

*Original Article*

## High prevalence of fenfluramine-related aortic regurgitation in women with end-stage renal disease secondary to Chinese herb nephropathy

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### Abstract

**Background.** Non-controlled studies have noted a high prevalence of valvular regurgitation in patients with Chinese herb nephropathy; most of these patients had taken appetite suppressants. We aimed to determine the prevalence of valvular regurgitation and the role of appetite suppressants in patients with Chinese herb nephropathy.

**Methods.** This case-controlled echocardiographic study included 40 patients with end-stage renal failure due to Chinese herb nephropathy and 37 age-matched controls with end-stage renal disease due to nephropathy of other origin. Quantification of cumulative doses of appetite suppressants was performed.

**Results.** Aortic regurgitation was detected in 52.5% of patients with Chinese herb nephropathy,  $72 \pm 1$  months after stopping appetite suppressants, and in 21.6% of controls ( $P=0.009$ ). No difference was found in the incidence of mitral or tricuspid regurgitation. A history of slimming medication was the only significant determinant for aortic regurgitation ( $P=0.009$ ). Higher cumulative doses of Chinese herbs, (dex)fenfluramine and diethylpropion were observed in patients with Chinese herb nephropathy with, when compared to those without, aortic regurgitation. The dose–response relationship between the cumulative dose of drugs and the presence of aortic regurgitation was significant for fenfluramine only (chi-square = 5.16,  $P=0.024$ ).

**Conclusions.** Six years after stopping appetite suppressants, aortic regurgitation remains highly prevalent among patients with end-stage Chinese herb nephropathy. The dose-related association with fenfluramine intake strongly confirms a determinant pathogenic role of anorectic drugs.

**Keywords:** appetite suppressants; aortic regurgitation; Chinese herb nephropathy; fenfluramine

### Introduction

Several studies support an association between appetite suppressants and cardiac valve abnormalities [1,2]. However, some concerns have been raised regarding the precise role of anorectic drugs in the pathogenesis of the valvular disease [3]. In addition, even if the role of anorectic drugs is acknowledged, recent data have suggested that valve damage from diet drugs may improve or even disappear with time [4,5]. Aortic regurgitation is the most prevalent cardiac valve abnormality that has been related to anorectic drugs. Interestingly, a puzzling association between aortic regurgitation and Chinese herb nephropathy was reported in Belgium some years ago [6]. This nephropathy is a rapidly progressive interstitial fibrosis of the kidneys and was first reported in 1993 in women who had taken slimming pills containing Chinese herbs and appetite suppressants [7]. The kidney disease was related to the fact that these pills contained the nephrotoxic Chinese herb *Aristolochia fangchi* [8].

Soon after the initial report of valvular heart disease associated with appetite suppressants [9], the fact that patients with Chinese herb nephropathy had also received anorectic drugs (fenfluramine alone or associated with other compounds) prompted us to hypothesize that valvular lesions observed in these patients could in fact be due to the intake of appetite suppressants [10]. At the time of the present study, 43 patients with end-stage renal failure related to Chinese herb nephropathy had been admitted to our department. Since cumulative doses of appetite suppressants had been recorded for the purposes of studying the nephropathy [11], we chose to use this constructed database with long-term follow-up, first, to determine the prevalence of valvular regurgitation late after stopping appetite suppressants, and, second, to further clarify the possible relationship between appetite suppressants and valvular regurgitation. However, as valvular heart disease may also be related to metabolic and haemodynamic disturbances in relation to end-stage renal

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disease [12,13], we also compared the prevalence of valvular regurgitation in patients with end-stage Chinese herb nephropathy and in age-matched controls with end-stage renal disease from another origin.

## Subjects and methods

### Patients

Forty-three patients with Chinese herb nephropathy followed at our nephrology department had reached end-stage renal failure at the time of the present study (from December 1997 to February 1999), among whom three refused to undergo echocardiography. Of the remaining 40 patients, seven were receiving dialysis and waiting for a kidney transplant, and 33 had undergone successful transplantation. All were women who had been prescribed slimming pills containing powdered Chinese herbs and appetite suppressants during the period when these herbs were commonly distributed in Belgium (1990–1992). The diagnosis of Chinese herb nephropathy was based on a history of intake of these pills and on the occurrence of rapidly progressive deterioration of previously normal renal function, and was confirmed by typical histological data [14] obtained from renal biopsy or nephrectomy specimen.

Thirty-seven controls with a functional kidney transplant ( $n=30$ ) or on chronic dialysis ( $n=7$ ) for end-stage renal failure due to an origin other than Chinese herb nephropathy were studied [Table 1, glomerular disease ( $n=12$ ); chronic interstitial nephritis ( $n=14$ ); vascular ( $n=3$ ); congenital ( $n=3$ ); post-partum cortical necrosis ( $n=1$ ); unknown ( $n=4$ )]. This control group was selected from the database of all patients living in Belgium and treated in our centre for terminal renal failure from December 1997 to January 2001 ( $n=733$ ). To establish the control group, we used the following exclusion criteria: male gender, age outside the range of ages of the patients with Chinese herb nephropathy (42–69 years), any history of slimming pill intake, a history of valvular heart disease diagnosed before 1990, a diagnosis of kidney disease associated with a higher prevalence of valvular abnormalities, such as autosomal dominant polycystic kidney disease and lupus erythematosus. Two of the eligible patients were reluctant to undergo cardiac investigations and

were also excluded. Three patients included in the study underwent valvular surgery after 1990; two for mitral regurgitation (one patient with Chinese herb nephropathy and one control) and one for aortic regurgitation (belonging to the Chinese herb nephropathy group).

All patients gave oral consent for participation in this study.

### Echocardiography and Doppler imaging

Doppler echocardiography study was prospectively performed on a Hewlett Packard Sonos 5500 system. In patients with previous valvular surgery, preoperative recordings were reviewed. Measurements were made according to the recommendations of the American Society of Echocardiography [15], and taken from the mean of three cardiac cycles. Left ventricular mass index was calculated according to the formula of Devereux *et al.* [16].

Aortic regurgitation was considered to be present by Doppler examination when a holodiastolic flow originating from the aortic valve was visualized in the left ventricular outflow tract. The ratio of the height of the aortic regurgitation jet at its origin to the size of the left ventricular outflow tract was used for grading: mild (1–24%), moderate (25–46%), moderate-to-severe (47–64%), and severe ( $\geq 65\%$ ) [17]. When the regurgitant signal was not holodiastolic, either due to its small size or limited duration, aortic regurgitation was graded as trace.

Mitral and tricuspid regurgitation were quantified using colour flow mapping of the regurgitant jet using orthogonal planes from parasternal and apical views [18] and graded as none, trace ( $< 2 \text{ cm}^2$ ), mild ( $\geq 2$  to  $< 5 \text{ cm}^2$ ), moderate ( $\geq 5$  to  $< 10 \text{ cm}^2$ ), or severe ( $\geq 10 \text{ cm}^2$ ). Trace aortic regurgitation and trace-to-mild mitral and tricuspid regurgitation were considered as physiological leaks.

In the present study, we evaluated the number of patients presenting with aortic regurgitation of mild or greater severity, mitral regurgitation of moderate or greater severity, and tricuspid regurgitation of moderate or greater severity, as initial studies on appetite suppressant-related valvulopathies also reported cases of tricuspid regurgitation [9]. All examinations were recorded by a cardiologist (P.U.), aware of the aetiology of the renal failure, but unaware of the cumulative doses of appetite suppressants. Studies were stored on VHS videotape for off-line analysis, which was

**Table 1.** Clinical characteristics and echocardiographic data

Parameters	Patients with CHN ( $n=40$ )	Control group ( $n=37$ )	<i>P</i> -value
Mean age (years)	52.5 ± 1.1	53.3 ± 1.2	0.61
Body-mass index <sup>a</sup> (kg/m <sup>2</sup> )	26.2 ± 0.7	25.3 ± 0.9	0.40
Duration of dialysis (months)	22.6 ± 3.0	49.6 ± 7.0	0.0005
Duration post transplantation (months)	25.2 ± 2.6 ( $n=33$ )	46.0 ± 5.9 ( $n=30$ )	0.001
Mean plasma creatinine of transplanted patients (mg/dl)	1.39 ± 0.04 <sup>b</sup>	1.41 ± 0.08 <sup>b</sup>	0.85
Mean arterial blood pressure (mm Hg)	106 ± 2	103 ± 2	0.34
Heart rate (beats/min)	75 ± 2	75 ± 2	0.91
Left ventricular end-diastolic diameter (mm)	46.4 ± 0.7	46.8 ± 1.0	0.77
Fractional shortening (%)	42.5 ± 1.1	40.9 ± 1.1	0.31
Left ventricular ejection fraction (%)	72.6 ± 1.2	71.1 ± 1.3	0.40
Left ventricular mass index (g/m <sup>2</sup> )	118.3 ± 5.2	125.0 ± 4.0	0.32
Left atrium diameter (mm)	39.0 ± 0.8	40.3 ± 0.8	0.26
Aortic root diameter (mm)	31.3 ± 0.4	30.8 ± 0.6	0.48

Values are mean ± SEM; CHN, Chinese herb nephropathy.

<sup>a</sup>The body-mass index is the weight in kilograms divided by the square of the height in metres.

<sup>b</sup>Four transplanted patients in each group had proteinuria > 500 mg/day.

performed by a second cardiologist (D.P.), unaware of any clinical data. Concordant results on the presence or absence of regurgitation (i.e. aortic regurgitation of mild or greater degree, mitral and tricuspid regurgitation of moderate or greater degree) were observed by the two cardiologists in 100% of the aortic valves, 96% of the mitral valves and 94% of the tricuspid valves. The eight discrepancies were adjudicated by a consensus reading, favouring the conclusions of the blinded observer in four cases.

### Evaluation of exposure

In the framework of the study of Chinese herb nephropathy and associated urinary carcinoma, all prescriptions delivered from 1990 to 1992 were obtained from the pharmacists with the help of the Belgian Ministry of Public Health, and were reviewed. The most common treatment consisted of a mixture of Chinese herbs (*Stephania tetrandra* inadvertently replaced by the nephrotoxic *Aristolochia fangchi*) [8] in various concentrations, and appetite suppressants (fenfluramine and diethylpropion); in addition, some patients also received dexfenfluramine ( $n=16$ ), phentermine ( $n=7$ ) and acetazolamide ( $n=29$ ). For each patient, the cumulative doses were calculated and expressed as the mean ingested dose of each compound (in grams).

### Statistical analysis

Results are expressed as mean  $\pm$  SEM. The demographic characteristics of both groups (patients with Chinese herb nephropathy and controls) were compared using the Student's *t* or Fischer's exact tests for continuous and nominal variables, respectively. Two-tailed *P*-values were considered significant if  $<0.05$ . To test the trend in a  $k \times 2$  table of contingency, a chi-square test of linear tendency was used [19].

## Results

Our survey confirmed that, besides Chinese herbs, all patients with Chinese herb nephropathy had been prescribed fenfluramine as well as diethylpropion. Sixteen patients had also taken dexfenfluramine, seven phentermine and 29 acetazolamide. Cumulative doses of all compounds were available, except in one case where only the dose of Chinese herbs was quantified. Thirty-nine patients (98%) received the medications for at least 6 months and 27 (68%) for at least 1 year. No patient reported taking slimming drugs after 1993; echocardiographic studies were performed, for the purposes of this study, a mean of  $72 \pm 1$  months after the patients had stopped taking appetite suppressants.

Table 1 lists the clinical characteristics of the patient populations. None of the parameters was statistically different between the two groups, except for the duration of dialysis and the duration post-transplantation.

### Prevalence of valvular disease

None of the M-mode echocardiographic parameters was found to be statistically different among the two groups (Table 1).

As shown in Table 2, the prevalence of aortic regurgitation was significantly higher in patients with Chinese herb nephropathy as compared to controls ( $P=0.009$ ). In contrast, the prevalence of mitral or tricuspid regurgitation was similar in the two groups: mitral regurgitation was found in three patients with Chinese herb nephropathy and in four controls ( $P=0.70$ ). Tricuspid regurgitation was detected in three patients and in four controls ( $P=0.70$ ). Among patients with Chinese herb nephropathy, aortic regurgitation was the sole abnormality in 18 patients, was associated with mitral regurgitation in two patients, and with both mitral and tricuspid regurgitation in one patient. Two patients with Chinese herb nephropathy had isolated tricuspid regurgitation.

### Predictive factors for developing aortic regurgitation

To detect factors predicting aortic regurgitation, clinical and echocardiographic data were compared in patients with and without aortic regurgitation (Table 3). A history of slimming regimen and duration of the transplant period were the sole significant determinants of aortic regurgitation. In order to determine the role of the duration of the transplant period, a repeat echocardiogram could be performed in 18 of the 21 transplanted patients with aortic regurgitation after a mean additional delay of  $41.9 \pm 4.0$  months. Aortic regurgitation persisted in all cases, and the total duration of the transplant period of the 29 patients with aortic regurgitation increased to  $42.8 \pm 7.0$  months ( $P=0.42$  vs patients without aortic regurgitation).

In patients with Chinese herb nephropathy, significantly higher cumulative doses of Chinese herbs ( $P=0.046$ ), fenfluramine ( $P=0.038$ ) and dexfenfluramine ( $P=0.029$ ) were found in patients with, as compared to patients without, aortic regurgitation (Table 4). There was a close relationship between the cumulative intake of fenfluramine and of Chinese herbs ( $P<0.0001$ ). The dose-response relationship between the cumulative dose of fenfluramine and the

**Table 2.** Grading of valvular regurgitation

Valve	Regurgitation grade	Number of patients (%)	
		Patients with CHN ( $n=40$ )	Control group ( $n=37$ )
Aortic	None-trace	19 (47) <sup>a</sup>	29 (78)
	Mild	10 (25)	4 (11)
	Moderate/moderate-to-severe	10 (25)	4 (11)
	Severe	1 (3)	0 (0)
Mitral	None, trace or mild	37 (92)	33 (89)
	Moderate	2 (5)	3 (8)
	Severe	1 (3)	1 (3)
Tricuspid	None, trace or mild	37 (92)	33 (89)
	Moderate	3 (8)	4 (11)
	Severe	0 (0)	0 (0)

CHN, Chinese herb nephropathy.

<sup>a</sup> $P=0.009$  vs controls.

**Table 3.** Risk factors for developing aortic regurgitation

	Aortic regurgitation		<i>P</i> -value
	Absent ( <i>n</i> = 48)	Present ( <i>n</i> = 29)	
Slimming regimen (no/yes)	29/19	8/21	0.009
Duration of dialysis (months)	40 ± 6	29 ± 4	0.18
Duration of the transplant period (months)	36.5 ± 4.2	16.8 ± 3.6	0.002
Age (years)	52.1 ± 0.9	54.0 ± 1.4	0.24
Mean arterial blood pressure (mm Hg)	105 ± 1	103 ± 2	0.47
Body mass index (kg/m <sup>2</sup> )	26.1 ± 0.7	25.2 ± 0.8	0.43
Left ventricular mass index (g/m <sup>2</sup> )	118 ± 3	127 ± 7	0.20
Aortic root diameter (mm)	30.9 ± 0.5	31.4 ± 0.5	0.46

Mean ± SEM for all continuous variables.

presence of aortic regurgitation showed a significant linear trend (Table 5; chi-square = 5.16, *P* = 0.024) whereas the linear trend for the dose–response relationship between the cumulative dose of Chinese herbs, categorized in four linearly increasing intervals (0–99, 100–199, 200–299 and ≥300 g) and the risk of developing aortic regurgitation did not reach statistical significance (chi-square = 2.82, *P* = 0.095).

## Discussion

This work is the first case-controlled echocardiographic study with a long-term follow-up on the prevalence of aortic regurgitation in end-stage renal failure after the intake of anorectic drugs. Indeed, a comprehensive review of the medical prescription obtained for the study of Chinese herb nephropathy [11], provides an accurate estimate of the cumulative doses of appetite suppressants taken. Our work shows that fenfluramine intake was the only significant determinant for the development of aortic regurgitation in our cohort of end-stage renal disease patients. Moreover, the occurrence of aortic regurgitation in patients with Chinese herb nephropathy was significantly related to the cumulative dose of fenfluramine

**Table 4.** Cumulative doses of slimming pill components and the risk of developing aortic regurgitation

	Aortic regurgitation		<i>P</i> -value
	Absent	Present	
<i>Stephania</i> <sup>a</sup>	171 ± 18 (19)	227 ± 20 (21)	0.046
Fenfluramine	11 ± 2 (19)	18 ± 3 (20)	0.038
Dexfenfluramine	2 ± 1 (7)	6 ± 1 (9)	0.029
Phentermine	12 ± 5 (2)	14 ± 6 (5)	0.85
Diethylpropion	13 ± 2 (19)	17 ± 2 (20)	0.14
Acetazolamide	34 ± 6 (15)	38 ± 7 (14)	0.70

Cumulative doses are expressed in grams (mean ± SEM). The numbers in parentheses refer to the number of patients prescribed the component.

<sup>a</sup>In fact, *Aristolochia*, see Depierreux *et al.* [14].

**Table 5.** Relationship between the risk of developing aortic regurgitation and the cumulative dose of fenfluramine categorized in four linearly increasing intervals

Cumulative dose of fenfluramine (g)	Aortic regurgitation			
	Absent	Present	Total	% Present
0–6.9	7	3	10	30
7–13.9	6	4	10	40
14–20.9	5	8	13	62
≥21	1	5	6	83
Total	19	20	39	
Linear trend	Chi-square = 5.16, <i>P</i> = 0.024			

and not to that of Chinese herbs. Therefore, the role of Chinese herbs in the pathology of aortic regurgitation is at most minimal when compared to that of fenfluramine.

Age-related mild valvular regurgitation may occur in normal subjects [20], end-stage renal disease is associated with a high prevalence of cardiac abnormalities [12,13], left ventricular dysfunction and dilatation resulting from chronic hypertension may complicate the course of renal disease and induce mitral regurgitation [12], and premature valve calcification may occur [13]. However, all these biases were addressed in our study by considering an age-matched control group with terminal renal failure of other origin. Although this strategy resulted in two fairly similar groups, controls had a longer history of dialysis as compared to patients with Chinese herb nephropathy. This characteristic would potentially increase the prevalence of valvular regurgitation in the controls, leading to an underestimated difference between groups and thus would reinforce, rather than negate, the significance of our observations. Moreover, a trend towards a longer history of dialysis in patients without aortic regurgitation as compared to patients with aortic regurgitation (40 ± 6 vs 29 ± 4 months, respectively) makes the duration of dialysis an unlikely determinant of aortic regurgitation in this series. Since the duration of transplant period was shorter in patients with aortic regurgitation, we reviewed the subsequent repeat echocardiography performed in this subset of patients. Aortic regurgitation persisted in all transplant recipients with aortic regurgitation that underwent a follow-up echocardiography, after a mean additional delay of 41.9 ± 4.0 months, allowing us to rule out the hypothesis of a ‘transplantation-induced’ reversibility of valvular regurgitation.

Several studies support an association between appetite suppressants and valvular abnormalities [1,2]. However, wide variations in the estimates of prevalence exist [1,2].

The prevalence of valvular regurgitation in patients with Chinese herb nephropathy in the present study exceeds previous estimates among users of appetite suppressants. This high prevalence may be explained, first, by the contribution of renal disease, which is

suggested by the substantial prevalence of valvular regurgitation observed in controls and, second, by the duration of the slimming regimen that was particularly long in our patients [2].

Finally, our work demonstrates for the first time, that aortic regurgitation persists long after the discontinuation of the anorectic agents, contrasting with some reports that this adverse effect may resolve over time [4,5]. We suggest that the long duration of treatment and the high doses of appetite suppressants, as well as the metabolic disturbances associated with renal failure, may have altered the potential for reversal of the valvular lesions.

*Conflict of interest statement.* None declared.

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