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Peritoneal dialysis in refractory end-stage congestive heart failure: a challenge facing a no-win situation

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Better is what the eyes can see than what can be imagined.

Ecclesiastes VI

Abstract

Background. Current medical therapeutic strategies for refractory congestive heart failure (CHF) in the population of 65 years and older with contraindications for heart transplantation are limited. Peritoneal dialysis applied to CHF patients with or without renal impairment showed clinical functional improvement.

Methods. A single centre, prospective but non-randomized study in 20 patients with severe congestive heart failure refractory to optimal pharmacological therapy [New York Heart Association (NYHA), class IV] was performed between 2000 and 2003. The mean age was 65.71 ± 7.66 years. The patients had a baseline glomerular filtration rate of 14.84 ± 3.8 ml/min. Fifteen patients were diabetics (type I, 10; type II, five). For all patients, the baseline ejection fraction was <35% (31.2 ± 4.7%). The mean Charlson's co-morbidity index was 7.8 ± 1.8. Patients were treated initially by 2–5 sessions of continuous veno-venous haemofiltration (CVVH) or sequential haemofiltration (SHF). Automated peritoneal dialysis (APD) was started after implantation of a Tenckhoff catheter. Three APD sessions/week (8 h each), with 15–20 l of dialysis fluid (PDF) per session (10.35 ± 3.05 l of 1.5% lactated glucose and 8.95 ± 2.95 l of 4.25% glucose PDF), were performed. Total follow-up ranged between 7 and 35 months (mean 19.80 ± 7.37).

Results. After 1 year of follow-up, all patients showed haemodynamic improvement: significant improvement of left cardiac work index (2.33 ± 0.69 to 2.59 ± 0.47 kg min/m^2), reduction of the systolic times ratio (61.14 ± 12.57 to 39.18 ± 13.44%), lower thoracic fluid contents (0.04 ± 0.005 to 0.003 ± 0.0001 Ω) as well as a regression from NYHA class IV to class I. Need for hospitalization for CHF decreased from 157 to 13 days.

Conclusions. Peritoneal dialysis appears to be a promising therapeutic tool for patients affected by refractory CHF. Clinical improvement of cardiac function may be related to clearing blood from middle molecular weight myocardial depressant substances, including atrial natriuretic peptide. Prospective multicentre trials are needed to confirm these encouraging results.

Keywords: apoptosis; atrial natriuretic peptide; cytokines; haemofiltration; heart failure; peritoneal dialysis

Introduction

The prevalence of congestive heart failure (CHF) in the population ≥65 years old is persistently increasing. The calculated increment of prevalence in the coming 40 years indicates, at least for the USA, an approximate number of 77.2 million patients affected by CHF compared with 34.8 million patients identified 3 years ago [1]. The apparent paradox of this gloomy prediction facing substantial progress in interventional cardiology may well derive in qualifying the epidemic as a disease of medical progress. Indeed, improved care of cardiac patients may result in more people surviving acute heart conditions and, consequently, being alive for longer, enough finally to reach the situation of a failing heart at an older age.

There are not very many current therapeutic strategies. Pharmacological treatment, including intermittent intravenous inotropic drugs, vasodilator/diuretic regimen, calcium and β-blocking agents as well as angiotensin-converting enzyme (ACE)

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inhibitors or antagonists is widely recommended [2]. Alternatively, for patients becoming refractory to optimal pharmacological therapy, heart transplantation, cardiomyoplasty and other surgical procedures represent the only possibility to keep them alive. However, not every patient with end-stage CHF is suitable for heart transplantation. On one hand, the scarcity of organs cannot cope with a continuously growing waiting list; on the other hand, the procedure is addressed to highly selected candidates, free from the long list of contraindications identified by currently accepted guidelines. To quote some of them, we should mention: insulin-requiring diabetes with evidence of end-organ damage, irreversible pulmonary hypertension, active peptic ulcer disease, recent malignancy, severe chronic obstructive pulmonary disease (COPD), peripheral or cerebro-vascular disease, systemic diseases and age over 65 years. This last point is quite critical since, as quoted before, at least in the USA, almost 13% of the population affected by CHF (34.8 million) is $\geq$65 years old.

This study is focused on the populations of cardiac patients that, due to a high co-morbidity index and contraindications for heart transplantation, have a gloomy prognosis. Indeed, the literature exposes evidence indicating that the 1-year mortality rate is ~74% [4]. It should be noted that most of them are critically ill, showing symptoms and signs defining the New York Heart Association (NYHA) class IV. Some recently published opinions propose to set in motion palliative hospice care and end of life options [3,4].

Quite frequently, nephrologists are involved in the therapy of these overhydrated, hyponatraemic, oligo-anuric and orthopnoeic patients. Different alternative therapeutic approaches have been used.

Continuous renal replacement therapies [continuous veno-venous haemofiltration (CVVH), slow continuous ultrafiltration and slow daily ultrafiltration] have being used basically to overcome the acute situation of overhydration in oliguric cardiac-decompensated patients. Some groups applied these techniques as a maintenance therapy, even on a daily basis. Besides the logistic problems and the considerably high costs derived from day after day haemofiltration, results in terms of survival were poor. After treating 52 patients, Canaud *et al*. [5] reported that only 18 survived for periods longer than 3 months. So far, haemofiltration and haemodialysis are effective as an acute rescue therapy, but ineffective as a long-term treatment.

More than 50 years ago, Scheneierson [6] published the first case report using peritoneal dialysis (PD) as a successful rescue therapy in a patient affected by severe CHF. Since then, the literature shows that PD has been applied to ~282 overhydrated, cardiac patients who lost adequate functional power of their diseased hearts, as an acute rescue therapy or as a long-term maintenance treatment. Even though most reports deal with small numbers of patients, it appears evident that both intermittent (IPD) and continuous ambulatory peritoneal dialysis (CAPD) substantially contributed in improving the quality and extension of life in otherwise dying patients [7]. This therapeutic approach was used successfully in patients with or without chronic renal insufficiency [8]. Some of the reported patients free of relevant renal involvement were able to undergo heart transplantation, due to substantial improvement of their haemodynamic parameters [8]. Other patients with contraindications for cardiac transplantation took a favourable turn, showing long survival time, improved quality of life as well as a substantial reduction in hospitalization days [9].

So far, the general notion that can be perceived from the already published experience supports the contention that PD, applied to cardiac patients showing severe CHF refractory to optimal pharmacological therapy, is effective, since it prolongs life and offers improved quality of life and results in a quite significant reduction of hospitalizations due to heart failure.

Subjects and methods

Patients

A single centre, prospective non-randomized study in 20 patients, showing symptoms and signs of severe congestive heart failure refractory to optimal pharmacological therapy (NYHA class IV), was performed in our centre between 2000 and 2003. The mean age of this patient population was 65.7 ± 7.6 years. The initial MDRD glomerular filtration rate calculated from serum creatinine was 14.84 ± 3.8 ml/min. All patients had different degrees of chronic renal failure. Fifteen out of the 20 patients were diabetics (type I, 10; type II, five). The zero time ejection fraction evaluated by echocardiography was <35% (31.2 ± 4.7%). The mean Charlson's co-morbidity index was 7.8 ± 1.8 (range 6–13). It should be noted that a score >5 implies an 85% mortality rate after the first year of follow-up. All 20 patients had a long history of arterial hypertension. Fourteen had severe coronary heart disease and 12 showed signs and symptoms of marked peripheral vascular disease. According to currently accepted criteria, none of these patients would have been considered as a candidate for heart transplantation [10].

Therapeutic schedule

Initially, patients were treated by means of 2–5 sessions of CVVH or sequential haemofiltration (SHF). As soon as dry weight was attained, a Tenckhoff catheter was surgically implanted and automated peritoneal dialysis (APD) was started. Patients underwent three APD sessions/week (8 h each), using 15–20 l of peritoneal dialysis fluid (PDF) in each session (10.35 ± 3.05 l of 1.5% lactated glucose and 8.95 ± 2.95 l of 4.25% glucose PDF). The total period of follow-up ranged between 7 and 35 months [mean $\pm$ SD, 19.80 ± 7.37 months; 95% confidence interval (CI) 16.35 ± 23.25 months], resulting in 396 months of therapy in 20 patients.

Bioimpedance studies

Evaluation of haemodynamic parameters and thoracic fluid contents was performed by means of transthoracic

cardio-bio-impedance (CardioScreen Version 3/1, Medizinische Mesteenik. Ilmenau, Germany) [11,12] and substantiated the clinical assessment.

Statistical analysis

Results are presnted as the arithmetic mean ± SD. Differences between two groups of continuous variables were analysed using the Mann–Whitney test. Analysis of differences between proportions was performed by means of the Fisher's exact test.

Results

Mean ultrafiltration rate was 2102 ± 505 ml/session (95% CI 2009–2195). There was a substantial improvement in patients' clinical condition.

At the end of the first year of follow-up, their functional capabilities were defined as class I (NYHA).

A significant increase of the mean stroke volume index (Figure 1) as well as a substantial reduction of the systolic times ratio (Figure 2) was observed.

These changes are quite relevant, and in line with the already published evidence showing a substantial agreement between systolic times ratio and ejection fraction evaluated by echocardiography (Figure 2) [13]. This contention is supported further by the significant improvement of the left cardiac work index (Figure 3). So far, clinical and haemodynamic parameters indicate a marked recovery of systolic left ventricular function. Fluid overload was remarkably corrected in most patients, as shown in Figure 4. Evaluation of thoracic fluid contents by means of transthoracic cardio-bio-impedance has been defined as a reliable method for evaluating dialysis-induced changes of intra- and extravascular fluids. The main advantage of the method lies on the registration of fluid balance simultaneously with the haemodynamic parameters.

The first year mortality was 10%, substantially lower than that expected according to the co-morbidity index. The overall mortality during the 396 months of follow-up in the 20 patients was 30%. Two patients were transferred to haemodialysis during the observation period. The incidence of peritonitis was 0.27 episodes/patient/year. The mean survival time of patients who died was 21.33 ± 8.16 months (median, 22 months; mode, 20 months). The mean whole follow-up for the surviving patients at the end of the observation period was 15.90 ± 6.25 months (median, 15 months; mode, 15 months). In spite of the limited size of the sample, the Gaussian distribution of data related to survival may suggest that these results could be reproducible if applied to a larger similar population of patients.

The total number of hospitalization days due to CHF during 1 year before starting APD was 157, whereas the corresponding figures for the whole period of dialytic therapy were only 13 ($P < 0.001$, Fisher's exact test).

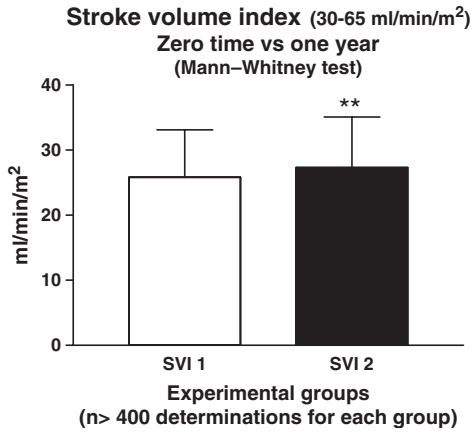

Fig. 1. Stroke volume index. Comparison of results at zero time (SVI 1) and at the end of the first year of follow-up (SVI 2).

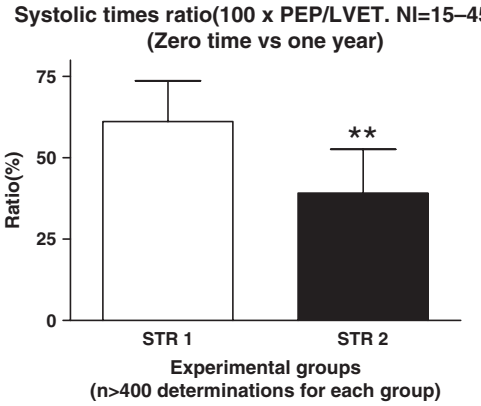

Fig. 2. Systolic times ratio evaluated by means of cardio-bio-impedance. The columns offer mean values of data obtained at zero time (STR 1) and at the end of the first year of follow-up.

Discussion

How and why can PD be so effective in refractory CHF? Clinical and haemodynamic improvement, achieved in four non-compliant patients (problems related to fluid intake), suggest that fluid overload may be more a consequence rather than a cause behind the progression of CHF.

Indeed, cytokines and humoral factors are involved in the development and progression of CHF, some of them with demonstrated specific myocardial depressant activity. Atrial natriuretic peptide (ANP), tumour necrosis factor-α (TNF-α), interleukin (IL)-1 and IL-6 have been shown to induce apoptosis of cardiac myocytes and/or to have negative inotropic effects [14]. Circulating levels of ANP are also related to left ventricular mass and function, and are useful in predicting mortality [15].

Loss of cardiac myocytes through apoptosis, induced by ANP and other humoral factors, appears to be a fundamental step in the chain of events that launch and/or aggravate heart failure [16].

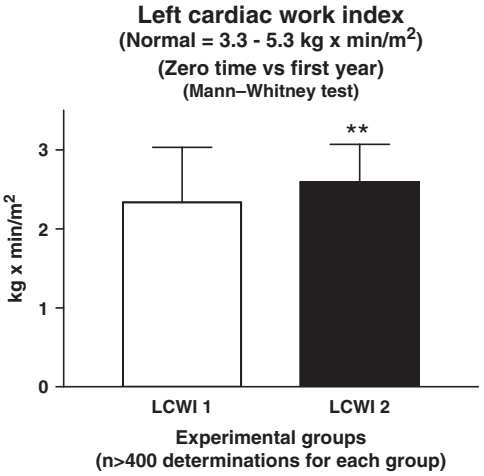

Fig. 3. Left cardiac work index estimated by means of cardio-bio-impedance (LCWI 1 = zero time; LCWI 2 = end of the first year of follow-up).

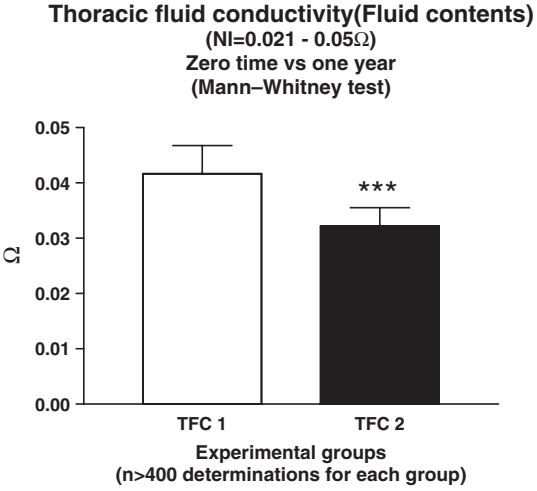

Fig. 4. Thoracic fluid contents evaluated using transthoracic bio-impedance. Values represent the mean ± SD of data obtained at zero time (TFC 1) and after 1 year of follow-up (TFC 2).

Some groups tried to challenge the progress of heart failure using anticytokines. However, clinical trials performed on patients with NYHA class II or IV heart failure failed to show improvement and, in some cases, their clinical condition was adversely affected [17]. Failure of this anticytokine monotherapy may be explained by the large number of identified and, most probably, by additional still unidentified circulating mediators involved in progression of the myocardial cell loss.

The molecular weight of myocardial depressant factors ranges between 500 and 20 000–30 000 Da. [18]. There is enough evidence indicating that the peritoneum is permeable to middle molecular weight solutes. ANP's chain is composed of 17–28 amino acids, the molecular weight of TNF-α is ∼17 kDa and that of Myocardial Depressant Factor (MDF) is near 700–800 Da. At this point, it is relevant to mention that transperitoneal transfer and removal from blood of TNF-α [19] and ANP [20] has been demonstrated.

So far, all this information suggests that removal of middle molecular weight substances (MDF, TNF, cytokines and ANP) from the blood, affecting the life cycle of myocardial cells as well as their contractile capabilities, may well explain both the improved quality of life and survival seen in cardiac patients treated with PD. This critical aspect of the problem is now being investigated in our laboratory.

A look at the future

In spite of recently published sceptical inferences hypothesizing that PD may not be the optimal choice for new chronic uraemic patients having an undefined history of CHF [21], the experience and information accumulated since Scheneirson [6] raises a more optimistic hope. It is true that the analysis of small groups of heterogeneous patients, treated in different centres, and also using heterogeneous dialytic methodologies, is ill suited for reaching scientifically based evidence useful for developing the required therapeutic guidelines. However, given the magnitude and severity of the morbidity and mortality of refractory CHF, a multicentre prospective study applying PD to patients with refractory CHF is urgently required. It should basically include subjects having a Charlson co-morbidy index >5 and, therefore, not fulfilling the requirements for listing for heart transplantation. For these patients, dialytic therapy should be added to the state of the art of conventional medical therapy. It is the opinion of the authors that a control group should not be required and could be even unethical, since, without the dialytic procedure, those patients will eventually be part of the unavoidable 85% mortality rate within their first year of follow-up. It is of note that heart transplantation as a life-saving therapeutic measure was never compared in randomized clinical studies with any of the conventional medical therapies [4].

Finally, if the results of such a study were to be convincing, progress in both life-saving, cost-effective therapy and pathophysiology of congestive heart failure could follow.

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Conflict of interest statement. None declared.

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