

A Standard, Noninvasive Monitoring of Hematocrit Algorithm Improves Blood Pressure Control in Pediatric Hemodialysis Patients

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Accurate dry weight assessment is difficult in pediatric hemodialysis patients but is essential to prevent chronic fluid overload, hypertension, and cardiovascular morbidity. A noninvasive monitoring (NIVM) of hematocrit-guided ultrafiltration algorithm was studied prospectively in 20 pediatric hemodialysis patients. The algorithm targeted the first 50% of total goal ultrafiltration to be removed during the first hour of dialysis with a maximum blood volume change of 8 to 12% per hour. The second 50% was removed during the remaining treatment time with a maximum blood volume change of 5% per hour. Data that were collected at baseline and 6 mo included weight, BP, number of antihypertensive medications, 24-h ambulatory BP monitoring (ABPM), echocardiogram, and ultrafiltration-associated symptoms. Sixteen of 20 enrolled patients completed the study. No difference was seen between baseline and 6-mo weight, predialysis casual BP, nighttime ABPM, or left ventricular mass index. There was a decrease in postdialysis casual systolic BP, daytime ABPM, number of antihypertensive medications prescribed, and rate of intradialytic events related to ultrafiltration (all $P \leq 0.05$). Adoption of a standardized NIVM-guided algorithm led to (1) improved ABPM profiles, (2) decreased antihypertensive medication burden, and (3) decreased ultrafiltration-associated symptoms. Wider use of NIVM-guided ultrafiltration may decrease cardiovascular morbidity in pediatric hemodialysis patients.

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Cardiovascular morbidity and mortality remain high in both children (1–3) and young adults (4–6) who are on long-term hemodialysis (HD). Left ventricular (LV) hypertrophy is common in pediatric HD patients (7) and is a known risk factor for cardiovascular mortality in adults (8). Of the risk factors for developing LV hypertrophy, hypertension and chronic volume overload are two of the most significant (9).

Despite the known significance of chronic volume overload as a contributor to hypertension in HD (10), both estimating and achieving dry weight in pediatric HD patients can be difficult for a number of reasons, not the least of which is growth while on dialysis. A technique that may help attain better control of volume status is continuous noninvasive monitoring of the hematocrit (NIVM). NIVM has been proposed as a more accurate method of estimating the dry weight in both adults and children (11–14). An NIVM-directed ultrafiltration (UF) algorithm was believed to reduce the hospitalization rate for severe fluid overload in a pediatric HD population at a

single center, although the patients studied had already been receiving NIVM before the algorithm was introduced in that dialysis unit (15).

More accurate determination of dry weight and more consistent attainment of dry weight during HD should improve BP control in this population. However, little is known about the effects of using NIVM on cardiovascular parameters in children who are on HD. The aim of this study, therefore, was to evaluate prospectively the effects of introducing an NIVM-guided UF algorithm on BP control and LV mass (LVM) in pediatric HD patients who previously were naïve to NIVM. It was hypothesized that the introduction of NIVM during HD would result in improved BP control and reduced LVM.

Materials and Methods

Study Design

This was an uncontrolled prospective study that compared clinical data before and after institution of a standardized NIVM protocol at two pediatric HD centers (Columbus Children's Hospital, Children's Hospital at Montefiore). Patients were used as their own controls because of the limited number of individuals available and the variations in age, size, and underlying disease. NIVM was performed using the CRIT-LINE instrument (Hema Metrics, Kaysville, UT), which calculates the hematocrit using a photometric technique that is based on the absorption and scattering of light by erythrocytes (16,17). Under the

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assumption that the total red cell volume remains constant during the HD session, changes in the hematocrit will be inversely proportional to changes in the blood volume.

Inclusion criteria were age between 6 and 21 yr, being on chronic HD therapy for at least 1 mo, and expectation of remaining on HD for the 6-mo study period. Exclusion criteria were previous use of NIVM, planned living-donor renal transplant within the study period, and a history of noncompliance with attending HD treatments. The study adhered to the Declaration of Helsinki and was approved by the local institutional review board at each center. Written informed consent was obtained for each patient before enrollment.

Baseline data were collected during a period of 1 wk, during which NIVM data were recorded electronically during HD treatments, but the HD unit staffs were blinded to the recordings. During the baseline period, adjustments to the HD prescription were made as indicated by conventional clinical criteria. The baseline period was followed by a 6-mo intervention period, during which a standardized NIVM-guided UF algorithm was followed during each HD session.

NIVM Algorithm

Under the NIVM algorithm, 50% of the total UF goal was removed during the first hour of treatment, with a maximum blood volume change limited to 8 to 12% per hour. The second 50% of the UF goal was removed during the remaining treatment time, with the maximum change in blood volume limited to 5% per hour. This algorithm was based on previous work that suggested that adverse intradialytic events such as hypotension were less likely in children using this algorithm (18). Dialysis nurses from the two participating centers were trained in use of the NIVM algorithm at Texas Children's Hospital before the study. For ensuring adherence to the NIVM algorithm, all NIVM blood volume curves were reviewed by an investigator outside the two participating units (S.L.G.), with feedback provided to the participating units as necessary.

Once a week, UF was minimized 15 min before the end of the treatment to assess for plasma refilling. Depending on whether the plasma volume readily refilled during UF minimization (indicated by a decrease in hematocrit), the dry weight was adjusted. Similarly, after an intradialytic morbidity event, UF was minimized to assess whether the event was due to inadequate plasma refilling. If the hematocrit readily decreased indicating an easy plasma refill, then the dialysis nurse would resume UF. The decision to pause and resume UF or institute other interventions such as administering a fluid bolus to address intradialytic morbidity events were left to the discretion of the dialysis unit staffs.

Outcome Measures

Variables that were measured with each HD session during the baseline and intervention periods included the following: Number of dialysis-associated morbidity (DAM) events, estimated dry weight, pre- and post-HD weight, and pre- and post-HD casual BP. The mean weights and casual BP during 1 wk were used in the data analysis. DAM events were defined as the occurrence of hypotension, dizziness, cramping, headache, nausea, or vomiting that required a nursing intervention (saline bolus, hold/stop UF, terminate HD early, or Trendelenburg positioning).

Within 1 mo before and after the study period, 24-h ambulatory BP monitoring (ABPM) was performed. ABPM data were recorded using an oscillometric device (Spacelabs 90217 monitors; Spacelabs Medical, Redmond, WA). The monitors were placed on the patients after HD and worn for the next 24 h. The monitors were programmed to record BP every 20 min from 6 a.m. to midnight and every 30 min from

midnight to 6 a.m. LVM index (LVMI) was measured within 4 mo of starting NIVM and within 3 mo after the study period (mean 7 mo between measurements). LVM was measured using standard two-dimensional guided M-mode echocardiography according to criteria that were established by the American Society of Echocardiography (19). LVMI ($\text{g}/\text{m}^{2.7}$) was indexed to patient height raised to the 2.7 power to account for body size, as described elsewhere (20).

To facilitate comparing BP among children of various sizes, casual BP was indexed using the values from recently published guidelines on hypertension in children (21). The BP index is calculated by dividing the patient's measured BP by the age-, gender-, and height-specific 95th percentile value as described previously (22,23). A BP index ≥ 1 indicates that the patient has hypertension. ABPM measurements were indexed to the 95th percentile for gender and height using values published by Soergel *et al.* (24).

Statistical Analyses

Data in this study are expressed as mean \pm SD unless otherwise specified. Two-sided paired *t* test was used to compare pre- and post-study weight, BP, and LVMI data. χ^2 analysis was used to compare frequency of DAM events and the use of antihypertensive medications. $P \leq 0.05$ was accepted as statistically significant for all analyses.

Results

Patients

A total of 20 patients were enrolled between the two centers (eight in Columbus and 12 in the Bronx). The mean age of the patients was 17.5 ± 2.8 yr (range 10 to 20 yr). Nine patients were female, and 11 were male. The cause of ESRD included FSGS ($n = 7$), HIV nephropathy ($n = 4$), other glomerulonephritides ($n = 3$), obstructive uropathy/dysplasia ($n = 3$), and other ($n = 3$). The median time spent on HD before study enrollment was 11.5 mo (range 1 to 64 mo). One patient had converted from peritoneal dialysis to HD 1 mo before entering the study. His HD prescription (including dry weight) did not change for 2 wk before enrollment. The remaining patients had been on HD for at least 4 mo. Sixteen of the 20 patients completed the 6-mo intervention period (six in Columbus and 10 in the Bronx). The reasons for dropout included deceased-donor renal transplant ($n = 2$), switch in dialysis modality to peritoneal dialysis ($n = 1$), and transfer out of the dialysis unit ($n = 1$). Review of the NIVM hematocrit and blood volume curves demonstrated that the targeted UF algorithm was followed in 92% of all HD treatments.

DAM

Eight patients (four at each center) had at least one DAM event during the baseline observation period. During the baseline period, these patients had a total of 26 events during 1 wk. At the end of the study period, this subgroup had a total of eight events during 1 wk ($P = 0.03$). Of these eight patients, five had fewer, one had more, and two had the same number of events. The eight patients who did not have any DAM events at baseline had a total of five DAM events during 1 wk at the end of the study period, which was not significantly different from the baseline period ($P = 0.16$). These five events were observed in three of the eight patients, whereas the other five remained free of DAM events.

BP Control

The change in pre- and post-HD casual BP index is shown in Figure 1. One month after initiation of the NIVM protocol, there was a decrease in mean post-HD diastolic BP (DBP) index (0.76 ± 0.22 versus 0.71 ± 0.20 ; $P = 0.04$) and a trend toward decreased mean post-HD systolic BP (SBP) index (0.93 ± 0.13 versus 0.88 ± 0.14 ; $P = 0.06$). The post-HD BP did not change significantly for the remainder of the study. The mean pre-HD SBP index did not change significantly at 1 mo but did decrease during the study period. The pre- and postintervention BP for the 16 patients who completed the study period are summarized in Table 1. There was no statistically significant difference between baseline and 6-mo pre- and post-HD casual BP index, with the exception of a lower post-HD SBP index at the end of the study period (0.93 ± 0.13 versus 0.86 ± 0.11 ; $P = 0.04$). The pre-HD SBP index and post-HD DBP index also were lower, but the differences did not reach statistical significance ($P = 0.08$ for both).

The results of ABPM are summarized in Figure 2. Compared with the baseline period, the patients had a significantly lower ABPM index after the 6-mo study period for daytime SBP and DBP ($P = 0.05$ for both). Although the nocturnal SBP and DBP indices also decreased, these differences did not reach statistical significance (SBP index, $P = 0.09$; DBP index, $P = 0.10$). Also noted on the ABPM studies was blunted nocturnal dipping, which did not change before and after intervention (7.9 ± 9.1 versus $4.2 \pm 7.9\%$; $P = 0.33$).

Antihypertensive medication use is summarized in Table 2. During the baseline period, eight of the 16 patients were taking a total of 19 antihypertensive medications. At the end of the intervention period, these same eight patients were taking a total of just eight antihypertensive medications. Six of these eight patients each were taking fewer antihypertensive medications than at baseline, and the other two were taking the same medications. None of these eight patients were switched from one class of antihypertensive agent to another. Two of the eight patients who were not taking antihypertensive medications during the baseline period each were taking one medication at the end of the study. One of these two patients was not hypertensive but was started on an angiotensin-converting enzyme

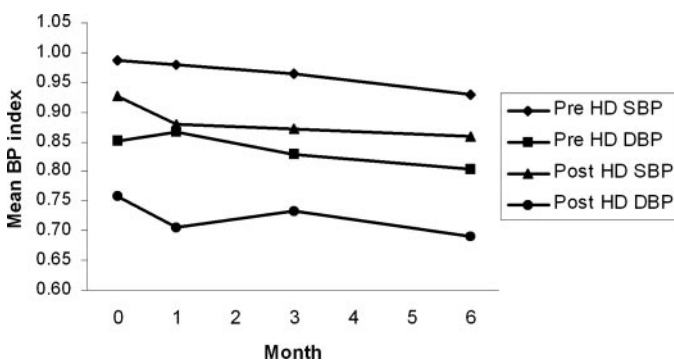


Figure 1. Change in casual BP during the 6-mo study period. Month 0 represents the baseline period. Mean BP index represents the mean over the last week of the respective study month. DBP, diastolic BP; HD, hemodialysis; SBP, systolic BP.

inhibitor for afterload reduction as a result of decreased cardiac function. The total of 10 prescribed antihypertensive medications was decreased significantly compared with the baseline period ($P = 0.04$).

LVMI

Both pre- and post-echocardiogram data were available in 11 of the 16 patients. There was no significant difference in LVMI between the baseline and 6-mo studies (41.6 ± 16.9 versus 41.2 ± 14.3 g/m^{2.7}; $P = 0.64$).

Volume Control

One month after starting the NIVM protocol, there was a significant increase in the total UF achieved (2.67 ± 1.86 versus 3.33 ± 1.38 L; $P = 0.04$), although this was not accompanied by a significant change in post-HD weight (49.25 ± 16.28 versus 49.10 ± 16.17 kg; $P = 0.62$). Comparing the baseline period and postintervention period, no significant difference was found between estimated dry weight (48.84 ± 16.83 versus 48.78 ± 15.92 kg; $P = 0.89$) or total UF (2.67 ± 1.93 versus 2.95 ± 1.30 L; $P = 0.29$). There also was no difference in post-HD weight (49.25 ± 17.14 versus 49.24 ± 15.63 kg; $P = 0.98$).

Discussion

Although long-standing hypertension in pediatric ESRD is an independent predictor of mortality (25), uncontrolled hypertension still is a common problem that affects 65% of pediatric HD patients (26). Compounding the difficulty of achieving adequate BP control is the tendency to develop more DAM events with more aggressive attempts at volume control. The current study demonstrates improved BP control, as measured by casual BP, ABPM, and antihypertensive medication requirements, 6 mo after the institution of an NIVM-guided UF algorithm during HD at two pediatric dialysis centers. Of note, these improvements in BP were achieved even as the rate of DAM events significantly decreased for the patients.

This study confirms previous findings of a reduction in the number of intradialytic symptoms related to UF in both children and adults using NIVM (18,27). In a pediatric study by Jain *et al.* (18), the data were more convincing in children who weighed <35 kg. The patients in our study mostly were older adolescents, with a mean age of 17.5 yr and a mean estimated dry weight of 48.84 kg. Only four of 16 patients weighed <35 kg, and of those four, three were between 30 and 35 kg. Of the eight patients who had DAM events at baseline and then improved, only one weighed <35 kg. Therefore, our study extends previous findings in young children by demonstrating that NIVM also is effective in reducing DAM events in older children and adolescents. Four patients had more DAM events during the postintervention period compared with the baseline period. The small number made it difficult to find any meaningful differences from those who improved.

Using historical age-matched controls, Michael *et al.* (11) showed that use of NIVM was associated with less need for non-angiotensin-converting enzyme inhibitor antihypertensive medication use in children who were on HD. Our study also confirms that routine use of NIVM can lead to a decreased

Table 1. Effect of NIVM algorithm on outcome parameters^a

Outcome Variable	Baseline	End of Study	<i>p</i> ^b
Estimated dry weight (kg)	48.84 ± 16.83	48.78 ± 15.92	NS
Pre-HD weight (kg)	51.69 ± 18.74	52.11 ± 16.65	NS
Post-HD weight (kg)	49.25 ± 17.14	49.24 ± 15.62	NS
Casual pre-HD SBP index	0.99 ± 0.16	0.93 ± 0.12	0.08
Casual pre-HD DBP index	0.85 ± 0.24	0.79 ± 0.19	NS
Casual post-HD SBP index	0.93 ± 0.13	0.86 ± 0.11	0.04
Casual post-HD DBP index	0.76 ± 0.22	0.69 ± 0.15	0.08
LVMI (g/m ^{2.7} ; <i>n</i> = 11)	41.6 ± 16.9	41.2 ± 14.3	NS

^aDBP, diastolic BP; HD, hemodialysis; LVMI, left ventricular mass index; NIVM, noninvasive monitoring of hematocrit; SBP, systolic BP. BP index equals measured BP divided by the 95th percentile value.

^b*P* > 0.10 is reported as NS.

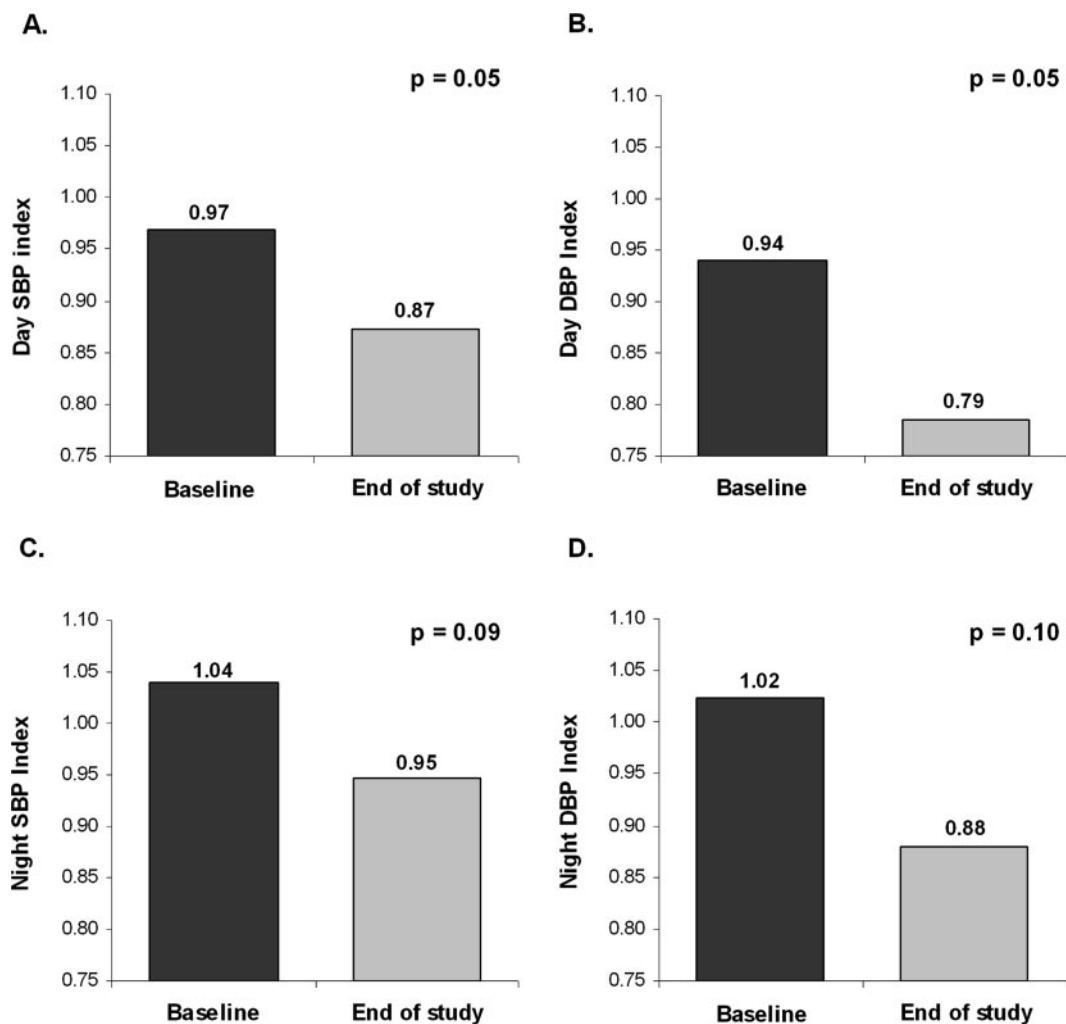


Figure 2. Effect of noninvasive monitoring (NIVM) algorithm on ambulatory BP monitoring (ABPM) profile. (A) Daytime SBP index. (B) Daytime DBP index. (C) Nighttime SBP index. (D) Nighttime DBP index. All BP were indexed to ABPM 95th percentile values for gender and height (24).

burden of antihypertensive medication use. Despite being on fewer antihypertensive medications as a group, there is evidence of decreased mean casual post-HD (and perhaps pre-HD) BP. The benefits on post-HD BP were seen as early as 1 mo

after initiation, possibly indicating an improvement in achieving dry weight. This is supported by the increased total UF achieved at 1 mo but not supported by the lack of change in post-HD weight.

Table 2. Number of antihypertensive medications prescribed by category for all patients who completed the study ($n = 16$)

Antihypertensive Medication Category	Baseline	End of Study
ACEI/ARB ^a	7	4
Calcium channel blocker	6	3
β blocker	3	1
Central α agonist (clonidine)	3	2
Total	19	10

^aACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.

To our knowledge, this study is the first to demonstrate the beneficial effect of NIVM on ambulatory BP. The daytime BP was statistically improved. The nighttime BP also improved but did not reach statistical significance, whereas nondipping did not improve at all. ABPM has been shown to correlate better with future cardiovascular morbidity and mortality than casual BP measurements in adults (28,29). Nondipping, which has been reported to be prevalent in both children and adults who are on long-term HD (30,31), still was present after the 6 mo of NIVM-guided ultrafiltration in this study.

A somewhat surprising finding was that the improvement in BP parameters was observed despite no significant change in estimated dry weight or achieved post-HD weight. The improvement in BP cannot be explained by increased use of antihypertensive medications because there was a significant decrease in the use of such medications. One possible explanation is that the patients grew during the study period and gained true weight. If that is the case, then achieving the same post-HD weight 6 mo later actually may represent an improvement in that the patients then were closer to their real weight and less fluid overloaded. The mean age at study enrollment was 17.5 yr; 10 boys and six girls completed the study. According to the Centers for Disease Control and Prevention growth curves (32), a healthy 17.5-yr-old boy typically gains 1 kg during the next 6 mo, and a healthy 17.5-yr-old girl typically gains 0.2 to 0.5 kg during the next 6 mo. Although our patients certainly are not healthy, they still could gain true weight, especially because the pubertal growth spurt often is delayed in ESRD toward later adolescence. This confirms the difficulty of accurately estimating target dry weight using conventional clinical criteria.

It was hypothesized that an improvement in BP and fluid control would lead to an improvement in LVMI on echocardiography; however, no such difference was found between the baseline and 6-mo studies. The 6-mo period may not have provided enough time to observe a significant change in LVMI. It also is possible that the degree of improvement that was achieved in daytime ABPM was not sufficient to achieve improvement in LVMI. Even with the improvement in BP, the patients in this study maintained their nondipping status on ABPM, which has been shown to be associated independently with increased LVMI in adult HD patients (31). Another expla-

nation may be that if there was no improvement in volume overload or anemia, then this may have mitigated any improvement in LVM as a result of improved BP control.

There are several limitations to this study. First, the small number of patients limits the power of the study and its conclusions. Second, there was no control group receiving standard HD without the use of NIVM for comparison. However, even if such a group existed, it still would have been difficult to draw conclusions because blinding the dialysis nursing staff would not have been feasible because of the nature of the intervention. Third, this study was a short-term study, and it remains to be seen whether the beneficial effects of NIVM that were observed during the study period would persist on a long-term basis. Finally, the generalizability of this study remains to be proved. A recent randomized, controlled, nonblinded trial on the use of NIVM in adult HD patients paradoxically showed increased mortality and hospitalization compared with the control group (33). The reason for the discrepancy between that study and this one is not clear. One obvious difference is patient age, with a mean age in the adult study of approximately 59 yr. A limitation of the adult study was that use of the monitoring and intervention algorithm was encouraged but not mandated, and its implementation was variable. In our study, 92% of the HD sessions followed the prescribed UF algorithm.

Conclusion

The NIVM-guided UF algorithm that was used in this study resulted in an improved ABPM profile, reduced need for antihypertensive medication use, and decreased rate of UF-related DAM events in a group of pediatric HD patients. Although additional data from larger studies with longer follow-up clearly are needed to confirm and extend the findings of this study, our data suggest that wider adoption of this NIVM-guided UF algorithm may decrease risk for cardiovascular morbidity and improve outcomes in pediatric HD patients.

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Disclosures

None.

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