Hemodynamic Tolerance of Intermittent Hemodialysis in Critically Ill Patients

Usefulness of Practice Guidelines

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Poor hemodynamic tolerance of intermittent hemodialysis (IHD) is a common problem for patients in an intensive care unit (ICU). New dialysis strategies have been adapted to chronic hemodialysis patients with cardiovascular insufficiency. To improve hemodynamic tolerance of IHD, specific guidelines were progressively implemented into practice through the year 1996 in our 26-bed medical ICU. To evaluate the efficiency of these guidelines we retrospectively compared all IHD performed during the years before (1995) and after (1997) implementation of these recommendations. Forty-five patients underwent 248 IHD sessions in 1995 and 76 patients underwent 289 IHD sessions in 1997. The two populations were similar for age, sex, chronic hemodialysis (26% versus 17%), and secondary acute renal failure. In 1997, patients were more severely ill with a higher SAPS II (50 $\pm$ 17 versus 59 $\pm$ 24; p = 0.036), and more patients required epinephrine or norepinephrine infusion before dialysis sessions (16% versus 34%; p $<$ 0.0001). The compliance to guidelines was high, inducing a significant change in IHD modalities. As a result, hemodynamic tolerance was significantly better in 1997, with less systolic blood pressure drop at onset (33% versus 21%, p = 0.002) and during the sessions (68% versus 56%, p = 0.002). IHD with hypotensive episode or need for therapeutic interventions were less frequent in 1997 (71% versus 61%, p = 0.015). The ICU mortality was similar (53.3% in 1995 versus 47.3% in 1997; p = 0.52) but death rate in 1997, but not in 1995, was significantly less than predicted from SAPS II (47.3% versus 65.6%; p = 0.02). Length of ICU stay was also reduced for survivors in 1997 (p = 0.04). Implementation of practice guidelines for intermittent hemodialysis in ICU patients lessens hemodynamic instability and may improve outcome.

Despite advances in renal replacement therapy, the mortality of acute renal failure (ARF) in critically ill patients remains very high (1). This poor outcome appears to be related to the high prevalence of associated organ failures and to underlying diseases. In these patients, hypotensions should be avoided to prevent a reduction in tissue oxygen delivery that may lead to organ dysfunction (2–4). This is particularly important for the kidney in case of ARF, because of the impairment of renal blood flow autoregulation. In case of acute tubular necrosis, hypotension induces new ischemic tubular damage and further reduces the glomerular filtration rate (5). Therefore, renal replacement therapy should be kept as safe as possible to avoid a delay in recovery of renal function and improvement of other organ failures (6). Maintaining hemodynamic stability is probably one of the most important aspect of this technique as well as one of the most difficult challenges (7).

(*Received in original form July 21, 1999 and in revised form November 30, 1999*)

This study was presented in part at the American Thoracic Society International Conference, San Diego, April 23–28, 1999.

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Am J Respir Crit Care Med Vol 162. pp 197–202, 2000
Internet address: www.atsjournals.org

Nevertheless, the best blood purification method for patients in an intensive care unit (ICU) remains a source of controversy. Contrarily to continuous techniques, intermittent hemodialysis (IHD) is empirically felt by many intensivists to induce hemodynamic instability. Most often, hypotension results from the underlying disease process and is exacerbated by the hemodialysis procedure (6). It has been suggested that the use of continuous methods in critically ill patients with ARF and multiple organ failures could help to improve hemodynamic tolerance (8, 9). Several studies, particularly in sepsis, argue to an improvement of hemodynamic parameters following the initiation of hemofiltration, which is able to remove some majors mediators of the inflammatory response (10–13). Nevertheless, comparative data on the hemodynamic tolerance of continuous techniques and IHD are scarce. In the only randomized crossover study to date, Misset and coworkers (14) showed that hemodynamic response to continuous hemofiltration and IHD was similar.

In addition to the development of continuous techniques, advances in hemodialysis technology now allows us to better adapt individual dialytic regimens to patients' needs. These new dialysis strategies have been developed for chronic hemodialysis patients with cardiovascular instability to reduce procedure-related hypotensions (15). Adapted dialysis strategies, however, are not systematically used in intensive care units, and their usefulness has not been well assessed (16, 17). The aim of this study was to evaluate if application of these guidelines in critically ill patients could improve hemodynamic tolerance of IHD.

METHODS

The medical ICU of Henri Mondor hospital is a 26-bed unit in a 1,000-bed university hospital. Because hemodialysis can be performed 24 h a day in the Department of Nephrology, patients suffering from uncomplicated ARF are most often managed in this department. Only patients who have an additional organ failure, mostly respiratory and hemodynamic, are admitted to the medical ICU. In this closed unit, continuous or intermittent renal replacement therapy is available and orders for hemodialysis sessions are provided by critical care physicians. ICU nurses are trained for dialysis techniques and the nurse in charge of the patient organizes, primes, and runs the IHD session. In case of IHD-related hypotension, nurses are allowed to reduce the rate of ultrafiltration and to raise the patient's legs to increase cardiac refilling. If symptomatic hypotension persists, a therapeutic intervention, that is, saline or colloid infusion, or initiation or increase of vasoactive drugs, is ordered by the physician in charge of the patient. Hemodialysis monitoring uses specific charts for recording of hemodynamic parameters every 30 min or more frequently in case of hemodynamic instability, therapeutic interventions, blood flow and ultrafiltration (UF) rates, session duration, and total ultrafiltration achieved. In addition, a special registry is filled by the nurses and contains administrative and relevant medical information on every dialysis session performed in the unit.

Guidelines Development

Since 1995, we have developed and implemented into routine practice, practice guidelines for different specific conditions in our ICU.

These recommendations concerned diagnostic or therapeutic procedures, and/or aimed at minimizing iatrogenic complications or reducing ICU costs. All guidelines were submitted to the medical ICU staff for in depth discussion, and, when approved by consensus, were included in a pocket book for individual use, given to ICU physicians and to the new residents at each rotation on arrival every 6 mo.

In 1996, we developed new practice guidelines to adapt intermittent hemodialysis conditions to critically ill patients, and after two meetings with the medical staff, all ICU physicians reached a consensus. Guidelines were published as a list of interventions aimed at improving hemodynamic stability during hemodialysis sessions. Most of those were indicated for routine use during sessions, and others were recommended only in case of poor hemodynamic tolerance during the session for the most unstable patients. The compliance to these two types of recommendations was evaluated. Additional recommendations were suggested but their use was not evaluated. Table 1 gives a list of these recommendations.

Implementation of Hemodialysis Guidelines

The first step to implement guidelines into practice has been to improve hemodialysis order forms. Before the hemodialysis session, the physician in charge of the patient had to indicate the session duration and sequential UF if necessary, the total amount and rate of ultrafiltration required, the blood flow rate, the dialysate sodium concentration, and temperature. In 1997, cuprophane membranes were no longer available and only cellulose acetate dialyzers were used (CA 170; Baxter, Maurepas, France). To facilitate implementation, the rationale for this new hemodialysis approach was explained in several teaching sessions to nurses and physicians. Repeated informal follow-up training was also performed. Lastly, a medical referent was designated and available for any questions and technical needs.

Evaluation of Guidelines Efficacy

Because the guidelines were developed and implemented into clinical practice through the year 1996, we retrospectively compared the tolerance of hemodialysis sessions performed over the year before, 1995, chosen as an historical control with those over the year following implementation of recommendations, 1997. In these periods of study, intermittent hemodialysis was carried out with the same Monitral SC dialysis system, providing ultrafiltration control (Hospal, Lyon, France). Bicarbonate baths with the same calcium concentration (1.75 mmol/L) were used for all IHD. Almost all sessions were performed using a single femoral catheter and a double-pump single-pass system. Dialysate flow rate was fixed at 500 ml/min in all sessions.

All sessions performed in 1995 and 1997 were identified through the registry, and the hemodialysis conditions were retrospectively recorded through the hemodialysis order forms and monitoring charts. Between the two periods of the study, there was no change in the supervision of IHD sessions nor in the recording of hemodynamic parameters by nurses on the specific charts. To assess the patient's severity of illness on ICU admission, age, sex, preexisting chronic hemodialysis, Simplified Acute Physiology Score (SAPS II) (18), and MacCabe score (19) were recorded for each patient. The patient's status before each hemodialysis sessions was characterized by recording the need for mechanical ventilation or inotropic support, and the baseline systolic arterial pressure. The major end-point of this analysis was the hemodynamic tolerance of hemodialysis sessions, which was assessed by recording all hypotensives episodes and the need for therapeutic interventions: saline or colloid infusion and initiation or increase of vasoactive drugs. A fall in systolic blood pressure was defined by a > 10% drop from the baseline value. The net ultrafiltration rate per session and the body weight variations over the length of dialysis treatment were collected to compare the ultrafiltration efficiency. Secondary end-points were mortality and length of stay in the ICU.

TABLE 1

INTERMITTENT HEMODIALYSIS PRACTICE GUIDELINES

Recommendations for systematic use
Use only modified cellulosic membranes in place of cuprophane
Connect simultaneously both lines of the circuit filled with 0.9% saline to the catheter
Set dialysate sodium concentration $\geqslant$ 145 mmol/L
Limit the maximal blood flow at 150 ml/min with a minimal session duration of 4 h
Set dialysate temperature $\leqslant$ 37° C
Advice for the most hemodynamically unstable patients
Start session by dialysis and continue with ultrafiltration (UF) alone
Cool dialysate at 35° C
Additional recommendations
Stop vasodilator therapy
Start session without ultrafiltration, then adapt UF/h rate according to hemodynamic response
Strictly adapt ultrafiltration order to patient's volemia and weight loss requirement

TABLE 2

PATIENTS' CHARACTERISTICS ON ICU ADMISSION

	1995 (*n = 45*)	1997 (*n = 76*)	p Value
Age, yr	57 ± 15*	60 ± 15	0.3
Male/female	13/32	18/58	0.5
Chronic hemodialysis patients, n (%)	12 (27)	13 (17)	0.2
ARF occurring during ICU stay,† n (%)	5 (11)	8 (11)	1
SAPS II score	50 ± 17	59 ± 24	0.04
MacCabe 3 classification,‡ n (%)	5 (11)	18 (28)	0.02

Definition of abbreviations: ARF = acute renal failure; ICU = intensive care unit; SAPS = simplified acute physiology score.

* Values are expressed as mean ± SD.

† Acute renal failure occurring during ICU stay was defined by a need for hemodialysis occurring after the first week in the ICU.

‡ MacCabe 3 = underlying disease fatal within 1 yr.

Statistical Analysis

Continuous variables were expressed as percentages, and categorical variables as means ± SD. A p value of 0.05 or less in a two-tailed test was considered to indicate significance. Percentages were compared with use of the chi-square test, and means with the Student's *t* test. Nonparametric tests were used when the conditions for parametric tests were not fulfilled (i.e., Mann–Whitney test for continuous variables).

RESULTS

Forty-five patients underwent 248 IHD sessions in 1995 and 76 patients underwent 289 IHD sessions in 1997. The two populations were comparable in terms of age, sex, chronic hemodialysis, and ARF occurring during the ICU stay, defined as a need for dialysis after the first week in the ICU (Table 2). Patients treated in 1997 were more severely ill as evidenced by a higher mean SAPS II score and MacCabe classification, as well as a greater number of patients who required epinephrine or norepinephrine before starting hemodialysis (Table 3). Mean baseline systolic blood pressure (SBP) was similar between the two groups. Blood urea nitrogen level and serum creatinine concentration before the first IHD session were similar (34 ± 14 mmol/L in 1995 versus 34 ± 15 mmol/L in

TABLE 3

PATIENTS' CHARACTERISTICS BEFORE EACH HEMODIALYSIS SESSION

	1995 (*n = 248*)	1997 (*n = 289*)	p Value
Epinephrine/norepinephrine use, n (%)	41 (16)	99 (34)	< 0.001
Mechanical ventilation, n (%)	183 (74)	192 (67)	0.06
Baseline systolic blood pressure, mm Hg	125 ± 24*	121 ± 23	0.09

* Values are expressed as mean ± SD.

TABLE 4

PRACTICE GUIDELINES IMPLEMENTATION

Dialysis Sessions Procedures	1995 (*n* = *248*)	1997 (*n* = *289*)	p Value
Duration, h	4.2 ± 1.0*	5.0 ± 1.5	< 0.001
Blood flow rate, ml/min	163 ± 52	156 ± 37	0.11
Isovolemic connection, n (%)	45 (18)	289 (100)	< 0.001
Dialysate sodium ⩾ 145 mmol/L, n (%)	†	195 (67)	
Dialysate temperature ⩽ 37° C, n (%)	†	289 (100)	
Sequential ultrafiltration, n (%)	0	43 (15)	
Cool dialysate, n (%)	0	38 (13)	

* Values are expressed as mean ± SD.
† Parameter not ordered in 1995.

1997, p = 0.98, and 498 ± 220 μmol/L in 1995 versus 556 ± 249 μmol/L in 1997, p = 0.22).

Compliance to guidelines was high and induced a significant change in the intermittent hemodialysis technique in 1997, with an increase of session duration, a systematic use of isovolemic connection, a limitation of bath temperature to ⩽ 37° C, a high bath sodium concentration ordered in two-thirds of IHD, and a wider use of sequential ultrafiltration and cool dialysate (Table 4).

Figure 1 shows that hemodynamic tolerance was significantly better in 1997 than in 1995. Systolic blood pressure (SBP) drop occurred less often at onset (33% versus 21% of IHD, p = 0.002) and during sessions (68% versus 56% of IHD, p = 0.002). Because the frequency of SBP recording by nurses could vary between sessions, we also analyzed the frequency of hypotensive episodes among the total number of SBP recorded per session, and found it was also less in 1997 (27% versus 19%, p < 0.001). In 1997 fewer patients undergoing IHD required saline or colloid infusion (16.5% versus 7.3%, p < 0.001), with a similar need for initiation (6.5% versus 3%) or increase (17% versus 18%) of inotropic drugs per IHD. Lastly, the number of hemodialysis sessions with hemodynamic impairment, defined by either SBP fall, saline or colloid infusion, or initiation or increase of vasoactive drugs, was less in 1997 (71% versus 61%, p = 0.015). Comparing hemodynamic stability only during the first IHD session of the patients showed that hypotension per first session was also significantly less in 1997 (27% versus 19%, p = 0.02), as well as the number of first IHD patients with a drop in SBP (p = 0.006) and patients needing saline or colloid administration (p = 0.046). Only drop in SBP at onset was not significantly different (p = 0.11) (Figure 1).

The ultrafiltration rate per hour was similar (362 ± 237 versus 383 ± 697 ml/h, p = 0.6) but fluid depletion requisite was more often reached in 1997: required UF minus real UF amounted to +135 ± 434 ml in 1995 versus −11 ± 515 ml in 1997 (p = 0.005). Mean body weight loss over the entire period of renal replacement therapy (body weight at the date of starting renal replacement therapy minus body weight at the date of ending renal replacement therapy) was available for 29 patients in 1995 and 39 patients in 1997, and was significantly greater in 1997 (−1,700 g) than in 1995 (+50 g), p < 0.001.

Despite a higher severity in 1997, the ICU mortality of these groups of patients remained similar over the 2 yr (53.3% versus 47.3% in 1995 and 1997, respectively, p = 0.52) (Table 2). The mortality rate in 1995 did not differ from the predicted death rate by SAPS II (9) (53.3% versus 45.9%, p = 0.53), whereas the observed mortality was significantly lower than predicted in 1997 (47.3% versus 65.6%, p = 0.02). Also, the median length of stay in survivors (n = 31) was significantly shorter in 1997: 11 versus 7 d (p = 0.04).

DISCUSSION

These guidelines were developed because hypotension secondary to hemodialysis is a frequent problem in ICU patients. In most ICU patients with ARF, the underlying disease is a cause of hemodynamic instability (e.g., sepsis, cardiogenic shock) before initiation of renal replacement therapy. Moreover, several additional factors often contribute to absolute or relative hypovolemia, such as bleeding, gastrointestinal tract

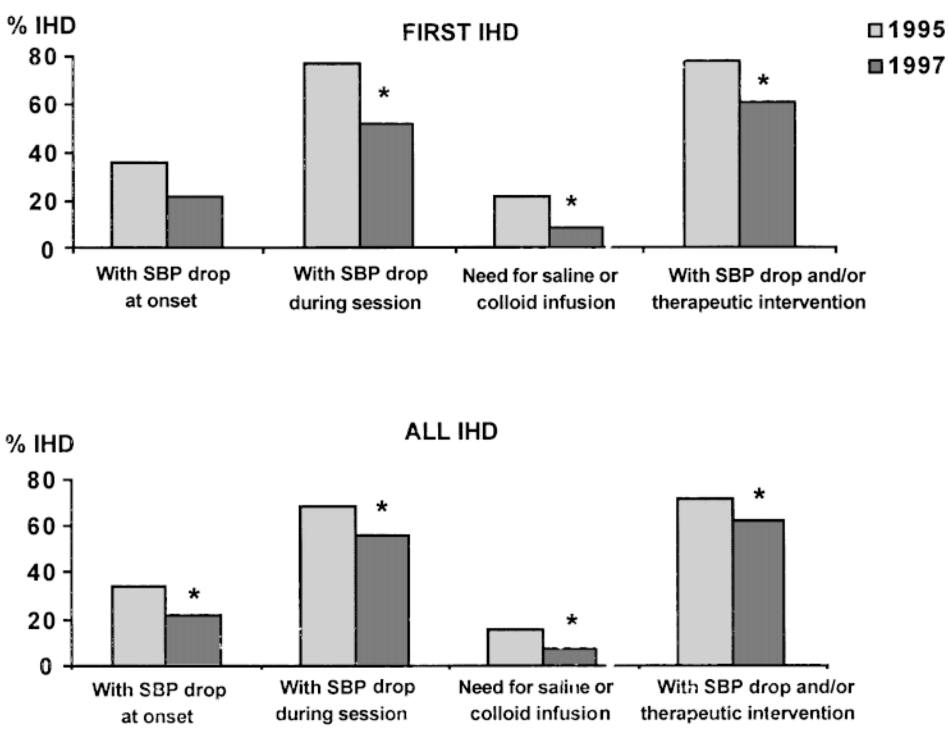

Figure 1. Comparison of hemodynamic tolerance to intermittent hemodialysis (IHD) sessions performed during the year before (1995, *open bars*) and after (1997, *gray bars*) guidelines implementation, either for the first IHD session for each patient (*upper panel*) or for all IHD sessions (*lower panel*). Hemodynamic tolerance was defined by a drop in systolic blood pressure (SBP) of at least 10% or the need for saline or colloid infusion.

paralysis, and administration of sedatives drugs. During the hemodialysis session, several procedure-related factors may exacerbate this preexisting hemodynamic instability including ultrafiltration, osmolar shifts, and temperature changes (20). Risks associated with transient but repeated hypotensions include occurrence of new organic ischemic injuries contributing to the multiple organ system dysfunction syndrome, and a delayed recovery of renal function (5, 6). In addition, hemodynamic instability during the procedure often leads to a premature termination of the intermittent hemodialysis session, and therefore to an inability to effectively remove fluids and solutes (16). In addition to the blood purification methods used, the dialytic conditions and settings probably have a large influence on its safety. To our knowledge, this study is the first evaluation of an optimized intermittent hemodialysis strategy in ICU patients. This study demonstrates the usefulness of the implementation of practice guidelines to change IHD procedures. Despite a higher severity, patients managed with the new hemodialysis strategy had better hemodynamic stability (Figure 1). The practice guidelines are based on dialysis strategies experienced in chronic hemodialysis patients suffering from cardiovascular insufficiency (15). Surprisingly, such guidelines have not been formally implemented in critically ill patients, who are even more at risk for intradialytic hypotension. Probably because of the lack of specific assessment of these guidelines in ICU patients, the lack of specific recommendations for these patients, and other reasons, these guidelines were not applied in a systematic fashion in our unit. Because of a closed organization of many medical or surgical ICUs, it is important to stress that it may be useful to introduce guidelines, developed with organ specialists when needed, and adapted to the multiorgan failure of critically ill patients and their different organ support therapies. Our study shows that hemodynamic tolerance to IHD may vary according to the conditions under which hemodialysis is performed.

Various procedures of adapted dialysis strategy may be useful to preserve myocardial function and plasma volume during fluid removal, and to adapt vascular resistances. Several invasive hemodynamic studies in ARF patients have shown an impairment of the myocardial performance during acetate-based dialysis, and a poorer hemodynamic tolerance compared to bicarbonate bath (21). Several factors, such as a rapid rate of solute removal, may induce a fall in plasma osmolality, promoting osmotic water movement into the cells and therefore inducing a reduction in plasma volume (22). To avoid rapid solute removal, we limited the hemodialysis blood flow rate and increased the duration of the session to preserve the delivered dialysis dose. Likely, one of the more useful guidelines to prevent hypotension induced by a fall in plasma osmolality is to increase the sodium bath concentration (23–25). High dialysate sodium concentration prevents a major reduction in plasma osmolality, promotes fluid shift from the interstitial to the intravascular compartments, and preserves plasma volume. In our guidelines, in addition to the minimal sodium concentration required at 145 mmol/L, we advised that the dialysate sodium concentration should be raised as the ultrafiltration rate was increased, and that ultrafiltration might be strictly adapted to the weight loss necessity. During guideline teaching sessions with staff, we advised that except in patients with cardiac insufficiency, fluid removal should be avoided at the early stage of hemodynamic disorders, unless required by respiratory distress or severe hypoxemia. After the implementation of guidelines, we observed that in 32 of 76 first IHD sessions, UF was not ordered, whereas in 1995 only 9 of 45 first sessions were performed without ultrafiltration.

Cooling the dialysate to lower body temperature and increase vascular resistances is another means to reduce the risk of intradialytic hypotension. Several studies have shown that hypothermia increases peripheral vascular resistances, resulting in better preservation of arterial blood pressure during dialysis without apparent deleterious effect (26–28). More important, however, is to avoid warming up the patient during dialysis, which promotes vasodilatation and hypotension (29). Our recommendations therefore included not only using cool dialysate for the more unstable patients but also a limitation of bath temperature to $\leq 37°$ C for all IHD. Performing ultrafiltration alone, without diffusive solute removal, may also contribute to improved hemodynamic tolerance to volume depletion, because of a better adaptation of total vascular resistances (30).

Using biocompatible membranes is another aspect of dialytic conditions adapted to patients with multiple organ system failure, which may influence patient's outcome. Two prospective comparative studies have suggested that in critically ill patients with ARF, the mortality and delay of recovery from renal failure could be reduced by using a biocompatible synthetic membrane in place of cuprophane (31, 32). Because of their high flux, the use of synthetic membranes during intermittent hemodialysis requires a pyrogen-free dialysate, because of the risk of backleak. For this reason, we used a modified cellulosic membrane, whose compatibility is better than cuprophane, in place of a synthetic membrane.

The retrospective nature of our study may have limited our ability to identify episodes of poor hemodynamic tolerance. All data were retrospectively recorded, and the risk of underestimating of a brief episode of hemodynamic impairment was probably the same between the two periods of the study. Moreover, recommendations for staff nurses, supervision methods, and recording of hemodynamic therapeutic interventions by nurses during IHD sessions were the same in 1995 and 1997. However, we defined hemodynamic impairment not only as episodes of hypotension, but also by either the need for saline or colloid infusion or by an initiation or an increase of vasoactive drugs even if no hypotension was recorded on the charts by nurses. Hemodynamic tolerance to IHD remained better in 1997, both using hypotensive episodes and a larger definition. All patients with episodes of hypotension did not necessarily need fluid infusion or drug intervention. Some episodes of hypotension were cured by decreasing the UF rate alone or raising the legs of the patients; other episodes were not treated because, despite a greater than 10% fall, the SBP remained above 100 mm Hg. This was the case in about one-third of the recorded episodes of hypotension in our study.

The design of our study does not permit us to determine which recommendation was especially useful for improving hemodynamic tolerance. We established a global program for the improvement of IHD management, then assessed the impact of all the guidelines. To our knowledge, only the use of variable sodium and UF regimens, combined with continuous plasma volume monitoring, allowing an instantaneous adaptation of sodium concentration and UF rate to patients' volemia, has been shown in prospective studies in intensive care patients with ARF to improve hemodynamic stability (25).

In our study, the significant changes observed in hemodialysis procedures in 1997 argue for their influence in the hemodynamic response (Table 4). We included chronic hemodialysis patients in our analysis because once they have an acute illness needing ICU admission, they experience problems during hemodialysis similar to ARF patients. The fact that more patients were treated by epinephrine or norepinephrine in 1997 does not seem to be the reason for their better tolerance, as baseline systolic blood pressure was similar or slightly lower in this group (Table 3). More likely, it reflects a higher severity in cardiovascular dysfunction. Moreover, the decreased need for saline or colloid infusion in 1997 was not offset by an increase of vasoactive drugs. The mean UF rate per hour, which was similar between the two periods, cannot explain the difference in hemodynamic tolerance. In addition, fluid depletion was more efficient in 1997. Indeed, in 1995 the poor tolerance of dialysis sessions often led to shorter hemodialysis duration and to increased fluid administration. Thus the expected ultrafiltration level was rarely reached in 1995, which may have contributed to patients receiving more hemodialysis sessions. The use of isovolemic connection during which patients received about 250 ml of saline fluid did not impair the efficiency of fluid depletion and contributed to preventing hypotensive episodes at the onset of sessions (Figure 1). We also compared hemodynamic response during the first IHD session, which may be considered to have an increased risk for hypotension, and found that guidelines were similarly useful (Figure 1).

In 1997, patients were more severely ill. This finding may lead to an underestimate of the actual benefit of the implementation of guidelines on hemodynamic tolerance. Despite this higher severity, and although ICU mortality remained similar, the observed mortality became significantly lower than predicted by SAPS II score in 1997 (18). It has been suggested that late onset of ARF during ICU stay, which is not taken into account by the scoring system calculated on admission, could lead to an underestimation of this predicted mortality (1). In addition, delayed ARF seems to be an independent risk factor of death in critically ill patients (1). In our study, ARF occurring late during the ICU stay had the same prevalence in 1995 and in 1997 (Table 2), and cannot explain this difference between predicted and observed mortality. Because of the nonrandomized nature of the study, the two populations were not perfectly matched, and, although this difference favored the early period, such a study design does not allow us to conclude that the implementation of practice guidelines was directly responsible for the decrease in mortality. However, a better control of hemodynamic tolerance and a better net efficiency of ultrafiltration may have contributed to the reduction in ICU length of stay, and thus may have influenced patients' outcome.

We conclude that in critically ill patients with renal failure necessitating renal replacement therapy, hemodynamic response to intermittent hemodialysis is strongly dependent on the strategy used. We have shown that despite the overall severity of ICU patients, adaptation of this technique to prevent hemodynamic impairment resulted in improved hemodynamic tolerance. The assessment of tolerance to renal replacement therapy must include the conditions in which they are performed. Furthermore, our study argues for the usefulness of practice guidelines to change ICU procedures and to improve the management of patients. The satisfactory compliance to the guidelines indicates their practicality. Nevertheless, the success of practice guidelines is dependent on the efficiency of a continuous information program for the staff and a close follow-up of compliance to and adaptation of the guidelines.

***Acknowledgment*:** The authors wish to thank all the personnel of the Intensive Care Unit who participated to the implementation of these dialysis guidelines. They particularly thank the three nurses involved in this process: Sylviane Ba, Pascale Baraffe, and Yaelle Karsenti.

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