The Role of Blood Pressure Control on Hemodialysis Patients Survival

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Cardiovascular events are by far the first cause of death in hemodialysis (HD) patients. On top of classical risk factors, the dialysis population is exposed to specific risk factors linked to chronic renal failure and/or to its treatment. The most powerful among them are certainly extracellular volume and blood pressure control.

Is it possible to control blood pressure on dialysis, and if so, How?

According to the Tassin experience using a 3×8 hours per week hemodialysis schedule, the blood pressure can indeed be controlled in a large majority of dialysis patients[1]. This is achieved with less than 5% of patients on antihypertensive treatment[2]. The mean pre-dialysis blood pressure value of over one thousand long HD patients without antihypertensive drugs is 128/79, within normal range according to the 6th Joint National Committee on blood pressure evaluation[3]. Furthermore the ambulatory blood pressure is also normal at least for circadian and daytime values [4]. The nighttime values are slightly elevated due to the lack of nocturnal dip in about half of the patients on long HD.

So, hypertension can be controlled in more than 90% of the patients. This is not a "center effect". It has indeed been reported by most units in the early 70's when everybody was still using long dialysis & low salt diet[5-7]. It is still reported and published by those who continue to use a long dialysis, e.g. Manchester[8] or Christchurch[9]. A medication-free blood pressure control is also reported by most groups using daily dialysis whether short[10] or long[11]. But in standard short HD today out of a few units[12, 13] medication-free blood pressure control is seldom achieved.

The first and essential way by which dialysis allows to control blood pressure is by controlling the extracellular volume (ECV). Guyton[14] brilliantly described the effect of sodium load in chronic renal failure dog. The ECV under the effect of a Na^+ load increases sharply. This leads to an increased cardiac output without change in total peripheral resistances but with an increased blood pressure and natriuresis so that the extracellular volume overload is tapered down. After a fortnight of sodium load the cardiac output gets back to normal but the total peripheral resistances increase so that the blood pressure and the natriuresis remain high, reducing further the ECV overload. After some weeks the animal is hypertensive but not obviously volume overloaded, e.g. usually presenting without edema. That a moderate extracellular volume change can induce an important blood pressure change is a crucial practical point.

For a closer look at the extracellular volume/ blood pressure relationship, one can follow the first HD year of 700 patients started on dialysis in Tassin (Fig. 1). The extracellular volume as expressed by post-dialysis weight (shown in column) drops sharply of about 2 kilos (2 liters) within the first HD month while pre-dialysis

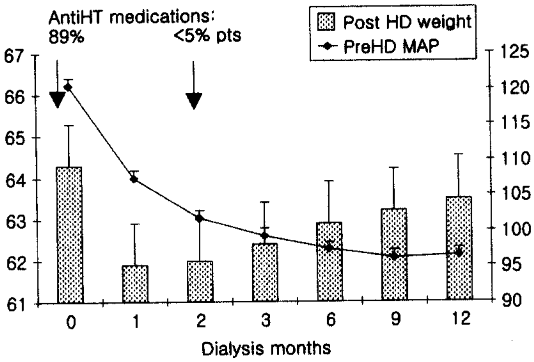

Fig. 1. *Evolution of post-dialysis weight and pre-dialysis mean arterial pressure in 712 patients first long hemodialysis (3×8 hr/wk) year in Tassin.*

MAP (displayed in plain line) also decreases. After 2 months almost all patients are off anti-hypertensive medication, post-dialysis weight is stable, blood pressure continues to decrease. Then the curves cross over: blood pressure decreases gently for several months while post-dialysis weight increases. This weight gain is not due to an increase in extracellular volume but to the increase in lean and fat body mass subsequent to anabolism induced by the start of dialysis.

The respective effects of session duration and volume control on blood pressure are illustrated by a study we did with the group of Stockholm [15] in which 64 long HD Tassin patients were compared with 54 short HD Stockholm patients. All long HD patients were normotensive, as well as 26 of short HD patients who were also normotensive. On the other hand 28 of the 54 short HD patients were hypertensive.

The ECV evaluated by multi-frequency bio-impedance between 2 dialysis sessions showed a significantly lower ECV in normotensive patients (although the difference with the higher blood pressure subgroup was not huge). We concluded that all normotensive patients, whatever their dialysis duration long or short, shared the common feature of having reached their “dry weight”.

Hemodialysis dry weight

Dry weight (DW) is the ideal post dialysis weight that must be achieved to maintain a constantly normal blood pressure without antihypertensive medication.

What the nephrologist is trying to do in terms of ECV and blood pressure control is to mimic the sophisticated native biofeedback mechanism whereby the kidney using ECV and blood pressure information regulates -through perfectly adapted natriuresis and hormonal interventions - the extracellular volume and the blood pressure. The physician or person in charge of the dialysis treatment uses the same pieces of information - extracellular volume and blood pressure - to prescribe the dry weight, which is translated into an ultrafiltration rate to return the extracellular volume back to normal.

Dry weight can be clinically assessed[16] using blood pressure and extracellular volume repeated evaluation. Achieving DW needs 3 major steps : a low salt diet, too often forgotten today[17] reducing the interdialytic weight gain; a nil or slightly negative diffusive Na^+ balance using a reasonably low dialysate sodium i.e. about 5 mmol/L lower than patient's natremia as shown by Locatelli[18]; and of course an adequate ultrafiltration. This last means today is often used alone and considered the only tool at hand to control the sodium balance. In fact, ideally, it should only be the fine tuning button of the volume control system in HD.

End-stage renal failure does affect blood pressure control by other means than by just controlling body Na^+ content and extracellular volume. In other words extracellular volume excess does not explain each and every case of dialysis hypertension. Hypertension may be related to a change in Na^+ distribution without volume overload but with an increased intracellular Na^+ content[19]; to renin-angiotensin II inappropriate over activity[20]; to sympathetic over activity[21]; to inhibition of Nitric Oxide-related vasodilatation[22]; to other endothelium-derived factors such as endothelin[23]; or to other factors (prostaglandin, bradykinin…). But altogether these non-volume related factors explain only a tiny part of hypertension cases on HD[24].

HTN control impact on dialysis patients mortality

On Fig. 2 the Tassin population has been split in 2 equal cohorts of patients according to the integrated pre-dialysis mean arterial pressure. The 1st cohort had a low normal blood pressure (<97 mmHg, mean=89 mmHg) while the second cohort had a normal to high-normal blood pressure (>97 mmHg, mean=105 mmHg) before the session. The mortality was significantly lower in the low blood pressure subgroup ($p<0.001$). The difference was mostly explained by the cardiovascular mortality much lower in the low blood pressure subgroup (12.7 vs. 38.1 cardiovascular deaths per 1,000 patient-years, $p<0.001$). Most literature reports since the early days of maintenance dialysis[25,26] up to now[27,28] also have shown a clear-cut relationship between hypertension and mortality.

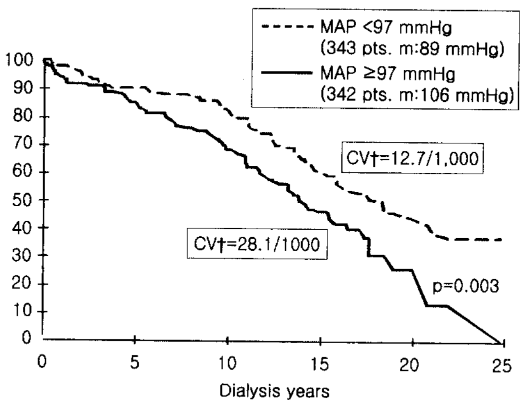

Fig. 2. *Mortality and cardiovascular (CV) death rate as a function of predialysis integrated mean arterial pressure (MAP) in 685 Tassin patients (mean MAP respectively 89 and 106 mmHg).*

Hypertension is very common in dialysis patients, it is a risk factor for stroke, coronary disease, left ventricular hypertrophy and congestive heart failure. The mortality related to hypertension is mostly long-term as already shown for non-uremic patients in the Framingham study[29].

Opposite to this commonly held position several authors[30-33] state that the relationship between hypertension and mortality is not established and even that hypertensive patients tend to survive longer than normotensive or hypotensive ones.

Does OTA impact on mortality? The "U curve" phenomenon

First of all, of what hypotension are we speaking about? One must clearly separate 2 concepts. The hypotensive episodes occurring during the dialysis session are a pattern of poor tolerance of the intermittent procedure. They are common, troublesome, but their relevance to mortality is not clearly established out of the case of diabetic patients[34]. The permanent hypotension in hemodialysis patients is our concern and present topic[35,36].

Long-standing OTA in dialysis patient is not very common, although it seems to increase with dialysis vintage. It is a marker of poor clinical condition, frailty, and particularly of congestive heart failure. Low blood pressure (especially diastolic) is correlated with coronary risk[37] although no causal relationship has been established. Mortality associated with hypotension is short-term, some months to some years[30,31,33].

A "U curve" between blood pressure and mortality has been described in the HD patient by Zager some years ago[31] as it had been described earlier in non-uremic patients[38,39]. This curve relates mortality to blood pressure control, the lowest mortality is observed in normotensive patients. Mortality is higher in hypertension but also in hypotension.

How do Tassin data match with this U curve concept? Let's consider first the KM survival as a function of integrated pre-dialysis MAP values. If we split the population in 3 cohorts according to the pre-dialysis mean arterial pressure integrated values (Fig. 3), the higher the blood pressure, the higher the mortality. The subgroup of patients with the lowest MAP has the best survival, the intermediate MAP subgroup has an intermediate survival and the highest MAP subgroup has the worst survival.

So we just confirm here what we saw earlier on Fig. 1.

But if one uses the same database and correlates the survival with the initial MAP (instead of the integrated MAP value) at start of dialysis (Fig. 4) we get exactly the opposite results. The subgroup with the highest initial blood pressure has the best survival, the subgroup with the lowest initial blood pressure has the worst survival (especially in the first few months after starting hemodialysis therapy), and the intermediate subgroup has an intermediate survival. This stands true for 5 or 6 years.

At this point the curves cross over.

Let's now match chronologically the last analysis (Fig. 4) with the reports establishing a relationship between mortality and hypotension on dialysis. Salem et al.[30, 32] analyzed mortality at 1 and 2 years of follow-up, Port et al.[33] between 1 and 2.5 years, while Zager et al.[31] described the U curve after a mean follow-up of 2.3 to 5 years. So altogether the relationship between low or normal blood pressure and mortality is situated chronologically in the first part of the Kaplan-Meier survival curve. In other word these authors are right in reporting that initially hypertensive patients have a better survival than normo- or hypotensive ones within this time delay of 5-6 years.

But using blood pressure figures at the start of dialysis when about 90% of the patients are hypertensive is questionable. How does blood pressure at start indicate the effective patient exposure to hypertension? Hypertension at dialysis start can correspond to quite different clinical situations : a long-standing hypertension with a high cardiovascular risk; a few years of hypertension with a medium cardiovascular risk; or a

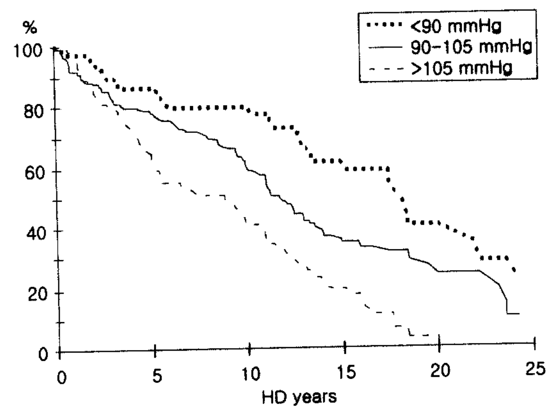

Fig. 3. Mortality in 882 Tassin patients splitted in 3 groups according to predialysis integrated mean arterial pressure (MAP) (mean MAP respectively ≤90, 90-105 and >105 mmHg).

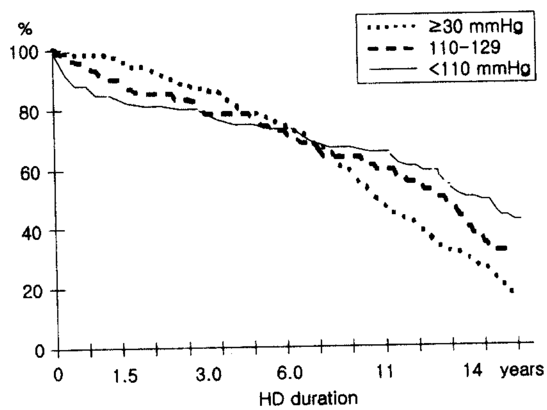

Fig. 4. Mortality in 882 Tassin patients splitted in 3 groups according to predialysis mean arterial pressure (MAP) at initiation of dialysis treatment (mean MAP respectively ≤110, 110-129 and ≥130 mmHg).

very short period of hypertension just before the start of dialysis treatment with no specific cardiovascular risk. On the other hand a normal or low blood pressure at start of dialysis may reveal a fortunate situation such as a salt losing nephropathy with no specific cardiovascular risk. But it may at opposite express a congestive heart failure resulting from the prolonged evolution of a very severe hypertension (the so-called "reverse causality"), with a very high mortality risk.

Therefore blood pressure level at start of dialysis is a very poor indicator of the true hypertension story and of the subsequent cardiovascular risk. This again has been already reported in non-uremic patients, in whom pre-treatment blood pressure is not a predictor of survival[40].

The apparent paradox of a 'U curve' between blood pressure and mortality in dialysis patients is due to the arbitrary and misleading display on the same curve of 2 unrelated facts occurring in different time settings (early and late on dialysis). That blood pressure is low or normal at start of dialysis in some patients with an early mortality is not an argument to suggest that hypertension should be left untreated in HD patient s… no more than the hypocholesterolemia occurring in the setting of denutrition (and subsequent mortality) is an argument to consider that hypercholesterolemia should be left untreated.

So to summarize our understanding on the role of hypertension on dialysis mortality :

- Hypotension is a marker of early mortality as in non-uremic patients[39] especially elder ones[41].
- Hypertension is a cause of late mortality on dialysis.
- The same U curve pattern exists out of HD and it has the same signification.
- The questionable risk of hypotension is "not a mandate to undertreat hypertension.

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