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Extracellular Volume and Cardiovascular Parameters in Chronic Hemodialysis Patients

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Thou mayst believe me, gentle reader, without swearing, that I could willingly desire this book (as a child of my understanding) to be the most beautiful, gallant, and discreet that might possibly be imagined; but I could not transgress the order of nature, wherein everything begets his like…

Miguel de Servantes Saavedra

Abstract

The increase in exracellular fluid volume (ECV) is predominantly seen in hemodialysis (HD) patients and correlates positively with increments in blood pressure (BP) and cardiovascular (CV) mortality. It predisposes to the left ventricular hypertrophy (LVH) and contributes to the diastolic heart failure and myocardial ischemia. Hypertension is evident in 70-90 % and LVH in 70 % of those patients commencing dialysis. Symptomatic ischemic coronary artery disease (CAD) and heart failure are present in one third of such patients. CAD and LVH predispose to diastolic dysfunction and systolic heart failure. It is thus not surprising that CV mortality among dialysis patients is much higher than in the general population.

The present series of studies was designed to examine the effects of HD and changes of ECV on the parameters used in the diagnosis of hypertension, myocardial ischemia and diastolic dysfunction in patients on chronic HD treatment.

In study **I**, interactions between changes in body weight, plasma atrial natriuretic peptide (pANP) and ambulatory blood pressure (ABP) were studied in 10 patients. The results showed a positive correlation between interdialytic weight gain and increase in interdialytic daytime systolic blood pressure (SBP). pANP did not correlate with this BP elevation. Diurnal variation was preserved in these patients.

In studies **II-III** the effect of HD with simultaneous ultrafiltration (UF) on QRS amplitude and dynamic vectorcardiographic parameters (dVCG) was evaluated in 15 patients. Simultaneous changes in ECV and blood volume (BV) were recorded. The increase in QRS amplitude during HD correlated with a reduction in ECV. Changes in the dVCG parameters QRS vector difference (QRS-VD) and ST change vector magnitude (STC-VM) were related to ECV and BV changes. The observed changes may give a false positive impression of myocardial ischemia. The parameter ST vector magnitude (ST-VM) was less markedly influenced by volume changes.

The separate effect of isolated UF and HD with minimal UF on dVCG parameters and Doppler-derived indices of left ventricular (LV) diastolic function were examined in 12 and 11 patients in studies **IV** and **V**. It was shown that isolated UF increased parameters QRS-VD and STC-VM but not ST-VM. The increase in QRS-VD bore a close relation to that in ECV. HD with minimal UF had no effect on any dVCG parameters. UF affected the parameters E (mitral inflow peak early diastolic velocity), A (mitral inflow peak late diastolic velocity), and isovolumic relaxation time (IVRT), which are used in evaluation of LV diastolic function. HD with minimal ultrafiltration as such does not have an effect on these parameters.

In conclusion, in patients on chronic HD changes in ECV have an effect on SBP, on some dVCG parameters and on Doppler-derived indices of LV diastolic function.

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Tiivistelmä (Abstract in Finnish)

Keinomunuaispotilaiden solunulkoinen nestetilavuus on suurentunut johtaen verenpaineen nousuun ja lisääntyneeseen sydän- ja verisuonitautikuolleisuuteen. Lisäksi solunulkoisen nestetilavuuden nousu aiheuttaa sydämen vasemman kammion liikakasvua, altistaa sydämen lepovaiheen toimintahäiriöille ja sydänlihaksen hapenpuutteelle. Noin 70–90 %:lla keinomunuaishoitoon tulevista potilaista on verenpainetauti ja/tai sydämen vasemman kammion liikakasvu. Heistä noin kolmasosalla on oireinen sepelvaltimotauti tai sydämen vajaatoiminta. Toisaalta sepelvaltimotauti ja sydämen vasemman kammion liikakasvu altistavat sekä sydämen lepo- että supistusvaiheen vajaatoiminnalle. Tämän vuoksi ei ole yllättävää, että keinomunuaishoidossa olevien potilaiden sydän- ja verisuonitautikuolleisuus on merkittävästi normaaliväestöä suurempi.

Tässä tutkimussarjassa tutkittiin keinomunuaishoidon ja solunulkoisen nestetilavuuden vaihtelun vaikutuksia pitkäaikaisessa keinomunuaishoidossa olevien potilaiden verenpainetta, sydänlihaksen hapenpuutetta ja sydämen lepovaiheen toimintaa mittaaviin muuttujiin.

Tutkimuksessa **I** selvitettiin kymmenen pitkäaikaisessa keinomunuaishoidossa olevan potilaan painon muutosten, sydäneteisten erittämän munuaisten natriumineritystä lisäävän peptidihormonin (pANP) veripitoisuuden muutosten ja toistomitatun verenpaineen yhteyttä. Tutkimuksessa havaittiin positiivinen yhteys keinomunuaishoitojen välisen painon nousun ja suurten valtimoiden sydämen supistuksen aikaisen korkeimman paineen (systolinen verenpaine) välillä. pANP:n pitoisuuden muutokset eivät olleet yhteydessä havaittuun verenpaineen nousuun. Tutkitetuilla potilailla oli havaittavissa verenpaineen vuorokausivaihtelua.

Tutkimuksessa **II** arvioitiin 15 potilaalla normaalin nestettä ja kuona-aineita samanaikaisesti poistavan keinomunuaishoidon vaikutusta sydämen kammioiden lepopotentiaalieron häviämistä sydänsähkökäyrässä edustavan voimakkaan heilahduksen (QRS-kompleksi) korkeuteen. Tutkimuksessa **III** analysoitiin edellä mainittujen potilaiden kolmiulotteisen sydänsähkökäyrän (vektorikardiografia) muutoksia keinomunuaishoidon aikana. Tutkimusten **II-V** aikana mitattiin samanaikaisesti sekä veritilavuuden että solunulkoisen nestetilavuuden muutoksia. QRS-kompleksin korkeuden nousu keinomunuaishoidon aikana oli yhteydessä samanaikaiseen solunulkoisen nestetilavuuden laskuun. Muutokset kolmiulotteisen sydänsähkökäyrän muuttujissa QRS-kompleksin vektoriero (QRS-VD), sekä S-poikkeaman ja T-poikkeaman välisen summavektorin suunnan muutoksen suuruus (STC-VM), olivat yhteydessä solunulkoisen nestetilavuuden ja veritilavuuden muutoksiin. Todetut muutokset saattavat antaa väärän vaikutelman sydänlihaksen hapenpuutteesta. Kolmiulotteisen sydänsähkökäyrän muuttuja S-poikkeaman ja T-poikkeaman välisen summavektorin pituuden muutoksen suuruus (ST-VM) ei muuttunut merkittävästi keinomunuaishoidon aiheuttamien nestemuutosten vaikutuksesta.

Tutkimuksessa **IV** tutkittiin 12 potilaalla keinomunuaishoidon avulla erillisen nesteenpoiston ja erillisen kuona-aineiden poiston vaikutusta kolmiulotteisen sydänsähkökäyrän muuttujiin. Keskeinen tulos oli, että eriytetty nesteenpoisto lisäsi muuttujien QRS-VD ja STC-VM arvoja, mutta ei vaikuttanut muuttujaan ST-VM. Muuttujan QRS-VD ja solunulkoisen nestetilavuuden muutosten välillä havaittiin tilastollinen yhteys. Eriytetty kuona-aineiden poisto ei vaikuttanut kolmiulotteisen sydänsähkökäyrän muuttujiin.

Tutkimuksessa **V** mitattiin 11 keinomunuaishoitopotilaalla edellä mainitussa tutkimusasetelmassa sydämen Doppler-kaikukuvauksella sydämen lepovaiheen aikaisia veren virtausnopeuden muutoksia. Keinomunuaishoidon aikainen nesteen poistuma vaikutti sydämen lepovaiheen toimintaa mittaaviin muuttujiin E (varhainen virtaus hiippaläppäaukossa), A (vasemman eteissupistuksen aiheuttama virtaus vasempaan kammioon) ja IVRT (aika aorttaläpän sulkeutumisesta hiippaläpän avautumiseen, eli vasemman kammion lihasjänteyden vähenemisaika). Pelkkä kuona-aineiden poisto ilman merkittävää nesteen poistoa ei vaikuttanut kyseisiin muuttujiin.

Yhteenvetona on todettavissa, että pitkäaikaisessa keinomunuaishoidossa olevilla potilailla solunulkoisen nestetilavuuden muutokset vaikuttavat systoliseen verenpaineeseen, eräisiin kolmiulotteisen sydänsähkökäyrän muuttujiin sekä joihinkin kaikukuvauksella mitattaviin sydämen lepovaiheen toimintaa mittaaviin muuttujiin.

Contents

Abbreviations

A	Mitral inflow peak late diastolic velocity
A`	Mitral annular late diastolic velocity
ABP	Ambulatory blood pressure
ABPM	Ambulatory blood pressure monitoring
ANP	Atrial natriuretic peptide
BIA	Bioelectrical impedance analysis
BNP	Brain natriuretic peptide
BP	Blood pressure
BV	Blood volume
cGMP	Cyclic guanosine 3´,5´-monophosphate
dVCG	Dynamic vectorcardiographic ischemia monitoring
CAD	Coronary artery disease
CO	Cardiac output
CRF	Chronic renal failure
CV	Cardiovascular
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
DT	Deceleration time
E	Mitral inflow peak early diastolic velocity
E`	Mitral annular early diastolic velocity
E/A	Early to late peak mitral inflow velocity
ECG	Electrocardiography
ECV	Extracellular fluid volume
ECW	Extracellular water
ESRD	End-stage renal disease
FS	Left ventricular fractional shortening
HD	Hemodialysis (diffusion combined with ultrafiltration)
HR	Heart rate
I	Current
IVCD	Inferior vena cava diameter
IVRT	Isovolumic relaxation time
IVST	Interventricular septum thickness
LAD	Left atrial diameter
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVPWT	Left ventricular posterior wall thickness
MAP	Mean arterial pressure

MIDA	Myocardial infarction dynamic analysis
NO	Nitric oxide
pANP	Plasma atrial natriuretic peptide
QRS-VD	QRS vector difference
R	Resistance
SBP	Systolic blood pressure
STC-VM	ST change vector magnitude
ST-VM	ST vector magnitude
ST-VM6	ST vector magnitude 60 ms after J-point
SV	Stroke volume
SVR	Systemic vascular resistance
U	Potential
UF	Ultrafiltration
VCG	Vectorcardiography

List of original publications

This thesis is based on the following original articles, which are referred to as **I-V** in the text:

I. S. Ojanen, K. Pietilä, A. Pasternack: Plasma atrial natriuretic peptide, body weight and twenty-four-hour blood pressure monitoring in chronic hemodialysis patients. Nephron 1996;73:174-178.

II. S. Ojanen, T. Kööbi, P. Korhonen, J. Mustonen, A. Pasternack: QRS amplitude and volume changes during hemodialysis. Am J Nephrol 1999;19:423-427.

III. S. Ojanen, T. Kööbi, A-M. Koivisto, P. Korhonen, J. Mustonen, A. Pasternack: Hemodialysis causes changes in dynamic vectorcardiographic ischemia monitoring parameters. Clin Nephrol 2000; 54:227-233.

IV. S. Ojanen, A-M. Koivisto, T. Kööbi, P. Korhonen, J. Mustonen, P Laippala, A. Pasternack: Isolated ultrafiltration affects dynamic vectorcadiographic ischemia monitoring parameters. Clin Nephrol 2002; 57:359-364.

V. S. Ojanen, V. Virtanen, T. Kööbi, J. Mustonen, A. Pasternack: The effect of isolated ultrafiltration on Doppler-derived indices of left ventricular diastolic function. Nephrol Dial Transplant 2004; 19:3130-3136.

Introduction

The exceedingly high cardiovascular (CV) mortality rate among patients with end-stage renal disease (ESRD) is a public health problem and a challenge for kidney disease research. In the 45-54 year age group, the CV mortality rate among dialysis patients is about 65 times higher than in the general population (Levey et al. 1998). It is estimated that cardiovascular diseases (CVD) account for 40 to 50 % of all ESRD mortality (Herzog 2000, Finne et al. 2001).

In view of the poor long-term survival, a more aggressive strategy is needed for the detection of CVD in ESRD patients. Advanced methods, ambulatory blood pressure monitoring (ABPM), dynamic vectorcardiographic ischemia monitoring (dVCG) and Doppler echocardiography, are nowadays available for the detection of hypertension, coronary artery disease (CAD) and heart failure. The present study was designed to evaluate the effects of extracellular fluid volume (ECV) and hemodialysis (HD) on the results of these methods in patients on chronic HD treatment.

Fluid retention is not the only, but certainly a prominent factor in the pathogenesis of CVD in ESRD patients. These patients have an increased salt sensitivity and they react with a significant increase in blood pressure (BP) if given a diet containing much sodium (Koomans et al. 1985). ECV and blood volume (BV) are expanded in renal failure and correlate to elevated BP (Kim et al. 1980). The prevalence of hypertension increases as renal failure progresses being present in 80-90 % of patients on dialysis (Mailloux et al. 1998). Studies using ABPM indicate that a substantial number of ESRD patients have also lost the normal diurnal variation in BP. The relation between ECV expansion (body weight), BV and diurnal variation is evaluated in this thesis.

Many patients commencing dialysis suffer from coexistent CAD (Jungers et al. 1997), which is associated with a worse prognosis (Foley et al. 1995). In uremic patients, myocardial ischemia can occur even in the absence of significant CAD by reason of increased oxygen demand, impaired autoregulation, decreased capillary density and small-vessel disease. The recognition of CAD in ESRD is complicated by the fact that many of these patients are asymptomatic (Bennet et al. 1978) and have left ventricular hypertrophy (LVH) -related electrocardiographic (ECG) abnormalities. On the other hand, ST-segment changes are observed in 15 to 61 % of HD patients when investigated by ambulatory Holter monitoring (Kremastinos et al. 1992, Singh et al. 1994, Conlon et al. 1998). Changes in the volume of ultrafiltrate removed have been thought to play an important role in the background to these findings (Kremastinos et al. 1992, Singh et al. 1994). In this thesis, the use of the dVCG ischemia monitoring system, myocardial infarction dynamic analysis (MIDA), is evaluated during HD with and without ultrafiltration (UF).

Fluid retention also inevitably leads to dilatation of the heart compartments and a direct relationship is found between BV and left ventricular (LV) diameter in HD patients (Chaignon et al. 1981). LVH is present in about 70 % of ESRD

patients, and as many as 70 % of HD patients may have diastolic dysfunction of the LV. Doppler-derived indices are used for the estimation of LV diastolic function, but earlier studies suggest that some of them are dependent on fluid status. In this thesis, the effects of UF and HD without of UF on Doppler-derived indices of LV diastolic function are assessed.

1 Review of the literature

1.1 Fluid status and its determination in hemodialysis patients

1.1.1 Extracellular volume expansion

In the HD patient's fluid status there is a continuous disequilibrium characterized by a rapid reduction in ECV during dialysis and followed by its slow increase between dialysis sessions. As the glomerular filtration rate declines, ECV expands being predominantly increased in almost all anuric HD patients (Vasavada et al. 2003).

Fluid intake is the most important determinant of weight gain between HD sessions. The over-riding stimulus to thirst is effective plasma osmolality, of which the serum sodium concentration is the major determinant (Tomson 2001). The ECV is entirely dependent on the amount of sodium in the body (Mees 1995). Theoretically, a 1 % increase in sodium concentration would cause an increase in ECV of 0.5 liters. As the plasma is a part of the ECV, BV take place concomitant with it. The ECV-BV relationship is not however linear, since BV within the vascular system cannot increase indefinitely, while there is no apparent limit to expansion of the ECV (Guyton et al. 1996). An ECV excess of more than 10 % of body weight may not cause evident edema.

In HD patients excess salt and water can only be removed by intermittent UF. Over the past 15-20 years there has been an increase in the prescribed dialysate sodium concentration to reduce intradialytic symptoms such as hypotension and muscle cramps (Leunissen et al. 1996, Charra 2007). However, a high dialysate sodium gradient is related to higher interdialytic weight gains and BP in HD patients (Daugirdas et al. 1985, Charra 2007). Recently, lower dialysate sodium has been advocated to decrease BP (Krautzig et al. 1998, Song et al. 2002, de Paula et al. 2004, Thein et al. 2007).

1.1.2 Determination of fluid status

Estimating the dry weight correctly is of the most importance in dialysis patients to minimize both symptomatic hypotension during dialysis and hypertension and volume overload during the interdialytic period (Perazella 1999).

1.1.2.1 Dry weight

The term dry weight was used for the first time in the literature in 1967 (Thomson et al. 1967). Traditionally dry weight is defined as the lowest weight a patient can tolerate without the development of symptoms or hypotension in the absence of overt fluid overload (Henderson 1980). However, the presence of hypotension alone does not necessarily mean that dry weight has been achieved. Kim and associates (1970) showed that hypotension might occur in dialysis patients even though they are grossly overhydrated and edematous.

The current definition accentuates the value of interdialytic BP: the dry weight is that body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis despite retention of salt and water (Wizemann et al. 1995, Charra et al. 1996, Charra 1998). In addition, at dry weight the patient has no clinical signs or symptoms of fluid overload or hypovolemia.

It is also important to note, that in many patients dry weight varies over time. During the first months of HD treatment, it is the net result of two opposing processes, i.e. control of the ECV to reverse hypertension on the one hand and increase in the `dry mass` as a result of anabolism induced by HD treatment on the other (Chazot et al. 1999). Dry weight can also fluctuate with intermittent illnesses and with changes in lean body mass and body fat.

1.1.2.2 Clinical assessment

At present dry weight is in most centers determined clinically. However, several investigators have found the clinical determination of dry weight difficult, unreliable or insensitive (Kouw et al. 1993, Leunissen 1995, Spiegel et al. 2000). For example, edema may not be detectable until the ECV has risen by 30 % above normal, corresponding to 4-5 liters. Thus, other modalities have been evaluated in an effort to estimate dry weight more objectively.

1.1.2.3 Natriuretic peptides

1.1.2.3.1 Atrial natriuretic peptide

De Bold et al. (1981) demonstrated that infusion of atrial (but not ventricular) tissue extracts of normal hearts into rats causes rapid natriuresis and diuresis. Atrial natriuretic peptide (ANP) was the first member of a family of peptides with potent natriuretic, diuretic and vasorelaxant activities (Laragh 1985). Endogenous paracrine/autocrine factors such as endothelin-1, nitric oxide, or angiotensin II liberated in response to atrial wall stretch, rather than direct stretch, appear to be responsible for activation of ANP secretion in response to volume load (Ruskoaho et al. 1997). Due to its relatively low molecular weight, ANP can theoretically be removed through the dialysis membrane. However, it has been shown that ANP hardly changes during isovolemic dialysis and its secretion rate probably lies well above the removal rate through the dialysis membrane (Lauster et al. 1990, Mallamaci et al. 1994).

Larger increases in ANP levels can be observed during acute and chronic ECV overload. In ESRD patients the plasma concentration of ANP is increased several fold compared to healthy controls, which might be due to volume expansion, decreased renal clearance and prolonged plasma half time (Kojima et al. 1987, Woolf 1989). Rascher and associates (1985) were the first to suggest its possible role in determining fluid status in HD patients. ANP levels are elevated before and after dialysis in HD patients compared to healthy controls, and levels are significantly lower after HD (Andersson et al. 1988, Ishikura et al. 1996, Wolfram et al. 1996, Plum et al. 2001).

Katzarski and associates (1999a) have investigated the effect of fluid removal during HD and the interaction between intravascular volume and ANP in 16 HD patients. They conclude that the usefulness of the plasma atrial natriuretic peptide (pANP) level in assessment of fluid status in HD patients is limited, since age and factors other than those directly related to volume influence the concentration of ANP. ANP has also been found to be elevated in normovolemic HD patients with mitral valve insufficiency compared to normovolemic patients without this disorder making ANP levels difficult to interpret in this setting (Leunissen et al. 1993). Thus, the persistent postdialysis ANP elevation might be due to inadequate dry weight achievement or the presence of altered left atrial hemodynamics. pANP levels are useful parameters for fluid overload only in HD patients with normal left atrial function.

1.1.2.3.2 pro-Atrial natriuretc peptides

Pro-ANP peptides are also elevated in dialysis patients and decrease during the dialysis session when fluid is removed. It has also been found that high flux cellulose-triacetate dialyser reduces plasma levels of pro-ANP peptides significantly, whereas ANP is not affected. According to their molecular weight and size, elimination across the membrane is unlikely and membrane absorption is the possible explanation (Franz et al. 2001).

In a study by Franz and colleagues (2000), patients with altered LV hemodynamics displayed significantly higher plasma concentrations of all pro-ANP fragments and ANP than patients with normal cardiac function. HD patients with moderate or severe hypertension had higher concentrations of pro-ANP peptides and ANP than patients with normal BP or those with only mild hypertension. Cellulose-triacetate dialysers reduced plasma levels of pro-ANP 1-30, pro-ANP 31-67, and pro-ANP 1-98 significantly more than polysulfone dialysers, but ANP levels were not different. The investigators concluded that circulating ANP and pro-ANP fragments are influenced by a variety of factors such as ESRD, HD treatment, dialyser membrane material, cardiac dysfunction and hypertension (Franz et al. 2000).

1.1.2.3.3 Cyclic guanosine 3´,5´-monophosphate

Like ANP, cyclic guanosine 3´,5´-monophosphate (cGMP) is also released in response to an increased wall stress in the right and left atrium of the heart. cGMP acts as a second messenger for ANP, which stimulates its production by activation of membrane-bound guanylate cyclase. Since cGMP is more stable in serum at room temperature than ANP, it has been proposed that cGMP would be a better marker than ANP for the assessment of fluid status (Jaeger et al. 1999a).

Lauster and associates (1990, 1992, 1993) concluded that the cGMP value determined immediately after HD is a sensitive marker for overhydration in patients with ESRD. However, others have not confirmed this conception, since the levels of cGMP are also influenced by altered left atrial hemodynamics (Leunissen et al. 1993). In addition, several other natriuretic peptides stimulate the production of cGMP and its specificity is thus low. Due its relatively low molecular weight, cGMP can theoretically be removed through the dialysis membrane. Plum and colleagues (1990) have shown that plasma cGMP decreases during isovolemic HD and thereby underestimates post-dialysis hydration.

1.1.2.3.4 Brain natriuretic peptide

At present, the mammalian natriuretic peptide system including ANP, brain natriuretic peptide (BNP) and C-type natriuretic peptide has been described. BNP is a natriuretic hormone homologous to ANP. It is synthesized in the brain and heart by a process similar to that producing ANP and the actions of the two are similar (Mukoyama et al. 1991). In many recent studies an increase in plasma BNP levels in dialysis patients has been observed (Nishikimi et al. 2001, Fagugli et al. 2003a, Lee et al. 2003) when compared with those of controls. In a study by a group under Nishikimi (2001) plasma BNP levels before and after HD directly correlated with the degree of body fluid retention only on mondays suggesting that marked predialytic fluid retention due to one extra interdialytic day may elicit a higher BNP secretion. However, several other studies have not reported BNP reduction after HD (Kohse et al. 1993, Ishikura et al. 1996, Lee et al. 2003). Fagugli and associates (2003a) found an association between BNP and ECV in HD patients, but they excluded patients with congestive heart disease, valvular heart disease, atrial fibrillation, LV dysfunction and diabetes mellitus. BNP is highly specific for heart failure, since it is minimally expressed in the normal myocardium (Wiese et al. 2000). The highest concentration of the peptide is found in the atria, with the total ventricular amount of BNP being even higher due to greater mass of the ventricle. BNP gene expression in atria and ventricles is induced within one hour in response to overload (Mäntymaa et al. 1993, Magga et al. 1994, Hama et al. 1995, Nakagawa et al. 1995). Since cardiac function is a major determinant for BNP plasma levels, it would appear to have only a limited role in the assessment of overhydration in HD patients.

1.1.2.4 Blood volume monitoring

UF during dialysis removes fluid from the intravascular compartment and results in a progressive decline in BV (Koomans et al. 1984). Absolute BV may be determined by measuring the concentration of an injected tracer or dye, which is distributed homogeneously in the vascular compartment. This method is both invasive and intermittent and is not suitable for routine application in the monitoring and control of BV (Johner et al. 1998).

Steuer and colleagues (1993) have described a simple, practical and reliable optical multiple-wavelenght method to measure real-time continuous changes in BV. The method is based on measuring the change in hematocrit. Since erythropoietin does not have any short-term effects on hematocrit, the increase in hematocrit during HD is inversely proportional to the change in BV. Four main profiles of BV decrease during HD sessions have been observed (Santoro et al. 1996). Profile types have been used to detect an inadequately high dry weight (Lopot et al. 1996). A flat BV profile throughout dialysis in a patient who tolerates the session hemodynamically well suggests that that patient has not yet

attained dry weight and the steepest BV reduction is related to hypovolemia (Jaeger et al. 1999a).

It has also been suggested that such monitoring may allow the prescribed dry weight to be achieved more safely without hypotension (DE Vries et al. 1993, DE Vries et al. 1994). On the other hand, interindividual (Santoro et al. 1996) and intraindividual (Krepel et al. 2000) variability in BV changes as a response to the UF rate makes it unlikely that a single value of BV will reliably predict the occurrence of dialysis-induced hypotension (Basile 2001). Santoro and colleagues (1995) have studied BV trends after UF stops. They conclude that the profiles of BV changes after these UF stops define the individual capacity for plasma refilling and may have the great advantage of optimizing the patient's dry weight.

1.1.2.5 Bioimpedance analysis

The bioelectrical impedance analysis (BIA) is used for the assessment of volume status and evaluation of hemodynamic changes and transcompartmental fluid shifts during HD. It is also a simple means of assessing nutritional status (Chertow et al. 1995, Kushner et al. 1996). Kouw and associates (1992) using multiple frequency BIA, having data from 29 HD patients and 31 control subjects, found that HD patients had markedly expanded predialytic ECV compartments compared with controls. Others have confirmed these results (Spiegel et al. 2000, Chen et al. 2002).

In some reports, BIA prediction of total body water in HD patients has been shown to correlate very well with dilution techniques (Ho et al. 1994, Cooper et al. 2000). However, in other studies an unacceptably wide range of agreement has been found between BIA and tracer dilution techniques (Arkouche et al. 1997, Cox-Reijven et al. 2001). In the last mentioned study the disagreement between techniques was augmented in patients with the largest relative magnitude of body water compartments. Nevertheless, BIA adequately predicted acute changes in ECV during isolated UF as well as during HD with UF. It is important to note that BIA does not accurately predict absolute water loss during dialysis (Di Iorio et al. 2004). However, both whole-body and segmental BIA can be used to track relative changes in ECV with 2 % to 3 % precision error (Gudivaka et al. 1999, Chanchairujira et al. 2001).

Bioimpedance measurement has certain limitations. The optimal time to perform BIA in relation to HD is uncertain and the timing of BIA measurement has been ranged from immediate post-HD to 1.5 hours post-HD (Fisch et al. 1996, Katzarski et al. 1996, Zhu et al. 1999). Immediately after dialysis BIA may underestimate ECV, since at that time fluids shift from the legs towards the trunk and the trunk contributes only 5 % to total resistance. However, in a recent study by Di Iorio and colleagues (2004) it was found that BIA variables remained constant and highly reproducible over the 120 minutes after the end of HD.

In addition, measurement of high-frequency impedance is affected by temperature, electrolyte, red cell and protein concentration changes during

dialysis (Scharfetter et al. 1997). However, a group under Sinning (1993), using single-frequency BIA measurement, found no correlation between changes in electrolytes, whereas changes in hematocrit and serum protein values had a high correlation to a measured resistance.

In comparison with inferior vena cava diameter (IVCD) and BV changes, BIA may be the most accurate means of assessing fluid changes in HD patients (Kraemer et al. 2006). A protocol using a combination of BIA and on-line BV monitoring in assessment of dry has been described for clinical practice (Jaeger et al. 1999b).

1.1.2.6 Inferior vena cava diameter and collapsibility

The echocardiographic examination of the IVCD and collapsibility has been proposed as a non-invasive method for estimating intravascular volume (Cheriex et al. 1989, Brennan et al. 2006). A group under Ando (1985) was the first to show the relationship between the amount of water removed and the IVCD in HD patients. IVCD has been validated against right atrial pressure and total BV in ESRD patients, and the post-dialysis IVCD reliably predicts hemodynamic changes during HD (Kouw et al. 1993, Leunissen et al. 1993). Some limitations to IVCD and collapsibility measurement should be noted. Mandelbaum and associates (1996) found a wide interindividual variation and single measurements are not helpful in individual patients. As IVCD is a derivative of right atrial pressure, the presence of tricuspidal insufficiency or right side heart failure also limits its use (Moreno et al. 1984). IVCD increases at least 2 hours after HD due to refilling from interstitial fluid and shortly after HD may overestimate an underhydrated status (Tetsuka et al. 1995, Katzarski et al. 1997).

1.1.2.7 Radioisotopes

ECV values obtained by the dilution technique are considered as reference values for comparison with alternate measurement techniques (Ellis 2000). Bromide is the most commonly used tracer for the measurement of ECV. It should be noted that labelled traces, which diffuse over the ECV, also penetrate into the intracellular space to a variable degree, thus introducing errors in measurement (Boer 1984, Leunissen et al. 1993). Accuracy for the assessment of ECV by bromide is around $\pm$ 5 % (van Kreel 1994). The use of these techniques is, however, limited in clinical practice since they are time-consuming, cannot be repeated frequently and usually mean exposure to radioactivity.

1.2 Body fluid dynamics during dialysis

During an HD session of 3-5 h several liters of fluid may be removed by UF and this in some cases may exceed the total circulating plasma volume. During normal HD (diffusion combined with UF), plasma water removal induces a progressive reduction in plasma volume and a decrease in cardiac stroke volume (SV) (Kinet et al. 1982). The resultant hypovolemia is followed by refilling: a water shift from the interstitial and cellular spaces toward the vascular compartment (Santoro et al. 1998).

Fluid removal by UF results in a decrease in plasma hydrostatic pressure and a rise in plasma protein concentration and oncotic pressure. Both of these changes promote vascular refilling from the interstitial space to the vascular compartment. At the same time, due to diffusive loss of urea and other small solutes, the osmolality of the fluid returning to the patient will fall, leading to a movement of water into the cells. This effect and water loss by UF leads to ECV depletion and refilling will decrease.

During HD treatment, plasma volume would theoretically remain constant if refilling equals the UF rate. However, refilling is probably never completed during a dialysis session and there is a delay with plasma refilling lagging behind UF (Keshaviah et al. 1984). It has been shown that the post-dialysis re-equilibration between BV, intracellular fluid volume and ECV appears to take 3 to 5 hours (Olthof et al. 1992).

The refilling rate depends on the following factors (Katzarski et al. 1996): individual state of hydration (Koomans et al. 1984), UF rate (Mann et al. 1990), dialysate sodium concentration (Mann et al. 1990), total protein balance (Schneditz et al. 1992, Enzmann et al. 1994) and capillary permeability (Schneditz et al. 1992).

In view of the large number of factors that are involved in regulation of the plasma refilling rate, the individual variability in refilling is substantial. During a regular UF rate (10-15 ml/min) applied for 4 h in nearly normohydrated patients, the individual BV decrease may vary from 10 to 30 % (Koomans et al. 1996).

A rapid reduction in plasma osmolality, which causes ECW (extracellular water) to move into the cells, can be avoided in sequential UF and isovolemic dialysis. During isolated UF the plasma returning to the patient is reduced in volume but not changed in osmolality. The resulting rise in plasma oncotic pressure results in fluid movement from the interstitial fluid and the cells into the reduced vascular space. The last effect will lead to enhanced plasma refilling and minimize the degree of plasma volume depletion (Jones et al. 1977, Keshaviah et al. 1982).

1.3 Hemodynamic changes and monitoring during hemodialysis

1.3.1 Cardiovascular reactivity

When refilling from the interstitial tissue to the intravascular compartment during UF is inadequate, a decline in plasma volume results and other compensatory mechanisms are required to maintain BP (Passauer et al. 1998). A normal CV response is a activation of the sympathetic nervous system. This response results in an increase in systemic vascular resistance (SVR) and venous tone, and a translocation of sequestered blood from the splanchnic and cutaneous circulation to the central BV maintaining adequate cardiac filling (Greenway et al. 1986, van Kuijk et al. 1995).

Sympathetic activation also increases the heart rate (HR) and cardiac contractility, which results in maintained cardiac output (CO). However, cardiac rate changes appear to be less important in maintaining CO under conditions of decreased filling than in normal physical activity (Daugirdas 1991).

Arterial hypotension results if the normal sympathetic nervous system response is impaired. In persistently hypotensive patients, parasympathetic dysfunction is accompanied by sympathetic impairment. These patients are not able to increase the HR and/or SVR adequately in response to UF (Takahashi et al. 1996, Armengol et al. 1997). A sudden withdrawal of sympathetic activity can also occur once a critical reduction in BV has been reached. The result is vasodepressor syncope (Bezold-Jarisch reflex) with bradycardic hypotension (Converse et al. 1992a).

1.3.2 Non-invasive hemodynamic monitoring

A thorough evaluation of a patient's hemodynamic profile would be ideal to optimize volume management in HD. Impedance methods to assess hemodynamics have been available since the 1960s. Thoracic bioimpedance (impedance cardiography) is a non-invasive technology, which tracks changes in cardiac SV and thus estimates CO. The thoracic bioimpedance methods are those most widely used, but their levels of agreement with invasive methods have varied substantially (Atallah et al. 1995, Jensen et al. 1995). In whole-body impedance cardiography most of the body participates in the impedance measurement. In a study by Kööbi and associates (1997) a close agreement between whole-body impedance cardiography and thermodilution in the measurement of CO in patients with CAD was found. This method has not been validated in HD patients.

The ultrasound dilution technique is a novel means of measuring CO and SVR in HD patients. The method has been verified to be accurate and reproducible in HD patients (Krivitski et al. 1999). Also CO measured by ultrasound velocity was in good agreement with invasive measurement in an animal model (Kisloukhine et al. 1996).

A number of studies (Santoro et al. 1990, Pizzarelli et al. 1995, Straver et al. 1998, Miltenyi et al. 2001, Hoeben et al. 2002) using non-invasive hemodynamic monitoring during HD have provided an opportunity to gain more insight into the pathophysiology of intradialytic hemodynamics. However, until recently there are no data demonstrating their benefits in improving hemodynamic control in HD (Ishibe et al. 2004).

1.4 Blood pressure and hypertension in hemodialysis patients

1.4.1 Epidemiology

Hypertension is estimated to occur in 70 % to 90 % of chronic HD patients in the USA, Europe and Finland (Raine et al. 1992, Salem 1995, Finne et al. 2001, Rocco et al. 2001). Patients with chronic renal failure (CRF) also have a higher incidence of increased pulse pressure and isolated systolic hypertension than the general population (London et al. 1992).

In the majority of HD patients hypertension is not adequately controlled. A group under Cheigh (1992) used ABPM to evaluate 53 HD patients BP and found that only 15 % maintained BP within the normal limits. In the Hemodialysis Study the mean baseline predialysis BP was 152/82 mmHg and in predialysis patients in the Modification of Diet in Renal Disease Study only 54 % had BP $\leq$ 140/90 mmHg (Hebert et al. 1997, Cheung et al. 2004). Mittal and colleagues (1999) found that 80 % of hypertensive HD patients had a BP greater than 150/90 mmHg despite antihypertensive medications.

1.4.2 Pathogenesis

The pathogenesis of hypertension in ESRD is a combination of volume expansion and increased SVR. Various factors, including renin-angiotensin-aldosterone, nitric oxide (NO), endothelin-1 and Na^+, K^+-ATPase inhibitor and increased sympathetic nervous activity, are proposed to increase SVR in patients with chronic kidney failure (Mailloux et al. 1998, Salem 2002). Nonetheless,

hypervolemia is clearly the most important factor in the pathogenesis of hypertension in HD patients.

1.4.2.1 The role of extracellular volume and sodium

In 1960, Scribner initiated chronic HD treatment for terminal renal failure. His first patient had malignant hypertension, which was cured by controlling his ECV with a combination of dietary sodium restriction and UF. The patient remained normotensive for the next 11 years he survived on dialysis (Scribner et al. 1960, Scribner 1990).

Other historical data on hypertension in HD patients likewise support the central role of salt and water retention in the pathophysiology of hypertension in ESRD. During the 1960s the control of BP was achieved in a majority of patients by long HD sessions and low-salt diet and the percentage of hypertensive patients was low (Vertes et al. 1969, Charra et al. 2003). In the 1980s and 1990s HD sessions were shortened and the sodium concentration in the dialysate was higher, the diet was liberalized and the percentage of patients with hypertension rose to over 50 % (Perez-Garcia et al. 2001). At present the prevalence of hypertension in HD patients ranges from 70 to 90 % and almost all of them are volume-overloaded (Mittal et al. 1999, Rahman et al. 1999, Mailloux 2001).

The first evidence for the role salt and water retention in the pathogenesis of hypertension ESRD comes of a study by Kempner (1949), in which a sodium-free rice diet was successfully managed to control hypertension in patients with vascular disease. In patients on Kempner`s diet ECV is normal (Murphy 1950). Later Coleman and Guyton (1969) showed that in anephric dogs the sodium load leads to hypertension characterized initially by increased plasma volume and CO. This is followed by increased SVR, which maintains the hypertension (Coleman et al. 1969). The response to salt and water loading is not uniform in ESRD. A study by Kim and associates (1972) showed four different hemodynamic profiles in response to fluid and salt overload leading to hypertension in patients on HD.

Several studies on renal patients have investigated the relationship between hypertension and fluid overload. Already 40 years ago, Blumbeg et al. (1967) observed a strong association between fluid overload and hypertension. Hypertensive HD patients also have an expanded ECV compared to normotensive (Lins et al. 1997, Katzarski et al. 1999b, Chen et al. 2002), the difference being approximately 2-3 liters (Katzarski et al. 1999b). Ŏzkahya and colleagues (1999) reported that additional UF and strict control of sodium intake resulted in normalization of BP in the majority of their HD patients. Studying 120 HD patients not receiving antihypertensive drugs Ventura and Sposito (1997) found a direct correlation between change in mean BP and volume expansion. In addition, Fishbane and coworkers (1996) found volume overload to play an important role in the hypertension of HD patients. A group under Leypoldt (2002) observed an association of the intradialytic decrease in body weight and the intradialytic decrease with plasma volume with predialysis and

postdialysis BP. Recently, in a study having data from over 32 000 dialysis sessions in 442 subjects with a follow-up to six months, it was observed that every 1 % increase in percentage of interdialytic weight gain was associated with a 1.00 mmHg increase in predialysis SBP, 0.65 mmHg decrease in postdialysis SBP and 1.66 mmHg increase in SBP during dialysis (Inrig et al. 2007).

The relationship between volume status (interdialytic weight gain) and BP in HD patients has been questioned in many studies (Sherman et al. 1993, Luik et al. 1994a, Luik et al. 1994b, Savage et al. 1997, Alvarez-Lara et al. 2001). A summary of studies on the association between weight gain during the interdialytic period and ambulatory blood pressure (ABP) is presented in Table 1.

Table 1. Summary of studies reporting association between interdialytic weight gain and ambulatory blood pressure.

Author	Number of patients	Weight gain (kg)	Interdialytic period (h)	Correlation with weight gain and BP (+/-)
Kooman et al. 1992	22	2.8 ± 1.4	48	-
Luik et al. 1994a,b	20	2.8 ± 1.6	72	-
Rodby et al. 1994	33	2.3	48	-
Chazot et al. 1995	40	1.2 ± 0.8	35 ± 2.9	-
Huisman et al. 1995	12	2.3 ± 1.2	64 ± 19	-
Lingens et al. 1995	18	1.5	42-71	-
Coomer et al. 1997	36	2.3 ± 1.4	48	-
Savage et al. 1997	27	1.6 ± 0.8	48	-
Ventura et al. 1997	167	1.8 ± 0.7	44-68	+ MBP
Mitra et al. 1999	40	1.3 ± 0.7	48	-
Sorof et al. 1999	12	1.0 ± 0.3	44	+ SBP
Fagugli et al. 2003b	110	2.6 ± 1.1	24	- (ECV+, SBP)
Santos et al. 2003	71	2.3 ± 1.0	48	-

MBP = mean blood pressure, SBP = systolic blood pressure, ECV = extracellular fluid volume.

There are many reasons why weight gain between dialysis sessions in most studies bears little relationship to BP. One may be that the relationship between ECV and BP is not linear. When ECV is normal, a small fluid load (1-2 kg) will go unnoticed, but a slightly greater load (3-4 kg) will increase BP. There is also a delay of several weeks or months between the normalization of ECV and the gradual decrease in SVR and BP (Charra 1998, Charra et al. 1998, Özkahya et al. 1999). Further, Luik and colleagues (1997) found that interdialytic fluid loading increased intravascular volume and CO but reduced SVR, resulting in no change in interdialytic BP (Luik et al. 1997). Hence, autoregulation of systemic blood flow as postulated by Cuyton (1990) may not be applicable for short-term interdialytic fluid changes in HD.

However, the long-term changes in volume status could have a different effect on BP as compared to short-term interdialytic fluid changes. The best clinical evidence for volume overload in the pathogenesis of hypertension in HD patients comes from Tassin, France. Using an 8-hour dialysis three times per week with moderate salt restriction, BP was normalized in more than 90 % of over a 1000 patients treated over a 30-year period (Chazot et al. 1995, Charra et al. 1999). Further, in a recent study Katzarski and associates (2003) investigated the effect of the removal of fluid excess on BP monitored continuously during 48 hours in HD patients. During a study period of 3-4 months systolic blood pressure (SBP) and diastolic blood pressure (DBP) were reduced only in the patient group who showed a reduction in ECV.

1.4.2.2 Lag phenemenon

Failure to find an association between ECV and BP may be due in part to a delay of several weeks or months between the normalization of ECV and the gradual decrease in SVR and BP (Charra 1998, Charra et al. 1998, Ŏzkahya et al. 1999). This lag phenomenon may arise from retention of vasoconstrictive circulating factors such as asymmetric dimethylarginine and Na^+, K^+-ATPase inhibitors, which may remain elevated because of the large volume of distribution, ineffective removal and persistent expression caused by a volume- mediated stimulus (Khosla et al. 2004). These factors are proposed to be a link between increased ECV and increased SVR in the pathogenesis of hypertension in the HD population (Boero et al. 1988, Tojo et al. 2000). Another explanation for the lag phenomenon may be linked to the reduction of sodium bound in the interstitial matrix lining the intimal surfaces of blood vessels (Shaldon 2006). This sodium store slowly leaks out and takes months to become normal if the patient is maintained on a 5 g salt intake per day.

A reduction in SVR and BP in patients treated with prolonged dialysis time has been observed in a one study. Luik and coworkers (1998) studied whether the good BP control in patients on long as compared to patients on short dialysis was associated with differences in ECV. IVCD, LV diameter index and ANP were not significantly different in patients on long dialysis compared to those on short. The investigators concluded that patients on long dialysis have adequate BP control, which seems mainly to be caused by a low SVR. The data suggest that also factors other than a lower fluid state contribute to the good BP control in patients on long dialysis. It is possible that longer dialysis times provide better removal of these vasoconstrictive substances and therefore improve BP control. Such a view is supported by the observation that 25 % of the normotensive Tassin patients treated with long dialysis had elevated postdialysis ECV in a study by Katzarski and group (1999b). In addition, a one study has shown that the use of short dialysis sessions with highly efficient HD treatments was associated with levels of BP control similar to those with conventional thrice-weekly HD treatment (Velasquez et al. 1998).

1.4.3 Assessment of blood pressure

There are great uncertainties regarding the best method for measuring BP (manual vs. monitored) and the best time (before dialysis, during dialysis, after dialysis, interdialytic) for collecting reliable BP readings in HD patients (Mailloux et al. 1998).

1.4.3.1 Sources of error

Some sources of error in the measurement of BP are unique to HD patients. The dialysis access may limit the measurement of BP to the arm with weaker blood flow, or it is also possible to have access in both arms. The environment of a busy HD unit may have a significant influence on the predialysis BP. Further, only a single BP measurement is usually taken rather than the average of three, patients may not rest before measurement, adequate cuff size or placement may not be used and the patient may not be asked about eating, drinking, smoking or exercising in the previous half hour (Agarwal 2002). A group under Rahman (2002) compared BP readings in 270 HD patients obtained following the usual routine in an HD unit with those obtained following standard guidelines for BP measurement. Their result implies that a given reading obtained in the dialysis unit may have been approximately 20 mmHg less than or 49 mmHg greater than the standardized BP reading. In addition, predialysis and postdialysis BP levels are influenced by intradialytic decreases in body weight and plasma volume and interdialytic weight gain (Fishbane et al. 1996, Ventura et al. 1997, Leypoldt et al. 2002, Vasavada et al. 2003).

1.4.3.2 Dialysis unit measures

Regardless of many limitations in measurement, pre- and postdialysis BP readings are normally used to represent BP behavior in HD patients. Some studies have found that predialysis BP correlates with interdialytic BP (Conion et al. 1996, Agarwal 1999). The postdialytic BP has been observed in some studies to give the best approximation of interdialytic values (Kooman et al. 1992, Mitra et al. 1999). Data obtained by Coomer and associates (1997) showed that both pre- and postdialysis BP correlate significantly with mean ABP. However, many studies using ABPM have concluded that dialysis unit BP cannot be used to predict interdialytic BP (Rodby et al. 1994, Huisman et al. 1995, Zoccali et al. 1999, Agarwal et al. 2001b). The current opinion is that HD unit BP can be used only in a quantitative sense. It can indicate the presence of hypertension, but cannot accurately predict the ABP (Agarwal et al. 2001b, Agarwal 2002).

1.4.3.3 Home monitoring

In free-living ambulatory hypertensive patients without renal disease, home BP monitoring correlates with ABP better than office BP (Kleinert et al. 1984). The use of home BP monitoring in HD patients has been assessed in a study by Agarwal (1999) involving 20 HD patients and comparing home BP measurements to 44-hour interdialytic measurements as well as pre- and post dialysis unit measurements. Agarwal found an excellent correlation ($r^2 = 0.8$) between average systolic and diastolic ABP and home blood pressures. ABP correlated fairly well with predialysis SBP ($r^2 = 0.73$), while the poorest correlation was with postdialysis BP ($r^2 = 0.34$). Using interdialytic ABPM recording as the reference standard Agarwal et al. (2006) observed that home SBP of ≥ 150 mmHg has the best combination of sensitivity and specificity to diagnose hypertension in HD patients. In patients with CRF not in HD an average home BP of approximately 140/80 mmHg appears to be the best correlate of hypertension defined by means of ABPM (Andersen et al. 2005).

1.4.4 Ambulatory blood pressure monitoring

The main problem in assessing HD patients BPs is that casual BP values taken around the dialysis session correlate poorly with the values of an ABPM session. The technique of ABPM allows better assessment of overall BP and a better correlation with the end-organ damage than isolated clinic readings (Zoccali et al. 1998, McGregor et al. 1999, Cannella et al. 2000, Agarwal 2007). ABPM is likely to assume a more prominent role in the care of renal patients.

1.4.4.1 Normal values

Several large meta-analyses of normotensive and hypertensive populations provide a useful normal range for ABPM (Staessen et al. 1996). The average awake BP by ABPM is normally ≤ 130/80 and values ≥ 135/85 mmHg should be considered as diagnostic for the presence of hypertension (Verdecchia et al. 1998, Ritz et al. 2001). Average nighttime ABPM values ≥ 120/70 mmHg are considered hypertensive.

1.4.4.2 Interdialytic BP profile

The predominant pattern of BP behavior observed in HD patients is a progressive increase in BP during the interdialytic period and absence of nocturnal fall in BP (Table 2).

Table 2. *Summary of studies reporting the profile of interdialytic blood pressure in hemodialysis patients.*

Author	Number of patients	Interdialytic BP	Casual BP correlated with ABP	Dipping BP	Rapid predialytic BP increase
Kooman et al. 1992	22	D1=D2	post-dialysis	↓, D1=D2	+
Luik et al. 1994[a,b]	20	D3>D2 (NT) D3=D2 (HT)	nr	→, D1=D2 NT=HT	nr
Rodby et al. 1994	33	D1=D2	none	→	nr
Chazot et al. 1995	40	NBP2>NBP1	nr	↓, NBP2>NBP1	nr
Huisman et al. 1995	12	D3>D2>D1	none	↓	-
Lingens et al. 1995	18	DBP1=DBP2 NBP2>NBP1	none	nr	+
Coomer et al. 1997	36	D2>D1	none	↓	nr
Savage et al. 1997	27	D2>D1 or D1=D2	nr	nr	nr
Ventura et al. 1997	167	D2>D1	nr	nr	nr
Mitra et al. 1999	40	D2>D1	post-dialysis	↓, NBP2>NBP1	+
Sorof et al. 1999	12	D2>D1	none	↓	nr
Santos et al. 2003	71	D2>D1	none	↓, D1=D2	nr

ABP = ambulatory blood pressure, D1-3 = BP in monitoring days 1-3, DBP = daytime blood pressure, NBP = nighttime blood pressure, NT = normotensive, HT = hypertensive, nr = not reported, ↓= dipping status worsened, →=dipping status stable.

In some studies, however, BP has not been seen to increase during the interdialytic period (Kooman et al. 1992, Rodby et al. 1994) or increases only in some patients (Luik et al. 1994a, Luik et al. 1994b, Savage et al. 1997). Some authors have observed only a nocturnal increase in BP during the interdialytic period (Chazot et al. 1995, Lingens et al. 1995). In most studies, casual BP correlates weakly with the mean ABP (Rodby et al. 1994, Huisman et al. 1995, Lingens et al. 1995, Coomer et al. 1997, Sorof et al. 1999, Santos et al. 2003), but post-dialysis BP may predict the average interdialytic BP (Kooman et al. 1992, Mitra et al. 1999). In some cases, a rapid predialytic increase in BP was observed (Kooman et al. 1992, Lingens et al. 1995, Mitra et al. 1999).

1.4.4.2.1 Nocturnal changes in BP

Non-dippers are defined as those subjects whose mean sleeping BP does not fall by 10 % or rise during sleep. The normal decrease in BP during the night is blunted in 74-82 % of patients with advanced renal disease or undergoing dialysis treatment (Luik et al. 1994b, Goldsmith et al. 1997, McGregor et al. 1999, Peixoto et al. 2002). Farmer and colleagues (1997) have found a clear association between the number of non-dippers and the degree of renal function impairment. In their study in 380 patients, the difference in prevalence of nocturnal dipping reached statistical significance once plasma creatinine rose above 400 μmol/l. Non-dipping is independent of the underlying renal disease (Baumgart et al. 1991).

Studies of the effect of volume expansion on the diurnal variation in BP in HD patients have yielded contradictory results. In a study by a group under Narita (2001), the decreased nocturnal BP fall seen in 76 % of non-diabetic HD patients was associated with increased ECV even in those without overt overhydration. Likewise Sorof and associates (1999) report similar results in children receiving HD. In turn, many other results argue against the role of increased ECV in the pathogenesis of non-dipping (Luik et al. 1994a, Luik et al. 1994b, Chazot et al. 1995, Katzarski et al. 1999b, McGregor et al. 1999, Fagugli et al. 2001). Fagugli and group (2001) reported normalization of BP and reduction in ECV in 12 patients on short daily HD, but observed no difference in night-day ratio in SBP. Normotension achieved either by long and slow HD does not seem to protect against the loss of nocturnal dip in BP. In spite of the much smaller expansion in ECV in comparison with patients on conventional HD (Katzarski et al. 1999b), 50-75 % of patients on long dialyses are non-dippers (Chazot et al. 1995, McGregor et al. 1999).

Another etiological factor may be sleep apnoea. This disorder occurs in at least 60 % of ESRD patients and is associated with lack of fall in nocturnal BP (Kraus et al. 1997). In a study by Zoccali and colleagues (1998), nocturnal hypoxemia in HD patients was associated with altered BP profile independently of arterial pressure. Sleep apnoea is not improved by conventional modes of dialysis, but is corrected by nocturnal HD (Hanly et al. 2001). Unfortunately, no data are available concerning the impact of nocturnal HD on the diurnal variation in BP.

The lack of fall in nocturnal BP in HD patients could be also related to an increased sympathetic nervous system activity (Converse et al. 1992b, Nielsen et al. 1995, Liu et al. 2003).

1.4.4.2.2 Daytime variation in BP

There are also diurnal variations in BP in HD patients other than the nocturnal change. A rapid increase in BP has been recorded just before the HD session (Kooman et al. 1992, Lingens et al. 1995, Mitra et al. 1999). The last mentioned

authors suggest the white-coat phenomenon as an explanation. They observed the white-coat effect in almost 40 % of arrival pressure. This effect may also be more common in renal patients than in general hypertensive population (Rosansky et al. 1995). In a study by Huisman and colleagues (1995), BP did not increase sharply in the hours before dialysis, but in seven of the 12 patient studied it continuously declined up to 5-6 h after dialysis. Agarwal (1999) later confirmed the result. Controversies exist related to changes in BP during the interdialytic days. In some studies, daytime BP has not differed between the 1st and the 2nd interdialytic day (Kooman et al. 1992, Rodby et al. 1994, Lingens et al. 1995). Contrary to these reports, a pattern of progressive rise in BP during the interdialytic period has been observed in other studies (Huisman et al. 1995, Sorof et al. 1999, Santos et al. 2003). Agarwal (1999) reported that the initial decrease in BP during the first interdialytic day was compensated next morning by an increase to the predialysis levels. Figure 1 presents some typical SBP profiles in HD patients.
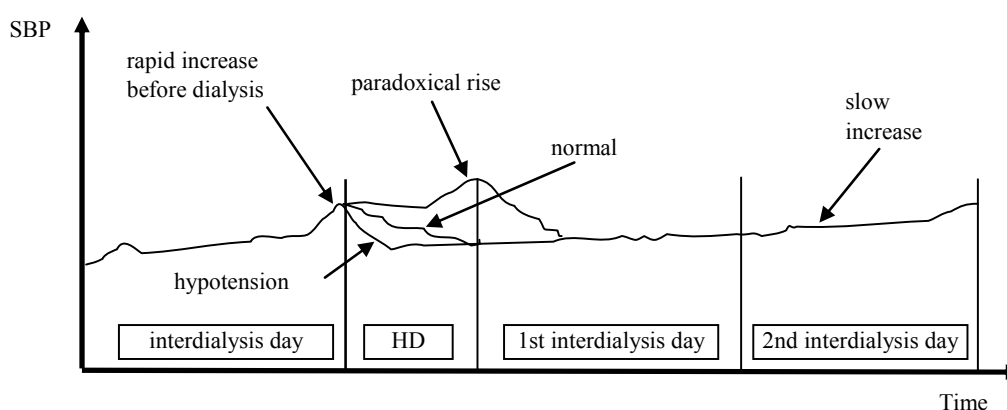
Figure 1. *Various systolic blood pressure profiles during hemodialysis and the interdialytic period. HD = hemodialysis, SBP = systolic blood pressure.*

1.4.4.3 Left ventricular hypertrophy

In studies using echocardiography the frequency of LVH is reported to range from 60 to 75 %. Several cross-sectional studies have shown that BP elevation in HD patients is a clear risk factor for LVH (Erturk et al. 1996, Zoccali et al. 1998, McGregor et al. 1999, Cannella et al. 2000, Fagugli et al. 2003b). In the studies in question, the association between ABP data and LVH was stronger than between casual BP and LVH. On the other hand, in a study by Zoccali et al. (1999) pre-dialysis BP was at least as strong predictor of left ventricular mass (LVM) as 24-h AMBP. Non-dipper status has also been associated with LVH in HD patients (McGregor et al. 1999, Liu et al. 2003).

Blunted diurnal BP variation leads to an increased BP load and predisposes to the development of LVH. In an elegant prospective study by Covic and associates (2000), the effect of abnormal diurnal BP variability on

echocardiographically derived serial measurements of the LV was examined in 60 stable chronic HD patients over a 12-month period. Those patients with reduced diurnal BP variability developed a dilated LV.

A close relationship exists between LVH and impaired LV diastolic relaxation. The patients most susceptible to HD hypotension are characterized by both LVH and diastolic dysfunction (Raine 1996).

1.4.5 Intradialytic hypertension

In some hypertensive HD patients, BP rises further during UF. This paradoxical rise is explained by the fact that the kidneys react to volume contraction by activating the renin-angiotensin system and further increase the SVR (Charra et al. 2003). Other mechanisms have also been suggested: activation of norepinephrine, increased sympathetic activity, hypercalcemia increasing vasoconstriction, brain ischemia secondary to hypovolemia, increased CO, erythropoietin and intradialytic removal of antihypertensive medications (Fellner 1993, Lewin 1993, Gunal et al. 2002).

Agarwal and colleagues (2001a) demonstrated that the renin-angiotensin system is activated in these patients and thrice-weekly lisinopril effectively reduces BP. The role of the renin-angiotensin system in the genesis of intradialytc hypertension is however questioned in a study by Cirit and associates (1995). They assessed seven volume-overloaded HD patients with paradoxical hypertension. These patients were not responsive to antihypertensive drugs, including ACE-inhibitors. Intensified more frequent UF led to the disappearance of the paradoxical BP rise and antihypertensives were withdrawn in all cases. These observations stress the importance of volume control on paradoxical hypertension in HD patients. However, one recent study suggests that the physiological changes in intradialytic hypertension patients are characterized by an inappropriately increase in SVR due to elevation of endothelin-1 and a decrease in NO (Chou et al. 2006).

1.4.6 Sodium and dialysis regimen in the treatment of hypertension

The mainstay in the treatment of hypertension in HD patients is to normalize ECV and maintain dry weight through control of fluid, salt intake and UF.

1.4.6.1 Sodium restriction

The clinical relation between salt, ECV and BP in patients with renal failure is manifest. Increasing salt loading from 0.5 g per day to 10 g per day causes an increase in ECV of approximately 1.5 liter and on the other hand, a 1.0 liter reduction in ECV reduces mean arterial pressure (MAP) by 10 mmHg (Cianciaruso et al. 1996). Kempner (1949) first reported the benefit of a reduced dietary salt intake (250-300 mg per day) in controlling hypertension in patients with CRF.

In the Tassin unit BP is controlled in 95 % of the patients without medication using a long 8-hour, thrice-weekly dialysis schedule with a mean salt intake of 5 g per day and a dialysate sodium of 138 mmol/l (Laurent et al. 1998, Charra 2007). It is obvious that the results obtained in Tassin cannot be reproduced without salt restriction. The overall survival is better in the Tassin unit than in a conventional HD unit (Innes et al. 1999). In addition, two other groups have obtained normal BP without medication by means of long HD and reduced salt intake (Goldsmith et al. 1996, Ŏzkahya et al. 1998). However, it is also possible to lower BP and reduce or even discontinue antihypertensive medication without prolongation of dialysis time (Krautzig et al. 1998). These last-mentioned authors reported a decrease in pre-dialysis SBP and DBP in eight patients when dialysate sodium was reduced from 140 to 135 mmol and dietary salt intake was restricted to 6 g per day.

Conventional relatively short dialysis (three times weekly for at least 4 hours) can also achieve normal BP, while salt intake is restricted to less than 6 g per day without contemporaneous change in dialysate sodium concentration (Ŏzkahya et al. 1999). Lowering only the dialysate sodium concentration without extra intervention to dietary salt restriction may not be sufficient to improve BP control (Kooman et al. 2000).

The most important effect of a reduction in dialysate sodium concentration and a salt-restricted diet is a reduction in thirst and interdialytic weight gain (Fishbane et al. 2002, Kooman et al. 2003). An increase in interdialytic weight gain in compliant patients with salt restriction should not be more than 1.5 kg.

1.4.6.2 Dialysis regimen

Frequent and prolonged HD has been uniformly shown to control hypertension in ESRD patients more effectively than conventional HD. In comparison to this latter, a daily schedule (six times a week for 2 h) results in better control of BP (Buoncristiani et al. 1988, Mastrangelo et al. 1998, Traeger et al. 1998, Woods et al. 1999, Kooistra 2003). BP decreases mainly in hypertensive patients and in those undergoing treatment with antihypertensive medications (Woods et al. 1999, Kooistra 2003). Fagugli and coworkers (2001) conducted a randomized two-period crossover study to compare the effect of short daily HD versus standard thrice-weekly dialysis. A significant reduction in 24-hour BP during

daily HD was observed. In a study by Maduell and group (2003) patients were changed from conventional three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. A reduction in both SBP and DBP was observed albeit without achieving statistical significance.

Thrice weekly long HD also results in excellent BP control in the majority of patients without the need for antihypertensive drugs (Chazot et al. 1995, Laurent et al. 1998, McGregor et al. 1999, Luik et al. 2001). McGregor and associates (2001) conducted a randomized crossover trial to establish whether home HD was associated with better BP control than standard HD. Pre- and postdialysis systolic, ambulatory SBP and DBP were all higher with standard than with home HD. Weight, ECV and neurohormones did not differ between these treatments.

Long-term nocturnal HD, which uses longer and more frequent sessions than conventional HD, lowers clinic BP (Pierratos 1999, Williams et al. 1999). Chan and associates (2003) studied 18 consecutive patients before and 1 and 2 months after conversion from conventional HD to nocturnal (six 8-hour sessions per week) HD. Nocturnal HD lowered 24-hour MAP, total SVR and plasma norepinephrine. The Chan and group (2002) also studied the effects of nocturnal HD in LVH. Reductions in BP with nocturnal HD were seen to be accompanied by a regression of LVH. Conversion of patients from nocturnal HD to daily short HD results in poorer BP control (Pierratos 1999).

1.5 Myocardial ischemia in hemodialysis patients

1.5.1 Epidemiology and risk factors

Patients on dialysis have a very high rate of CAD. Forty percent of the 1846 patients on HD enrolled in the Hemodialysis Study had CAD at study initiation (Cheung et al. 2000). In the Wave II Dialysis Morbidity and Mortality Study of the United States Renal Data system 32 % of 4024 patients starting dialysis had history of CAD (Foley 2003). The prevalence of CAD ranges to 36 % in diabetic patients on maintenance HD (Koch et al. 1997a) and to 88 % in diabetic transplant candidates over the age of 45 (Manske et al. 1992, Wizemann 1996).

Several studies have documented an increasing prevalence of traditional coronary risk factors in patients with chronic kidney disease and in ESRD (Longenecker et al. 2002, Shlipak et al. 2002, Goicoechea et al. 2005). However, in patients with ESRD, such factors account only partly for the very high CV mortality rate (Cheung et al. 2000). Non-traditional risk factors such as inflammation, hyperhomocysteinemia, hyperphosphatemia, sympathetic nervous system overactivity and anemia are uremia-related factors, which increase in prevalence as kidney function declines and may contribute to the excess risk of CVD in CRF (Menon et al. 2005).

To explain the accelerated atherosclerosis, cardiac remodelling and hypertrophy and progression of renal disease Bongartz and coworkers (2005) have recently proposed the renin-angiotensin system, the balance between NO and reactive oxygen species, inflammation and the sympathetic nervous system as actual links in combined heart and renal failure.

1.5.2 Effects of hemodialysis on myocardial ischemia

Myocardial ischemia is caused by a limitation of coronary flow reserve generally induced by significant coronary artery stenosis. However, in 27 % of HD patients ischemic symptoms are attributable to non-atherosclerotic disease (Rostand et al. 1984). Many non-traditional risk factors for CAD in HD patients may play a role in the development of coronary ischemia without significant coronary artery stenosis. In the setting of endothelial dysfunction, increased vessel calcium content and hypercoagulation, normal hemodynamic autoregulation to preserve flow in the coronary bed may not occur (Schreiber 2001). Patients with end-stage diabetic nephropathy have been observed to have a reduced coronary flow reserve despite angiographically normal coronary arteries (Ragosta et al. 2004).

Hypovolemia during the HD session reduces cardiac filling, SV and CO. Most ESRD patients have LV diastolic dysfunction, when even a mild reduction in filling may result in a marked reduction in CO and BP and augment the risk of myocardial ischemia (Wizemann 1996). Myocardial ischemia can on the other hand aggravate LV diastolic dysfunction (Cohen-Solal 1998). Further, hypovolemia activates the sympathetic system, which induces vasoconstriction and an increase in myocardial contractility and HR (Santoro et al. 1998). Tachycardia leads to shortening of the diastolic period and perfusion time, predisposing to myocardial ischemia.

Hypervolemia is also clearly the most important factor in the pathogenesis of hypertension in HD patients. This is associated with increased workload and oxygen demand on the LV and is therefore likely to aggravate myocardial ischemia during the HD session. Correction of hypervolemia by UF increases the ejection fraction and diminishes ST-segment changes (Wizemann 1996).

The prevalence of LVH is very high, up to 70 %, among dialysis patients and predisposes to the nonatherosclerotic ischemic heart disease (London et al. 2001). Interstitial fibrosis is a prominent finding in uremic heart disease, contributes to the development of LVH, and in very advanced stages may restrict diffusion of oxygen (Amann et al. 1994a, London 2003). Small-vessel smooth-muscle hypertrophy and endothelial abnormalities described in LVH would further predispose to ischemia (Amann et al. 1997, Parfrey 1999). LVH also results in increased perfusion requirements, predisposing to myocardial ischemia during the HD session (Jaradat et al. 2002).

A decrease of 1.3-2 kPa in arterial oxygen tension has been noted in patients undergoing HD. This fall may not be tolerated by HD patients having CVD, and

oxygen therapy may be required (Cardoso et al. 1988, DE Broe et al. 1988, Yap et al. 1998). It is also worth of noting that the prevalence of sleep apnoea syndrome ranges from 50-70 % in HD patients and was found to be associated with severe CAD in a recent study (Jung et al. 2005).

1.5.3 Effects of hemodialysis on ECG and vectorcardiogram

Most patients on chronic HD treatment exhibit abnormal ECG (Diskin et al. 1981, Abe et al. 1996). HD itself seems to induce changes on both the standard ECG (Diskin et al. 1981, Ono et al. 1983, Wizemann et al. 1983, Shapira et al. 1992, Madias et al. 2003a) and the vectorcardiogram (Tarjan et al. 1975, Ishikawa et al. 1979, Vitolo et al. 1987). The most frequent changes during HD treatment are a decrease, flattening or inversion in T wave in 30-50 % of patients, an increase in QRS amplitude (R wave) in 60-75 % of patients and changes in the QTc time in 55-60 % (Diskin et al. 1981, Ono et al. 1983, Shapira et al. 1992). Asymptomatic ST-segment changes suggesting myocardial ischemia are also present in 22-45 % of patients (Diskin et al. 1981, Shapira et al. 1992, Abe et al. 1996). Dialysis may also cause changes in P wave duration (Shapira et al. 1992, Szabo et al. 2002).

In many studies, the major change observed in standard ECG induced by HD is an increase in QRS amplitude (Diskin et al. 1981, Ono et al. 1983, Wizemann et al. 1983, Fuenmayor et al. 1993, Madias et al. 2003a). Ishikawa and colleagues (1979) have reported that the amplitude of the R waves in the vectorcardiographic leads X,Y, and Z, the sum of the R wave amplitudes of the three leads and the magnitudes of the maximal QRS vector in the three planes were all significantly augmented after dialysis. Vitolo and associates (1987) also observed that all vectorcardiographic measurements except maximal vector on the horizontal plane showed a statistically significant increase during HD. An increase in QRS amplitude after HD has also been observed on body surface maps (Kinoshita et al. 1993).

Daniel Brody investigated the effect of intracardiac blood mass on the ECG (Brody 1956). The Brody effect is based on the inhomogenity of the tissues. The resistivity of the intracardiac blood is about 1.6 Ωm, that of the cardiac muscle about 5.6 Ωm and lungs about 10-20 Ωm (Malmivuo et al. 1995, Madias et al. 2003a). The lungs thus behave as electrical insulators, whereas blood acts as a conductor. During the initial phases of ventricular depolarization, the excitation wave advances radially, whereas in the later phases tangential forces predominate. The radial forces predominantly generate the surface potentials and represent the most important determinant of QRS voltage. Since intracardial blood augments these radial forces, the whole QRS complex, and especially its initial phase, increases when the BV rises (Voukydis 1974).

According to Brody's conception, a decrease in intracardiac blood or heart volume will lead to a decrease in the QRS potentials and on the other hand, an enlarged heart is associated with increased surface potentials. Millard and

coworkers (1978), who reduced the volume of the LV by venesection, noted the decrease in QRS amplitude and reinforced Brody's theory. Reduction in heart volume by intravenous diuresis (Vancheri et al. 1989), by reduction of the venous return (Castini et al. 1996) or rapid sinus caroticus pacing (Daniels et al. 1984) has also been found to diminish QRS amplitude. There is also an assumption that reduction in heart size will increase the distance between the heart and the precordial ECG leads and thus lower QRS amplitude. In contrast to Brody effect, decrease in LV dimensions during HD is associated with increase in QRS amplitude. Changes in QRS amplitude during HD have proved to correlate with changes in LV dimensions in one study (Vitolo et al. 1987) but not in two others (Fuenmayor et al. 1993, Kinoshita et al. 1993).

Blood resistivity is in direct relation to hematocrit and thus changes in hematocrit are expected to affect the transmission of cardiac forces, resulting in changes in QRS voltage. Raising hematocrit in experimental animal studies (Nelson et al. 1972, Hodgkin et al. 1977) and due to blood transfusion in anemic patients (Rosenthal et al. 1971) decreases radial forces and QRS amplitude according to the Brody effect. In any case, an inverse relation has been observed in HD patients (Vitolo et al. 1987, Oreto et al. 1992, Kinoshita et al. 1993). Thus, the Brody theory does not explain the increase in QRS amplitude during HD.

An increase in QRS amplitude during exercise tests has been reported to indicate myocardial ischemia (Bonoris et al. 1978a, Bonoris et al. 1978b). Myocardial ischemia may provoke an increase in end-diastolic volume of LV or LV dyskinesia and QRS amplitude may be augmented due the Brody effect (Brody 1956). However, groups under Battler (1979) and Ohlmeier (1983) found no evidence of the existence of the Brody effect in humans during exercise. The most significant increase in QRS amplitude over leads V5 and V6 during HD would favour myocardial ischemia as a causative factor (Diskin et al. 1981, Ono et al. 1983). Diskin's group (1981) reported that 45 % of their patients on HD developed depression of the ST-segment and 75 % an increase in QRS amplitude. The authors concluded that the increase in QRS amplitude is associated with myocardial ischemia based on the considerable proportion of patients having CAD in their population. In contrast, in another study the relative constancy of the precordial leads during HD in comparison with limb and augmented limb leads would argue against ischemia as a cause of increased QRS complex (Dudley et al. 1990). Further, in many other studies QRS amplitude variations during HD have not been attributed to myocardial ischemia (Wizemann et al. 1983, Fuenmayor et al. 1993, Kinoshita et al. 1993, Madias et al. 2003a).

A positive correlation has been reported between an increase in QRS amplitude and weight loss or UF volume during HD (Ono et al. 1983, Vitolo et al. 1987, Kinoshita et al. 1993). In turn, no such correlation has been found in some other reports (Diskin et al. 1981, Fuenmayor et al. 1993). In one study, the correlation of the sums of the QRS amplitude changes of all ECG leads and weight loss was moderate, but there was no correlation with the net volume removed (Madias et al. 2003a). One reason for these discrepancies may be the sensitivity of QRS amplitude to changes in body weight or volume removed. In those studies in which the weight change correlated positively with an increase

in QRS amplitude the mean weight decrease during HD was 2.2 kg, while in studies with no correlation, the mean decrease in weight was only 1.2 kg.

An augmentation of the QRS complex in patients with congestive heart failure responding to diuretic induced diuresis has recently been documented (Madias 2005). Conversely, an association of marked reduction in the amplitude of the QRS complex with progressive weight gain due to development of peripheral edema has also been reported (Madias et al. 2001, Madias et al. 2003c, Madias et al. 2003b). The mechanism underlying the QRS changes in these contexts is associated with changes in the water content of the tissues. Increased water content in the tissues reduces resistance (R) to conduction, which in the presence of stable current (I) according the Ohm's law ($U = R*I$) leads to low potentials (U) and QRS amplitudes (Rudy et al. 1979). Indeed Madias and coworkers (2003c) have reported a good cross-correlation of weights, QRS amplitudes and the electrical properties (resistance/reactance/impedance) of the body during the course of treatment for heart failure. In addition, they found statistically significant correlations between weight loss and net fluid removed and the change in the QRS complex in the course of 26 HD sessions in one patient (Madias et al. 2003a). However, further studies with a large number of patients are needed to clarify the relationship between the electrical properties of tissues and QRS amplitude in HD patients.

1.5.4 Diagnosis of myocardial ischemia

1.5.4.1 Clinical symptoms

Advanced CAD may be found in HD patients with minimal or no symptoms. Schmidt and associates (2001) have reported a low sensitivity (65 %) and specificity (66 %) of angina pectoris in 42 patients undergoing chronic HD and 42 patients after renal transplantation. Studies of patients on HD indicate that asymptomatic ischemia is most prevalent in those with diabetes mellitus (Joki et al. 1997, Koch et al. 1997a, Koch et al. 1997b). Such discrepancy between coronary angiographic findings and symptoms may be due to autonomic neuropathy (Jassal et al. 1998). CAD should also be suspected in dialysis patients with dialysis hypotension, heart failure, exceptional dyspnea or arrhythmias (Goldsmith et al. 2001). Conversely, many patients on HD may have angina symptoms with no CAD. The reason for this is that the heart with open coronary arteries in renal failure is more susceptible to ischemic injury as a result of impaired microvascular adaptation, impaired metabolic adaptation and inappropriately high sympathetic activity (Amann et al. 2003).

1.5.4.2 Troponins

Cardiac troponin T and I are the most sensitive and specific laboratory markers of myocardial cell injury and have replaced creatine kinase MB as the gold standard (Jaffe et al. 2000, Hamm et al. 2002). The appropriate use of these enzymes is less clear in patients with ESRD, since in their case elevations of troponin T, and to a less extent also troponin I, are frequently found without clinical evidence of myocardial disease (Li et al. 1996, McLaurin et al. 1997, Apple et al. 2002). Several possible causes have been presented for the difference in the increase in troponin T compared with troponin I. Impaired renal clearance of troponin T fragments may explain elevated troponin T levels in ESRD patients (Diris et al. 2004). In addition, a higher relative concentration of myocardial troponin T and /or an easier release from the myocardium might explain the difference (Chapelle et al. 2002, Peetz et al. 2003). High serum troponin T levels may also be caused by leakage from hypertrophic cardiomyocytes in LVH (Mallamaci et al. 2002).

There are limited data available in the HD population relating cardiac troponin status and angiography findings. In a prospective study enrolling 224 HD patients coronary angiography was undertaken for 65 to determine the prevalence and severity of CAD according to troponin T concentration (DeFilippi et al. 2003). Elevated levels of troponin T were strongly associated with diffuse CAD. Elevated concentrations of cardiac troponins are also associated with severe coronary artery calcification in asymptomatic HD patients (Jung et al. 2004).

A number of observational studies have also found especially the troponin T level to be strongly associated with a risk of incident CV events in HD patients (Ooi et al. 2001, Apple et al. 2002, Mallamaci et al. 2002, Khan et al. 2005). In a study by Apple and associates (2002) elevated versus normal troponin T defined by any cut-off concentration was associated with a 2- to 5-fold increase in all-cause mortality. Surprisingly, no differences in the relative risk of mortality were found between patients with or without a known history of CAD or diabetes.

In the absence of an acute coronary event, elevated pre-dialysis troponin T levels are relatively consistent. A small increase over time is common and may reflect progression of CAD or LVH (Mallamaci et al. 2002, Conway et al. 2005). Levels more than double from the baseline may indicate acute coronary syndrome. To distinguish between troponin elevations due to chronic conditions or acute coronary syndrome, serial measurement of troponin concentrations in ESRD patients is proposed to obtain a baseline value for comparison (Hamm et al. 2002, Conway et al. 2005).

1.5.4.3 Electrocardiography

ECG alterations are frequently observed in patients on HD and the resting ECG may not be useful as a screening test for CAD in these patients (Schmidt et al.

2001). A group under Abe (1996) reported that 65 % outpatients receiving HD evinced abnormalities in resting ECG: changes in PQ and QRS intervals, QRS-amplitude and non-specific changes in ST-segment and T-waves. In addition, repolarization abnormalities caused by LVH may mask ischemic changes in ECG. There is also the impact of HD therapy on ECG (Severi et al. 2003). ST-segment depression on the ECG at rest did not distinguish patients with or without CAD in diabetics on HD treatment (Koch et al. 1997a). In this latter study, one third of patients without angiographic evidence of CAD had non-specific ECG changes. The sensitivity of ST-segment depression at resting ECG was 52 %. In any case, in a recent study by Sharma and colleagues (2005) a significantly higher proportion of patients with severe CAD in coronary angiography had an abnormal baseline ECG (p = 0.001) when compared to those showing no CAD seen in angiography. Further, in a study by a group under Nakamura (2000) the incidence of CAD was significantly greater in HD patients who showed a depression of the ST-segment in repeated ECG recordings during the HD session than in a negative-ST group. Event-free survival was also poorer in the positive-ST group. ST-segment depression tends to occur predominantly at the end of a dialysis (Nakamura et al. 2000).

1.5.4.4 Holter monitoring

From 15 to 60 % of patients on HD treatment display transient and mostly asymptomatic ST-segment depression on Holter monitoring (Kremastinos et al. 1992, Abe et al. 1996, Conlon et al. 1998, Severi et al. 2003). Holter readings in HD patients cannot always be accepted as evidence of myocardial ischemia, since in some studies the presence or absence of deviation in ST-segment depression did not predict the presence or absence of CAD (Kremastinos et al. 1992, Singh et al. 1994, Conlon et al. 1998). Moreover, Severi and associates (2003) have reported an influence of HD on ECG. Further, in many studies ST changes are mostly found during and immediately after dialysis (Zuber et al. 1989, Kremastinos et al. 1992, Narula et al. 2000) and may result from electrolyte shifts.

There are also factors favouring the conception that ST-segment changes in HD patients are due to CAD. Firstly, CAD is very prevalent in patients with ESRD, and recent studies have shown an excellent correlation between ST depression recorded during Holter monitoring and other simultaneous objective evidence of ischemia in the general population. Secondly, HD patients with CAD have two separate ischemic peaks in monitoring, the first during early morning and the second in the late afternoon contemporary with the time of dialysis (Cice et al. 2003). Thirdly, the use of high-dose diltiazem proved able to reduce both ischemic peaks in HD patients with CAD (Cice et al. 2003). Fourthly, chest discomfort, a diagnosis of angina pectoris or a previous myocardial infarction have been observed to be more prevalent in patients showing ST-segment changes (Abe et al. 1996, Narula et al. 2000). Fifthly, in some studies ST

depression is mostly unrelated to HD timing (Abe et al. 1996, Conlon et al. 1998, Conlon et al. 2000).

Further studies including coronary angiography in a larger number of patients are needed to clarify whether ST changes during HD reflects occult coronary disease, or electrocardiographic responses to major transcellular shifts in potassium, calcium or magnesium (Goldsmith et al. 2001).

Table 3. *Summary of studies reporting ST-segment findings on Holter monitoring in hemodialysis patients.*

Author	Number of patients	Angina symptoms before the study (%)	Angina symptom during Holter (%)	Number of patients with ST changes (%)	Number of patients with ST changes during HD (%)
Zuber et al. 1989	32	nr	4 (13)	8 (25)	8 (25)
Kremastinos et al.1992	45	12 (27)	17 (38)	7 (16)	7 (16)
Abe et al. 1996	72	11 (15)	nr	43 (60)	11 (26)
Conlon et al. 1998	67	25 (37)	0	16 (23)	1 (1)
Conlon et al. 2000	31	nr	nr	10 (32)	1 (3)
Narula et al. 2002	38	6 (16)	0	17 (45)	13 (34)

nr = not reported.

1.5.4.5 Exercise ECG testing

Exercise ECG testing has evolved into a modality of considerable importance in the evaluation of patients with known or suspected CAD. However, this approach is not generally recommended for HD patients by reason of the markedly reduced exercise capacity of most such subjects, the high prevalence of non-specific changes due to LVH and frequent abnormalities in the rest ECG. While Schmidt and colleagues (2001) performed exercise stress ECG in 79 patients undergoing chronic HD or after renal transplantation, only 18 of them were able to reach a sufficient exercise level. In two other studies, patients with diabetes were evaluated prior to renal transplantation to determine the risk of CV complications. Only 6/80 (7.5 %) and 12/60 (12 %) of these patients achieved an adequate rise in HR (Morrow et al. 1983, Philipson et al. 1986). The overall sensitivity of the stress ECG to detect coronary artery stenosis >70 % was only 30-35 % in two recent studies among renal transplant candidates (Schmidt et al. 2001, Sharma et al. 2005).

1.5.4.6 Echocardiography

It is recommended that all ESRD patients be evaluated for LV systolic function and valvular disease after HD initiation (Herzog 2003). The most cost-effective test is echocardiography. If the echocardiograph confirms a wall motion abnormality in a distribution consistent with usual coronary artery flow, exercise echocardiography may not be required for the diagnosis of CAD (Sorrell 2001). A normal resting echocardiogram result without a finding of regional wall motion disturbance does not exclude CAD in the uremic population.

Dobutamine stress echocardiography offers a non-exercise method of detecting ischemia. It is independent of exercise capabilities and has been suggested as the screening tool of choice (Logar et al. 2003). The timing of dobutamine stress echocardiography in respect of the HD session has not been studied. The usefulness of this technique in detecting CAD has been studied in renal transplant canditates (Reis et al. 1995, Herzog et al. 1999, Sharma et al. 2005). In these studies dobutamine stress echocardiography was compared with coronary angiography and a sensitivity of 75-95 % and a specificity of 71-94 % of dobutamine stress echocardiography for CAD diagnosis was reported.

1.5.4.7 Dynamic vectorcardiography

Approximately 75 % of all ischemic episodes in stable or unstable CAD are silent (Deedwania et al. 1991). Even using repeated ECGs in conjunction with chest pain, most episodes of ischemia will be overlooked. Therefore, a variety of technologies for continuous monitoring of the ST-segment, for example dVCG, have been introduced (Lindahl 1999).

1.5.4.7.1 Method

Vectorcardiography (VCG) is based on eight electrodes recording a three-lead ECG (X, Y and Z) where each lead is a summation of electrical forces at 90 deg angles with two, i.e. an orthoglonal system (Dellborg 2001). Ernest Frank presented the lead system for VCG registrations used today in 1956 (Frank 1956). Five years later the superiority of VCG compared with conventional ECG for the diagnosis of acute myocardial infarction was reported (Wolff et al. 1961). Hodges presented the non-on-line VCG registration in 1974 (Hodges et al. 1974) and on-line dynamic vectorcardiographic registration (dVCG) was adopted for clinical use in 1986. The monitoring system consists of a microprocessor-controlled data acquisition module, a computer, a monitor and a laser printer. ECG signals are continuously collected from eight conventional body surface electrodes applied to the patient's chest according to the Frank lead system (Dellborg et al. 1990, Lundin et al. 1992).

For clinical use three variables, QRS vector difference (QRS-VD), ST vector magnitude (ST-VM) and ST change vector magnitude (STC-VM), shown in Figure 2 are collected, compared with the reference complex, measured and presented on trends. Trend curves showing ischemia parameters are updated during a pre-chosen period of 10-240 s. QRS-VD reflects changes in the shape of the QRS complex. ST-VM displays the actual deflection of the ST-segment from the isoelectric baseline, no matter whether it is an elevation or depression. ST-VM is measured 20 ms and 60 ms after the termination of the QRS complex (J-point). STC-VM constitutes the length of the difference vector between the initial and the current vector (Lundin et al. 1992, Norgaard et al. 2000). By calculating ST and QRS changes, ischemia is monitored in the entire heart.
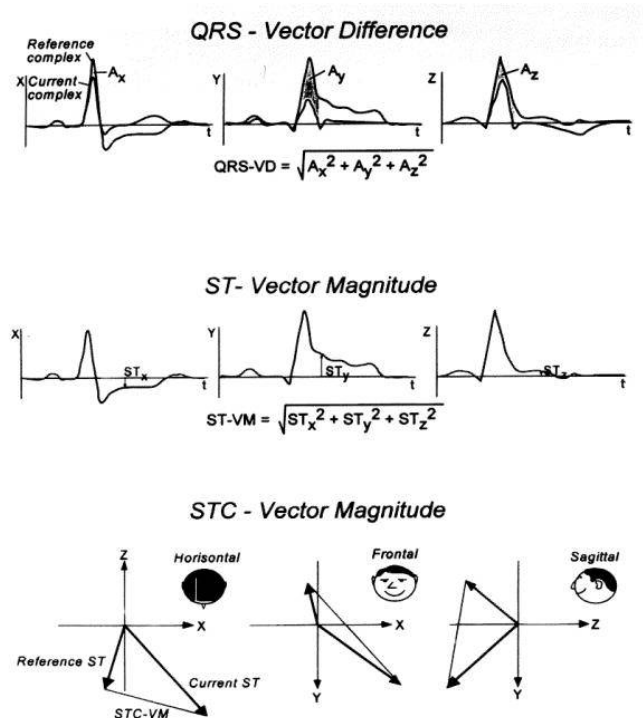
Figure 2. *Vectorcardiographic variables QRS-VD, ST-VM and STC-VM used in dVCG monitoring. Obtained from Lundin et al. 1997. Reprinted with permission of S Karger AG, Basel.*

A QRS-VD ischemic episode is defined as a transient change >15 µVs from the patient baseline (Lundin et al. 1992, Norgaard et al. 2000). A QRS-VD end value of > 15 µVs is regarded as indicative of acute myocardial infarction. An ischemic episode is defined as an ST-VM and/or STC-VM increase >50 µV >1min from patient baseline and over three ST-VM/STC-VM episodes during a 24 hour registration identifies high-risk patients (Jensen et al. 1994, Andersen et al. 1996, Jensen et al. 2002). STC-VM has been found to be the most sensitive parameter for monitoring ischemia (Jensen et al. 2000). Using coronary

angioplasty as the model of myocardial ischemia it has been demonstrated that both ST-VM and STC-VM give a reasonable estimation of myocardial ischemia, but ST-VM gives no information additional to STC-VM (Jensen et al. 1994, Jensen et al. 2000). Lundin and colleagues (1998) investigated the ability of dVCG monitoring to detect myocardial ischemia after an episode of unstable CAD. In their trial the sensitivity, specificity and total accuracy in identifying patients with a positive dobutamine stress test by VCG were: 38 %, 91 % and 63 % for QRS-VD; 59 %, 88 % and 73 % for ST-VM; 84 %, 79 % and 82 % for STC-VM. In addition, STC-VM changes and a positive dobutamine stress echocardiograph predicted 3-vessel disease equally well as determined by coronary angiography.

1.5.4.7.3 Clinical implications

The reliability of dVCG in the detection of myocardial ischemia in the ESRD population has not been studied hitherto. However, in the general population dVCG is known to be more sensitive than conventional ECG in the detection of myocardial ischemia during coronary angioplasty (Jensen et al. 1994), after an episode of unstable CAD (Lundin et al. 1998) and after coronary surgery (Dahlin et al. 2001). There are at least two reasons for the superiority of the technique. Firstly, ischemic changes from the posterior area are better presented in dVCG than in standard ECG due to different positioning of the leads (Hurd et al. 1981). Secondly, ischemia sometimes causes only directional ST vector changes (Jensen et al. 1994) and in contrast to dVCG standard ECG does not bring out these changes. However, when patients in whom transient ischemic episodes had been detected by continuous standard ECG and dVCG were compared, the groups were similar in terms of signs of myocardial damage, occurrence of exercise-induced ischemia and presence of severe coronary lesions (Jernberg et al. 2001). dVCG is also a valuable tool for diagnosing and monitoring patients with suspected CAD and bundle branch block (Eriksson et al. 1997).

The method helps in early detection of myocardial ischemia and in differentiating between extra-cardiac chest pain and acute coronary disease (Lundin et al. 1992, Gustafsson et al. 1996, Gustafsson et al. 2000). It also differentiates patients with unstable angina from those with myocardial infarction. In a study by a group under Gustafsson (1996) dVCG was compared with resting 12-lead ECG on admission in patients admitted to hospital because of suspicion of acute myocardial infarction. Compared with ECG on admission, the dVCG recording after 6 h showed a significantly greater sensitivity: 86 % compared with 62 %. dVCG was especially useful in patients with non-diagnostic ECG on admission. In another study in patients with chest pain and suspected acute myocardial infarction, but without ST elevation on resting 12-lead ECG, 2 h dVCG had 44 % sensitivity and 90 % specificity in detecting acute myocardial infarction (Gustafsson et al. 2000). If dVCG was positive on admission, the sensitivity was 100 % for the detection of acute myocardial infarction.

dVCG also provides important information for risk stratification in unstable coronary syndromes (Andersen et al. 1996, Jernberg et al. 2002, Norgaard et al. 2004). Abrahamsson and associates (2001) compared the prognostic value of several different vectorcadiographic parameters. In a one-year follow-up of a total of 323 patients, ST-VM maximun >144 μV had a 78 % specificity and a 52 % sensitivity to predict death or myocardial infarction. In a meta-analysis of three studies involving almost 1000 patients Akkerhuis and colleagues (2001) evaluated the risk of unfavourable outcome in patients with unstable angina and recurrent ischemia detected by continuous ECG. Ischemic episodes were detected in 27 % of patients. The authors concluded that the relative risk of death or myocardial infarction at 5 and 30 days increased by 25 % for each additional ischemic episode per 24 h.

Even very small variations in ST-segment shift during the first hours of ST-elevation myocardial infarction provide prognostic information for cardiac events from 1 month up to 5 years (Lundin et al. 1994, Johanson et al. 2001, Jensen et al. 2003). The maximum ST-VM during 24 h monitoring seems to predict myocardial infarction and death within one year better than the number of ST-VM and STC-VM episodes (Abrahamsson et al. 1999). However, Lundin and colleagues (2000) found that the maximum value of ST-VM and STC-VM and number of episodes of these parameters yielded prognostic information. The occurrence of at least one STC-VM episode during the first 24 hours of dVCG seems to predict CV death or myocardial infarction better than ST depression on admission ECG (Andersen et al. 1996). Johansson and colleagues (2003) studied the prognostic value of ST-segment resolution in 752 patients after thrombolysis, and 88 % of deaths in their trial were correctly predicted after one-hour registration of dVCG.

1.5.4.7.4 Limitations

Different body positions cause major changes in QRS-VD but affect ST-VM and STC-VM only to a minor degree (Dellborg et al. 1992, Jensen et al. 1997, Gannedahl et al. 1997a, Norgaard et al. 1999). Thus, QRS-VD cannot be used as a single marker of ischemia.

Acute changes in fluid status and cardiac volumes have an effect on R wave voltage. In a study by Vitolo and coworkers (1987) the effects of acute changes in cardiac volumes on cardiac voltages were assessed in 18 chronically uremic patients by means of a vectorcardiographic and scalar Frank leads recording, immediately before, at the 90th and 180th minute, and immediately after HD. During HD all voltages considered except R wave in the X lead increased significantly. When the amount of fluid removed was restored at the end of HD, these cardiac voltages decreased parallel to the increase in LV diameters.

Inter- and intraobserver variation for interpretation of dVCG trend curves was low in a study by Lundin and associates (1997). However, the number of dVCG episodes varied between observers especially in patients with low

suspicion of ischemic heart disease. The interobserver difference regarding estimation of STC-VM, ST-VM and ORS-VD episodes were 0.5, 0.6 and 1.1.

For the detection of myocardial ischemia, the standard ECG and derived ECG have shown good agreement (Gannedahl et al. 1997b), but there is one significant difference. The amplitudes in the precordial leads are lower in the derived ECG than in the standard 12-lead ECG and may in some cases conceal the presence of LVH (Drew et al. 1992, Gannedahl et al. 1997b).

1.5.4.8 Coronary angiography

Coronary angiography is the gold standard for the diagnosis of CAD. Unfortunately, in ESRD patients many arteries are diffusely diseased and focal lesions are often complex in shape, limiting the accuracy of this technique (Sorrell 2001). Very high-risk ESRD patients should be considered for coronary angiography even with a negative non-invasive test (Danovitch et al. 2002). Subjects with cardiac symptoms (dyspnoea, angina, refractory heart failure, hemodynamic instability during dialysis) or evidence of previous myocardial infarction, unexplained LV dysfunction, diabetes of long duration and asymptomatic patients having multiple (3 or more) risk factors for CAD are defined as very high risk patients (Elsner 2001, Danovitch et al. 2002). Asymptomatic patients with ESRD and diabetes mellitus require special attention since approximately one-third to one-half of them has significant CAD in angiography (Ramanathan et al. 2005).

In a recent register study by a group under Chertow (2004) 57 284 elderly (age 65 to 89 yr) individuals with acute myocardial infarction from the Cooperative Cardiovascular Project were classified by the presence or absence of chronic kidney disease. Mortality was significantly higher among chronic kidney disease cases (53 versus 26 %). Fewer patients with chronic kidney disease underwent coronary angiography (25 versus 47 %) despite the observation that a similar proportion of patients were defined as appropriate for angiography by standard criteria. Thus, there may be a large relative decrease in utilization of coronary angiography among patients with chronic kidney failure.

Repeated use of angiography is necessary in this patient group, since in a the retrospective study of 26 patients Gradaus and colleagues (2001) reported that during a follow up of 12-60 months 50 % of patients showed a relevant progression of CAD.

1.5.4.9 Non-invasive methods versus coronary angiography

A summary of studies reporting the sensitivity and specificity of non-invasive methods in comparison with coronary angiography for the diagnostics of CAD in ESRD patients is presented in Table 4. It is quite difficult to compare reliably different studies, since in some studies high-risk symptomatic patients with

multiple risk factors are included while in others all patients have been asymptomatic. In addition, the differences in age and the prevalence of diabetes vary greatly in the different studies. Further, the number of patients in some studies is quite small. Non-invasive screening tests for CAD in patients ESRD seem to have limited value because of their low sensitivity. The diagnostic accuracy of the new method combining dipyridamole-exercise thallium for detecting CAD is promising in non-diabetics and in those without non-cardiac exercise limitations (Dahan et al. 1998, Dahan et al. 2002).

Table 4. The ability of non-invasive tests to predict coronary artery disease in patients with end-stage renal disease.

Method Author	Number of patients	Sensitivity %	Specificity %	Comments
Clinical symptoms				
Joki et al. 1997	24	73	46	HD 100 %, DM 63 %
Koch et al. 1997[a]	105	24	82	HD 100 %, DM 100 %
Schmidt et al. 2001	84	65	66	KTP 50 %, HD 50 %, DM 51 %
Sharma et al. 2005	125	51	59	EKTP 45 %, HD 55 %, DM 39 %
ECG				
Joki et al. 1997	24	75	63	HD 100 %, DM 63 %
Koch et al. 1997[a]	105	52	70	HD 100 %, DM 100 %
Nakamura et al. 2000	61	47	100	ST-segment depression in repeated ECG during HD
Schmidt et al. 2001	84	67	52	KTP 50 %, HD 50 %, DM 51 %
Sharma et al. 2005	125	77	58	EKTP 45 %, HD 55 %, DM 39 %
Holter				
Kremastinos et al. 1992	45	0	76	ST-segment ↑ or ↓ during HD, DM?
Exercise ECG				
Schmidt et al. 2001	18	30	100	Could be performed in only 18/84 (21 %)
Sharma et al. 2005	125	35	64	EKTP 45 %, HD 55 %, DM 39 %
Echocardiography				
Schmidt et al. 2001	77	38	92	
Stress echocardiography				
Reis et al. 1995	30	95	86	Dobutamine, HD 61 %, PD 39 %, Angiography in 30/97 for clinical indications
Herzog et al. 1999	50	75	71	Dobutamine, EKTP, DM 78 %, HD 92 %
Dahan et al. 2002	44	83	84	Dipyridamole-exercise, HD 100 %, DM 11 %
Sharma et al. 2005	125	88	94	Dobutamine, EKTP 45 %, HD 55 %, DM 39 %
Dipyridamole isotope stress test				
Boudreau et al. 1990	80	86	79	EKTP, DM 100 %
Marwick et al. 1990	45	37	73	EKTP
Vandenberg et al. 1996	47	53	73	EKTP, DM 100 %
Dahan et al. 1998	60	92	89	Combined with exercise, HD 100 %, DM 14 %
Schmidt et al. 2001	55	80	37	
Dahan et al. 2002	44	92	91	Combined with exercise, HD 100 %, DM 11 %

HD = hemodialysis, PD = peritoneal dialysis, DM = diabetes mellitus, KTP = undergone kidney transplantation, EKTP = on evaluation for kidney transplantation, ECG = electrocardiography

1.6 Diastolic dysfunction of the left ventricle in hemodialysis patients

1.6.1 Definition

Diastolic dysfunction refers to abnormal mechanical properties of the LV and is defined as an abnormality of distensibility, filling or relaxation of the LV during diastole (Aurigemma et al. 2004). Due to impaired capacity of the LV to accept blood left atrial pressure increases. Abnormalities in diastolic function can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function (Zile et al. 2002). Diastolic heart failure is defined as a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction and abnormal diastolic function (Zile et al. 2002). However, it is a worth noting, that subtle abnormalities of systolic function are observed in patients with "pure" diastolic dysfunction (Yip et al. 2002, Yu et al. 2002, Clements 2005, Vinereanu et al. 2005) and that nearly all patients with symptomatic systolic dysfunction show evidence of diastolic dysfunction (Hart et al. 2000). This indicates the common coexistence of systolic and diastolic dysfunction in a spectrum of different severity in the pathophysiological process of heart failure (Yu et al. 2002).

1.6.2 Epidemiology

In a cross-sectional survey of 2042 randomly selected residents of Olmstedt County aged 45 years or older, 21 % of the population had mild, 7 % had moderate and 6 % severe diastolic dysfunction (Redfield et al. 2003). The prevalence of diastolic dysfunction increases with age, with an approximate incidence of 15 % to 25 % in patients <60 years of age, 35 % to 40 % in those between 60 and 70 years of age, and 50 % in patients >70 years of age (Luchi et al. 1982, Wong et al. 1989, Lubien et al. 2002).

The high prevalence of diastolic dysfunction in patients older than 70 years is associated with the high prevalence of hypertensive heart disease. The prevalence of diastolic dysfunction is more common in patients with CVD, diabetes or abnormal systolic function and is equally common in men and women (Redfield et al. 2003).

Disturbed LV diastolic function has been reported as many as in 70 - 80 % of patients on HD included in cross-sectional studies (Himelman et al. 1988, Foley et al. 1999, London et al. 2001, Zoccali et al. 2001). It is prevalent in adults (Johnstone et al. 1996, Schroeder et al. 1997, Wright et al. 2003) and children (Goren et al. 1993, Mitsnefes et al. 2004) with mildly to moderately impaired

renal function. Further, the prevalence of diastolic dysfunction increases with deteriorating renal function (Stewart et al. 2005, Mark et al. 2006).

1.6.3 Risk factors

Age, diabetes mellitus, hypertension and LV mass are independent predictors of diastolic dysfunction in patients with ESRD (Fathi et al. 2003). About 80 % of dialysis patients have LVH and a strong correlation between LVH and diastolic dysfunction has been observed in these patients (Fujimoto et al. 1994, Wizemann et al. 1994). In one study, age was more likely to explain the fall in diastolic function in patients with progressive renal disease than an increase in LVH (Stewart et al. 2005). Diabetes, independently of LVH, is also related to diastolic dysfunction in patients with CRF (Miyazato et al. 2005). Some uremia-related factors such as parathyroid hormone may have an influence on the pathogenesis of diastolic dysfunction in CRF (McMahon et al. 1996).

1.6.4 Pathophysiology

Diastolic dysfunction refers to abnormalities in the process of active relaxation and passive elastic properties of the LV. The initial abnormality is a slowing of myocardial relaxation and a reduction in the suction effect in early rapid filling (Ommen et al. 2003). Thus, a relative shift of LV filling to the latter part of the diastole takes place. Abnormalities in relaxation will result in an increase in left atrial pressure during tachycardia (exercise) and acute presentation of pulmonary edema (Lainchbury et al. 1999, Phillips et al. 2001). Diastolic dysfunction during the late filling phase of the diastole can be a result of decreased LV compliance (Deswal 2005). Compliance of the LV reflects the passive elastic properties of LV during the blood flow across the mitral valve. When LV compliance is impaired, high left atrial pressure is needed to maintain adequate CO. The consequence of this is retrograde transmission of elevated pressure into the pulmonary vascular system, leading to pulmonary congestion and dyspnea (Hart et al. 2000).

Myocardial relaxation is slow or incomplete in the occurrence of high SBP, high plasma volume and increased venous return (Gillebert et al. 2000). In Guyton's model in renal failure, the sodium load leads to hypertension characterized by increased plasma volume and CO. This is followed by increased SVR, which maintains the hypertension (Coleman et al. 1969). Thus, Guyton's model may explain transitional changes in myocardial relaxation in HD patients.

Interstitial myocardial fibrosis is a prominent finding in subjects with diastolic dysfunction (Merx et al. 2005). Excessive deposition of the aminoterminal propeptide of type III procollagen is observed in the myocardium in patients with LV diastolic dysfunction (Rossi et al. 2004) and angiotensin II

has been shown to increase collagen synthesis in cardiac fibroblasts and to be associated with increased stiffness (Diez et al. 2002). Macrophage-mediated inflammation (Kuwahara et al. 2004) and activation of the chymase pathway (Matsumoto et al. 2003) are suggested to play a central role in the pathogenesis of myocardial fibrosis. Several other factors such as parathyroid hormone, endothelin, increased sympathetic nerve discharge and increased plasma catecholamines are known to contribute to myocardial fibrosis in CRF (Bernardi et al. 1985, Amann et al. 1994b, Demuth et al. 1998).

1.6.5 Diagnosis

There is a high prevalence and a rising incidence of diastolic dysfunction in the ageing dialysis population. The diagnosis of diastolic dysfunction is important in that it yields prognostic information (Bella et al. 2002, Redfield et al. 2003) and treatment can be modified, although the optimal treatment has not yet been defined (Kitzman 2002a, Yusuf et al. 2003, Carson et al. 2005). However, in the future chronic chymase inhibition (Matsumoto et al. 2003) and peroxisome proliferator-activated receptors alpha or -gamma agonists (Kim et al. 2003) may become an important strategy in the prevention of LV diastolic dysfunction.

1.6.5.1 Clinical symptoms and signs

The guidelines of American College of Cardiology for the evaluation and management of heart failure suggest that the diagnosis of diastolic heart failure be based on the finding of typical symptoms and signs of heart failure with preserved systolic function (Hunt et al. 2005). Zile and colleagues (2001) have demonstrated that at least one abnormal index of diastolic function was present in Doppler echocardiography in patients with heart failure and normal systolic function.

Even severe diastolic dysfunction is often asymptomatic (Fathi et al. 2003, Redfield et al. 2003). Moreover, the majority of patients show symptoms only in stress conditions (Packer 1990, Kitzman 2002a, Kitzman et al. 2002b). Further, there is no difference in the prevalence of specific symptoms and signs in systolic versus diastolic heart failure (McDermott et al. 1995, Vasan et al. 1995). Moreover, there is also a lack of specificity in heart failure symptoms and many patients may have some other reason such as obesity or lung disease than diastolic dysfunction for their symptoms (Caruana et al. 2000, Banerjee et al. 2002, Lubien et al. 2002). In summary, diastolic heart failure cannot be distinguished from systolic heart failure based on symptoms or clinical signs of heart failure.

1.6.5.2 Natriuretic peptides

BNP is a cardiac neurohormone secreted from the ventricles in response to ventricular volume and pressure overload (Cheung et al. 1998, Maeda et al. 1998). BNP is metabolized by natriuretic peptide receptors and degraded by plasma endopeptidases (Almirez et al. 1999). Glomerular filtration rate has independent effects on both plasma BNP and N-terminal-proBNP concentrations in patients with CKD, but N-terminal-proBNP appears to be more affected by declining kidney function (Vickery et al. 2005).

In the general population, N-terminal-proBNP can reliably detect the presence of at least moderate or severe diastolic dysfunction (Cabanes et al. 2001, Lubien et al. 2002, Alehagen et al. 2003, Hammerer-Lercher et al. 2004, Tschope et al. 2005). In a cross-sectional study of HD patients with presence of echocardiographic or electrocardiographic evidence of cardiomyopathy, neither BNP nor ANP was statistically significantly elevated in patients with LV diastolic dysfunction (Mark et al. 2006). Nor did DeFilippi and associates (2005) find any relationship between diastolic dysfunction and N-terminal-proBNP levels in patients with CRF. In one recent study LV diastolic function in HD patients was measured by electrocardiagraphic-gated 99mTc-MIBI myocardial SPECT and the peak filling rate was an indicator of LV diastolic function (Tadokoro et al. 2006). In this study, the plasma BNP levels correlated with the peak filling rate, suggesting that the plasma BNP level reflects diastolic function. At present, there is no sufficient evidence of the relevance of natriuretic peptides for the diagnosis of diastolic dysfunction in patients with CRF.

1.6.5.3 Two-dimensional and M-mode echocardiography

According to the criteria of the European Study Group of Diastolic Heart Failure a diagnosis of diastolic heart failure requires the presence of normal or only mildly abnormal LV systolic function (Paulus 1998). In practice, an estimate of LV size and ejection fraction can be obtained with M-mode and two-dimensional echocardiography. Indices of LV diastolic function such as early diastolic time interval and the diastolic wall motion index are abnormal in patients on maintenance HD (Fujimoto et al. 1994). The motion of the posterior LV wall is diminished in patients with restrictive diastolic dysfunction (Upton et al. 1976). The rapid early filling ceases abruptly and there are no further expansion of the left ventricular wall (Feigenbaum 1989). However, these indices require complex, high-quality images and calculations, and are thus not easily used for clinical applications (Schmidt et al. 2000). In a comparison of M-mode echocardiography and Doppler echocardiography in assessing early diastolic filling, the two methods measure different aspects and should be regarded as complementary rather than interchangeable (Lee et al. 1991).

Two-dimensional echocardiography has also been used to assess LV diastolic performance. Unfortunately, this method, similar to M-mode echocardiography

also requires high-quality images and complex calculations, and has not been widely applied in clinical practice (Zoghbi et al. 1987, Schmidt et al. 2000).

Normal left atrial size and ejection fraction in patients with dyspnoea suggest that it is highly unlikely that they are suffering from elevated filling pressures and diastolic heart failure (Quinones 2005). Conversely, increased left atrial size and volumes usually indicate diastolic dysfunction in patients with hypertension (Rossi et al. 2002) and increased ventricular mass (Ammash et al. 2000). Left atrial size is also an independent determinant of LV filling pressure in patients with CAD (Appleton et al. 1993). In stable patients undergoing HD left atrial volume index may be a useful parameter to differentiate normal from pseudonormal mitral flow (Barberato et al. 2007).

1.6.5.4 Doppler transmitral velocities

Kitabatake and associates (1982) first described the use of the Doppler transmitral velocity technique to study LV diastolic function. Nowadays the Doppler transmitral velocity measurement has become the Rosetta stone for clinicians in diagnosing diastolic dysfunction (Nishimura et al. 1997).

The normal mitral inflow velocity wave consists of two peaks, the E (mitral inflow peak early diastolic velocity) wave in early diastole and the A wave in late diastole. The left atrial preload (Choong et al. 1987, Courtois et al. 1988a, Gillebert et al. 2000), minimal LV diastolic pressure (Appleton et al. 1988, Courtois et al. 1988b), compliance of the left atrium and the rate of ventricular relaxation (Choong et al. 1988) influence the peak E velocity. A decrease in preload with a reduction in left atrial pressure reduces E velocity and the relation is roughly linear (Choong et al. 1988). Further, less complete relaxation reduces the left atrial pressure gradient and E velocity (Lainchbury et al. 1999). Choong and colleagues (1988) have also demonstrated that increasing LV systolic pressure (afterload) is associated with a decline in E velocity. The peak E velocity may be increased either by elevated left atrial pressure or by the low LV minimal diastolic pressure caused by rapid LV relaxation mostly observed in young adults (Zile et al. 2002). Values for peak E velocity are usually in the range of 1.0-1.2 m/s in young adults, falling progressively with age to 0.5 m/s or less in the elderly (Benjamin et al. 1992).

As the LV fills in the early diastole, there is a rise in pressure, which exceeds the left atrial pressure, causing a deceleration of flow. The deceleration time (DT) is the interval between the peak E velocity and the intersection of the deceleration of flow within the baseline. DT tends to be prolonged by impaired LV relaxation and shortened by increased filling pressure (Shimizu et al. 1998, Mottram et al. 2005). DT is more or less HR-independent, since it decreases by less than 20 % with a 100 % increase in HR (Chung et al. 2006). However, the determination of DT at heart rates over 120/min (Chung et al. 2006), or at mitral flow velocities over 0.2 m/s at the start of atrial contraction (Appleton et al. 2000), becomes unreliable due to fusion of the E and A waves. DT increases with age (Schirmer et al. 2000, Hees et al. 2004, Sim et al. 2004). In adults with

cardiac disease, DT provides an accurate estimate of LV operating stiffness (Little et al. 1995, Nishimura et al. 1996, Garcia et al. 2001) and contains information regarding chamber viscosity and relaxation (Kovacs et al. 1987). DT also predicts survival and LV remodelling after acute myocardial infarction (Ueno et al. 2002, Temporelli et al. 2004). Early DT prolongation in asymptomatic elderly subjects is associated with increased relative wall thickness and enhanced ANP increments after central volume expansion, and may represent a precursor to symptomatic diastolic heart failure (Margulies et al. 1999). Prolonged DT of early filling is also a powerful independent marker of poor prognosis in patients with LV systolic dysfunction (Temporelli et al. 2004).

With atrial contraction, left atrial pressure rises and increases the transmitral pressure gradient, producing the mitral A (mitral inflow peak late diastolic velocity) velocity curve. A wave velocity reflects the pressure gradient between the LV and the atrium. The A wave is determined by atrial systolic function, atrial preload and LV operating compliance (Smiseth et al. 2000). Volume loading increases left atrial pressure and the peak mitral A velocity (Choong et al. 1988). The duration of the A wave shortens with a decrease in LV chamber compliance (Matsuda et al. 1990, Rossvoll et al. 1993), since the reduced LV filling during the early diastole results in less LV pressure and the atrium contracts into low pressure and a more compliant chamber (Appleton et al. 2000). A transmitral A wave velocity rises with age (Henein et al. 2002) and with an increase in HR (Appleton 1991). A shortened A wave DT is a useful index of elevated LV filling pressure (Tenenbaum et al. 1996).

The ratio of early to late peak filling velocities (E/A ratio) is the parameter mostly widely used in clinical practice to assess LV diastolic function. In a normal middle-aged subject, the E velocity is slightly greater than the A velocity (Schirmer et al. 2000).

Isovolumic relaxation time (IVRT) is defined as the time interval between aortic valve closure and mitral valve opening, during which LV pressure falls with no change in volume. The IVRT reflects the rate of LV relaxation and increases with impaired relaxation. The IVRT is dependent not only on the rate of ventricular relaxation, but also on the LV pressure at the time of aortic valve closure (afterload), the atrial pressure at the time of mitral valve opening (preload) and the HR (Appleton et al. 1988, DeGroff 2002). Elevation of the filling pressure and an increase in HR shortens the IVRT (Regolisti et al. 1997). The IVRT correlates significantly with the acceleration of the E wave and the E/A ratio (Brecker et al. 1992). It is an early indicator of LV dysfunction and may increase before there are any changes in the E/A ratio (Brecker et al. 1992, Mandinov et al. 2000). A study in hypertensive and normotensive rats has demonstrated a close correlation between IVRT and invasive relaxation indices (Slama et al. 2005). Further, in another animal model IVRT as measured by Doppler echocardiography was found to reflect LV relaxation only during constant preload. During volume loading prolongation of IVRT, as a sign of slowing of relaxation, was counteracted by an earlier opening of the mitral valve leaving IVRT unchanged (Myreng et al. 1990). With an end-diastolic pressure of 30 mmHg, IVRT is zero and thus patients with normal IVRT may have considerable diastolic dysfunction. IVRT is significantly prolonged in patients

with CAD (Hashimoto et al. 1996), in hypertension (Lewis et al. 1980) and in patients with hypertrophic cardiomyopathy (Maron et al. 1987). Ageing results in a prolongation of the IVRT, so that in the elderly this is approximately double that in children (Maron et al. 1987, Myreng et al. 1989, Prasad et al. 2005).

1.6.5.5 Mitral annulus motion velocities in tissue Doppler

Doppler tissue imaging measures the velocity of the mitral annulus motion during the diastole. Myocardial fibers have a common insertion on the fibrous mitral annulus and the mitral annular motion in the longitudinal axis is determined by the sum of longitudinally oriented fibers (De Boeck et al. 2003). Thus, the mitral annulus velocity represents the velocity of changes in the LV long axis dimensions. In healthy persons, the mitral annular motion during the diastole is almost a mirror image of the transmitral flow pattern and consists of two negative velocities E` (mitral annular early diastolic velocity) and atrial A` (mitral annular late diastolic velocity) (Lainchbury et al. 1999). Velocities at both the septal and lateral mitral annulus are used in clinical practice. However, Peverill and associates (2004) investigated the relationship between septal and lateral annular velocities and found no close correlation.

The E` velocity behaves as an index of LV relaxation and is inversely correlated to the time constant of relaxation (Rodriguez et al. 1996, Oki et al. 1997, Nagueh et al. 1999), whereas A` is primarily determined by left atrial contractility and afterload (Nagueh et al. 2001). Diastolic velocities E` and A` rapidly decrease during acute ischemia, show a rebound increase after reperfusion, and display distinct patterns based on the presence or absence of obstructive CAD in the associated vessel (Bach et al. 1996, Derumeaux et al. 1998, Nagueh et al. 2004). A significant relationship also prevails between E` and the beta-adrenergic receptor density and interstitial fibrosis in patients with CAD (Shan et al. 2000). The ratio of E velocity to E` correlates with LV filling pressures (Nagueh et al. 1997, Nagueh et al. 1998, Sundereswaran et al. 1998, Nagueh et al. 1999). In a study by Nagueh and associates (1997) a mitral annulus E/E` ratio greater than 10 was associated with the most optimal sensitivity (91 %) and specificity (81 %) for elevated pulmonary capillary wedge pressure. Further, Ommen and group (2000) have shown that an E/E` ratio over 15 identifies increased LV end-diastolic pressure. The E/E` ratio showed a better correlation with LV end-diastolic pressure than did any other Doppler variables for all levels of systolic function. However, in a study by Poerner et al. (2004) the E/E` ratio showed no significant differences between patients with normal and elevated LV end-diastolic pressure. The E/E` ratio can be used to estimate pulmonary capillary wedge pressure with reasonable accuracy in sinus tachycardia and even with complete merging of E and A velocities (Nagueh et al. 1998). In patients with chronic kidney disease Doppler tissue imaging has been shown to identify significantly more patients with diastolic dysfunction than conventional echocardiography (Hayashi et al. 2006).

Normal ageing causes a decrease in E` and a substantial increase in A` myocardial velocities, and thereby the E/E` ratio decreases (Rodriguez et al. 1996, Henein et al. 2002). An increase in HR reduces E`, but increases A` (Nagueh et al. 2004). The main limitation of the method is that the E` is a regional index and errors can occur when results are extrapolated to the entire ventricle.

1.6.5.6 Effects of hemodialysis on Doppler indices

1.6.5.6.1 Doppler transmitral velocities

A number of studies have investigated the influence of HD on Doppler LV diastolic filling indices (Rozich et al. 1991, Sadler et al. 1992, Gupta et al. 1993, Sztajzel et al. 1993, Chakko et al. 1997, Uusimaa et al. 1999, Agmon et al. 2000, Chamoun et al. 2002, Dincer et al. 2002, Graham et al. 2003, Ie et al. 2003, Koga et al. 2003, Barberato et al. 2004, Hayashi et al. 2004, Hung et al. 2004b, Hung et al. 2004a, Galetta et al. 2006, Vignon et al. 2007). In all of these studies, HD with UF results in a marked decrease in E wave velocity. However, the authors have produced conflicting results on the influence of HD for the A wave velocity, E/A ratio, DT and IVRT. Table 5 summarizes the effects of HD on LV diastolic filling indices.

Table 5. *Summary of previous studies on the effects of hemodialysis on left ventricular Doppler diastolic filling indices.*

	Rozich et al. 1991	Sadler et al. 1992	Gupta et al. 1993	Sztajzel et al. 1993	Chakko et al. 1997	Uusimaa et al. 1999	Agmon et al. 2000	Chamoun et al. 2002	Dincer et al. 2002	Graham et al. 2003	Ie et al. 2003	Koga et al. 2003	Barberato et al. 2004	Hayashi et al. 2004	Hung et al. 2004a	Hung et al. 2004b	Oğuzhan et al. 2005	Galetta et al. 2006	Vignon et al. 2007
PATIENTS																			
Number	16	24	15	12	13	12	13	20	62	17	10	32	21	13	40	128	30	20	37
Age (yr)	57	52	27	41	62	54	62	44	42	55	54	72	53	59	53	59	41	51	52
Time on HD (mo)	31	35		61			26		65	13	29	40		30		59		56	64
HEMODIALYSIS																			
Duration (h)			4	3-4	3-4	4-5			4-5	4		3-4		3-4.5	4	4		3.5-4	
Fluid removed (l)							3.1		2.5		2.2		2.2						3.0
Weight change (kg)			1.4 **	3.0 ***	3.4 ***	3.0 ***		2.1 ***		1.6 ***				2.3 ***	2.6 ****	2.6 ***	3.9 ***	3.0 ***	3.0
MITRAL INFLOW pre/post HD																			
E (cm/s)	55/39 **	87/66 ***		95/63 **	97/81 *	87/57 ***	91/62 ***	116/103 *	89/65 **	84/68 ***	65/52 **	68/59 *	95/78 ***	88/69 **	95/70 ***	91/67 ***	100/85 ***	59/59 ns	
A (cm/s)	64/69 ns	85/83 ns		80/74 ns	91/95 ns	84/73 *	91/80 *	93/92 ns	79/74 ns	95/87 ***	86/82 ***	94/92 ns	101/98 ns	89/86 ns	80/72 ***	105/100 ***	76/71 *	68/74 ns	
E/A	0.9/0.6 **	1.1/0.8 ***	1.5/1.3 *	1.2/0.9 **	1.2/0.9 *		1.2/1.0 *	1.3/1.2 *	1.2/0.9 **	0.9/0.8 **	0.8/0.5 **	0.7/0.6 *	1.0/0.8 ns	1.0/0.8 ns	0.9/0.8 ***	0.9/0.7 ***	1.4/1.3 ***	0.9/0.8 ns	1.0/0.8 *
DT (ms)		199/221 ***	248/184 ***		217/229 ns		195/240 ***	239/246 ns	185/231 **			217/251 ns	276/264 ns		192/212 *	191/210 ***			194/271 *
IVRT (ms)	58/73 **	92/99 ns	80/57 **			90/118 **	100/113 ns	76/85 *	88/117 **				119/134 ns	101/93 ns	90/107 ***	88/110 ***	91/93 ns	86/89 ns	81/105 ns

* = p<0.05, ** = p<0.01, *** = p<0.001, ns = non-significant, E = mitral inflow peak early diastolic velocity, A = mitral inflow peak late diastolic velocity, E/A= early to late peak mitral inflow velocity, DT= deceleration time, IVRT = isovolumic relaxation time.

Changes in left atrial diameter (LAD) and LV end-diastolic dimension reflect changes in left atrial pressure and preload during HD (Kinet et al. 1982). In several studies in HD patients, preload reduction after dialysis was manifested by a decrease in body weight, in LAD and in the LV end-diastolic dimension. An acute reduction in left atrial pressure by transient inferior caval occlusion (Courtois et al. 1988b) or by nitroclyserin infusion (Choong et al. 1987) results in a decrease in E wave velocity. These observations support the pathogenetic role of left atrial pressure in changes in E wave velocity during UF. In a study by a group under Chakko (1997), diastolic Doppler filling parameters were measured before and after hemodialyses, performed once with and once without fluid removal. The decrease in E wave velocity occurred only with fluid removal and correlated with weight loss, indicating that the change is a result of reduction in preload. The preload dependence of the E wave is also supported in the study of Sadler and coworkers (1992), who observed that only those HD patients who lost one or more kilograms during HD had a significant decrease in peak E wave velocity. Further, the volume replacement after HD with normal saline solution returned E velocity to baseline.

Some studies have reported that in addition to changes in E wave also changes in A wave significantly differ with respect to the varying amount of UF (Uusimaa et al. 1999, Agmon et al. 2000, Dincer et al. 2002, Graham et al. 2003, Hung et al. 2004b, Hung et al. 2004a, Oğuzhan et al. 2005). In a study by Hung and colleagues (2004b) changes in both E and A wave were greatest in patients with a high UF. In addition, Hsiao and associates (2005) found that both E and A wave decrease significantly when the amount of fluid removed during HD is larger than 2 kilograms. Nonetheless, many studies have reported no change or only a trend towards a decrease in A wave velocity after HD with UF (Rozich et al. 1991, Sadler et al. 1992, Sztajzel et al. 1993, Chakko et al. 1997, Chamoun et al. 2002, Ie et al. 2003, Koga et al. 2003, Barberato et al. 2004, Hayashi et al. 2004, Galetta et al. 2006). The discrepancy may be related to differences in changes in HR, since rise in HR is associated with an increase in A wave velocity (Appleton 1991). However, in many HD studies an increase in HR seems to stand in relation to an decrease in A wave (Agmon et al. 2000, Hung et al. 2004b, Hung et al. 2004a). In patients on HD an increase in HR is the major hemodynamic compensatory mechanism to intravascular volume depletion (Bos et al. 2000, Maggiore et al. 2000, Braunschweig et al. 2006). Thus, during HD with very high intravascular volume depletion a decrease in A wave due to a reduction in preload may be counteracted by the increase in HR.

The HR response to intravascular volume reduction may vary in different patients. Andrulli and coworkers (2002) studied 123 patients on chronic HD who were considered prior normotensive, intradialytic hypotension-prone or hypertensive. Heart rates increased until the end of dialysis in all groups, but variation was much less in the intradialytic hypotension-prone and hypertensive groups. It is also possible that autonomic neuropathy will blunt the HR response to reduced preload or hypovolemia (Mallamaci et al. 1986, Takahashi et al. 1996). In addition, patients on HD and patients with diastolic dysfunction have reduced HR variability (Arora et al. 2004). The effects of HR on the transmitral

flow velocity pattern can be markedly different, depending on whether withdrawal of parasympathetic tone or sympathetic stimulation is the cause of the increase in HR (Appleton 1991).

The baseline values of the A wave may affect its changes during UF. The greatest changes in A wave peak velocity are found in those exhibiting the largest A waves at baseline (Courtois et al. 1988b, Ruffmann et al. 1990, Sadler et al. 1992). The results of a study by Yilmaz and group (2002) suggest that improved left atrial mechanical function after HD may enhance A wave velocity. Moreover, inter-individual variation in the behavior of the A wave during HD may be considerable (Sztajzel et al. 1993).

As the contribution of atrial contraction to total diastolic filling is only 30 %, a normal mitral inflow A wave is smaller then the E wave, with an E/A ratio greater than 1 (Hamlin et al. 2004). In a half of the studies presented in the Table 5 pre-dialytic E/A ratio is less than 1. After HD the ratio is reduced due to a more significant decrease in the E than the A wave. The reduction in preload can correct the pseudonormal pattern of the E/A ratio and hence after dialysis an E/A ratio less than 1 has been observed in most studies. The high prevalence of low pre- and post-dialytic E/A ratios is in line with the high prevalence of diastolic dysfunction in patients on HD.

Previous studies in HD patients have reported conflicting results on the effect of HD on DT and IVRT. However, most have demonstrated either a statistically significant increase or a trend towards an increase in DT and IVRT (Table 5). The longer duration of IVRT and DT may be attributed to the lower transmitral driving pressure resulting from reduced filling volume (Sadler et al. 1992). A reduction in driving pressure would result in delayed mitral valve opening and prolongation of IVRT and DT (Rozich et al. 1991). A second possible explanation is that the increase in serum concentrations of calcium during HD impairs LV relaxation and prolongs DT and IVRT (Rostand et al. 1988, Rozich et al. 1991, Näppi et al. 1999).

1.6.5.6.2 Mitral annular velocities in tissue Doppler

Contrasting data have been presented regarding HD induced changes on the mitral annular velocities in tissue Doppler (Table 6).

Table 6. Summary of studies on the effects of hemodialysis on mitral annular velocities.

MITRAL ANNULAR VELOCITIES (pre/post HD)	Agmon et al. 2000	Dincer et al. 2002	Graham et al. 2004	Ie et al. 2003	Hayashi et al. 2004	Hung et al. 2004b	Oğuzhan et al. 2005	Galetta et al. 2006
E`septal (cm/s)	6.1/4.1 ***	8.3/6.1 ***	6.2/6.1 ns	6.0/4.0 *	5.3/5.5 ns	6.9/5.7 ***	6.2/5.1 ***	7.6/5.9 ***
E`lateral (cm/s)	10.2/8.4 ***	10.6/8.3 ***	9.1/8.6 ns			9.0/8.0 ***	6.7/5.5 ***	10.3/7.1 ***
A`septal (cm/s)	8.3/8.1 ns	10.0/9.5 ns	10.6/10.4 ns	10.0/10.0 ns	7.5/7.3 ns	9.6/9.5 ns	5.5/5.6 ns	8.8/9.7 ns
A´lateral (cm/s)	11.3/10.3 ns	12.3/12.1 ns	10.9/10.6 ns			10.8/10.4 ***	4.4/4.7 ns	9.5/9.9 ns

*= p<0.05, ** = p<0.01, *** = p<0.001, ns = non-significant, E`= mitral annular (septal or lateral) early diastolic velocity, A`= mitral annular (septal or lateral) late diastolic velocity.

Most studies have demonstrated a significant decrease in E` and the E`/A` ratio after HD (Agmon et al. 2000, Dincer et al. 2002, Ie et al. 2003, Hung et al. 2004a, Oğuzhan et al. 2005, Galetta et al. 2006). On the other hand, groups under Graham (2003) and Hayashi (2004) observed no change in E` or E`/A` ratio following HD. A´ does not change during HD with UF. However, in one study A`lateral velocity, but not A´septal, has been shown to be affected by HD (Hung et al. 2004a).

The different responses in E` are assumed to be related to the different amounts of fluid removed during HD (Graham et al. 2003). There was a lower removal of fluid in a study by Graham and associates (2003), but not in a study by Hayashi and group (2004), compared with other studies. Changes in HR and BP may also influence E`and A` velocities. In the aforementioned study by Graham and colleagues (2003), HD resulted in no significant changes in HR or BP. In other studies, fluid removal has led to a significant decrease in BP and an increase in HR. Hayashi and associates (2004) report no hemodynamic changes after HD. Another possible mechanism underlying differences in the behavior of E` might be reduced coronary flow reserve, which may cause stunning and diastolic dysfunction due to hemodynamic stress at the time of dialysis (Galetta et al. 2006). The prevalence of CAD in the study populations varied largely ranging from 0 to 62 %.

1.6.6 Clinical implications

Echocardiographic findings of diastolic dysfunction may predict mortality also in HD patients. In a 4.25-year prospective study carried out with 40 diabetic and 28

non-diabetic patients starting HD, pseudonormal or restrictive patterns of LV diastolic dysfunction associated with mortality (Zaslavsky et al. 2005). Such adverse patterns of LV diastolic filling were observed in 41 % of non-survivors in comparison to 10 % of survivors.

Dialysis hypotension is prevalent in patients with diastolic dysfunction (Ruffmann et al. 1990). In HD patients with diastolic dysfunction, it is difficult to fill a stiff heart with blood during diastole, when the filling pressure is reduced (Daugirdas 2001). In addition, the majority of patients with diastolic dysfunction have a very limited ability to increase SV via the Frank-Starling mechanism. As a result, even a slight reduction in volume during UF can induce a fall in LV filling pressure and dialysis-associated hypotension.

On the other hand, HD patients with diastolic dysfunction have a mean left ventricular end diastolic pressure at rest approximately double that of healthy subjects (Wizemann et al. 1993). Thereby hypervolemia can result in a steep increase in LV pressure and cardiac backward failure, causing pulmonary edema (Passauer et al. 1998, Wizemann et al. 1998).

Atrial fibrillation is the most common sustained arrhythmia during dialysis, occurring in up to 11 % of treatments (Atar et al. 2006). Diastolic dysfunction is associated with an increased risk of atrial fibrillation (Thamilarasan et al. 2000, Tsang et al. 2002). The development of atrial fibrillation during dialysis causes hemodynamic deterioration, especially in elderly patients. Hemodynamic impairment is in part explained by shortening of the diastole and impaired LV filling (Zebe 2000).

The association between chronic kidney disease and CV death is accounted for, in part, by higher rates of serious arrhythmias. These are also associated with underlying structural heart disease, including diastolic dysfunction (Kayatas et al. 1999, McCullough et al. 2004). It is also important to note, that tachycardia during dialysis may worsen the diastolic dysfunction, since it reduces the time for complete relaxation. An increase in plasma calcium during standard HD may also cause acute impairment of diastolic filling (Virtanen et al. 1998a, Näppi et al. 1999).

2 Aims of the study

The purpose of the present study was to study the effects of extracellular fluid volume and hemodialysis

1. on plasma atrial natriuretic peptide and ambulatory blood pressure **(I)**.

2. on dynamic vectorcardiography parameters **(II, III, IV)**.

3. on the diastolic function of the left ventricle **(V)**.

3 Patients and methods

3.1 Patients

The participants in studies **I-V** were selected from among patients on chronic HD treatment in the Tampere University Hospital Dialysis Unit. The subjects were clinically stable, had no obvious symptoms of CAD or were not disposed to hypotension during HD treatment. In the recruitment, the author evaluated the ability of all patients on chronic HD treatment at that time in the unit to participate in different studies. Due to demanding study protocols, only a minority of patients were selected. In comparison to other patients in the unit, more females and fewer patients with DM were recruited to studies **IV-V**. The clinical characteristics of the patients are shown in Table 7.

Table 7. *Clinical characteristics of patients participating in studies.*

Study number	Number of subjects	Sex (F/M)	Age (years)	Time on hemodialysis (months)[a]	Dialysis time (hours)	ADPKD	CGLN	DN	Other
I	10	6/4	55 (20-73)	18 (2-72)	4	5	4	0	1
II, III	15	6/9	63 (36-76)	25 (1-66)	4.1 (3.5-5)[a]	2	5	6	2
IV	12	7/5	56 (32-76)	14 (1-59)	2.5+2.5	2	7	1	2
V	11	6/5	56 (32-76)	13 (1-59)	2.5+2.5	2	6	1	2

ADPKD = adult dominant polycystic kidney disease, CGLN = chronic glomerulonephritis, DN = diabetic nephropathy, [a] = mean (range).
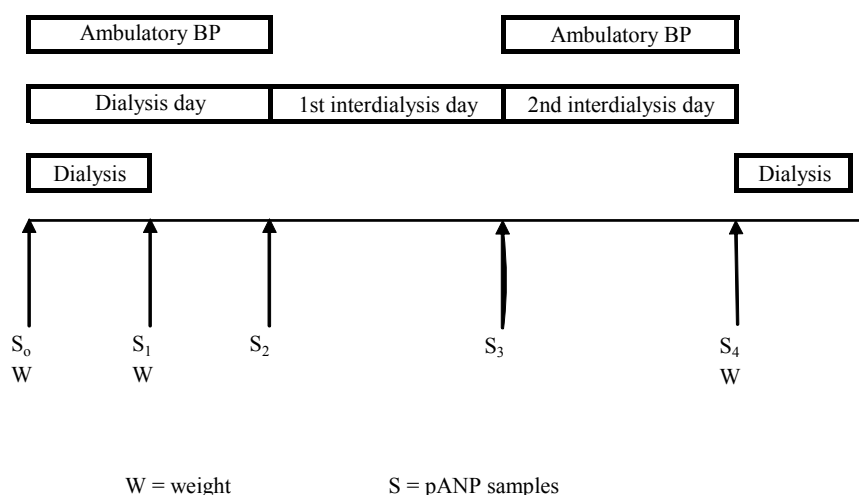
Initially the same patients were included in studies **IV** and **V**. However, one patient was excluded from study **V** due to poor visibility on echocardiography. In study **I**, all patients had received antihypertensive treatment before maintenance HD was started, but only two required antihypertensive treatment after the initiation of HD. In studies **II** and **III**, all except one patient had history of hypertension and seven of them a history of CAD. In studies **IV-V,** three of the patients had a history of CAD. The diagnosis of CAD was based on the presence of one or more of the following criteria: a positive history of typical angina pectoris chest pain with characteristic findings in exercise testing, documented pathological Q waves on the ECG, coronary artery stenosis greater than 50 % of the lumen diameter on angiography, a prior history of coronary artery angioplasty

or bypass surgery. Patients were asked to report symptoms suggestive of myocardial ischemia during the monitoring.

3.2 Methods

3.2.1 Study protocols

The subjects were studied as outpatients in the Tampere University Hospital Dialysis Unit. In study **I**, ABP recording was started 1 h before HD and continued for the next 24 hours. ABP was not recorded on the first interdialytic day, but was performed on the second interdialytic day and continued next 24 hours to the following HD. Blood samples for pANP analyses were taken and patients` weight was measured, as presented in Figure 3.

| Ambulatory BP | | Ambulatory BP |

| Dialysis day | 1st interdialysis day | 2nd interdialysis day |

| Dialysis | | Dialysis |

S_0 S_1 S_2 S_3 S_4
W   W   W

W = weight   S = pANP samples

Figure 3. *Protocol of study I.*

In studies **II-IV** HD-related changes in body weight, biochemical blood variables, BV, ECW and myocardial ischemia parameters registered by dVCG were analysed. Studies **IV** and **V** were undertaken to assess the role of isolated UF and HD with minimal UF in changes in parameters reflecting myocardial ischemia as registered by dVCG (**IV**) and indices in LV diastolic function (**V**).

In studies **I-III**, HD was performed simultaneously with UF. In studies **IV-V**, the 5 h dialysis session was divided into a 2.5 h period of UF (UF phase) and a 2.5 h period of dialysis with minimal UF (HD phase). In studies **II-V**, patients were settled in bed after weighing, and ECG and impedance measurement

electrodes were attached. After a 15-min resting period basal ECW was determined, the fistula cannulated and blood samples collected for analyses. Blood samples were taken before and after dialysis (**II-III**) or before and after UF and HD phases (**IV-V**). On-line VCG was started immediately prior to dialysis and on-line BV monitoring was commenced simultaneously with UF. During the dialysis session patients were allowed to sit only during eating. The recording of ECG data was time-synchronized with BV, ECW and hemodynamic registration. Body weight was again registered immediately after discontinuation of the dialysis session.

In study **I**, two patients receiving antihypertensive medication were asked to discontinue antihypertensive therapy two weeks before the study day. The medication was allowed to continue in studies **II-V**.

3.2.2 Hemodialysis procedures

The Fresenius 2008 E or Gambro AK 10B dialysis apparatus was used in study **I** and a volumetrically UF controlling Fresenius 4008E HD machine in studies **II-V**. Patients were dialysed for 4 h (**I**), 3-5 h (**II-III**) or 5 h (**IV-V**). In study **I**, each patient was dialyzed by the same type of dialysator as before throughout the study. The type of dialyser membrane used was cellulosynthetic, cellulose acetate, polymethylmethacrylat or polysulfone. In studies **II-V** all patients used cellulose acetate membrane hollow fiber dialyzers (Ca 130/170 series, Baxter Healthcare, Round Lake IL, USA). The composition of the dialysate in every study was Na 140 mmol/l, K 2 mmol/l, Ca 1.5 mmol/l, Mg 0.5 mmol/l, Cl 111 mmol/l and HCO3 33 mmol/l. The dialysate flow was fixed at 500 ml/min and the dialysate temperature was 36.5^0C. The blood flow rate was prescribed individually. The UF rate was kept constant in studies **I-III** and patients were ultrafiltrated until their clinically determined dry weight was reached. In studies **IV-V** the 5-h treatment session was divided into two parts. During the first 2.5 h (UF phase) dialysate flow was turned off and the UF volume was determined individually to reach patients` clinically defined dry weight. At the end of the UF phase patients were allowed to eat and during the next 2.5 h (HD phase) only the fluid volume they gained during the meal was removed. Body weight was registered immediately before and immediately after dialysis (**II-IV**).

3.2.3 Ambulatory blood pressure monitoring

In study **I** ABP was recorded using a non-invasive fully automatic recorder (Novacor Diasys 2000, France). The device measures BP by an auscultatory method. The cuff was placed on the contra-lateral arterio-venous fistula mid-arm. Conventional SBP and DBP ('office pressure') was recorded after a 15-minute

supine rest by a regular auscultatory technique. Optimal cuff placement was achieved through comparison between three conventional auscultatory standard cuff methods and ABPM device BP measurements. The difference in means under 5 mmHg was accepted to start ABPM. ABPM was performed twice. On the first study day, mid-week dialysis day, the recorder was placed approximately 1 h before dialysis. During dialysis (4 h) BP was measured every 10 min, during daytime (14-22 h) every 15 min and during the night (22-6 h) every 30 min. During the second interdialytic day monitoring, patients were told to rest for 4 h at the time of HD treatment on the first day to simulate dialysis. They were instructed to follow their usual daily activities and to keep a diary. The average and the day-night difference in systolic and diastolic BP were calculated and the average SBP and DBP computed for the whole 24-hour period in both recordings.

3.2.4 Dynamic vectorcardiography

In studies **II-IV** the patients were monitored with continuous dVCG over the whole HD session. A computerized MIDA system (MIDA 1000, Ortivus Medical, Täby, Sweden) was used for analysis of QRS complex and ST-segment changes. To obtain ECG signals eight conventional ECG electrodes were applied to the chest after careful skin preparation according to the Frank lead system. Three variables, QRS-VD, ST-VM and STC-VM, were generated by averaging at one-minute intervals the recorded ECG signals, compared with the reference complex, measured and presented on trend graphs. In addition, the 12-lead-derived ECG was calculated from the X, Y and Z leads. The collected data were automatically stored on the hard disk of the MIDA computer, later transferred, and stored in another computer for statistical analyses. In study **I**, ST-VM6 elevation > 100 µV and in studies **II-III** ST-VM6 and / or STC-VM increase > 50 µV and QRS-VD changes over 15 µVS were considered to reflect ischemia. The recorded dVCG data were time-synchronized with BV and ECV registration.

3.2.5 Echocardiography

In study **V** a two-dimensional M-mode and Doppler transthoracic echocardiographic examination was performed three times (before, after HD, and after the UF phases) by a single experienced observer using a General Electric Vingmed ultrasound unit with a 2.5 MHz transducer (GE Vingmed, Horton, Norway). The following parameters were assessed for measurements of LV and left atrial dimensions: LAD, LVEDD, LVESD, IVST and LVPWT. LVH was defined as LVMI (left ventricular mass index) over 134 g/m^2 for males and over 110 g/m^2 for females at the end of the UF phase (Devereux et al. 1986). Systolic dysfunction was defined as FS (left ventricular fractional shortening) < 25

percentage. Left atrial enlargement was determined as a LAD (left atrial diameter) over 40 mm after UF (Braunwald et al. 2001). The transmitral inflow velocities were recorded by pulsed-wave Doppler echocardiography in the apical four-chamber view with the sample volume placed at the level of the mitral leaflet tips. The following indices were measured or calculated: E, A, the E/A ratio. IVRT was measured as the time from closure of the aortic valve to the onset of mitral valve opening. Normal values for IVRT are age-dependent. Prolongation of IVRT was defined as follows: $IVRT_{<30y}$ >92 ms, $IVRT_{30-50y}$ >100ms, $IVRT_{>50y}$ >105 ms. The mitral DT was measured from the peak of the early diastolic mitral flow velocity to its extrapolation at baseline. Abnormal values were $DT_{<50y}$ >220 ms and $DT_{>50y}$ >280 ms. The criteria for diagnosing diastolic heart failure were based on a working group report of the European Study Group on Diastolic Heart Failure (Paulus 1998). The study group has previously reported the reproducibility of M-mode and Doppler echocardiography earlier (Virtanen et al. 1998b).

3.2.6 Blood volume monitoring

In studies **II-V** BV changes were monitored noninvasively and continuously with CRIT-LINE instrument (In-Line Diagnostics, Riverdale, UT, USA) using an on-line optical reflection method based on the reflection of infrared light by erythrocyte membranes. On the assumption that the red blood cell mass is essentially constant during the dialysis session, BV and hematocrit are inversely and linearly related to each other. Hematocrit measurement was made through a sterile plastic disposable blood chamber (PN 2231, In Line Diagnostics) placed in the blood circuit between the arterial blood tubing and the dialyzer. The hematocrit as an indicator of percentage change in BV was calculated every 20 sec.

3.2.7 Extracellular water and hemodynamic monitoring

Whole-body bioimpedance was used to estimate changes in ECW in studies **II-V** and hemodynamic responses in study **V**. Determination of whole-body impedance was made using the whole-body impedance cardiography channel of the CircMon B202 device (JR Medical Ltd, Tallinn, Estonia). Two pairs of electrically connected electrodes were placed immediately proximally to the wrists and ankles (Kööbi et al. 1997). A 30 kHz 0.7 mA alternating current was applied to the external pair of electrodes and the voltage measured from the inner pair. Five-minute impedance measurements were made before the beginning of the dialysis, during the procedure at 15 (**II-III**) or 30 min intervals (**IV-V**) and at the end of the session. During the measuring, the patient was always in supine

position, arms at the sides without touching the body. In study **V**, the following hemodynamic parameters were measured: HR, SV and CO. SBP and DBP measured by a manual sphygmomanometer and their values entered into a CircMon B202 database.

3.2.8 Mathematical formulas

In study **I**, mean values for SBP, DBP, pANP, change in body weight and the day-night difference in SBP and DBP were calculated. In studies **II-V**, ECW was calculated from the generally accepted impedance index H^2/R, where H is the height of the patient and R the estimated baseline impedance. In study **V**, SVR was calculated according to the formula: SVR = 79.96 (MAP/CO). MAP was calculated as follows: DBP + 1/3(SBP-DBP). In study **V**, LVM was calculated according to the formula of Devereux and Reichek (1986): LVM(g) = $1.04[(LVEDD+IVST+LVPWT)^3-(LVEDD)^3]$-13.6. LVM was corrected for body surface area to give the LVMI. Fractional shortening was determined as FS (%) = (LVEDD-LVSD)x100/LVEDD.

3.2.9 Laboratory measurements

In study **I**, pANP values were measured before and after HD, 24 h, 48 h and 72 h from the start of the first dialysis session. Patients were kept in supine position for 30 min before blood sampling. pANP sample were analysed in Medix CO. Laboratories using the ELISA method with Peninsula antibody. Normal values for pANP were under 65 ng/l. In studies **II-III**, hemoglobin, hematocrit, sodium, chloride, magnesium, potassium, ionized calcium, phosphate, venous blood pH, and bicarbonate ion (HCO3$^-$) before and after HD were determined using standard automated techniques (Kodak Ektachem 700, Technicon H2, Hitachi 717, ABL 500, CIBA Corning 634). In studies **IV-V**, blood samples were taken before and after UF and HD phases and analytical procedures were carried out with a same automated technique as in studies **II-III**.

3.2.10 Statistical analyses

Results are expressed as mean, standard deviation (± SD), or standard error of mean (± SEM) in study **I**. Student`s two-tailed t-test for paired data was applied to evaluate the difference between pre- and post-treatment values. In Study **V**, Bonferroni adjustment was used in statistical comparisons. To evaluate the association between variables logistic regression analysis and Pearson`s

correlation coefficient were used. In study **I**, differences between means of multiple groups were tested with analysis of variance (ANOVA). In studies **III-IV**, the subject-specific slopes from the mixed models for BV and ECW as covariates in mixed models for dVCG parameters were used to ascertain the effect of change in BV and ECW on changes in ECG parameters. In studies **II-IV**, the influence of fluid and food ingestion and body position changes on dVCG parameters was taken into account by eliminating the periods in question from analyses. In all studies, statistical analyses were carried out with the statistical software Statgraphics® Plus for Windows 7.0. PROC MIXED in the SAS System for Windows 6.12 software was used in studies **III-IV** for fitting linear mixed models.
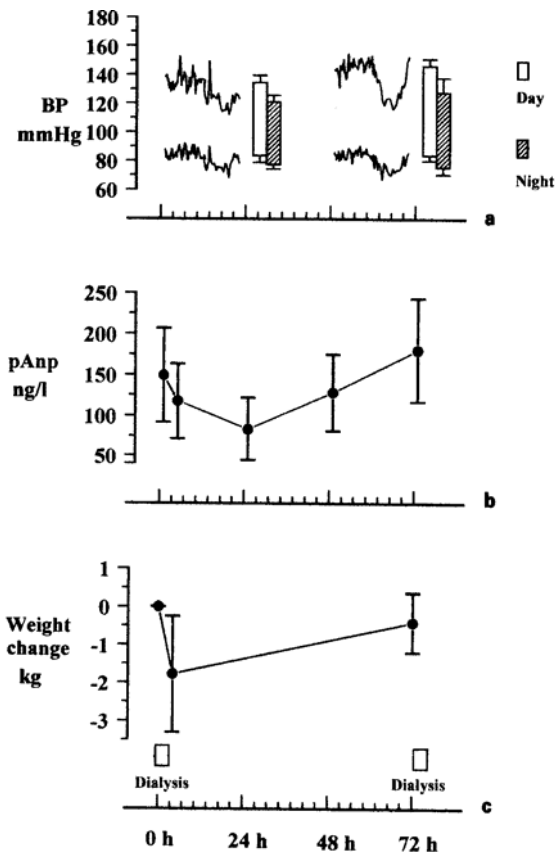
3.2.11 Ethical considerations

All patients gave an informed consent to participate and the Tampere University Hospital ethical committee approved the study protocols.

4 Results

4.1 The effects of volume changes and hemodialysis on pANP and ABP

Average changes in SBP, DBP, pANP concentrations and body weight observed in study **I** are presented in Figure 4.

Figure 4. *Mean values (±SEM) of SBP and DBP, day and night BP (a), pANP (b) and body weight change (c) in 10 HD patients (**I**).*

During HD the mean decrease in body weight was 1.7 ± 0.5 kg (p = 0.005) and the mean UF volume was 2.4 ± 0.7 l. The interdialytic weight gain was 1.3 ± 0.2 kg (p = 0.03). During the HD session, pANP decreased in seven patients and increased mildly in three. The mean pANP concentration decreased during the HD session from 149.7 ± 18.2 to 117 ± 0.1 ng/l (p = 0.15). After the HD session

pANP decreased in every patient, and the lowest mean pANP concentration, 83 ± 12.2 ng/l, was measured 20 h after completion of HD. The decrease was statistically significant (p = 0.001) compared with predialytic values. Thereafter, pANP increased constantly in every patient and reached its highest mean value, 180 ± 14.9 ng/l, before the next dialysis session. The body weight decrease (r = 0.65, p = 0.04) and the UF volume (r = 0.58, p = 0.07) during dialysis correlated with the simultaneous pANP decrease. The relationship between changes in body weight and pANP was still stronger (r = 0.72, p = 0.019) when the maximal pANP decrease was compared with weight reduction during the HD session. No correlation was observed (r = 0.11, p = 0.77) between interdialytic weight gain and pANP accumulation.

During the second interdialytic day the daytime SBP increased significantly (p = 0.039) compared to that of the dialysis day. The absolute increase was 12.5 ± 4.8 mmHg. This phenomenon was observed in 5/10 patients. Nighttime SBP rose significantly in only 3/10 and the overall nighttime BP increase was insignificant. However, there was a sharp BP elevation immediately prior to the second dialysis. Changes in DBPs were minimal. There was a positive correlation between interdialytic weight gain and SBP increase (r = 0.61, p = 0.06). No correlation (r = -0.07, p = 0.85) was noted between pANP and SBP elevation.

The day-night difference in SBP was 11.3 ± 4.8 mmHg on the dialysis day and 19.3 ± 3.1 mmHg on the second interdialytic day. Both differences were statistically significant. On the dialysis day, a significant day-night SBP difference was observed in 8/10 patients and on the second interdialytic day in 6/9 patients. The corresponding differences in diastolic pressures were 7.1 ± 1.8 and 8.7 ± 1.8 mmHg and they were significant in 5/10 and 4/9 patients.

4.2 The effects of volume changes and hemodialysis on dynamic vectorcardiography parameters

4.2.1 Changes in vectorcardiography parameters

In study **II**, the effect of HD with contemporaneous UF on QRS-VD was evaluated. The mean QRS-VD increased from 4.16 ± 2.40 to 15.60 ± 7.0 μV (p<0.001) (Figure 5). The QRS-VD change was due to a change in amplitude, since the duration of the QRS complex did not significantly alter.
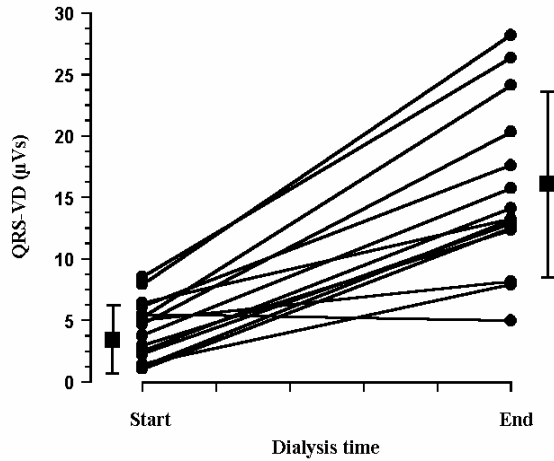
*Figure 5. QRS vector difference (QRS-VD) changes in 15 patients during dialysis (**II**).*

In study **III**, during the HD with combined UF QRS-VD increased during the dialysis session from 3.5 ± 3.0 to 14.4 ± 6.0 µVs, (Δ % 75.5 ± 49.6), (p <0.001) and STC-VM from 6.5 ± 5.3 to 27.3 ± 19.7 µV, (Δ % 72.5 ± 68.5), (p <0.001). Deviating from these two parameters, the ST-VM6 change from 85.5 ± 56.1 to 88.8 ± 76.3 µV, (Δ % 3.8 ± 26.5) was not significant (Figure 6).
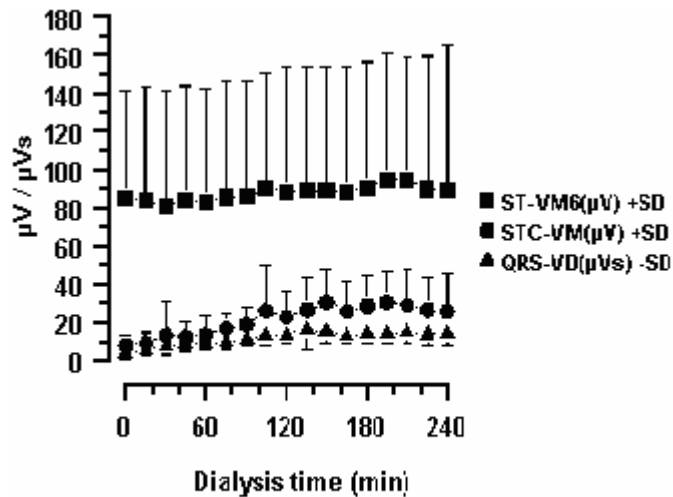
*Figure 6. Mean changes (± SD) in QRS-VD, STC-VM, ST-VM6 during HD (**III**).*

Conversely, according to the linear mixed model QRS-VD and STC-VM showed a statistically significant linear trend (time effect for QRS-VD p = 0.0001 and for STC-VM p = 0.0004). In contrast, no statistically significant change was noted in ST-VM6 during dialysis (time effect p = 0.5635).

In study **IV**, the absolute and percentage changes in VCG during the isolated UF phase were: +8.6 ± 5.8 (Δ % 59.9 ± 13.7) for QRS-VD, +7.3 ± 5.1 (Δ % 40.5 ± 22.6) for STC-VM and + 0.9 ± 12.7 (Δ % 0.6 ± 12.8) for ST-VM6. No statistically significant changes were observed in QRS-VD, STC-CM or ST-VM6 during the HD phase (Figure 7).
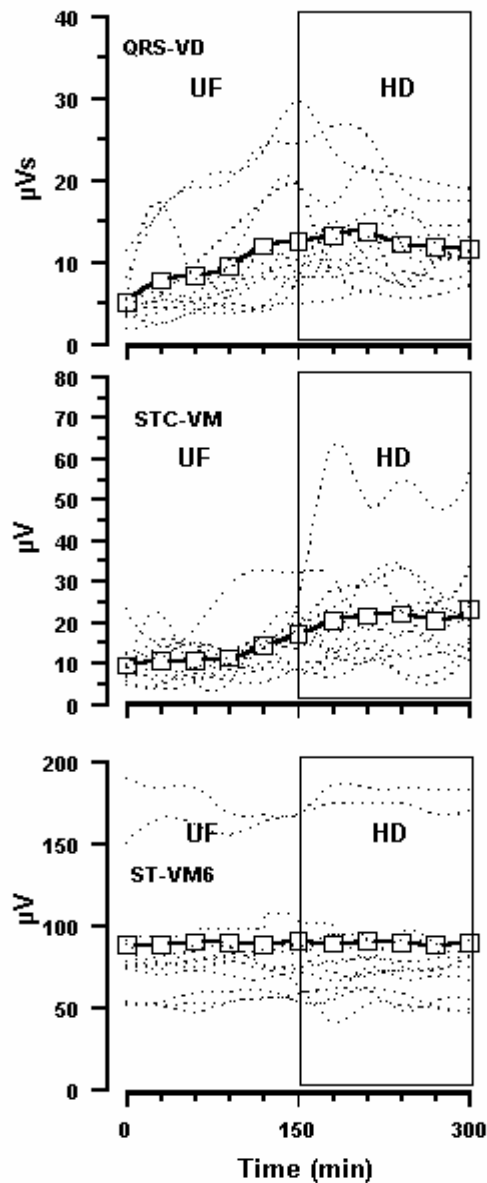
Figure 7. *Changes in QRS-VD, STC-VM and ST-VM5 in 12 patients during UF and HD phases. Bold line signifies mean trend (**IV**).*

According to the linear mixed model, no statistically significant change was noted in ST-VM6 within the UF phase (time effect $p = 0.986$). In contrast, QRS-VD and STC-VM showed a statistically significant linear trend (time effect for

QRS-VD p < 0.0001 and for STC-VM p < 0.0001. As summary of the percentage changes in dVCG parameters during HD with combined UF, isolated UF and HD with minimal UF is presented in Table 8, **(III-IV).**

Table 8. *Percentage changes in vectorcardiographic parameters during hemodialysis with combined ultrafiltration, isolated ultrafiltration and HD with minimal ultrafiltration (III-IV).*

QRS-VD			STC-VM			ST-VM6		
HD+UF	UF	HD	HD+UF	UF	HD	HD+UF	UF	HD
75.5 ±	59.9 ±	0.6 ±	72.5 ±	40.5 ±	11.1 ±	3.8 ±	0.6 ±	2.87 ±
49.6	13.7	12.8	68.5	22.6	55.6	26.5	12.8	16.8
p<0.001	p<0.001	ns	p<0.001	p<0.001	ns	ns	ns	ns

HD+UF = hemodialysis with combined ultrafiltration, UF = isolated ultrafiltration, HD = hemodialysis with minimal ultrafiltration, ns = non-significant.

4.2.2 Volume changes

In studies **II-III**, the mean body weight reduction was 1.89 ± 1.04 kg (p<0.001) and the mean volume removed by UF 2.36 ± 0.96 liters. In the analyses of the raw data, slightly different results in studies **II** and **III** were observed in the changes in BV and ECW during HD. In the first analysis (**II**) the mean ECW loss was 8.6 ± 3.7 % (p<0.001) and 7.1 ± 2.9 % (p<0.001) in the second (study **III**). The mean reduction percent in BV was 6.1 ± 5.3 %, p< 0.001 (**II**) and 5.0 ± 5.6 %, p< 0.001, (**III**). The differences were due to some minor differences in the time synchronization of the abundant raw data in these two analyses. Figure 8 illustrates mean changes in BV and ECW during combined UF hemodialysis in study **III**.
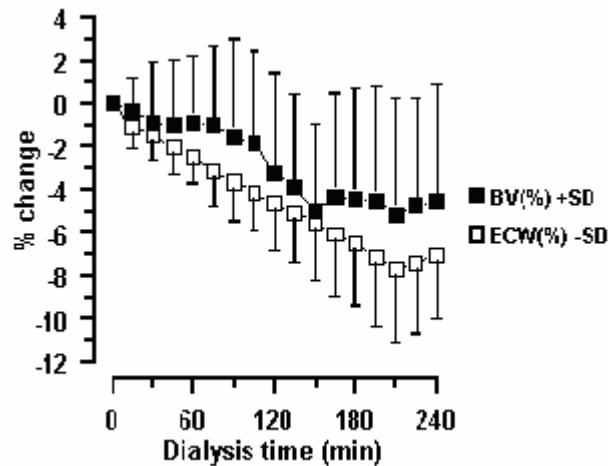
Figure 8. Mean changes (± SD) in blood volume (BV) and extracellular water (ECW) during combined UF hemodialysis (***III***).

In study **IV**, during the first 2.5 h of the study session isolated UF removed on average 1.80 ± 0.72 l fluid. The mean ECW decline at the same time was 8.0 ± 2.3 %, (1.0 ± 0.3 l), ($p < 0.0001$) and the mean diminution of BV 7.6 ± 3.4 %, ($p < 0.0001$). The mean volume removed by ultrafiltration during the HD phase was 0.25 ± 0.93 l. The mean ECW declined at the same time by 0.7 ± 1.8 % (0.1 ± 0.23 l), ($p = 0.829$) and the mean BV increased by 2.8 ± 3.0 %, ($p < 0.0001$). In study **V** in which eleven of the original twelve patients were selected for analyses, the mean amount of fluid removed during the UF phase was 1.82 ± 0.75 l (range: 1.06–3.50 l; 667 ± 356 ml/hour; range: 432–1400 ml/hour). The mean ECW decline at the same time was 7.9 ± 2.4 % ($p < 0.001$) and the mean diminution of BV 7.8 ± 3.4 % ($p < 0.001$). The mean amount of fluid removed during the HD phase was 0.25 ± 0.91 l (range: 0–0.30 l; 93 ± 45 ml/hour; range: 0–132 ml/hour). During this phase, ECW declined by 0.6 ± 1.8 % ($p = $ ns) and BV increased by 2.9 ± 2.8 % ($p < 0.001$). Figure 9 illustrates changes in BV and ECW during studies **IV-V**.
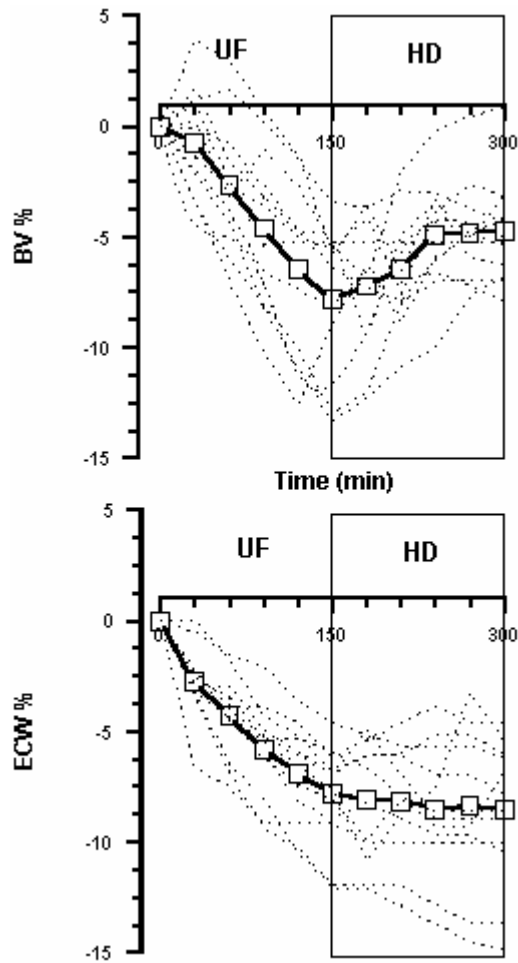
Figure 9. *Changes in blood volume (BV) and extracellular water (ECW) in 12 patients during UF and HD phases. Bold line represents a mean trend (**IV-V**).*

As summary of the percentage changes in ECW and BV during HD with combined UF, isolated UF and HD with minimal UF is presented in Table 9.

Table 9. *Summary of percentage changes in extracellular water and blood volume during hemodialysis with combined ultrafiltration, isolated ultrafiltration and hemodialysis with minimal ultrafiltration (**II-V**).*

	HD+UF	UF	HD
ECW change	- 7.1 ± 2.9	- 8.0 ± 2.3	- 0.7 ± 1.8
	p<0.001	p<0.001	ns
BV change	- 5.0 ± 5.6	- 7.6 ± 3.4	+ 2.8 ± 3.0
	p< 0.001	p< 0.001	p< 0.0001

HD+UF = hemodialysis with combined ultrafiltration, UF = isolated ultrafiltration, HD = hemodialysis with minimal ultrafiltration, ns = non-significant.

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In studies **II-III**, the relation between dVCG parameters and volume changes change in body weight correlated with the change in QRS-VD (r = -0.55, p < 0.05), STC-VM (r = -0.45, p = 0.09) and ST-VM6 (r = 0.37, p = 0.17). In study **II**, the correlation between changes in QRS-VD versus ECW, BV and weight change for a single patient was also calculated (Table 10).

*Table 10. Correlation of QRS vector difference versus extracellular water, blood volume and weight change during hemodialysis with combined ultrafiltration (**II**).*

Patient number	QRS-VD vs ECW	QRS-VD vs BV	Weight change kg (%)
1	-0.91***	-0.74***	-1.3 (-1.9)
2	-0.97***	-0.98***	-3.7 (-4.8)
3	-0.86***	-0.92***	-3.5 (-5.3)
4	-0.97***	-0.93***	-2.0 (-3.7)
5	-0.86***	-0.83***	-0.6 (-0.8)
6	-0.94***	-0.73***	-0.8 (-1.3)
7	-0.97***	-0.22***	-1.9 (-2.7)
8	-0.91***	-0.82***	-1.8 (-2.0)
9	-0.80***	-0.23**	-0.5 (-0.8)
10	-0.87***	-0.75***	-3.0 (-3.3)
11	-0.88***	+0.11 ns	-2.4 (-2.7)
12	-0.67**	-0.66***	-0.4 (-0.5)
13	-0.96**	-0.78***	-2.3 (-2.8)
14	-0.76***	-0.89***	-1.8 (-2.3)
15	-0.88***	-0.78***	-2.3 (-3.0)

*QRS-VD = QRS vector difference, BV = blood volume, ECW = extracellular water, ** = p <0.01, *** = p <0.001, ns = non-significant.*

In most of the patients studied, the change in QRS-VD during HD with combined UF correlated significantly with the changes in BV and ECW. In some patients, however, the correlation between QRS-VD and BV was poor. All these patients (no. 7, 9 and 11) had a very small BV change (0 %, + 1 %, +1 %) compared to the loss of ECW (-10 %, -3 %, -7 %).

To study more extensively connections between dVCG parameters and volume changes, linear mixed models were used. In study **III**, changes in both ECW and BV had an effect on the change in QRS-VD and in STC-VM, but not on those in ST-VM6. In study **IV**, the change in ECW was related to QRS-VD during the UF phase and no relation was observed between dVCG parameters and BV changes (Table 11).

*Table 11. Statistical significance (p values) of vectorcardiographic parameter changes as a function of blood volume and extracellular water changes during dialysis with combined ultrafiltration (UF+HD) and dialysis with isolated ultrafiltration (UF) (**III-IV**).*

	BV_{HD+UF}	BV_{UF}	ECW_{HD+UF}	ECW_{UF}
QRS-VD	0.0001	0.5010	0.0001	0.0033
STC-VM	0.0001	0.1342	0.0331	0.1027
ST-VM6	0.2222	0.5190	0.5385	0.5561

QRS-VD = QRS vector difference, STC-VM = ST change vector magnitude ST-VM6 = ST vector magnitude 60 ms after J-point, BV = blood volume, ECW = extracellular water.

4.2.3 Biochemical variables

In addition to volume changes, changes in plasma concentration of biochemical variables during the HD may also have an effect on dVCG parameters. Changes in major biochemical variables in studies **II-V** are presented in Table 12.

*Table 12. Changes in biochemical variables during combined ultrafiltration hemodialysis and during hemodialysis with separate ultrafiltration and hemodialysis phases (**II-V**).*

	HD+UF	UF	HD
Hcr	0.01 ± 0.0 ns	0.03 ± 0.02 $p<0.0001$	$- 0.01 \pm 0.02$ $p<0.005$
K	-1.56 ± 0.61 $p< 0.001$	0.04 ± 0.50 ns	$- 1.21 \pm 0.55$ $p< 0.0001$
Na	$1.14 \pm 3.3.9$ ns	0.7 ± 1.67 ns	0.3 ± 1.07 ns
Krea	-479 ± 144.35 $p<0.001$	$- 71.9 \pm 53.22$ $p<0.001$	$- 334.0 \pm 165.30$ $p< 0.0001$
Urea	-15.0 ± 3.66 $p<0.001$	$- 2.2 \pm 1.73$ $p< 0.01$	$- 8.9 \pm 2.78$ $p<0.0001$
iCa	0.06 ± 0.10 $p<0.05$	0.04 ± 0.04 $p< 0.005$	0.03 ± 0.06 $p<0.05$
pH	0.10 ± 0.07 $p<0.001$	0.02 ± 0.04 ns	0.07 ± 0.02 $p<0.0001$
HCO3	5.56 ± 2.43 $p<0.0001$	0.57 ± 1.86 ns	4.67 ± 1.41 $p< 0.0001$

HD+UF = hemodialysis with combined ultrafiltration, UF = isolated ultrafiltration, HD = hemodialysis with minimal ultrafiltration, ns = non-significant. Values are given as means ± 1 SD.

Statistical correlations between changes in dVCG parameters and biochemical variables in studies **II-IV** are presented in Table 13. In studies **II-III**, laboratory parameters reflecting volume and osmotic changes during HD correlated with the QRS-VD and STC-VM changes. However, no significant correlations were seen between changes in dVCG parameters and biochemical variables during isolated UF or HD with minimal UF (**IV**).

Table 13. *Statistical correlations (R) between changes in vectorcardiographic parameters and biochemical variables during combined ultrafiltration hemodialysis, hemodialysis with minimal ultrafiltration and isolated ultrafiltration (**III-IV**).*

	QRS-VD R (p)			STC-VM R (p)			ST-VM6 R (p)		
	HD+UF	UF	HD	HD+UF	UF	HD	HD+UF	UF	HD
Hkr	**0.56**	0.38	0.23	0.41	0.02	0.15	-0.16	-0.19	-0.01
	p= 0.04	ns	ns	ns	ns	ns	ns	ns	ns
Hb	**0.63**	0.46	0.17	**0.54**	0.21	0.20	0.16	0.21	0.24
	p=0.02	ns	ns	**p=0.05**	ns	ns	ns	ns	ns
K	-0.35	0.45	0.41	-0.13	0.04	0.22	0.26	0.08	0.29
	ns	ns	ns	ns	ns	ns	ns	ns	ns
Na	**-0.59**	0.25	0.18	**0.58**	-0.05	-0.32	-0.14	-0.26	-0.31
	p=0.03	ns	ns	**p=0.03**	ns	ns	ns	ns	ns
Krea	0.29	0.55	0.46	0.09	0.36	0.54	0.37	-0.24	-0.05
	ns	ns	ns	ns	ns	ns	ns	ns	ns
Urea	**-0.62**	0.26	0.62	**0.54**	0.18	0.33	0.24	-0.09	-0.02
	p=0.02	ns	ns	**p=0.05**	ns	ns	ns	ns	ns
iCa	-0.12	-0.19	0.45	-0.37	0.17	-0.40	0.27	0.34	-0.31
	ns	ns	ns	ns	ns	ns	ns	ns	ns
pH	0.33	-0.15	0.09	-0.21	-0.45	-0.17	-0.03	0.13	0.03
	ns	ns	ns	ns	ns	ns	ns	ns	ns
HCO$_3$	0.40	-0.26	0.35	0.30	0.15	-0.39	0.05	0.01	-0.11
	ns	ns	ns	ns	ns	ns	ns	ns	ns

ns = non-significant. **Bold** *= statistically significant.*

4.2.4 Myocardial ischemia

ST-VM6 and/or STC-VM increase >50 µV and QRS-VD changes over 15 µVs are considered to reflect myocardial ischemia. No ischemic ST-VM6 changes were found during HD with combined UF, HD with isolated UF or HD with minimal UF (**III-IV**). A QRS-VD increase >15 µVs was found in 4/15 patients in studies **II-III** and in 3/12 patients during the UF phase, but in none within the HD phase in study **IV**. In studies **II-III**, two of the four patients with a QRS-VD increase over 15 µVs had a history of CAD. In study **IV**, none of the three patients showing a QRS-VD increase over 15 µVs at the time of the UF phase had a history of CAD. In study **III**, neither of the two patients with STC-VM

increase over 50 µV had a history of CAD. No ischemic changes in STC-VM were observed in the course of the UF - or HD phases. None of the patients studied had symptoms of myocardial ischemia during the studies. Further, there were no differences in the change in dVCG parameters during the dialysis session between patients with or without CAD (**III**, Figure 10).
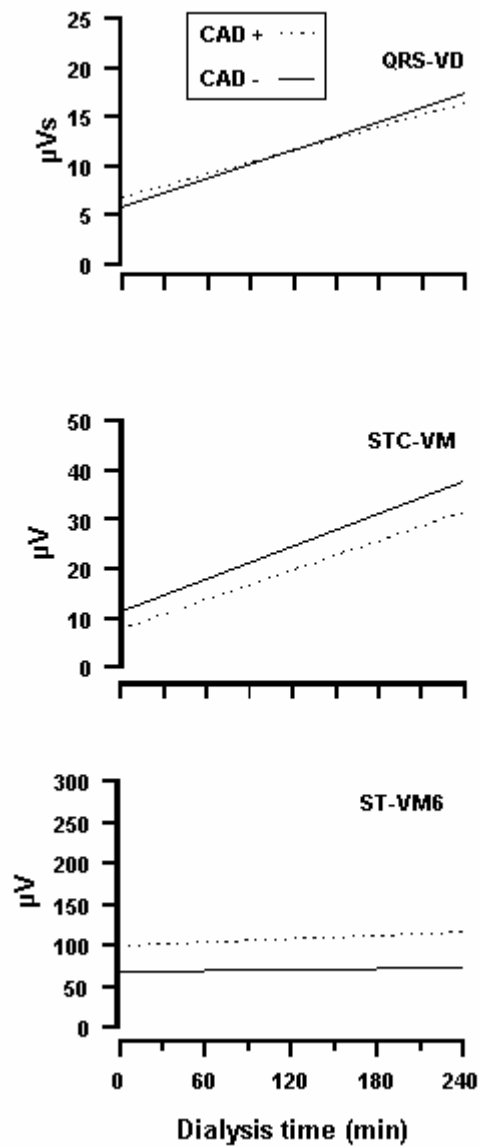
Figure 10. *Mean linear trends of QRS-VD, STC-VM and ST-VM6 changes during hemodialysis in patients with (+) and without (-) coronary artery disease (CAD)* ***(III)****.*

4.3 The effects of volume changes and hemodialysis on the Doppler-derived indices of diastolic function of the left ventricle

The effects of isolated UF and HD with minimal UF on cardiac parameters are listed in Table 14.

Table 14. *Effects of isolated ultrafiltration (UF) and hemodialysis with minimal ultrafiltration (HD) on Doppler and M-mode echocardiography indices and the statistical significance of the changes (p values)* **(V)**.

Parameters	Before UF	After UF and before HD	After HD	*p*-value before UF vs after UF	*p*-value before HD vs after HD	*p*-value before UF vs after HD
E (m/s)	0.82 ± 0.2	0.62 ± 0.2	0.72 ± 0.2	0.003	0.0018	ns
A (m/s)	0.72 ± 0.2	0.63 ± 0.2	0.70 ± 0.3	0.042	ns	ns
E/A	1.18 ± 0.4	1.07 ± 0.4	1.12 ± 0.4	ns	ns	ns
DT (ms)	175 ± 83	244 ± 119	209 ± 98	ns	ns	ns
IVRT (ms)	142 ± 40	171 ± 55	169 ± 47	0.03	ns	ns
LVEDD (mm)	58.2 ± 5.0	55.6 ± 9.4	56.6 ± 6.7	ns	ns	ns
LVESD (mm)	41.2 ± 7.9	40.6 ± 11.6	39.7 ± 6.8	ns	ns	ns
LAD (mm)	44.8 ± 5.51	41.2 ± 6.91	40.4 ± 6.19	ns	ns	ns
IVST (mm)	12.6 ± 1.9	12.8 ± 2.31	13.0 ± 2.19	ns	ns	ns
LVPWT (mm)	11.7 ± 1.62	11.1 ± 1.56	10.9 ± 1.10	ns	ns	ns
LVMI (g/m^2)	198.0 ± 39.5	203.4 ± 86.8	174.8 ± 31.5	ns	ns	ns
FS (%)	29.5 ± 9.23	27.9 ± 9.08	29.8 ± 6.79	ns	ns	ns

ns = non-significant. Data are presented as mean ± SD, paired t test before vs after.

During the UF phase, E decreased from 0.82±0.2 to 0.62±0.2 m/s (p = 0.003) and A from 0.72±0.2 to 0.63±0.2 m/s (p = 0.042). The change in their ratio (E/A) from 1.18±0.4 to 1.07±0.4 was not statistically significant. At the time of UF, other echocardiographic indicators of diastolic function IVRT and DT lengthened, but DT insignificantly. During the HD phase, an increase in E from 0.62±0.2 to 0.72±0.2 m/s (p = 0.018) was the only statistically significant change in the parameters of diastolic function. A increased insignificantly from 0.63±0.2 to 0.70±0.3 m/s, as also the change in E/A was not significantly (from 1.07±0.4 to 1.12±0.4). When pre- and post-study values were compared, the changes in E from 0.82±0.2 to 0.72±0.2, in A from 0.72±0.2 to 0.70±0.3 and in E/A from 1.18±0.4 to 1.12±0.4 were statistically insignificant. The changes in E, A and in the E/A ratio are illustrated in Figure 11 and the changes in IVRT and DT in Figure 12.
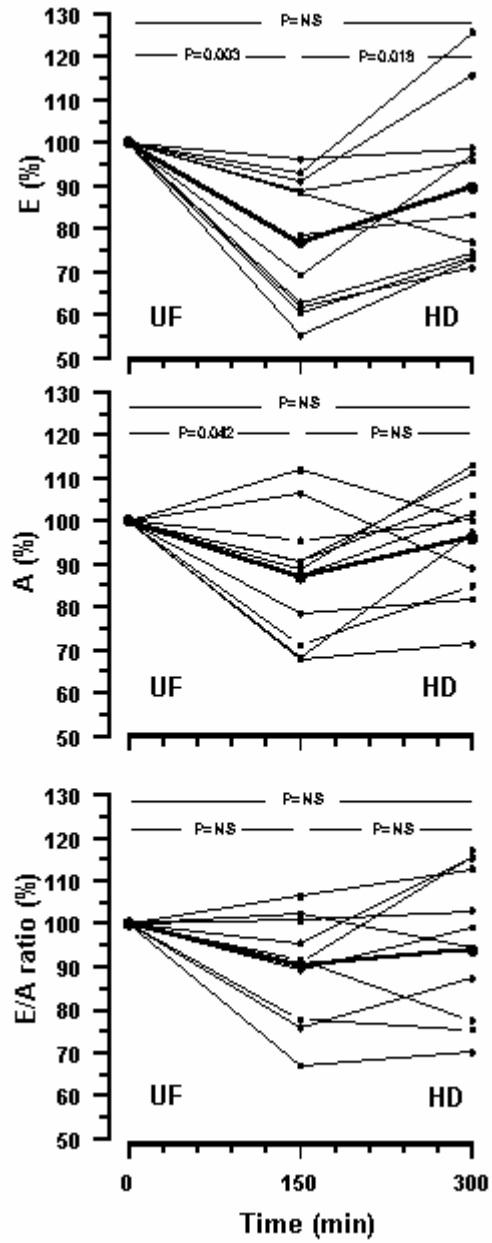
Figure 11. *Percentages of changes in E, A and the E/A ratio in 11 patients during UF and HD with minimal UF. The bold line is the mean of the changes (**V**).*
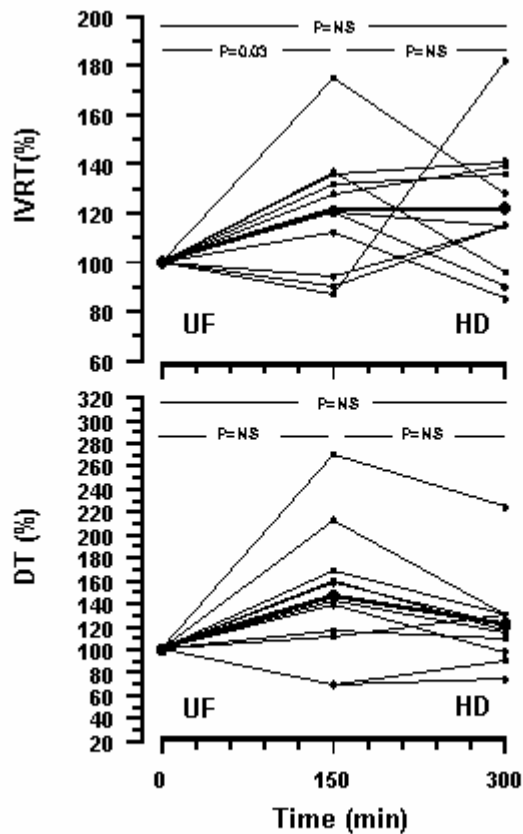
Figure 12. *Percentages of changes in IVRT and DT in 11 patients during UF and HD with minimal UF. The bold line is the mean of changes (**V**).*

During the UF phase, LAD decreased insignificantly from 44.8±5.51 to 41.2±6.9 as also during the HD phase from 41.2±6.9 to 40.4±6.19. In this study population, LVH was detected in every patient and left atrial enlargement in five out of 11. The systolic function of the heart was impaired in four patients and remained abnormal during the study in all of them.

During UF, CO decreased clearly due to diminution of HR and SV. A decrease in SV reflects changes in ECW and especially in circulating BV. During the HD phase, SV and CO increased simultaneously with the increase in BV. There were no changes in SBP or DBP during the UF or HD phases. The changes in systemic hemodynamic variables are presented in Table 15.

Table 15. *Effects of isolated ultrafiltration (UF) and hemodialysis with minimal ultrafiltration (HD) on systemic hemodynamic parameters and the statistical significance of changes (p-values)* **(V).**

Parameters	Before UF	After UF and before HD	After HD	p before UF vs after UF	p before HD vs after HD	p before UF vs after HD
HR (beats/min)	69.5 ± 13	66.3 ± 11	71.8 ± 13	0.006	0.003	ns
SV (ml)	67.8 ± 14	62.5 ± 12	68.5 ± 13	ns	ns	ns
CO (l)	4.8 ± 1.4	4.2 ± 1.2	5.0 ± 1.4	0.024	0.000	ns
SBP (mmHg)	164 ± 28	157 ± 36	162 ± 33	ns	ns	ns
DBP (mmHg)	90 ± 12	88 ± 15	88 ± 23	ns	ns	ns
SVR (dyns/cm^5)	2037 ± 747	2231 ± 888	1908 ± 843	ns	0.018	ns

HR = heart rate, SV = stroke volume, CO = cardiac output, SBP = systolic blood pressure, DBP = diastolic blood pressure, SVR = systemic vascular resistance, ns = non-significant.

No statistically significant correlations were observed between the changes in E or A and the changes in hemodynamic parameters during the UF and HD phases. Furthermore, the changes in the dimensions of the heart did not correlate with those of E and A. However, in the analysis of the whole group there were close and logical Pearson correlations between the changes in the means of E, A, SV and HR during both the UF (r = 0.99, p<0.001) and HD (r = 0.99, p<0.001) phases. During the UF phase, the change in E showed some correlation with the amount of UF (r = 0.45, p = 0.17) and the change in BV (r = 0.44, p = 0.17).

Changes in biochemical parameters during the UF and HD phases are presented in Table 13. There was an inverse correlation between the changes in plasma ionized calcium and the changes in E during the UF phase (r = –0.64, p = 0.04). In addition, the changes in HCO3 correlated negatively with changes in E during the UF phase (r = –0.71, p = 0.01).

The E/A ratio was abnormal in only one patient at the start of the study. This ratio changed during the study in two cases from normal to abnormal and in one from abnormal to normal. At the outset, DT was abnormal in two patients. It changed from normal to abnormal in three patients during the UF phase but normalized in two of them during the HD phase. IVRT was abnormal in 10 out of 11 patients throughout the study and the IVRT of the one normal patient changed to abnormal during the HD phase.

5 Discussion

5.1 General considerations regarding study subjects and design

Due to the use of many technical devices and long, demanding study protocols the patients recruited to this study had to be selected from among those who were co-operative and in a stable clinical condition. For example, about 15-20 percent of the patients in the unit had hypotensive episodes during HD treatment and could not be recruited. Further, in study **I** patients having Cimino fistulas in both arms had to be excluded. In addition, patients not capable of staying still during ECW monitoring were excluded. In studies **II-III** 40 percent of patients had diabetic nephropathy and none in study **I**.

Since the number of patients in the present series was small, the question arises of possible selection biases in the studies. However, the objective here was to study correlations between different factors, e.g. ECW to dVCG parameters and the patients served as their own control. Thereby, the representativeness of the study population in comparison with the whole HD population in the unit may not be the key element. In studies **IV-V,** a comparison was made between the study population and other HD patients in the unit and the mean weight changes and mean UF did not differ. The cohort in studies **IV-V** included fewer patients with diabetes and more patients with glomerulonephritis and adult dominant polycystic disease compared with the HD population in the unit. From the physiological standpoint, the relevance of the results is strengthened through the exclusion of hemodynamically unstable patients. In studies **IV-V**, elimination of the effect of refilling during the HD phase would have required a study design in which isovolemic dialysis is followed by UF alone. No such design was carried out, because during isovolemic dialysis the rapid rate of solute removal results in an abrupt fall in plasma osmolality which contributes to the development of hypotension during the quite short UF phase (Bergström et al. 1976).

5.2 Volume changes, pANP and blood pressure

5.2.1 Volume changes

The results of study **I** show an increase in daytime SBP during the second interdialytic day compared to that of the dialysis day. This increase correlated with interdialytic weight gain. In patients on chronic HD, a positive correlation between increased ECW or weight gain and hypertension has been reported only in some studies (Fishbane et al. 1996, Lins et al. 1997, Katzarski et al. 1999b, Ŏzkahya et al. 1999, Chen et al. 2002, Leypoldt et al. 2002). In addition, only a small number of studies have found a relationship between ABP and weight gain during the interdialytic period (Ventura et al. 1997, Sorof et al. 1999). In most studies no relationship has been observed between volume status (weight gain) and ABP in HD patients (Kooman et al. 1992, Luik et al. 1994a, Luik et al. 1994b, Rodby et al. 1994, Chazot et al. 1995, Huisman et al. 1995, Lingens et al. 1995, Coomer et al. 1997, Savage et al. 1997, Santos et al. 2003).

The use of antihypertensive medication is suggested to be an important confounder explaining the discrepancies in the results, since vasoactive medication could reduce vascular resistance and change the effect of increased volume on BP (Santos et al. 2003). Indeed, in a study by Ventura and Sposito (1997) volume expansion was directly correlated with mean BP only in patients not receiving antihypertensive drugs. In the present study, none of the patients was on antihypertensive medication at the time of the study. In addition, the basal levels of ECW and BP in the patients studied may account for the differences, since hypertensive patients are more sensitive to an increase in BP during the volume gain than normotensive ones (Ventura et al. 1997). In the state of increased ECW, a quite small fluid volume will increase BP (Ritz 1999). In the present study, BP was well controlled and it is justifiable to believe that most of the patients were at their true dry weight and no very substantial changes in BP were expected during the interdialytic period.

Data collected from the US Renal Data System strongly support the conception that interdialytic weight gain is an important factor affecting BP in HD patients. In one large study population there was a positive correlation between BP and interdialytic weight gain in patients with severe hypertension, but not in normotensive patients (Rahman et al. 2000). In another study by Rahman`s group (1999) there was a linear increase in DBP with increasing interdialytic weight gain only in hypertensive patients.

Groups under Fagugli (2001) and Chen (2002) have found an association between BP and fluid overload, which was measured by BIA as ECV %. A relationship between ECV and BP was likewise observed when Swedish normotensive and hypertensive HD patients were compared with normotensive patients in Tassin (Katzarski et al. 1999b). In a prospective study of 3-4 months

SBP and DBP were reduced only in HD patients who showed a reduction in ECV (Katzarski et al. 2003).

In summary, the results of study **I** bespeak a role for volume retention in the pathogenesis of hypertension in HD patients.

5.2.2 pANP and blood pressure

In a number of studies evaluating BP in HD patients, ANP levels in plasma have been used as an indicator of volume status. Antonicelli and colleagues (1989) found that pre- and post HD pANP levels were higher in hypertensive than in normotensive patients. Fishbane and coworkers (1996) verified the finding. In their study HD patients with dialysis refractory hypertension had very high pre- and postdialytic pANP levels in comparison to normotensive HD patients. Patients with any history of cardiac disease were excluded from the study.

In the present study, the increase in daytime SBP did not correlate with changes in ANP. However, ANP may have an effect on BP regulation during the interdialytic period. Luik and associates (1997) found that interdialytic fluid loading increased intravascular volume and CO but reduced SVR, resulting in no change in interdialytic BP. ANP may be the factor which reduces SVR, since the chronic hypotensive effect of ANP is primarily mediated by a reduction in SVR (Melo et al. 2000). ANP has also been shown to exert a generalized sympatholytic effect, and ANP-mediated attenuation of CV sympathetic tone could be the effector mechanism for the chronic vasodilatory action of this hormone (Lang et al. 1991, Melo et al. 2000).

In animal studies, ANP infusion has been shown to shifts fluid from the intravascular to the interstitial compartment and reduce BP (Maack 1996). Also in patients on chronic HD, intravenous pharmacological doses of ANP shifts fluid from the intravascular to the interstitial space and reduces BV and BP (Jespersen et al. 1990). Wallin and colleagues (2004) observed a close correlation between serum ANP, BV and SBP during HD, which resulted in a significant decrease in weight. Mallamaci and group (1994) tested the effect of ANP infusion on the hemodynamic response in HD patients. Doubling of the pANP concentration did not affect SBP, DBP or HR. In studies by groups under Deray (1990) and DE Châtel (1991) changes in pANP during HD did not correlate with the changes in BP. Further, pANP levels were similar in hypotensive and normotensive HD patients (Armengol et al. 1997).

There was a prolonged decrease in pANP after the HD session in the present study. Although pANP remains at a low-level 2 h after dialysis (Wallin et al. 2004), a prolonged decrease has not previously been described. Dialysis increases LV contractility (Chaignon et al. 1982, Nixon et al. 1983) and improves left atrial mechanical function (Yilmaz et al. 2002). In addition, the correction of acidosis may reduce ANP secretion from the atrium (Tavi et al. 1999). Thus, HD possibly reduces ANP secretion.

Wallin and coworkers (2004) measured central BV, CO, SV and serum ANP before, immediately after and 2 hours after HD. They observed that the circulatory performance, as indicated by a high HR, small SV and low SBP, was depressed two hours after HD. In spite of this, serum ANP remained low, indicating that low atrial pressure and reduced atrial distension are responsible for the delayed decrease in ANP concentration.

In the aforementioned study by Wallin`s group (2004) HD resulted in a significant increase in HR and a reduction in SV and CO. It is hence also possible that in the present study acute hemodynamic stress during the dialysis session kept pANP levels inappropriately high in relation to changes in preload and atrial stretch. The decrease in pANP due to volume reduction would thus become manifest only after these acute hemodynamic changes had ceased. This probably also explains why in three of our patients pANP increased during HD.

In summary, the role of pANP in the CV responses to acute ECV changes is unclear and the lack of correlation between ANP and BP levels suggests that ANP is not implicated in the pathogenesis of hypertension in HD patients.

5.2.3 Day-night difference in blood pressure

In contrast to most other studies, here the day-night difference in BP was preserved and persisted in most patients during the interdialytic period. Volume overload has been thought to constitute the main reason for loss of diurnal variation in BP in HD patients, although the exact cause is unclear (Baumgart et al. 1991, Elisaf et al. 1996, Narita et al. 2001). The present study does not support the conception of volume expansion as an etiologic factor in non-dipping.

In spite of the interdialytic weight gain, patients in the present study exhibited no more non-dipping profiles in the second interdialytic day than in the first. In addition, Luik and associates (1994b) have reported a clear nocturnal BP reduction in HD patients. As in the present study, antihypertensive medication was stopped some weeks prior to the study to exclude the influence of medication on BP diurnal variation (Luik et al. 1994b).

It can be postulated that patients in study **I** did not lose their normal diurnal BP variation due to quite small interdialytic weight gain. An average weight gain in the present study was 1.3 kg and about 2.8 kg in a Luik`s study (1994b). Thus, even a rather marked increase in interdialytic weight seems not to reduce BP variability (Luik et al. 1994b). Further evidence exists against the role of volume excess in the etiology of non-dipping in HD patients. In the Tassin HD population, most patients are non-dippers despite small interdialytic weight gain (Chazot et al. 1995). Normalization of BP and reduction of ECW on short daily HD (Fagugli et al. 2001) or extended HD (Fagugli et al. 2006) do not restore the normal day-night BP ratio.

The nightly BP decline is most severely blunted in hypertensive HD patients (Kooman et al. 1992, Elisaf et al. 1996). Hence, the reason why most patients in study **I** evinced near-normal diurnal BP variation could be that their BP was well

controlled. The finding in the current study that the BP variation in one patient returned to normal after reduction of BP by antihypertensive medication supports this theory. On the other hand, around 60 % of the Tassin patients have a non-dipping BP profile despite normotension (Chazot et al. 1995).

Factors other than volume expansion may cause a loss of diurnal-nocturnal BP variation in HD patients. The prevalence of autonomic neuropathy and diabetes in the study population and the age of the patients studied may have an effect on BP variability. Non-dipping is for instance linked to autonomic dysfunction in these patients (Liu et al. 2003). Increased sympathetic nervous activity (Converse et al. 1992b) may be the reason for the loss of nocturnal increase in pANP and increase in nocturnal BP in ESRD patients (Portaluppi et al. 1992). In a study by under Lingens (1995) ANP correlated with both mean daytime BP and nighttime BP in pediatric HD patients.

There may also be other reasons for the contradictory results on BP variation in HD patients. The definition of night, the frequency of BP measurements during the nighttime and the statistical method to demonstrate the diurnal pattern of BP varies in different studies. One confusing factor is the reproducibility of the decrease in BP during sleep. In one recent study, up to 43 % of the subjects changed their dipping category within or between interdialytic periods (Peixoto et al. 2000). In contrast, the night/day systolic ratio was highly reproducible in 168 non-diabetic Italian patients on HD (Tripepi et al. 2005).

The rapid rise in BP which occurred just prior to the next dialysis has also been described in previous studies (Kooman et al. 1992, Lingens et al. 1995, Mitra et al. 1999). The effect seems not to be dependent on weight gain (Mitra et al. 1999). Factors such as arousal and emotional reactions with the initiation of dialysis in a busy environment may play a role in the pathogenesis of the phenomenon.

In summary, interdialytic weight gain does not induce loss of the circadian rhythm of BP in HD patients. Diurnal BP variation is preserved as long as BP is adequately controlled either by volume control or by drug treatment. A rapid rise in BP often occurs immediately prior to the next dialysis.

5.3 Dynamic ischemia monitoring

5.3.1 Volume changes

The results of studies **II-IV** indicate that QRS amplitude and dVCG parameters QRS-VD and STC-VM are greatly dependent on volume changes. QRS-VD and STC-VM, but not ST-VM, alter significantly during HD with UF or during

isolated UF. An increase in QRS amplitude during HD with simultaneous UF was observed in study **II**. HD without UF did not affect any of these parameters.

In earlier studies, an increase in QRS amplitude after HD has been observed on standard ECG (Diskin et al. 1981, Ono et al. 1983, Wizemann et al. 1983, Fuenmayor et al. 1993, Madias et al. 2003a), on VCG (Ishikawa et al. 1979, Vitolo et al. 1987) and on body surface maps (Kinoshita et al. 1993). Some authors (Ono et al. 1983, Vitolo et al. 1987, Kinoshita et al. 1993), but not all (Diskin et al. 1981, Fuenmayor et al. 1993) have found a relationship between increase in QRS amplitude and reduction in body weight. One explanation for the different results might be variations in methodology. In earlier studies evaluation of the BV reduction on HD was based on singular body weight and hematocrit measurement. In the present study continuous BV measurement and ECW determinations at 15-min intervals were used. Another reason for the conflicting results may be the quantity of weight reduction. In study **II,** the mean weight decrease was 1.9 kg and in studies with no correlation between QRS amplitude and body weight the decrease was much lower.

According to the Brody effect, a decrease in intracardiac blood or heart volume will lead to decrease in QRS potentials (Brody 1956). However, in the present study a marked reduction in BV was followed by an increase in QRS amplitude. Ishikawa and colleagues (1983) investigated the influence of sauna bathing on body surface potentials and found that sauna caused an increase in QRS amplitude, which was accompanied by a reduction in circulating BV and a decrease in heart intracavitary BV. These findings are compatible with the results of some other studies (Vitolo et al. 1987, Oreto et al. 1992). The result of the present study is in conflict with the Brody effect and the Brody theory may thus not explain the increase in QRS amplitude during HD with UF.

In study **II**, a close connection was found between changes in QRS amplitude and changes in ECW. Thus, the mechanism of the augmentation of QRS amplitude during HD with UF may be associated with changes in water content in the tissues (ECW). During HD-related UF the water content of tissues is reduced, with the result that the electrical resistance of extracardial tissues increases and shunting of the electrical current diminishes. The increased resistance in the presence of a stable current leads to an increase in QRS amplitude (Rudy et al. 1979). The results of studies **II-IV** are in agreement with those of Bayley and Berry (1962), who showed in a nonhomogeneous conductivity model that an increase in "body trunk" resistivity causes an increase in body surface potentials.

The results of the present series indicate that QRS-VD is the most sensitive of the dVCG parameters to the influence of volume changes. Nevertheless, in study **IV** QRS-VD correlated to ECW but not to BV during isolated UF. A close relation between changes in ECW and QRS-VD is reasonable, since it is precise ECW, which conducts electrical current to the body surface. The lack of correlation with BV and QRS-VD is due to the refilling effect shifting continually fluid from the interstitial space to the blood compartment with various amounts and timing in individual patients. The refilling was continuous during study **IV**, but was clearly visible during the HD phase.

An increase in STC-VM during HD with UF (**III**), but not during isolated UF (**IV**), was related to changes in both ECW and BV. Certain factors could explain this discrepancy. The increase in STC-VM was much less marked during isolated UF than during HD with UF. The rate and timing of UF were also different in these studies. Finally, the individual variation in the trend of STC-VM was fairly large in the isolated UF study (**IV**).

In study **II,** parallel QRS-VD and ST-VM artefacts related to changes in body position were observed. These findings are not fully compatible with results of earlier studies in which different body positions caused major changes in QRS-VD but affected ST-VM and STC-VM only to a minor degree (Dellborg et al. 1992, Jensen et al. 1997, Gannedahl et al. 1997a, Norgaard et al. 1999). It is obvious that body position changes cause variations in heart and electrode positions, which can affect dVCG parameters. However, a QRS-VD increase in sitting or upright position may not be solely explained by positional changes. During head up tilt, blood is shifted from the thorax to the lower body and the electrical resistance of the tissues around the heart increases, partly explaining the positional increase in QRS-VD. On the other hand, in the present studies ST-VM was not dependent on changes in BV or ECW. The reason may be that ST-VM is generated during the isoelectric phase of cardiac electrical activity. If the initial deviation of the ST-segment from the isoelectric phase is zero, then volume-related amplitude changes would not appear. It is thus obvious that the cause for the similar behavior of QRS-VD and ST-VM during body position changes cannot be completely explained on the basis of the present findings.

5.3.2 Biochemical parameters

An essential finding in the present series was that HD with minimal UF had no effect on any dVCG parameters. On the other hand, during HD with UF or during isolated UF only parameters which stand in relation to changes in volume or osmotic pressure, had some correlation to QRS-VD or STC-VM.

The sodium-induced changes in ECG are of little clinical significance, as the levels necessary to alter action potential are incompatible with life (Cooksey et al. 1977). There are few studies evaluating the effect of sodium on dVCG parameters. Ono and associates (1983) have demonstrated that an increase in QRS amplitude and depression of the ST-segment are significantly more frequent when patients are dialysed with a low sodium dialysate (133 mEq/l) than when the sodium concentration is raised (141 mEq/l). Their conclusion was that when a low sodium dialysate (133 mEq/l) is used, intravascular refilling is not rapid enough to prevent hypovolemia, and this may lead to myocardial ischemia. During UF a dialysate sodium concentration higher than that of the serum maintains ECV better than a lower sodium dialysate (DE Vries et al. 1994). Therefore, the increase in QRS amplitude is not so marked and for the same reason ST-segment changes, if they occur, are milder. Additional sodium in the contrast medium in patients undergoing cardioangiography does not change QRS-

VD more than a normal sodium concentration (Flinck et al. 1994). Severe hyperkalemia (over 6.5 mmol/l) may widen the QRS complex and reduce its amplitude (Surawicz 1967). Plasma potassium concentrations decreased significantly after HD with UF and during isolated UF, but no significant correlation was found between dVCG parameters and potassium. In the present studies, the mean plasma concentrations were clearly under the level mentioned above.

5.3.3 Myocardial ischemia

In studies **II-IV**, some of the patients evidenced QRS-VD or STC-VM changes, which fulfilled the criteria of myocardial ischemia. These changes were most probably related more to volume changes than to myocardial ischemia, since they were dependent on changes in ECW and BV. If these changes on dVCG parameters were caused by ischemia, they would presumably be more serious in patients with CAD. In addition, none of the patients studied had symptoms of coronary ischemia during the HD session. However, it must be taken into account that myocardial ischemia can exist in HD patients without any symptoms. There is furthermore an argument, which counters the role of myocardial ischemia in the pathogenesis of QRS-VD and STC-VM changes during the HD session. Myocardial ischemia sometimes causes only directional ST vector changes and in non-HD patients STC-VM may detect myocardial ischemia with a higher sensitivity than ST-VM (Jensen et al. 1994). However, in another study STC-VM and ST-VM quite congruently detected myocardial ischemia (Lundin et al. 1998), and it is reasonable to assume that simultaneous changes in ST-VM and STC-VM will be observed during ischemia. Likewise, Bos and coworkers (2000) have demonstrated in nine chronic HD patients that during isolated UF the balance between cardiac oxygen supply and demand did not decrease, but improved slightly despite substantial changes in hemodynamics.

Earlier studies have demonstrated that the value of using QRS-VD for the detection of myocardial ischemia is limited, because several mechanisms other than ischemia or volume changes also cause changes in the QRS complex (Rosenthal et al. 1971, Sutherland et al. 1983, Feldman et al. 1985). The results of the present studies indicate that QRS-VD and STC-VM are not reliable in screening for myocardial ischemia during the HD session. On the other hand, the ST-VM was not influenced by volume changes and should be more suitable for the detection of myocardial ischemia during the HD session.

Myocardial ischemia is suggested to increase QRS amplitude (Diskin et al. 1981, Ono et al. 1983). However, no objective evidence of myocardial ischemia was presented in the studies in question. Likewise, in the present studies myocardial ischemia was not absolutely excluded. The serologic diagnosis of myocardial ischemia is difficult since in HD patients elevations of troponins are frequently found without clinical evidence of myocardial disease (Li et al. 1996, McLaurin et al. 1997, Apple et al. 2002). For this reason, measurements of

troponin concentrations were not used as a marker of myocardial ischemia in the present series.

The ability of dVCG and two-channel Holter monitoring to detect ischemic episodes has been compared in non-uremic patients with unstable angina pectoris (Dellborg et al. 1995). The authors concluded that dVCG detected ischemia with higher sensitivity than did Holter ECG. There are no data comparing these two methods during the HD session. In many recent studies (Zuber et al. 1989, Kremastinos et al. 1992, Shapira et al. 1992, Singh et al. 1994, Conlon et al. 1998) non-ischemic ST-segment changes during the HD session on Holter monitoring seem to be highly prevalent. Thus, dVCG may be a more specific method for the detection of myocardial ischemia than Holter in HD patients.

5.4 Doppler-derived indices of diastolic function

In study **V**, HD with isolated UF resulted in a marked decrease in E and A wave velocity but not in the E/A ratio. Isolated UF markedly reduced BV, which in turn is closely associated with changes in preload and left atrial pressure. There was also a trend towards a reduction in LAD and LVEDD, which equally reflects changes in left atrial pressure (Kinet et al. 1982). Hence, the present findings indicate that a change in preload and left atrial pressure has an effect on both E and A wave velocity.

5.4.1 E and A wave velocities

The most prominent changes were detected in the peak E wave velocity. This finding is similar to those recorded in earlier studies evaluating the effect of HD on Doppler echocardiographic parameters (Rozich et al. 1991, Sadler et al. 1992, Gupta et al. 1993, Sztajzel et al. 1993, Chakko et al. 1997, Uusimaa et al. 1999, Agmon et al. 2000, Chamoun et al. 2002, Ie et al. 2003, Barberato et al. 2004, Hayashi et al. 2004, Oğuzhan et al. 2005, Vignon et al. 2007). In addition to the changes in the preload and left atrial pressure, the decrease in E wave velocity may be explained by an increase in afterload (Choong et al. 1988). According to study **V**, in which BP did change, this mechanism is not probable.

Most studies have reported that dialysis-related reduction in preload does not reduce A wave velocity. However, in some studies has also A wave velocity diminished, albeit usually less than E wave velocity (Dincer et al. 2002, Graham et al. 2003, Hung et al. 2004b, Hung et al. 2004a). The maximal velocity of the A wave depends among other factors on HR and the contractility of the left atrium (Nishimura et al. 1997). A decrease in HR, even within the physiological range, reduces atrial velocities. Although patients in study **V** evinced significant

decreases in heart rates and A wave velocity during the UF phase, no correlation was observed between these parameters.

The normal hemodynamic response in HD patients to intravascular volume depletion is an increase in HR. The HR response to BV reduction during HD with UF has varied in different studies. In some, there was no change in HR (Rozich et al. 1991, Gupta et al. 1993, Sztajzel et al. 1993, Chakko et al. 1997, Chamoun et al. 2002, Graham et al. 2003, Koga et al. 2003, Vignon et al. 2007). On the other hand, other reports have shown a clear increase in HR (Agmon et al. 2000, Hung et al. 2004b, Hung et al. 2004a, Galetta et al. 2006). Hemodynamic changes during isolated UF are different from those observed during conventional dialysis with UF. During UF without dialysis, much more rapid UF is tolerated without a fall in BP or increase in pulse rate (Bergström et al. 1976). This is the reason why the HR decreased during isolated UF in study **V**. The decrease may explain the marked reduction in A wave velocity.

The myocardium increases its strength of contraction in response to an increase in HR (Bombardini 2005). Therefore, the decrease of HR during isolated UF in the present study may have caused a reduced contractility of the atrium and the observed decrease in A wave velocity. Isolated UF as such does not have an effect on myocardial contractility and SV decreases with a decrease in preload (Nixon et al. 1983). In contrast, conventional HD with or without UF increases atrial and LV myocardial contractility (Nixon et al. 1983, Yilmaz et al. 2002, Hayashi et al. 2004). It is hence highly probable that the decrease in the contractility of the myocardium with a simultaneous decrease in HR explains the pronounced diminution of the A wave during isolated UF.

One confusing factor in the results of the different studies may be the wide interpatient variation of the HR response to BV reduction (Andrulli et al. 2002). A co-existent background disease may also determine the myocardial response to HD. In a study by Govind and coworkers (2006) systolic and diastolic myocardial function improved only in patients who did not have type 2 diabetes and/or CAD (Govind et al. 2006). In addition, the baseline values of A wave and LV filling pressures seem to have on effect on the behavior of the A wave (Courtois et al. 1988b, Ruffmann et al. 1990, Sadler et al. 1992, Hurrell et al. 1997). The conception that an association between volume changes and A wave velocity observed during isolated UF is supported by observations that changes in both E and A wave are most striking in HD patients with a high UF rate (Hung et al. 2004a, Hsiao et al. 2005). In addition, the decrease in A wave velocity is mainly observed in studies in which BP diminishes, probably reflecting a considerable reduction in the preload (Agmon et al. 2000, Hung et al. 2004b, Hung et al. 2004a). In the current study, however, the decrease in A wave velocity was not associated with a decrease in BP. In animal studies (Courtois et al. 1988b) and in subjects with normal diastolic function (Nishimura et al. 1997), an acute decrease in preload reduces the E and A peak velocities proportionately. On the other hand, acute volume loading in non-dialysis patients increases both E and A wave velocities (Stoddard et al. 1989).

Uremic serum acutely induces impaired recovery of cardiac myocyte calcium concentration and impairs relaxation (Periyasamy et al. 2001). Thus, the

elimination of uremic substances during HD may enhance the diastolic function of the heart. In the present study both E wave and A wave velocities increased during the HD phase, although the increase in the A wave was not statistically significant. However, these increases may be due more to the fluid refilling from the extracellular space to the blood space than to the removal of uremic toxins.

In the present study, a very mild but statistically significant rise was observed in the plasma concentration of ionized calcium correlating with the decrease in E during the UF phase. This rise in ionized calcium may be due to the Donnan effect, wherein a change in the concentration of negatively charged albumin causes a small parallel change in the concentration of positively charged calcium (Thode et al. 1983). A more profound increase in plasma calcium than observed here may impair LV relaxation in patients with CRF and in patients on combined UF-HD (Virtanen et al. 1998a, Näppi et al. 1999). In contrast in one study, an increase in ionized calcium during HD without UF did not lead to a change in Doppler parameters of LV diastolic function (Ie et al. 2004). It appears that changes in the parameters of LV diastolic function during isolated UF are related to changes in preload but not to changes in ionized calcium.

In summary, both E wave and A wave velocity are dependent on preload. E and A wave velocities were so consistently dependent on preload that their ratio was not affected by isolated UF or HD with minimal UF.

5.4.2 Isovolumic relaxation time and deceleration time

The predialytic IVRT was prolonged in 10 out of 11 patients studied (**V**). IVRT is also load-dependent, since a decrease in left atrial pressure leads to delayed mitral valve opening and prolongs IVRT (Rozich et al. 1991, Sadler et al. 1992, Nishimura et al. 1997). The finding in the present study that IVRT was further lengthened during the UF phase is in accordance with such a mechanism. The prolongation of IVRT is associated with LVH, which was present in all of the patients studied. Increased LV chamber stiffness and prolongation of IVRT also occurs during myocardial ischemia (Barry et al. 1974, Aroesty et al. 1985). Ischemia is an unlikely explanation for the prolongation of IVRT, since no real ischemic changes were found in dVCG monitoring during the study.

The behavior of DT during the study was similar to that of IVRT. In contrast, a group under Chakko (1977) observed no change in DT during isolated UF. As a whole, earlier studies have yielded conflicting results regarding the behavior of IVRT and DT during HD (Gupta et al. 1993, Agmon et al. 2000, Chamoun et al. 2002, Graham et al. 2003, Hung et al. 2004b, Hung et al. 2004a). However, most have demonstrated either an increase or a trend towards an increase in DT and IVRT. The prolongation of IVRT and DT during HD, as in the UF phase in the current study, obviously reflects more changes in the fluid state than deterioration in relaxation. Changes in preload due to refilling during the HD phase were obviously too slight to affect IVRT or DT. The increase in the plasma concentration of calcium during the UF phase is apparently too small to impair

LV relaxation and to prolong DT and IVRT (Rostand et al. 1988, Rozich et al. 1991, Näppi et al. 1999).

In summary, the results of this study demonstrate that the LV diastolic filling parameter IVRT, and lesser DT, are affected by UF and preload but not by HD.

5.4.3 Hemodynamic changes

At the start of study **V**, patients were overloaded with fluid and were in a hyperdynamic CV state. Fluid retention increased preload and led to pseudonormalisation of echocardiographic parameters of the LV diastolic function. Thus, there was an abnormal predialytic increase in the velocities of E and A waves and a diminution in the IVRT and DT. The diminution of preload during the UF phase led to notable hemodynamic responses: HR, SV and CO decreased, reflecting the recovery of the patients from the hyperdynamic state. UF abolished the pseudonormalisation of the LV diastolic function parameters and values with higher accuracy were measured at the end of the UF phase. Refilling from the tissues during the HD phase increased BV and the changes in HR, SV and CO were opposite to those observed in the UF phase.

In summary, changes in the parameters of diastolic function during UF obviously do not reflect deterioration in diastolic function but rather recovery from the hyperdynamic CV state caused by fluid retention.

6 Summary and conclusions

1. In hemodialysis patients weight gain between two dialysis sessions increases the daytime systolic blood pressure but not the diastolic blood pressure. Diurnal blood pressure variation is maintained as long as blood pressure is adequately controlled either by volume control or by drug treatment.

2. The increase in QRS amplitude during a hemodialysis session is significantly correlated to reduced extracellular fluid volume and the mechanism involved is most probably augmentation of electrical resistance caused by loss of interstitial fluid. This hemodialysis related increase in QRS amplitude should not be taken as an indicator of left ventricular hypertrophy or myocardial ischemia unless clinical symptoms or other indices are present.

3. During hemodialysis treatment changes in the dynamic vectorcardiographic ischemia monitoring parameters QRS-VD and STC-VM are mostly related to extracellular fluid volume and blood volume changes, and may give a false-positive impression of myocardial ischemia. The ST-VM trend is less influenced by volume changes.

4. Isolated ultrafiltration leads to an increase in the dynamic vectorcardiographic ischemia monitoring parameters QRS-VD and STC-VM. The increase in QRS-VD is closely related to changes in extracellular fluid volume. Hemodialysis with minimal ultrafiltration has no effect on dynamic vectorcardiographic ischemia monitoring parameters. During hemodialysis ultrafiltration causes changes in dynamic vectorcardiographic ischemia monitoring parameters and may give a false-positive impression of myocardial ischemia.

5. In hemodialysis patients ultrafiltration affects parameters used to evaluate left ventricular diastolic function (E, A, IVRT). However, the E/A ratio is not affected by isolated ultrafiltration or hemodialysis with minimal ultrafiltration. IVRT seems to indicate left ventricular diastolic dysfunction before and after ultrafiltration and is not affected by hemodialysis. The appropriate time to evaluate left ventricular diastolic function in dialysis patients calls for further studies, but it could be some hours after dialysis, when plasma refilling is over and there is not yet an weight gain.

7 Acknowledgements

I am truly grateful to the entire personnel of the Department of Nephrology for their mental and practical help during this study.

I am most thankful to Robert MacGilleon, M.A., for careful and educational revision of the English language of the original communications and this thesis.

I am very thankful to Sisko Kammonen and Raila Melin at the Medical Library of the University of Tampere for their professional help.

I appreciate the skilful secretarial work of Miss Päivi Laaksonen.

I owe my deepest gratitude to my beloved wife Ulla and my lovely daughters Outi, Maija and Aino for their never failing support throughout these years. Without this support and this thesis would not have been completed.

I wish to thank my pug Robert for his warm friendship and constant staring during our common nighttime visits to the refrigerator during this study.

Finally, I wish to honor the memory of my recently passed brother Taisto who already logged the day of this dissertation on his diary.

Kangasala, November 2007

Seppo Ojanen

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Plasma Atrial Natriuretic Peptide, Body Weight and Twenty-Four-Hour Blood Pressure Monitoring in Chronic Hemodialysis Patients

Abstract

In this study we investigated the interactions between volume changes (body weight), plasma atrial natriuretic peptide (pANP) and ambulatory blood pressure (BP) in 10 patients with end-stage renal disease undergoing regular hemodialysis (HD) treatment three times weekly. Most patients retained their diurnal BP variation when their BP was adequately controlled. Interdialytic weight gain was 1.3 ± 0.2 kg and the day-time systolic BP increased 12.5 ± 4.8 mm Hg on the second interdialytic day. pANP did not correlate ($r = -0.07$, $p = 0.85$) with this BP elevation, but there was a fairly strong positive correlation ($r = 0.61$, $p = 0.06$) between interdialytic weight gain and systolic BP. The mean pANP level decreased from 149.7 ± 18.2 to 117 ± 0.1 ng/l during HD and continued its decrease to 83 ± 12.2 ng/l at 20 h after an HD session. The total decrease from 149.7 ± 18.2 to 83 ± 12.2 ng/l was statistically significant ($p = 0.001$). Since the lowest pANP value was found 20 h after completion of the dialysis session, body weight is a more reliable indicator of volume reduction during HD than pANP. The results indicate that in HD patients weight gain between two dialysis sessions increases the day-time systolic BP but not the diastolic BP. Diurnal BP variation is maintained as long as BP is adequately controlled either by volume control or by drug treatment.

Introduction

The prevalence of hypertension in patients with end-stage renal disease ranges from 70 to 90% [1]. In most patients, hypertension is controlled by adequate hemodialysis (HD) and fluid restriction, and only 10–20% of HD patients are considered to require antihypertensive agents [2]. Isolated blood pressure (BP) readings will not show all clinically important BP features that occur during dialysis and the interdialytic period. Ambulatory BP monitoring may be more suitable, and results obtained with this technique would seem to indicate that hypertension is in fact inadequately controlled in most HD patients treated for hypertension [2] and that the normal day-night BP variation may be absent in HD patients [3]. This nocturnal hypertension is correlated with left ventricular hypertrophy [4] and suggested to lead to additional cardiovascular mortality.

The pathogenesis of hypertension in HD patients is multifactorial, but sodium-volume excess is considered to

Table 1. Clinical data of the patients studied

	Patients									
	1	2	3	4	5	6	7	8	9	10
Name	E.M.	L.U.	P.V.	L.M.	P.J.	S.K.	S.A.	U.A.	V.R.	A.M.
Sex	male	female	female	female	male	female	female	male	female	male
Age, years	67	56	67	30	32	62	57	73	55	48
Type of kidney disease	shock kidney	APKD	ADPKD	chronic glomerulo-nephritis	chronic glomerulo-nephritis	chronic glomerulo-nephritis	ADPKD	chronic kidney failure	ADPKD	ADPKD
Time on dialysis, y:m	6:0	1:7	0:2	0:11	0:6	0:6	1:10	0:10	0:5	2:5
Type of dialyzer membrane	polysulfone (F-40)	cellulose acetate (Ca 170)	cellulo-synthetic (Moderato)	cellulose acetate (Ca 130)	cellulose acetate (Ca 170)	polysulfone (HFL-F6)	cellulose acetate (Ca 130)	cellulose acetate (Ca 130)	PMMA (B2-1.0H)	polysulfone (HFL-F8)
Diuresis/day, ml	1,100	350	1,300	0	0	1,500	1,200	450	1,550	0
Kidney transplantation before dialysis	no	no	no	yes	yes	np	no	no	no	yes
Antihypertensive medication										
Before dialysis	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
On dialysis	no	no	no	no	no	no	yes	yes	no	no

ADPKD = Adult dominant polycystic kidney disease; PMMA = polymethylmethacrylate.

be the most important cause [5]. On the other hand, many vasoactive substances are known to modify the BP of HD patients [6]. One of these is atrial natriuretic peptide (ANP), which is a potent vasodilator. Plasma ANP (pANP) concentrations are elevated in patients with end-stage renal disease and in HD patients [7, 8]. The most likely reason for this is volume expansion, not decreased renal excretion. Infusion of pharmacological doses of ANP into normal and hypertensive subjects leads to a rapid and sustained reduction in BP, but the role of pANP as a BP regulator in HD patients is controversial [9, 10]. Our purpose was to study the interdependencies of volume excess, pANP and BP using ambulatory blood pressure monitoring.

Patients and Methods

Ten clinically stable patients on regular HD were studied. All were treated as outpatients and were able to pursue their daily activities. Their main clinical data are presented in table 1. The patients' median age was 56.5 years (range 20–73). They had been on HD for an average of 1.6 (range 0.2–7.7) years. All patients had used antihypertensive treatment before maintenance HD was started, but only 2 (S.A. and U.A.) still required antihypertensive therapy after the initiation of HD. Their antihypertensive medication was discontinued 2 weeks before the study.

The design of the study is presented in figure 1. BP was measured using the Novacor Diasys 2000 continuous ambulatory blood pressure apparatus, which measures BP by auscultatory means. On the first study day, the recorder was placed approximately 1 h before dialysis. During dialysis (4 h) BP was measured every 10 min, during day-time (14–22 h) every 15 min and during the night (22–6 h) every 30 min. On the second monitoring day, patients were told to rest for 4 h at the time of the HD treatment on the first day to simulate dialysis.

Patients were dialysed for 4 h using the Fresenius 2008E or Gambro AK 10B dialysis apparatus. The ultrafiltration rate was programmed to reach the patients' optimal dry weight. Each patient continued to use the same type of dialysator as before throughout the study. Sodium bicarbonate was used as dialysate buffer.

The pANP values were measured as shown in figure 1. Patients were kept in the supine position for 30 min before blood sampling. pANP sampels were analysed in Medix Co. Laboratories using the ELISA method with Peninsula antibody. Normal values for pANP were under 65 ng/l, and values over 120 ng/l in hemodialysis patients reflected hypervolemia according to our laboratory's own control material.

Values are expressed as mean ± SEM. A paired Student's t test was used to estimate differences in pANP and weight. Linear regression analysis was used to evaluate correlations with weight and pANP. ANOVA was used for multiple comparisons. The statistical calculations were made using the Statgraphics (ver. 7.0) statistical package. Differences at the 95% level were considered significant. Significance is given as p values.
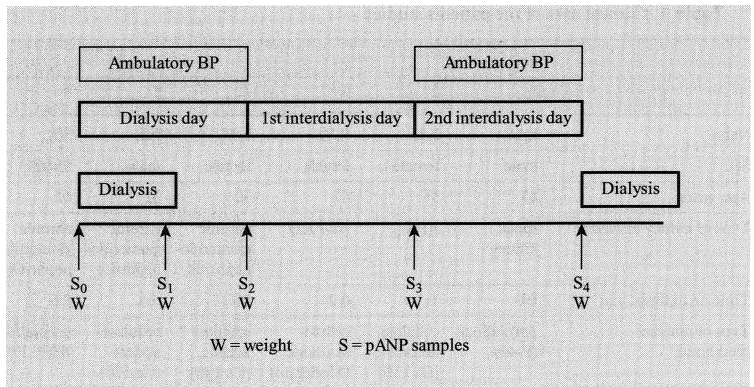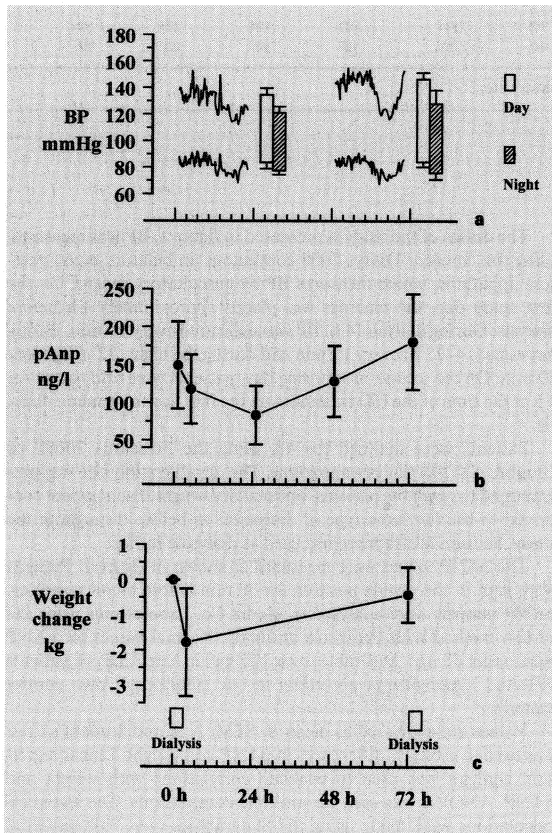
Fig. 1. Protocol of the study.

Fig. 2. Mean values of systolic and diastolic BP, day and night BP (a), pANP (b) and body weight change (c) in the 10 HD patients studied.

Results

Day-Night Blood Pressure Difference

The day-night difference in systolic BP was 11.3 ± 4.8 mm Hg on the dialysis day and 19.3 ± 3.1 mm Hg on the second interdialytic day. Both differences were statistically significant. On the dialysis day, a significant day-night systolic BP difference was observed in 8/10 patients and on the second interdialytic day in 6/9 patients. The corresponding differences in diastolic pressures were 7.1 ± 1.8 and 8.7 ± 1.8 mm Hg and they were significant in 5/10 and in 4/9 patients. Patient U.A. had high BP values with antihypertensive treatment and he had no diurnal BP variation. Later, with the patient on antihypertensive medication, a repeat continuous ambulatory BP measurement was made, and the mean 24-hour BP was 154/79 mm Hg and a clear day-night BP variation was present.

Weight and ANP

Body weight decreased by 1.7 ± 0.5 kg (p = 0.005) during dialysis and the interdialytic weight gain was 1.3 ± 0.2 kg (p = 0.03). The mean pANP concentration decreased during the HD session from 149.7 ± 18.2 to 117 ± 0.1 ng/l (p = 0.15). pANP decreased during HD in 7 patients and increased mildly in 3. After the HD session pANP decreased in every patient, and the lowest mean pANP concentration 83 ± 12.2 ng/l was measured 20 h after the session. This decrease was statistically significant (p = 0.001) compared with the predialytic value. Thereafter, pANP increased constantly and reached its highest mean value 180.4 ± 14.9 ng/l before the next dialysis session.

The body weight decrease during dialysis correlated positively (r = 0.65, p = 0.04) with the simultaneous pANP decrease. This relationship was still stronger (r = 0.72, p = 0.019) when maximal pANP decrease was compared with weight reduction during the HD session. No correlation was observed (r = 0.11, p = 0.77) between interdialytic weight gain and pANP accumulation.

Increase in Day-Time Systolic BP during the Second Interdialytic Day

Average changes in systolic and diastolic BP and pANP concentrations are presented in figure 2. During the second interdialytic day the day-time systolic BP increased significantly (p = 0.039) compared to that of the dialysis day. The absolute increase was 12.5 ± 4.8 mm Hg. This phenomenon was observed in 5/10 patients. Night-time systolic BP rose significantly in only 3/9 patients. The overall night-time sytolic BP increase was insignificant, although there was a sharp BP elevation just before the second dialysis. Changes in diastolic BPs were very small. There was a fairly strong positive correlation between interdialytic weight gain and systolic BP increase (r = 0.61, p = 0.06). No correlation (r = –0.07, p = 0.85) was noted between pANP and systolic BP elevation.

Discussion

Ambulatory 24-hour BP measurement is a new and refined method to investigate BP changes over a long period. It is the only way to identify those patients who have lost their diurnal BP variation and are at risk of developing cardiovascular complications.

Using ambulatory BP monitoring, we observed a systolic BP elevation on the second postdialytic day in patients on regular HD three times weekly. It correlated positively with weight gain, indicating that BP was volume dependent. The systolic BP increase at that time did not correlate with pANP elevation. Probably pANP is not a major BP regulator in this setting, or the connection is masked by some other confounding hemodynamic factor (see later). A similar observation was made in two earlier studies [11, 12]. However, in one study [10], a positive correlation was obtained. Antonicelli et al. [13] found that pANP levels were higher both before and after dialysis in hypertensive patients on maintenance HD than in normotensive patients. They noted a positive correlation between pANP levels and systolic BP in hypertensive patients.

Although all our patients had been hypertensive before starting on HD, only 2 continued antihypertensive treatment during maintenance HD. In the others, BP was controlled by volume reduction during HD. Consequently, most of our patients could be regarded as normotensive provided that adequate volume status was maintained. The sharp BP elevation immediately prior to the next dialysis session found in this study was also recorded in other studies [13, 14].

Hasegawa et al. [15] found that the pANP concentration changed very little during the 24 h following HD treatment, but that it increased very rapidly during the 24 h that followed a dialysis session. We observed that pANP continued to decrease during 20 h after dialysis. This phenomenon has not been described previously. HD may lead to secondary hemodynamic changes which oppose the effect of volume reduction on pANP and keep pANP levels inappropriately high during the dialysis session. The decrease in pANP due to volume reduction would thus become manifest only after these acute hemodynamic changes ceased. This probably also explains why in 3 of our patients pANP increased during HD.

We found that the day-night difference in BP persisted in most patients. According to Baumgart et al. [3] and Kooman et al. [16], the circadian BP rhythm is disturbed in patients with chronic renal failure undergoing HD. Baumgart et al. [3] proposed that volume expansion is the major determinant in the pathogenesis of blunted diurnal BP variations. The reason why most of our patients had near-normal diurnal BP could be that their BP was well controlled. This conception is supported by the findings of Kooman et al. [16], who observed that the nocturnal decline in BP was most severely blunted in hypertensive patients. To test this hypothesis, we applied an extra ambulatory BP monitoring in one of our patients who was hypertensive in the original study period but whose BP was normalized by drug treatment. His BP variation reappeared.

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QRS Amplitude and Volume Changes during Hemodialysis

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Abstract

Background: According to several studies the QRS amplitude of the ECG increases during hemodialysis. The detailed background to this phenomenon has not been defined. Two main mechanisms have been suggested: myocardial ischemia and volume changes. New noninvasive technologies make possible a comparison of QRS complex changes synchronously with myocardial ischemia and extracellular water (ECW)/blood volume (BV) changes during hemodialysis. *Methods:* In this study hemodialysis-related changes in body weight, biochemical blood variables, BV, ECW, ST segment and QRS complex were analyzed in 15 patients (age 36–76, time on dialysis 0–6 years) undergoing chronic hemodialysis treatment. QRS complex and ST segment changes were measured using a dynamic vectorcardiographic monitoring system. The ECG parameters measured were QRS vector difference (QRS-VD) and ST vector magnitude (ST-VM6). Bioimpedance analysis was used to detect changes in the ECW. Continuous measurement of BV changes was implemented using an on-line optical reflection method based on the reflection of infrared light by erythrocyte membranes. Blood hemoglobin (B-Hb), hematocrit (B-Hcr), plasma sodium (P-Na), chloride (P-Cl), magnesium (P-Mg), potassium (P-K), ionized calcium (P-iCa), phosphate (P-Pi), creatinine (P-Crea) and urea (S-Urea) were monitored. *Results:* The mean QRS-VD increase during the dialysis session was almost fourfold (372 ± 300%) from 4.16 ± 2.40 to 15.60 ± 7.0 µVs ($p < 0.001$). This change was due to a change in amplitude, since the duration of the QRS complex did not alter significantly. The correlation between the changes in QRS-VD and body weight from the start to the end of the dialysis session was moderate and statistically significant ($r = -0.55$, $p < 0.05$). The correlation between the changes in QRS-VD and ECW varied from $r = -0.67$ to -0.97, being statistically significant in all patients ($p < 0.001$). The correlation between BV and QRS-VD was assessed at one minute intervals during the dialysis and varied from $r = -0.22$ to -0.98, being significant in 14 of the 15 patients ($p < 0.001$). Significant ST segments alterations (ST-VM6 elevation > 100 µV) did not occur during dialysis. Laboratory parameters reflecting volume and osmotic changes during hemodialysis correlated with QRS-VD change: B-Hcr ($r = 0.56$, $p < 0.05$), B-Hb ($r = 0.63$, $p < 0.05$), P-Na ($r = 0.62$, $p < 0.05$) and S-Urea ($r = -0.62$, $p < 0.05$). *Conclusions:* The increase in QRS complex amplitude during hemodialysis is correlated to reduced ECW. The mechanism involved is most probably augmentation of electrical resistance of the tissues around the heart caused by loss of interstitial fluid.

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Introduction

According to several studies the QRS amplitude of the ECG (electrocardiography) increases during hemodialysis. The precise background to this phenomenon has not been defined. Two main mechanisms have been suggested: myocardial ischemia [1, 2] and volume changes [3, 4]. Earlier studies were based on single ECG and body weight registrations. New noninvasive techniques, however, allow dynamic on-line ECG, ECW (extracellular water) and BV (blood volume) recordings. The aim of the present study was to relate the QRS amplitude alterations to changes in ECW, BV and blood chemistry as well as to myocardial ischemia during hemodialysis. This was done by means of continuous registration of vectorcardiography, ECW (bioimpedance analysis) and BV (hematocrit). A pronounced correlation was observed between ECW loss and increase in QRS amplitude during hemodialysis.

Subjects and Methods

Subjects

Fifteen hemodialysis patients (6 women and 9 men) were studied. Their mean age was 63 years (range 36–76) and they had been on hemodialysis for a mean time of 25 months (range 1–66). The etiology of end-stage renal failure as chronic glomerulonephritis (n = 5), polycystic kidney disease (n = 2), diabetic nephropathy (n = 6), interstitial nephritis (n = 1) and bilateral nephrectomy due to renal carcinoma (n = 1). All except one patient had a history of hypertension and 7 had coronary artery disease. Ten were using cardiovascular medication (calcium channel blockers n = 6, beta-blockers n = 6, long-acting nitrates n = 5, ACE inhibitors n = 1, alpha-blockers n = 1) which was allowed to continue during the study. All patients signed an informed consent of participation. The study was approved by the Ethics Committee of Tampere University Hospital.

Hemodialysis Procedure

Patients were dialyzed three times a week for 3.5–5 h (mean 4.1 h) by the Fresenius 4008E (Fresenius AG, Bad Hamburg, Germany) delivery system. Cellulose acetate membrane hollow fiber dialysers (Ca 130/170 series, Baxter Healthcare, Round Lake, Ill., USA) were used. The composition of the dialysate was: Na 140 mmol/l, K 2 mmol/l, Ca 1.5 mmol/l, Mg 0.5 mmol/l, Cl 111 mmol/l, HCO_3 33 mmol/l. The dialysate temperature was 36.5 °C. The blood flow rate was prescribed individually (range 250–350 ml/min). The dialysate flow was fixed at 500 ml/min and the ultrafiltration rate was kept constant during dialysis. All patients were ultrafiltrated until their clinically determined dry weight was reached.

On-Line Vectorcardiography Monitoring

We used a computerized system (MIDA 1000, Ortivus Medical, Täby, Sweden) for on-line dynamic analysis in QRS complex and ST segment changes during dialysis. The on-line vectorcardiography recordings were started before the commencement of dialysis and extended over the whole hemodialysis session. To obtain ECG signals eight conventional ECG electrodes were applied to the chest of the patients according to the Frank lead system [5] and three orthogonal leads X, Y and Z were continuously recorded and analyzed. The trends at 1-min intervals for QRS vector difference (QRS-VD) and ST vector magnitude (ST-VM6) were generated by averaging the recorded ECG signals. QRS-VD is a parameter affected by all changes in the QRS complex shape. The current QRS complex was compared to the initial QRS complex and the area difference (A) was calculated from the X, Y and Z leads. The values were fed to the formula:

$$QRS\text{-}VD = \sqrt{A_x^2 + A_y^2 + A_z^2}$$

and the resulting QRS-VD plotted as a trend graph. ST magnitude was measured at every averaged beat 60 ms after the J-point and calculation proceeded in the same manner as in QRS-VD.

Blood Volume Monitoring

On the assumption that the red blood cell mass is essentially constant during the dialysis session, BV and hematocrit are inversely and linearly related to each other. Hematocrit was monitored noninvasively and continuously during each session with a CRIT-LINE instrument (In-Line Diagnostics, Riverdale, Utah, USA). This device uses a transmissive photometric technique to determine hematocrit on the basis of both absorption properties of hemoglobin and the scattering properties of red blood cells passing through the blood chamber. Hematocrit measurement was made through a sterile plastic disposable blood chamber (PN 2231, In Line Diagnostics) placed in the blood circuit between the arterial blood tubing and the dialyzer. The hematocrit as an indicator of %ΔBV was calculated every 20 s.

Extracellular Water Volume Monitoring

Bioelectric impedance analysis (BIA) was used for ECW estimation. The determination of whole-body impedance was made using the whole-body impedance cardiography channel of the CircMon B202 device (JR Medical, Tallinn, Estonia). Two pairs of electrically connected electrodes were affixed proximally to the wrists and ankles. A 30-kHz 0.7-mA alternating current was applied to the external pair of electrodes and the voltage was measured from the inner pair. ECW was calculated from the impedance index H^2/R, where H is the height of the patient and R the estimate whole-body impedance [6]. Impedance measurements were taken 5 min before the beginning of dialysis, during the procedure at 15-min intervals and at the end of the session. During the measuring the patient was always in supine position, arms at the side without touching the body, legs separated so that there was no contact between them.

Blood Analyses

Blood samples were taken before and after hemodialysis for hemoglobin (B-Hb), hematocrit (B-Hcr), sodium (P-Na), chloride (P-Cl), magnesium (P-Mg), potassium (P-K), ionised calcium (P-iCa), phosphate (P-Pi), creatinine (P-Crea), and urea (S-Urea) measurement using standard automated techniques (Kodak Ektachem 700, Technicon H2, Hitachi 717, ABL 500, CIBA Corning 634).

General Procedure

After weighing, patients were settled in bed and ECG and impedance measurement electrodes were attached after careful skin preparation. After a 15-min resting period basal ECW was determined, the fistula cannulated and blood samples collected for analyses. On-
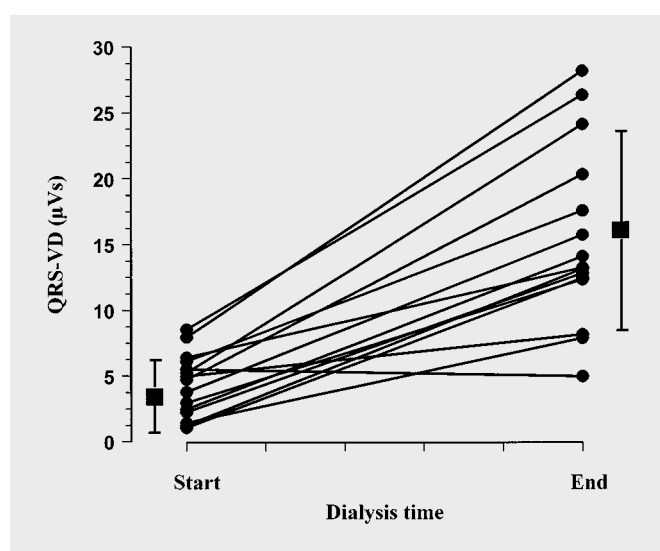
line vectorcardiography was started immediately prior to dialysis and blood volume monitoring was commenced simultaneously with ultrafiltration. During the dialysis session patients were allowed to sit only during eating. The recording of ECG data was time-synchronized with blood volume and ECW registration. During the dialysis averaged BV data were collected every 20 s, averaged ECG data at 1-min and ECW data at 15-min intervals. Body weight was again registered immediately after discontinuation of the dialysis session.

Statistical Analysis

Data were analyzed using paired t test and regression analysis. A significance level of $p < 0.05$ was considered statistically significant. The results are expressed as means ± SD (range). QRS-VD and ST-VM6 transitions caused by body position changes were removed before statistical analysis.

Results

The mean QRS-VD increase during the dialysis session (fig. 1) was almost fourfold (372 ± 300%), from 4.16 ± 2.40 to 15.60 ± 7.0 µV ($p < 0.001$). The QRS-VD change was due to a change in amplitude, since the duration of the QRS complex did not alter significantly. The mean body weight reduction was 1.89 ± 1.04 kg ($p < 0.001$; 2.78 ± 1.54%) and the mean volume removed by ultrafiltration 2.36 ± 0.96 litres. The mean ECW loss was 1.13 ± 0.54 litres ($p < 0.001$; 8.56 ± 3.79%) and the mean reduction percent in BV was 6.06 ± 5.29% ($p < 0.001$). The correlation between the changes in QRS-VD and body weight from the start to the end of dialysis was moderate and statistically significant ($r = -0.55$, $p < 0.05$). The correlation between QRS-VD and ECW change, when calculated for a single patient from 15-min values during dialysis, was moderate and statistically significant in each patient, varying from $r = -0.67$ to -0.97 ($p < 0.001$) (table 1). The correlation between BV and QRS-VD was assessed every minute during dialysis and proved statistically significant in 14 of the 15 patients, varying from $r = -0.22$ to -0.98 ($p < 0.001$). In one patient (No. 11) the correlation between the changes in QRS-VD and BV was positive and statistically insignificant ($r = 0.11$, $p = $ n.s.). All patients with poor correlation between QRS-VD and BV (No. 7, 9 and 11) had a very small BV change (0%, +1%, +1%) compared to the loss of ECW (–10%, –3%, –7%). There were no notable ST segment alterations (ST-VM6 elevation > 100 µV) during the dialysis session as shown in figure 2, representing a typical case. QRS-VD and ST-VM6 were highly sensitive to artefacts related to body position changes (fig. 3) and this phenomenon will be further debated in the discussion. Laboratory parameters reflecting volume and osmotic changes during hemo-

dialysis correlated with the QRS-VD changes: B-Hcr ($r = 0.56$, $p < 0.05$), B-Hb ($r = 0.63$, $p < 0.05$), P-Na ($r = 0.62$, $p < 0.05$) and S-Urea ($r = -0.62$, $p < 0.05$). P-K decreased ($p < 0.001$) and P-iCa concentration increased ($p < 0.05$) significantly during the dialysis, but these parameters did not correlate with the increase in QRS-VD.
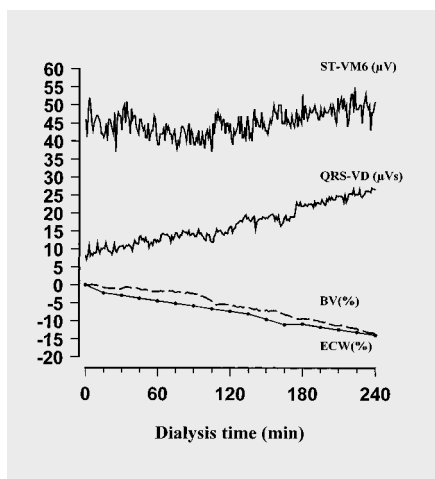

Fig. 1. QRS vector difference (QRS-VD) changes during dialysis.

Table 1. Correlation of QRS vector difference (QRS-VD) versus extracellular water (ECW), blood volume (BV) and weight change during dialysis

Patient No.	QRS-VD vs. ECW	QRS-VD vs. BV	Weight change kg (%)
1	−0.91**	−0.74**	−1.3 (−1.9)
2	−0.97**	−0.98**	−3.7 (−4.8)
3	−0.86**	−0.92**	−3.5 (−5.3)
4	−0.97**	−0.93**	−2.0 (−3.7)
5	−0.86**	−0.83**	−0.6 (−0.8)
6	−0.94**	−0.73**	−0.8 (−1.3)
7	−0.97**	−0.22**	−1.9 (−2.7)
8	−0.91**	−0.82**	−1.8 (−2.0)
9	−0.80**	−0.23*	−0.5 (−0.8)
10	−0.87**	−0.75**	−3.0 (−3.3)
11	−0.88**	0.11	−2.4 (−2.7)
12	−0.67*	−0.66**	−0.4 (−0.5)
13	−0.96*	−0.78**	−2.3 (−2.8)
14	−0.76**	−0.89**	−1.8 (−2.3)
15	−0.88**	−0.78**	−2.3 (−3.0)

* $p < 0.01$, ** $p < 0.001$.

Fig. 2. Patient (No. 4) case representing typical ST vector magnitude (ST-VM6), QRS vector difference (QRS-VD), blood volume (BV) and extracellular water (ECW) changes during dialysis.
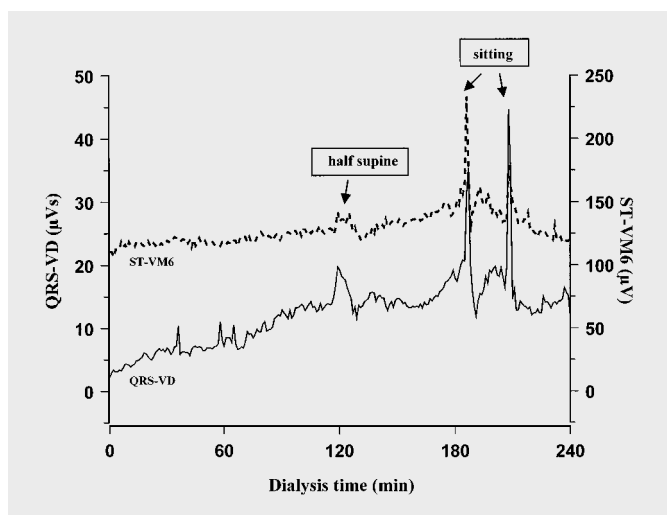
Fig. 3. QRS vector difference (QRS-VD) and ST vector magnitude (ST-VM6) artefacts related to body position changes in patient 13.

Discussion

The main result of the present study was that the increase in QRS amplitude during hemodialysis correlated significantly with the changes in body weight, BV and especially with changes in ECW, and also with biochemical parameters reflecting volume and osmotic changes.

In two earlier studies [1, 7], no correlation was found between changes in body weight and QRS amplitude dur-

ing dialysis, whereas some other studies [2–4] have shown a relationship between increase in QRS amplitude and reduction in body weight. In these studies the evaluation of the blood volume reduction on hemodialysis were based on singular body weight and hematocrit measurements. To explain those conflicting results we used continuous BV measurement and ECW determinations repeated at 15-min intervals.

In ECG changing potentials of an electrical field generated by the heart are recorded. The heart is surrounded by various tissues – lungs, muscles, fat, bones and vascular bed – which form a resistance between the heart and electrodes on the body surface shunting the heart generated electrical current. Thus electrodes placed on the surface of the body do not directly record the electrical activity of the heart itself. The ability of the tissues to conduct electric current significantly depends on their resistivity. Because ECW conducts electrical current with great ease, the resistance of the tissues surrounding the heart depends mainly on their ECW content. During hemodialysis-related ultrafiltration the water content of tissues is reduced, with the result that the electrical resistance of extracardial tissues increases and the shunting of the electrical current diminishes. The strong inverse relation between changes in QRS amplitude and ECW volume gives reason to suggest that the shunting effect of extracellular volume is the major factor influencing QRS amplitude during hemodialysis. Our findings are in agreement with those of Bayley and Berry [8], who showed on a nonhomogeneous conductivity model that the increase in 'body trunk' resistivity causes an increase in body surface potentials. Ishikawa et al. [9] investigated the influence of sauna bathing on body surface potentials and found that sauna caused an increase in QRS amplitude which was accompanied by a reduction in circulating blood volume and a decrease in heart intracavitary blood volume. These results were in conflict with the Brody effect [10], according to which a decrease in QRS amplitude should follow in this case. In our opinion, this phenomenon in QRS can be explained by the dehydration of body tissues. Tissue dehydration during hemodialysis or sauna bathing results in an increase in the resistance of the tissues surrounding the heart and thus to a decrease in the shunting effect on these tissues.

The above explanation in QRS amplitude increase during hemodialysis is supported by the relation of dialysate sodium concentration and QRS amplitude noted by Ono et al. [2] and Wizemann et al. [11]. Ono et al. [2] perceived a positive correlation between an increase in QRS amplitude and the weight loss/dry weight ratio of

patients only after standard sodium dialysis. They also observed that an increase in QRS amplitude and depression of the ST segment are significantly more frequent when patients are dialyzed with a standard sodium dialysate than when the dialysate sodium concentration is increased compared to the serum sodium concentration. Their conclusion was that, when a standard sodium dialysate is used, intravascular refilling is not rapid enough to prevent hypovolemia and which leads to myocardial ischemia. Our inference is that during ultrafiltration a dialysate sodium concentration higher than that of serum maintains ECW volume better than a lower sodium dialysate and thus the increase in QRS amplitude is not so remarkable and for the same reason ST segment changes, if they occur, are milder. Since we observed no prominent ST segment alterations we do not consider myocardial ischemia a reason for QRS amplitude rise as Diskin et al. [1] and Ono et al. [2] did.

Body position changes can also cause variations in heart and electrode positions, which can affect the QRS amplitude. In any case a QRS-VD increase in sitting or upright position cannot be explained solely by positional changes, since during head-up tilt blood is shifted from the thorax to the lower body and the electrical resistance of the tissues around the heart increases, partly explaining this positional increase in the QRS amplitude of the ECG (fig. 3).

Plasma potassium decreased and calcium concentration increased significantly during the hemodialysis session. Nonetheless, these factors, which are in principle able to modify the ECG, did not correlate with the increase in QRS-VD, while a correlation was observed between B-Hb, B-Hcr, P-Na, S-Urea and QRS-VD. These parameters all stand in relation to changes in volume or osmotic pressure and thus even these results fit to our theory of the volume dependence of the QRS-VD.

In summary, the increase in QRS amplitude during a hemodialysis session is significantly correlated to reduced ECW and the mechanism is most probably augmentation of electrical resistance caused by loss of interstitial fluid. This hemodialysis-related increase in QRS amplitude should not be taken as an indicator of left ventricular hypertrophy or myocardial ischemia unless clinical symptoms or other indices are present.

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ORIGINAL

Hemodialysis causes changes in dynamic vectorcardiographic ischemia monitoring parameters

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Abstract. Aims: The aim of this study was to establish whether changes in parameters reflecting myocardial ischemia QRS vector difference (QRS-VD), ST change vector magnitude (STC-VM) and ST vector magnitude (ST-VM6) during hemodialysis (HD) registered by MIDA (myocardial infarction dynamic analysis) are related to changes in blood volume (BV), extracellular water (ECW) and blood biochemistry. Patients and methods: Fifteen hemodialysis (HD) patients were studied. Computerized vectorcardiography was used for on-line dynamic analysis of ST segment and QRS complex changes. BV changes were monitored non-invasively and continuously with the CRIT-LINE instrument. Bioelectric impedance analysis (BIA) was used for ECW estimation. Blood samples were taken before and after hemodialysis for hemoglobin (B-Hb), hematocrit (B-Hcr), sodium (P-Na), chloride (P-Cl), magnesium (P-Mg), potassium (P-K), ionized calcium (P-iCa), phosphate (P-Pi) and astrup measurement. Results: During dialysis treatment QRS-VD, ST-VM6 and STC-VM did not change in parallel. According to the linear mixed model, no statistically significant changes were noted in ST-VM6 during dialysis (time effect $p = 0.5635$). On the other hand, QRS-VD and STC-VM showed a statistically significant linear trend (time effect for QRS-VD $p = 0.0001$ and for STC-VM $p = 0.0004$). Changes in both ECW and BV affected the change in QRS-VD and in STC-VM. Conclusion: During HD treatment changes in the vectorcardiographic ischemia monitoring parameters QRS-VD and STC-VM are mostly related to ECW and BV changes and may give a false positive impression of myocardial ischemia. The ST-VM6 trend is less markedly influenced by volume changes.

Introduction

ST segment changes are observed in 15.5% to 61% of hemodialysis (HD) patients when investigated by ambulatory Holter monitoring [Conlon et al. 1998, Kremastinos et al. 1992, Shapira and Bar-Khayim 1992, Singh et al. 1994, Zuber et al. 1989]. These changes have not correlated with either perfusion defects on radioisotope scans or angiographic findings. Changes in the plasma concentration of potassium and magnesium and in the volume of ultrafiltrate removed have been thought to play an important role in the genesis of these Holter ECG findings [Kremastinos et al. 1992, Singh et al. 1994]. Holter monitoring may thus not be reliable in screening for myocardial ischemia during the HD session. MIDA (myocardial infarction dynamic analysis) is a new widely used vectorcardiographic (VCG) ischemia monitoring system, which enables three-dimensional on-line signal registration. On MIDA registration QRS complex and ST changes are analyzed on-line to detect ischemia. In a recent study [Ojanen et al. 1999] we demonstrated that the increase in QRS complex amplitude during the HD session correlated with extracellular water (ECW). The aim of this new analysis was to ascertain whether ST changes registered by this new technique are also related to changes in ECW, blood volume (BV), and blood biochemistry induced by HD.

Table 1.   Clinical characteristics of patients.

Patients (number)	Sex (f/m)	Age (years)	Kidney disease	Time on hemodialysis (y : m)	Coronary artery disease ( )	Left ventricular hypertrophy ( )	Cardiovascular medication
1	f	36	CGLN	5 : 2	–	–	–
2	f	47	CGLN	0 : 1	–	–	cb
3	m	72	CGLN	0 : 3	+	+	bb + ab + ni
4	f	62	CGLN	0 : 6	–	–	–
5	m	64	CGLN	2 : 10	+	–	bb + cb + ni
6	m	65	ADPKD	0 : 2	+	–	–
7	m	59	ADPKD	4 : 11	–	+	–
8	m	61	DN	2 : 1	+	–	bb + cb
9	m	67	DN	0 : 6	–	–	–
10	m	70	DN	0 : 2	+	+	bb + ab + ni
11	f	66	DN	3 : 9	+	+	cb + ni
12	m	68	DN	0 : 10	+	+	ni
13	f	76	DN	1 : 3	–	+	bb + cb+ acei
14	f	66	TIN	1 : 6	–	–	cb
15	m	66	nephrectomy	5 : 6	–	–	bb

CGLN = chronic glomerulonephritis, ADPKD = adult dominant polycystic kidney disease, DN = diabetic nephropathy, TIN = tubulo-interstial nephritis. ab = alpha blocker, bb = beta blocker, cb = calcium blocker, ni = long acting nitrates, acei = angiotensin-converting enzyme inhibitor.

Patients and methods

Fifteen HD patients were studied. Patient characteristics are shown in Table 1. Their mean hematocrit level was 0.36   0.05. The diagnosis of coronary artery disease (CAD) was based on the presence of one or more of the following criteria:

− a positive history of typical angina pectoris chest pain with characteristic findings in exercise testing,
− documented pathological Q waves on the ECG,
− coronary artery stenosis greater than 50% of the lumen diameter on angiography,
− a prior history of coronary artery angioplasty or bypass surgery.

Patients were asked to report about symptoms of myocardial ischemia during the monitoring. Cardiovascular medication was allowed to continue during the study. All patients gave informed consent to participate in the study, which had been approved by the Ethics Committee of Tampere University Hospital.

Patients were dialyzed three times a week for 3.5 – 5 h (mean 4.1 h) by the Fresenius 4008E (Fresenius AG, Bad Homburg, Germany) delivery system. Cellulose acetate membrane hollow fiber dialyzers (Ca 130/170 series, Baxter Healthcare, Round Lake, IL, USA) were used. The composition of the dialysate was: Na 140 mmol/l, K 2 mmol/l, Ca 1.5 mmol/l, Mg 0.5 mmol/l, Cl 111 mmol/l, HCO_3 33 mmol/l. The dialysate temperature was 36.5 C. The blood flow rate was prescribed individually (range 250 – 350 ml/min), but the dialysate flow was fixed at 500 ml/min and the ultrafiltration rate kept constant during dialysis. All patients were ultrafiltrated until their clinically determined dry weight was reached.

We used a computerized system (MIDA, Ortivus Medical, Täby, Sweden) for on-line dynamic analysis of QRS complex and ST segment changes during dialysis. The on-line vectorcardiography recordings commenced in the advance of dialysis and extended over the whole HD session. To obtain ECG signals eight conventional ECG electrodes were applied to the chest according to the Frank lead system [Frank 1956] and three orthogonal leads X, Y and Z were continuously recorded and analyzed. The trends in one minute intervals for QRS vector difference (QRS-VD), ST change vector magnitude (STC-VM) and ST vector magnitude (ST-VM6) were generated by averaging the recorded ECG signals. QRS-VD is a parameter affected by all

changes in QRS complex shape. STC-VM constitutes the spatial difference vector between the initial and the current ST vector. ST-VM6 magnitude measures ST segment changes in every averaged beat 60 milliseconds after the J-point. Since all these parameters are measured in the X, Y and Z directions, ischemia can be detected in the entire heart. ST-VM6 and/or STC-VM increase > 50 V and QRS-VD changes over 15 VS were considered to reflect ischemia [Dellborg et al. 1991].

On the assumption that the red blood cell mass is essentially constant during dialysis, BV and hematocrit are inversely and linearly related to each other. Hematocrit was monitored non-invasively and continuously during each session with the CRIT-LINE instrument (In-Line Diagnostics, Riverdale, UT, USA). The instrument uses a transmissive photometric technique to determine hematocrit on the basis of both the absorption properties of hemoglobin and the scattering properties of red blood cells passing through the blood chamber. Hematocrit measurement was through a sterile plastic disposable blood chamber (PN 2231, In-Line Diagnostics) placed in the blood circuit between the arterial blood tubing and the dialyzer.

Bioelectric impedance analysis (BIA) was used for ECW estimation. Determination of whole-body impedance was made using the whole-body impedance cardiography channel of the CircMon B202 device (JR Medical Ltd., Tallinn, Estonia). Two pairs of near electrodes were placed immediately proximaly to the wrists and ankles [Kööbi et al. 1997]. A 30 kHz 0.7 mA alternating current was applied to the external pair of electrodes and the voltage measured from the inner pair of electrodes. ECW was calculated from impedance index H^2/R, where H is the height of the patient and R the estimated whole-body impedance. Five-minute impedance measurements were made before the beginning of dialysis, during the procedure at 15 min intervals and at the end of the session. During the measuring the patient was always in supine position, arms at the sides without touching the body.

Blood samples were taken before and after hemodialysis for hemoglobin (B-Hb), hematocrit (B-Hcr), sodium (P-Na), chloride (P-Cl), magnesium (P-Mg), potassium (P-K), ionized calcium (P-iCa), phosphate (P-Pi) and venous blood pH, and bicarbonate ion (HCO_3^-) measurement using standard automated techniques (Kodak Ektachem 700, Technicon H2, Hitachi 717, ABL 500, Ciba Corning 634).

After weighing, the patients were settled in bed and ECG and impedance measurement electrodes attached after careful skin preparation. After a 15-min resting period basal ECW was determined. On-line vectorcardiography was started immediately prior to dialysis and blood volume monitoring was commenced simultaneously with ultrafiltration. During dialysis session patients were permitted to sit only during eating. The influence of fluid and food ingestion during the treatment session was taken into account by eliminating this period from the analyses. The recording of ECG data was time-synchronized with BV and ECW registration. During dialysis, averaged BV data were collected every 20 sec, averaged ECG data in 1 min and ECW data in 15 min intervals. Body weight was registered immediately after discontinuation of dialysis.

To compare pre- and post-dialysis values in different parameters, the paired sample t-test was used. Association between laboratory and ECG parameters was evaluated using linear regression. To establish in greater detail whether there was a significant change in ECG parameters, BV and ECW during dialysis, linear mixed models for repeated measurements [Verbeke et al. 1997] were used. To ascertain the effect of change in BV and ECW on the changes in ECG parameters, we used the subject-specific slopes from the mixed models for BV and ECW as covariates in mixed models for ECG parameters. We allowed interaction between time and slope, which reveals whether the change in BV and ECW described as a slope could explain the change in ECG parameters. Linear mixed models were fitted using the Proc Mixed in SAS System for Windows version 6.12. A significance level of $p < 0.05$ was considered statistically significant. Results are expressed as means SD (range).

Results

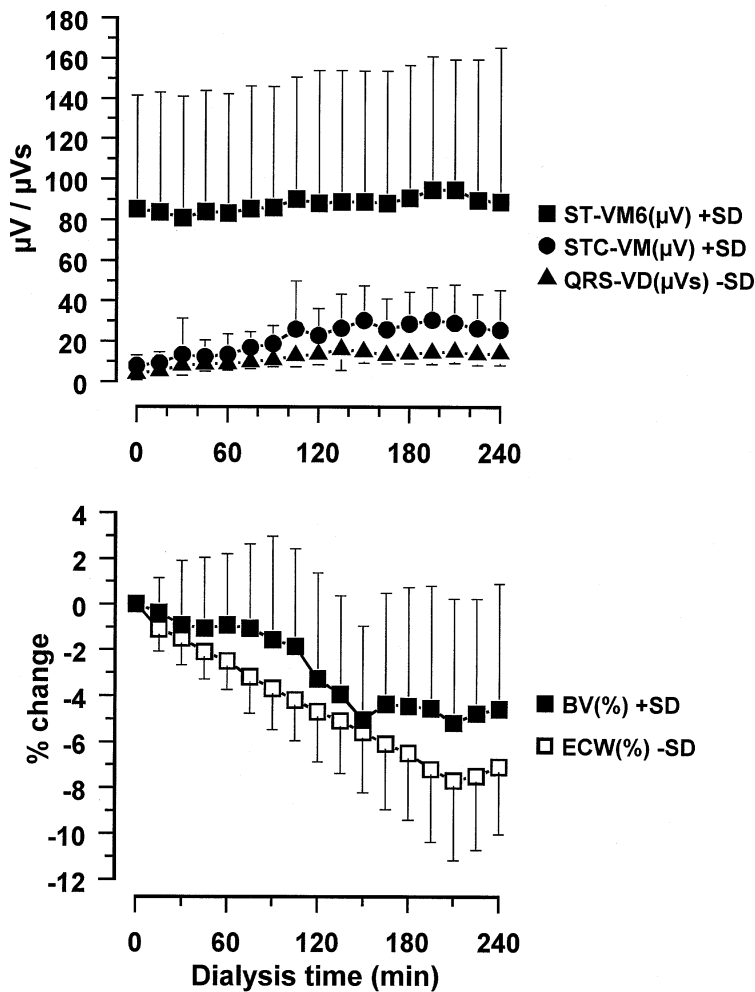During dialysis treatment QRS-VD, ST-VM6 and STC-VM did not change in par-

Figure 1. Mean changes (± SD) in QRS-VD, STC-VM, ST-VM6, blood volume (BV) and extracellular water (ECW) during hemodialysis.

Figure 2. Linear trends of QRS-VD, STC-VM and ST-VM6 change during hemodialysis. Bold line is a mean trend.

allel. QRS-VD increased during dialysis session from 3.5 ± 3.0 to 14.4 ± 6.0 μVs, (Δ% 75.5 ± 49.6), (p < 0.001) and STC-VM from 6.5 ± 5.3 to 27.3 ± 19.7 μV, (Δ% 72.5 ± 68.5), (p < 0.001). Deviating from these two parameters, the ST-VM6 change from 85.5 ± 56.1 to 88.8 ± 76.3 μV, (Δ% 3.8 ± 26.5) was not significant (Figure 1). The mean body weight reduction was 1.89 ± 1.04 kg (2.78 ± 1.54%), (p < 0.001) and the mean volume removed by ultrafiltration 2.36 ± 0.96 l. The mean ECW decline was 7.1 ± 2.9%, (p < 0.001) and the mean diminution of BV 5.0 ± 5.6%, (p < 0.001). Change in body weight correlated with the change in QRS-VD (r = –0.55, p < 0.05), STC-VM (r = –0.45, p = 0.09) and ST-VM6 (r = 0.37, p = 0.17).

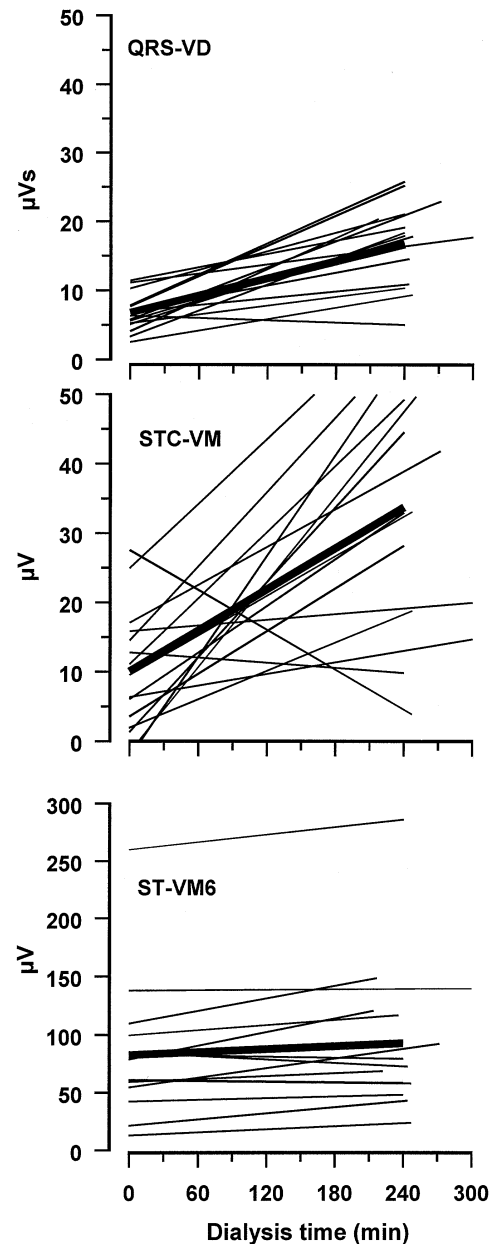According to the linear mixed model, no statistically significant change was noted in

ST-VM6 during dialysis (time effect p = 0.5635). In contrast, QRS-VD and STC-VM showed a statistically significant linear trend (time effect for QRS-VD p = 0.0001 and for STC-VM p = 0.0004), giving an impression of aggravation of ischemia (Figure 2).

When investigating the relation between ECG parameters and volume changes, we noted that changes in both ECW and BV had an effect on the change in QRS-VD and in STC-VM. This was not seen in ST-VM6 (Table 2).

Table 2. Statistical significance (p values) of vectorcardiographic parameter (QRS-VD, STC-VM, ST-VM6) changes as a function of blood volume (BV) and extracellular water (ECW) changes during dialysis.

	BV	ECW
QRS-VD	0.0001	0.0001
STC-VM	0.0001	0.0331
ST-VM6	0.2222	0.5385

Table 3. Statistical correlations between changes in vectorcardiographic parameters (QRS-VD, STC-VM, ST-VM6) and biochemical variables.

	QRS-VD R (p)	STC-VM R (p)	ST-VM6 R (p)
Hkr	0.56 (p = 0.04)	0.41 (NS)	−0.16 (NS)
Hb	0.63 (p = 0.02)	0.54 (p = 0.05)	0.16 (NS)
K	−0.35 (NS)	−0.13 (NS)	0.26 (NS)
Na	−0.59 (p = 0.03)	0.58 (p = 0.03)	−0.14 (NS)
Cl	0.43 (NS)	0.37 (NS)	−0.03 (NS)
ionCa	−0.12 (NS)	−0.37 (NS)	0.27 (NS)
Mg	−0.30 (NS)	−0.26 (NS)	0.55 (p = 0.04)
pH	0.33 (NS)	−0.21 (NS)	−0.03 (NS)
HCO_3^-	0.40 (NS)	0.30 (NS)	0.05 (NS)

No ischemic ST-VM6 changes (ST-VM6 increase > 50 V) were found during dialysis. QRS-VD increase > 15 Vs was found in 4/15 patients and STC-VM elevation > 50 V in 2/15 patients. There were no differences in the change of MIDA parameters during dialysis session between patients with or without CAD (Figure 3). Neither of those two patients with STC-VM increase over 50 V during dialysis and two of the four patients with QRS-VD increase over 15 Vs had a history of CAD. None of the 15 patients had symptoms of coronary ischemia during dialysis.

Statistical correlations between changes in vectorcardiographic parameters (QRS-VD, STC-VM, ST-VM6) and biochemical variables are presented in the Table 3.

Discussion

In a recent study the ability of on-line VCG and two-channel Holter monitoring to detect ischemic episodes was compared in non-uremic patients with unstable angina pectoris [Dellborg et al. 1995]. The authors concluded that VCG detected ischemia with
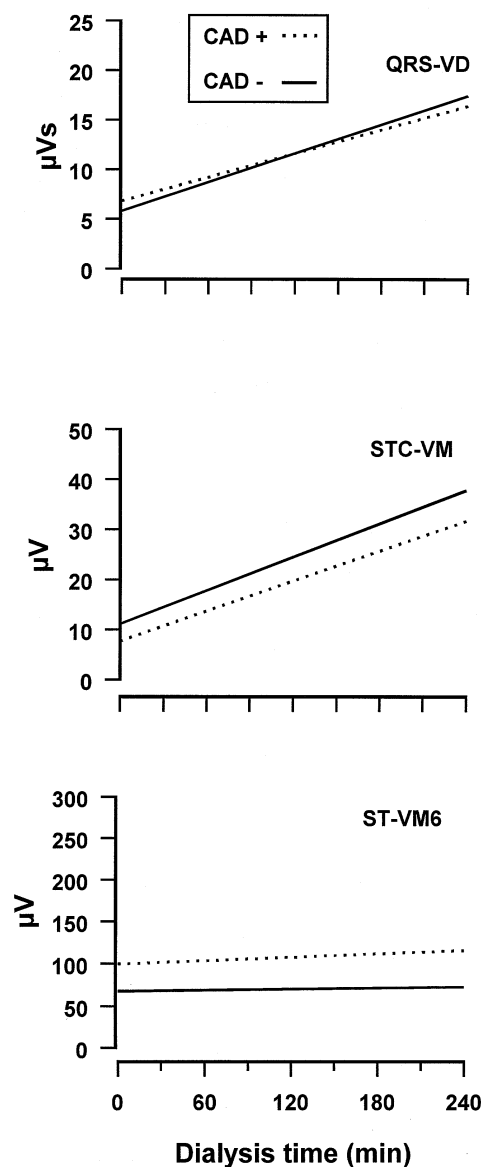

Figure 3. Mean linear trends of QRS-VD, STC-VM and ST-VM6 changes during hemodialysis in patients with (+) and without (–) coronary artery disease (CAD).

higher sensitivity than Holter ECG did. It is also assumed that in non-HD patients STC-VM detects myocardial ischemia with a higher sensitivity than ST-VM6, since ischemia sometimes causes only directional ST vector changes without simultaneous ST-VM6 changes [Jensen et al. 1994]. The value of using QRS-VD for the detection of myocardial ischemia is limited, because several mechanisms other than ischemia cause changes in the QRS complex [Feldman et al. 1985, Rosenthal et al. 1971, Sutherland et al. 1983].

In our study QRS-VD changes in 4/15 patients and STC-VM changes in 2/15 fulfilled the criteria of ischemia without concurrent ischemic changes in ST-VM6. The changes in QRS-VD and STC-VM were most probably related to volume changes, since both QRS-VD and STC-VM changes were dependent on changes in ECW and BV, while ST-VM6 did not. In a previous study we have shown and discussed how volume changes affect the amplitude and direction of the recorded vectors [Ojanen et al. 1999]. In most cases, differently from QRS-VD and STC-VM, the ST-VM6 is formed from the isoelectric phase of cardiac electrical activity. If the initial deviation of the ST segment from the isoelectric line is zero, volume related amplitude changes will not appear. Thus, in these cases ST-VM6 is less susceptible to volume-related alteration. We did not find any reasonable explanations for the relation between electrolytes and MIDA parameters. The correlations between Hb/Hcr and MIDA parameters were, however, logical as they most probably were due to volume changes.

In spite of the fact that QRS-VD and STC-VM changes were clearly dependent on changes in ECW and BV, we cannot absolutely exclude myocardial ischemia during dialysis. However, there are several reasons to assume, that our patients did not develop ischemia. First, there was no difference in MIDA parameters in patients with or without CAD, and if the changes in MIDA parameters would have been caused by ischemia, they would presumably have been more serious in patients with CAD. Secondly, none of the patients had symptoms of coronary ischemia during dialysis. Further, if the changes in the MIDA parameters during dialysis would have been caused by ischemia, they most likely would have changed in a parallel direction. Finally, ST-VM6 did not change during dialysis although the ST-segment is the classical and most widely used ECG marker of myocardial ischemia.

We did not measure serodiagnostic markers of myocardial ischemia in this study, as we are not aware of any parameter that would be more sensitive than MIDA in the detection of slight myocardial ischemia. The serologic diagnosis of myocardial ischemia is difficult in patients with end-stage renal disease because of false positive elevations in CK and troponin T. It has been estimated, for example, that 29% of patients on hemodialysis have elevated serum troponin T concentrations without evidence of myocardial injury [Bhayana et al. 1995, Haller et al. 1996, McLaurin et al. 1997]. CK-MB also may be misleading in renal failure due to non-specific enzyme elevations in 5 – 50% of renal patients [Robbins et al. 1997]. Troponin I seems to be the most specific of the currently available biochemical markers of myocardial injury in dialysis patients, but its level begins to rise only 6 – 8 h after myocardial ischemia [Martin et al. 1997].

In summary, our results would indicate that during HD treatment changes in the vectorcardiographic ischemia monitoring parameters QRS-VD and STC-VM, which are mostly related to ECW and BV changes, and may give a false positive impression of myocardial ischemia. The ST-VM6 trend is less influenced by volume changes.

Acknowledgements

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ORIGINAL

Isolated ultrafiltration affects dynamic vectorcardiographic ischemia monitoring parameters

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Abstract. Aims: The present study was undertaken to assess the role of isolated ultrafiltration (UF phase) and hemodialysis with minimal ultrafiltration (HD phase) in changes in parameters reflecting myocardial ischemia: QRS vector difference (QRS-VD), ST change vector magnitude (STC-VM) and ST vector magnitude (ST-VM6) registered by MIDA (myocardial infarction dynamic analysis). Patients and methods: Twelve patients on maintenance hemodialysis were first ultrafiltrated for 2.5 h without dialysis (UF) followed by a 2.5-hour session of hemodialysis with minimal ultrafiltration (HD). Computerized vectorcardiography (VCG) was used for on-line dynamic analysis of ST segment and QRS complex changes. Blood volume (BV) changes were monitored non-invasively and continuously with the CRIT-LINE instrument. Whole-body bioelectric impedance analysis (BIA) was used for extracellular water (ECW) estimation. Results: During the UF phase QRS-VD and STC-VM showed a statistically significant increasing linear trend (time effect for both QRS-VD and STC-VM $p < 0.0001$, while no changes were noted in ST-VM6; time effect $p = 0.986$). During the HD phase none of these parameters changed (time effect for QRS-VD $p = 0.855$, for STC-VM $p = 0.275$ and for ST-VM6 $p = 0.976$). During the UF, phase changes in QRS-VD were in close relation to those in ECW. Conclusion: Isolated ultrafiltration leads to an increase in the VCG ischemia monitoring parameters QRS-VD and STC-VM. The increase of QRS-VD is related to changes in ECW. Hemodialysis with minimal ultrafiltration has no effect on VCG ischemia monitoring parameters.

Introduction

MIDA (myocardial infarction dynamic analysis) is a new, widely used vectorcardiographic (VCG) ischemia monitoring system which makes possible 3-dimensional on-line signal registration. On MIDA registration, QRS complex and ST changes are analyzed on-line to detect ischemia. Vectorcardiography (VCG) appears to be as sensitive as standard 12-lead ECG (sECG) in the diagnosis of acute myocardial infarction or ischemia, and more sensitive in the diagnosis of inferior infarction [Edenbrandt et al. 1990]. VCG also might be useful in the early diagnosis of acute myocardial infarction, especially in patients with non-diagnostic sECG [Gustafsson et al. 1996].

However, MIDA may not be a reliable method of screening for myocardial ischemia during the HD session. Our recent studies demonstrated that during HD treatment the increase in QRS complex amplitude and changes in the VCG ischemia monitoring parameters QRS-VD and STC-VM are related mainly to ECW and BV changes. They may thus give a false positive impression of myocardial ischemia [Ojanen et al. 1999, 2000]. The ST-VM6 trend is less influenced by volume changes.

Since during normal hemodialysis fluid removal and solute removal are coincidental events, it is difficult to accurately separate their respective effects on VCG ischemia monitoring parameters. The idea of the present study was to distinguish ultrafiltration from dialy-

Table 1.   Clinical characteristics of patients.

Patients	Sex	Age	Kidney disease	Time on hemodialysis	Coronary artery disease	Cardiovascular medication
(number)	(f/m)	(years)		(y : m)	(±)	
1	f	68	ADPKD	0 : 2	–	bb
2	f	67	ADPKD	4 : 10	–	–
3	m	47	CGLN	0 : 7	–	bb + ata
4	m	51	CGLN	0 : 5	+	–
5	f	76	CGLN	0 : 3	+	–
6	f	47	CGLN	0 : 8	–	bb + cb
7	m	67	CGLN	0 : 6	–	bb
8	f	53	CGLN	0 : 4	–	bb
9	f	32	CGLN	0 : 11	–	bb + ata
10	m	51	DN	0 : 10	+	bb + acei
11	f	67	NS	3 : 6	–	bb + ata
12	m	42	SA	0 : 11	–	–

ADPKD = adult dominant polycystic kidney disease, CGLN = chronic glomerulonephritis, DN = diabetic nephropathy, NS = nephrosclerosis, SA = secondary amyloidosis, acei = angiotensin converting enzyme inhibitor, ata = angiotensin II receptor antagonist, bb = beta blocker, cb = calcium blocker, ni = long-acting nitrates.

sis, and thus gain a more profound conception of their isolated effects on MIDA parameters.

Patients and methods

Twelve HD patients were studied; their characteristics are shown in Table 1. The diagnosis of coronary artery disease was based on the presence of one or more of the following criteria: a positive history of typical angina pectoris chest pain with characteristic findings in exercise testing, documented pathological Q waves on the ECG, coronary artery stenosis greater than 50% of the lumen diameter on angiography, a prior history of coronary artery angioplasty or bypass surgery. Patients were asked to report on symptoms of myocardial ischemia during monitoring. Cardiovascular medication was allowed to continue during the study. All patients gave informed consent to participate in the study, which had been approved by the Ethics Committee of Tampere University Hospital.

The HD machine used here was a Fresenius 4008E (Fresenius AG, Bad Homburg, Germany), which controls ultrafiltration volumetrically. Cellulose acetate membrane hollow fiber dialysers (Ca 130/170 series, Baxter Healthcare, Round Lake, IL, USA) were used. The composition of the dialysate was: Na 140 mmol/l, K 2 mmol/l, Ca 1.5 mmol/l,

Mg 0.5 mmol/l, Cl 111 mmol/l, HCO_3 33 mmol/l, dialysate temperature 36.5 °C. The blood flow rate was prescribed individually (range 250 – 350 ml/min).

The 5-hour treatment session was divided into 2 parts. During the first 2.5 hours (UF phase) the dialysate flow was turned off and the ultrafiltration volume (mean 1801 ml, range 1600 – 3500) determined individually to reach patients' clinically defined dry weight. At the end of the UF phase patients were allowed to eat, and during the next 2.5 hours (HD phase) only the fluid volume they gained during the meal was removed (mean 247 ml, range 0 – 300). Dialysate flow was fixed at 500 ml/min during the HD phase.

We used a computerized system (MIDA 1000, Ortivus Medical, Täby, Sweden) for on-line dynamic analysis of QRS complex and ST segment changes. The on-line VCG recordings commenced in advance of the UF phase and extended over the whole HD phase. To obtain ECG signals, 8 conventional ECG electrodes were applied to the chest according to the Frank lead system [Frank 1956] and 3 orthogonal leads X, Y and Z were continuously recorded and analyzed. The trends at one-minute intervals for QRS vector difference (QRS-VD), ST change vector magnitude (STC-VM) and ST vector magnitude (ST-VM6) were generated by averaging the recorded ECG signals. QRS-VD is a parame-
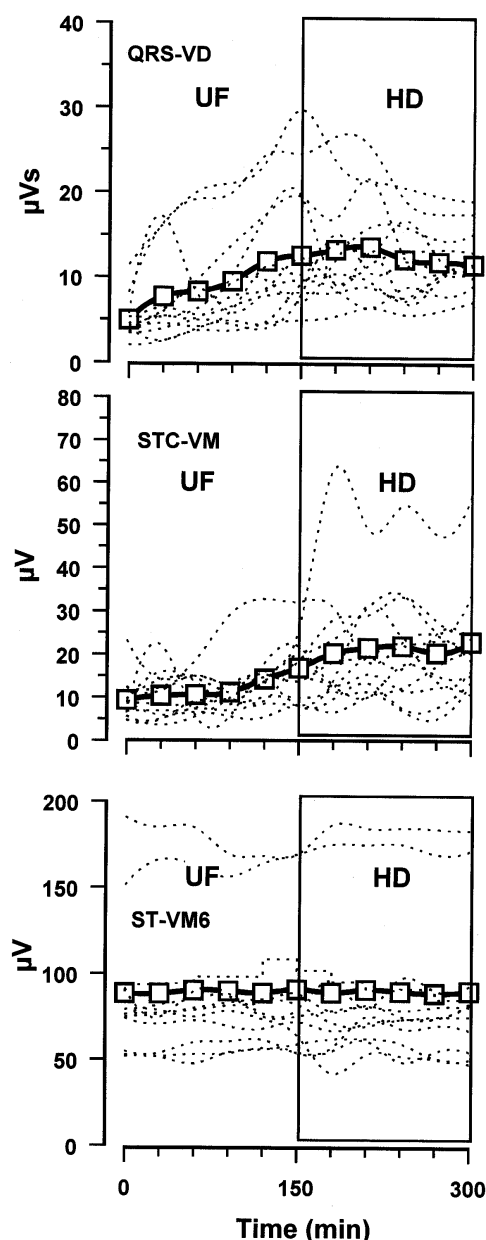
Figure 1. Changes in QRS-VD, STC-VM and ST-VM6 during UF and HD phases. Bold line is a mean trend.

ter affected by all changes in QRS complex shape. STC-VM constitutes the spatial difference vector between the initial and the current ST vector. ST -VM6 magnitude measures ST segment changes in every averaged beat 60 ms after the J point. Since all these parameters are measured in the X, Y and Z directions, ischemia can be detected throughout the entire heart. ST-VM6 and/or STC-VM increases > 50 μV and QRS-VD changes over 15 μVS were considered to reflect ischemia [Dellborg et al. 1991].

Blood volume (BV) was monitored non-invasively and continuously during each session with the CRIT-LINE instrument (In-Line Diagnostics, Riverdale, UT, USA).

Bioelectric impedance analysis (BIA) was used for ECW estimation. Determination of whole-body impedance was done using a commercially available device (B202, JR Medical Ltd., Tallinn, Estonia). Five-minute impedance measurements were made before the beginning of the UF phase, at 30-min intervals during the UF and HD phases and at the end of the HD phase.

The recording of ECG data were time-synchronized with BV and ECW registration. Averaged BV data were collected every 20 sec, averaged ECG data at 1-min and ECW data in 30-min intervals.

Blood samples were taken before and after the UF and HD phases for hematocrit (B-Hcr), urea nitrogen (P-Urea), creatinine (P-Crea), sodium (P-Na), potassium (P-K), ionized calcium (P-iCa), phosphate (P-Pi) and venous blood pH, and bicarbonate ion (HCO_3^-), and measurements were made using standard automated techniques (Kodak Ektachem 700, Technicon H2, Hitachi 717, ABL 500, Ciba Corning 634).

To compare pre- and post-values in different parameters during UF and HD phases, the paired samples t-test was used. Associations between laboratory, BV, ECW and MIDA parameters were evaluated using linear regression. To establish in greater detail whether there were significant changes in ECG parameters, BV and ECW during dialysis, linear mixed models for repeated measurements [Verbeke and Molenberghs 1997] were used. Linear mixed models were fitted using the PROC MIXED in SAS System for Windows version 6.12. A significance level of $p < 0.05$ was considered statistically significant. Results are expressed as means ± 1 SD.

Results

During the UF phase QRS-VD, ST-VM6 and STC-VM did not change in parallel. According to the linear mixed model, no statistically significant change was to be noted in ST-VM6 within the UF phase (time effect $p = 0.986$). In contrast, QRS-VD and STC-VM showed a statistically significant linear trend

Table 2. Absolute and percentage changes in vectorcardiographic parameters (QRS-VD, STC-VM, ST-VM6) during UF and HD phases.

Parameter	Change	
	UF phase	HD phase
QRS-VD		
μVs	8.6 ± 5.8*	−0.9 ± 12.7
%	59.9 ± 13.7*	−0.6 ± 12.8
STC-VM		
μV	7.3 ± 5.1*	5.6 ± 12.4
%	40.5 ± 22.6*	11.1 ± 55.6
ST-VM6		
μV	0.9 ± 12.7	−0.4 ± 11.9
%	0.6 ± 12.8	−2.9 ± 16.8

Values are given as means ± 1 SD, * = p < 0.0001.

Table 3. Statistical significance (p values) of vectorcardiographic parameter (QRS-VD, STC-VM, ST-VM6) changes as a function of extracellular water (ECW) and blood volume (BV) changes during the UF phase.

Parameter	ECW	BV
QRS-VD	0.0033	0.5010
STC-VM	0.1027	0.1342
ST-VM6	0.5561	0.5190

Figure 2. Changes in blood volume (BV) and extracellular water (ECW) during UF and HD phases. Bold line is a mean trend

$p = 0.855$, for STC-VM $p = 0.275$ and for ST-VM6 $p = 0.976$ (Figure 1). The absolute and percentage changes in MIDA parameters within the UF and HD phases are presented in Table 2.

Changes in STC-VM or ST-VM6 reflecting ischemia (increase > 50 μV) were not observed during the UF or HD phases. A QRS-VD increase > 15 μVs indicative of ischemia was found in 3/12 patients during the UF phase, but in none during the HD phase. None of the 3 patients in question had a history of CAD coronary artery disease. None of the 12 patients evinced clinical symptoms of coronary ischemia during the study.

The mean volume removed by ultrafiltration during the UF phase was 1.80 ± 0.72 l. The mean ECW decline at the same time was 8.0 ± 2.3%, (1.0 ± 0.3 l), (p < 0.0001) and the mean diminution of BV 7.6 ± 3.4%, (p < 0.0001). The mean volume removed by ultrafiltration during the HD phase was 0.25 ± 0.93 l. The mean ECW declined at the same time by 0.7 ± 1.8%, (0.1 ± 0.23 l), (p = 0.829) and the mean BV increased by 2.8 ± 3.0%, (p < 0.0001) (Figure 2). During the UF phase, the change in ECW was related to QRS-VD, but no relation was observed between other VCG parameters and blood volume changes (Table 3). Changes in biochemical variables during the UF and HD phases are presented in Table 4. No significant correlations were seen between changes in MIDA parameters and biochemical variables.
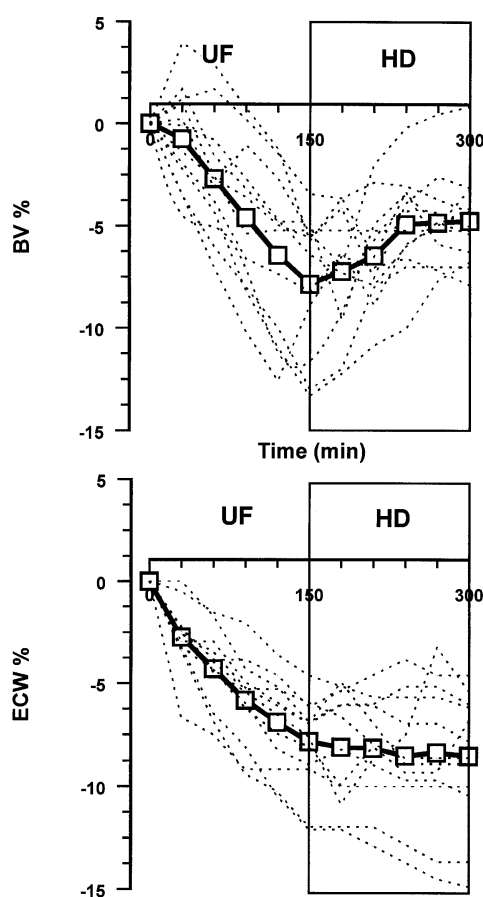
Discussion

The results of the present study indicate that QRS-VD is the most sensitive of the MIDA parameters to the influence of changes in ECW. This is in agreement with earlier re-

(time effect for both QRS-VD and STC-VM p < 0.0001). No statistically significant changes were observed in QRS-VD, STC-VM or ST-VM6 during the HD phase. During this phase the time effect for QRS-VD was

Table 4.   Changes in biochemical parameters and the statistical significance of the change (p values) during UF and HD phases.

Parameters	Change	
	UF phase	HD phase
Hcr	0.03 ± 0.02 (p < 0.0001)	–0.01 ± 0.02 (p < 0.005)
K mmol/l	0.04 ± 0.50 (p = NS)	–1.21 ± 0.55 (p < 0.0001)
Na mmol/l	0.7 ± 1.67 (p = NS)	0.3 ± 1.07 (p = NS)
Krea μmol/l	–71.9 ± 53.22 (p < 0.001)	–334.0 ± 165.30 (p < 0.0001)
Urea mmol/l	–2.2 ± 1.73 (p < 0.01)	– 8.9 ± 2.78 (p < 0.0001)
Pi mmol/l	–0.24 ± 0.17 (p < 0.005)	–0.73 ± 0.35 (p < 0.0001)
iCa mmol/l	0.04 ± 0.04 (p < 0.005)	0.03 ± 0.06 (p < 0.05)
pH	0.02 ± 0.04 (p = NS)	0.07 ± 0.02 (p < 0.0001)
HCO_3	0.57 ± 1.86 (p = NS)	4.67 ± 1.41 (p < 0.0001)

Values are given as means ± 1 SD.

ports indicating that QRS-VD is very sensitive to many factors, such as changes in body position, left ventricular chamber size, contrast injection and ventricular conduction velocity [Feldman et al. 1985, Jensen et al. 1997, Sutherland et al. 1983]. However, STC-VM is also, albeit to a lesser degree than QRS-VD, influenced by changes in, for example, body position [Norgaard et al. 2000]. The present results also confirm our earlier findings that ST-VM6 is not related to changes in ECW or BV [Ojanen et al. 2000].

It was demonstrated here that QRS-VD correlated to ECW but not to BV. The result is reasonable since ECW conducts electrical current to the body surface. The lack of correlation with BV is due to the refilling effect, in which refilling continually shifts fluid from the interstitial space to the blood compartment with various amount and timing in individual patients. Although the refilling was continuous during the study, it was clearly perceptible during the HD phase, when ECW did not change but BV increased (Figure 2).

In our previous study in patients in combined ultrafiltration-dialysis, the increase in STC-VM was related to changes in ECW and BV [Ojanen et al. 2000]. Although there was a trend in the present study, the increase in STC-VM during the UF phase was not related to changes in ECW and BV. Certain factors could explain this discrepancy. The increase in STC-VM was much less marked in the current study than in our earlier study, and the rate and the timing of the ultrafiltration were very different in these two studies. Finally, the individual variation in the trend of STC-VM was quite large in the present case.

An important finding here was that changes in electrolytes have no notable effect on MIDA parameters. This result is congruent with our earlier findings in patients on combined ultrafiltration-dialysis [Ojanen et al. 2000]. In earlier studies using 12-lead ECG or Holter recording during combined ultrafiltration dialysis, no correlations have been observed between changes in electrolytes and ST depression [Shapira and Bar-Khayim 1992, Singh et al. 1993]. The reason why the change in plasma potassium level had no effect on MIDA parameters is not obvious. Severe hyperkalemia (6.5 mmol/l or over) may widen the QRS complex [Surawicz 1967] and decrease the amplitude of the QRS complex, and so in theory could have an effect on QRS-VD. In our study, however, the mean plasma potassium concentrations were clearly under the level mentioned above.

In conclusion, isolated ultrafiltration leads to an increase in the VCG ischemia monitoring parameters QRS-VD and STC-VM. The increase in QRS-VD is closely related to changes in ECW. Hemodialysis with minimal ultrafiltration has no effect on VCG ischemia monitoring parameters. The clinical implication of the study is that during hemodialysis treatment it is ultrafiltration that causes changes in VCG ischemia monitoring parameters which may give a false positive impression of myocardial ischemia.

Acknowledgments

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Original Article

The effect of isolated ultrafiltration on Doppler-derived indices of left ventricular diastolic function

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Abstract

Background. Haemodialysis (HD) is associated with acute changes simultaneously in fluid status (ultrafiltration) and in many biochemical parameters (dialysis). Reports on the effects of these changes on left ventricular (LV) diastolic function are scant. This study evaluated the effect of isolated ultrafiltration (UF) and subsequent HD with minimal fluid removal on Doppler-derived indices of LV diastolic function in patients who were asymptomatic and stable on HD.

Methods. In 11 HD cases, the 5 h treatment session was divided into a 2.5 h period of fluid removal without dialysis (UF phase) and 2.5 h of dialysis with minimal fluid removal (HD phase). We examined the following parameters of LV diastolic function echocardiographically: early rapid filling (Emax), atrial peak filling (Amax), Emax/Amax ratio, isovolumic relaxation time (IVRT) and deceleration time of the E-wave (DT).

Results. During the UF phase, Emax decreased from 0.82 ± 0.2 to 0.62 ± 0.2 m/s ($P = 0.003$), Amax decreased from 0.72 ± 0.2 to 0.63 ± 0.2 m/s ($P = 0.042$) and the ratio Emax/Amax did not change ($P = NS$). During the HD phase, Emax increased from 0.62 ± 0.2 to 0.72 ± 0.2 m/s ($P = 0.018$), Amax increased from 0.63 ± 0.2 to 0.70 ± 0.3 m/s ($P = NS$) and the Emax/Amax ratio remained unchanged ($P = NS$). IVRT was prolonged in 10 out of 11 patients at the start of the UF phase and it was further prolonged from 142 ± 40 to 171 ± 55 ms ($P = 0.03$) during the UF phase. IVRT did not alter during the HD phase ($P = NS$). During the UF phase, DT increased from 175 ± 83 to 244 ± 119 and it decreased from 244 ± 119 to 209 ± 98 in the HD phase, but both changes were statistically insignificant. No statistically significant correlations were observed between the changes in the Doppler indices of diastolic function and changes in biochemical parameters during the HD phase.

Conclusions. UF affects the parameters Emax, Amax and IVRT used to evaluate LV diastolic function. The changes in Emax and Amax during the HD phase are due to fluid refilling from tissues into the blood space, HD as such having no effect on Doppler indices. However, isolated UF or HD does not affect the Emax/Amax ratio. Emax and IVRT seem to be the most volume-sensitive parameters.

Keywords: haemodialysis; isolated ultrafiltration; left ventricular diastolic function

Introduction

It has been accepted generally that the principal functional disorder in uraemic cardiomyopathy in patients on renal replacement therapy is left ventricular (LV) diastolic dysfunction. Its prevalence appears to be 30–60% [1,2]. It results from impaired LV diastolic relaxation and decreased LV compliance. Diastolic function is of considerable importance in the haemodynamic response to hypovolaemia, and dialysis patients with reduced LV compliance are particularly sensitive to haemodialysis (HD) hypotension [2–4]. The aim of this study was to explore the impact of ultrafiltration (UF) during dialysis on Doppler-derived indices of LV diastolic function in patients who are asymptomatic and stable on HD.

Diastolic LV function can be assessed non-invasively using pulsed Doppler analysis of flow across the mitral valve during diastole. Normally, as the mitral valve opens, ventricular relaxation occurs, with a rapid increase in flow leading to an early peak (Emax), followed by a later increase, to the atrial peak (Amax), which reflects atrial contraction. When the relaxation of the LV is reduced, Emax decreases. Thus, the second (atrial contraction) phase becomes compensatorily

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more important, resulting in a lowered Emax/Amax ratio.

Many previous studies have evaluated the effect of HD on LV diastolic function [5–8]. Emax, Amax, the Emax/Amax ratio, deceleration time (DT) and isovolumic relaxation time (IVRT), Doppler-derived indices, have been used to estimate function. In clinical practice, the Emax/Amax ratio is the most commonly used parameter [9], but its assessment value is limited in dialysis patients, since the pattern of LV diastolic filling is significantly altered by changes in preload [10]. Earlier studies suggest the preload-dependence of rapid early diastolic filling, but no significant change in the maximum velocity of the A-wave [5–8]. A decrease in the Emax/Amax ratio during UF might, thus, be interpreted erroneously to indicate deterioration of LV diastolic function.

Although HD entails acute changes both in preload (ultrafiltration) and in many biochemical parameters, the separate effects of HD and UF on diastolic function have not been studied adequately. In one study two incomparable dialyses were performed on different days: HD with and without fluid removal [11]. In our study, UF without dialysis and dialysis with only minimal UF were carried out sequentially during one session and simultaneous changes in LV diastolic function parameters were examined echocardiographically.

Subjects and methods

The study cohort consisted of 11 patients [six females and five males, aged 32–76 years (mean age ± SD: 55.9 ± 13.8 years)] with end-stage renal disease who were on regular maintenance HD for 4–5 h thrice weekly, with a mean time on dialysis of 13 ± 6 months. The clinical characteristics of the studied patients and the other patients in the unit are summarized in Table 1. Table 2 compares weight changes and UF rates between these two groups. All patients were in sinus rhythm, in a stable haemodynamic state and were allowed to continue their usual medications.

The machine used for HD was a Fresenius 4008E (Fresenius AG, Bad Homburg, Germany), which controls UF volumetrically and which was fitted with cellulose acetate membrane hollow-fibre dialysers (Ca 130/170 series; Baxter Healthcare, Round Lake, IL, USA). The dialysate consisted of Na 140 mmol/l, K 2 mmol/l, Ca 1.5 mmol/l, Mg 0.5 mmol/l, Cl 111 mmol/l, HCO$_3$ 33 mmol/l, used at 36.5°C. The blood flow rate was individually prescribed (range: 250–350 ml/min).

The study session took place 43–45 h after a standard dialysis. A 5 h treatment session was divided into two parts. During the first 2.5 h (UF phase) the dialysate flow was turned off and the UF volume (mean: 1819 ml; range: 1060–3500 ml) was determined individually to yield a patient's clinically defined dry weight. At the close of the UF phase, patients were allowed to eat and during the next 2.5 h (HD phase) only the fluid volume they gained during the meal was removed (mean: 254 ml; range: 0–300 ml). Dialysate flow was fixed at 500 ml/min during the HD phase.

M-mode, two-dimensional and Doppler echocardiographic examinations were performed before and after the UF and after the HD phases by a single experienced observer (V.V.) using a Wingmed ultrasound unit with a 2.5 MHz transducer. The following parameters were assessed: left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVST) and left ventricular posterior wall thickness (LVPWT). Left ventricular mass

Table 2. Comparison of mean weight changes (kg) and mean UF (ml) between the studied patients and other HD patients in the unit

	PrevpostdW	PredW	PostdW	Wgain	Wred	UFtot
Studied patients (n = 11)	73.4	75.0	73.1	1.6	1.9	2073
SD	13.9	14.2	14.0	1.0	0.7	742.7
Other HD patients (n = 46)	73.6	75.0	73.2	1.5	1.8	2146
SD	20.4	20.8	20.2	1.0	1.1	1106.9

PrevpostdW, weight after the previous dialysis; PredW, weight before the study dialysis or normal dialysis (in the other HD patients in the unit); PostdW, weight after the study dialysis or normal dialysis (in the other HD patients in the unit); Wgain, weight gain between the previous dialysis and the study dialysis or normal dialysis (in the other HD patients in the unit); Wred, weight reduction during the dialysis; UFtot, total UF during the study dialysis or normal dialysis (in the other HD patients in the unit).

Table 1. Clinical characteristics of the studied patients and other HD patients in the unit

	Mean age	Sex		Diagnosis						Medication			
	Years	F	M	CGLN	DN	ADPKD	NS	AMYL	Other	ACEI	ATA	BB	CB
Studied patients (n = 11)	55.9	6	5	6	1	2	1	1	0	1	3	7	1
%		55	45	55	9	18	9	9	0	9	27	65	9
Other HD patients (n = 46)	59.2	15	31	10	18	4	3	2	9	5	6	28	19
%		33	67	22	39	9	7	4	20	11	13	61	41

F, female; M, male; CGLN, chronic glomerulonephritis; DN, diabetic nephropathy; ADPKD, adult dominant polycystic disease; NS, nephrosclerosis; AMYL, amyloidosis; ACEI, angiotensin-converting enzyme inhibitor; ATA, angiotensin-II-receptor antagonist; BB, beta-blocker; CB, calcium blocker.

(LVM) was calculated according to the formula of Devereux *et al.* [9]:

$$LVM(g) = 1.04\,[(LVEDD + IVST + LVPWT)^3$$
$$- (LVEDD)^3] - 13.6$$

LVM was corrected for body surface area to give the LVM index (LVMI). Left ventricular hypertrophy (LVH) was defined as an LVMI $>134\,g/m^2$ for males and $>110\,g/m^2$ for females at the end of the UF phase [12]. Left ventricular fractional shortening (FS) was defined as:

$$FS(\%) = (LVEDD - LVSD) \times 100/LVEDD$$

Systolic dysfunction was defined as an FS $<25\%$. Left atrial enlargement was defined as a left atrial diameter $>40\,mm$, after UF [13].

The mitral inflow velocity was measured by pulsed-wave Doppler echocardiography in the apical four-chamber view. The following indices were measured or calculated: maximal early diastolic flow velocity (Emax); maximal late atrial flow velocity (Amax); the Emax/Amax ratio; iso-volumic relaxation time (IVRT), measured as the time from the closure of the aortic valve to the onset of mitral valve opening; and the rate of decrease in velocity fol-lowing the E-velocity, measured as the deceleration time (DT). The criteria for diagnosing diastolic heart failure were based on the working group report of the European Study Group on Diastolic Heart Failure [14]. The reproducibility of M-mode and Doppler echocardiography has been published earlier by our group [15].

A whole-body impedance cardiograph (CircMon^{TM} B202 device; JR Medical Ltd, Tallinn, Estonia) was used to estimate changes in extracellular water (ECW) and haemodynamic responses, as described elsewhere [16,17]. The following haemodynamic parameters were measured: heart rate (HR), stroke volume (SV) and cardiac output (CO). Systolic (SBP) and diastolic blood pressure (DBP) (measured by a manual sphygmomanometer) and their values were entered into CircMon^{TM} B202 database. Systemic vascular resistance (SVR) was calculated accord-ing to the formula $SVR = 79.96\,(MAP/CO)$. Five-minute impedance measurements were made before the start of the UF phase, at 30 min intervals during the UF and HD phases and at the end of the HD phase. Blood volume (BV) was monitored non-invasively and continuously during each session with the CRIT-LINE^{TM} instrument (In-Line Diagnostics, Riverdale, UT, USA). During the study, averaged BV data were collected every 20 s and ECW data every 30 min.

Blood samples were taken before and after the UF and HD phases for haematocrit (B-Hct), sodium (P-Na), potas-sium (P-K), ionized calcium (P-iCa), phosphate (P-Pi) and venous blood pH and bicarbonate ion (HCO_3^-), quantifica-tion being done with standard automated techniques (Kodak Ektachem 700, Technicon H2, Hitachi 717, ABL 500, CIBA Corning 634).

To compare changes in different parameters during the study, we used the two-way paired samples *t*-test with a Bonferroni adjustment. Associations between laboratory, BV, ECW, haemodynamic and echocardiographic param-eters were evaluated using linear regression. A *P*-value of <0.05 was considered statistically significant. Results are expressed as means $\pm$ SD.

All patients gave informed consent to participate in the study, which had been approved by the Ethics Committee of Tampere University Hospital.

Results

Figure 1 illustrates changes in BV and ECW during the study. The mean amount of fluid removed during the UF phase was 1.82 ± 0.75 l (range: 1.06–3.50 l; 667 ± 356 ml/h; range: 432–1400 ml/h). The mean ECW decline at the same time was $7.9 \pm 2.4\%$ ($P < 0.001$) and the mean diminution of BV was $7.8 \pm 3.4\%$ ($P < 0.001$). The mean amount of fluid removed during the HD phase was 0.25 ± 0.911 (range: 0–0.30 l; 93 ± 45 ml/h; range: 0–132 ml/h). During the HD phase, ECW declined by $0.6 \pm 1.8\%$ ($P = NS$) and BV increased by $2.9 \pm 2.8\%$ ($P < 0.001$).

The effects of isolated UF and HD with minimal UF on cardiac parameters are listed in Table 3. During the UF phase, Emax decreased from 0.82 ± 0.2 to 0.62 ± 0.2 m/s ($P = 0.001$) and Amax from 0.72 ± 0.2 to 0.63 ± 0.2 m/s ($P = 0.014$); the change in their ratio
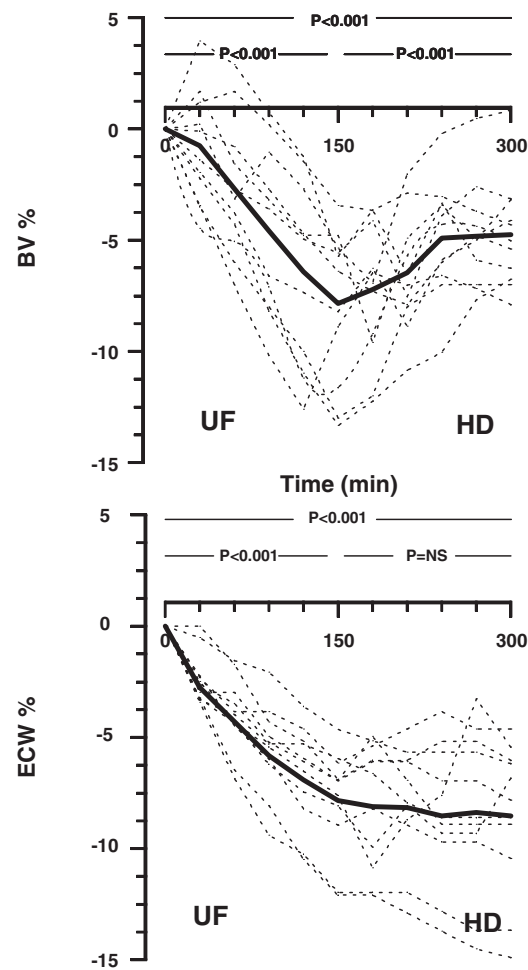
Fig. 1. Percentages of changes in BV and ECW during UF and HD with minimal UF. The bold line is the mean of the changes.

Table 3. Effects of UF and HD on Doppler and M-mode echocardiography indices and the statistical significance of the changes (*P*-values)

Parameters	Before UF	After UF and before HD	After HD	P-value before UF vs after UF	P-value before HD vs after HD	P-value before UF vs after HD
Emax (m/s)	0.82 ± 0.2	0.62 ± 0.2	0.72 ± 0.2	0.003	0.0018	NS
Amax (m/s)	0.72 ± 0.2	0.63 ± 0.2	0.70 ± 0.3	0.042	NS	NS
Emax/Amax	1.18 ± 0.4	1.07 ± 0.4	1.12 ± 0.4	NS	NS	NS
DT (ms)	175 ± 83	244 ± 119	209 ± 98	NS	NS	NS
IVRT (ms)	142 ± 40	171 ± 55	169 ± 47	0.03	NS	NS
LVEDD (mm)	58.2 ± 5.0	55.6 ± 9.4	56.6 ± 6.7	NS	NS	NS
LVESD (mm)	41.2 ± 7.9	40.6 ± 11.6	39.7 ± 6.8	NS	NS	NS
LAD (mm)	44.8 ± 5.51	41.2 ± 6.91	40.4 ± 6.19	NS	NS	NS
IVST (mm)	12.6 ± 1.9	12.8 ± 2.31	13.0 ± 2.19	NS	NS	NS
LVPWT (mm)	11.7 ± 1.62	11.1 ± 1.56	10.9 ± 1.10	NS	NS	NS
LVMI (g/m²)	198.0 ± 39.5	203.4 ± 86.8	174.8 ± 31.5	NS	NS	NS
FS (%)	29.5 ± 9.23	27.9 ± 9.08	29.8 ± 6.79	NS	NS	NS

Data are presented as means ± SD, paired *t*-test before *vs* after.

(Emax/Amax) from 1.18 ± 0.4 to 1.07 ± 0.4 was not statistically significant ($P = $ NS). At the time of UF, other echocardiographic indicators of diastolic function, IVRT and DT, lengthened, but DT insignificantly. During the HD phase, an increase in Emax from 0.62 ± 0.2 to 0.72 ± 0.2 m/s ($P = 0.018$) was the only statistically significant change in the parameters of diastolic function. Amax increased from 0.63 ± 0.2 to 0.70 ± 0.3 m/s ($P = $ NS), while Emax/Amax did not change significantly (from 1.07 ± 0.4 to 1.12 ± 0.4; $P = $ NS). When pre- and post-study values were compared, the changes in Emax from 0.82 ± 0.2 to 0.72 ± 0.2, in Amax from 0.72 ± 0.2 to 0.70 ± 0.3 and in Emax/Amax from 1.18 ± 0.4 to 1.12 ± 0.4 were statistically insignificant. The changes in Emax, Amax and in the Emax/Amax ratio are illustrated in Figure 2 and the changes in IVRT and DT in Figure 3.

During the UF phase, left atrial diameter decreased from 44.8 ± 5.51 to 41.2 ± 6.9 ($P = $ NS) and during the HD phase from 41.2 ± 6.9 to 40.4 ± 6.19 ($P = $ NS). In this study population, LVH was detected in every patient and left atrial enlargement in five out of 11. The systolic function of the heart was impaired in four patients and remained abnormal during the study in all of them.

The changes in systemic haemodynamic variables and laboratory values are presented in Tables 4 and 5, respectively.

No statistically significant correlations were observed between the changes in Emax or Amax and the changes in haemodynamic parameters during the UF and HD phases. Furthermore, the changes in the dimensions of the heart did not correlate with those of Emax and Amax. However, if we analyse the whole group, there were close and logical Pearson correlations between the changes in the means of Emax, Amax, SV and HR during both the UF ($R = 0.99$, $P < 0.001$) and HD ($R = 0.99$, $P < 0.001$) phases.

During the UF phase, the change in Emax showed some correlation with the amount of UF ($R = 0.45$, $P = 0.17$) and the change in BV ($R = 0.44$, $P = 0.17$).
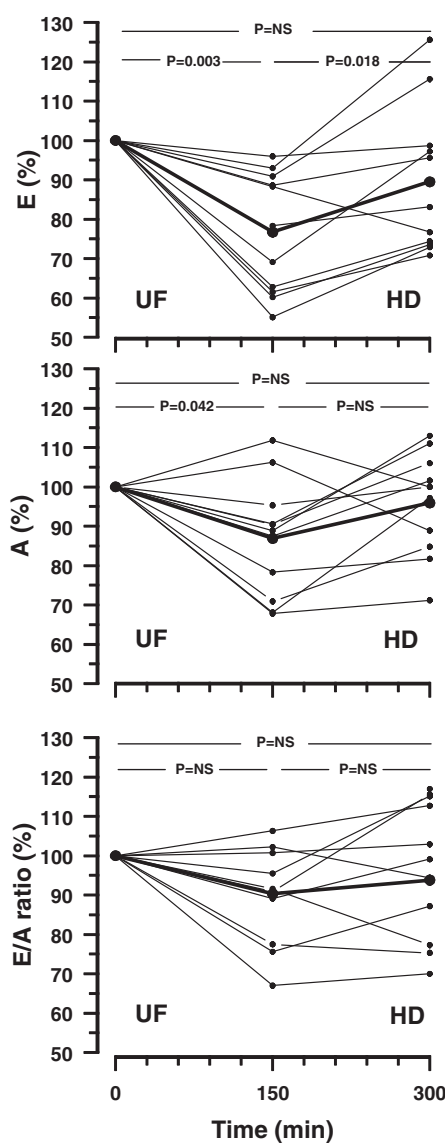
Fig. 2. Percentages of changes in Emax, Amax and the Emax/Amax ratio during UF and HD with minimal UF. The bold line is the mean of the changes.

There was an inverse correlation between the changes in plasma iCa and the changes in Emax during the UF phase ($R = -0.64$, $P = 0.04$). Also, the changes in HCO_3 correlated negatively with changes in Emax during the UF phase ($R = -0.71$, $P = 0.01$).
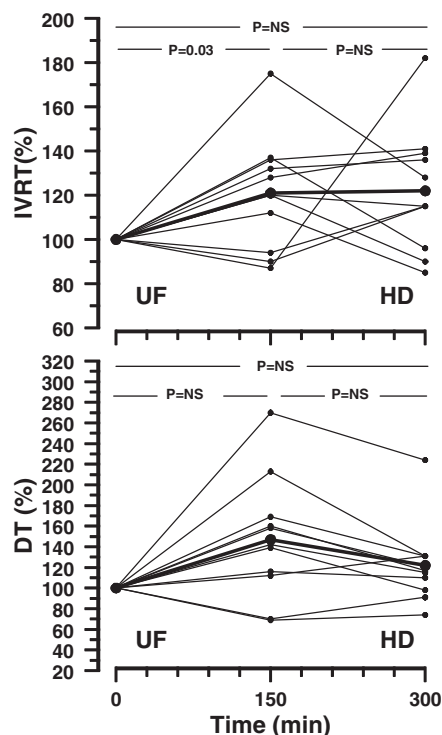
Fig. 3. Percentages of changes in IVRT and DT during UF and HD with minimal UF. The bold line is the mean of the changes.

There was no significant relationship between other biochemical parameters and pulsed Doppler indices during the study.

The Emax/Amax ratio was abnormal in only one patient at the start of the study. This ratio changed during the study in two cases from normal to abnormal and in one from abnormal to normal. At the start of the study DT was abnormal in two patients. DT changed from normal to abnormal in three patients during the UF phase but normalized in two of them during the HD phase. IVRT was abnormal in 10 out of 11 patients throughout the study and the IVRT of that one normal patient also changed to abnormal during the HD phase.

Discussion

The only essential external factor that changed during the UF phase was fluid balance, which in turn is closely associated with changes in preload. Our study thus indicates that a change in preload has an effect on Emax, Amax, IVRT and DT, but not on the Emax/Amax ratio. The constancy we observed in the Emax/Amax ratio is at odds with earlier reports showing that fluid removal during standard dialysis with UF reduces mainly Emax velocity and, thus, the Emax/Amax ratio [5–8,11,18]. It is necessary, however, to point out that in some of those studies Amax velocity diminished also, albeit clearly less than Emax [6,18].

The already-known dependency of Emax on preload was confirmed in our study, but the marked diminution of Amax during UF was a new finding.

Table 4. Effects of UF and HD on systemic haemodynamic parameters and the statistical significance of changes (*P*-values)

Parameters	Before UF	After UF and before HD	After HD	*P*-value before UF *vs* after UF	*P*-value before HD *vs* after HD	*P*-value before UF *vs* after HD
HR (beats/min)	69.5 ± 13	66.3 ± 11	71.8 ± 13	0.006	0.003	NS
SV (ml)	67.8 ± 14	62.5 ± 12	68.5 ± 13	NS	NS	NS
CO (l)	4.8 ± 1.4	4.2 ± 1.2	5.0 ± 1.4	0.024	0.000	NS
SBP (mmHg)	164 ± 28	157 ± 36	162 ± 33	NS	NS	NS
DBP (mmHg)	90 ± 12	88 ± 15	88 ± 23	NS	NS	NS
SVR (dyn·s/cm^5)	2037 ± 747	2231 ± 888	1908 ± 843	NS	0.018	NS

Data are presented as means $\pm$ SD, paired *t*-test before *vs* after.

Table 5. Effects of UF and HD on biochemical parameters and the statistical significance of changes (*P*-values)

Parameters	Before UF	After UF and before HD	After HD	*P*-value before UF *vs* after UF	*P*-value before HD *vs* after HD	*P*-value before UF *vs* after HD
Hct (%)	0.35 ± 0.04	0.38 ± 0.04	0.37 ± 0.04	0.000	0.000	0.03
Urea (mmol/l)	19.7 ± 5	17.4 ± 5	8.5 ± 3	0.006	0.000	0.000
K (mmol/l)	5.0 ± 0.8	5.0 ± 1.0	3.8 ± 0.5	NS	0.000	0.000
iCa (mmol/l)	1.20 ± 0.1	1.24 ± 0.1	1.27 ± 0.1	0.009	NS	0.009
HCO_3 (mmol/l)	23.3 ± 3	23.9 ± 2	28.7 ± 2	NS	0.000	0.000
pH	7.40 ± 0.03	7.42 ± 0.04	7.48 ± 0.03	NS	0.000	0.000

Data are presented as means $\pm$ SD, paired *t*-test before *vs* after.

The maximal velocity of the A-wave depends on, among other factors, heart rate and the contractility of the left atrium [10]. A decrease in heart rate, even within the physiological range, reduces atrial velocities. Our patients evinced significant decreases in heart rates during the UF phase and increases during the HD phase, but no correlation was observed between changes in heart rate and Amax. Myocardial contractility does not usually decrease during normal HD and may even increase [19]. The situation is different in isolated UF, during which cardiac output decreases according to the Frank–Starling mechanism, i.e. stroke volume decreases concomitantly with a decrease in preload [19]. It is thus possible that the concomitant decreases in the contractility of the left atrium and of the heart rate during isolated UF explain the considerable diminution of the A-velocity. An increase seen in A-velocity during the UF phase in two patients may be due to the somewhat lower fluid removal they underwent. The increases in Emax and Amax during the HD phase were obviously due to fluid refilling from the extracellular space into the blood space.

Our study confirmed the observation of Chakko and colleagues [11], that HD without fluid removal has no effect on LV diastolic filling parameters. To eliminate the effect of refilling during the HD phase would have required a study design in which isovolaemic dialysis is followed by UF alone. We did not want to do that, because during isovolaemic dialysis the rapid rate of solute removal results in an abrupt fall in plasma osmolality that contributes to the development of hypotension during the quite short UF phase. It is also worthy of remark that the main focus of our study was on the UF phase and only the Emax of Doppler-derived indices of diastolic function changed significantly during the HD phase.

We observed a very mild but statistically significant rise in the plasma concentration of ionized calcium during the UF phase, correlating with the decrease in Emax. This rise may be due to UF and the Donnan effect [20], wherein a change in the concentration of negatively charged albumin causes a small parallel change in the concentration of positively charged calcium.

A long IVRT reflects a reduction in LV relaxation and usually it is associated with myocardial ischaemia or LV hypertrophy, of which the latter was present in all of our patients [21]. In spite of the fact that a high preload shortens IVRT [10], it was prolonged in 10 out of 11 of our patients at the start of the UF phase. IVRT further lengthened during this phase, for a decrease in left atrial pressure leads to delayed mitral valve opening. It is also known that myocardial ischaemia prolongs IVRT [21]. Ischaemia is an unlikely explanation here, since in a previous study we concluded that isolated UF does not cause myocardial ischaemia [22]. The behaviour of DT during that study was similar to that of IVRT. Earlier studies have yielded conflicting results regarding the behaviour of IVRT and DT during dialysis [7,11,23]. In the current study, the prolongation of IVRT and DT during the UF phase obviously did not reflect deterioration in relaxation, but rather a return to the patient's normal state. Changes in preload due to refilling during the HD phase were obviously too slight to affect IVRT or DT.

The changes in preload during the UF phase led to notable haemodynamic responses: HR, SV and CO decreased, reflecting the recovery of the patients from the hyperdynamic cardiovascular state at the start of the UF phase. Refilling from the tissues during the HD phase increased BV and the changes in HR, SV and CO were the opposite of those observed in the UF phase. It is apparent, however, that the increase in cardiac output during the HD phase is also dependent on an increase in heart rate and a decrease in SVR. It is also very logical that haemodynamic parameters Emax and Amax changed in parallel, although not statistically significantly, when their changes were analysed in separate patients.

As to the interpretation of these results, it is noteworthy, first, that for this study we recruited only patients in a stable haemodynamic state. Therefore, the cohort included fewer patients with diabetes and more patients with glomerulonephritis and adult dominant polycystic disease compared with the HD population in the unit (Table 1). However, it is important to point out that there were no differences in weight changes and UF volumes between these groups (Table 2). Secondly, although this study design allowed us to evaluate the effects of pure UF on Doppler-derived indices of diastolic function, due to refilling the HD phase was not completely isovolaemic. Thirdly, the cohort was rather small, since we were unable to recruit more patients from our unit into this exploratory study, which was quite demanding of them. Thus, some of the correlations and results may simply be due to the small sample size; however, they should not be dismissed as unimportant. Also, due to the small number of patients, we used the Bonferroni correction in statistical comparisons; therefore, we want to highlight the information that can be acquired directly from Figures 1–3, which clearly show the main trends of the findings.

In summary, the results of this study demonstrate that the LV diastolic filling parameters Emax, Amax and IVRT are significantly affected by UF and preload but not by HD. Emax and Amax were so consistently dependent on preload that their ratio was not affected by isolated UF or HD with minimal UF. We further conclude that the changes during UF in the parameters of diastolic function obviously do not reflect deterioration in diastolic function but rather recovery from the hyperdynamic cardiovascular state caused by fluid retention. Unlike the Emax/Amax ratio, IVRT seems to be volume-sensitive and fluid removal during UF probably reveals the real values of IVRT. The clinical implication of our findings is that the individual's state of hydration must be taken into consideration when interpreting Doppler-derived indices of LV diastolic function in HD patients.

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