Cardiovascular morbidity and mortality: reduction by long hemodialysis, the Tassin experience.

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Long hemodialysis (HD), 3 x 8 to 12 hours per week on 1 sq-m flat plate cuprophane dialysers, has been the empirical most achieved form of dialysis in the 70’s, the “gold standard” [1]. Technical advances, changing scientific views on uremia pathophysiology [2], and economical pressure to make a better use of the scarce dialysis stations have led to the apparition and wide expansion of “short” dialysis [3]. In Tassin the 8-hour hemodialysis (HD) has remained the unique treatment method for almost all patients whether in the unit or at home since 1968. After more than three decades of follow-up, the overall results of the empirical long slow HD representing more than 6500 patient-years of experience are worth reviewing.

**Tassin experience summary**

Three sessions of seven to eight hours per week are performed overnight during the sleep or in the day time according to patient’s possibility and preference. Home dialysis has been used in a large portion of the population up to the 80’s (at which time 50% of the patients dialyzed at home). Then, multiplication of dialysis units, transplantation rate increase and patients case-mix worsening have led to a steady decrease of the proportion of patients treated at home. Only 10% of Tassin patients are treated at home presently.

Until 1995 we used a poorly “biocompatible” setting including cuprophane® membrane, acetate buffer and plain softened water. Since 1996 bicarbonate buffer has progressively been substituted to acetate. Since 1998 low-flux polysulfone dialyzers have progressively replaced cellulosic ones. Finally in January 2001 a complete change occurred in the water treatment. It uses now a reverse osmosis treatment completed by an ultrafiltration system. Moderate (220 ml/min) blood flow has been used throughout the experience.

Since 1991 a “short” HD program has been set up as a complement of the long HD. It uses a 3x5 or 6h schedule with large area size dialyzers (1.7 to 2.5 sq-meter), and 300ml/min blood flow. This shortened schedule is presently used in 25% of Tassin patients.

Whatever the dialysis session duration the dose provided is large: the mean delivered urea Kt/V using second generation Daugirdas method [4] is 2.0 per session, 6.0 per week [5]. The mean normalized protein catabolic rate is over 1.2. The mean protein and calories intake are 1.2 g/kg and 32 kcal/kg/day respectively. The patients are requested to maintain a low salt diet. No salt is added to the food and processed food is avoided. Accordingly, the average sodium chloride intake is 5 to 6 g per day. On the other hand the patients are not requested to restrain from drinking. Using a reasonable (138 mmol/L) dialysate sodium, the mean interdialytic weight gain is 1.7 kg (2.5% of mean dry weight).

All antihypertensive medications are stopped in over
95% patients within the two first months of HD. It is a crucial point of the method that during the initial few weeks of dialysis the antihypertensive treatment is tapered down and stopped in each and every patient in conjunction with the lowering of his extracellular volume to achieve "dry weight" and normotension [6].

As in many units worldwide Tassin incident population profile has changed drastically over calendar years. The mean age at start increased from 36 years in 1968 to 66 in 1999. During the same period diabetes mellitus and nephrosclerosis prevalence in the incident population crept up from 5 to 53% and the proportion of patients with cardiovascular comorbidity (myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, and peripheral vascular disease) increased from 6 to 61% of incident patients.

![Demographic evolution 5 calendar cohorts](image)

**Mortality data**

Due to the increase in risk factors, the crude mortality expressed as a Kaplan-Meier survival curve [7] has steadily increased along calendar years. The mean half-life of the cohort of patients starting HD between 1968 and 1975 was 17.5 years. It dropped to only 5 years for the most recent cohort (starting HD after 1992) [5]. But this compares patients almost free of comorbid conditions (first cohort) to aged sick patients with heavy comorbid conditions (last cohort). A realistic view of the mortality evolution in a given unit must take into account the changing demographic and comorbid patterns of the population.

To achieve this correction, the patients' risk level must be stratified according to identifiable patients risk factors. The Standardized Mortality Ratio (SMR) adjusts for age, race, sex and cause of renal failure using the United States Renal Data System (USRDS) standard mortality table as the reference [8]. For each calendar year the ratio between observed and expected deaths numbers according to the standard table is calculated. A SMR value inferior to one translates a better than expected survival. The average observed mortality in Tassin is 0.45 of the expected value according to US standards for grossly similar patients. It has remained fairly stable around this value over the last 12 calendar years (Table 1) in spite of the worsening case-mix.

<table>
<thead>
<tr>
<th>Calendar year</th>
<th>O/E death†</th>
<th>SMR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>24143.7</td>
<td>0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1990</td>
<td>14/42.4</td>
<td>0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1991</td>
<td>18/44.7</td>
<td>0.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1992</td>
<td>15/46.1</td>
<td>0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1993</td>
<td>23/47.7</td>
<td>0.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1994</td>
<td>20/50.3</td>
<td>0.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1995</td>
<td>23/57</td>
<td>0.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1996</td>
<td>27/56.4</td>
<td>0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1997</td>
<td>25/48.5</td>
<td>0.52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1998</td>
<td>26/47.6</td>
<td>0.55</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1999</td>
<td>27/67.5</td>
<td>0.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2000</td>
<td>31/69.9</td>
<td>0.44</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

†O/E: observed i/ expected number

Comparing Tassin mortality to the only available long-term French series of 4-5hr hemodialysis reported by Degoulet et al. several years ago [9] shows that long HD mortality was lower (52.4 vs. 99 deaths per 1000 pt-yrs, p<0.001). There was no difference in several specific (infection, cancer, or others) causes of mortality between the two series but for the cardiovascular mortality which was much lower on long than on short HD (19.8 vs. 44.6 cardiovascular deaths per 1000 pt-yrs, p<0.001).

We splitted Tassin long dialysis population in 2 cohorts (equal in number) according to integrated predialysis mean arterial pressure (MAP) calculated over the whole dialysis treatment time, and then we analyzed their respective Kaplan-Meier survival. The subgroup of patients with the lowest MAP (n=382 pts; mean predialysis MAP=89 mm Hg) had a significantly lower mortality (p=0.003) than the subgroup with a slightly more elevated MAP (n=383 pts; mean predialysis MAP=103 mm Hg). The difference in survival was mainly explained by a lower cardiovascular mortality in the lower MAP subgroup, 12.7 vs. 28.1 cardiovascular deaths per 1000 pt-yrs (p<0.01).

The Cox proportional hazard model [10] analyzing the
Table 2

Proportional Hazard Cox model of mortality of 786 patients

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient</th>
<th>95% Confidence Interval</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start</td>
<td>0.049</td>
<td>(0.033, 0.067)</td>
<td>1.050</td>
<td>(1.033, 1.069)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.606</td>
<td>(0.131, 1.081)</td>
<td>1.833</td>
<td>(1.139, 2.947)</td>
</tr>
<tr>
<td>CV(1) antecedent</td>
<td>0.631</td>
<td>(0.204, 1.057)</td>
<td>1.879</td>
<td>(1.226, 2.878)</td>
</tr>
<tr>
<td>MM(2) index 0.404</td>
<td>(-0.681, -0.128)</td>
<td>0.668</td>
<td>1.165</td>
<td>(0.706, 1.964)</td>
</tr>
<tr>
<td>KW urca</td>
<td>0.153</td>
<td>(-0.348, 0.675)</td>
<td>1.165</td>
<td>(0.506, 1.880)</td>
</tr>
<tr>
<td>Mean MAP(3)</td>
<td>0.033</td>
<td>(-0.084, 0.007)</td>
<td>0.971</td>
<td>(0.938, 0.993)</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>-0.029</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1): CV = Cardiovascular antecedent (Myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, peripheral ischemia)
(2): MM = Middle Molecule
(3): MAP = Mean Arterial Pressure

same patients survival shows (Table 2) that age, cause of renal failure and cardiovascular antecedents are very powerful predictors of mortality. These factors are not amenable to medical action as treatment-related factors. Among treatment-related factors urea Kt/V is not a significant predictor of survival. At opposite, the more time-dependent middle molecule index calculated using Babb’s method based on vitamin B12 clearance [11] is significantly correlated to survival (the higher the middle molecule removal rate, the longer the survival) [12]. This interesting feature has been confirmed recently in a subset of the USRDS population [13]. But the strongest predictors of mortality are serum albumin and even more predialysis MAP. For each 10 mm Hg increment of the predialysis MAP the risk of death increases by 34%.

So, a long HD allows for a long survival. This long survival is mainly due to a low cardiovascular mortality. The main feature of long HD which could explain this result is the good blood pressure control.

Is BP control really good in long slow hemodialysis?

The mean observed casual predialysis BP calculated from all values of each patient (128/79 mm Hg) is within the normal range advised by the Vth Joint National Committee on BP [14]. Besides, ambulatory BP monitoring values are also within normal range at least for daytime (121/72 mm Hg) and circadian values (119/71 mm Hg). However the night time values (118/67 mm Hg) are slightly more elevated than normal (106/64 mm Hg) due to the lack of nocturnal dip in 50% of the patients.

One cannot exclude some “center effect” in the achieved results. But all units where a long dialysis was in use in the 60’s [15-18] as those where it is still in use today [19-22] report the same excellent patients survival and low
A long HD allows for a long survival.

This long survival is mainly due to a low rate of CV mortality

The main feature of long HD which could explain this is BP control

Mean predialysis BP values in all 970 long HD pts. (antiHT therapy in <5% of pts after 3 months HD)

- Mean casual pre dialysis BP=128/79 mmHg
  MAP=86 mmHg
  Advised normal BP= 120-129/80-84 mmHg
  (VI th Joint National Committee BP)

- ABPM Circadian Daytime Nighttime
  Tassin* 119/71 121/72 116/67
  Staessen 116/72 123/76 106/64

*Chuzel & al, Am J Cardiol 1991; 67-172

How and Why does a long HD improve BP control?

Due to the intermittent nature of HD the patient oscillates between a “wet (saline overloaded) state” just before, and a “dry” (saline depleted) state just after the session. During the few hours of HD the plasma compartment is ultrafiltered down to a nadir. Refilling from interstitial space lags some hours behind. At the very end of the session the patient is hypovolemic. He returns to normovolemia a few hours later when refilling is completed. The hill-and-valley unphysiologic rhythm of intermittent HD is a critical issue which leads to conditions favoring alternately hypertension and hypotension.

TASSIN

ACHIEVING NORMAL ECV

Long slow HD not only reduces hypertension but also hypotension episodes. Hypotensive episodes prevalence is less in long than in short HD. This appears in our own unit when comparing 8 hour (7% of hypotension episodes) to 5 hour (13% hypotensive episodes) sessions, but even more in units using shorter sessions (20% or more hypotensive episodes). The reduction of both hypertension and hypotension by a longer (or probably more frequent) session has a

How and Why does a longer dialysis improve BP control?

Normotension can be reached in long HD by achieving a normal ECV, in other words, “dry weight”. This implies a low salt diet to avoid excessive interdialytic weight gain, a reasonable dialysate sodium (about 138 mmol/l) to achieve a nil diffusive sodium balance, and a sufficient ultrafiltration. This is the most powerful tool we have at hand but it is also the weakest one because it is limited by the patient refilling capacity, therefore by time.
Hypertension also aggravates left ventricular hypertrophy and decreases left ventricular function. This reduces the capacity of the heart to adapt its output to the acute changes in volume. Eventually antihypertensive drugs are added, which potentiate further hypertension during ultrafiltration. Altogether interdialytic hypertension and intradialytic hypotension keep on amplifying each other. Hemodialysis duration reduction behaves as an amplifier of BP variability.

**Does hypertension impact on mortality in hemodialysis?**

The question sound curious given Framingham and many other studies evidence in non-uremic patients, and the natural answer is yes, hypertension increases mortality. In the dialysis setting many studies have shown that mortality decreases with control of hypertension [9, 24-29]. According to these studies hypertension is very common in dialysis, it is a risk factor for stroke, coronary disease, left ventricular hypertrophy and congestive heart failure. And it is of note that mortality associated with hypertension is a long-term effect (210 years) in non-uremic [30] as in hemodialysis patients [28, 29, 31].

On the other hand, according to others studies the relationship between hypertension and mortality is not established [32-37]. Furthermore, according to several of them, it is hypotension and not hypertension which is related to mortality. What do we know about hypotension on dialysis? First hypotension (excluding the hypertensive episodes during the session) is not very common in HD. Second, it is a marker of poor clinical condition, especially congest-

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**Shorter D: the Blood Pressure Issue**

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**Hypertension in Dialysis Patients**

- HT is very common in HD
- Low BP is a marker of poor clinical condition (CHF, frailty)
- Low BP correlates with increased coronary risk (causal relation not established)
- Mortality associated with hypotension is mostly short-term

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**TASSIN**

**YES!**

- Most reports show a clear-cut relation HT/mortality
  - Elkhou et al., J Mt Sc 1977; 1:333
  - Haire et al., Cardiovasc Med 1978; 3: 1153
  - Despollet et al., J Nephrol 1992; 31: 103
  - Ritz et al., J Nephrol 1992; 31: 203
  - Charra et al. J Nephrol 1992; 31: 1029
  - Mazza et al., J Nephrol 2000, 58: 2147

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**TASSIN**

**Incidents per 100 dialysis as a function of session duration (370000 sessions)**

<table>
<thead>
<tr>
<th>HD Hours</th>
<th>Diaphane</th>
<th>Bergamo</th>
<th>Tassin</th>
<th>Tassin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>4,3</td>
<td>4</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Cramps</td>
<td>20,8</td>
<td>21,8</td>
<td>7,0</td>
<td>12,9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10,2</td>
<td>11,0</td>
<td>2,1</td>
<td>2,0</td>
</tr>
<tr>
<td>Headache</td>
<td>4,4</td>
<td>4,5</td>
<td>0,6</td>
<td>0,5</td>
</tr>
</tbody>
</table>

**TASSIN**

<table>
<thead>
<tr>
<th>HD Hours</th>
<th>Intra dialytic time</th>
<th>Inter dialytic time</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF rate</td>
<td>HYPERTENSION</td>
<td>Patient’s poor HD acceptance</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Daily fluid balance</td>
<td>Dry weight description</td>
</tr>
<tr>
<td>Spine infusion</td>
<td>Hypertension</td>
<td>Diuretic</td>
</tr>
<tr>
<td>Anti HTA medications</td>
<td>Hypertension</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Described dry weight</td>
<td>Hypertension</td>
<td>Over weight</td>
</tr>
<tr>
<td>Over weight</td>
<td>Hypertension</td>
<td>Thirst</td>
</tr>
</tbody>
</table>

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**TASSIN**

**Shorter D: the Blood Pressure Issue**

**TASSIN**

**Hypertension in Dialysis Patients**

- HT is very common in HD
- Low BP is a marker of poor clinical condition (CHF, frailty)
- Low BP correlates with increased coronary risk (causal relation not established)
- Mortality associated with hypotension is mostly short-term
ve heart failure or frailty. Third, a low BP, especially diastolic, may be - as for non-uremic patients - a coronary risk factor but causal relationship is not established. Fourth and last, the mortality associated with hypotension is mostly short-term (some months or some years). Which is the killer? Hypertension or hypotension?

Altogether if we plot mortality against mean arterial pressure, the lowest mortality correlates with normotension. Mortality is higher in hypertension, but also in hypotension. In fact this “U curve” pattern is misleading, more an intellectual construction than a reality: - First because we artificially display on the same curve all mortality whether short- (hypotension) or long-term (hypertension); - Second because different studies use different BP estimates to correlate with mortality. This second point can be illustrated using our own population data. If we observe the Tassin Kaplan-Meier mortality curve as a function of BP in 3 subgroups of patients according to their “integrated” mean predialysis MAP (i.e. calculated all over their maintenance dialysis time), the lowest BP subgroup has the best survival, the highest BP subgroup has the worst survival, the intermediate BP subgroup has an intermediate survival. But if we take for the same patients the value of BP at start of dialysis as the predictor of mortality, we come out with an inverse correlation. The patients with a low initial MAP have the highest mortality, the patients with the highest initial MAP have the lowest mortality, and the intermediate initial MAP subgroup has an intermediate mortality. It is of note that after 5-6 years of follow-up this relationship

Kaplan-Meier mortality curve as a function of BP in 3 subgroups of patients according to their “integrated” mean predialysis MAP (i.e. calculated all over their maintenance dialysis time), the lowest BP subgroup has the best survival, the highest BP subgroup has the worst survival, the intermediate BP subgroup has an intermediate survival. But if we take for the same patients the value of BP at start of dialysis as the predictor of mortality, we come out with an inverse correlation. The patients with a low initial MAP have the highest mortality, the patients with the highest initial MAP have the lowest mortality, and the intermediate initial MAP subgroup has an intermediate mortality. It is of note that after 5-6 years of follow-up this relationship

Is ECV control the necessary and sufficient condition of BP control in HD?

- a Na+ (ECV) overloaded HD patient is almost always hypertensive
- a hypertensive HD patient is almost always Na+ (ECV) overloaded
- a normotensive HD patient is almost always at dry weight

# BUT...
A normal BP is a mandatory condition to assert that dry weight has been achieved. As a matter of fact, a sodium (or ECV) overloaded patient is almost always hypertensive, a hypertensive HD patient is almost always sodium (or ECV) overloaded, and a normotensive HD patient is almost always at dry weight. But a reduced or normal ECV can coexist with an increased BP (white coat effect).

Is ECV the necessary & sufficient condition of low CV morbidity/mortality?

In HD other factors than BP control may influence CV morbidity & mortality:
- Serum phosphorus control (MM dose) vs CV mortality

P<0.001
Mean serum P<1.6mmol/l
Mean serum P>1.6mmol/l

- dGMM & other vasoactive substances clearance (SM dose)
- other factors: vascular calcifications...

Is BP control the necessary and sufficient condition of a low cardiovascular morbidity and mortality on HD?

Here the answer is, of course, no. For instance as suggested recently by Block [23] a high serum phosphate and/or CaP04 product is correlated with a high cardiovascular mortality on HD. We compared the cardiovascular mortality in two Tassin subgroups of patients adjusted for age, diabetes, cardiovascular comorbidity and blood pressure. Cardiovascular mortality is significantly lower (p<0.01) in the subgroup of patients whose predialysis serum phosphate is normal (>1.60 mmol/l before dialysis) than in those where it exceeds 1.6 mmol per liter.

Many other factors do affect cardiovascular morbidity and mortality. Some are linked to the treatment, others to the patient, his life style, his disease, or his comorbidity. These factors probably explain why cardiovascular problems continue to plague long HD patients in spite of their good BP control. Among them lack of nocturnal dip, vascular calcifications, and left ventricular hypertrophy probably explain why although lower than in standard HD, the cardiovascular mortality in Tassin remains much (4 times) higher than in a standard French adjusted non uramic population.

To make a long story short, we have used Tassin data to focus on cardiovascular morbidity and mortality factors, and the way dialysis can modify them. The data show that BP extremes can be reasonably well controlled in almost all patients by increasing the dialysis session time (or alter-
natively by increasing the frequency al' sessions?). This allows 10% a reduced cardiovascular morbidity and mortality. But the result is not perfecto the normal nyctemeral rhythm al' BP is not restored in half 0' the patients. left ventricular hypertrophy persists also in about half 0' the patients, vascular calcifications are common. But al' course 1 really “optimum” dialysis needs other conditions. Out of the ECV and BP control on which wc [ou­ sed. it needs small and middle molecule large clearnnces.

Comment Vigo (B Charra)

All alike thanks lo Carlos GOMEZ-ALAMILLO and the organizing commiuce for giving us a chance to uend this exciting meeting with you. I shall use the Tassin data on Sh HD to discuss the CV morbidity & mortality on HD.

The same unchanged 3X8hr HD has been used since over the last 35 yrs. It provides a Kr/V 0' about 2 per sess­ ien. 6 per week. und a normalized PCR 0' about 1.2. The mean protein and calories intakes are large, but the sodium intake is restricted. The mean intake is 5g sodium chloride per day. The mean interdialytic weight gain is less than 2 kg. An essential feature is that no until-IT medicion is used in 95% 0' pts after the 2nd month of dialysis. AntiHT drugs are systematically withdrawn in each ami every pt al start 01' dialysis.

If the treatment has rellained the same. the population 0' pts has changed a lot along years as everywhere else. 1 split here our population in 5 calendar cohons frall 1968 lo 1999: DM (yellow) and nephrosclerosis (blue) have become increasingly common. The mean age at 01' (reel) proportion 0' pts with CV cOlllorbidity (grssel) increased steeply. Due to the increasing risk factors the crude mortality has increased along years.

As shown by the KM survival curves ofthese 5 cohorts crude 1110rtal mortality becomes worse and worse. This is the 1st and this is the last cohort curve with mean half life of 17 and 5 yrs respectively. But 01' course we are comparing oranges and bananas young fit pts almosl free 01' comorbi­ dity here (sho\W) ami aged. sick pts with a heavy comorbidity there A fair outcome analysis must take into account the change in case-mix by stratifying the pts into risk groups as done with the Standardize<l vlortality Ratio (SMR) shown now.

SMR adjusting 01' age. race and cause 01' renal faililre uses the standard USRDS mortality table to calculate one yr after the other the ratio between the observed and the expected number of deaths. It rellained stable all along the last 12 years in spite of the change in case mix. around half 0' the expected number al' deaths.

If we compare Tassin mortality to the only available (very old) long term French series on 4-5 hr dialysis. it appears lha! long HD mortality is about 50% lower.

Furthermore. this difference is explained by a large 2 in CV mortality is 3fold lower in Long HD.

Now. if we split our own population in 2 equal cohons of pts according to the median preHD MAP(integrated valuc) the subgroup with the lowest BP has a significantly lower mortality than the other subgroup. This difference in survival is mostly explained by a large difference in CV mortality: 12.6 vs 28.5 CV deaths/ llllli pr-yrs.

So. long HD allows for a long survival. This long sur­ vival is mainly due to a low CV mortality. The main feature 01' long HD which could explain this result is the BP control.

Now is BP control really good in long slow HD?

Overall SP control is quite good witholl need for antiHT drugs. Tassin mean casual preclialysis BP is 128 over 79 within normal range according to Sixth Joint Nationa! Committee on BP eval. Ambulatory BP monitoring valves are also within normal range as defined by Slaessen except 01' the absence 01' nocturnal dip in about 50% pts. This is not a center effect.

- the same control 01' SP without amb HT control was achie­ ved in 90% 0f pts in the early 70's and is still by those who continue using long HO today ...
- But also ver' often by those who usc claily dialysis whether shon or long achieve a betler than usual control 01' BP.

How & Why does a longer (and probably a more frequent) dialysis improve BP control?

NormoTf\ can be reached in long HD by achieving a normal ECV. in other words. DW. This implies a low salt diet to avoid excessive interdialytic \V gain. a reasonable dial/sate Na to achieve a nil diffusive sodium balance. and a sufllcient UF. This is the mosl powerful tool but it is also the weakest because it is limited by the patient refilling capacity therefore by lime. Let spend some minutes on this.

Oue to the intennittent nature 0' HD the pt oscillates between a “wet (saline overloaded) state” just before. ami
a "cry" (salino deplcted) suue just after the session. During the few hrs 01' HD plasma space is UFtter, lo a nadir (show). Refilling Ircm intratissular space lags snrne hours behind. So at the very end 01' the run the pt is hypovolemic, he return to normovolemia a few hours later when refilling is completed. This unphysiology of intermittent HD is a critical issue which leads alternatively to hypertension and hypotension. 

To complete this view I must point at the fact that long slow HD not only reduces HTA but also OTA episodes. As displayed here hypotensive episodes prevalence is less in long than in short HD session. It is clear in our own unit when comparing Shr (7% OTA) to 5 hr (13%) sessions. but even more lor even shorter sessions (20% or more OTA). The reduction olb01.h HTA and OTA by a longer 01" probably more frequenu session has a logic.

When session time decreases. UF rate lncrcases a aTA gets more common. This has 2 effects: The pt with a p00r perfccion r uccptance all' HD & asks or shorter sessions. The RN has to cut down the UF rate/give saline so that prescribed DV is not achieved. The physician wrongfully reevaluate DW. Orten he increases diyalysate Na which reduces the diffusive loss of Na, & leads to increased osmolality. thirst & weight gain. Altogether the pt does not get 10 DW but is overloaded & HT. He needs more UF. eventually antiHT drugs which potentiate further OTA. Intercdialytic Ht' & intradialytic aTA keep on amplifying each other in a vicious circle...

Does HTA impact on mortality in HD? The question sounds curious given Framingham and many other studies evidence in non-uremic patients. and the natural answer is

YES HTA increases mortality in dialysis. many studies (a few of whom only are displayed here) have shown that mortality decreases with control ol 'HTA

According to these studies HT is very common in HD. it is a risk factor for ror stroke, coronary disease. left ventricular hyponerphy and congestive heart failure. And it is ol' note that mortality associated with hYPtension is a long-term effect (20 years).

On the other hand. according to others studies. solleol' thcll shown here. the relationship between HTA and 1110rality is NOT established. And according to several ol' them. conversely. it is OTA and NOT HTA which is related to mortality. What can be said about this paradox? and first. what do we know about aTA on dialysis? First aTA (excluding ol' course hypotensive episodes during the session) is not very ODIM1mon in HD. it is a II11aker ol' poor snchina condition: especially CHF or frailty. A low BP especially diastolic may be as ror non-uremic pts a coronary risk factor but a causal relationship is not established. The mortality associated with hypotension is mostly short-term.

So which is the killer? HTA or UTA?

Altogether if we plot the mortality (yellow line) against MAP. the lowest mortality correlates with norm101 tension. Mortality is higher in 1ITA. but also with hypotension. In fact this U curve is misleading: -1 st. because we artificially display 011 the same curve all' mortality whether short- (OTA) or long-term (HTA): -2 nd. because studies use 0BP estinates lo correlate with monalily. I shall illustrate this second point with our own population.

This is Tassin KM mortality curve as a function ol' BP in 3 sub-groups of pl'S according to their mean predialysis MAP calculated all over their mainenance dialysis time: the low BP subgroup (green) has the best survival. the high BP subgroup rorange: the worst, the intermediate. an intermedia­diate survival. It is something I already presentcased earlier. Now if we take for the sake of this pts their initial predialysis sI1AP as predictor.

We come out with an inverse correlation: initially the pts with a low initial MAP (green) have the highest morbility & conversely. Alter 5-6 yrs 01' FU this relationship inversed. One must point al the fact that al start ol' HD when 90% 01' pts are HT, a low BP is a marker ol' severe heart disease or fraility which correlates with early mortalily. Mazzucchi from Uruguay showed the same thing in a recent paper (but mortality was...).

So altogether aTA is a marker of short-term 1110rality. HTA is a cause of long-term mortality. the same U curve pattern has been described in non urcemic patients.

Anyway the questionable risk induced by hypotension is not a mandate to undertreal HTA whose risk is well established.

I have 2 remaining questions to address: the Jst (me: Is ECV control the necessary and sufficient condition ol' SP control in HD? A normal SP is a mandato1' condition to assert that D1V has been achieved: as a matter ol' fact a Na+ (ECV) overloaded patient is almost always hypertensive. a hyper­tensive 1-ID patient is almost always Na+ (ECV) overloaded and a normotensive HD patient is almost always at dry weight. But.

A reduced or normal ECV can coexist with an increased SP (while COart effect, renovascular HTA. pheochromocytoma. hypercalcemia...). and on the other hand an increased ECV can coexist with a normal ol' decreased BP (antihypertensive Tl. CHF and so forth...).

So. Volume Xs is by far the 1St determinanl of HTA in dialysis but other factors do exist that must be kept in mind.

2nd Question now: Is BP control the necessary and sufficient condition olo' a low cardiovascular morbidity and mortality on HD. 1're the ansVer is 01' course NO.

For instance as suggested recently by Block a high serum phosphorus and/or Ca×P product is correlated the high CV Illortalily ol' HD. As an illustration I compared here the CV mortality in 2 Tassin subgroups of pl'S adjusted rol' age. D1V and CV comorbidity & BP. It is significantly lower in pl'S whose predialysis serum phosphorus is normal than in those where it exceeds 1.6 ml11ol per liter. Other
Iactors do affect CV morbidity and mortality.
Some are linked to the treatment others to the patient, his Jire style, his discase, his comorbidity, and so forth. These factors probably explain why in spite of a very good BP control cardiovascular problems continue to plague long HD pts. Among them lack of nocturnal clip, vascular calcifications, LVH that probably explain why although lower than in standard HD, the CV mortality in Tassin remains much higher than in a standard French adjusted population.

To make a long story short, I used Tassin data to focus on CV morbidity & mortality factors, and the

way dialysis can modify them.
But of course optimal dialysis needs additive interconnected conditions. Out of ECV and BP control which I focused, it needs small and middle molecule large clearances, adequate nutrition, and probably severa! other conditions. Each of these conditions is mandatory. Any of them if not fulfilled may wreck the whole ship. But we must keep in mind that everywhere including in Tassin the CV mortality remains by fur the first cause of death, the one we must control first. It is on this that we must plan any perspective policy aiming at beuer results.

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