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Long-term blood pressure monitoring and echocardiographic findings in patients with end-stage renal disease: reverse epidemiology explained?

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ABSTRACT

Background: In patients with end-stage renal disease (ESRD) hypertension is common and often leads to left ventricular (LV) hypertrophy and diastolic dysfunction, but hypotension at the onset of dialysis is associated with increased mortality. We studied blood pressure data over longer periods of time in patients on haemodialysis and related them to echocardiographic outcome, in order to elucidate these contradictory findings.

Methods: In 50 haemodialysis patients mean arterial pressure (MAP) and pulse pressure (PP) were calculated in the first three months of haemodialysis, the complete period from the start of haemodialysis until echocardiography and the last three months of haemodialysis before echocardiography. Hypertension load, pulse pressure and interdialytic weight gain were quantified and related to echocardiography.

Results: LV mass index was associated with MAP in all three periods, and also with the hypertension load, PP and PP load. In patients with LV dilatation, MAP and PP averaged over the complete period of dialysis were 5 to 7 mmHg higher than in patients without LV dilatation. Blood pressure parameters were the same in patients with or without LV diastolic dysfunction or systolic dysfunction. Systolic dysfunction was more frequent in patients undergoing long-term haemodialysis treatment. Interdialytic weight gain was not associated with any of the echocardiographic variables.

Conclusion: When long-term blood pressure values are considered, hypertension is associated with parameters of early cardiac damage such as increased LV mass index and not with parameters of advanced heart failure such as systolic dysfunction. This supports the hypothesis that the presence of advanced heart failure reciprocally influences blood pressure in a negative way, thereby explaining the 'reverse epidemiology' of blood pressure and mortality in ESRD.

KEYWORDS

Echocardiography, end-stage renal disease, heart failure, haemodialysis, left ventricular hypertrophy

INTRODUCTION

The high mortality among patients with chronic renal failure is mainly attributed to an increased incidence of atherosclerotic cardiovascular events.[1] In population-based studies, hypertension is one of the strongest risk factors for cardiovascular morbidity and mortality. In contrast to the general population, high blood pressure is not associated with increased mortality in patients on haemodialysis: on the contrary, patients with hypotension at the onset of dialysis or during specified short periods of time have a 1.5 to 3 times higher probability of death in follow-up periods of three to seven years.[2-4] This counter-intuitive finding,[4,5] known as reverse epidemiology,[6] has even lead to discussion in the literature as to whether or

not hypertension in haemodialysis patients should be treated as vigorously as in patients without renal disease.[7-9] If hypotension is considered to be the result of forward failure, it is explainable that a low blood pressure during a fixed period of time is associated with higher mortality: the low blood pressure cohort will contain the largest proportion of patients with severe forward failure. Forward failure can thus be seen as the confounding variable causing both hypotension and increased mortality.

In patients with end-stage renal disease, information is lacking regarding the development of forward failure, manifesting as systolic dysfunction and hypotension. One would expect that patients with significant hypertension at the start of dialysis first develop left ventricular (LV) hypertrophy and subsequently systolic dysfunction, ultimately resulting in hypotension. Blood pressure data in dialysis patients over longer periods of time are scarce, and successive information on cardiac performance even more so.

In our centre – a large outpatient centre for haemodialysis and peritoneal dialysis – we consequently registered blood pressure values and interdialytic weight gain in patients on haemodialysis for the last 13 years. The aim of this cohort study was to observe the relation of blood pressure with various echocardiographic characteristics of heart disease: we hypothesise that high blood pressure is associated with early signs of cardiac dysfunction, and that hypótension may become prominent when a stage of more advanced heart failure has developed.

Table 1 *Patient characteristics*

	Patients (n=50)
Age (years)	58.7 ± 12.4*
Gender (male/female)	32/18
Body mass index (kg/m²) ± SD	23.4 ± 3.6
Causes of end-stage renal disease (%)	
• Glomerulonephritis	10
• Interstitial nephritis	22
• Cystic kidney diseases	20
• Other congenital and hereditary kidney diseases	4
• Renal vascular disease	12
• Diabetes mellitus	4
• Other multisystem diseases	6
• Other	4
• Unknown	18
• Duration of renal replacement therapy (years)	4.0 (0.5-29.0)
• Diabetes mellitus (%)	8
Smoking (%)	
• Ever	46
• Never	54
Hypercholesterolaemia (%)†	34
History of cardiac disease (%)‡	66

***Males 55.1 ± 12.5, females 62.5 ± 11.8 years. †Defined as a total cholesterol ≥6 mmol/l or treatment with cholesterol-lowering drugs. ‡Defined as overt angina pectoris, myocardial infarction, cardiac hypertrophy, valvular dysfunction or heart failure.**

METHODS

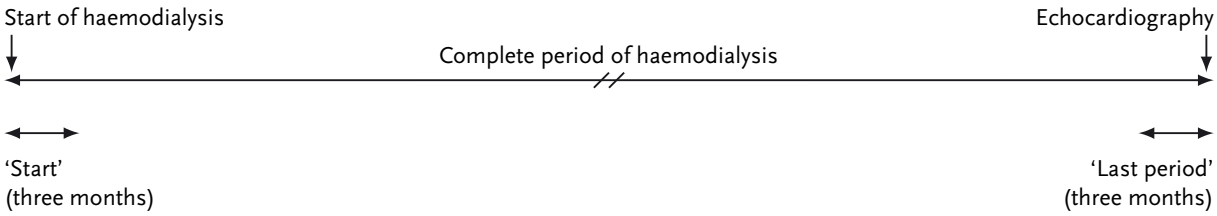
Patients

Patients from our haemodialysis department who underwent echocardiography between June 1999 and June 2003 (n=50) were selected for this study. Patient characteristics are shown in *table 1*. At the time of echocardiography, 42 patients were treated with haemodialysis three to four times a week and eight patients with haemodialysis more than four times a week. Overall, median time on renal replacement therapy was 4.0 years with a range of 0.5 to 29.0 years (mean ± SD 7.0 ± 7.6 years). Twenty-two patients had been on dialysis for ≤3 years, eleven for 3 to 6 years, five for 6 to 10 years, eight for 10 to 20 years and four for >20 years. Patients' medical history, family history and cardiovascular risk factors were recorded. Hypercholesterolaemia was defined as a total cholesterol of ≥6 mmol/l or the use of cholesterol-lowering drugs. Cardiac history was considered positive if a patient had experienced angina pectoris or a myocardial infarction, or was known to have cardiac hypertrophy, valvular dysfunction or heart failure before echocardiography was performed (*table 1*).

Blood pressure and interdialytic weight gain

Blood pressure was recorded in a computerised database for our entire population from the start of renal replacement therapy until the time of echocardiography. This database included systolic and diastolic blood pressure values predialysis and postdialysis at every dialysis session, at least three times a week. Predialysis blood pressure was measured upon arrival to the clinic, generally 10 to 15 minutes before puncture of the fistula. Postdialysis blood pressure was measured after disconnection from the dialysis monitor, thus after reinfusion of the blood. Mean arterial pressure (MAP) and pulse pressure (PP) were calculated before and after a dialysis session over three time intervals: a) the first three months of haemodialysis; b) the complete period from the start of haemodialysis until echocardiography; c) the last three months of haemodialysis before echocardiography was performed (*figure 1*). The intradialytic declines in MAP and PP were calculated by subtracting the values after haemodialysis from the values before haemodialysis; the result was expressed as a percentage of the predialysis MAP and PP. To obtain a measure of the 'hypertension load' for an individual patient, the percentage of time on haemodialysis

Figure 1 *Time intervals of blood pressure recordings*



treatment in which predialysis MAP was >120 mmHg was calculated. A MAP ≥100 mmHg has been demonstrated to increase the risk of cardiac pathology.[9] Because our population had a high average MAP (>100 mmHg) we chose a cut-off level of 120 mmHg to study the influence of high blood pressure. Analogously, as a measure of the pulse pressure load, the percentage of time on haemodialysis treatment in which predialysis PP was ≥75 mmHg was calculated. This cut-off level was chosen because a PP of ≥75 mmHg is associated with a higher risk of cardiac disease.[10]

The difference between predialysis and postdialysis body weight was considered indicative of interdialytic weight gain (IDWG) between the sessions; this value was expressed as a percentage of the dry weight of a patient. Again, as a measure of volume overload the percentage of time on dialysis in which relative IDWG was ≥4% was calculated.[11]

Echocardiographic assessment

Two-dimensional and M-mode echocardiographic examinations were performed using a Philips Sonos 5500 (Philips Andover, Massachusetts, USA) with a 3.5 MHz transducer. Echocardiographic examinations were performed to obtain information on heart function as part of the routine work-up of patients on haemodialysis. The examination was performed on a midweek nondialysis day. All examinations were assessed by an independent physician. At least three consecutive cardiac cycles were analysed for each patient. The echocardiographic parameters obtained from two-dimensional and M-mode recordings were interventricular septal thickness (IVST), LV posterior wall thickness (LVPWT), LV internal dimension (LVIDD) all at end diastole, LV internal dimension at end systole (LVIDS), and left atrial dimension (LAD). End-diastolic LV dimensions were used to calculate LV mass by a formula validated by necropsy comparison ($r = 0.90$, $p<0.001$)[12] and to assess relative wall thickness (posterior wall thickness to chamber ratio).[13] To account for the impact of body size, LV mass was indexed for body surface area (LV mass index).[14] Fractional shortening, a parameter of LV contractility which is comparable with ejection fraction, was calculated according to the formula: ((LVIDD – LVIDS) / LVIDD) x 100%.[15] Ejection fraction was not measured because it requires biplane analysis, which is frequently not feasible in haemodialysis patients. The presence of LV hypertrophy, LV dilatation, LV diastolic dysfunction, and LV systolic dysfunction were carefully assessed in each patient.

Statistical analysis

Calculations were made with SPSS for windows (release 11.5, 2002). Parameters were given as mean ± SD, unless they showed a skewed distribution, in which case they were presented as median (range). Continuous variables were analysed by means of regression and correlation, continuous and categorical variables by means of t-tests and relations between categorical variables by χ^2 tests or Fisher's exact tests where appropriate. As a first step, univariate analysis was performed to discover relationships between different variables and the echocardiographic parameters. Next, the variables that showed a significant association were analysed in a multivariate model to eliminate the influence of potential confounders. All tests were two-tailed, and a p value of 0.05 or less was considered to indicate significance.

RESULTS

The predialysis MAP, averaged over the complete period from the start of haemodialysis until echocardiography, was 104 ± 10 mmHg. Predialysis MAP was higher in the first three months of haemodialysis, and lower in the last three months of dialysis before echocardiography (*table 2*). Postdialysis MAP was 8 to 9 mmHg lower than predialysis MAP, and showed the same trend over time. The percentage of time on dialysis in which severe hypertension existed was quite low (median 6%). The intradialytic fall in MAP (predialysis minus postdialysis MAP) did not change throughout the complete dialysis period. Predialysis PP remained the same throughout the dialysis period; postdialysis PP decreased somewhat, so that the intradialytic PP difference showed a trend towards increase. Interdialytic weight gain was somewhat lower in the first three months of dialysis, probably explained by an effect of residual diuresis.

Table 2 *Blood pressure and interdialytic weight gain characteristics*

	Start of dialysis**	Complete period of dialysis**	Last period of dialysis**
MAP predialysis (mmHg)	108 ± 11	104 ± 10	102 ± 12
MAP postdialysis (mmHg)	99 ± 16	96 ± 9	93 ± 11
MAP >120 mmHg predialysis (%)*	3 (0-86)	6 (0-60)	0 (0-56)
Intradialytic MAP difference (%)	8.7 ± 7.6	8.6 ± 5.1	7.7 ± 6.5
PP predialysis (mmHg)	65 ± 17	64 ± 16	64 ± 17
PP postdialysis (mmHg)	58 ± 14	55 ± 14	53 ± 14
PP ≥75 mmHg predialysis (%)*	20 (0-100)	15 (0-93)	16 (0-100)
Intradialytic PP difference (%)	11 ± 13	15 ± 10	16 ± 12
Interdialytic weight gain (%)	2.2 ± 1.2	2.5 ± 1.0	2.5 ± 1.1
Interdialytic weight gain ≥4% (%)*	3 (0-100)	5 (0-75)	3 (0-85)

MAP = mean arterial pressure; PP = pulse pressure. *Median percentage of dialysis sessions with these values. **See also text: 'start' refers to the first three months of haemodialysis, 'complete period' to the complete period from start of haemodialysis until echocardiography, and 'last period' to the last three months of haemodialysis before echocardiography was performed.

The results of echocardiography are given in *table 3*, in which the parameters are put in order as expected to occur *in vivo* in heart failure.[16] Most of the parameters were abnormal, especially those of early stage cardiomyopathy such as LV hypertrophy and LV diastolic dysfunction. LV mass index was slightly increased in men, and more increased in women. This was preferentially due to an increase in end-diastolic volume, rather than to concentric LV hypertrophy: LV internal dimension at end diastole was increased, LV dilatation occurred frequently and there was no increase in LV posterior wall thickness, nor in relative wall thickness, and only a slight increase in interventricular septal thickness. Severe heart failure, of which the echocardiographic parameters are given at the bottom of *table 3*, was less frequently present.
In eight patients there were no signs of LV hypertrophy, diastolic dysfunction, systolic dysfunction or diminished fractional shortening. Thirteen patients had only structural abnormalities: they had LV hypertrophy and/or diastolic dysfunction but preserved systolic function; five patients had LV hypertrophy and diminished systolic function (structural and functional abnormalities). Of the remaining 24 patients 14 had LV dilatation with preserved systolic function and ten had LV dilatation and diminished systolic function (also structural and functional abnormalities).
Results of a univariate regression analysis showed that LV mass index was associated with MAP in the first three months of dialysis and in the complete period of dialysis (*table 4*). Also the hypertension load (time with MAP >120 mmHg) was positively correlated with LV mass index, and we found the same for PP and PP load (time with PP ≥75 mmHg), although correlations for the latter were weak. Other results of the univariate regression analysis were the predominant negative associations of MAP and PP with fractional shortening. Although not all associations reached significance, it seemed that the higher the MAP and PP, the lower the fractional shortening, a sign of LV dysfunction. Furthermore, the larger the fall in MAP during dialysis, the lower the fractional shortening appeared to be (β -0.45, p=0.006, *table 4*). Correlations with blood pressure parameters and LV mass in the three months before echocardiography were not significant.
When patients were divided according to presence or absence of LV hypertrophy, there were remarkable differences in the blood pressure parameters throughout their dialysis life (*table 5*): although the differences did

Table 3 *Cardiac parameters, arranged according to supposed pathophysiology of heart failure*[15]

Echocardiographic variables	Mean ± SD/%	Normal value
LV hypertrophy (%)	62	0
LV mass index, men (g/m²)	136 ± 40	<132
LV mass index, women (g/m²)	140 ± 40	<101
LV diastolic dysfunction (%)	44	0
LV posterior wall thickness (cm)	0.97 ± 0.14	0.7-1.1
Interventricular septal thickness (cm)	1.13 ± 0.20	0.7-1.1
Relative wall thickness	0.36 ± 0.07	<0.45
LVIDD (cm)	5.6 ± 0.7	3.6-5.4
LV dilatation (%)	48	0
LA dimension (cm)	4.5 ± 1.1	2.3-4.5
LV systolic dysfunction (%)	28	0
LV fractional shortening (%)	33 ± 8	25-45

LV = left ventricular; LVIDD = LV internal dimension at end diastole; LA = left atrial.

Table 4 *Results of univariate regression analysis*

	LVMI		LV fractional shortening	
	β	P	β	P
MAP – start	0.51	0.001	-0.25	0.13
MAP – complete period	0.50	0.001	-0.27	0.10
MAP >120 – start*	0.34	0.03	0.08	0.62
MAP >120 – complete period*	0.37	0.02	-0.10	0.55
Intradialytic MAP difference – start	0.15	0.42	-0.09	0.62
Intradialytic MAP difference – complete period	0.20	0.22	-0.45	0.006
PP – start	0.34	0.04	-0.44	0.007
PP – complete period	0.36	0.02	-0.24	0.15
PP ≥75 – start*	0.25	0.12	-0.38	0.02
PP ≥75 – complete period*	0.24	0.14	-0.22	0.19

LV = left ventricular; LVMI = LV mass index; MAP = mean arterial pressure; PP = pulse pressure. The extensions 'start', and 'complete period' refer to the first three months of dialysis and the complete period from start of dialysis until echocardiography, respectively. *Percentage of dialysis sessions with these values.

Table 5 *Blood pressure and pulse pressure in patients with and without left ventricular hypertrophy*

	LVH absent (n=19)	LVH present (n=31)	P
MAP – start (mmHg)	108 ± 9	108 ± 12	0.99
MAP – complete period (mmHg)	101 ± 11	106 ± 8	0.08
MAP – last period (mmHg)	99 ± 13	103 ± 11	0.24
MAP >120 – start (%)*	11 ± 21	19 ± 23	0.23
MAP >120 – complete period (%)*	9 ± 12	12 ± 15	0.50
MAP >120 – last period (%)*	5 ± 1	10 ± 17	0.34
Intradialytic MAP difference – start (mmHg)	8 ± 6	11 ± 8	0.36
Intradialytic MAP difference – complete period (mmHg)	9 ± 6	9 ± 5	0.98
Intradialytic MAP difference – last period (mmHg)	6 ± 7	10 ± 7	0.09
PP – start (mmHg)	63 ± 13	66 ± 19	0.55
PP – complete period (mmHg)	61 ± 12	66 ± 17	0.21
PP – last period (mmHg)	61 ± 16	65 ± 17	0.38
PP ≥75 – start (%)*	20 ± 22	33 ± 34	0.13
PP ≥75 – complete period (%)*	19 ± 23	33 ± 29	0.09
PP ≥75 – last period (%)*	25 ± 29	28 ± 29	0.73

LVH = left ventricular hypertrophy; MAP = mean arterial pressure; PP = pulse pressure. The extensions 'start', 'complete period' and 'last period' refer to the first three months of dialysis, the complete period from start of dialysis until echocardiography, and the last three months of dialysis before echocardiography was performed, respectively. *Percentage of dialysis sessions with these values.

not reach significance, MAP, PP, hypertension load and pulse pressure load were consistently higher in patients with LV hypertrophy, compared with the patients without LV hypertrophy. MAP and PP in the complete period of dialysis were 5 mmHg higher in patients with LV hypertrophy than in patients without. Analogously, patients with LV dilatation had a higher MAP and PP averaged over the complete dialysis period, compared with patients with normal LV dimensions (MAP 107 ± 8 *vs* 102 ± 10 mmHg respectively, p=0.04; PP 68 ± 15 *vs* 61 ± 16 mmHg respectively, p=0.16).

There was no obvious difference in blood pressure parameters in patients with and without LV diastolic dysfunction or LV systolic dysfunction, with one exception: patients with LV systolic dysfunction had a higher intradialytic fall in MAP averaged over their complete dialysis period compared with patients with normal LV systolic function (12 *vs* 7 mmHg, respectively, p=0.02).

The interdialytic weight gain variables were not associated with any of the echocardiographic outcomes.

In a multivariate regression analysis the characteristics sex, age, body mass index, presence of diabetes mellitus or

history of cardiac disease did not influence the associations between MAP and the various echocardiographic findings. Total duration of renal replacement therapy (< or ≥5 years) had no influence on presence of LV hypertrophy or LV dilatation. LV diastolic dysfunction seemed more frequent in patients with haemodialysis of short duration (p=0.06). Long-term haemodialysis was associated with LV systolic dysfunction (p=0.04, *table 6*).

DISCUSSION

This study shows that increased blood pressure, averaged over the complete period of renal replacement therapy, was associated with an increased LV mass index. An analogous association with LV mass index was found for hypertension load and pulse pressure load. Patients with LV dilatation had a 6 mmHg higher mean blood pressure throughout their dialysis life than patients without, and patients with LV hypertrophy had a 5 mmHg higher mean blood pressure and pulse pressure than patients without, although the latter was not statistically significant, probably due to the small number of patients. However, in this study no significant associations were present between blood pressure and characteristics of functional cardiac damage, such as LV systolic dysfunction, i.e. not with hypertension, nor with hypotension.
When we studied the relation between cardiac parameters and duration of dialysis, it appeared that LV hypertrophy and diastolic dysfunction were present in the majority of patients, possibly already when patients started renal replacement therapy. On the other hand, we found that LV systolic dysfunction developed after patients had been on haemodialysis for some time, because this was more often present in patients who had been on haemodialysis ≥5 years. This could not be explained by a difference in age, or in cardiovascular history.

Interdialytic weight gain was not a predictor of LV hypertrophy or cardiac damage. We presume that either the interindividual variation of interdialytic weight gain was so large that it concealed any possible relation,[11] or that the influence of weight gain was indeed less substantial than one would expect from a clinical point of view.
Our study confirms that in patients with end-stage renal failure, hypertension and elevated PP predict the development of LV hypertrophy[17,18] and diastolic dysfunction.[19] Furthermore, others have demonstrated that volume overload as imposed by the creation of an arteriovenous fistula contributes to LV hypertrophy.[20] The opposite has also been found: reduction of volume overload by conversion to daily nocturnal haemodialysis leads to control of hypertension, reduction in PP and reduction in LV mass index.[21] Our results and previous findings clearly indicate that both blood pressure and pulse pressure, provided that their cumulative influence is considered over longer periods of time, increase cardiac afterload. This underscores the harmful effects of hypertension on cardiac morbidity and mortality. Foley *et al.* studied the echocardiographic risk factors for the development of heart failure in patients who underwent echocardiography at baseline and at one year after starting dialysis therapy.[22] An increase in LV mass index and a decrease in fractional shortening in one year were indeed associated with subsequent development of cardiac failure. However, the striking finding of this study was that these associations were independent of blood pressure levels. Furthermore, hypotension predicts mortality in epidemiological studies that considered blood pressure recordings over a short period of time, e.g. one week or one year.[2-4]
Therefore the issue is to explain why hypertension is associated with LV hypertrophy and LV dilatation, why neither hypertension or hypotension are associated with systolic dysfunction, and why hypotension is associated with increased mortality in patients on haemodialysis.

Table 6 *Prevalence of echocardiographic parameters according to duration of renal replacement therapy*

	Total duration of renal replacement therapy <5 years (n=29)	Total duration of renal replacement therapy ≥5 years (n=21)	P
Age (years)	56.9 ± 12.7	60.0 ± 12.3	0.38
Positive cardiovascular history (%)	62	71	0.49
LV hypertrophy (%)	66	57	0.55
Abnormal LVMI (%)	92	80	0.35*
LV diastolic dysfunction (%)	55	29	0.06
LV dilatation (%)	55	38	0.23
LV systolic dysfunction (%)	17	43	0.04

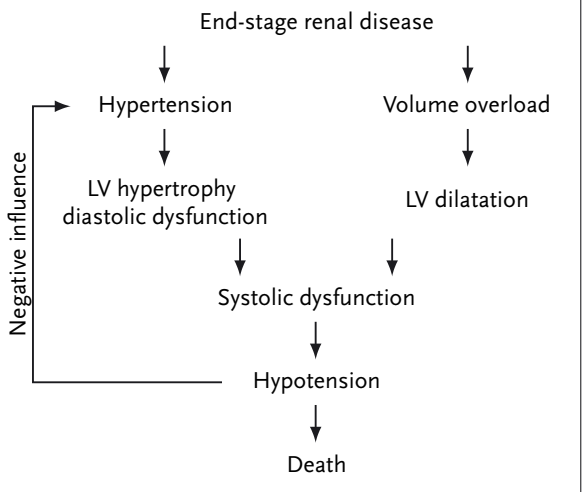
LV = left ventricular; LVMI = LV mass index. *Fisher's exact test.

Because the evidence for the detrimental effects of hypertension in the general population is overwhelming, it is unlikely that hypotension directly causes poor survival in end-stage renal disease. From a clinical point of view one could imagine that long-standing hypertension, almost invariably present in patients in their predialysis phase, has already caused heart failure at the onset of dialysis in some patients and consequently increased mortality with hypotension as a sign of forward failure (selection bias). That systolic dysfunction was independent of blood pressure parameters in our study could be explained by a negative effect of cardiac failure on the blood pressure parameters (reverse causation). This will entangle the relation between blood pressure and characteristics of heart failure. The results of our study support this hypothesis, depicted in *figure 2*: hypertension is associated with LV hypertrophy, and at a later stage longstanding haemodialysis is associated with advanced cardiac dysfunction.[22,23] Indeed we found that diminished fractional shortening, i.e. LV dysfunction, was associated with lower MAP and PP.

Interestingly, in support of our hypothesis we found that MAP seems to decrease in the course of a dialysis life (*table 2*). We realise that the present study was not designed to study the course of blood pressure in time. Further studies are recommended using a study design with a refined time scale in combination with echocardiography to precise this phenomenon.

The present retrospective cohort study did not include the patients who died from cardiac failure before echocardiography could be performed. Therefore it is possible that the patients with the most serious cardiac damage were not represented, and the hypotheses need confirmation in prospective studies in larger patient cohorts. Still, a small part of the reverse epidemiology in end-stage renal disease seems to be explained by the present findings.

Figure 2 *The association between hypertension and mortality in ESRD is entangled by ensuing hypotension*



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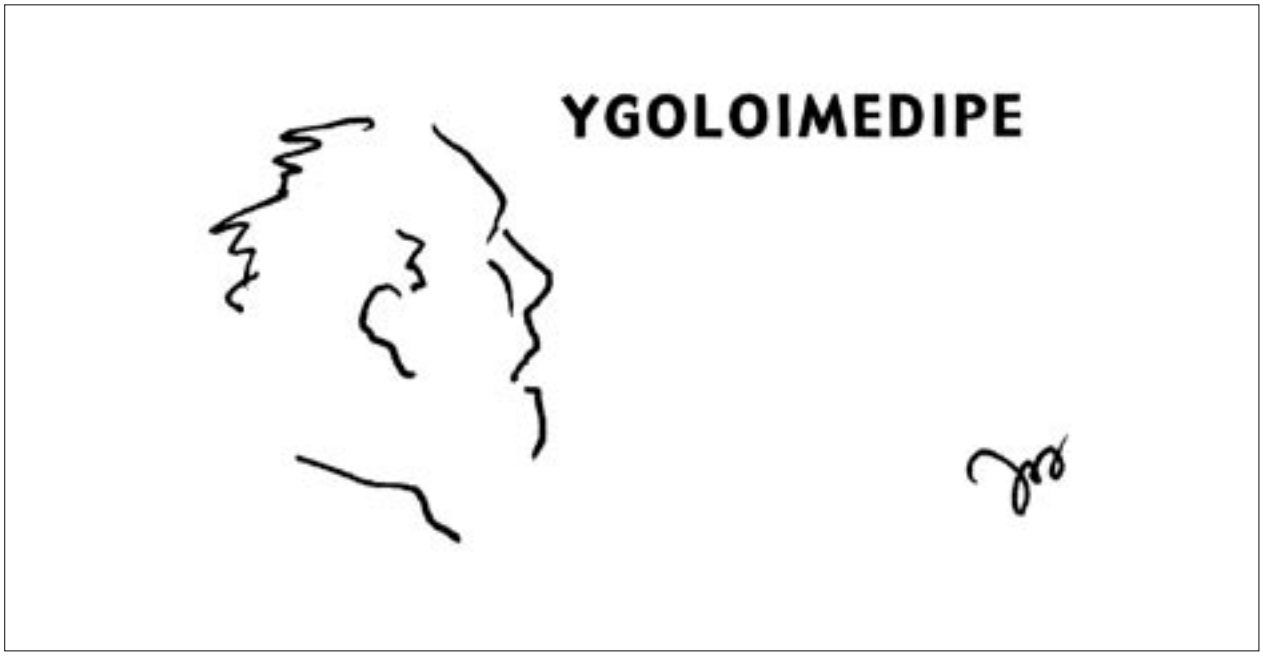

Borsboom, et al. Reverse epidemiology of blood pressure in ESRD.