Effect of Beta-Blocker Cardioselectivity on Vascular Refilling in Hemodialysis Patients

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Keywords

Hemodialysis · β -Blocker · Carvedilol · Vascular refilling · Absolute blood volume · Intradialytic morbid events

Abstract

Background: β -Blockers are the most frequently prescribed cardioprotective drugs in hemodialysis (HD) patients, despite their weak evidence. We sought to evaluate the effects of β -blockers on vascular refilling during HD treatments and examine whether carvedilol, for being noncardioselective and poorly dialyzable, associates more impact than others.

Methods: The study was performed in a cohort of maintenance HD patients from a tertiary center. All patients had previous β -blocker prescription. We conducted a prospective crossover study and measured vascular refilling volume (V_{ref}) and vascular refilling fraction (F_{ref}) in 2 circumstances: under β -blocker treatment (βb profile) and without β -blocker effect (non- βb profile). **Results:** Twenty patients were included, 10 of whom were treated with carvedilol. Predialysis values were comparable between the 2 profiles. Although the βb profile showed lower V_{ref} and higher ABV drop, these differences did not reach statistical significance. Data showed an increase in F_{ref} in the non- βb profile ($70.01 \pm 6.80\%$ vs. $63.14 \pm 11.65\%$; $p = 0.015$). The βb profile associ-

ated a significantly higher risk of intradialytic hypotension (IDH) (risk ratio 2.40; 95% CI: 1.04–5.55). When analyzing separately the carvedilol group, patients dialyzed under drug effect experienced a significant impairment in V_{ref} , F_{ref} , and refilling rate. **Conclusions:** Administering β -blockers before HD associated a higher risk of IDH and a decrease in F_{ref} . Patients dialyzed under carvedilol effect showed an impaired refilling, probably related to its noncardioselectivity and lower dializability.

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Introduction

Cardiovascular (CV) disease is a major cause of morbidity and mortality among hemodialysis (HD) patients, with a prevalence up to 3 times higher than that observed in other groups at risk [1]. There is wide evidence showing beneficial effect of cardioprotective medications, such as β -blockers, in decreasing CV morbidity and mortality in general population. However, most clinical trials that analyze β -blockers' cardioprotective effectiveness exclude dialysis patients due to the risk of side effects [2–5]. Despite the poor evidence, β -blockers remain the most common CV medications prescribed in HD patients, based on their

Table 1. Pharmacokinetics of β -blockers included in the study (15–19)

	Cardioselectivity	Lipid solubility	Elimination	Half-life ($T_{1/2}$), h	Maximum plasma concentration (T_{max}), h
Moderate dialyzability					
Atenolol	Yes	Low	Kidney	6–8	2–4
Metoprolol	Yes	Moderate	Liver	3–4	1.5–2
Low dialyzability					
Bisoprolol	Yes	Low	Liver, kidney	10–12	2–4
Carvedilol	No	Moderate	Liver	6–8	1.5–2

proven efficacy in patients with normal kidney function [6]. Their mechanisms of action include [7] blood pressure (BP) lowering (due to a decrease in cardiac output), anti-ischemic action (by reducing heart rate, cardiac contractility, and systolic blood pressure), antiarrhythmic activity, inhibition of renin release and angiotensin II production (which also contributes to BP control), and left ventricular ejection fraction improvement [8, 9].

Only 2 randomized controlled trials (RCTs) have explored β -blockers' benefits in HD patients [10]: one comparing carvedilol to placebo in HD patients with congestive heart failure and dilated cardiomyopathies, showing a reduction in morbidity and mortality in the carvedilol group [11, 12]; and a second study comparing atenolol to lisinopril therapy in HD patients with left ventricular hypertrophy and hypertension, which showed atenolol's superiority in preventing CV morbidity and all-cause hospitalizations [13]. A third RCT by Roberts et al. [14] comparing carvedilol to placebo attempted to compare all-cause mortality and CV event incidence; however, they were unable to recruit planned sample size. It should be taken into account that effectiveness may differ among agents, as intradialytic kinetic is likely to vary between β -blockers: while the literature shows that atenolol and metoprolol are highly dialyzable, bisoprolol and carvedilol clearances remain lower [15]. It is also important to consider β -blocker selectivity: atenolol, metoprolol, and bisoprolol show cardioselectivity, while carvedilol is considered noncardioselective (Table 1) [16–20].

Intradialytic hypotension (IDH) is a frequent complication during HD treatments, occurring in up to 20% or more of dialysis sessions, and it associates significant morbidity secondary to end-organ hypoperfusion [21]. It is the clinical manifestation of a drop in absolute blood volume (ABV) due to ultrafiltration (UF) rate, not compensated by vascular refilling volume (V_{ref}) from interstitial to

intravascular compartment. The use of β -blockers may impair intradialytic physiologic compensatory responses to ABV drop and contribute to IDH development [22]. However, there is scarce evidence supporting this hypothesis, as ABV and V_{ref} measurement has not been easily accessible to direct investigation for years [23]. Recently, a new methodology has been reported that allows clinicians to easily and noninvasively calculate ABV and estimate V_{ref} based on the infusion of 240 mL of purified dialysate and the analysis of RBV changes [24, 25]. A first retrospective study conducted by our group suggested that HD patients under β -blocker treatment tend to have lower vascular refilling fraction (F_{ref}) [26]. It is the aim of this study to analyze how β -blockers modify vascular refilling during HD treatments and examine whether carvedilol, for being noncardioselective and poorly dialyzable, has more influence on intradialytic hemodynamics than other β -blockers.

Materials and Methods

Participants

The study was performed in a cohort of maintenance HD patients from a tertiary center and was approved by the local ethics committee. Inclusion criteria were ages >18 years, previous β -blocker prescription, and ability to read informed consent. All subjects were dialyzed thrice a week under online hemodiafiltration modality and high-flux dialysis membranes.

Study Design

We conducted a prospective crossover study, using the blood volume biosensor (BVM) included in 5008 online hemodiafiltration monitors (FMC[®]; Bad Homburg, Germany). Every patient had ABV, V_{ref} , and F_{ref} measured in 2 different circumstances: under β -blocker treatment (βb profile) and without β -blocker effect (non- βb profile). For the βb profile, patients were asked to take the β -blocker 2 h before the dialysis treatment (according to average drug maximum plasma concentrations), and for the non- βb profile, β -blockers were discontinued following each drug half-life

(Table 1). Measures were performed in a randomized order, all of them in the first dialysis treatment of the week. Dialysate temperature was maintained constant at 36.0°C. UF volume was established according to clinical criteria.

ABV, V_{ref} and F_{ref} Measurement

ABV at the beginning (ABV_b) and at the end (ABV_e) of the dialysis treatment, V_{ref} and F_{ref} were calculated using the methodology recently proposed by Kron et al. [24, 25]: RBV was continuously monitored by BVM. Treatments were started without UF. Within the first 15 min of the treatment, ABV_b was calculated by infusing 240 mL of ultrapure dialysate into the venous blood line, at a rate of 200 mL/min. Blood flow was reduced to 50 mL/min during bolus administration. RBV was recorded before and immediately after the procedure. Once the measure is completed, UF must be started, adding the volume infused for the test in order to achieve dry weight.

Initial ABV was calculated as

$$\text{ABV}_b = \frac{V_{\text{bolus}}}{10 \times (\text{Post RBV} - \text{Pre RBV})},$$

where ABV_b is measured in liters (L), V_{bolus} is the volume of the bolus infused (measured in milliliters, mL), and Pre-RBV and Post-RBV are the RBV measured immediately before and after the bolus infusion (measured in percentage, %).

For calculating ABV_e , there is no need to infuse another bolus, and only RBV must be recorded in the last 15 min (Final RBV). The ABV_e equation has been corrected according to a recently published erratum [27]:

$$\text{ABV}_e = \frac{\text{ABV}_b \times \text{Final RBV}}{100},$$

where Final RBV is RBV measured in the last 15 min.

Once we determine Initial ABV and Final ABV, V_{ref} can be estimated as

$$V_{\text{ref}} = V_{\text{uf}} + \text{Final ABV} - \text{Initial ABV}.$$

Vascular refilling fraction (F_{ref}) is calculated as the ratio of V_{ref} to prescribed UF volume:

$$F_{\text{ref}} (\%) = \frac{V_{\text{ref}}}{V_{\text{uf}}}.$$

IDH Definition

There is yet no evidence-based consensus in the definition of IDH: while some definitions are based exclusively on systolic blood pressure (SBP) or mean arterial pressure reduction, others require associated symptoms or dialysis staff intervention [28–33]. In order to be able to compare more easily, we agreed to use IDH definition proposed by Kron et al. [24, 25], also applied in previous studies from our group: an SBP decrease above 20 mm Hg during HD (calculated as the difference between predialysis and lowest blood pressure) accompanied or not by symptoms [34, 35].

Statistical Analysis

Results are expressed as mean $\pm$ standard deviation, median, or percentage, as appropriate. Each patient serves as his/her own control. Normal distribution of the data was determined using the Shapiro-Wilk test. The paired t test was performed to compare matched data. All analyses were carried out using SPSS Version 20.0. The significance was set at $p < 0.05$.

Results

Patient Characteristics

A total of 20 individuals receiving maintenance HD were included in the study. Overall, study patients had a mean age of 74.9 ± 8.0 years, 16 were men, and the most common end-stage renal disease (ESRD) cause was diabetic nephropathy ($n = 9$), followed by nephrosclerosis ($n = 5$). Mean HD vintage was 26.6 ± 24.5 months. CV disease was frequent among the cohort: 14 patients had atrial fibrillation, 12 had ischemic cardiopathy, and 17 patients had cerebrovascular disease. According to inclusion criteria, all patients had previous β -blocker prescription: 2 patients were receiving atenolol, 4 patients metoprolol, 4 bisoprolol, and 10 patients had carvedilol prescription. Other antihypertensive drugs prescribed were calcium channel blockers ($n = 14$), α -blockers ($n = 10$), and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers ($n = 5$).

Mean HD duration was 219.00 ± 14.92 min, with a mean UF rate of 836.98 ± 275.52 mL/h and a specific UF rate of 12.67 ± 4.53 mL/kg/h. Sixteen patients had a functioning arteriovenous fistula while the remaining 4 had a central venous catheter. Mean blood flow was 350 ± 39.74 mL/min.

Primary Analysis

Predialysis and postdialysis hemodynamic data are shown in Table 2. An overall analysis of the data did not show statistical differences between the 2 profiles (non- β b profile and β b profile) when comparing mean specific ABV_b (92.89 ± 24.26 mL/kg and 90.17 ± 15.34 mL/kg, respectively, $p = 0.585$) or mean specific ABV_e (79.30 ± 23.52 mL/kg and 75.14 ± 14.12 mL/kg, respectively, $p = 0.376$). UF was also similar in both conditions, with a mean value of 3.089 ± 1.071 mL for the non- β b profile and 2.972 ± 1.147 mL for the β b profile ($p = 0.365$). Although the β b profile showed lower V_{REF} and higher ABV drop, these differences did not reach statistical significance. However, a significantly higher F_{REF} in the non- β b profile was observed ($70.01 \pm 6.80\%$ vs. $63.14 \pm 11.65\%$; $p = 0.015$).

IDH Incidence

Predialysis SBP was similar in both profiles (143.5 ± 23.7 mm Hg in the non- β b profile and 144.4 ± 21.2 mm Hg in the β b profile). However, IDH was significantly more frequent when patients were under β -blocker treatment: 60% patients (33.3% were receiving bisopro-

Table 2. Predialysis and postdialysis volume data comparing non- β b profile and β b profile

	Non- β b profile	β b profile	Paired <i>t</i> test <i>p</i> value
UF volume, mL	3.080 $\pm$ 1.071	2.972 $\pm$ 1.147	0.365
Initial absolute blood volume, L	6,17 $\pm$ 1.39	6.00 $\pm$ 0.96	0.590
Initial specific absolute blood volume, mL/kg	92.89 $\pm$ 24.26	90.17 $\pm$ 15.34	0.585
Final absolute blood volume, L	5.27 $\pm$ 1.39	4.99 $\pm$ 0.89	0.332
Final specific absolute blood volume, mL/kg	79.30 $\pm$ 23.52	75.98 $\pm$ 14.09	0.357
Absolute blood volume drop, L	0.90 $\pm$ 0.30	1.01 $\pm$ 0.33	0.079
Vascular refilling volume, L	2.18 $\pm$ 0.85	1.96 $\pm$ 0.99	0.061
Refilling fraction, %	70.01 $\pm$ 6.80	63.14 $\pm$ 11.65	0.015

Table 3. Predialysis and postdialysis volume data for the carvedilol group

	Noncarvedilol profile	Carvedilol profile	Paired <i>t</i> test <i>p</i> value
UF volume, mL	3.005 $\pm$ 1.263	2.820 $\pm$ 1.111	0.083
Initial absolute blood volume, L	5.79 $\pm$ 0.78	5.72 $\pm$ 0.76	0.812
Initial specific absolute blood volume, mL/kg	88.10 $\pm$ 15.31	86.50 $\pm$ 12.23	0.774
Final absolute blood volume, L	4.92 $\pm$ 0.91	4.69 $\pm$ 0.71	0.473
Final specific absolute blood volume, mL/kg	74.66 $\pm$ 15.09	71.03 $\pm$ 11.48	0.495
Absolute blood volume, drop L	0.88 $\pm$ 0.37	1.03 $\pm$ 0.42	0.193
Vascular refilling volume, L	2.13 $\pm$ 0.92	1.69 $\pm$ 0.87	0.014
Refilling fraction, %	70.14 $\pm$ 6.55	59.54 $\pm$ 12.72	0.043
Refilling rate, mL/h	593 $\pm$ 263	478 $\pm$ 253	0.014

lol, 50% carvedilol, and 16.7% metoprolol) in the β b profile versus 25% patients (25% were being treated with bisoprolol, 50% with carvedilol, and 25% metoprolol) in the non- β b profile (risk ratio 2.40; 95% CI: 1.04–5.55).

Effect of Carvedilol on Vascular Refilling

Ten of the 20 patients included in the study had a carvedilol prescription, with a median dose of 12.5 mg per day (6.25–50). Carvedilol impact on hemodynamics analysis showed that when patients were not under its effect (noncarvedilol profile), they presented a significantly higher V_{ref} than when they had been previously exposed to the drug (carvedilol profile) (2.13 ± 0.92 L vs. 1.69 ± 0.87 L, respectively; $p = 0.014$). Similar results were found for F_{ref} ($70.14 \pm 6.55\%$ vs. $59.54 \pm 12.72\%$, respectively; $p = 0.043$) and refilling rate (593 ± 263 mL/h vs. 478 ± 278 mL/h; $p = 0.014$). Data are shown in Table 3.

Discussion

This study evaluated the effect of β -blockers on intradialytic hemodynamics among individuals receiving maintenance HD. To date, there are no previous studies comparing the effect of β -blockers on V_{ref} and F_{ref} in the dialysis population, as its measurement has not been easily available in clinical practice. Since Kron et al. [24] published their new methodology to assess vascular refilling during HD treatments, several authors have been using it to provide an in-depth understanding of hemodynamics during HD [34–38]. A first observational study conducted by our group, including a cohort of 31 dialysis patients, showed lower F_{ref} in patients under previous β -blocker treatment (mean F_{ref} of 67.82% in patients under β -blockers vs. 80.59% in patients without these drugs; $p = 0.007$) [26]. In an attempt to avoid biases, as patients receiving β -blockers might have CV comorbidities that affect their F_{ref} , we performed this crossover study to deeply investigate the relationship between β -blockers and vascular refilling.

The results show that β -blocker use among dialysis patients led to a higher risk of IDH if administered before the HD session, when compared to performing the same HD treatment without the effect of the drug (risk ratio 2.40; 95% CI: 1.04–5.55). This may be related to the fact that β -blockers impair intradialytic physiologic compensatory responses to ABV drop caused by UF, such as reduction of cardiac output and reduction of pre- and post-synaptic vasoconstrictor nerve activity, with a secondary increase in hydrostatic pressure in the capillary bed that may inhibit refilling [39]. A primary analysis showed a slightly lower V_{ref} in the βb profile when compared to non- βb profile, with a nonsignificant greater ABV drop. Moreover, data showed a significantly lower F_{ref} in the βb profile when compared to the non- βb profile (63.14 ± 11.65 vs. $70.01 \pm 6.80\%$; $p = 0.015$). These data corroborate the findings of the previously mentioned study conducted by our group [26].

We studied separately patients under carvedilol treatment, as out of the β -blockers included in the study, it is the only noncardioselective and low dialyzable, which might enhance its systemic effect. There are scanty data about the effect of carvedilol on intradialytic hemodynamics in HD patients. In the Beta-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) trial, Roberts et al. [14] attempted to advance our knowledge on carvedilol effects on HD patients compared to placebo; nevertheless, they could not recruit planned sample size: among 1,443 patients screened, only 354 met eligibility, and just 91 provided consent and finally 72 entered the 6-week run-in period. Of these, only 49 participants tolerated carvedilol therapy and progressed to randomization [14]. Cice et al. [12] also performed an RCT, mentioned elsewhere, comparing carvedilol to placebo in HD patients, showing left ventricular function and clinical status improvement. Despite its proven long-term CV benefits, no study to date has analyzed carvedilol's immediate effect on V_{ref} and F_{ref} . In this study, we found evidence that being dialyzed under carvedilol effect associated a significant impairment in V_{ref} , F_{ref} and refilling rate when compared to noncarvedilol profile. Some authors recommend that highly dialyzable β -blockers such as atenolol should be administered after HD in order to achieve longer effect, as lowering its plasma concentration during the dialysis treatment may affect patient's survival outcome [40, 41]. Since carvedilol seems to impair vascular refilling, it could also be beneficial to take this drug postdialysis in order to improve patients' hemodynamics and technique tolerance. However, larger studies are needed.

Conclusion

Administering β -blockers before HD associated a higher risk of IDH due to a greater decrease in F_{ref} . Out of β -blockers, patients dialyzed under carvedilol effect showed a lower V_{ref} and F_{ref} , probably related to its non-cardioselectivity and lower dializability. Patients might benefit from having carvedilol administered after HD.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board at which the studies were conducted (IRB Approval No. 212/19) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institute's committee on human research. Informed consent was obtained from the patients to publish.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Álvarez Nadal, Marta, contributed to conception and design of the work; acquisition and analysis of data; interpretation of data; drafting the work; revising the work critically; final approval. Viera Ramírez, Elizabeth Romelia, contributed to acquisition and analysis of data; drafting the work. García Vallejo, María, contributed to acquisition and analysis of data; drafting the work. Martín Capón, Irene, contributed to interpretation of data; drafting the work. Fernández Lucas, Milagros, contributed to conception and design of the work; interpretation of data; revising the work critically; final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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