Does Blood Pressure Control by Gentle Ultrafiltration Improve Survival in Hemodialysis Patients?

Bernard Charra, Guillaume Jean, Jean-Marc Hurot, Charles Chazot, Thierry Vanel, Jean-Claude Terrat, Guy Laurent

Centre de Rein Artificiel, Tassin, France

A gentle ultrafiltration can be achieved using a long and slow hemodialysis. It is easier to achieve gentle ultrafiltration if the interdialytic weight intake is moderate (i.e.*, if the patient maintains a low sodium diet) and if diffusion allows for a negative or nil sodium balance during the session (* i.e.*, dialysate sodium < 140 mmol/L). A gentle ultrafiltration allows control of blood pressure by reducing the extracellular volume to its ideal level, the "dry weight," at the end of the session. Controlling blood pressure reduces cardiovascular mortality, which is by far the foremost cause of death in hemodialysis.*

Controlling blood pressure means reducing the occurrence of both hypertension and hypotension. Hypotension has been reported to correlate with mortality in hemodialysis as much as or more than hypertension itself. This "U-curve" phenomenon is not paradoxical. It displays two distinct facts on the same figure: an increased early mortality in hypotensive patients (hypotension is a marker of frailty or congestive heart failure, both of which cause increased mortality) and, on the other hand, the well-established, long-term increased mortality in hypertensive patients. Hypotension is not a mandate to undertreat hypertension.

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Key words

Hypertension, hypotension, mortality

Introduction

Can the gentle ultrafiltration (UF) achieved by long slow hemodialysis (HD) improve survival? The Tassin experience with long-session HD allows us to address this question by answering several dependent questions: Does long-session HD allow blood pressure (BP) control by gentle UF? Does long-session HD improve survival? Is it really by controlling BP that gentle UF improves survival? Is hypertension (HT) the real danger, or is it rather hypotension (OT), as is sometimes suggested?

In Tassin, the same long slow HD has been used for 30 years: 3 × 8 hours per week using cellulosic membranes, a 138-mmol/L sodium dialysate, and an acetate buffer. Mean Kt/V is 2.0 per session, and normalized protein catabolic rate greater than 1.2. The mean protein and calorie intakes are large, and the only diet restriction is salt (mean NaCl intake, 5 g per day). The mean interdialytic weight gain is 1.6 kg. No antihypertensive medication is used in 95% of patients after the second HD month. We have reported in detail elsewhere the different aspects of this policy [1,2].

Correspondence to:
Bernard Charra, MD, Centre de Rein Artificiel de Tassin, 42 Avenue du 8-Mai-1945, 69160 Tassin, France.
email: bcharra@aol.com

Does long gentle UF allow control of BP, and if so, why?

In our experience, BP control does not require antihypertensive drugs. In the Tassin population the mean casual predialysis BP is 128/79 mm Hg, within normal range [3]. Ambulatory BP monitoring values are also in the normal range, except for the absence of a nocturnal dip in about 50% of patients [4].

This good control of BP using long-session HD is not a center effect. It was regularly reported in the 1960s by most groups using long-session HD [5–7]. Nowadays, normotension is also regularly achieved by those who still use long-session HD [8,9] or daily dialysis [10,11]. On the other hand, with shortened HD sessions, the impaired BP control reported by Kramer [12] and Wizemann [13] has been widely confirmed. In 1999, HT prevalence was commonly greater than or equal to 70% [14,15].

At the other end of the BP spectrum, 8-hour HD allows for a low intradialytic morbidity. Hypotension episodes are less common than in shorter conventional HD. Long-session HD allows for good control of both HT and OT. When the session time is reduced in order to achieve dry weight (DW), the UF rate needs to be increased, and OT becomes more common. This has several consequences: the patient has a poor perception and acceptance of HD and asks for a shorter session; the nurse has to cut down the UF rate and/or give saline, therefore the prescribed DW is not achieved; the physician wrongly re-evaluates DW. Often, to reduce OT and cramps, the physician also increases dialysate sodium. This leads to increased thirst and interdialytic weight gain. Ultimately, the patient does not achieve DW, is saline overloaded and hypertensive, and needs to use a higher UF rate during the next treatment; thus the vicious cycle continues. Antihypertensive drugs may be added, but they are poorly efficient in the saline overload state and further potentiate the tendency to OT during dialysis. Interdialytic HT and intradialytic OT continue to amplify each other in a vicious circle. Reducing HD time acts to further amplify BP variations.

To consider more specifically the relationship between extracellular volume (ECV) and BP, Fig. 1 summarizes the Tassin experience of the first dialysis year in the entire population. During the first HD month, ECV (expressed as postdialysis weight) drops sharply due to UF and a strict low salt diet. Predialysis mean arterial pressure (MAP) decreases

more slowly over months. Knowledge of the lag time between change in ECV and BP is of utmost importance [16]. Antihypertensive drugs are stopped in 95% of patients after 2 months. After that time, weight increases. This reflects a lean and fat body mass gain due to dialysis-induced anabolism [17].

The effect of changing the dialysis schedule in the same group of patients illustrates the importance of prolonging session duration and using a low UF rate. One hundred and twenty-four dialysis patients were treated in Tassin for at least 6 months while waiting for a kidney transplant. They were unselected; all had been treated for at least 6 months using a "short" dialysis schedule (≤ 5 hours per session, three times weekly). Half (65 patients) received antihypertensive medications. After 3 months of long-session HD, their mean postdialysis weight was reduced by 0.5 kg, their average predialysis MAP had fallen from 112 mm Hg initially, to 102 mm Hg, and antihypertensive treatment had been stopped in all but 1 patient. Thereafter, predialysis MAP continued to decrease, reaching 92 mm Hg at 12 months, while weight re-increased by about 2 kg due to anabolism.

Conversely, 49 long-session HD Tassin patients were switched to a 3 × 5-hour schedule. All had been dialyzing 3 × 8 hours for more than 6 months. All were normotensive without antihypertensive medication. Dialyzer area and blood flow were increased to maintain an unchanged Kt/V. After 1 year the Kt/V was grossly unchanged (1.79 vs 1.89). Predialysis MAP had increased significantly, from 87 to 98 mm Hg, in spite of a mean 2.5-kg reduction in DW and the introduction of antihypertensive medications in 4 patients.

A long-session HD (associated with a low salt diet and reasonable dialysate sodium) with a low UF rate allows control of BP. The limiting factor in achieving normal ECV and BP on short-session HD is patient intolerance of high UF rates.

Does a gentle HD with slow UF improve survival, and if so, why?

Although the treatment has remained the same in Tassin, patient characteristics have changed over the years. Diabetes and nephrosclerosis, which together represented 5% of the etiologies in the incident end-stage renal disease population in 1968, were observed in 38% of patients in 1990, and 68% in 1999. The mean age at start of dialysis has increased from 36 years in 1968 to 63 years in 1999. The proportion of patients with cardiovascular comorbidity at HD start increased from 10% to 61%. As shown in Table I, the case-mix worsening has particularly accelerated in the past 10 years. Due to the increasing risk factors, crude mortality has worsened over the years. Among patients started on dialysis before 1975, 25% had died at 11 years of treatment, while among those started after 1990, 25% had died after 2 years.

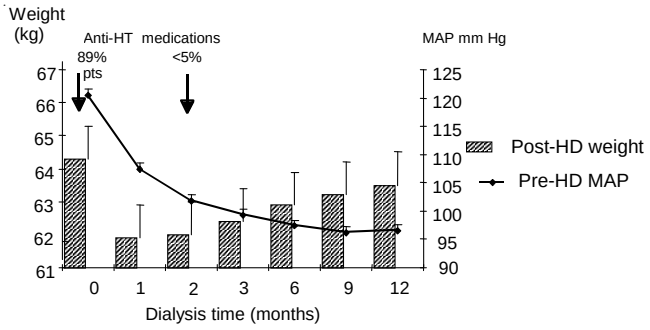

FIGURE 1 Evolution of postdialysis weight (SEM) and predialysis mean arterial pressure (MAP) (SEM) during the first hemodialysis (HD) year. HT = hypertensive.

Comparing the crude mortality of the young fit patients of the early cohorts, almost free of comorbidity, to the aged sick patients with heavy comorbidity now prevalent gives a wrong idea of treatment-related mortality. A fair outcome analysis must take into account the changing case-mix by stratifying patients into risk groups, as done with the Standardized Mortality Ratio (SMR) [18] shown in Table II. In the past decade, in spite of the patients' worsening clinical condition (Table I), the SMR has remained stable (about 50% lower than expected mortality for USRDS patients).

Comparing Tassin mortality to the only available long-term French series on 4- to 5-hour dialysis [19] shows that mortality was about 50% lower in the patients treated using long-session HD. The difference is explained mainly by cardiovascular (CV) mortality (19.8 CV deaths per 1000 patient-years in Tassin vs 44.6 in all of France).

According to these facts, long-session HD allows use of a lower UF rate, leading to good control of BP with less HT and less OT, and to a longer survival, due mainly to reduced CV mortality.

Is it by controlling BP that the methods using a low UF rate improve dialysis mortality?

The better survival observed in Tassin than in many other series is due essentially to a lower CV mortality, which depends at least in part on BP control. If we split the total Tassin population into two equal cohorts of patients according to median predialysis MAP (calculated from all treatments), the subgroup with the lower predialysis MAP (mean 89 mm Hg) has a lower mortality ($p < 0.0001$) than the subgroup with a slightly more elevated MAP (mean 107 mm Hg). The difference is explained essentially by a large difference in CV mortality (12.6 vs 28.5 CV deaths per 1000 pt-yrs). Many authors have come to the same conclusion. Control of HT in HD patients reduces the risk of stroke [20], coronary disease [21], congestive heart failure (CHF) [22], and left ventricular hypertrophy (LVH) [23]. According to many reports, HT reduces the overall survival of HD patients [24–29].

Is hypertension the significant mortality risk factor in dialysis, or is hypotension?

According to the literature, OT is infrequent in the nonuremic population. A Medline search showed that referenced papers

TABLE I Evolution of demographic and comorbid factors in Tassin for years 1989–1998.

Calendar year	*1989*	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*
Diabetes (%)	12.8	18.4	17.1	26.4	20.5	26.7	21.1	25.5	31.3	36.0
Nephrosclerosis (%)	25.6	21.1	24.4	22.6	25.6	20.0	28.1	26.0	21.9	20.5
Other/unknown (%)	61.5	60.5	58.5	50.9	53.8	53.3	50.9	48.5	46.9	43.5
Age at start (years)	54.1	55.4	56.0	56.5	58.4	59.7	62.1	61.5	63.4	65
Cardiovascular antecedents (%)	41	46	47	50	54	57	55	58	61	63

TABLE II Standardized mortality ratio in Tassin, 1989–1998.

Year	*O/E deaths*	*SMR*	p *Value*
1989	23/43.7	0.53	<0.005
1990	14/42.4	0.33	<0.001
1991	18/44.7	0.40	<0.001
1992	15/46.1	0.33	<0.001
1993	23/47.7	0.48	<0.001
1994	20/50.3	0.40	<0.001
1995	23/57	0.40	<0.001
1996	27/56.4	0.51	<0.001
1997	25/48.5	0.52	<0.001
1998	26/47.6	0.55	<0.005

O/E = observed number/expected number; SMR = standardized mortality ratio; *p* values relate to expected versus observed mortality.

relating mortality to low BP number 20 times fewer than those relating mortality to high BP. Hypotension is essentially an immediate prognostic factor in shock, whatever its origin. Other types of hypotension (e.g., postural, postprandial) do not appear to be established risk factors, except for patients with specific frailties or CV diseases. In these cases OT is a factor for short-term (3-years) mortality [30]. In the general population, HT appears as a major long-term mortality factor [3,31,32]. Only very severe HT has an impact on short-term mortality [33]. Hypertension prevention is considered one of the most effective means of reducing general population mortality [34].

In the dialysis population, mortality decreases with HT control. On the other hand, according to many authors [35–40] the relationship between HT and mortality has not been established. Furthermore, several studies show OT, not HT, is related to mortality. This gives rise to a "U-curve" phenomenon [39,41] as reported in nonuremic patients [30]. The U-curve phenomenon in the general population has been the source of many questions [42,43]. Definitive answers are still pending [44], but the general consensus [45,46] is that low BP, especially diastolic, correlates with increased coronary risk, but that no causal relation is established. Even if it were definitely proven that treatment-related OT is a hazard to the patient, it would not be "a mandate to undertreat HT" [43].

In dialysis patients, the correlation of diastolic OT with cardiac mortality [47–49] may be due to the associations between LVH and mortality [50], and between LVH and OT [51,52]. Congestive heart failure has also been associated with both mortality [22,53] and OT [54,55]. Hypotension-associated mortality in dialysis occurs especially in the first years of follow-up [40,56] and does not preclude HT from being a powerful long-term mortality risk factor [40].

From a methodological point of view, relating CV mortality to BP using the same clinical database may lead to different results, according to which BP measurement is used as "predictor." Tassin data illustrate this point. We analyzed the survival of the same patients taking two different BP values.

Figure 2 shows the Kaplan–Meier mortality curve as a function of predialysis MAP calculated for each patient from all treatments. The MAP values define three subgroups of patients. The demographic and comorbid characteristics of these three subgroups are reported in Table III. The low MAP subgroup is not different by age or prevalence of diabetes mellitus, but it includes more female patients and fewer smokers. The duration of HT (in years) preceding start of dialysis was shorter than in the other two subgroups. Cardiovascular comorbidity (coronary, cerebrovascular, and peripheral vascular disease) was also significantly less prevalent than in the other two subgroups. The intermediate (between 90 and 105 mm Hg) and high MAP subgroups differed only by a significantly higher proportion of diabetics and longer exposure to HT before dialysis in the high MAP subgroup. The low MAP subgroup (predialysis MAP < 90 mm Hg) had the best survival; the intermediate subgroup showed an intermediate survival curve; and the high MAP subgroup (predialysis MAP ≥ 105 mm Hg) had the shortest survival.

Let us now consider for the same patients the initial predialysis MAP (at start of HD) as predictor. Three subgroups

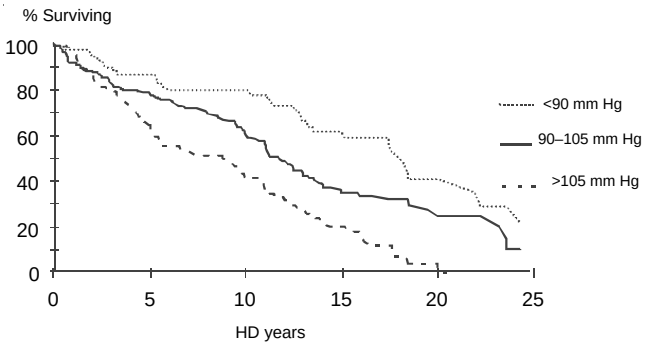

FIGURE 2 Kaplan–Meier mortality curve as a function of predialysis mean arterial pressure calculated for each patient from all hemodialysis (HD) treatments.

TABLE III Demographics and comorbidity of three blood pressure subgroups during maintenance hemodialysis (HD).

Blood pressure subgroup	*Low*	*Medium*	*High*
Blood pressure (mm Hg)	<90	90–105	≥105
Number of patients	215	484	266
Age at HD start (SD)	49.6 (18.0)	52.6 (17.3)	52.8 (13.9)
Female (%)	49.5[a,b]	28.4	30.1
Diabetes mellitus (%)	12.4	10.1[c]	18.4
Hypertension (years)	3.6 (6.2)[a,b]	5.1 (6.4)[c]	7.2 (6.2)
CV comorbidity (%)	27.3[a,b]	37.9	42.5
Smokers (%)	23.7[a,b]	43.9	45.1

CV = cardiovascular.
[a] $p < 0.05$, Low versus Medium.
[b] $p < 0.05$, Low versus High.
[c] $p < 0.05$, Medium versus High.

of patients were again compared. Their respective demographic and comorbid features are displayed in Table IV. The low BP subgroup of patients is slightly older than the high MAP subgroup; the medium BP group has more patients with diabetes mellitus than the other two groups. The highest percentage of smokers is in the high subgroup, followed by the medium and the low subgroups. No other significant differences were found between subgroups. The initial survival trend observed in these three predialysis MAP subgroups (Fig. 3) is opposite to that of the three integrated BP subgroups. The patients with the lowest initial MAP (predialysis MAP < 110 mm Hg) had the highest mortality. The patients with the highest initial MAP (predialysis MAP >130 mm Hg) had the lowest mortality. Patients with an intermediate predialysis MAP had an intermediate mortality. After 5 or 6 years of follow-up, the mortality curves cross over and the relationship between BP and mortality inverts. Thus cross-sectional and longitudinal BP data may lead to opposite mortality estimates.

Other methodological problems occur in analyzing HD mortality as a function of BP. Blood pressure varies in the short term according to the dialysis cycle and measurement conditions. It also varies seasonally [57]. Even more relevant to the U-curve phenomenon, BP varies in the long term

TABLE IV Demographics and comorbidity of three blood pressure subgroups at the start of hemodialysis (HD).

	Low	*Medium*	*High*
Blood pressure (mm Hg)	<110	110–129	≥130
Number of patients	295	340	336
Age at HD start (SD)	55.4 (17.1)[a]	53.6 (16.2)	50.4 (14.8)
Female (%)	31.4	38.9	29.0
Diabetes mellitus (%)	31.3[b]	46.1[c]	25.2
Hypertension (years)	4.9 (7.2)	5.7 (6.5)	5.5 (6.2)
CV comorbidity (%)	42.1	39.6	34.0
Smokers (%)	28.5[a,b]	44.6[c]	49.6

[a] $p < 0.05$, Low versus High.
[b] $p < 0.05$, Low versus Medium.
[c] $p < 0.05$, Medium versus High.

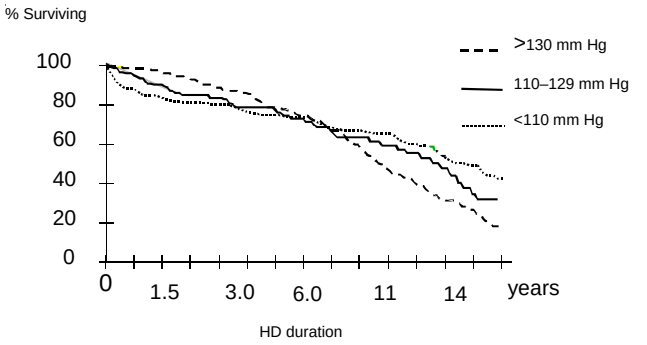

FIGURE 3 Kaplan–Meier mortality curve as a function of initial predialysis mean arterial pressure at start of hemodialysis (HD).

according to dialysis treatment duration. Typically, 70% – 90% of new HD patients are hypertensive at the start of treatment. Through the first months of HD (as ECV is reduced), BP decreases progressively, reaching a normal level in a variable proportion of patients (30% – 95%) after a few months. The predialysis MAP through 15 years' dialysis of 139 Tassin patients is displayed in Fig. 4. The initially high (mean 124 mm Hg) mean predialysis MAP decreased within the first few weeks of dialysis, then remained fairly stable (about 95 mm Hg) after the third month of dialysis treatment. This graphic makes clear that taking the MAP at days 1, 30, or 120 of HD as the predictor of mortality will lead to completely different results.

Another point that needs to be considered is the time interval between exposure to HT and its effect on mortality. We mentioned the fact that the OT relationship to mortality, if any, is short-term. It is the opposite for HT. The Framingham study showed that it takes over 10 years to observe the benefit of controlling HT in the general population [32]. Hypertension target-organ damage usually takes 5 – 7 years to appear [30]. There is no reason to believe that dialysis patients should be different than nonuremic patients.

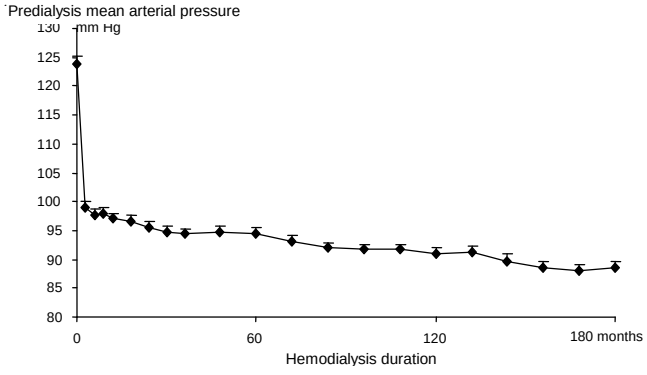

FIGURE 4 Long-term (180 months) evolution of predialysis mean arterial pressure in 139 Tassin hemodialysis patients.

Another common practical problem arises from the fact that the BP status of HD patients before they start HD is often unknown. The same cross-sectional BP value at start of dialysis can correspond to completely different BP situations in the previous years, that is, a different BP-related risk profile. Using the BP value at start of HD treatment as a predictor of mortality is obviously more a clairvoyant's than a doctor's task.

After 40 years' development of maintenance HD, hypertension still appears a very common and dangerous condition, leading to very high mortality. Hypotension is a tiresome event that hampers the delivery of optimal treatment and may increase CV morbidity. Both hypertension and hypotension prevalences are reduced by using long slow dialysis, or daily dialysis treatment. Controlling blood pressure appears today to be the most promising lifesaving strategy for improving survival on HD.

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