Journal of the American Heart Association

ORIGINAL RESEARCH

Progression of Carcinoid Heart Disease in the Modern Management Era

Emilie Baron, MD; Catherine Szymanski, MD, PhD; Hélène Hergault, MD; Céline Lepère, MD; Olivier Dubourg, MD; Marie Hauguel-Moreau, MD; Nicolas Mansencal, MD, PhD

BACKGROUND: The development of carcinoid heart disease (CaHD) is still relatively unclear. It is difficult to define an optimal follow-up for patients without any cardiac involvement at baseline. The aim of this study was to assess the prevalence and natural history of CaHD by annual echocardiographic examinations.

METHODS AND RESULTS: We studied 137 consecutive patients (61±12 years, 53% men) with proven digestive endocrine tumor and carcinoid syndrome between 1997 and 2017. All patients underwent serial conventional transthoracic echocardiographic studies. Right-sided and left-sided CaHD were systematically assessed. We used a previous validated echocardiographic scoring system of severity for the assessment of CaHD. An increase of 25% of the score was considered to be significant. Mean follow-up was 54±45 months. Prevalence of CaHD was 27% at baseline and 32% at 5-year follow-up. Disease progression was reported in 28% of patients with initial CaHD followed up for >2 years (n=25). In patients without any cardiac involvement at baseline, occurrence of disease was 21%. CaHD occurred >5 years from the initial echocardiographic examination in 42% of our cases, especially in patients presenting with new recurrence of a digestive endocrine tumor. An increase of urinary 5-hydroxyindoleacetic acid by 25% during follow-up was identified as an independent predictor of CaHD occurrence during follow-up (hazard ratio [HR], 5.81; 95% CI, 1.19–28.38; *P*=0.03), as well as a maximum value of urinary 5-hydroxyindoleacetic acid >205 mg/24 h during follow-up (HR, 8.41; 95% CI, 1.64–43.07; *P*=0.01).

CONCLUSIONS: Our study demonstrates that in patients without initial CaHD, cardiac involvement may occur late and is related to serotonin. Our data emphasize the need for cardiologic follow-up in patients with recurrence of the tumor process.

Key Words: carcinoid heart disease ■ valvular heart disease ■ tricuspid regurgitation ■ digestive endocrine tumor

Digestive endocrine tumor is a rare disease.[1–3] Patients presenting with this tumor and a carcinoid syndrome may develop carcinoid heart disease (CaHD).[4] This complication is associated with decreased survival, and thus being able to determine whether the patient has cardiac involvement is essential for better management and prognosis.[2,5–8] Echocardiography is the leading examination to detect the presence of this valvular heart disease.[3] Most studies assessing the prevalence of CaHD were performed in the 1990s and 2000s, before several therapeutic advances.[8] Thus, the development of CaHD is still relatively unclear. Previous studies have reported that the development of CaHD was related to an increased level of serotonin, previous use of chemotherapy, and the presence of a patent foramen ovale (PFO).[9–11] However, it is difficult to define an optimal follow-up for patients initially free from cardiac involvement. The aim of this study was to assess the prevalence and the progression of CaHD nowadays by annual echocardiographic follow-up.

Correspondence to: Nicolas Mansencal, MD, PhD, AP-HP, Hôpital Universitaire Ambroise Paré, Service de Cardiologie et des Maladies Vasculaires, Centre de référence des cardiomyopathies et des troubles du rythme cardiaque héréditaires ou rares, 9 avenue Charles de Gaulle, 92100 Boulogne, France. E-mail: nicolas.mansencal@aphp.fr

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020475

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- With the improvement of prognosis of patients presenting with digestive endocrine tumors, late onset of carcinoid heart disease is possible.
- The only independent marker of late occurrence of carcinoid heart disease is a significant increase of urinary 5-hydroxyindoleacetic acid during follow-up.

What Are the Clinical Implications?

- The need for prolonged cardiology follow-up is recommended in patients presenting with recurrence of the tumor process with significant increase of urinary 5-hydroxyindoleacetic acid levels (key role of serotonin).

Nonstandard Abbreviations and Acronyms

5-HIAA	5-hydroxyindoleacetic acid
CaHD	carcinoid heart disease
PFO	patent foramen ovale

METHODS

Study Population

The data that support the findings of this study may be available from the corresponding author upon reasonable request. Between 1997 and 2017, 137 consecutive patients with histologically proven digestive endocrine tumor and carcinoid syndrome were referred to our institution (reference center of cardiomyopathies). All patients had complete transthoracic echocardiographic evaluation. Entry criteria included age>18 years, proven digestive endocrine tumor, carcinoid syndrome, and echocardiographic follow-up.

Clinical data regarding the patient, the characteristics of the tumor (primary tumor site, presence of metastases), biomarkers, and treatment (surgical resection of the tumor, chemotherapy, somatostatin analog) were retrospectively collected from patients' medical records. During follow-up, serial imaging evaluation (ultrasound, computed tomography scan, magnetic resonance imaging, coloscopy) was performed to assess the progression of this disease (new appearance or significant increase of tumor size). Treatment was administered according to guidelines. Results of NT-proBNP (N-terminal pro-B-type natriuretic peptide) were available and collected in 46 patients (22 patients with CaHD and 24 patients without CaHD).

The metabolite of serotonin (urinary 5-hydroxyindoleacetic acid [5-HIAA]; normal value 40 mg/24 h) was performed at baseline and during follow-up (every 6 months). For these dosages, foods rich in tryptophan (eg, bananas, avocados, plums, eggplants, tomatoes, pineapples, walnuts, kiwis) and medications that can increase 5-HIAA were avoided.[3] Variation of urinary 5-HIAA levels was the difference between the maximal value of 5-HIAA before the development of CaHD and the value of 5-HIAA at baseline. An increase of urinary 5-HIAA by 25% during follow-up was considered to be significant.

Echocardiographic Protocol

Transthoracic echocardiography was performed once per year for each patient, unless otherwise indicated. All echocardiographic examinations were recorded and read by the same investigator (N.M.), who was blinded to clinical data. We systematically assessed right- and left-sided CaHD.

Right-sided CaHD was defined as tricuspid or pulmonary valvular injury (ie, thickening, retraction, reduced valvular mobility) associated with tricuspid regurgitation or stenosis or pulmonary regurgitation or stenosis. Right-sided CaHD was also defined by a right ventricular enlargement with endocardial thickening or a metastatic carcinoid tumor to the heart. Patients without abnormality of valvular mobility were not considered to have right-sided CaHD. Left-sided CaHD was defined as significant mitral or aortic regurgitation associated with a reduction in mitral or aortic valvular mobility.

Contrast transthoracic echocardiography searching for a right-to-left atrial shunt through a PFO was performed at the end of conventional transthoracic echocardiography. The contrast protocol consisted of the injection of agitated 5% glucose solution through an upper-extremity vein. A PFO was affirmed when >8 microcavitations passed from the right to the left atrium within the first 3 cardiac cycles after contrast appearance in the right atrium, at rest and after a cough test or Valsalva maneuver. Several injections were used to detect PFO with different echocardiographic views (parasternal short axis, apical 4-chamber, and subcostal views).

Carcinoid Heart Disease Severity Scoring System

Both right- and left-sided CaHD were quantified using a validated scoring system (Table S1).[10,12] This scoring system assessed the anatomy of the valves and quantified valvular heart disease. All quantifications were performed according to the recommendations.[13,14] The right ventricular size was assessed in an apical 4-chamber view. A 2-dimensional right-to-left ventricular end-diastolic area ratio <0.6 was considered as normal, between 0.6 and 1 as moderate right ventricular dilatation, and >1 as severe dilatation.[15]

The score for right-sided CaHD ranged from 0 (no CaHD) to 20 (major CaHD), and the score for left-sided CaHD ranged from 0 (no CaHD) to 10 (major CaHD). The overall score of CaHD was 0 to 30. An increase of 25% of the score was considered to be significant. The study was approved by the Institutional Data Protection Authority of Paris Saclay University Hospitals. Because of the retrospective enrollment, written informed consent from the patients was waived.

Statistical Analysis

Normally distributed continuous variables were expressed as mean±SD. Categorical variables were summarized as frequency percentages and absolute numbers. Comparisons between groups were performed with the chi-square test, unpaired *t* tests, Wilcoxon test, and Fisher's exact test, as appropriate. The end points were the prevalence of CaHD at the first echocardiographic evaluation and at the end of follow-up. Linear regression analysis was used to investigate the relation between laboratory markers and CaHD.

We performed a survival analysis with a Cox model, to identify independent predictors of CaHD occurrence during follow-up. For multivariable analyses, an epidemiological approach was adopted, and factors thought to be important for the end points were entered in multivariable analyses: age, sex, PFO, an increase of urinary 5-HIAA by 25% during follow-up and a maximum value of urinary 5-HIAA >205 mg/24 h during follow-up (third quartile). A value of $P<0.05$ was considered statistically significant. Data were analyzed with STATA 8.0 (STATA Corp., College Station, TX).

RESULTS

Baseline Characteristics

Baseline data among the 137 consecutive patients with histologically proven digestive endocrine tumor and carcinoid syndrome are presented in Table 1. Mean age at diagnosis was 61±11 years. All the patients presented with at least 1 metastasis and had at least 1 symptom associated with the carcinoid syndrome:

Table 1. Characteristics of All Included Patients and Characteristics of Patients Presenting With or Without Carcinoid Heart Disease

Characteristics	All patients (n=137)	No CaHD (n=88)	CaHD (n=49)	*P* value
Age, y, mean±SD (range)	61±12 (24–88	60±12 (24–85)	64±10 (40–88)	0.05
Men, n (%)	73 (53)	48 (54.5)	25 (51)	0.69
Primary tumor site, n (%)				
Foregut	6 (4)	5 (6)	1 (2)	0.42
Stomach	3 (2)	2 (2)	1 (2)	0.99
Pancreas	3 (2)	3 (3)	0 (0)	…
Midgut	118 (86)	73 (83)	45 (92)	0.15
Ileojejunum	79 (58)	48 (55)	31 (63)	0.32
Proximal colon	39 (28.5)	25 (28)	14 (29)	0.98
Hindgut (distal colon+rectum)	8 (6)	5 (6)	3 (6)	0.99
Bronchial	3 (2)	3 (3)	0 (0)	…
Other	2 (1.5)	2 (2)	0 (0)	…
Metastases, n (%)				
Hepatic	120 (87)	76 (86)	44 (90)	0.56
Peritoneal	28 (20)	18 (20)	10 (20)	0.99
Ovarian	5 (4)	2 (2)	3 (6)	0.35
Other	22 (16)	14 (16)	8 (16)	0.95
Patent foramen ovale, n (%)	43 (31)	16 (18)	27 (55)	<0.0001
Treatment, n (%)				
Somatostatin analog	112 (82)	72 (82)	40 (82)	0.98
Hepatic artery embolization	40 (29)	22 (25)	18 (37)	0.15
Chemotherapy	37 (27)	20 (23)	17 (35)	0.13
Urinary 5-HIAA, mg/24 h, mean±SD				
At baseline	220±316	91±97	452±423	<0.0001
Peak	324±392	109±106	709±423	<0.0001
Variation during follow-up	104±248	19±55	257±362	<0.0001

5-HIAA indicates hydroxyindoleacetic acid; and CaHD, carcinoid heat disease.

flushing in 118 (86%) patients, secretory diarrhea in 80 (58%) patients, and wheezing in 14 (10%) patients.

Prevalence of CaHD and Baseline Echocardiographic Characteristics

At baseline, the prevalence of CaHD was 27% (n=37). All patients with initial CaHD had right-sided heart disease, and 16% (n=6) of them also had left-sided CaHD. Tricuspid regurgitation was present in 89% (n=33) and tricuspid stenosis in 32% (n=12). Pulmonary regurgitation was present in 59% (n=22), and pulmonary stenosis was found in 35% (n=13) (Figure 1A). Tricuspid stenosis was always associated with tricuspid regurgitation. On the other hand, pulmonary stenosis could occur without pulmonary regurgitation (n=2;

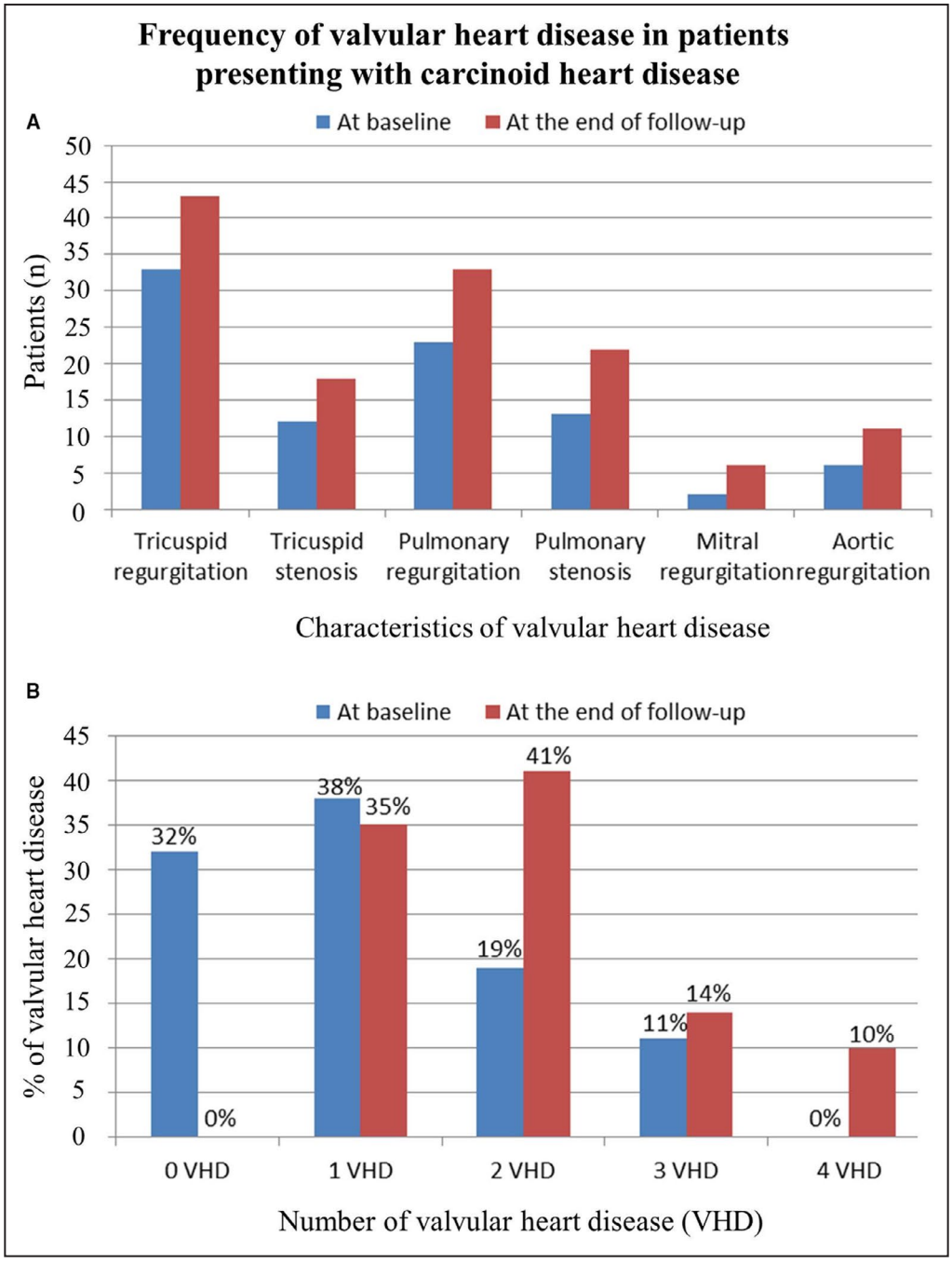

Figure 1. Frequency of valvular heart disease in patients presenting with CaHD (A) and frequency of valvular heart disease according to the number of valves involved at baseline and at the end of follow-up in patients followed up for >1 year (B).
CaHD indicates carcinoid heart disease; and VHD, valvular heart disease.

15%). Regurgitant valvular heart disease was twice more frequent than stenotic valvular heart disease: 55 pulmonary or tricuspid regurgitations versus 25 pulmonary or tricuspid stenoses.

Progression of CaHD and Echocardiographic Characteristics During Follow-up

The mean duration of follow-up was 54±45 months (range, 12–192 months). Prevalence of CaHD was 32% at 5-year follow-up and 36% (n=49) at the end of follow-up (Table 1, Figure 1B, Figure 2). The number of patients with <5 years of follow-up and without CaHD was 30 (22%). Urinary 5-HIAA levels were significantly higher in patients presenting with CaHD (median, 346 [interquartile range, 112–703] versus 49 [interquartile range, 32–87] mg/24 h; *P*<0.0001; Figure 3). Patients without initial CaHD but developing CaHD during follow-up had normal urinary 5-HIAA levels at baseline (median, 93 [interquartile range, 49–111] mg/24 h) and significantly increased urinary 5-HIAA levels during follow-up (median, 664 [interquartile range, 433–800] mg/24 h; *P*<0.0001; Figure 3). Median NT-proBNP was significantly higher in patients with CaHD (1856 ng/L versus 107 ng/L in patients without CaHD; *P*<0.001).

Among patients with initial CaHD followed up for >2 years (n=25), significant disease progression was observed in 28% of cases (n=7), whereas 52% (n=13) of patients presented with no variation of their score, and 20% (n=5) had a <25% increase of the score. Significant correlations were observed between urinary 5-HIAA and the scoring system (Figure 4).

In patients without any cardiac involvement at baseline and followed up for >2 years (n=56), CaHD occurred during follow-up in 21% (n=12) (Tables 2 and 3). Mean time of CaHD occurrence was 65±50 months (range, 12–168 months). The onset of CaHD occurred >5 years from the baseline echocardiography in 42%. In patients with late occurrence of CaHD, there was always recurrence of digestive endocrine tumor and carcinoid syndrome. Furthermore, 83% of patients developing CaHD during follow-up presented with variations of urinary 5-HIAA levels >5N versus 22% in patients with CaHD at baseline (*P*=0.0002) versus 1% in patients without CaHD at baseline and during follow-up (*P*<0.0001).

On the other hand, in patients with normal echocardiography for >3 years (n=41; mean follow-up, 90±32 months [range, 48–192 months]), without any significant increase of urinary 5-HIAA levels (variation during follow-up, 19±55 mg/24 h; *P*=0.42) and without resurgence of the tumor process, no patient developed CaHD.

Figure 1B shows the prevalence of valvular heart disease in patients with CaHD during follow-up. Right-sided CaHD increased almost 2-fold. Tricuspid regurgitation remained the most common valvular disease. Left-sided CaHD strongly increased: Aortic regurgitation and mitral regurgitation showed a 3- to 6-fold increase at the end of follow-up compared with baseline. Of the 12 patients developing left-sided CaHD, 75% (n=9) had a PFO, and all had hepatic metastases. Compared with baseline, there was a 2-fold increase in patients with bivalvular heart disease (41% versus 19%, respectively, at the end of follow-up and at baseline). There were 11% of patients with valvular heart disease involving the 4 valves at the end of follow-up (versus 0% at baseline) (Figure 1B).

On multivariate survival analysis (Table 4), a 25% increase of urinary 5-HIAA during follow-up was identified as an independent predictor of CaHD occurrence during follow-up (hazard ratio [HR], 5.81, 95% CI, 1.19–28.38, *P*=0.03), as well as a maximum value of urinary 5-HIAA above 205 mg/24 h during follow-up (HR, 8.41, 95% CI, 1.64–43.07, *P*=0.01). Age was not significantly associated with CaHD occurrence (HR, 1.00; 95% CI, 0.92–1.07; *P*=0.90). Being a man was significantly associated with CaHD occurrence (HR, 4.76; 95% CI, 1.18–19.24; *P*=0.03).

DISCUSSION

Our study is one of the first to investigate exhaustively the echocardiographic characteristics during follow-up of patients presenting with digestive endocrine tumors and carcinoid syndrome in the modern era. The main results are (1) CaHD is an ongoing disease involving echocardiographic follow-up; (2) serotonin plays a key role in the development of CaHD; (3) no patient developed CaHD in the case of ≥3 years of normal echocardiographic examinations, no significant increase of urinary 5-HIAA levels, and absence of resurgence of the tumor process; (4) with the improvement of prognosis of patients presenting with digestive endocrine

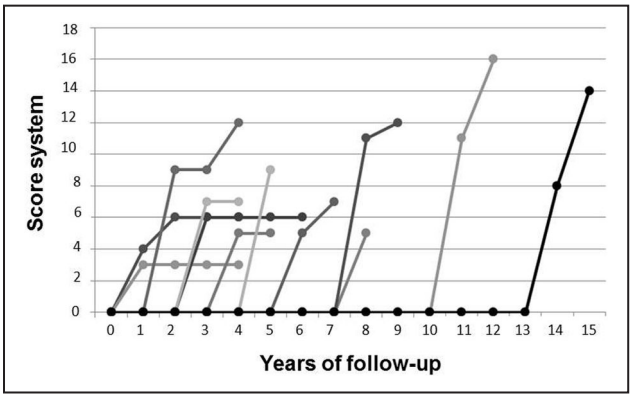

Figure 2. Evolution of scoring system in patients without initial CaHD and presenting with occurrence of CaHD during follow-up.
CaHD indicates carcinoid heart disease.

tumors, late onset of CaHD is possible, and the only independent marker of late occurrence of CaHD is a significant increase of urinary 5-HIAA during follow-up.

Carcinoid heart disease is a rare disease characterized by the plaque-like deposit of fibrous tissue,[16,17] mostly on the endocardium of right-sided valvular cusps, as the lung inactivates carcinoid substances.[18] CaHD can develop in the case of digestive endocrine tumor associated with carcinoid syndrome. As multimodality imaging is used increasingly in many cardiac diseases including CaHD,[19] transthoracic echocardiography remains the exam of choice, and it was recently confirmed as the gold standard for the diagnosis and follow-up of CaHD.[3] Prevalence of CaHD has been assessed in several previous studies with a wide range of results, from 20% to 60%.[3,8,12,20] In our study, the prevalence of CaHD at baseline was relatively low (27%), but reached 36% during follow-up. At 5-year follow-up, this prevalence was 32% and could be underestimated because 22% of patients without CaHD did not complete the follow-up period. About 30% of patients with a long follow-up experienced an increase of their disease as shown in previous studies.[3,4,12,21] This increased prevalence during follow-up highlights the need for an initial echocardiographic follow-up in patients suffering from digestive endocrine tumor and carcinoid syndrome. Left-sided CaHD may develop in the case of PFO, bronchial localization of the primary tumor or poorly controlled carcinoid (with very significant liver metastases).[22] In our series, during follow-up, 9% (n=12) of patients developed left-sided CaHD: all of them had liver metastases, 75% (9 patients) had a PFO, and none had bronchial carcinoid tumor. The presence of PFO then appears to be one of the most

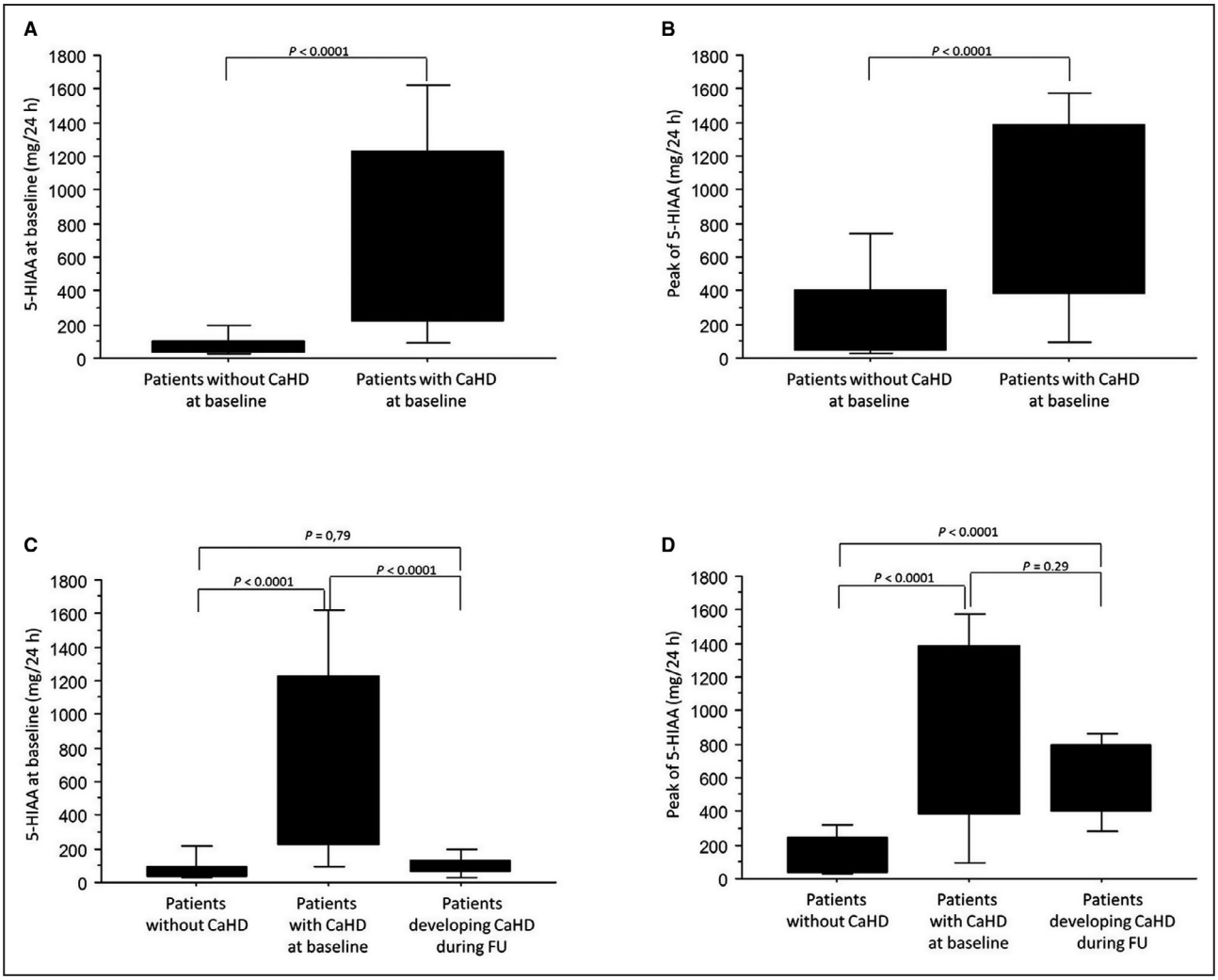

Figure 3. Urinary 5-HIAA levels.
A, At baseline, in patients with or without CaHD. **B**, During follow-up, in patients with or without CaHD. **C**, At baseline, in patients without CaHD, in patients with CaHD at baseline and in patients developing CaHD. **D**, During follow-up, in patients without CaHD, in patients with initial CaHD, and in patients developing CaHD. 5-HIAA indicates 5-hydroxyindoleacetic acid; CaHD, carcinoid heart disease; and FU, follow-up.

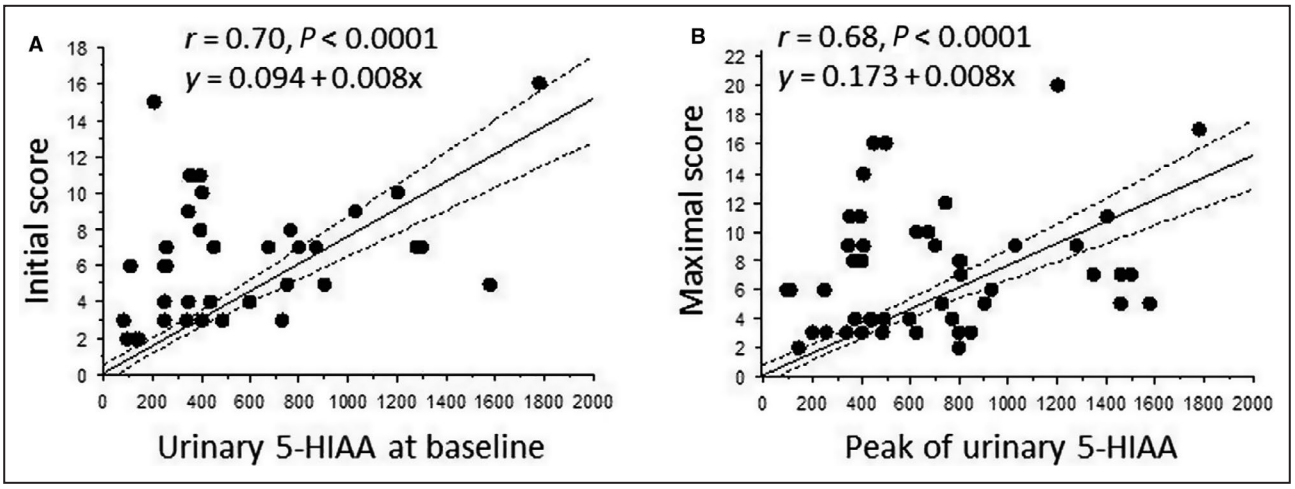

Figure 4. Correlations between urinary 5-HIAA levels at baseline and initial echocardiographic score for the assessment of CaHD (A) and correlations between peak of urinary 5-HIAA and maximal echocardiographic score (B).
5-HIAA indicates 5-hydroxyindoleacetic acid; and CaHD, carcinoid heart disease.

important factors in the development of left-sided CaHD and should be systematically assessed by contrast echocardiography.[23]

Previous studies have clearly demonstrated the role of serotonin using an assay of urinary 5-HIAA in CaHD,[9,11] and in our study, we also found a significant increase of serotonin in patients presenting with CaHD. However, in a previous study, we reported that CaHD may progress in the first 3 years after the initial management of digestive endocrine tumor despite accurate therapeutic management.[12] Interestingly, no patient with ≥3 years of normal echocardiographic examinations and therapeutic management of carcinoid syndrome and tumor developed CaHD. However, there is a lack of data regarding the long-term progression of CaHD, possibly explained by the

Table 2. Characteristics of Patients Presenting With Carcinoid Heart Disease at Baseline and Patients Developing Carcinoid Heart Disease During Follow-up

Characteristic	CaHD at baseline (n=37)	CaHD during follow-up (n=12)	*P* value
Age, y, mean±SD (range)	65±11 (40–88)	61±10 (51–86)	0.28
Men, n (%)	19 (51)	6 (50)	0.94
Valvular injury, n (%)			
Tricuspid			
Regurgitation	33 (89)	10 (83)	0.63
Stenosis	12 (32)	6 (50)	0.27
Pulmonary			
Regurgitation	23 (62)	10 (83)	0.29
Stenosis	13 (35)	9 (75)	0.02
Mitral regurgitation	2 (5)	4 (33)	0.03
Aortic regurgitation	6 (16)	5 (25)	0.11
Patent foramen ovale	21 (57)	6 (42)	0.68
Maximum valvular score	7.5±4.2 (2–20)	6.6±4.0 (2–16)	0.26
Treatment, n (%)			
Somatostatin analog	30 (81)	10 (83)	0.99
Hepatic artery embolization	9 (24)	9 (75)	0.004
Chemotherapy	9 (24)	8 (67)	0.02
Urinary 5-HIAA, mg/24 h, mean±SD			
At baseline	568±426	95±55	<0.0001
Peak	718±456	678±317	0.68
Variation during follow-up	151±300	582±353	<0.0001

5-HIAA indicates hydroxyindoleacetic acid; and CaHD, carcinoid heart disease.

Table 3. Characteristics of Patients Without Carcinoid Heart Disease and Patients Developing Carcinoid Heart Disease During Follow-up

Characteristic	No CaHD during follow-up (n=88)	CaHD during follow-up (n=12)	*P* value
Age, y, mean±SD (range)	60±12 (24–85)	61±10 (51–86)	0.79
Men, n (%)	48 (54.5)	6 (50)	0.77
Primary tumor site, n (%)			
Foregut	5 (6)	0 (0)	…
Stomach	2 (2)	0 (0)	…
Pancreas	3 (3)	0 (0)	…
Midgut			
Ileojejunum	48 (55)	9 (75)	0.30
Proximal colon	25 (28)	2 (17)	0.51
Hindgut (distal colon+rectum)	5 (6)	1 (8)	0.55
Bronchial	3 (3)	0 (0)	…
Other	2 (2)	0 (0)	…
Metastases, n (%)			
Hepatic	76 (86)	11 (92)	0.96
Peritoneal	18 (20)	4 (33)	0.46
Ovarian	2 (2)	2 (17)	0.11
Other	14 (16)	2 (17)	0.99
Patent foramen ovale, n (%)	16 (18)	6 (42)	0.02
Treatment, n (%)			
Somatostatin analog	72 (82)	10 (83)	0.99
Hepatic artery embolization	22 (25)	9 (75)	0.002
Chemotherapy	20 (23)	8 (67)	0.005
Urinary 5-HIAA, mg/24 h, mean±SD			
At baseline	91±97	95±55	0.84
Peak	109±106	678±317	<0.0001
Variation during follow-up	19±55	582±353	<0.0001

5-HIAA indicates hydroxyindoleacetic acid; and CaHD, carcinoid heart disease.

relatively high short-term mortality of the patients in the first series. In the modern management era, the life expectancy of patients with carcinoid syndrome has increased.[8,24] In our study, we found that recurrence of digestive endocrine tumor and carcinoid syndrome may occur during follow-up and this modification of clinical status should prompt echocardiographic examinations again. Indeed, late occurrence of CaHD after 5 years of follow-up appeared in 42% of cases of CaHD during follow-up (mean follow-up: 65±50 months) and, in 2 patients, this progression was assessed 11 and 14 years after the first echocardiographic examination, with a severe progression score. We found that the only independent marker of late occurrence of CaHD was a significant increase of urinary 5-HIAA during follow-up, highlighting the key role of serotonin in CaHD. In clinical practice, and according to our study findings, the need for prolonged

Table 4. Multivariable Analyses for Predicting the Late Occurrence of Carcinoid Heart Disease

Variables	No carcinoid heart disease	Occurrence of carcinoid heart disease	*P* value
	HR	HR (95% CI)	
Age	1.00	1.00 (0.92–1.07)*	0.90
Male	1.00	4.76 (1.18–19.24)	0.03
Variation of urinary 5-HIAA levels >25%	1.00	5.81 (1.19–28.38)	0.03
Peak of urinary 5-HIAA >205,mg/24 h	1.00	8.41 (1.64–43.07)	0.01

*For an increase of age by one unit, since age was included as a linear variable in the model. 5-HIAA indicates hydroxyindoleacetic acid; and HR, hazard ratio.

cardiology follow-up is recommended, particularly in case of significant increase of urinary 5-HIAA levels during follow-up.

The main limitation of our single-center study is its limited number of patients. However, this disease is particularly uncommon, explaining the few available data concerning CaHD. Nonetheless, all echocardiographic examinations were performed by the same experienced investigator according to a standardized protocol, allowing complete assessment of CaHD in routine practice. A previous study has demonstrated the usefulness of NT-proBNP in CaHD.[25] The increase of NT-proBNP may suggest the presence of CaHD, and echocardiographic examination is needed to confirm this suspicion of CaHD. In our study, the assay of BNP was not available for the first included patients, and we did not systematically perform this assay. However, in the light of our results and in agreement with an expert statement,[3] a significant increase of urinary 5-HIAA levels during follow-up may lead to assay of NT-proBNP and if necessary (N-terminal pro-BNP >260 ng/mL) to echocardiographic examination. Finally, although foods and medications that could affect urinary 5-HIAA levels were discouraged, rigorous control over these factors was not feasible.

CONCLUSIONS

The prevalence of CaHD is still substantial in the case of carcinoid syndrome, even with modern therapies. Our study demonstrates that in patients without initial CaHD, cardiac involvement may occur late, despite normal initial echocardiographic assessments. Our data suggest the need for prolonged cardiology follow-up in patients presenting with recurrence of the tumor process with significant increase of urinary 5-HIAA levels.

ARTICLE INFORMATION

Received March 2, 2021; accepted September 30, 2021.

Affiliations

Department of Cardiology, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Centre de référence des cardiomyopathies et des troubles du rythme cardiaque héréditaires ou rares, Université de Versailles-Saint Quentin (UVSQ), Boulogne, France (E.B., C.S., H.H., O.D., M.H., N.M.); INSERM U-1018, CESP, Team 5 (EpReC, Renal and Cardiovascular Epidemiology), UVSQ, Villejuif, France (C.S., O.D., M.H., N.M.); and Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, AP-HP, Paris, France (C.L.).

Sources of Funding

None.

Disclosures

Dr Hauguel-Moreau reports personal fees from Biotronik outside the submitted work. The remaining authors have no disclosures to report.

Supplementary Material

Table S1

REFERENCES

1. Kaltsas G, Caplin M, Davies P, Ferone D, Garcia-Carbonero R, Grozinsky-Glasberg S, Hörsch D, Tiensuu Janson E, Kianmanesh R, Kos-Kudla B, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pre- and perioperative therapy in patients with neuroendocrine tumors. *Neuroendocrinology*. 2017;105:245–254. doi: 10.1159/000461583
2. Hassan SA, Banchs J, Iliescu C, Dasari A, Lopez-Mattei J, Yusuf SW. Carcinoid heart disease. *Heart*. 2017;103:1488–1495. doi: 10.1136/heartjnl-2017-311261
3. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, Cuthbertson DJ, Dobson R, Grozinsky-Glasberg S, Steeds RP, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. *J Am Coll Cardiol*. 2017;69:1288–1304. doi: 10.1016/j.jacc.2016.12.030
4. Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC, Kvols LK. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation*. 1993;87:1188–1196. doi: 10.1161/01.CIR.87.4.1188
5. Steeds RP, Sagar V, Shetty S, Oelofse T, Singh H, Ahmad R, Bradley E, Moore R, Vickrage S, Smith S, et al. Multidisciplinary team management of carcinoid heart disease. *Endocr Connect*. 2019;8:R184–R199. doi: 10.1530/EC-19-0413
6. Hayes AR, Davar J, Caplin ME. Carcinoid heart disease: a review. *Endocrinol Metab Clin North Am*. 2018;47:671–682. doi: 10.1016/j.ecl.2018.04.012
7. Silaschi M, Barr J, Chaubey S, Nicou N, Srirajaskanthan R, Byrne J, Ramage J, MacCarthy P, Wendler O. Optimized outcomes using a standardized approach for the treatment of patients with carcinoid heart disease. *Neuroendocrinol*. 2017;104:257–263. doi: 10.1159/000446213
8. Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. *Circulation*. 2005;112:3320–3327. doi: 10.1161/CIRCULATIONAHA.105.553750
9. Moller JE, Connolly HM, Rubin J, Seward JB, Modesto K, Pellikka PA. Factors associated with progression of carcinoid heart disease. *N Engl J Med*. 2003;348:1005–1015. doi: 10.1056/NEJMoa021451
10. Mansencal N, Mitry E, Forissier J-F, Martin F, Redheuil A, Lepère C, Farcot J-C, Joseph T, Lacombe P, Rougier P, et al. Assessment of patent foramen ovale in carcinoid heart disease. *Am Heart J*. 2006;151:e1131 doi: 10.1016/j.ahj.2006.02.019
11. Buchanan-Hughes A, Pashley A, Feuilly M, Marteau F, Pritchard DM, Singh S. Carcinoid heart disease: prognostic value of 5-hydroxyindoleacetic acid levels and impact on survival - a systematic literature review. *Neuroendocrinology*. 2021;111:1–15. doi: 10.1159/000506744
12. Mansencal N, Mitry E, Bachet JB, Rougier R, Dubourg O. Echocardiographic follow-up of treated patients with the carcinoid syndrome. *Am J Cardiol*. 2010;105:1588–1591. doi: 10.1016/j.amjcard.2010.01.017
13. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr*. 2017;30:303–371. doi: 10.1016/j.echo.2017.01.007
14. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392. doi: 10.1016/j.echo.2017.02.009
15. Mansencal N, Joseph T, Vieillard-Baron A, Qanadli S, Jardin F, Lacombe P, Jondeau G, Dubourg O. Comparison of different echocardiographic indices secondary to right ventricular obstruction in acute pulmonary embolism. *Am J Cardiol*. 2003;92:116–119. doi: 10.1016/s0002-9149(03)00485-5
16. Roberts WC. A unique heart disease associated with a unique cancer: carcinoid heart disease. *Am J Cardiol*. 1997;80:251–256. doi: 10.1016/S0002-9149(97)00340-8
17. Simula DV, Edwards WD, Tazelaar HD, Connolly HM, Schaff HV. Surgical pathology of carcinoid heart disease: a study of 139 valves from 75 patients spanning 20 years. *Mayo Clin Proc*. 2002;77:139–147. doi: 10.1016/S0025-6196(11)62328-8

18. Gustafsson BI, Hauso O, Drozdov I, Kidd M, Modlin IM. Carcinoid heart disease. *Int J Cardiol*. 2008;129:318–324. doi: 10.1016/j.ijcard.2008.02.019
19. Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, Davar J. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. *Circ Cardiovasc Imaging*. 2010;3:103–111. doi: 10.1161/CIRCIMAGING.109.886846
20. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Analysis of 150 patients with carcinoid syndrome seen in a single year at one institution in the first decade of the twenty-first century. *Am J Cardiol*. 2008;101:378–381. doi: 10.1016/j.amjcard.2007.08.045
21. Bhattacharyya S, Schapira AH, Mikhailidis DP, Davar J. Drug-induced fibrotic valvular heart disease. *Lancet*. 2009;374:577–585. doi: 10.1016/S0140-6736(09)60252-X
22. Bhattacharyya S, Davar J, Dreyfus G, Caplin ME. Carcinoid heart disease. *Circulation*. 2007;116:2860–2865. doi: 10.1161/CIRCULATIONAHA.107.701367
23. Connolly HM, Schaff HV, Mullany CJ, Rubin J, Abel MD, Pellikka PA. Surgical management of left-sided carcinoid heart disease. *Circulation*. 2001;104:I36–40. doi: 10.1161/hc37t1.094898
24. Kerstrom G, Hellman P, Hessman O. Midgut carcinoid tumours: surgical treatment and prognosis. *Best Pract Res Clin Gastroenterol*. 2005;19:717–728. doi: 10.1016/j.bpg.2005.05.005
25. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. *Am J Cardiol*. 2008;102:938–942. doi: 10.1016/j.amjcard.2008.05.047

SUPPLEMENTAL MATERIAL

Table S1. Right- and left-sided CaHD scoring system of severity.

Right-sided CaHD scoring system	
Tricuspid and pulmonary anatomies (score for each valve)	Score
Normal	0
Mild immobility	1
Moderate to severe immobility	2
Thickened or fixed	3
Tricuspid and/or pulmonary regurgitation (score for each valve)	
No or trivial regurgitation	0
Mild regurgitation	1
Moderate regurgitation	2
Severe regurgitation	3
Tricuspid and/or pulmonary stenosis (score for each valve)	
No significant stenosis	0
Mild stenosis	1
Moderate stenosis	2
Severe stenosis	3
Right ventricular size	
Normal	0
Mild or moderate dilatation	1
Severe dilatation	2
Right-sided CaHD score: minimal = 0; maximal = 20	

Left-sided CaHD scoring system	
Mitral and aortic anatomies (score for each valve)	Score
Normal	0
Mild immobility	1
Moderate to severe immobility	2
Thickened or fixed	3
Mitral and/or aortic regurgitation (score for each valve)	
No or mild regurgitation	0
Moderate regurgitation	1
Severe regurgitation	2
Left-sided CaHD score: minimal = 0; maximal = 10	
Global CaHD score: minimal = 0; maximal = 30	
CaHD: carcinoid heart disease	
Ref. 12	