NDT
Nephrology Dialysis Transplantation

Original Article

Intermittent haemodiafiltration in refractory congestive heart failure: BNP and balance of inflammatory cytokines

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Abstract

Background. Elevated plasma levels of cytokines have been associated with an increased risk of congestive heart failure (CHF) even in people without history of myocardial infarction. Here we have tested the hypothesis that effective removal of pro-inflammatory cytokines in patients with advanced CHF unresponsive to diuretic treatment is associated with diuresis restoration and with a significant reduction of B-type natriuretic peptide (BNP) circulating levels.

Methods. We prospectively enrolled 10 patients with decompensated CHF (NYHA classes III–IV). Five patients unresponsive to diuretic treatment underwent a short course of intermittent haemodiafiltration (iHDF), whereas five patients responsive to diuretics were treated with intravenous boluses of furosemide. Renal function was similar between the two groups.

Results. Excess body fluids were removed in both groups always resulting in a reduction of pulmonary congestion and peripheral oedema. NYHA class improved in all patients, but one treated by intravenous boluses of furosemide. Only patients treated with iHDF showed a significant reduction of circulating interleukin-8 and monocyte chemoattractant protein-1. After the end of iHDF treatment, patients showed consistent restoration of diuretic responsiveness to significantly lower doses of oral furosemide up to one month of follow-up. Plasma levels of BNP before treatment were significantly higher in the iHDF group, lowering significantly in both groups after treatment.

Conclusions. Our results suggest that HDF is an effective treatment for patients with advanced CHF when cytokines have to be cleared and diuretic responsiveness needs to be restored. In our experience, iHDF is a cost-effective option when compared with continuous ultrafiltration methods because it can be performed in a routine dialysis unit without adjunctive costs for machinery or personnel training.

Keywords: BNP; congestive heart failure; cytokines; furosemide; haemodiafiltration

Introduction

Congestive heart failure (CHF) is the end product of a vicious circle in which reduced cardiac output and impaired salt and renal water excretion have a negative impact on each other [1,2].

The management of patients with advanced CHF classically consists of sodium intake and physical activity restriction and treatments include angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, digitalis, diuretics and nitrates [3]. Loop diuretics, have long been accepted as first-line treatment of patients with severe CHF and extreme fluid retention [4,5]. Diuretics are essential despite the fact that these drugs stimulate the renin–angiotensin–aldosterone axis leading to adaptive responses that may be counter productive. However, a lack of response to diuretics is a common event, particularly in elderly patients with advanced disease. When diuretic resistance occurs, proposed therapeutic options include higher oral doses of loop diuretics or their intravenous constant infusion [6], concomitant dopamine infusion aimed at increase renal blood flow [7], or a combination of different diuretic classes providing a synergistic effect [8–10]. Extracorporeal ultrafiltration (UF) is a particularly helpful procedure allowing a sustained clinical improvement. UF reduces pulmonary and peripheral oedema, mechanical lung function improves, right atrial

pressure and pulmonary wedge pressure decrease, neurohumoral activation is reset towards a more physiological condition, and diuretic response improves. During a UF session, patients are exposed to rapid variations of body fluid composition. Since fluid is withdrawn from the intravascular compartment, blood volume falls during the procedure. The transient lowering of blood volume elicits compensatory mechanisms, such as the process of intravascular refill, which are aimed at minimizing such a reduction [11,12].

B-type natriuretic peptide (BNP) represents the biologically active fragment of the amino-terminal pro-B-type natriuretic peptide. Both peptides have mainly been used as diagnostic markers of suspected heart failure. Ventricular stretch and wall tension are thought to stimulate the secretion of such natriuretic peptides. Consequently, plasma concentrations are increased in patients with diseases characterized by expanded fluid volume (e.g. CHF). As accurate measurement of body fluid composition requires a sophisticated apparatus and techniques beyond the scope of most clinical practices, bioelectrical impedance analysis (BIA) is, instead, a relatively simple method for the examination of body fluids [13,14]. BIA is based on the principle that the electrical conductivity through the body is much greater in all body fluids and electrolytes.

Recent studies have identified the importance of biologically active molecules, such as neurohormones, as mediators of disease progression in CHF. It has become apparent that another group of biologically active molecules such as the cytokines are also expressed in the setting of heart failure [15–18]. In many forms of cardiomyopathic left ventricular (LV) dysfunction, there is a rapid myocardial expression of pro-inflammatory cytokines such as interleukin 1, interleukin 8 (IL-8) and tumour necrosis factor-alpha (TNF-α), which mediate, via specific receptors, various processes as gene expression, cell growth or apoptosis [19–21]. Myocardial expression of cytokines contributes to depression of contractile performance and adverse LV remodelling. Cytokine-induced depression of contractile performance appears to result from sphingosine production, which interferes with myocardial calcium handling. The activity of inflammatory cytokines is also influenced by anti-inflammatory cytokines such as transforming growth factor TGF-β and interleukin-10 (IL-10), which can downregulate the production of several inflammatory cytokines from macrophages and other cells [22,23]. Several studies have shown that haemodiafiltration (HDF) using porous synthetic membranes removes a wide range of circulating inflammation mediators [24,25]. Limited evidence supports the notion that this treatment can also influence circulating plasma concentrations of various mediators such as cytokines [26].

In this work, we have tested the hypothesis that effective removal of pro-inflammatory cytokines in patients with advanced CHF unresponsive to diuretic treatment is associated with a significant reduction of BNP circulating levels and diuresis restoration.

Methods

Patients

Ten patients with CHF (New York Heart Association functional classification, NYHA, classes III–IV) have been included into the study. Four patients had ischaemic heart disease, and six patients had idiopathic dilated cardiomyopathy. All patients had symptoms of dyspnoea with radiological evidence of pulmonary venous congestion and cardiomegaly, recent body weight (BW) gain (>5 kg in the last month), generalized oedema and ingravescent oliguria. Long-term medications included digoxin ($n = 4$), diuretics ($n = 10$), ACEI ($n = 8$), nitrates ($n = 4$) and amiodarone ($n = 3$). Short-term medications used for cardiac decompensation included dopamine ($n = 6$) and dobutamine ($n = 4$) in different combinations and doses. During the study period, medications were not changed. This study was approved by the Ethical Committee of the 'Fondazione IRCCS Policlinico San Matteo', Pavia, Italy. Informed consent was obtained from each patient after a detailed explanation on haemodiafitration, and the clinical and research purposes of the study was given.

Five patients (all NYHA class IV) aged 57 ± 12 years and unresponsive to oral diuretic treatment underwent a short course of intermittent haemodiafiltration (iHDF group), whereas five patients (four NYHA class III, and one NYHA class IV) aged 49 ± 13 years ($P = NS$ *vs* HDF) and responsive to oral diuretics were treated with intravenous boluses of furosemide (FUR group). The FUR group received furosemide as intravenous boluses of 160 ± 80 mg for 8 ± 5 days. Daily dosage of furosemide was defined according to urinary volume, aterial blood pressure values, severity of clinical signs and symptoms of pulmonary congestion. Renal function was similar between the two groups (Table 1). Serum and urinary laboratory parameters were measured daily.

Six healthy volunteers were studied as controls (CON group).

Eligibility criteria of HDF group

According to the definition of refractory CHF [27], CHF, as applied to the Framingham criteria and fulfilling the NYHA functional classification for CHF [28], all patients had uncompensated CHF (dyspnoea, weakness, lower limb oedema or anasarca), NYHA functional class IV that was unresponsive to treatment with oral high doses of furosemide or combinations of diuretics (thiazides, loop diuretics and spironolactone), ACEI, digitalis, beta-blockers and nitrates. Eligible patients had been under such treatment for at least 2 weeks before enrolement into the study. Patients were judged unresponsive, when despite the increase of oral furosemide dosage alone or in combination with other diuretics they showed a progressive reduction of urine volume with constant increase of BW and impairment of CHF clinical signs. None was taking non-steroidal anti-inflammatory drugs.

Haemodiafiltration

HDF was performed by using a Hospal Prisma CRRT (Mirandola, Italy). During HDF, blood was pumped

Table 1. Anthropometric, clinical and laboratory data, before (at entry, BAS), after treatment (T-end) and after 30 days (30-d)

	iHDF			FUR		
	BAS	T-end	30-d	BAS	T-end	30-d
Age (year)	51.5 ± 9.4	–	–	43.0 ± 11.6	–	–
Weight (Kg)	76.8 ± 6.1	65.7 ± 3.9*	67.1 ± 5.7*	78.6 ± 5.4	69.4 ± 6.6*	70.9 ± 5.7*
S-creatinine (mg/dl)	1.9 ± 1.6	1.4 ± 0.6	1.6 ± 0.4	1.2 ± 0.5	1.3 ± 0.8	1.2 ± 0.3
Serum BUN (mg/dl)	56.8 ± 12.4	37.8 ± 7.41*	47.0 ± 10.3*	31.1 ± 7.7	62.5 ± 11.0	29.7 ± 8.4
Serum Na (mEq/l)	132.2 ± 2.7	136.7 ± 3.11	35.7 ± 4.0	133.2 ± 5.1	135.4 ± 4.9	138.2 ± 3.7
Serum K (mEq/l)	3.6 ± 0.5	3.4 ± 0.8	3.7 ± 0.2	3.7 ± 0.4	3.5 ± 0.6	4.1 ± 0.5
Urinary Na (mEq/24)	38.2 ± 19.4	96.5 ± 28.6*	84.0 ± 17.9*	46.1 ± 13.5	102 ± 24.6*	99.3 ± 18.4*
LV EF (%)	14.0 ± 1.5	16.5 ± 1.0*	–	16.0 ± 1.0	17.5 ± 2.0	–
Furosemide os mg/day	180 ± 114	–	75 ± 38*	125 ± 61	–	94 ± 58

*$P < 0.05$ vs BAS.

through the haemofilter with an AN-69 membrane (M-100, Hospal, Italy), surface area $1 m^2$, inserted into an extra-corporeal circuit connected to a double lumen Y-shaped catheter positioned in a femoral vein. A peristaltic pump was regulated to maintain a blood flow of $130 ± 20$ ml/min. The reinfusion rate was 1500 ml/h and dialysate flow was 2500 ml/h. Heparinization was individualized with an initial priming dose of standard heparin between 2000 and 4000 UI, which was followed by continuous infusion rate of 500–1000 IU/h during the HDF sessions. In all patients, the procedure was terminated when haematocrit increased by 10% from baseline values (>3l of ultrafiltrate in all cases/session). Mean time duration of a single HDF session was $220 ± 49$ min for 4–6 sessions.

BIA measurements and procedure

Stature was measured with a movable anthropometer to a precision of 0.1 cm, and BW was measured by a portable spring scale to a precision of 0.1 Kg.

Bioelectrical parameters of resistance (R) and reactance (Xc) were measured by impedance analyzer (BIA/STA, Akern, Firenze, Italy) that emitted $800 \mu A$ and 50 kHz alternating sinusoidal currents. Current injector electrodes were positioned in the middle of the dorsal surfaces of the right hand and foot, proximal to the metacarpal–phalangeal and metatarsal–phalangeal joints, respectively. Detector electrodes were placed medially on the posterior side of the right wrist, between the distal prominence of the radius and the ulna and between the medial and lateral malleoli at the right ankle. The total time for one BIA patient analysis was ~5 min. All measurements were taken by the same experienced operator, before and after HDF or intravenous furosemide therapy.

Left ventricular function assessment

Transthoracic echocardiographic assessment was performed by a single experienced physician blinded to the rest of tests and clinical data, using a Hewlett–Packard Sonos 2000 scanner with a 2.5 MHz transducer. Measurements were taken according to recommendations of the American Society of Echocardiography. Intraobserver variability was 9%. Left ventricular ejection fraction [LVEF] was calculated using modified Simpson's rule. Left ventricular systolic dysfunction was defined as LVEF < 45%.

Cytokine ELISA assays

Plasma cytokine levels were assessed by enzyme-linked immunosorbent assay (ELISA). Antibody pairs were used according to supplier protocols. Anti-monocyte chemoat-tractant protein-1 (MCP-1) and anti-TGF-β monoclonal (MoAb) coating and biotynilated polyclonal (PolyAb) detecting antibodies were purchased from R&D System (MN, USA) and used at the following concentrations: MCP-1: MoAb clone 23007.111 at 1 μg/ml, PolyAb at 50 ng/ml (assay sensitivity 2.4 pg/ml); TGF-β, MoAb clone 9016.2 at 4 μg/ml, PolyAb at 50 ng/ml (assay sensitivity 1.9 pg/ml). IL-8 assay was performed with reagents purchased from Endogen (Woburn, MA, USA) as follows: IL-8 MoAb clone 3IL8-H10 at 1 μg/ml, detecting MoAb clone I8-S2 at 50 ng/ml (assay sensitivity 2 pg/ml). IL-10 assays were conducted with reagents purchased from Immunokontact (Frankfurt am Main, Germany) as follows: IL-10 MoAb clone 9016.2 at 4 μg/ml, detecting MoAb clone JES3-1248 at 50 μg/ml (assay sensitivity 1.6 pg/ml).

BNP assay

Venous blood samples were taken to measure BNP, after patients had been lying supine for 30 minutes, before (BAS) and after treatments (T-end), and after one month (30-d) of follow-up. All samples were measured in a single batch by an experienced technician using a standard commercially available radioimmunoassay kit (Peninsula, UK).

Follow up

During the 30-day Follow-up period, one of the five patients from the iHDF group died of irreversible CHF. One patient from the FUR group was readmitted into the hospital presenting a higher NYHA functional class than at discharge. The remaining patients maintained the same NYHA functional class achieved at the time of hospital discharge, four out of five from the iHDF group and two out of five from the FUR group, respectively. Three out of five HDF patients and three out of five FUR patients received beta-blockers, whereas all patients continued ACEI. After hospital discharge, 80 mEq sodium daily dietary intake and 1 l daily oral fluids were suggested to all patients from both groups. BW (morning, before breakfast) and 24-h urinary volume measurements were performed daily.

Table 2. BIA data of the patients investigated before (BAS) and after (T-end) the treatment

	iHDF		FUR	
	BAS	T-end	BAS	T-end
R (Ω)	431.2 ± 103.6	502.2 ± 83.2	488,2 ± 137.7	476.0 ± 89.7
Xc (Ω)	32.2 ± 9.4	43.5 ± 5.5*	38.2 ± 6.9	51.2 ± 3.8*
R/H (Ω/m)	242.3 ± 64.9	282.2 ± 51.6	277.4 ± 78.3	270.4 ± 51.7
Xc/H (Ω/m)	19.8 ± 6.0	24.4 ± 3.2*	21.7 ± 4.1	29.1 ± 1.9*
Phase angle (°)	4.2 ± 1.6	5.1 ± 1.4	4.5 ± 1.9	6.3 ± 2.1

*$P < 0.05$ *vs* BAS.

Statistical analysis

All quantitative data are expressed as mean ± standard deviation. Statistical analysis was performed using analysis-of-variance (ANOVA) models for balanced designs and repeated measures ANOVA models. Paired *t*-tests on the equality of means were also performed (Student's *t*-test). A two-tailed *p*-value <0.05 was considered statistically significant. Pearson's correlation coefficients between BNP and cytokine (IL-8 and MCP-1) plasma levels were also calculated. *P*-values <0.05 were considered statistically significant. All analyses were performed using the statistical package Stata 8.0 (Stata Corporation. College Station, Texas 77845 USA, 2003).

Results

Basal pre-treatment clinical parameters were similar in both iHDF and FUR groups (Table 1). After either treatment, clinical and radiological features of CHF significantly improved in both groups. NYHA class improved in all patients but one from the FUR group. All patients showed insufficient natriuresis despite high oral doses of furosemide alone or in combination with thiazides or potassium-sparing diuretics. Post-treatment increase of daily diuresis was observed in both groups (data not shown). Natriuresis also increased in both groups, although Na and K levels remained within normal laboratory ranges (Table 1). Serum creatinine levels did not show significant differences before and after treatment in both groups (Table 1).

All HDF sessions were performed safely, without side effects or haemodynamic instability. Mean time duration of HDF sessions was 235 ± 46 min, and mean total fluid volume removed was 3980 ± 1420 ml (range 3000–5800), resulting at the end of iHDF cycle in a mean BW reduction of 11850 ± 8420 ml (range 6500–23000 ml). A significant improvement of diuretic responsiveness after treatment was observed in iHDF patients only and consistently up to 1 month of follow-up (Table 1).

Mean duration of intravenous furosemide therapy (FUR group) was 8 ± 5 days resulting in a mean reduction of BW of 8050 ± 3740 ml (range 3200–12000 ml; *P* = NS *vs* iHDF).
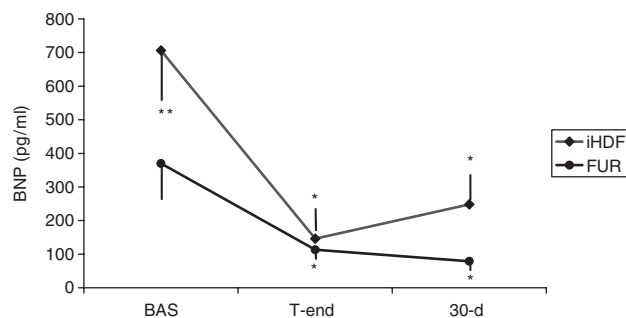

Fig. 1. BNP plasma levels of CHF patients on hemodiafiltration treatment (iHDF) and on diuretic treatment (FUR), before (BAS) and after therapy (T-end), and after 30 days (30-d). *$P < 0.05$ *vs* BAS. **$P < 0.05$ *vs* FUR.

Body fluid balance after HDF or FUR treatments

A significant reactance increase was demonstrated after treatment in both iHDF and FUR groups when compared with basal values (Table 2). Similarly, CHF patients before both treatments showed lower reactance/height ratio values than after treatments. There was no difference between pre- and post-treatment in both groups when other BIA parameters such as resistance, resistance/height and phase angle were analysed (Table 2). These results indicated that fluid overload in iHDF and FUR groups was effectively reversed.

Circulating BNP levels

Elevated pre-treatment circulating BNP levels (Figure 1) were found in both groups. The iHDF patients showed higher pre-treatment BNP levels (706.3 ± 205.6 pg/ml) when compared with FUR patients (370.6 ± 148.8 pg/ml, *P* < 0.01). A significant post-treatment decrease of BNP levels was observed in both groups at T-end (iHDF 146.8 ± 96.3 pg/ml, *P* < 0.001 *vs* pre-treatment; FUR 55.6 ± 39 pg/ml, *P* < 0.0016 *vs* pre-treatment in both groups). Such a significant decrease was also observed after 30 days of follow-up (iHDF 248.2 ± 136.3 pg/ml; FUR 79.5 ± 37.0 pg/ml, *P* < 0.001 *vs* pre-treatment in both groups).
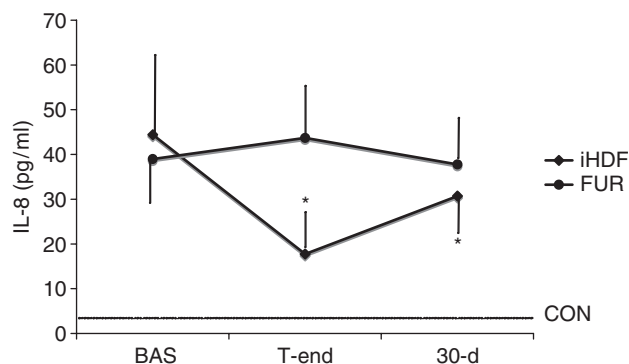
Fig. 2. IL-8 plasma levels of normal subjects (CON, dotted line), and CHF patients on haemodiafiltration treatment (iHDF) and on diuretic treatment (FUR), before (BAS), after therapy (T-end) and after 30 days (30-d). *$P < 0.05$ vs BAS.

Fig. 3. MCP-1 plasma levels of normal subjects (CON, dotted line), and CHF patients on haemodiafiltration treatment (iHDF) and on diuretic treatment (FUR), before (BAS), after therapy (T-end) and after 30 days (30-d).
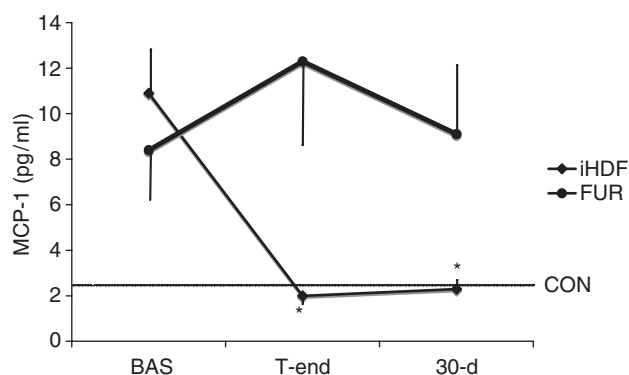*$P < 0.05$ vs BAS.

Circulating cytokine levels

Pre-treatment IL-8 circulating levels (Figure 2) exceeded significantly in iHDF (45.6 ± 32.1 pg/ml) and in FUR (39.1 ± 23.1 pg/ml) patients when compared with CON (2.7 ± 1.3 pg/ml; $P < 0.05$ vs iHDF and FUR). IL-8 in iHDF patients lowered significantly, both at T-end (17.8 ± 9.7 pg/ml, $P < 0.04$ vs pre-treatment) and at 30d (30.7 ± 15.5 pg/ml, $P < 0.04$ vs pre-treatment). FUR patients did not show differences in post-treatment circulating IL-8 levels (31.9 ± 28.7 pg/ml).

When compared with CON (2.4 ± 0.5 pg/ml), pre-treatment circulating levels of MCP-1 (Figure 3) were higher in both study groups (iHDF 10.9 ± 4.4 pg/ml, $P < 0.005$; FUR 8.4 ± 3.7 pg/ml, $P < 0.01$ vs CON). A significant lowering of post-treatment MCP-1 circulating levels was observed only in iHDF patients both at T-end (2.0 ± 0.5 pg/ml, $P = 0.005$) and at 30d (2.3 ± 0.4 pg/ml, $P < 0.005$). Circulating levels of anti-inflammatory cytokines (TGF-β and IL-10) in all CON and CHF patients but one of the HDF group was below the immunoassay detection limits.

Table 3. Pearson's correlation analysis between BNP and cytokine plasma levels before treatment (BAS), after treatment (T-end) and 30 days after treatment (30-d)

	N	R	P
BAS all patients			
BNP and IL-8	10	−0.4939	0.1468
BNP and MCP-1	10	0.2986	0.4020
IL-8 and MCP-1	10	−0.4072	0.2428
T-end iHDF patients			
BNP and IL-8	5	−0.7217	0.1687
BNP and MCP-1	5	−0.3313	0.5860
IL-8 and MCP-1	5	−0.5534	0.3332
T-end FUR patients			
BNP and IL-8	5	−0.2863	0.6405
BNP and MCP-1	5	0.8340	0.0791
IL-8 and MCP-1	5	−0.4763	0.4173
30-d iHDF patients			
BNP and IL-8	5	−0.6526	0.1275
BNP and MCP-1	5	0.4168	0.1603
IL-8 and MCP-1	5	−0.3927	0.3381
30-d FUR patients			
BNP and IL-8	5	−0.5932	0.2638
BNP and MCP-1	5	0.2446	0.4729
IL-8 and MCP-1	5	−0.1810	0.5903

N, number of patients; R, correlation coefficient; P, P-value.

Correlation between BNP and cytokine levels

The covariation in the magnitude of BNP with IL-8 or MCP-1 and the covariation in the magnitude of IL-8 with MCP-1 are not statistically significant, considering the 10 patients at baseline (BAS) and after treatments (at T-end and 30-d time, Table 3). We can conclude that, given this small sample size, we cannot reject the hypothesis of null correlation, and independence between these variables. The variation in one variable that is related to the variation in the others may be not influent in the relationship between type of treatment and BNP or cytokine levels.

Discussion

This study confirms that HDF treatment effectively removes fluid overload in patients with refractory CHF. Body fluid analysis by BIA also showed that extracellular fluid space was increased in CHF patients before therapy, and that hydration was normalized after HDF treatment.

As previously demonstrated UF improves respiratory function, and relieves ascites and peripheral oedema [3,29,30]. The benefits are usually obtained in a very short time, particularly when compared with any other available therapeutic approaches. In most patients, diuretic responsiveness can be regained, and in our study, furosemide dosages were reduced by ∼50% already the day after HDF. It has been reported that clinical beneficial effects of a single UF session last up to one month after the procedure [31].

Accumulating evidence indicates that pro-inflammatory cytokines play a pathogenic role in CHF by

influencing heart contractility, inducing hypertrophy, and promoting apoptosis or fibrosis, contributing to the continuous myocardial remodelling process. In our study, we analysed the pro-inflammatory cytokine network in patients with CHF. In part, our results confirmed previous findings showing elevated circulating levels of pro-inflammatory cytokines in CHF patients [15,16]. In particular, we have found a significant increase of circulating IL-8 and MCP-1 in CHF patients with NYHA classes III and IV. The inflammatory changes mediated by MCP-1 and IL-8 are essential and important in mediating chronic inflammation in cardiovascular disease. IL-8 and MCP-1 are relevant chemokines regulating migration and infiltration of monocytes/macrophages [32] also in injured arteries [33]. MCP-1 has been associated with chronic vascular inflammation, induces thrombosis, proliferation and migration of vascular smooth muscle cells, angiogenesis and oxidative stress.

Moreover, we have shown that pro-inflammatory cytokine circulating levels decreased significantly only in the HDF group and not in patients treated with intravenous diuretics. Several investigators have found an association between increased UF rates and cytokine removal [34]. Furthermore, filtration appears to augment adsorption [25], so that combined filtration/adsorption might be more effective than adsorption alone, at least when hollow-fibre dialysers are used. Although we observed a significant reduction of pro-inflammatory cytokines IL-8 and MCP-1 in iHDF patients, TGF-β and IL-10 levels remained unchanged and below detection limits even 30 days after treatment. Our data confirm that HDF effectively improves cardiac function and removes pro-inflammatory cytokines. In our opinion, iHDF removing pro-inflammatory cytokines can only partially improve the inflammatory state, and the advanced stage of heart failure of these patients cannot allow an increase of anti-inflammatory cytokine levels.

The activity of inflammatory cytokines is also influenced by anti-inflammatory cytokines such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) downregulating the production of several inflammatory cytokines from macrophages and other cells [15,16]. In contrast to enhanced levels of pro-inflammatory cytokines, we and others have demonstrated that CHF patients had decreased serum levels of the anti-inflammatory cytokines such as TGF-β and IL-10. Both these anti-inflammatory cytokines may have cardioprotective properties [35,36]. TGF-β seems to inhibit the release of TNF into the circulation after myocardial ischaemia, possibly acting synergistically with the suppressive effect of IL-10 [22,37]. TGF-β may also directly counteract damaging effects on the myocardium mediated by inflammatory cytokines [35]. IL-10 may also have potential beneficial effects in CHF patients by inhibiting the phagocyte pro-coagulant activity [36].

The significant and rapid reduction of circulating BNP levels, which we have found after HDF treatment, confirms the clinical data. In fact, the main stimulus for BNP peptide synthesis and secretion is cardiac wall stress [38]. Because increased wall stress is a common denominator of many cardiac diseases, it follows that BNP levels may serve as biochemical markers of these states. The more significant and rapid BNP reduction in HDF patients is probably due to rapid and important plasmatic volume reduction and subsequent cardiac wall stress. It is possible that HDF therapeutical effects are not only mediated by the direct effects on renal haemodynamics, but also by neurohormone modulation allowing an improved response to diuretics. This last mechanism could also justify the consistent reduction in BNP levels observed up to 30 days after discharge. Conversely, the severity of cardiac failure does not seem to be related to levels of MCP-1 and IL-8. It could be explained by the associated chronic renal failure that we also found in the patients with congestive heart failure that we investigated. BNP is constitutively released from ventricular myocytes and is a specific recognized cardiac biomarker whereas cytokines are non-specific markers of organ inflammation.

In summary, our data show that HDF is a safe and effective procedure allowing a rapid clinical and haemodynamic improvement. BNP plasma levels were significantly higher before treatment in the initially diuretic unresponsive HDF group and lowered significantly in both groups after treatment. Furthermore, iHDF patients showed a 4.8-fold reduction of BNP levels compared with a 3.2-fold lowering of the FUR group. In our experience HDF is a cost-effective option when compared with continuous ultrafiltration methods because it can be performed in a routine dialysis unit without adjunctive costs for machinery or personnel training.

In conclusion, this study expands on previous publications that have described elevated levels of pro-inflammatory cytokines in CHF by also demonstrating elevated circulating levels of IL-8 and MCP-1 and that their lowering after HDF is associated with a strong reduction of BNP and restoration of diuretic responsiveness.

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