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Daily hemodialysis: An underutilized technique despite its benefits

(L'hémodialyse quotidienne, une technique sous-utilisée malgré ses bénéfices hémodynamiques)

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Summary

Hemodialysis patients are at high cardiovascular risk, linked to both classic comorbidities (hypertension, diabetes, age) and chronic kidney disease itself. Their cardiovascular mortality is thus considerably higher than in the general population, partly due to the hemodynamic constraints induced by thrice-weekly hemodialysis, which is nevertheless performed in more than 90% of patients. This modality leads to alternating phases of acute hemodynamic stress during the session (with a risk of hypotension and ischemia) and chronic overload between sessions (promoting hypertension, pulmonary edema, and left ventricular hypertrophy).

Intensive hemodialysis (daily or prolonged) improves various parameters, which this article summarizes based on recent medical literature:

- Arterial hypertension: Meta-analyses and the FHN trial demonstrate a significant decrease in blood pressure and left ventricular hypertrophy, with a reduction in the use of antihypertensive drugs.
- Per-dialytic hypotension: Studies (FHN, RECAP, Murashima) show a decrease in the frequency of hypotensive episodes and improved hemodynamic stability due to lower volume variations.
- Myocardium: Conventional HD is particularly associated with myocardial stunning, a factor in ventricular dysfunction and mortality. Daily HD significantly reduces these contractile abnormalities.

- Post-dialysis recovery: Post-session fatigue, which is common and associated with excess mortality, is greatly reduced by daily HD (LONDON and FREEDOM studies), improving quality of life and psychological well-being.

Daily HD at home appears to be a promising option, facilitated by new devices; however, it is currently hindered by the lack of home visits by nurses to puncture the arteriovenous fistula. Nevertheless, it should be offered more widely, particularly to frail patients with refractory hypertension or those who do not tolerate conventional dialysis well.

Résumé

Les patients en hémodialyse présentent un risque cardiovasculaire (CV) majeur, lié à la fois aux comorbidités classiques (HTA, diabète, âge) et à la maladie rénale chronique elle-même. Leur mortalité CV est ainsi considérablement plus élevée que dans la population générale, en partie à cause des contraintes hémodynamiques induites par l'hémodialyse tri-hebdomadaire, pourtant pratiquée chez plus de 90 % des patients. Cette modalité entraîne en effet des phases alternées de stress hémodynamique aigu pendant la séance (avec risque d'hypotension, d'ischémie) et de surcharge chronique entre les séances (favorisant HTA, œdème pulmonaire et hypertrophie ventriculaire gauche).

L'hémodialyse intensive (quotidienne ou prolongée) améliore différents paramètres que cet article résume au vu de la littérature médicale récente :

- Hypertension artérielle : des méta-analyses et l'essai FHN démontrent une baisse significative de la pression artérielle et de l'hypertrophie ventriculaire gauche, avec une réduction du recours aux antihypertenseurs.
- Hypotension per-dialytique : les études (FHN, RECAP, Murashima) montrent une diminution de la fréquence des épisodes hypotensifs et une meilleure stabilité hémodynamique grâce à des variations volémiques plus faibles.
- Myocarde : l'HD conventionnelle est particulièrement associée au « stunning » myocardique, facteur de dysfonction ventriculaire et de mortalité. L'HD quotidienne réduit nettement ces anomalies contractiles.

- Récupération post-dialyse : la fatigue post-séance, fréquente et associée à une surmortalité, est fortement réduite par l'HD quotidienne (études LONDON et FREEDOM), améliorant qualité de vie et état psychologique.

L'HD quotidienne à domicile apparaît comme une option prometteuse, facilitée par de nouveaux dispositifs, bien qu'actuellement entravée, par l'absence de possibilité de passage d'infirmier(e)s à domicile pour la ponction de la fistule artérioveineuse. Elle devrait néanmoins être davantage proposée, notamment chez les patients fragiles, avec HTA réfractaire, ou tolérant mal la dialyse classique.

Keywords: home daily hemodialysis, daily hemodialysis

Mots-clés : dialyse à domicile quotidienne, hémodialyse quotidienne



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Introduction

It is well known that dialysis patients are at very high cardiovascular (CV) risk (CVR). Indeed, classic CVR factors (age, hypertension, diabetes, etc.) are a major cause of chronic kidney disease (CKD) and therefore of dialysis. Furthermore, CKD itself is now recognized as a high CVR factor in its own right. Nationally, according to the REIN registry [1], almost two-thirds of dialysis patients are aged 65 or over (65.7%). In almost half of cases (45%), the cause of CKD is hypertension, diabetes, or renovascular disease. The prevalence of coronary artery disease (approx. 25%), heart failure (23.3%), lower limb arteritis (23%), and stroke (12.8%) is also particularly high in this population.

As a result, dialysis patients have a particularly high rate of cardiovascular morbidity and mortality. A study of the European ERA-EDTA registry [2] shows that CV mortality in the dialysis population is 8.8 times higher than in the general population. Older studies showed an even higher level of risk (10 to 20 times higher) [3].

Despite this marked cardiovascular fragility, more than 90% of dialysis patients in France undergo a discontinuous purification process: hemodialysis (HD) three times a week [1]. However, this technique is characterized by two alternating phases of hemodynamic stress: an acute stress phase during the dialysis session itself, marked by a reduction in blood volume due to ultrafiltration (UF) and rapid hydroelectrolytic variations (with a risk of hypotension, ischemic organ damage, arrhythmia, etc.), and a phase of chronic hemodynamic stress, corresponding to the interdialytic period, marked by a risk of fluid overload, hypertension, pulmonary edema, and left ventricular hypertrophy in particular [4]. Foley's study [5] demonstrated that CV morbidity and mortality are significantly more frequent in dialysis patients at the end of the longest interdialytic interval (after 2 days without dialysis).

It therefore seems theoretically beneficial, in order to limit the risk of cardiovascular events, to limit volume variations and thus "spread" UF over a longer period of time, with a view to normalizing the patient's hydrosodium pool. This is also closer to physiological renal function, which is continuous. Several studies show a positive correlation between UF rate and cardiovascular morbidity and mortality in hemodialysis patients [6, 7]. In Flythe's article [6], the risk of all-cause and cardiovascular mortality increased significantly at UF rates >10 mL/kg/h. In Raimann's article [7], UF rates >760 mL/h were consistently associated with excess mortality. The "critical" UF rate appears to be lower than in Flythe's study, at around 7 mL/kg/h in patients with a dry weight of less than 100 kg. This correlation between UF and mortality was more linear when the hourly UF rate was related to the patient's body surface area rather than their dry weight.

So-called "intensive" HD, which consists of longer or more frequent sessions, could provide a solution to this problem. From a conceptual point of view, it allows dialysis to be performed with less volume fluctuation and therefore less CV stress.

In light of recent literature, it seems to us that daily hemodialysis remains underutilized despite its apparent benefits.

1. Benefits of “intensive” HD on high blood pressure

Hypertension is a frequent cause and consequence of CKD and persists in 50% to 90% of hemodialysis patients according to studies. This condition remains a major risk factor for CV morbidity and mortality in this population [8].

Meta-analyses by Liu [9] and Susantitaphong [10], of which the former compiles results from more than 22,000 patients, and the latter more than 900, show that long nocturnal hemodialysis [9] and frequent (≥ 3 times per week) or long (≥ 4 hours per session) HD [10] are superior to conventional HD (CHD, three times a week) for controlling hypertension, with a significant decrease in systolic (SBP) and diastolic (DBP) blood pressure (low in Liu’s study, and -14 and -7 mmHg in Susantitaphong’s study) and left ventricular hypertrophy (LVH), even though patients take fewer antihypertensive drugs.

The FHN (*frequent hemodialysis network*) study [11], published in 2015, analyzed the effect of intensive hemodialysis on hypertension. Patients were randomized into a group receiving HD six times a week or a group receiving CHD, with two sub-trials: one involving “daily” dialysis (“*daily trial*”) conducted on 245 patients, and the other involving nocturnal dialysis (“*nocturnal trial*”) with 87 patients. From the second month onwards, SBP and DBP decreased significantly in the intensive HD groups, by an average of approximately 7 and 4 mmHg, respectively, compared with CHD. This was correlated with a significant decrease in dry weight in the daytime HD group. This benefit was maintained throughout the study period (1 year), and the number of antihypertensive drugs prescribed was also slightly but significantly lower in patients included in the intensive HD arm. It should be noted that the decrease in numbers was particularly marked in the most hypertensive and anuric patients.

Several studies tend to show that blood pressure control is better with intensive HD, particularly daily HD (DHD). This is primarily because dry weight is easier to achieve gradually, spread over 5-6 days a week instead of 3. This mainly affects the volume component of hypertension.

2. Benefits of “intensive” HD on episodes of intradialytic hypotension

Intradialytic hypotension (IDH) mainly occurs when the plasma UF flow rate is higher than that of plasma refilling by the interstitial sector, especially due to the lack of adaptive hemodynamic response [12] (due to a pathological cardiocirculatory system, the use of antihypertensive agents, particularly sympathetic blockers, or autonomic neuropathy). Hypovolemia can also be aggravated by a transfer of water from the plasma sector to the intracellular sector when there is a significant difference in osmolarity (and particularly sodium concentration) between the patient’s blood and the dialysate [13].

The consequences may be clinically visible (malaise, CV accident) or, more insidiously, barely noticeable or imperceptible (silent organ damage) [14].

The definition of IDH has evolved over time and is inconsistent across different studies, which makes interpretation difficult. The *Table 1* reviews the definitions of this condition according to KDIGO 2020 [15]:

Table 1. Definitions of intradialytic-hypotension according to KDIGO 2020 [15]

KDOQI 2005 definition	Other definitions used in the scientific literature	KDIGO 2020 proposed definition
Decrease in SBP ≥ 20 mmHg or MBP ≥ 10 mmHg, <u>symptomatic</u> (cramps, headache, vomiting, or chest pain), <u>or requiring intervention</u> (reduction in UF/bolus of replacement fluid)	1) Drop in SBP accompanied by an intervention (administration of saline bolus, reduction in UF, or decrease in blood pump flow) 2) Drop in SBP of 20, 30, or 40 mmHg 3) Intradialytic SBP reaching a defined nadir (90, 95, or 100 mmHg)	Any symptomatic decrease in SBP or intradialytic minimum SBP < 90 mmHg
SBP: systolic blood pressure; MBP: mean blood pressure		

Flythe et al. published an article on this subject in 2015 [16]: data from 1,409 patients in the HEMO study and more than 10,000 patients in a dialysis center (“LDO” cohort) were used to study the associations between different definitions of IDH and mortality. Patients were considered to have IDH if they met the corresponding definition during at least 30% of dialysis sessions over the study period. Depending on the definition used, the frequency of IDH in the two cohorts ranged from approximately 10% (using the KDOQI definition: a ≥ 20 mmHg decrease in per-dialysis SBP with symptoms) to 69% (using the “Fall20” definition: a ≥ 20 mmHg decrease in per-dialysis SBP without symptoms, which may indeed be too sensitive, since a decrease in BP during the dialysis session is expected in patients arriving with fluid overload).

Within subgroups of patients with per-dialysis SBP up to 159 mmHg, the occurrence of per-dialysis hypotension, defined as a nadir < 90 mmHg (frequency of occurrence: approx. 10%), was most strongly associated with 1-year mortality, with a significant odds ratio (OR) of 1.32. In the subgroup of patients with per-dialysis SBP ≥ 160 mmHg, a nadir < 100 mmHg (frequency of occurrence: approx. 20%) was most strongly associated with 1-year mortality (significant OR of 1.29). Definitions that took into account symptoms, interventions, and BP variation during dialysis were not significantly associated with mortality.

Thus, the occurrence of IDH is frequent and associated with a poor prognosis. It is also associated with an increased risk of CV events [16], loss of residual renal function, vascular thrombosis [17], and poorer quality of life for the patient [18].

The FHN study [11] also looked at this issue. Hypotension during dialysis was defined as the occurrence of at least one episode of hypotension symptoms leading to a decrease in UF or the administration of a saline bolus. Using this definition, IDH was significantly less frequent in the daily daytime HD (10.8% of sessions), thrice-weekly long nocturnal HD (9.5%), and daily nocturnal HD (3.1%) groups compared to thrice-weekly daytime HD (13.6%). In each sub-trial (daily or nocturnal), the “intensive HD” and “conventional HD” groups were well balanced in terms of all key patient characteristics (age, sex, ethnicity, comorbidities, length of dialysis, residual renal function, vascular access).

Murashima’s retrospective study [19] was conducted in 12 patients who switched from thrice-weekly HD to DHD (median age 48 years; hypertension 100%, diabetes 33%). SBP and DBP were significantly more stable in DHD compared to conventional HD, with a mean variation during sessions of 10 mmHg vs. 13.2 mmHg for SBP, and 6.1 mmHg vs. 7.7 mmHg for DBP. Using the

2005 KDOQI definition, IDH was also less frequent in the DHD group, with a significant OR of 0.36.

Finally, in the French RECAP study [20], in 94 patients who switched to DHD, the frequency of IDH, defined as the occurrence of hypotension <90 mmHg, decreased from 14.3% to 2.7% of sessions in the first quarter, stabilizing at around 4±2% of sessions during the 2 years of follow-up.

These studies confirm the feeling that hemodynamics are more stable in intensive HD, and particularly in DHD, with less occurrence of IDH, probably due to less significant volume variations.

3. Direct benefits of “intensive” HD on the myocardium

Hemodialysis is associated with coronary perfusion disorders, which are themselves responsible for myocardial contractility abnormalities (“*stunning*”) and, ultimately, left ventricular dysfunction [21]. This has been demonstrated by measuring coronary flow in PET scans of hemodialysis patients, even though they have no significant abnormalities on coronary angiography [22, 23].

In a study of 70 hemodialysis patients [21], the frequency of myocardial stunning was very high: 64%. Patient age, UF volume, IDH, and troponin levels were significant and independent risk factors for stunning. Stunning was associated with increased mortality at 1 year and poorer left ventricular function.

The Jefferies study shows that DHD is also beneficial in terms of myocardial *stunning* [24]: 12 patients on CHD were compared with 34 patients on DHD (short-term in center: 12 patients; daytime at home: 12 patients; and nighttime at home: 10 patients). LVEF was similar at baseline in both groups. Patients underwent cardiac ultrasound before dialysis, 15 minutes before the end of dialysis, and after dialysis (15-30 minutes later). The results are presented in *Table II*.

↓ *Table II. Frequency and extent of myocardial stunning according to the dialysis technique used in the Jefferies study [24]*

Technique	CHD3 in center	CSD in center	Daytime HSD at home	Daily HN nighttime
Average duration per session (min)	204	142	209	467
Average UD (L)	4.1	2.6	1	1.1
% <i>stunning</i>	100	92	75	50
Average number of regions affected regions reached	4.8	4.6	3.3	3
CHD3: conventional thrice-weekly in-center hemodialysis ; CSD: in center short-daily hemodialysis five or more times per week ; HSD: at home five or more times per week ; HN: nocturnal dialysis at home five or more times per week.				

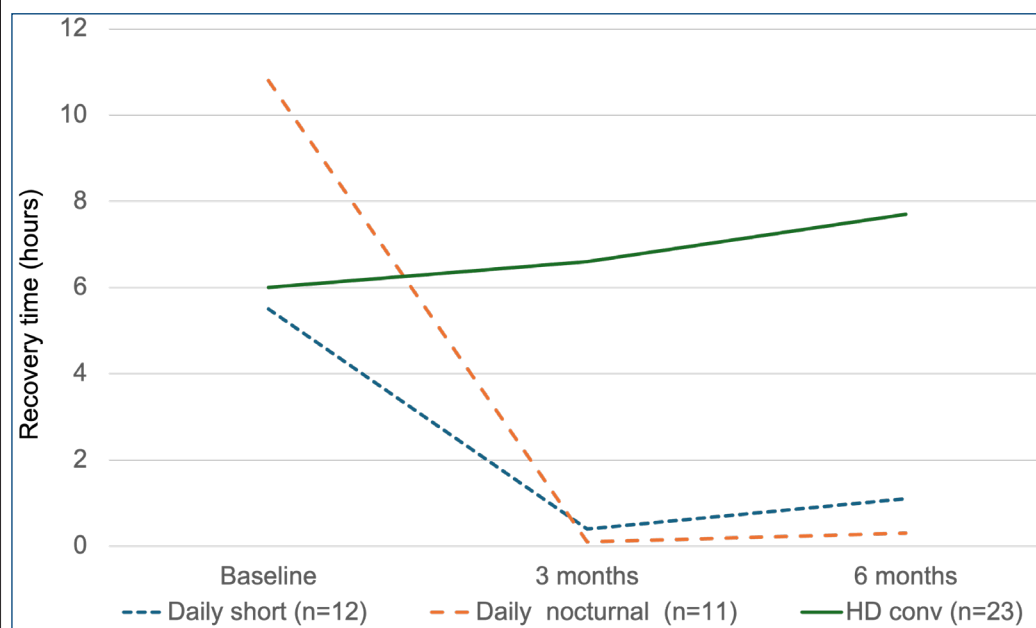
Myocardial contractility abnormalities were consistently found and more extensive in thrice-weekly HD, and less frequent and less extensive in HDQ. The occurrence of *stunning*, IDH, and SBP variability was positively correlated with UF rates, which were lower with daily dialysis techniques.

Thus, intensive hemodialysis, by reducing UF volumes and blood pressure variations, appears to limit myocardial *stunning* and preserve left ventricular function, resulting in a direct cardiovascular benefit.

4. Benefits of “intensive” HD on recovery after dialysis

Post-dialysis fatigue is very common (>80% according to an American study) [25] and is a major concern for dialysis patients, sometimes even more so than the fear of death [26]. According to the DOPPS study [27], the recovery time reported by patients is sometimes very long (>7 hours in 27% of patients), and this fatigue is associated with a significant increased risk of mortality (1 hour of recovery ↔ +5% risk of mortality) and hospitalization (1 hour of recovery ↔ +3% risk of hospitalization), as well as poorer quality of life.

In the prospective LONDON study [28], the recovery time after dialysis and quality of life were compared over an 18-month period, using questionnaires, in 23 patients who switched to HDQ vs. 22 patients who remained on conventional HD. The main results are presented in *Figure 1*.



↑ Figure 1. Change in post-session recovery time according to the dialysis technique used. Adapted from the LONDON study [28]. Shord daily and long dailys nocturnal performe 5_7 times/week. HD conv : 3 times/week

Recovery time decreased dramatically in patients who switched to daily dialysis, and this was evident as early as the third month of the study, while it remained stable and relatively long in patients who remained on conventional HD. There were also significant correlations between recovery time and fatigue, dialysis-induced stress, and quality of life.

The FREEDOM study [29] is a prospective, multicenter trial conducted in 239 dialysis patients. The benefits of switching to DHD on post-dialysis recovery time (via a questionnaire: “How long does it take you to recover from a dialysis session?”) and depressive symptoms, assessed using the Beck Depression Inventory scale, were studied. After 1 year, recovery time had significantly decreased, from an average of approximately 8 hours (476 min) to 1 hour (63 min), and the proportion of patients reporting a recovery time of <1 hour increased from 19% to 65%. A decrease in depressive symptoms was also observed.

Discussion

Numerous studies seem to confirm the intuition that hemodynamics are more stable and better controlled in DHD, with better control of hypertension, less occurrence of IDH, less myocardial stress, and better overall and mood tolerance. As a result, the patient's quality of life appears to be improved.

It also appears that phosphorus-calcium balance and potassium levels are better controlled with daily techniques [28, 30, 31]. Intensive techniques would therefore be particularly useful in reducing the risk of accidents and CV calcifications.

However, few studies are available on the benefits of DHD in terms of hard criteria such as cardiovascular morbidity and mortality or all-cause mortality. Several studies show a reduction in mortality with DHD compared to CHD, ranging from 36% to 66%, but most of these suffer from a lack of adjustment for confounding factors [30].

The Weinhandl study [30] is a retrospective cohort study that compared 1,873 patients on home HD with 9,365 patients on dialysis three times a week in a center, with satisfactory matching on many criteria of interest (length of dialysis, demographic characteristics, risk factors, and cardiovascular comorbidities). The results show that these patients represent a specific population within their dialysis center: they are younger, are more likely to be on the transplant list, suffer less from heart failure, are less likely to be hospitalized, and have been on dialysis for a shorter period. After an average follow-up of just under 2 years, better survival (HR 0.87, $p=0.01$) was found in patients receiving DHD compared to those with similar characteristics who were on dialysis three times a week in a center. The explanation for this difference in mortality remains somewhat enigmatic in this study, as the cause of death is often unknown. This benefit is particularly marked during the first 6 months of follow-up; thereafter, the difference in mortality in the intention-to-treat analysis is no longer significant. It should be noted that nearly a quarter of DHD patients discontinued this technique during the study period.

Thus, the lack of robust data and the significant methodological biases mean that the level of scientific evidence for the benefit of DHD in terms of hard criteria remains low. However, a long-term randomized trial comparing DHD and conventional HD seems difficult to envisage: this would likely create a conflict between the choice of purification technique, determined by the study, and the patient's own wishes.

The studies referenced here concern several DHD modalities, in particular low-flow DHD performed at home and DHD on conventional monitors with high dialysate flow, as is generally performed in centers. The benefits observed for one modality are not necessarily transferable to the other.

Given that DHD is conceptually more physiological and appears to be superior to thrice-weekly hemodialysis in terms of hemodynamic tolerance, it should be systematically offered to patients starting dialysis when they are presented with the various possible techniques for extrarenal purification. Patients should be informed of these advantages, especially since they are often frail, elderly, and prone to post-dialysis fatigue. This would be in line with the obligation to provide them with clear, honest, and appropriate information.

One way to reconcile DHD and quality of life is to offer home DHD. Significant progress has been made in recent years to reduce the amount of equipment required and eliminate the need for a large water treatment station at home, notably with the S3® and NxSTAGE PureFlow SL® systems, marketed by PHYSIDIA and FRESENIUS, respectively.

The inability to have a nurse come to the patient's home to perform AVF punctures is unfortunately still a major obstacle to the widespread adoption of this technique, even though it could be highly beneficial to the most fragile patients, not only from a hemodynamic standpoint, but also by sparing them repeated trips to a hemodialysis center, which must be considered an integral part of their hemodialysis treatment.

It is also important to offer intensive HD, particularly DHD, to patients already on thrice-weekly HD, especially if they have poor blood pressure control, poor hemodynamic tolerance, or significant post-dialysis fatigue.

Finally, DHD is not without risk: in particular, the arteriovenous fistula is used more frequently, and some studies, such as that by Weinhandl [30], warn of a potential increased risk of infection. Patients, their families, and caregivers must therefore be particularly well educated in aseptic technique and puncture technique.

Conclusion

So-called "intensive" hemodialysis, particularly daily hemodialysis, represents a promising alternative to conventional thrice-weekly hemodialysis for many patients. By allowing for gentler and more physiological purification, it contributes to better hemodynamic stability, more effective blood pressure control, a significant reduction in episodes of per-dialytic hypotension, reduced myocardial stress, and a noticeable improvement in post-dialysis comfort. These benefits are particularly relevant in a fragile, multi-pathological population with very high cardiovascular risk.

However, despite encouraging results, the level of evidence remains limited, particularly regarding the effects of intensive HD on long-term morbidity and mortality. It is therefore necessary to promote further randomized controlled studies to confirm these data.

In the meantime, clear and comprehensive information on the different dialysis modalities, including daily dialysis, must be systematically provided to patients in order to facilitate a shared decision that is tailored to their clinical needs and lifestyle.

Finally, the development of daily home hemodialysis, facilitated by technological innovation, paves the way for more individualized treatments, reconciling medical efficacy and quality of life. To take full advantage of this, structural and organizational barriers, particularly access to home nursing care, will need to be removed.

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Conflicts of interest

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