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Dietary and blood antioxidants in patients with chronic heart failure. Insights into the potential importance of selenium in heart failure

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Abstract

Background: Chronic heart failure (CHF) seems to be associated with increased oxidative stress. However, the hypothesis that antioxidant nutrients may contribute to the clinical severity of the disease has never been investigated. *Aims:* To examine whether antioxidant nutrients influence the exercise capacity and left ventricular function in patients with CHF. *Methods:* Dietary intake and blood levels of major antioxidant nutrients were evaluated in 21 consecutive CHF patients and in healthy age- and sex-matched controls. Two indexes of the severity of CHF, peak exercise oxygen consumption (peak VO_2) and left ventricular ejection fraction (LVEF), were measured and their relations with antioxidants were analysed. *Results:* Whereas plasma alpha-tocopherol and retinol were in the normal range, vitamin C ($P = 0.005$) and beta-carotene ($P = 0.01$) were lower in CHF. However, there was no significant association between vitamins and either peak VO_2 or LVEF. Dietary intake ($P < 0.05$) and blood levels of selenium ($P < 0.0005$) were lower in CHF. Peak VO_2 (but not LVEF) was strongly correlated with blood selenium: $r = 0.76$ by univariate analysis (polynomial regression) and $r = 0.87$ ($P < 0.0005$) after adjustment for age, sex and LVEF. *Conclusions:* Antioxidant defences are altered in patients with CHF. Selenium may play a role in the clinical severity of the disease, rather than in the degree of left ventricular dysfunction. Further studies are warranted to confirm the data in a large sample size and to investigate the mechanisms by which selenium and other antioxidant nutrients are involved in CHF.

Keywords: Nutrition; Peak exercise oxygen consumption; Left ventricular ejection fraction; Vitamin C; Selenium; Beta-carotene

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1. Introduction

The incidence of chronic heart failure (CHF), the common end-result of most cardiac diseases, is increasing steadily in many countries despite improvements in the prevention and treatment of most types of cardiopathies [1,2]. Unidentified factors may contribute to the age-adjusted rise in the number of CHF patients. For instance, CHF is now seen also as a metabolic problem with endocrine and immunological disturbances potentially contributing to the progression of the disease [3–5]. Only recently has it also been recognised that increased oxidative stress may contribute to the pathogenesis of CHF [6–10]. Clinical and experimental studies have indeed suggested that CHF may be associated with increased free radical formation [11,12] and reduced antioxidant defences [6] and that vitamin C may improve endothelial function in patients with CHF [13]. Also, in dietary trials in which the tested diet included high intakes of natural antioxidants, the incidence of CHF was reduced in the experimental groups [14,15] suggesting that antioxidant nutrients may play a role in CHF. As a matter of fact, selenium deficiency has been identified as a major factor in the aetiology of certain non-ischaemic CHF syndromes, especially in low-selenium soil areas such as eastern China (Keshan disease) and western Africa [16,17]. In Western countries, cases of congestive cardiomyopathy associated with low selenium have been reported in malnourished HIV-infected patients [18] and in subjects on chronic parenteral nutrition [19]. However, no study has examined the hypothesis that mild or moderate deficiency in antioxidant nutrients (vitamins and trace elements) may contribute to the severity of the disease and, for instance, influence the exercise capacity of CHF patients.

The main goals of this study were therefore to carefully evaluate the dietary habits of non-selected patients with CHF and to analyse the relationship between antioxidant nutrients and simple markers of exercise capacity [20] and of left ventricular dysfunction.

2. Subjects and methods

2.1. Subjects

We studied consecutive CHF patients (NYHA functional class II or III) adhering to a cardiac rehabilitation program. We retained only ambulatory patients with recent measurements of left ventricular ejection fraction (LVEF) and peak exercise oxygen consumption (peak $V\mathrm{O}_2$) as reliable indicators of the clinical severity of CHF. The diagnosis of CHF was based on a history of acute pulmonary oedema and objective evidence of left ventricular dysfunction (LVEF < 40%). Main exclusion criteria were the inability to exercise and major organ (liver and kidney) failure. We also studied age- and sex-matched healthy subjects to examine the relationship between dietary and blood antioxidants in subjects living within the same area as the patients, as well as the possibility that it is a low trace element soil area.

2.2. Exercise protocol and diet evaluation

All patients underwent symptom-limited upright bicycle exercise testing using a ramp protocol. Respiratory gas analysis (oxygen consumption and carbon dioxide production) was performed with a breath-by-breath apparatus. Peak $V\mathrm{O}_2$ was corrected for weight and expressed as ml/min per kg. Dietary habits of each patient were evaluated on at least two occasions using 24-h recall as previously described [21]. Average total energy intake was expressed in kJ per day and the intake of fats, carbohydrates and ethanol was done as a percentage of total energy intake. Intake of trace elements was evaluated using specific tables for selenium, zinc and copper intake [22]. Due to the lack of detailed and exhaustive tables for the trace elements, we used values corresponding to groups of foods rather than those of individual foods.

2.3. Laboratory measurements

Blood samples were obtained (in a fasting state, between 08.00 and 10.00 h) for routine biochemical and haematological determinations and using specific metal-free tubes for measurement of selenium, zinc and copper. Trace elements were measured by inductively coupled atomic emission spectroscopy (copper and zinc) or electrothermal atomic-absorption spectroscopy (selenium) as described [23]. Quality control for trace-element analysis was performed by comparison with reference standards and participation in an interlaboratory comparison study [24]. The reference values for normal adults in France are: selenium, 70–120 μg/l; zinc, 0.62–0.99 mg/l; copper, 0.88–1.20 mg/l. A reverse-phase high-performance liquid chromatography procedure was used for the quantitative measurement of serum carotenoids, retinol, alpha-tocopherol and two internal standards (tocol and echinenone). Chromatograms at four different wavelengths (292, 325, 450 and 473 nm) and spectra were monitored with a diode array detector, as described [25]. Plasma vitamin C concentrations were determined by high performance liquid chromatography with fluorimetric detection, in blood samples immediately put on ice, protected from light and stabilised in 5% metaphosphoric acid [26]. Chromatographic sepa-

ration was performed by isocratic elution using ODS-Hypersil C18 column [27].

2.4. Statistics

Results are shown as mean ± S.D. Unpaired Student's *t*-tests were used to compare the two groups in terms of nutrient intake and biological parameters. The relationship between dietary intake and blood concentrations of each nutrient, as well as the relationship between nutrients and clinical parameters were analysed by simple linear regression. The relationship between serum selenium and peak V_{O_2} were analysed by polynomial regression, then using a multilinear regression model with age, sex, LVEF and either copper or zinc as independent covariates.

3. Results

Twenty-one consecutive patients were included, 17 males and four females, aged 27–76 (Table 1). Most ($n = 19$) patients had post-ischaemic cardiomyopathy, the two other patients having idiopathic dilated cardiomyopathy. The healthy control group ($n = 18$, 15 males and 3 females, aged 34–68) was not different from the patient group for the age and main physiological variables. Data for trace elements were not available for one female patient. No CHF patient was cachectic or malnourished at the time of the study. None were smokers. None were taking any kind of supplements, including vitamin or trace-element antioxidant supplements. None exhibited severely impaired renal or liver function and none had overt diabetes (Table 2). As expected, the CHF patients differed from the healthy subjects in respect of blood metabolic parameters (uric acid, glucose and lipids). Regarding the trace elements in blood (dietary data are given below), the differences between groups were of borderline significance ($P < 0.05$) for copper and zinc and highly significant for selenium ($P < 0.0005$). Whereas retinol and alpha-tocopherol in blood were not different between the two groups (and within the normal range), beta-carotene and vitamin C levels were significantly lower in the CHF group (Table 3).

Table 1
Main clinical characteristics of the patients

	Mean	S.D.	Range
Body mass index (kg/m^2)	27.7	3.8	17.6–34.4
Blood pressure (mmHg)			
Systolic	128	21	90–100
Diastolic	83	12	60–100
Heart rate (b.p.m.)	79	13	60–120
LVEF (%)	29.3	6	21–40
Peak V_{O_2}	15.2	3	7.9–20.8
Medications (%)	45		
Digitalis	85		
Diuretics	85		
ACE inhibitors	85		
Beta blockers	20		
Calcium blockers	25		
Anticoagulants	50		
Antiplatelet agents	50		
Lipid-lowering drugs	25		

3.1. Analysis of dietary habits

Total energy, total fat, alcohol and protein intake

Table 2
Main biological characteristics of the two groups

	CHF ($n = 21$)	Control ($n = 18$)	*P*
Albumin (g/l)	44.1 (3.7)	44.5 (3.5)	0.74
Creatinine (μmol/l)	106 (31)	90 (35)	0.14
Uric acid (μmol/l)	451 (155)	316 (67)	0.002
Glucose (mmol/l)	7.1 (2.8)	5.5 (0.4)	0.01
Alkaline phosphatase (IU/l)	75.3 (35.6)	60.1 (17.4)	0.10
Bilirubin (μmol/l)	13.1 (4.2)	10.8 (4.2)	0.09
Total cholesterol (mmol/l)	5.7 (1.3)	5.2 (0.9)	0.14
HDL cholesterol (mmol/l)	1.2 (0.2)	1.5 (0.4)	< 0.005
Triglycerides (mmol/l)	2.1 (1.0)	1.1 (0.6)	0.0005
Apoprotein B (g/l)	1.2 (0.4)	1.0 (0.2)	0.08
Apoprotein AI (g/l)	1.4 (0.1)	1.7 (0.3)	0.007
Copper (mg/l)	1.15 (0.34)	0.97 (0.17)	< 0.05
Zinc (mg/l)	0.82 (0.12)	0.90 (0.09)	< 0.05
Selenium (μmol/l)	62.6 (13.9)	77.9 (10.7)	0.0004
Iron (μmol/l)	15.9 (6.4)	18.9 (3.5)	0.12
Ferritin (μg/l)	167 (163)	98 (33)	0.29
Calcium (mmol/l)	0.81 (0.07)	0.78 (0.05)	0.14
Magnesium (mmol/l)	2.33 (0.10)	2.34 (0.07)	0.69

Table 3
Blood antioxidant vitamins in the two groups

	CHF ($n = 21$)	Control ($n = 18$)	Normal range
Retinol (μm/l)	3.10 (3.25)	2.14 (0.65)	1.61–3.10
Alpha tocopherol (μm/l)	36.1 (13.3)	31.7 (10.2)	18.4–37.1
Vitamin C (mg/l)	7.0 (3.3)*	9.9 (2.5)	7.00–12.0
Beta carotene (μm/l)	0.39 (0.24)**	0.62 (0.29)	0.40–0.90
Alpha carotene (μm/l)	0.15 (0.11)	0.10 (0.10)	0.10–0.62
Lutein (μm/l)	0.46 (0.24)	0.48 (0.19)	0.41–1.01
Zeaxanthin (μm/l)	0.11 (0.06)	0.13 (0.06)	0.04–0.14
Beta crypoxanthin (μm/l)	0.25 (0.19)	0.35 (0.19)	0.08–0.62
Lycopene (μm/l)	0.50 (0.30)	0.53 (0.25)	0.13–0.99

*$P = 0.05$; **$P = 0.01$.

were not different in the two groups (Table 4) and were close to those of the average French adult population. The intake of vitamin C and beta-carotene were also not different between the two groups, suggesting that the differences in blood levels could not be explained by the diet. Mean selenium intake was lower in CHF patients whereas the intake of copper and zinc was similar in both groups. There was a positive correlation between selenium intake and blood levels: $r = 0.65$, $P = 0.001$ (Fig. 1). Thus, the low dietary intake accounted for the low blood selenium levels.

With vitamin C (but not with beta-carotene), there was a positive correlation ($P < 0.05$) between dietary intake and blood levels in the two groups: $Y = 7.17 + 52.65\ X$ (where X was the dietary vitamin C and Y the blood level) in the healthy group and $Y = 4.95 + 35.35\ X$ in the CHF group. The two regression lines are shown in Fig. 2 showing that the line for CHF was shifted downward. To quantify this lack of vitamin C in the CHF patients, the dietary vitamin C value measured in each CHF patient was entered into the equation of the healthy group. The 'expected' blood vitamin C was calculated and compared with the (measured) true value (paired t-test). The difference between the 'expected' (58.7 ± 16.5 μmol/l) and true (40.3 ± 18.8) values was higher than 17 μmol/l ($P < 0.0001$). Since dietary vitamin C is the main determinant of blood vitamin C (as shown by the strong positive correlation between the two variables) and because in the CHF patients the regression line is shifted downward, our data suggest that there is a relative depletion of vitamin C in CHF.

Using univariate analyses, we found no correlation between blood vitamin C and the other antioxidant nutrients (including vitamins and trace-elements). Using multivariate analyses, taking dietary vitamin C as a covariate, blood vitamin C was significantly associated with blood selenium (partial $r = 0.27$, $P = 0.05$) suggesting that the variation in blood selenium may explain approximately 10% of the variability of blood vitamin C.

Table 4
Main dietary characteristics of the two groups

	CHF ($n = 21$)	Control ($n = 18$)	P
Energy	9139 (2452)	9790 (2285)	0.39
(%) of energy			
Total fats	34.2 (8.8)	34.9 (6.5)	0.76
Carbohydrates	43.9 (9.4)	46.5 (6.1)	0.31
Alcohol	6.0 (7.5)	3.3 (5.4)	0.19
PUFA	5.3 (2.8)	5.0 (2.3)	0.76
MUFA	11.4 (3.7)	13.0 (3.3)	0.15
Saturated fat	13.4 (4.1)	13.0 (3.4)	0.75
Fibre (g/day)	14.4 (6.7)	19.8 (9.8)	< 0.05
Cholesterol (mg/day)	407 (189)	432 (277)	0.73
Ascorbic acid (mg/day)	139 (181)	118 (54)	0.63
Alpha-tocopherol (mg/day)	11.7 (7.8)	14.0 (5.2)	0.28
Retinol (μg/day)	318 (234)	378 (204)	0.39
Beta-carotene eq (μg/day)	4776 (4148)	3293 (3334)	0.22
Copper (mg/day)	1.22 (0.13)	1.37 (0.17)	0.48
Zinc (mg/day)	10.2 (3.7)	9.2 (3.0)	0.36
Selenium (μg/day)	63.7 (26.5)	80.9 (26.1)	< 0.05

PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids.

3.2. Relationship with clinical variables

We only found a trend towards a positive correlation between blood vitamin C and LVEF ($r = 0.36$, $P = 0.12$). No correlation was found between the trace elements and LVEF. Also, there was no correlation between peak VO_2 and either zinc or copper. In contrast, blood selenium was strongly correlated with peak VO_2. The best correlation in univariate analysis was observed using polynomial regression (Fig. 3, $r = 0.76$). The association between selenium and peak VO_2 was still stronger ($r = 0.87$, $P < 0.0005$) in a multilinear model in which age, sex and LVEF were entered as independent covariates and peak VO_2 as the dependent variable. This multivariate model explained 67% of the variability of peak VO_2 ($P < 0.005$). Zinc, copper and other antioxidants did not improve

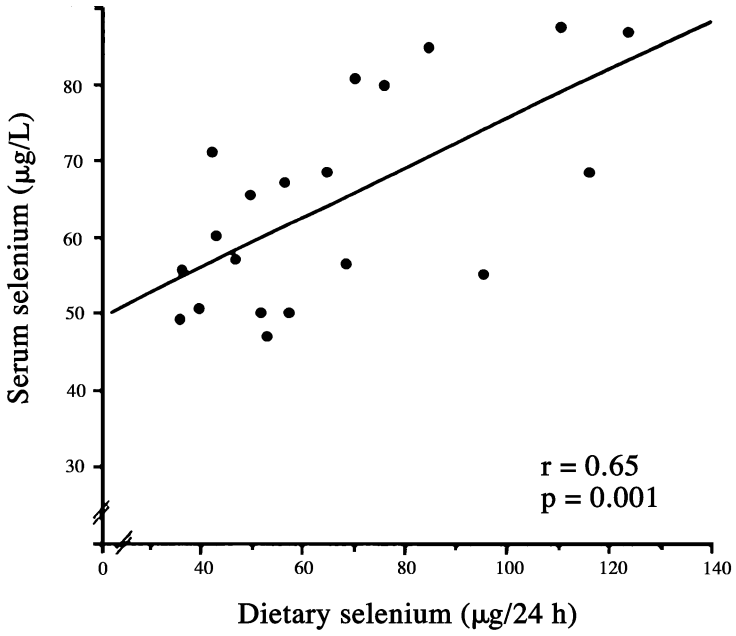

Fig. 1. Relationship between dietary intake and blood levels of selenium in patients with chronic heart failure.

the model. It is worth mentioning that the relationship between peak VO_2 and LVEF was significant (partial $r = 0.42$, $P < 0.05$) after adjustment for age, sex and selenium in this group of patients.

4. Discussion

4.1. Antioxidant vitamins

This study confirms previous reports in which CHF was associated with decreased levels of blood vitamin C [6] and increased oxidant stress [7,28,29]. Also, in line with a previous study is the fact that vitamin E levels were maintained [6]. There have been no previous reports about retinol, beta-carotene and other carotenoids in CHF and, in previous studies, dietary intake of antioxidant nutrients was not evaluated, although they are the main determinants of blood concentrations. This prevented a full interpretation of the data in these studies.

In the present study, the relative depletion in vitamin C in the CHF patients compared with the healthy controls was not explained by low dietary intake since there was no difference in dietary intake between the groups. This indicates that factors other than diet are involved, which include alteration in renal reabsorption, impaired cellular regulation of vitamin C and, more likely, loss of vitamin C sec-

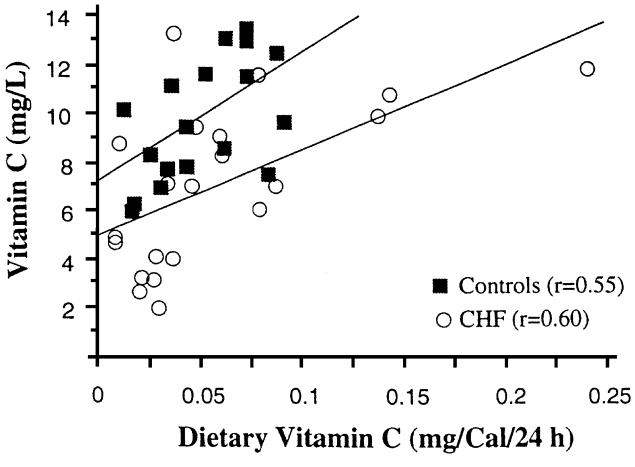

Fig. 2. Relationship between dietary intake and blood levels of vitamin C in patients with chronic heart failure and in healthy controls.

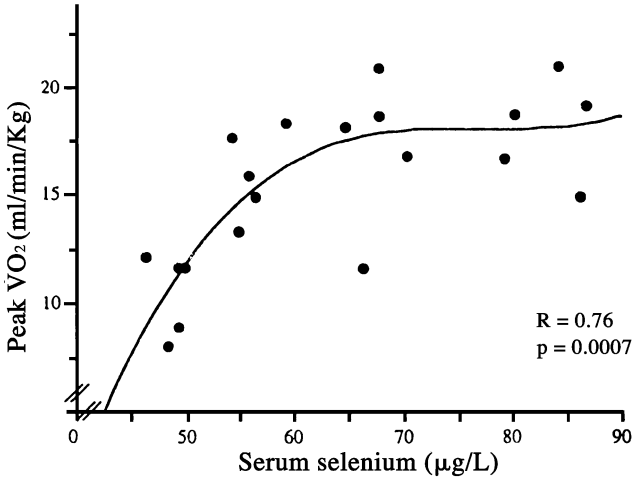

Fig. 3. Relationship between exercise capacity, evaluated by measuring peak exercise consumption (peak VO_2), and blood selenium in CHF patients.

ondary to the increased oxidant stress. Similar data were reported in diabetics [30] and smokers [31], two conditions associated with increased oxidant stress. In addition, the degree of depletion measured in our patients (none were smokers or diabetics) is in agreement with those reported [30–32], which gives confidence in the validity of our approach, a combined evaluation of dietary intake and blood levels.

Regarding beta-carotene, we also found no dietary explanation for the low blood level. In contrast with vitamin C, however, we found no significant relationship between dietary intake and blood level. In fact, only a small part of the variability in serum carotenoids has been explained by dietary and lifestyle factors [33]. The small sample size in this study and the fact that the existing tables to evaluate dietary carotenoids are not entirely satisfactory [33] may also explain the data.

Taken together, these data suggest that blood vitamin C (when analysed in relation with dietary intake) may be a sensitive indicator of oxidant stress in certain conditions and may serve as an indirect marker of it in the clinical setting, since most traditional methods to evaluate oxidant stress are often considered as being non-specific, inaccurate or unreliable [7,34,35]. A major issue, however, is the accuracy of measurements. As recently emphasised, vitamin C is easily oxidised in vitro and investigators must take care that any observed vitamin C decline actually occurred in the patients and not in the test tube [36]. Finally, another important issue raised by our findings relates to the absence of a significant relationship between vitamin C (and beta-carotene) and the clinical severity of CHF. Our data suggest that a moderate depletion in vitamin C (or beta-carotene) does not have any clinical implications. One study, however, showed that vitamin C might be beneficial in patients with CHF [13]. In addition, high consumption of natural antioxidant vitamins has been proposed to explain the low cardiovascular mortality rate in Mediterranean populations and in cardiac patients who adopt a Mediterranean or a vegetarian diet [14,15]. Finally, as recently stated, it is probably more important to monitor tissue (myocardium or storage organs) rather than plasma content of vitamins to detect the relationship between antioxidant vitamins and clinical complications [35]. Thus, further studies are warranted before saying that depletion in antioxidant vitamins can be disregarded in CHF.

4.2. Antioxidant trace elements

Plasma copper was slightly higher and zinc slightly lower in CHF than in healthy controls. On the other hand, dietary intakes were in the normal range and we found no significant relationship between dietary intake and blood levels in the two groups. It is not possible to say, however (and we do not wish to speculate), whether these copper and zinc abnormalities might contribute to the development of CHF or are simple markers for the chronic inflammation known to be associated with CHF [3,37,38]. Further studies are needed to address this point, since the implications for disease prevention are substantial.

In contrast with vitamin C and beta-carotene, the low selenium blood level in this study was mainly explained by a low consumption of selenium-rich foods. Also, the relationship between dietary and blood selenium were similar in the CHF and the healthy groups, indicating that there was no additional depletion of selenium (as seen with vitamin C). This emphasises the potential importance of dietary factors in CHF. The cardioprotective Mediterranean diet [15] is actually a selenium-rich diet (100 g of cooked octopus, the Greek national dish, provides approx. 100 μg of selenium) and increased consumption of selenium-rich marine or vegetable foods by cardiac patients has been shown to result in a reduced cardiac mortality rate in several trials [14,39]. This raises the question of the mechanism(s) by which selenium can influence cardiac mortality and eventually CHF. Selenium deficiency has been related to coronary heart disease and several mechanisms have been proposed. However, the evidence provided by case–control and prospective cohort studies remains controversial [19]. What about selenium and CHF?

4.3. Dietary selenium and CHF

Although sample size is small in this study, the strength and the shape of the correlation between selenium and exercise capacity suggests a causal relationship. A randomised trial is the appropriate next step to confirm the point. However, the relationship between selenium and peak VO_2 in our patients is linear only for selenium levels below 70 μg/l. With levels higher than 70 μg/l, peak VO_2 reaches a plateau suggesting that the causal relationship between selenium and exercise capacity (if it exists) would exist only when selenium levels are low. Thus, only patients with low selenium should be included in a trial. Another point is that CHF is now seen as a disease of the muscles, including skeletal and respiratory muscles [40], and not only of the heart muscle. Exercise and respiratory training actually resulted in significant improvements in peak VO_2 [41,42]. This means that, if the lack of selenium is responsible for the altered exercise capacity of our patients, it may be partly through muscle deconditioning. Thus, a rehabilitation program (with muscle reconditioning) should be included in a trial testing the beneficial effect of selenium on the exercise capacity of patients with

CHF. As a matter of fact, we found no correlation between selenium and LVEF, indicating that selenium was mostly involved in the symptoms of CHF (and peak VO_2) rather than in the development of the left ventricular dysfunction itself. This hypothesis is also in line with the history of Keshan disease [17,42–44], probably the best illustration of the role of selenium in CHF. Ge and Yang have pointed out that selenium deficiency (which may have resulted in the virus mutation that is the primary cause of the disease) is an essential cause, but not the only reason, for the occurrence of Keshan disease, an endemic cardiomyopathy in low-selenium soil areas [17,45]. In the Keshan area, the selenium status correlates with the clinical severity, rather than with the degree of left ventricular dysfunction, as assessed by echocardiographic studies. Other causes have been proposed but only selenium supplementation had a preventive effect in large trials and resulted in a reduced mortality rate [17,19,45]. In the endemic area, when the selenium levels of residents were raised to the typical levels in the non-endemic areas, clinically latent cases were still found and the echocardiographic prevalence of the disease remained high. Selenium deficiency is therefore considered a predisposing (or an aggravating) factor rather than a specific etiologic factor for the occurrence of the Keshan disease. What we learn from Keshan disease is therefore, that in patients with a known cause of CHF, even a mild deficiency in selenium may influence the clinical severity (the tolerance to exercise) of the disease. In our cases of CHF, however, the main cause of the low selenium level was unlikely to be the low selenium content of the soil but due to the diet of the patients.

4.4. What are the clinical implications of these data?

A selenium intake of approximately 80 μg/day is required in our CHF patients to obtain a blood concentration of 70 μg/l (Fig. 1). Beyond that point, higher blood levels are not associated with better exercise capacity (Fig. 3). An intake of 80 μg/day is higher than the current recommendations for healthy adults (55–70 μg/day) [46] and also higher than the intake (40 μg/day) considered as adequate for the prevention of Keshan disease in China [47]. Thus, in patients with CHF, dietary selenium requirements are probably higher than those recommended for the healthy population. This is a major practical point that needs confirmation.

The discrepancy between the symptoms of CHF and the degree of left ventricular dysfunction is a major issue for the management of patients with CHF [48]. The pathophysiology underlying the symptoms of CHF (dyspnea and muscle fatigue) is poorly understood, and treatments that correct the haemodynamics of heart failure do not reliably reduce the symptoms [48]. What about selenium in that context?

4.5. Exercise capacity, selenium and CHF

Selenium is an essential trace element and has a variety of functions. The main one is its role as an antioxidant in the enzyme glutathione peroxidase (GP), the major intracellular antioxidant. Selenium depletion results in a decrease in both GP activity and protein [49]. Until recently, studies on the function of selenium focused on GP. Recognition that several effects of selenium are not associated with GP has forced re-evaluation of its function. Another selenoprotein, designated Selenoprotein P, has been discovered which is postulated to be a major extracellular antioxidant [50]. More recently, the selenium-dependent thioredoxin reductase system has been proposed to contribute to ascorbate regeneration [51]. Thus, the selenium-dependent systems are crucial antioxidant defences in humans. On the other hand, CHF is associated with peripheral vasoconstriction [52] and impaired skeletal muscle metabolism [53], both attributed to the impaired vascular endothelial function [8,9,54]. Correction of endothelial dysfunction results in a significant increase in exercise capacity [55] and endothelial dysfunction in these patients is improved by vitamin C [13], thought to scavenge oxygen radicals and spare endogenous antioxidants from consumption [56]. The selenium-dependent systems act synergistically with vitamin C [57] to neutralise oxygen radicals and preserve endothelial function, which in turn may help to maintain exercise capacity. This may be a realistic interpretation of the close correlation we found between exercise capacity and selenium in this study.

Whereas the present data do not conclusively prove a causal relationship between selenium and low exercise capacity in patients with CHF, they should serve as a strong incentive to the initiation of studies testing the effects of natural antioxidants on the clinical severity of CHF. In the meantime, however, physicians would be well advised to measure selenium in patients with an exercise inability disproportionate to their cardiac dysfunction and before putting them on the waiting list for heart transplantation in the most severe cases.

References

[1] Cowie MR, Mostred A, Wood DA et al. The epidemiology of heart failure. Eur Heart J 1997;18:208–25.
[2] Gheorghiade M, Bonow RO. Chronic heart failure in the United States. Circulation 1998;97:282–9.
[3] Levine B, kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236–41.

[4] Niebauer J, Pflaum CD, Clark AL et al. Deficient insulin-like growth factor 1 in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. J Am Coll Cardiol 1998;32:393–7.
[5] Swan JW, Anker SD, Walton C et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527–32.
[6] Keith M, Geranmayegan A, Sole MJ et al. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol 1998;31:1352–6.
[7] Mallat Z, Philip I, Lebret M, Chatel D, Maclouf J, Tedgui A. Elevated levels of 8-iso-prostaglandin F2 alpha in pericardial fluid of patients with heart failure. A potential role for in vivo oxidant stress in ventricular dilatation and progression to heart failure. Circulation 1998;97:1536–9.
[8] Münzel T, Harrison DG. Increased superoxide in heart failure. A biochemical baroreflex gone awry. Circulation 1999;100:216–8.
[9] Singal PK, Khaper N, Palace V, Kumar D. The role of oxidative stress in the genesis of heart disease. Cardiovasc Res 1998;40:426–32.
[10] Givertz MM, Colucci WS. New targets for heart failure therapy: endothelin, inflammatory cytokines and oxidative stress. Lancet 1998;352(suppl I):34–8.
[11] Dhalla AK, Hill M, Singal PK. Role of oxidative stress in transition of hypertrophy to heart failure. J Am Coll Cardiol 1996;28:506–14.
[12] Bauersachs J, Bouloumié A, Fraccarollo D, Hu K, Busse R, Ertl G. Endothelial dysfunction in chronic myocardial infarction despite increased vascular endothelial nitric oxide synthase and soluble guanylate cyclase expression: role of enhanced vascular superoxide production. Circulation 1999;100:292–8.
[13] Hornig B, Arakawa N, Kohler C, Drexler H. Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure. Circulation 1998;97:363–8.
[14] Singh RB, Rastogi SS, Verma R et al. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow-up. Br Med J 1992;304:1015–9.
[15] de Lorgeril M, Salen P, Martin JL et al. Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction. Final report of the Lyon Diet Heart Study. Circulation 1999;99:779–85.
[16] Neve J. Selenium as a risk factor for cardiovascular diseases. J Cardiovasc Risk 1996;3:42–7.
[17] Ge K, Yang G. The epidemiology of selenium deficiency in the etiological study of endemic diseases in China. Am J Clin Nutr (Suppl) 1993;57:259S–263S.
[18] Chariot P, Perchet H, Monnet I. Dilated cardiomyopathy in HIV-infected patients. N Engl J Med 1999;340:732.
[19] Huttunen JK. Selenium and cardiovascular diseases. An update. Biomed Environ Sci 1997;10:220–6.
[20] Mancini D, LeJemtel T, Aaronson K. Peak $\dot{V}O_2$. A simple yet enduring standard. Circulation 2000;101:1080–2.
[21] de Lorgeril M, Renaud S, Mammelle N et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454–9.
[22] Lamand M, Tressol JC, Ireland-Ripert J, Favier JC, Feinberg M. Répertoire Général des Aliments. Table 4 (Table de composition minérale). INRA Editions, 1996, Paris, France, ISBN: 2-7380-0700-7.
[23] Nève J, Chamart S, Molle L. Optimization of a direct procedure for the determination of selenium in plasma and erythrocytes using Zeeman effect atomic absorption spectroscopy. In: Brätter P, Schramel P, editors. Berlin, Germany: Walter de Gruyter, 1987:349–58.
[24] Nève J, Thomassen Y, Van Damme M. Cooperative study on measurements of concentrations of selenium in freeze-dried blood. Pure Appl Chem 1992;64:765–80.
[25] Steghens JP, Van Kappel AL, Riboli E, Collombel C. Simultaneous measurement of seven carotenoids, retinol and alpha-tocopherol in serum by high-performance liquid chromatography. J Chromatogr 1997;694:71–81.
[26] Speek AJ, Schrijver J, Schreurs WHP. Fluorometric determination of total vitamin C in whole blood by high performance liquid chromatography with pre-column derivatization. J Chromatogr 1984;305:53–60.
[27] Lopez-Anaya A, Mayersohn M. Ascorbic acid and dehydroascorbic acid simultaneously quantified in biological fluids by liquid chromatography with fluorescence detection and comparison with a colorimetric assay. Clin Chem 1987;33:1874–8.
[28] McMurray J, Chopra M, Abdullah I, Smith WE, Dargie HJ. Evidence of oxidative stress in chronic heart failure in humans. Eur Heart J 1993;14:1493–8.
[29] Diaz-Velez CR, Garcia-Castineiras S, Mendoza-ramos E, Hernandez-Lopez E. Increased malondialdehyde in peripheral blood of patients with congestive heart failure. Am Heart J 1996;131:146–52.
[30] Will JC, Ford ES, Bowman BA. Serum vitamin C concentrations and diabetes: findings from the third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 1999;70:49–52.
[31] Lykkesfeldt J, Christen S, Wallock LM, Chang HH, Jacob RA, Ames BN. Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes. Am J Clin Nutr 2000;71:530–6.
[32] Smith JL, Hodges RE. Serum levels of vitamin C in relation to dietary and supplemental intake of vitamin C in smokers and nonsmokers. Ann NY Acad Sci 1987;498:144–52.
[33] Rock CL, Thornquist MD, Kristal AR et al. Demographic, dietary and lifestyle factors differently explain variability in serum carotenoids and fat-soluble vitamins: Baseline results from the sentinel site of the olestra post-marketing surveillance study. J Nutr 1999;129:855–64.
[34] Gutteridge JMC, Halliwell B. The measurements and mechanisms of lipid peroxidation in biological systems. Trends Biochem Sci 1990;15:129–35.
[35] Palace VP, Hill MF, Farahmand F, Singal PK. Mobilization of antioxidant vitamin pools and hemodynamic function after myocardial infarction. Circulation 1999;99:121–6.
[36] Padayatti SJ, Levine M. Vitamin C and myocardial infarction: the heart of the matter. Am J Clin Nutr 2000;71:1027–8.
[37] Sullivan JF, Blotcky AJ, Jetton MM et al. Serum levels of selenium, calcium, manganese, copper and zinc in various human diseases. J Nutr 1979;109:1432–7.
[38] Prasad AS. Zinc in human health: an update. J Trace Elem Exp Med 1998;11:63–87.
[39] Burr ML, Fehily AM, Gilbert JF et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: the Diet and Reinfarction trial (DART). Lancet 1989;334:757–61.
[40] Ferrari R. Origin of heart failure: cardiac or generalized myopathy? Eur heart J 1999;20:1613–4.
[41] Coats AJS. Exercise training for heart failure. Coming of age. Circulation 1999;99:1138–40.
[42] Bernardi L, Spadacini G, Bellwon J et al. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. Lancet 1999;351:1308–11.
[43] Inoko M, Konishi T, Matsusue S, Kobashi Y. Midmural fibrosis of left ventricle due to selenium deficiency. Circulation 1998;98:2638–9.

[44] de Lorgeril M, Salen P. Selenium and chronic heart failure. Circulation 2000;101:E74.
[45] Xu GL, Wang SC, Gu BQ et al. Further investigation on the role of selenium deficiency in the etiology and pathogenesis of Keshan disease. Biomed Environ Sci 1997;10:316–26.
[46] Recommended Dietary Allowances. Food and Nutrition Board, National Research council, 10ed. National Acad Press, 1989.
[47] Yang GQ, Xia YM. Studies on human dietary requirements and safe range of dietary intakes of selenium in China and their application in the prevention of related endemic diseases. Biomed Environ Sci 1995;8:187–201.
[48] Coats AJ. Origins of symptoms in heart failure. Cardiovasc Drugs Ther 1997;11(suppl 1):265–72.
[49] Takahashi K, Newburger PE, Cohen HJ. Glutathione peroxidase protein. Absence in selenium deficiency states and correlation with enzymatic activity. J Clin Invest 1986;77: 1402–4.
[50] Burk RF, Hill KE, Selenoprotein P. A selenium-rich extracellular glycoprotein. J Nutr 1994;124:1891–7.
[51] May JM, Mendiratta S, Hill KE, Burk RF. Reduction of dehydroascorbate to ascorbate by the selenoenzyme thioredoxin reductase. J Biol Chem 1997;272:22607–10.
[52] Zelis R, Flaim SF. Alterations in vasomotor tone in chronic heart failure. Prog Cardiovasc Dis 1982;24:437–59.
[53] Okita K, Yonezawa K, Nishijima H et al. Skeletal muscle metabolism limits exercise capacity in patients with chronic heart failure. Circulation 1998;98:1886–91.
[54] Drexler H. Endothelium as a therapeutic target in heart failure. Circulation 1998;98:2652–5.
[55] Hambrecht R, Fiehn E, Weigl C et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 1998;98:2709–15.
[56] Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci USA 1989;86:6377–81.
[57] Meister A. Glutathione-ascorbic acid antioxidant system in animals. J Biol Chem 1994;269:9397–400.