.001
Moderate or severe increase in right ventricular size — no. (%)	0	6 (40)	0.03	16 (46)	28 (80)	<0.001
Right atrial area — cm ²			0.01			0.06
Median	18	27		29	28	
Interquartile range	15–22	25–34		23–33	23–36	
Tricuspid valve						
Thickened, with severe immobility or fixed leaflets — no. (%)	0	7 (47)	0.01	14 (40)	26 (74)	0.002
Moderate or severe regurgitation — no. (%)	0	9 (60)	0.004	20 (57)	33 (94)	0.002
Ratio of regurgitant jet to right atrial area			0.01			0.09
Median	0.1	0.4		0.5	0.6	
Interquartile range	0.05–0.2	0.2–0.5		0.3–0.6	0.5–0.7	
Regurgitation velocity — m/sec			0.07			0.03
Median	2.5	2.9		2.6	2.8	
Interquartile range	2.1–2.8	2.8–3.1		2.3–2.8	2.3–3.1	
Pressure half-time — msec			0.71			0.18
Median	68	93		106	116	
Interquartile range	63–73	82–123		90–131	89–136	
Mean gradient — mm Hg			0.009			0.04
Median	0.8	3.1		3.4	3.6	
Interquartile range	0.5–1.8	2.4–5.4		1.9–4.2	2.6–5.5	
Right ventricular pressure — mm Hg			0.001			0.02
Median	26	47		41	47	
Interquartile range	22–35	40–52		37–48	38–53	
Pulmonary valve						
Thickened, with severe immobility or fixed cusps — no. (%)	0	8 (53)	0.009	18 (51)	24 (69)	0.04
Moderate or severe regurgitation — no. (%)	0	8 (53)	0.009	17 (49)	25 (71)	0.02
Diastolic forward flow — no. (%)	0	4 (27)	0.15	11 (31)	17 (49)	0.25
Peak velocity — m/sec			0.03			0.82
Median	0.9	1.2		1.6	1.8	
Interquartile range	0.8–1.2	1.0–1.9		1.4–1.9	1.4–2.1	
Mean gradient — mm Hg			0.09			0.32
Median	2.0	4.1		5.1	7.3	
Interquartile range	1.1–4.0	2.4–7.2		3.5–6.5	4.3–10.0	
Hepatic-vein systolic flow reversal — no. (%)	0	6 (40)	0.03	9 (26)	20 (57)	0.001
Cardiac score			<0.001			<0.001
Median	0	35		40	75	
Interquartile range	0–10	30–63		25–65	60–85	

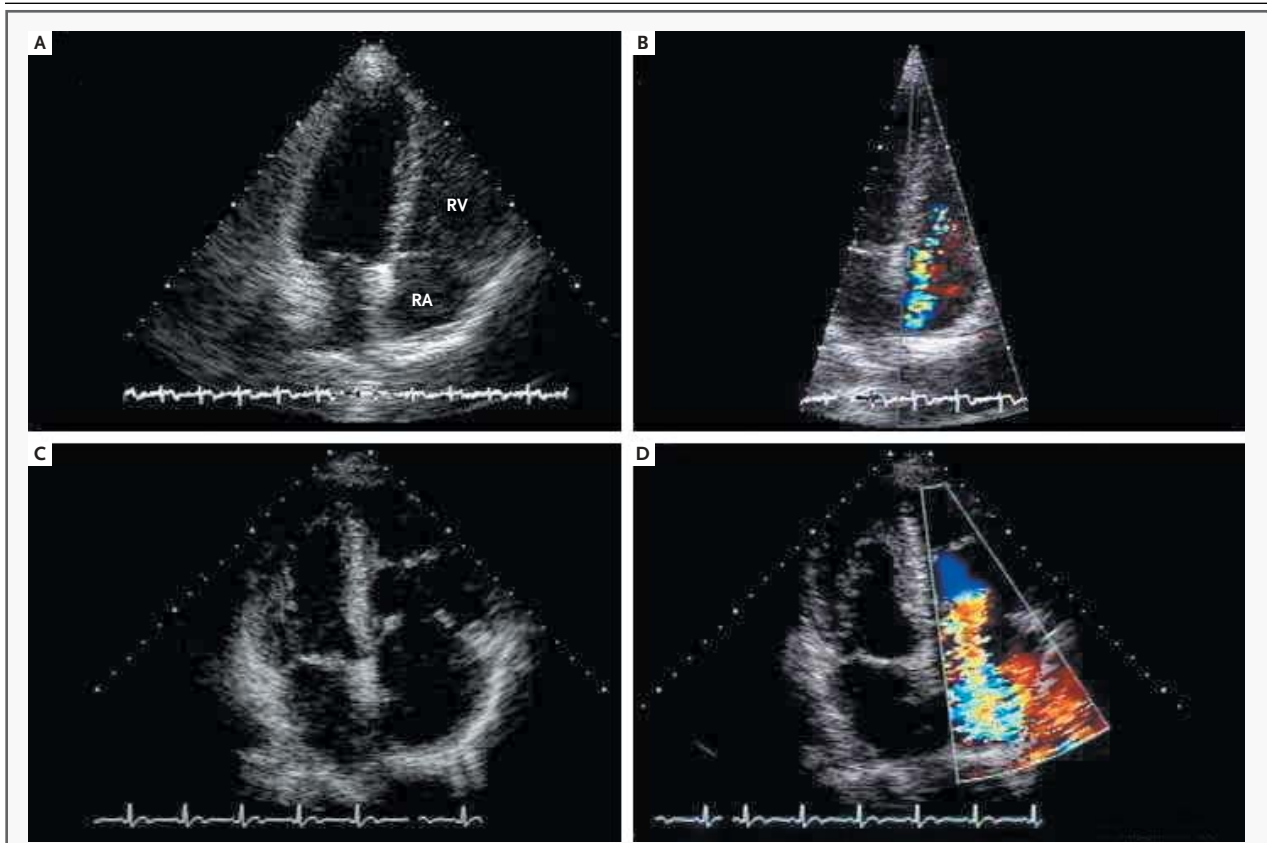


Figure 2. Example of Serial Echocardiographic Studies Showing an Increase in the Cardiac Score of More Than 25 Percent.

The base-line echocardiogram shows mild carcinoid involvement of the tricuspid valve (Panel A), leading to mild tricuspid regurgitation (Panel B). At base line, the 5-hydroxyindoleacetic acid (5-HIAA) level was 265 mg per 24 hours and the patient was undergoing treatment with cytotoxic chemotherapy. The following year, somatostatin treatment was initiated. With these interventions, the 5-HIAA level decreased and stabilized at values under 100 mg per 24 hours. After three years of follow-up, echocardiography revealed severe thickening and fixation of tricuspid leaflets (Panel C), leading to severe tricuspid regurgitation (Panel D). Right ventricular and atrial enlargement was also noted. The cardiac score was 15 at base line and 70 at follow-up. RA denotes right atrium, and RV right ventricle.

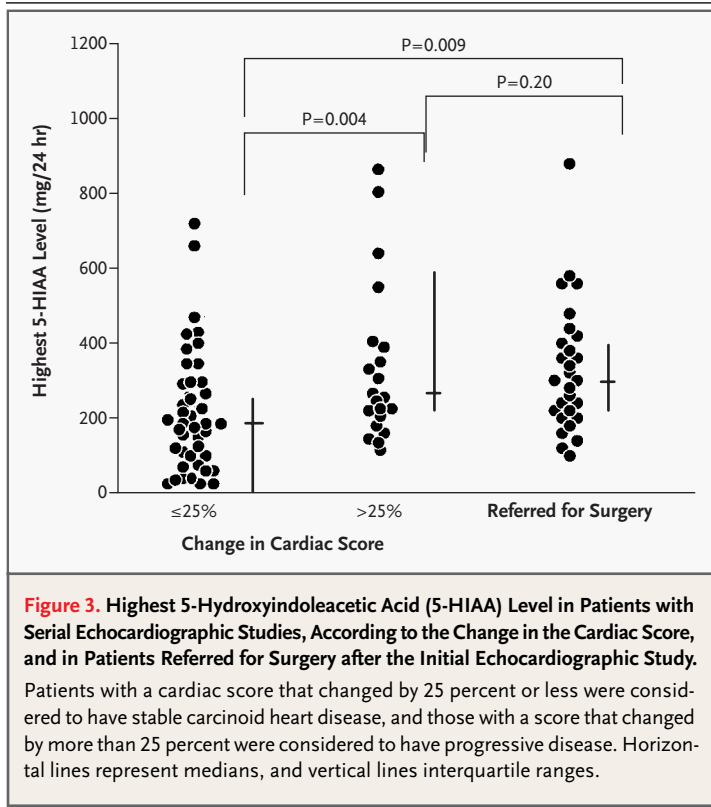
ac score was significantly higher in patients treated with cytotoxic chemotherapy than in patients who did not receive chemotherapy (Fig. 4). Thirteen of the patients whose cardiac score increased by more than 25 percent were treated with chemotherapy; in five of these patients (38 percent), biochemical regression occurred. Among the 23 patients who received chemotherapy, biochemical regression occurred in 8 patients (35 percent).

Clinical and radiographic features were similar in patients with serial echocardiographic studies and those referred for valve surgery (Table 3). Patients referred for surgery were more likely to have been treated with somatostatin than were patients with serial studies. In addition, patients referred for surgery had higher urinary 5-HIAA levels and were

more likely to have received chemotherapy than patients without progressive cardiac disease.

PREDICTORS OF PROGRESSIVE CARCINOID HEART DISEASE

A logistic-regression analysis of data from the patients with serial studies was performed to identify predictors of a change in the cardiac score that exceeded 25 percent. Age, the highest 5-HIAA level, the base-line 5-HIAA level, the interval between studies, the base-line cardiac score, and the presence or absence of tumor progression, biochemical progression, hepatic dearterialization, somatostatin treatment, and chemotherapy were entered in a stepwise logistic-regression model. Significant predictors were the highest recorded urinary



5-HIAA level (odds ratio, 1.08 for each increase of 25 mg per 24 hours [95 percent confidence interval, 1.03 to 1.13]; $P=0.009$) and chemotherapy (odds ratio, 3.65 [95 percent confidence interval, 1.74 to 7.48]; $P=0.001$). Biochemical progression was of borderline significance as a predictor ($P=0.06$).

DISCUSSION

Our findings suggest that although serotonin is related to the development of carcinoid heart disease, neither somatostatin therapy nor hepatic dearterialization prevents the progression of cardiac lesions. Moreover, the patients in our study who received cytotoxic chemotherapy had the highest risk of progressive heart disease.

Several studies have demonstrated that among patients with carcinoid tumors, those with cardiac involvement have higher levels of 5-HIAA, the by-product of serotonin degradation, than do patients without cardiac involvement.³⁻⁶ In addition, Denney et al. found that patients with the carcinoid syndrome in whom heart disease developed had higher 5-HIAA levels both before and after treatment with somatostatin analogues than did patients

without cardiac lesions.⁵ Our study confirms these findings and extends them to patients with preexisting heart disease. We found that the peak level of 5-HIAA was a significant predictor of progressive carcinoid heart disease and was also increased in patients with severe symptomatic heart disease who were referred directly for cardiac surgery. The formation of serotonin-induced carcinoid plaque appears to be mediated by serotonin receptor subtype 1B. This receptor induces fibroblast proliferation on in vitro stimulation¹² and has been detected in subendocardial cells,¹³ where stimulation leads to cell proliferation.¹⁴

However, there was a wide range of 5-HIAA levels among the patients in our study. Furthermore, 42 percent of patients with biochemical progression had no cardiac involvement or no worsening of cardiac lesions, and almost one fourth of the patients with biochemical regression had progressive cardiac disease. These findings suggest that the absolute increase in serotonin is an important factor in the development of cardiac lesions but that other factors, which may be environmental, inflammatory, or genetic, must be present before the lesions develop.

Somatostatin is a potent inhibitor of many processes, including the release of serotonin.¹⁵ In patients with the carcinoid syndrome, somatostatin analogues act by binding to somatostatin receptors,¹⁶ inhibiting the secretion of tumor by-products and relieving symptoms in more than 70 percent of patients.^{11,17,18} Hepatic dearterialization decreases the supply of blood to metastases, relieving symptoms and decreasing 5-HIAA levels.^{10,19} However, treatment with somatostatin analogues in the majority of our patients did not prevent the progression of cardiac lesions. Given the data suggesting that serotonin is involved in the development of cardiac lesions, a reasonable hypothesis is that early treatment with somatostatin might prevent the development of cardiac disease. Although the number of patients in our study was small, the results do not support this hypothesis, since carcinoid heart disease developed despite somatostatin treatment in six of nine patients. Thus, at least in some patients, somatostatin was ineffective in preventing the development of carcinoid heart disease. However, there was no control group in our study, and it is possible that somatostatin slowed the progression of cardiac disease.

Treatment with various combinations of cytotoxic agents has been minimally effective in patients

Table 3. Characteristics of the Patients with Serial Echocardiograms, According to the Change in the Cardiac Score, and Patients Referred for Surgery.

Variable	Patients with Serial Echocardiograms		P Value [†]	Patients Referred for Surgery (N=32)	P Value [†]
	≤25% Change (N=46)	>25% Change (N=25)			
Age at diagnosis — yr					
Median	58	52		59	
Interquartile range	50–67	43–60		43–65	
Female sex — no. (%)	16 (35)	8 (32)		9 (28)	
Interval from diagnosis to base-line study — yr					
Median	1.4	2.3		2.2	
Interquartile range	0.1–5.5	0.1–4.7		0.2–6.1	
Interval from base line to follow-up — yr					
Median	1.9	2.3		—	
Interquartile range	1.3–3.1	1.2–3.2			
Metastasis at base line — no. (%)					
Hepatic	42 (91)	23 (92)		31 (97)	
Nonhepatic	26 (57)	13 (52)		10 (31)	
Regression of tumor — no. (%)	5 (11)	2 (8)		—	
Progression of tumor — no. (%)	11 (24)	9 (36)		—	
Urinary 5-HIAA — mg/24 hr*					
At base-line study					
Median	115	166	0.005	195	0.01
Interquartile range	49–212	86–303		143–259	
Highest value					
Median	189	265	0.004	248	0.03
Interquartile range	75–286	209–593		193–362	
Biochemical regression — no. (%)	12 (26)	6 (24)		—	
Biochemical progression — no. (%)	9 (20)	10 (40)		—	
Treatment at base line — no. (%)					
Somatostatin analogue	22 (48)	17 (68)		29 (91) [‡]	<0.001
Hepatic dearterialization	20 (44)	10 (40)		17 (53)	
Chemotherapy	10 (22)	13 (52)	0.009	15 (47)	0.02

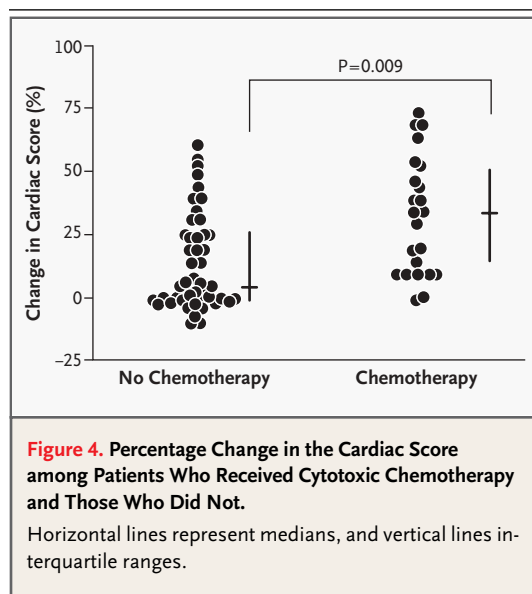
* 5-HIAA denotes 5-hydroxyindoleacetic acid.

[†] P values are for the comparison with patients with a change of 25 percent or less in the cardiac score.

[‡] P=0.03 for the comparison with patients with a change of more than 25 percent in the cardiac score.

with metastatic midgut carcinoid tumors.²⁰⁻²² In our study, logistic-regression analysis showed that patients treated with cytotoxic chemotherapy had an increased risk of progressive cardiac lesions. Also, chemotherapy was used more often in patients referred directly to cardiac surgery than in patients with no progression. Since chemotherapy is typically reserved for patients who do not have a response to other treatments,^{22,23} the apparently increased risk of progressive heart disease among these patients may reflect more aggressive disease. How-

ever, the fact that biochemical regression occurred in more than 30 percent of patients treated with chemotherapy, including patients with progressive carcinoid heart disease, suggests that the aggressiveness of the disease did not account for the increased risk. Several studies have shown that acute chemotherapy-induced emesis is caused by an increased release of serotonin from intestinal enterochromaffin cells.^{24,25} This increase, which is unaffected by somatostatin treatment, may be mediated by enterochromaffin-cell damage.²⁵ One might



speculate that cytotoxic chemotherapy induces transient bursts of serotonin released from hepatic metastases in patients with the carcinoid syndrome. In predisposed patients, chemotherapy may theoretically accelerate the progression of cardiac lesions. However, a prospective, randomized study would be required to establish this relationship.

A limitation of our study is the lack of well-accepted criteria for a worsening of carcinoid heart disease. We chose a 25 percent increase in an

echocardiographically determined score as the criterion for progression of heart disease. However, the group of patients we identified as having progressive carcinoid heart disease closely matched the group of patients with severe symptomatic carcinoid heart disease that warranted direct referral to cardiac surgery after the initial echocardiogram. In the study by Denney et al.,⁵ a semiquantitative scoring system was also used, although it did not include right ventricular size and function or Doppler signs of increased right atrial and right ventricular filling pressures. Our inclusion of right ventricular size and systolic function in the scoring system provided an additional assessment of right ventricular remodeling. With this approach, there is a risk of categorizing chronic stable valvular disease with right ventricular remodeling as progressive carcinoid heart disease. However, our findings suggest that right ventricular remodeling is accompanied by the progression of valvular lesions.

In summary, treatment with somatostatin, hepatic dearterialization, or both did not prevent the progression or development of cardiac lesions in our patients. Moreover, cytotoxic chemotherapy was associated with an elevated risk of progressive heart disease. The exact mechanism involved in the progression of carcinoid heart disease merits further investigation.

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