

*Original Article***Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs**

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Abstract

Background. Left ventricular hypertrophy (LVH) is very frequent in haemodialysis patients. Only few investigations have reported its regression, and only by the use of antihypertensive drugs. Because volume load is at least as important as pressure load, we investigated whether persistent strict volume control by ultrafiltration alone may be effective in improving LVH.

Methods. Using blood pressure (BP) and cardiac dimensions as a guide, we treated all hypertensive patients in our dialysis unit during the 3 times weekly dialysis sessions for 4 h per session with as much ultrafiltration as they could stand. If they gained too much weight an extra isolated ultrafiltration (UF) session was applied. Special attention was given to dietary salt restriction.

The study group of all 15 patients in whom echocardiographic assessment had been made at least 1.5 years previously was selected retrospectively, and we acknowledge that important confounding factors might not have been controlled for.

Cardiothoracic index (CTI) was estimated on the chest X-ray. Diameters of left atrium (LA), left ventricle systolic (LVS) and diastolic (LVD), interventricular septum (IVS), posterior wall (PW), and left ventricular mass index (LVMI) were estimated by standard echocardiographic methods.

Results. Mean arterial pressure of the study group had been lowered by UF before the first echocardiogram from predialysis 136 ± 11 to 101 ± 14 and from postdialysis 119 ± 8 to 92 ± 12 mmHg. During a mean follow-up period of 37 ± 11 months LVMI decreased from 175 ± 60 to 105 ± 11 g/m². CTI decreased further from 48 ± 3 to $43 \pm 4\%$, while significant decreases of LA (22.5 ± 3 to 19.9 ± 4 mm/m²), LVS (18.7 ± 4 to 15.9 ± 3 mm/m²) and LVD (28.3 ± 4 to 24.0 ± 3 mm/m²) were seen in all patients. There also was a further decrease in both pre- and postdialysis BP to $116 \pm 12/73 \pm 7$ and $105 \pm 7/65 \pm 3$ mmHg respectively.

Conclusion. The results of this uncontrolled retrospective study suggest that good long-term BP control and a decrease of LVM can be achieved by continuous efforts to control hypervolaemia. The decrease in volume may be even more important than pressure reduction to achieve this goal.

Key words: echocardiography; haemodialysis; hypertension; left ventricular hypertrophy; ultrafiltration

Introduction

Cardiac death is up to 20 times more frequent in uraemic patients than in the general population [1,2]. Left ventricular hypertrophy (LVH) has been identified as the most potent single risk factor in a general population [3], and the same applies to haemodialysis (HD) patients [4]. It is reported that LVH is mostly persistent and progressive, despite antihypertensive drug treatment [5]. Only two studies demonstrated regression in HD patients [6,7], but only with the use of antihypertensive drugs.

Generally the genesis and persistence of LVH in patients with hypertension is thought to be caused by the pressure load imposed upon the left ventricle by systemic hypertension. In HD patients, however, volume load also contributes to the maintenance of LVH. According to the LaPlace law, volume-increments lead to a proportional increase in wall thickness in order to normalize wall stress. The accompanying increase in muscle mass, however, needs to be considerably greater in volume overload as compared to pressure overload, because of the increased diameter of the left ventricular cavity. Thus although many other factors may be involved, slight but continued dilatation of the heart may be a dominant one.

Therefore we hypothesized that in HD patients in whom an acceptable blood pressure reduction (below 140/90 mmHg) has been achieved by reduction of fluid overload without antihypertensive drugs, and in whom signs of LVH are demonstrable, regression of LVH can be obtained by long-term adoption of such a policy.

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Subjects and methods

Four years ago, we started a programme consisting of re-emphasis on salt restriction, stopping all antihypertensive medication, intensified ultrafiltration (UF) during dialysis and occasional isolated UF sessions. As many patients interpret salt restriction as 'no added salt', we repeatedly explained its importance also to the family members. When they continued to gain too much weight between dialysis, an extra UF session was added, which also acted as a 'sanction' on non-compliance. Some patients who had been told by previous doctors 'that their blood pressure would never become normal any more' became more compliant when they realized the benefits of our approach. Thus, mean interdialytic weight gain of this group, which had been 2.8 ± 1.4 kg decreased to 1.6 ± 0.8 kg as a result of these efforts. Our aim was not only to normalize blood pressure, but also to achieve normal cardiac dimensions as evidenced by a cardiothoracic index (CTI) below 0.50, and normal dimensions of cardiac compartments measured by echocardiography. By this approach, satisfactory blood pressure (BP) levels were obtained in the large majority of the patients.

In the present study we collected all cases in whom an echocardiogram showing LVH at least 1.5 years before was available. None of them has been treated with drugs during the follow-up period. Only patients with haematocrit levels higher than 24% were admitted to the study. Fifteen patients (8 men and 7 women) fulfilled these criteria. Their mean age 40 ± 14 years. None had residual renal function. Eight of them were on erythropoietin treatment, which had been started between 6 and 18 months before the first echo. This had resulted in an increase of haematocrit (Hct) from of mean of 23.4 to 29.1% in these eight patients. The dose was not changed during follow-up.

The mean time on dialysis was 25 ± 11 months. They had been hypertensive during the early dialysis periods (pre-dialysis blood pressures $191 \pm 20/109 \pm 7$ mmHg) but at the time of the first echocardiography (as a result of the above-mentioned policy) blood pressure was as low as could possibly be achieved without severe complaints.

Blood pressures given in this article are the mean of at least three consecutive pre-dialysis recordings (sphygmomanometer). Haemodialysis was applied for at least 4 h thrice weekly, using mostly acetate dialysate with Na concentration 138 mEq/l. If necessary extra UF sessions were added.

Cardiothoracic index was calculated from a 2-ri chest X-ray. Echocardiography was performed using a Hewlett-Packard ultrasonoscope with a 2.5 MHz transducer. M-mode, two-dimensional Doppler recordings were simultaneously obtained with electrocardiography according to the recommendation of the American Society of Echocardiography. The echocardiographer was not always the same person, but he/she was not aware of previously recorded values. Left ventricular muscle mass (LVM) was calculated following the equation described by Devereux and Reichek [8]: $LVM = 1.04 \times [(IVS + LVDd + PWT)^3 - (LVDd)^3] - 136$ (g).

Statistical analysis: All results are reported according to an efficacy sample analysis. Data are expressed as mean \pm SD. The study group was determined by means of an unpaired Student's *t* test for quantitative variables. For comparisons of serial changes in BP, LVMI, LA, LVD etc., repeated-measures ANOVA was performed to examine treatment differences and interactions

Results

All of the patients had been previously hypertensive and sometimes overhydrated as evidenced by cardiac

dilatation and slight oedema (Table 1). The observation period started after maximal ultrafiltration had been applied and BP was below 140/90 mmHg postdialysis without drugs. Their average time on dialysis before this was achieved varied between 8 months and 4 years. None of the patients had had myocardial infarction and valve leakage was not detected.

The total follow-up period after the first echo varied between 19 and 76 months (mean 37 ± 15 months). During this time, continuous efforts were made to reduce BP further if necessary. This resulted in a gradual further improvement in several of the measured parameters. Table 1 also shows the main results at the start of intensified treatment and at the beginning, during and at the end of the observation period.

Mean predialysis BP values of the study group were $139 \pm 20/83 \pm 11$ mmHg at the beginning and $116 \pm 12/73 \pm 7$ mmHg at the end of observation period. Corresponding post-dialysis values were $126 \pm 8/75 \pm 10$ mmHg and $105 \pm 7/65 \pm 3$ mmHg respectively. This decrease in BP was accompanied by a decrease in the cardiac dimensions, even if they had been within normal limits at the beginning. Thus cardiothoracic index had been below 0.48 in half of the patients but decreased further in every subject (mean decrease from 0.48 to 0.43). The same tendency was seen for left atrial, left ventricular systolic, and diastolic diameters, which decreased by 10, 15 and 13% respectively (see Table 2). Despite these decreases, suggesting some further decrease in extracellular and blood volume, body-weight increased slightly (mean value 53 ± 13 kg before and 55 ± 12 kg after treatment), reflecting improved nutritional state. A small but not significant increase in haematocrit (28.4 ± 5 to 28.6 ± 4 , $P > 0.05$) was also present.

The most important finding was a decrease in wall thickness of the left-ventricle which concerned the posterior wall (-23.4%) as well as the interventricular septum (-23%) and occurred despite a decrease in ventricular diameter. Thus the calculated ventricular mass index decreased dramatically from 175 to 105 g/m².

No significant change in left ventricular ejection fraction was observed although an increase from 43 to 61% was noticed in the only patient whose value was below 50% (mean value for the group were 65% before and 68% after treatment).

Discussion

In terminal renal failure, both before and after the start of dialysis, LVH is frequent and initially correlates with blood pressure levels [9]. Despite blood-pressure reduction by drugs and/or dialysis, LVH remains, according to most authors [9,10]. Thus the possibility that factors other than hypertension are operative in renal patients should be considered. Changes in myocardial histology (fibrosis and decreased capillary density) have recently been described [1]. They are also present in uraemic animals and patients without

Table 1. Results of experimental group (n = 15) during haemodialysis

	BW (kg)	CTI (%)	Pre-dialysis		Post-dialysis		Haematocrit (%)
			SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	
At start of HD	55.7 ± 13.1	54 ± 3	191 ± 20	109 ± 7	163 ± 12	97 ± 7	26.7 ± 5.2
At first echo	53.2 ± 13.2	48 ± 2	139 ± 20	83 ± 11	126 ± 18	75 ± 10	28.4 ± 5
<i>P</i> ^a <	NS	0.001	0.001	0.001	0.001	0.001	NS
In between (n = 9)*	53.3 ± 12.5	45 ± 3	129 ± 16	80 ± 10	117 ± 13	70 ± 6	28.6 ± 4.2
<i>P</i> ^b <	NS	0.01	NS	NS	NS	NS	NS
At end of observation	55 ± 12	43 ± 4	116 ± 12	73 ± 7	105 ± 7	65 ± 3	28.6 ± 4.0
<i>P</i> ^c <	NS	0.001	0.001	0.001	0.001	0.001	NS

HD, haemodialysis; echo, echocardiogram; CTI, cardiothoracic index; SBP, systolic blood pressure; DBP, diastolic BP; BW, body-weight; NS, non-significant.

^aStart of HD *vs* first echo; ^bstart of HD *vs* in between (second echo); ^cfirst echo *vs* end of observation respectively. *Taken between 4 and 10 months after the first echo.

Table 2. Results of echocardiographic examinations measurements in experimental group (n = 15)

	LA (mm/m ²)	LVDd (mm/m ²)	LVSd (mm/m ²)	PWT (mm/m ²)	IVS (mm/m ²)	LVMI (g/m ²)
At first echo	22.5 ± 4.3	28.3 ± 3.8	18.7 ± 4.4	8.79 ± 1.57	8.73 ± 1.86	175 ± 60
<i>P</i> ^a <	0.05	0.05	NS	0.01	0.05	0.01
In between (n = 9)	20.5 ± 1.9	25.6 ± 2.5	17.4 ± 2.2	6.95 ± 1.2	7.29 ± 0.92	136 ± 70
<i>P</i> ^b <	NS	NS	NS	NS	NS	0.05
At end of observation	19.9 ± 3.9	24.0 ± 3.3	15.9 ± 2.9	6.73 ± 0.91	6.70 ± 0.90	105 ± 39
<i>P</i> ^c <	0.05	0.05	0.01	0.001	0.001	0.001

LA, left atrium diameter; LVDd, left ventricle end diastolic diameter; LVSd, left ventricle end systolic diameter; PWT, posterior wall thickness; IVS, interventricular septum thickness; LVMI, left ventricular mass index (results normalized for body surface area).

^aFirst echo *vs* second echo; ^bsecond echo *vs* end of observation; ^cfirst echo *vs* end of observation respectively.

hypertension, and may be (partly) irreversible. Factors responsible for these changes may be hyperparathyroidism, sympathetic activity [11], reflections of the pulse wave due to stiffened arteries [12] and anaemia. Although the mean Hct values did not change significantly after the first echo, it cannot be excluded that the previous rise in Hct in some patients contributed to improvement of LVH during the first months of observation.

Our hypothesis was that LVH is mainly caused by fluid overload in combination with high blood pressure and can be brought to regression by intensified UF and occasionally isolated UF sessions. The most important results of our study can be deduced from Tables 1 and 2. After a period of intensified UF (before the first echocardiogram was taken) we had reached acceptable blood pressure (pre-dialysis 139/83 and post-dialysis 126/75 mmHg), and clear decrease in cardiac volumes. Calculated left ventricular muscle mass was 175 ± 60 g/m², exceeding normal values considerably. After a prolonged period of HD and UF we reached (without drug) a calculated left ventricular muscle mass of 105 ± 39 g/m². In this period another 38% decrease of ventricular systolic cavity volume was accompanied by a decrease of the calculated muscle mass of 40%. It is known that volume changes of the heart can lead to errors in the calculation of the LVM [13] and consequently our results may have over-

estimated the real change. Yet this applies also to other studies [6,7] and the observed changes were too large to be explained by methodological error.

We would like to stress that we did not try to define 'dry weight' (which is notoriously difficult!) by one single parameter, but continuously tried to decrease blood pressure as much as possible without severe complaints. During this process the values for cardiac volume, as measured by X ray and echocardiography, which had been within the high range of normal at the time of the first echocardiogram, showed a progressive further decrease during continuing treatment in every patient. During this period, blood pressure became increasingly easier to control.

With few exceptions the majority of authors report increased internal dimensions of left ventricle cavities as being characteristic and frequent in haemodialysis patients. It is moderate in extent, the mean values lying around normal upper limit [12]. Foley *et al.* [10] recently identified left ventricular dilatation as an extremely strong risk factor. This probably implies that also lesser increments of cardiac diameters have an unfavorable effect on hypertrophy.

In the literature most publications seem to support irreversibility of LVH. One group of HD patients showed progression of hypertrophy and had a very bad prognosis [5]. Hüting *et al.* [14] followed 61 normotensive HD patients for 2.5 years and saw no

decrease in the LVH. Interestingly, left atrium dimension increased in that group. The same group [15] described a group of patients who had been normotensive due to excellent volume control for over 3 years, yet LVH persisted. A group of patients followed-up for 41 months after successful renal transplantation also showed no decrease in the degree of hypertrophy [16], but decrease in LVH was described in another study [17]. In our patients, like in those of the Lyon group [15,18] some LVH persisted, probably due to irreversible changes. The remaining discrepancies in the literature may be related to differences in patient populations.

To the best of our knowledge, only two publications reported regression of LVH in HD patients, but this result was attributed to the use of antihypertensive drugs. Canella *et al.* [6] reported on a group of eight patients who were treated simultaneously with a beta-blocker, a converting-enzyme inhibitor, and a calcium-channel blocker. After 24 month of treatment, decreases in BP, septum thickness (but not posterior wall), and left ventricular mass index were found. However, decrease in BP took many months to occur and there was also a striking decrease in left ventricular diastolic diameter from 62.6 to 54.9 mm. This raises the question of whether it was the drug treatment or a gradual decrease in intravascular volume that was responsible for the results. The authors indeed considered the latter possibility but found it unlikely because interdialytic weight gains were the same as in the control group. However, interdialytic weight gain is an indication of the patients' compliance, not of absolute volume control.

London *et al.* [7] compared the effect of two different drugs, a converting enzyme inhibitor and nitrendipine over 12 months, in a carefully conducted prospective study. A similar decrease in mean arterial pressure to 107 and 109 mmHg respectively was achieved. This resulted in significant decrease in LV mass index of -25% in perindopril-treated patients only. There was, however, also a striking decrease in LV diastolic diameter from 54.3 to 49.9 mm in that group, while this value remained the same in the nitrendipine-treated group. The authors attribute this to a decrease in preload caused by dilatation and increased compliance of the venous system. In other words some permanent redistribution of the blood volume was postulated. This result is very similar to that of Canella and a gradual decrease in blood volume may also have occurred in this study, somehow facilitated by the converting-enzyme blockade. Anyhow both studies support the importance of decreased left ventricular volume for the regression of hypertrophy.

The decreases reported in the present study were more pronounced. More importantly they were obtained without the use of antihypertensive drugs. It is well known that correction of anaemia can cause regression of hypertrophy in dialysis patients. Although the mean Hct values did not change significantly after the first echo, it cannot be excluded that the previous rise in Hct in some patients contrib-

uted to improvement of LVH during the first months of observation.

It could be argued that the 15 patients described in this study were unusually responsive to the applied treatment. However, the selection criterion was based on the accidental availability of two echocardiograms, because systematic application of this technique at that time was not possible for organizational and financial reasons. Of the remaining similarly treated 29 patients in our centre only three could not be adequately controlled without drugs (data not shown).

The fact that no hypotensive drugs were needed to control BP, while the percentage of drug-treated HD patients varies from 40 to 90% in world literature can only be explained by better awareness of our dialysis team of the need for volume control. Earlier publications indicated that at least 90% of hypertension in dialysis patients is volume dependent [19]. Since then this question has not been systematically investigated, but the virtual absence of hypertension in a large group of patients with good volume control [20] supports this view. While the latter group used long dialysis session, our results show that a similar result can be obtained by shorter sessions (shorter, for instance, than sessions in the Tassin experience [20]), provided the doctors are convinced of the necessity to reduce 'volume'.

Few attempts have been made to distinguish between the factors of 'pressure' and 'volume' or to identify volume retention as an independent risk factor. There is no doubt that 'silent' overhydration persists in many HD patients [21]. A recent review [22] came to the conclusion that same applies to CAPD patients: LVH did not regress during this treatment but is rapidly reversed after transplantation.

If volume-induced hypertension can be controlled by hypotensive drugs, the overhydration may not be corrected. In other words, lowering BP without correcting volume may be less effective in reducing LVH. On the other hand, decrease in LVH may facilitate blood-pressure control because LVH leads to decreased diastolic compliance, which favours sudden drops in blood pressure during ultrafiltration, making achievement of 'dry weight' more difficult. Such circulatory instability is also enhanced by antihypertensive drugs. These considerations are supported by the further decrease in blood pressure along with the progressive decreases in volume and muscle mass observed by us.

Our results illustrate that strict volume control not only decreases blood pressure, but also that it takes time and continuous efforts to reduce dilated cardiac compartments, which in turn facilitates blood pressure control, as was also emphasized by others [20]. The present study shows both the feasibility and the beneficial effects of such efforts.

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