THE EFFECT OF ACUTE INTRADIALYTIC EXERCISE ON CARDIOVASCULAR RESPONSES IN HEMODIALYSIS PATIENTS

BY

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DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Kinesiology & Community Health
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2017

Urbana, Illinois

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ABSTRACT

BACKGROUND: In patients with kidney failure requiring hemodialysis (HD) treatment, intradialytic exercise (IDEX, exercise during HD treatment) has been advocated for its feasibility and effectiveness for improving important health outcomes. However, IDEX as an adjunct therapeutic strategy is infrequently implemented, in part due to potential risks of IDEX.

PURPOSE: The purpose of this study was to evaluate the safety of IDEX by examining its effect on intradialytic cardiovascular (CV) hemodynamics.

METHODS: Intradialytic changes in brachial, aortic and cardiac hemodynamics and autonomic function were examined during a normal HD session without exercise, or when 30-minutes of cycling exercise was performed during the 1st- or 3rd-hour into HD in 12 HD patients.

RESULTS: IDEX performed during either the 1st- or 3rd- hour does not appear to exacerbate hemodynamic instability during HD. While there were transient increases in stroke volume, cardiac output and heart rate during IDEX, the intradialytic changes in brachial and aortic blood pressure (BP) parameters, cardiac hemodynamics and autonomic function were similar on days with and without IDEX. This null effect of IDEX on hemodynamic parameters during HD was demonstrated regardless of the timing of exercise and patients' underlying CV characteristics. Patient hydration status was correlated with the magnitude of BP drop and autonomic dysfunction, and increasing sympathetic activity was also correlated with drops in BP during HD.

CONCLUSION: These results indicate that IDEX does not exacerbate hemodynamic instability during HD regardless of hydration status and the timing of the exercise. We also observed the potential roles of overhydration and autonomic dysfunction on hemodynamic regulation during HD. These results should help to improve our understanding regarding the CV safety of IDEX.

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CHAPTER 1

INTRODUCTION

In patients with kidney failure requiring hemodialysis (HD) treatment, intradialytic exercise (IDEX, exercise during HD treatment) has been advocated for its feasibility and effectiveness for improving cardiovascular (CV) function, physical function and quality of life[1-3]. Despite promising preliminary evidence, IDEX as an adjunct therapeutic strategy is infrequently implemented and remains a poorly adopted area of practice, in part due to concerns many nephrologists have about the potential risks of IDEX[4, 5]. However, there is a lack of knowledge about what factors influence the safety of IDEX.

A primary concern with IDEX is its potential impact on hemodynamic variables during treatment. Hemodynamic instability is a perpetual problem for HD patients due to the significant volume of fluid (typically 2-5 L) that needs to be removed by ultracentrifugation during each dialysis session. Volume overload (VO) is very common in HD patients, mainly due to uncontrolled fluid intake and a high salt diet that stimulates thirst[6], as well as inadequate fluid removal during HD treatment. Chronic VO is associated with adverse clinical outcomes and is an independent determinant of mortality in HD patients[7, 8]. In patients with VO, the high target volume for fluid removal often exceeds the entire plasma volume pool, which in many cases

results in CV complications such as hypotensive episodes, especially in the last hour (3^{rd}~4^{th}) of HD treatment. Together with the delayed plasma refilling, inadequate CV compensation is suggested to be the main cause of adverse CV events during HD treatment. These events may lead to a vicious cycle of inadequate fluid removal during HD, subsequent fluid overload between HD sessions, and chronic cardiac and arterial impairment. Each of these are strong contributing factors for intra- and inter-dialytic CV complications.

Although IDEX may be considered an additional CV stress during HD, it also may help control HD-induced hemodynamic instability, especially intradialytic hypotension. This may be due to exercise-induced increases in cardiac output resulting from a variety of factors, including increased heart rate[9], increased myocardial contractility[10], elevated respiration rate[11], reduced afterload due to decreased total peripheral resistance, greater muscle pump-induced venous return[12] and shunting of blood flow from visceral organs[13], all of which combine to increase central blood flow.

By contrast, some patients experience a paradoxical increase in blood pressure (BP) during their treatment, known as intradialytic hypertension. Underlying causes of intradialytic hypertension are hypothesized to be hyperactivity of sympathetic outflow[14] and impaired vasodilatory capacity[15-17]. While it is possible that IDEX could exacerbate this problem, there is little evidence in the literature of adverse events caused by IDEX[4, 18]. Instead, intradialytic

hypertension could be attenuated after a bout of moderate intensity IDEX through the well-known phenomenon known as post exercise hypotension. Post exercise hypotension is characterized by reduced sympathetic activity, increased parasympathetic activity and decreased vascular responsiveness to elevated sympathetic outflow that persist up to 12 hours upon completion of exercise[19, 20]. Through this mechanism, IDEX could help compensate for the paradoxical increase in BP during HD.

To date, few studies have evaluated potential safety concerns of IDEX[21]. In particular, there is little data examining if: 1) a patient's hydration status impacts their hemodynamic response to exercise during treatment; 2) the hemodynamic response to exercise differs in patients prone to either intradialytic hypertension or hypotension; or 3) the timing of the exercise during HD (e.g., 1st vs 3rd hour) impacts the CV response during treatment. Providing more robust evidence for the safety and effectiveness of IDEX in patients with different hemodynamic characteristics, as well as evaluating the impact of exercising early vs late in the treatment, could help improve adoption of exercise training as a standard practice in HD clinics.

Thus, this study was performed to explore the safety of IDEX related to CV regulation in HD patients. Specifically, we examined the effects and timing of IDEX on BP changes during HD. and determined if patients with chronic over-hydration or under-hydration have an altered BP response to IDEX. We hypothesized that IDEX will not exacerbate hemodynamic instability

during HD in all patients, regardless of their underling CV characteristics or the timing of the exercise. We also examined potential mechanisms underlying the intradialytic BP responses to IDEX.

CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

2-1. High prevalence of ESRD and High CV morbidity and mortality in HD patients

The prevalence of end-stage renal disease (ESRD) has continuously increased over the last several decades. According to United State Renal Data System, there are currently about 640,000 ESRD patients in the U.S., with Medicare related expenditures for their treatment reaching $28.7 billion[22]. The majority of patients with ESRD (~90%) receive HD treatment as a renal replacement therapy in the U.S. in 2012[23]. The all-cause mortality rates adjusted for age, race and gender are seven- to eight-fold greater than the general population, and CV complications are responsible for more than the half of deaths in HD patients[24-26]. The contributing factors for the high prevalence of cardiovascular disease (CVD) and mortality include: 1) underlying causes of ESRD such as diabetes mellitus and hypertension; 2) pathophysiologic abnormalities secondary to ESRD such as anemia, hyperparathyroidism, mineral disorders, cardiac dilation, and muscle wasting; and 3) HD treatment-driven acute CV disturbances and inflammation[27]. Despite advances in both HD techniques and pharmacological therapies to treat co-morbidities, morbidity and mortality in this population remain extremely high[25]. This suggests additional therapeutic strategies are needed to improve the health and quality of life in HD patients.

2-2. CV Response and CV Complications during HD - Hemodynamic Instability

2-2-1. Normal CV response to HD

Excess fluid gained between HD sessions is removed through ultrafiltration during HD treatment. As a result of the plasma volume reduction, venous return and systemic peripheral vascular resistance are reduced, which causes decreases in stroke volume, cardiac output and mean arterial BP[28, 29]. Neurohumoral compensatory responses are critical in order to maintain central BP in the normal range, and thus, protect essential organs from ischemic insults. In response to progressive plasma volume loss, sensory signals from peripheral afferents are integrated in the central commend which initiates activation of sympathetic activity and a withdrawal of parasympathetic activity. As a consequence, heart rate and myocardial contractility increase which proportionally elevates cardiac output. In the vasculature, sympathoexcitation-driven vasoconstriction promotes plasma redistribution from the splanchnic and cutaneous circulation and thus increases central blood flow. Constriction of arterioles increases afterload and attenuates cardiac empting and may facilitate plasma refilling by lowering capillary pressure (See **Figure 1**). With any impairment in the CV compensatory mechanisms, CV complications including intradialytic hypotension and intradialytic hypertension can occur during a HD session. Impairment in baroreflex sensitivity, peripheral

vasopressor response, cardiac contractility, venous compliance and vascular perfusion capability, and delayed plasma refilling can each contribute to the risk of CV complications during HD treatment.

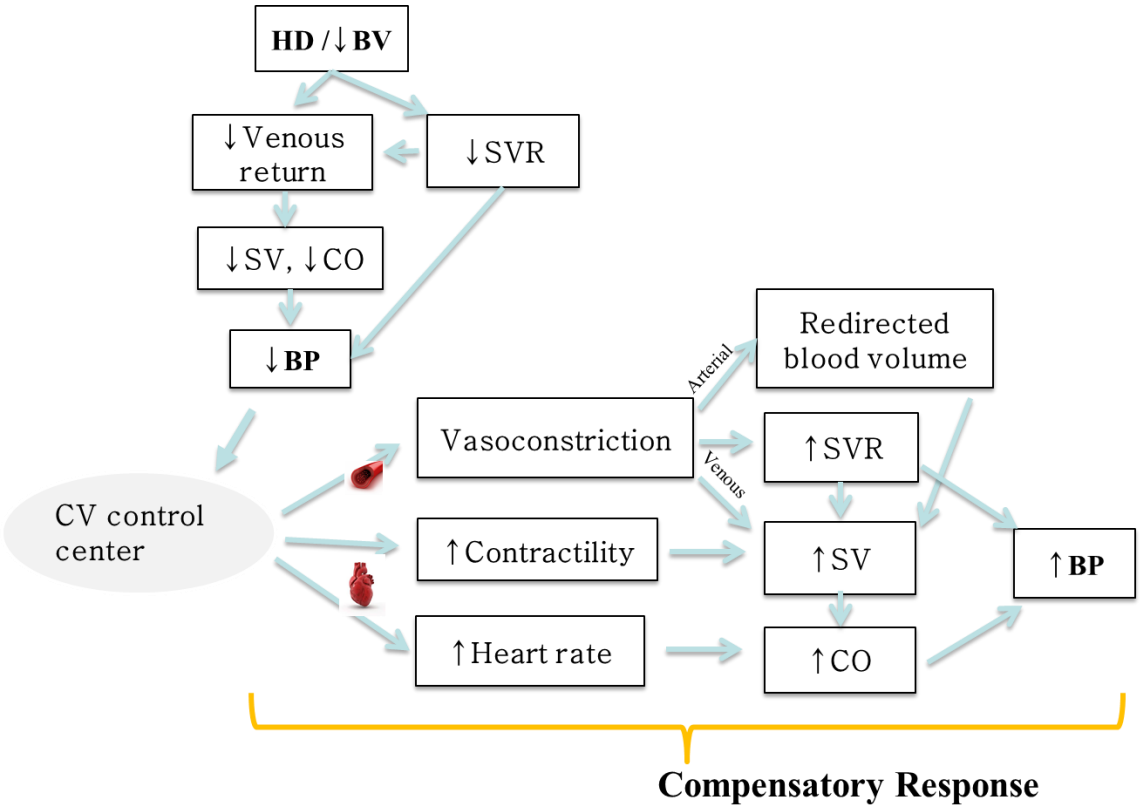

Figure 1. Normal hemodynamic response to HD treatment and CV compensatory response

HD: hemodialysis, **BV**: blood volume, **SV**: stroke volume, **CO**: cardiac output, **SVR**: systemic vascular resistance, **CV**: cardiovascular, **BP**: blood pressure

2-2-2. Intradialytic Hypotension (IDH)

Hypotension is the most common intradialytic complication, occurring in up to 30% of HD sessions[30]. When physical symptoms such as cramping present along with a reduction in BP, HD

treatment is often interrupted by stopping or slowing ultrafiltration, administration of saline, decreasing blood flow rate, or repositioning body posture, and this can have significant consequences. Reductions in ultrafiltration lead to incomplete removal of wastes and fluid during HD, while saline administration increases thirst, and thus fluid intake and accumulation. Furthermore, IDH increases the risk of further CV complications as a result of ischemic insult on the cerebral, mesenteric and coronary circulation, and is an independent risk factor for mortality in HD patients[31]. The main cause of intradialytic hypotension is an inadequate CV compensatory response to the plasma volume reduction. This includes a failure to increase heart rate, myocardial contractility and sympathetic nervous activity, inappropriate plasma refilling and peripheral vasoconstriction in response to progressive hypovolemia[32]. Although HD patients have elevated sympathetic activity at rest[33, 34], vaso-pressor response was found to be impaired by reduced function of renal afferent nerve endings and decreased alpha-adrenoreceptor density[35, 36]. This blunted pressor response, in turn, was suggested to increase the risk of IDH. In addition, sudden withdrawal of sympathetic activity has been reported in response to progressive plasma volume reduction during HD[37, 38]. This may occur partly due to cardiac depressor reflex. The mismatch between myocardial blood volume (gradually decreasing) and vigorous contractile force may activate cardiac mechanoreceptors and deactivate baroreceptors via vagal afferents. Patients with frequent IDH episodes have been shown to have impaired cardiac function[39],

decreased sympathetic tone[40, 41], increased arterial stiffness[42], impaired baroreflex sensitivity[43] and increased endotoxin [44] and systemic inflammation[42]. Although there is no definitive therapy to treat IDH, blood volume monitoring, vasoconstricting drugs, modification of dialysate composition and temperature, and adjustment of ultrafiltration rate and amount have been suggested to lower the development of IDH[30, 45-47]. However, blood volume monitoring has shown inconsistent benefits[48]. Vasoactive therapies such as selective α-1 adrenergic agonist midodrine and vasopressin have yielded effective results in some patients[45, 49]. However, increased total peripheral resistance reduces uremic toxin removal rate by decreasing capillary perfusion capacity, which raises a concern of decreased HD efficiency with the use of vasoconstricting agents. Moreover, HD prescription modification requires a high degree of clinical judgement and clinician involvement, which may limit its universal application in most HD clinics.

2-2-3. Intradialytic hypertension (IDHTN)

Paradoxical increases in BP during and immediately after a HD sessions, called intradialytic hypertension (IDHTN), occurs in 15~30% of HD sessions [50]. IDHTN is associated with increased risk of adverse outcomes including hospitalization and mortality in HD patients[51, 52]. The potential underlying mechanisms include: 1) traditional risk factors for hypertension that promote increases in peripheral vascular resistance such as hyperactivity of renin-angiotensin

aldosterone system, sympathetic over-activity, and endothelial dysfunction; and 2) ESRD-specific factors such as volume overload, volume-driven cardiac dilation and removal/filtration of anti-hypertensive medications during HD sessions[50, 53, 54]. Patients with IDHTN typically have increased sympathetic activity and reduced baroreceptor sensitivity[14], increased endothelin-1(a potent vasoconstrictor) and decreased nitric oxide levels[15-17]. Recently, Inrig et al., demonstrated that circulating levels of endothelial progenitor cells measured at the beginning of HD was severely decreased, and flow mediated vasodilatory capacity is also decreased. This indicates a reduced repair capacity for endothelial cells, and inadequate response to sheer stress, respectively, in patients with IDHTN[55]. Development of IDHTN was also associated with arterial stiffness[56] and VO[50, 53].

2-3. Intradialytic Exercise (IDEX): Health Benefits of IDEX

2-3-1. Decreased Physical Function and Inactivity

Accumulating evidence suggests that HD patients experience severely reduced physical functioning, which is associated with a poor prognosis and impaired QOL[57]. Exercise capacity has been shown to be approximately 50% of the level in healthy sedentary controls (ranging in 15.0 ~21.0 ml/kg/min of peak oxygen uptake)[58]. This is even lower than other clinical populations with co-existing medical problems such as severe anemia and diabetes mellitus, and

similar to values in heart failure patients[59, 60]. Patients with a VO2peak above a median value of 17.5ml/kg/min had 17% lower mortality rates than those below the median value after 3-years follow-up[57]. The marked reduction in functional fitness observed in HD patients is attributed to ESRD-driven health problems including anemia, metabolic disturbances, cardiac and arterial dysfunction, abnormal muscle metabolism, muscle wasting, malnutrition and inflammation[2, 58, 61-63]. In addition, a sedentary lifestyle is common and leads to progressive physical deconditioning in HD patients[64]. Physical deconditioning is associated with many skeletal muscular abnormalities and reduced cardiorespiratory function in HD patients[63]. Finally, self-reported sedentarism (those who never or almost never participate in physical activity during leisure time) in HD patients was associated with a 62% greater risk of mortality over 1 year compared to nonsedentary HD patients[59]. Similarly, engagement in regular physical activity (2~3 or 4~5 times/week) was associated with a 30% lower relative risk of mortality than compared to sedentary groups (>1time /week)[65] . Thus, any increment of physical activity is likely to be beneficial by potentially delaying of reversing physiological deconditioning imposed by either ESRD and/or inactivity.

2-3-2. Interdialytic vs Intradialytic exercise (IDEX)

Two types of exercise, in regard to timing of exercise, have been tried in HD patients; exercise outside of the HD clinic (interdialytic exercise) and exercise during HD treatment

(intradialytic exercise, IDEX). Interdialytic exercise has been generally performed in outpatient settings such as rehabilitation centers with targeted outcomes such as physical function, CV fitness, and disease-specific risk factors[2, 66]. While it allows various types and intensity of exercise for maximal benefits, low compliance and high drop-out rate have been noted from previous studies. Kouidi compared the two types (inter- vs intra-dialytic) of exercise programs and found that the magnitude of increase in aerobic capacity was greater in interdialytic exercise group, partly due to the higher exercise intensities achieved, but the adherence was poorer compared to IDEX training[67, 68]. IDEX has been advocated for its feasibility, time-efficiency and on-site supervision of medical staff. The convenience of not having to schedule additional visits might be particularly attractive to HD patients who already have a high burden of time commitments for regular HD treatment (3~5 hours/treatment, 3 times/wk). This extensive HD treatment time also represents a forced sedentary period when patients are in a hypercatabolic state due to the acute effects of the HD on systemic inflammation, as well as the loss of substantial amino acids caused by the dialysis filtration process. Thus, routine IDEX is not only a chance to increase physical activity levels but also may offset some of the unfavorable acute effects of HD treatment. While modest, the numerous health benefits of IDEX training has been shown for the last three decades[1-3]. By 2014, 24 randomized control trials of IDEX in HD patients had been conducted with 13 aerobic exercise, 7 resistance exercise and 4 combined

exercise trials[18]. The most popular form of IDEX has been aerobic cycling using an ergometer placed in front of the treatment chair. This has generally been done at a mild to moderate intensity, based on either RPE or maximal exercise testing. The duration of exercise typically varies from 15 – 45 minutes, though some studies have utilized exercise protocols ranging in duration between 1 to 4 hours.[18].

2-3-3. Benefits of IDEX on Physical Function

IDEX training has resulted in significant improvement in aerobic exercise capacity as measured by VO2peak in randomized controlled studies in HD patients[69-73]. The magnitude of improvement on VO2peak was greater with the combination of aerobic and resistance exercise than aerobic training alone, and also when the duration of training exceeded 6 months[18]. Exercise training also improved many indicators of physical functioning such as muscle strength[74, 75], 6-min walk test[92, 93], habitual and fastest gait speed, and performance on the sit-and-stand test[64, 76].

An interesting finding regarding the anabolic effect of exercise training in HD patients was that 9 weeks of aerobic IDEX training resulted in improvement in muscle strength and power, in addition to an increase in VO2peak levels[77]. These improvements in strength and power were seen despite the fact that the aerobic training was designed to improve cardiorespiratory fitness, and not strength. This somewhat unexpected benefit may have been due to the very severe physical deconditioning in HD patients.

Although this evidence suggests exercise training is feasible and is able to produce similar physiological changes seen in other clinical populations, the data should be interpreted with caution because of the selective inclusion criteria, small sample sizes, and lack of control groups in many of these studies. In particular, the subjects studied were generally highly functioning patients free of serious CV complications, which may limit extrapolating these results to the general HD population.

Furthermore, anabolic effects of exercise training have not been consistently demonstrated in HD patients. Although the number of randomized control trials lacks limiting the power to draw strong conclusion, several randomized controlled trials including both inter- and intra-dialytic exercise studies suggest that it is difficult to increase lean mass or muscle strength by exercise alone. Kouidi reported increases in fiber cross sectional area (CSA), capillary and mitochondrial density and VO2peak after a 6 months of combination of intense strength and aerobic exercise training on non-dialysis days[2]. However, other studies that did not reach either/both high intensity or volume of exercise demonstrated limited anabolic benefits of exercise training. Johansen investigated effects of either/both resistance interdialytic exercise and nandrolone, an anabolic steroid and found that quadriceps CSA was increased in the exercise groups combined with either placebo or nandrolone injections but improvement in whole body lean mass was only seen in the nandrolone group[78]. The PEAK study, a randomized control trial of resistance IDEX

training, reported significant improvements in muscle quality and strength but no improvement in thigh muscle CSA[74]. The factors leading to resistance to exercise-driven changes may include uremia-driven abnormalities in muscle metabolism and severe physical deconditioning that limits application of high intensity exercise. In addition, some have suggested that nutrition support might be necessary to maximize benefits of exercise in HD patients[79]. This is because many HD patients are malnourished and in a highly catabolic state, especially during HD. This is primarily due to inflammation, poor nutrition intake, and the intradialytic loss of amino acids[80]. Intradialytic nutritional support has been shown to improve muscle metabolism[81]. Pupim demonstrated that cycling initiated 15 min after starting an HD session resulted in an increased uptake of amino acids and net muscle protein gain compared to intradialytic nutrition support alone[82]. Similar results were seen with the combination of nutrition and resistance exercise[83]. However, the combination of intradialytic supplementation and 24 week of resistance training failed to show improvement in lean muscle mass[84]. Lastly, the excess extracellular fluid tends to confound the measurement of true muscle size due to the fluid-dependence of body composition measures.

2-3-4. CV Benefits of IDEX

The risk of CVD is 10-30 fold greater in HD patients compared to in the general population[25]. Cardiac abnormalities such as left ventricular (LV) hypertrophy, and systolic and

diastolic dysfunction are present in up to 80% of HD patients[85, 86]. These CV abnormalities independently predict adverse CV events and are the strongest predictor of mortality in this population[87, 88]. Exercise training as a part of a comprehensive treatment program has been shown to reduce the risk of CVD events in patients with established CVD and other chronic disease conditions[89, 90]. However, much less is known about the CV effects of exercise training in HD patients. Toussaint et. al., carried a prospective cross-over trial to investigate the effect of IDEX on arterial function in 19 HD patients. Half of the patients initially underwent 3 months of IDEX, while the other half remained sedentary during their treatment. After a one month washout period, the groups crossed over, so the previous exercisers no longer cycled, and vice versa. While there was a trend for an improvement in pulse wave velocity (PWV), a marker of arterial stiffness, during the exercise periods, it was not statistically significant. However, PWV did get worse during the control period in one of the two groups which led to a significant difference between post-exercise period and post-control period groups[91]. On the other hand, a randomized control trial by Koh et al., found no significant change in PWV, pulse augmented pressure, BP and HR after 6 months of IDEX, despite a modest increase in performance during the 6min-walk test[92]. The very low estimated workload (~35kal/sessions) may have influenced the negative findings. Only one study directly measured cardiac function adaptation with IDEX training and found a modest improvement in LV ejection fraction in HD patients[69]. As for BP

benefits, an uncontrolled study by Anderson et. al., showed 3 months of IDEX resulted in reductions in 44-hour ambulatory BP (systolic BP: 138.4 mmHg +/- 19.6 to 125.7 mmHg +/- 20.0 and diastolic BP: 83.2 mmHg +/- 10.2 vs. 74.7 mmHg +/- 9.0 at 0 and 3 months), as well as reductions in BP immediately before and after HD. A few randomized control trials included BP values as a study outcome with no reported post-intervention value[71] and no change after the intervention[75, 91, 92]. In addition, a study by Ouzouni et. al. reported a reduction in resting BP after 10 months of IDEX (systolic BP: 142.9 mmHg +/- 14.6 to 135.3 mmHg +/- 11.6 and diastolic BP: 86.8 mmHg +/- 7.8 vs. 79.2 mmHg +/- 7.7 at 0 and 10 months)[93]. Despite no significant reductions in BP after IDEX training, Painter and Miller have shown decreased use of antihypertensive medications[72, 94].

The paucity of exercise-related CV data might be due in part to complications associated with measuring CV parameters during dialysis. In particular, the significant fluid shifts between and during HD sessions in HD patients complicates these analyses. Many of the well-accepted CV clinical markers including BP, arterial compliance and myocardial contractility change their values depending on fluid volume status and, therefore, can be misrepresented in the presence of hyper-, hypo-volemia or altered cardiac geometry[95]. Standardization of measurement protocols and alternative methods with minimal fluid-dependence would help lower intra-patient

variability in CV measures, and allow for better characterization of exercise-induced changes in CV function in HD patients.

2-3-5. Benefits of IDEX on Autonomic Function

Abnormal autonomic regulation is frequently observed in HD patients, as generally reported by increased sympathetic activation[96-99]. Heart rate variability analysis provides information of cardiac autonomic modulation of heart rhythm by measuring beat-to-beat fluctuations in heart rate or variations in consecutive R-R intervals. Decreased heat rate variability has shown to be a risk factor for cardiac adverse events[100] and mortality in HD patients[101-104]. 6-months of exercise training in 60 HD patients significantly increased 24-hour heart rate variability which indicates increased cardiac vagal activity[58]. 10-months of combination of cycling and strength exercise training also led to an improvement in heart rate variability indices[69]. However, 12 weeks of aerobic training did not result in change in heart rate variability, suggesting the potential need for a longer period of exercise in order to cause changes in cardiac autonomic function[105]. IDEX training also yielded a marked improvement of baroreflex activity that was associated with the magnitude of improvement in patient's functional capacity.[70]

2-3-6. Benefits of IDEX on HD Adequacy

Adequacy of HD treatment is positively correlated with hospitalizations[106, 107] and mortality[108] in HD patients. Acute bouts of IDEX have resulted in increased removal of unwanted solutes, indicative of enhanced HD efficacy, as evidenced by reductions in post-HD rebound of urea, creatine and potassium[109], and increased phosphate removal[110-112]. Furthermore, compared to the usual HD care, chronic IDEX training resulted in higher HD adequacy (Kt/V) based on pooled analysis of 233 HD patients from 6 randomized control trails[18]. The underlying mechanisms are suggested to be increased diffusive flux in solutes from working muscles to blood stream[109]. However, the effect of IDEX on HD adequacy is inconclusive with null findings of urea clearance rate changes in several studies[110, 111, 113]. In addition to inherent high intra- and inter-variability of HD adequacy within patients, heterogeneity of exercise modality, equations and solutes used for calculation of HD efficiency, and subject inclusion criteria have been suggested to contribute to the conflicting results[112].

2-3-7. Psychological Benefits of IDEX

Severely reduced quality of life has been consistently reported[114, 115], and linked to poor morbidity and mortality in HD patients[116]. Functional limitations, ESRD-co-morbidities, extensive time-commitment to HD treatment, and a restrictive renal diet all contribute to the compromised quality of life in HD patients. IDEX training has resulted in favorable psychological adaptations in HD patients. Decreased subjective feeling of anxiety, depression,

fatigue and bodily pain and increased vitality has been reported in numerous studies that employing IDEX training[64, 117, 118]. Furthermore, quality of life was enhanced with improved perception of physical functioning, general health and mental health after an IDEX program in HD patients[64, 76, 119, 120].

2-4. Barriers to IDEX

Given the beneficial effects of exercise training, the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines included recommendations that "all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" in Guideline 14.2 and "the goal for activity should be for cardiovascular exercise at a moderate intensity for 30 minutes most, if not all, days per week" in Guideline 14.4. Despite the strong rationales, exercise during HD as an adjunct therapeutic strategy in HD is infrequently implemented and remains a poorly adopted area of practice. However, data on the prevalence of IDEX in clinical practice, either in the U.S. or abroad, is very limited[121 122].

Several studies have investigated perceived-barriers to increasing physical activity in HD patients and suggested combined roles of disease- , patient- and health-care personnel- oriented factors[4, 123-126]. Lack of interest and motivation was found to be the biggest perceived barrier to

engaging in exercise, although desires to improve medical conditions were still noted in HD patients[126]. On the other hand, clinicians self-reported that medical safety concerns relating to uncertainty of optimal exercise modality and comorbidity screening have limited their encouragement of IDEX for patients[4, 123]. Of note, nephrologists' perception regarding patients' interest in exercise was underappreciated. While 4% of patients expressed disinterest in exercise, 35% of nephrologists indicated patients would not be interested in exercise, and many of them doubt of effectiveness of exercise counseling to increase patients' physical activity levels. Similarly, safety concerns related to participating in physical activity was raised more in clinicians than patients (40% and 8% respectively)[123]. This may partly explain the deficit of exercise counseling by clinicians in most HD clinics[4]. According to reports from exercise intervention studies, the most common reason for dropouts and barriers for engaging in exercise programs was a lack of patient motivation, as opposed to health-related impairment[67, 68, 126]. Bennett sought to identify factors affecting sustainability of exercise program in HD patients. Inclusion of committed medical staff and dedicated exercise professionals as well as their encouragement during HD were found to be important components of successful continuation of exercise programs in the HD community[127]. Thus, increasing knowledge on safety aspects of IDEX may help facilitate exercise counseling by clinicians which could help raise patients' interest and motivation to increase physical activity levels in HD patients.

2-5. Risk and Adverse Events with IDEX

The risk of adverse events from participating in an exercise regime is elevated in HD patients given the high prevalence of ESRD-driven co-morbidities including CVD, hyperparathyroidism, muscle myopathy, neuropathy and bone disease. Furthermore, acute effects of the HD treatment itself may impact the risk for CV events during HD. HD generates considerable hemodynamic, electrolytic, and neuro-humoral stresses[128]. Specifically, HD can cause acute CV stress due to fluctuations in serum calcium concentrations[129], sympathetic hyperactivity[130], recurrent ischemia due to reduced coronary flow reserve[131], and endothelial dysfunction due to increased oxidative stress[132, 133]. While musculoskeletal injury is a common concern related to exercise, the potential increased risk of a life-threatening CV events may dissuade HD patients and their healthcare personnel from engaging in IDEX.

Generally, IDEX training in HD patients has been shown to be safe and well tolerated, although few studies have directly assessed safety concerns with IDEX. There has been no report of serious injuries as a result of participation in IDEX programs[127, 134]. Among seventeen randomized control trials that reported adverse events, three hypotensive events (two in the exercise groups and one in the control groups) and five musculoskeletal complications in the exercise groups were reported from three studies[73-75]. No overall significant effect of engaging in IDEX on incidences of adverse events was confirmed in a recent meta-analysis[18]. It should be

noted that study participants have been selective to relatively healthy, with low levels of comorbidities in general. Furthermore, the available studies were not designed to identify safety aspects of IDEX in HD patients. Nevertheless, cardiac rehabilitation programs historically have yielded minimal numbers of adverse cardiac events. The likelihood of adverse events can be minimized by using a progressive approach to an exercise regime, proper medical screening, and disease-specific considerations such as volume overload status by the medical team at the clinic[135].

2-6. Factors that May Affect Risk of CV Complications to IDEX

2-6-1. Volume Overload (VO) Status

One of the critical consequences of renal failure is retention of extra fluid due to the low or absent urine production. Removing this excess fluid is a primary purpose of each HD treatment. Accordingly, HD patients are exposed to frequent body fluid shifts driven by fluid removal during HD treatment and fluid retention between HD sessions. When inadequately treated over time, the excess volume raises BP in the vasculature and creates a substantial volume load to the heart. VO is very common in HD patients with the reported prevalence of 15~37% in HD patients[6]. However, this prevalence data was derived from quantitative assessments of intra and extracellular fluid volume estimated using bioimpedance analysis, which may underestimate a

patient's actual volume overload. In reality, it is very difficult to precisely determine a patient's true volume status. Indeed, a central tenet of nephrology practice is the belief that almost all patients with high BP, or who are on a BP medication to control BP, are likely to have chronic VO. Using this subjective criteria, more than 80% of all HD patient's in the U.S. may have chronic volume overloaded.

The high prevalence of VO is primarily due to inadequate fluid removal and uncontrolled fluid intake resulting from a high salt diet[6]. In patients with high fluid weight gain between HD sessions, the high target volume of fluid removal often exceeds the entire plasma volume pool, which in many cases results in CV complications such as hypotensive episodes, especially in the last hour (3~4th) of HD treatment. Together with the delayed plasma refilling, inadequate CV compensation is suggested to be the main cause of adverse CV events during HD treatment. This intolerance to HD treatment hinders complete correction of the volume gained between HD sessions, which subsequently contributes to development of chronic VO. VO-driven complications including hypertension and LV hypertrophy are highly prevalent, and likely contribute to the development of further CV manifestations in HD patients[136 85, 86]. Indeed, chronic VO has been shown to be associated with systemic hypertension and unfavorable arterial and cardiac remodeling, and is also an independent predictor of mortality in HD patients[137-139].

2-6-2. Autonomic Dysfunction

Chronic uremia affects autonomic control of the CV system, mainly as a result of central and/or peripheral uremic neuropathy[140, 141]. Chronically elevated SNS activity has been consistently reported in HD patients[38, 142] and as well as in mild to moderate chronic kidney disease patients[143-145]. Furthermore, increased SNS activity is believed to be both a cause and consequence of uncontrolled hypertension, and is linked to the ESRD progression and the increased risk of mortality in HD patients[38, 143, 145, 146]. Although the mechanisms involved in the elevated sympathetic tone in kidney patients remain poorly understood, it might be driven by signals from diseased kidneys that chronically trigger renal afferent nerve pathways[147-149]. Renal ischemia, hypoxia, adenosine, and angiotensinΠare considered the initial signals. Other pathophysiologic mechanisms for elevated SNS activity include an abnormally increased chemo-reflex and local skeletal muscle-reflex sensitivities[35], baroreflex dysfunction, decreased nitric oxide bioavailability[150, 151] and increased oxidative stress. In heart failure patients, abnormalities in peripheral reflex control and central neural integration at resting and during exercise are commonly seen[152-154] , and likely contribute to exercise intolerance[155]. Despite limited numbers, several studies have tested the role of autonomic control during dynamic exercise in HD patients. Park et. al., observed a greater increase in BP levels with moderate intensity isometric and rhythmic exercise (3 min of static handgrip exercise at 30% of maximum voluntary contraction) from baseline levels in ESRD patients compared to age-matched controls[142]. This abnormally

increased BP was mainly driven by an increase in heart rate, which indicates an impaired response to central command. Further experiments demonstrated that an elevated activation of exercise pressor reflex (metabo- and mechano- reflex) was partly responsible for the greater increase in BP levels after a bout of exercise in ESRD patients[156, 157]. Thus, augmented sympathetic outflows mediated by local muscle reflexes may compromise exercise tolerance in HD patients by overly-excited myocardial tissues, increased peripheral resistance and altered redistribution of blood flow. Particularly, the latter two complications can limit oxygen supply to active muscles contributing to the development of myopathy. In addition, impaired baroreceptor sensitivity is suggested to contribute to abnormal hemodynamic responses to exercise[43], although limited evidence exists in HD patients.

2-6-3. Vascular Abnormalities

HD patients have a number of vascular abnormalities characterized by accelerated vascular aging process, especially in the large arteries[158]. Markers of arterial stiffness including PWV and pulse pressure were positively associated with CV events and all-cause mortality[88, 159]. The potential pathophysiological vascular mechanisms in HD patients include increased intima-medial thickness, increased arterial stiffness and endothelial dysfunction from diminished synthesis and bioavailability of endothelial-derived nitric oxide[150], and from increased levels of ADMA, an inhibitor of endothelial nitric oxide synthase[160, 161]. The change in vascular tone has

an increasing role in maintaining circulatory stability when the total plasma volume and ventricular volume are critically low. The arterial maladaptation may predispose hemodynamic instability in response to exercise. These vascular abnormalities are likely to limit the efficiency of compensatory vaso-dilatory and vaso-constrictive capacity to stimuli such as hypovolemia and the concomitant exercise during HD.

2-6-4. Cardiac Abnormalities

HD patients have the high prevalence of cardiac structural and functional abnormalities such as LV hypertrophy, reduced LV contractility and compliance[85, 86]. These cardiac abnormalities increase the risk of CV complications during HD treatment, especially with concomitant exercise. LV hypertrophy and large artery stiffness reduce coronary flow reserve which consequently increases susceptibility to myocardial ischemic events during increased demand. The increased risk of myocardial ischemia during HD treatment has been indicated by abnormal echocardiogram such as ST-segment depression and elevated plasma markers of myocardial damage like cardiac troponin[162, 163]. In addition to the suboptimal blood supply to the myocardium, the role of cardiac dysfunction in producing abnormal exercise responses has been extensively studied in patients with heart failure. Exercise performance is shown to be compromised due to inadequate cardiac output with or without concomitant rise in ventricular filling pressure in cardiac patients. Heart failure patients have been shown to have decreased LV

contractility and blunted reductions in afterload that consequently lead to an attenuated reduction in end-systolic volume, and eventually a decreased cardiac output in response to exercise[164 165]. The inability of the heart to increase cardiac output to compensate for an increased metabolic demand during exercise leads to dyspnea (by increased LV filling pressure and impaired pulmonary gas exchange), decreased peripheral oxygen extraction (by impaired vasodilation), abnormal skeletal muscle metabolism (by increased ischemia-driven inflammation), and subjective symptoms of fatigue (by increased anaerobic metabolism and accumulation of lactate in skeletal muscle). All of these abnormal physiological responses contribute to decrease exercise tolerance in patients with cardiac disease. Studies showing decreased tolerance to HD treatment in patients with cardiac dysfunction suggest an increasing risk of CV complications with concomitant exercise. Van der Sande et. al., showed that HD patients with cardiac failure had a greater drop in BP during HD than HD patients without cardiac failure despite the same volume of intradialytic fluid removal[166]. However, no study has examined the role of the presence of cardiac abnormalities on hemodynamic response to IDEX in HD patients.

2-7. CV Response to Exercise

The main purposes of CV regulation during exercise are 1) to provide adequate oxygen supply to fulfill metabolic demand in exercising muscles and 2) to regulate systemic arterial BP

in order to maintain adequate perfusion pressure to vital organs[167]. Dynamic exercise engages both central and peripheral mechanisms to produce normal physiological responses for the increasing metabolic needs. Exercise involving large muscle mass induces metabolic vasodilation in skeletal muscle vasculature causing a drop in systemic vascular resistance. Despite the decreased vascular resistance, mean arterial BP has been shown to increase slightly during exercise in which autonomic control plays a critical role. Autonomic peripheral afferent signals from baroreflex, chemoreflex and skeletal muscle receptors are integrated at central command which causes augmented sympathetic nerve activity over parasympathetic nervous activity in the heart, adrenal gland, and the splanchnic and skeletal muscle vasculature during exercise. As a result, heart rate and myocardial contractility are increased as well as augmented venous return by muscle pumping action, which together contribute to increase cardiac output. In addition, sympathetic outflow causes peripheral vasoconstriction in non-exercising tissues and large blood vessels, which shunts blood flow to the active muscles where vasodilation has to occur to meet increasing oxygen needs in exercising skeletal muscles. This local vasodilation occurs despite an increased systemic sympathetic outflow (termed "functional sympatholoysis") because the redirected blood flow increases vascular shear stress on endothelium in skeletal muscle tissues which causes production of nitric oxide, a vasodilator. The magnitude of attenuation of sympathetic constriction is greater as the intensity increases[168, 169]. Adjustment

between cardiac output by preload, afterload, heart rate, and peripheral vascular tone is a critically important task of CV system to maintain homeostasis of systemic BP during exercise.

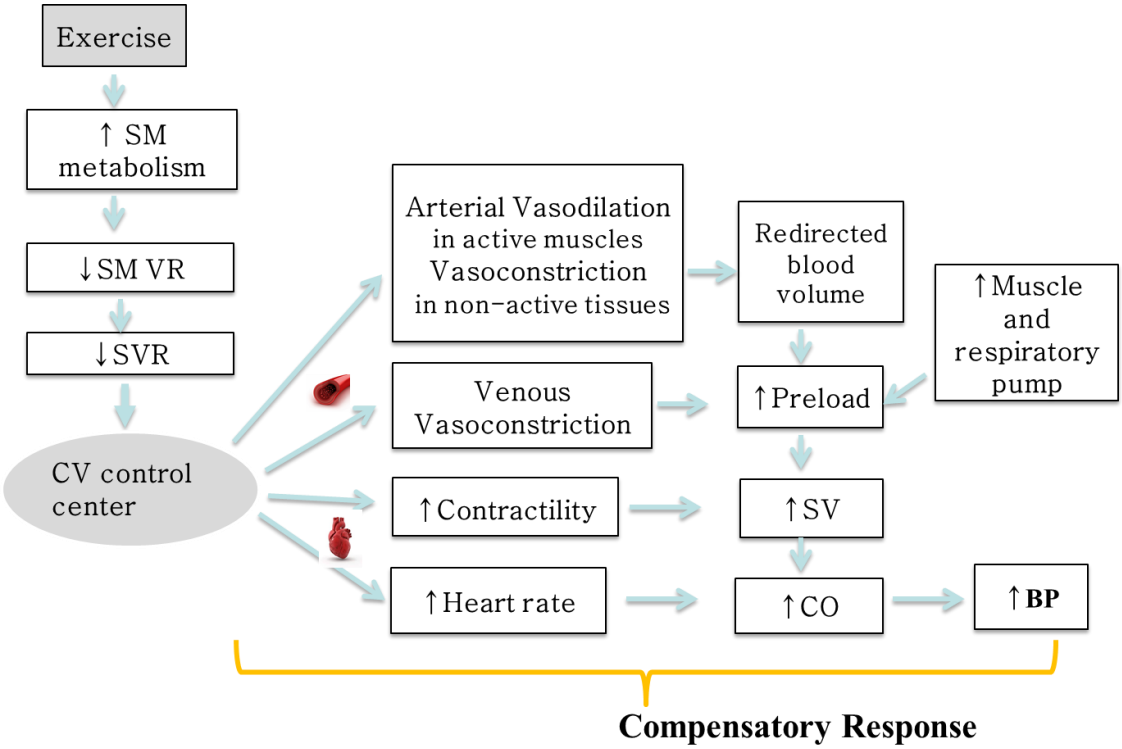

Figure 2. ***CV response to exercise and CV compensatory response***
SM: skeletal muscle, **SM VR**: skeletal muscle vascular resistance, **SV**: stroke volume, **CO**: cardiac output, **SVR**: systemic vascular resistance, **CV**: cardiovascular, **BP**: blood pressure

2-8. Potential CV Mechanisms by which IDEX may Help Hemodynamic Instability

Although exercise may act as an additive CV stress during HD, chronic exercise may help prevent adverse CV events during HD by improving CV function. Exercise training has shown to cause various favorable CV adaptations including reduced cardiac stress[170] and stiffness[171 172],

improved coronary vascular dysfunction[173], baroreflex sensitivity and arterial stiffness[174] in subjects with established CV disease. These factors interact to improve CV compensatory mechanisms. Furthermore, a bout of exercise elicits a complex series of CV adjustments to meet increasing metabolic needs that can, in turn, ameliorate hypotensive conditions during HD. Exercise causes increased sympathetic activity which leads to increased cardiac output resulting from a variety of factors including increased heart rate[9], increased myocardial contractility[10] and elevated respiration rate[11]. Considering depressed sympathetic activation during progressive blood volume loss is one of the main mechanisms of IDH[37, 38], exercise-induced-sympathoexcitation signaled by metabolic change (by chemo reflex) and mechanical change (by exercise pressor reflex) may help promote adequate autonomic input to prevent ischemia. In addition, other neurohumoral mechanisms including reduced afterload by decreased peripheral resistance, redirected blood flow from the organ system[13], and muscle pump-induced increased venous return[12] combine to increase central blood flow.

Moreover, increased venous return by non-neural pathways has been shown to be effective in treating hypotensive symptoms. Voluntary movements such as leg-crossing, muscle tensing, and foot wiggling while sitting increases BP in individuals with orthostatic hypotension[175, 176]. In HD patients, Yamamoto et al., applied an inflatable abdominal band and saw an attenuated drop in systolic BP of 16.7mmHg in 25 HD patients with uncontrolled orthostatic hypotension[177]. This

magnitude of improvement of systolic BP control is comparable to pharmacological therapies including midodrine, cool dialysis, and l-threo-3,4-dihydroxyphenylserine (which reduced the drop in systolic BP 10~15mmHg)[30, 46, 178, 179]. The main underlying mechanism is suggested to be shifting blood pool from the abdominal vascular bed to the central vasculature to increase venous return, as evidenced by increased ejection fraction and a fall in atrial natriuretic peptide concentration[177].

The post exercise recovery process, driven by continued elevation of skeletal muscle perfusion, oxygen delivery and uptake, may help control IDHTN after a bout of IDEX. The phenomenon known as post exercise hypotension is characterized by reduced sympathetic activity, increased parasympathetic activity and decreased vascular responsiveness to elevated sympathetic outflow, and persists up to 12 hours upon completion of exercise[19, 20]. The length of hypotensive effect is shown to last longer in hypertensive than normotensive subjects[180, 181]. Given that the underlying causes of IDHTN include hyperactivity of sympathetic outflow[14], impaired vasodilatory capacity by decreased nitric oxide activity[15-17], and increased arterial stiffness[55, 56], IDEX may produce compensatory CV responses that helps control abnormal hemodynamic response during and after HD treatment in patients with IDHTN.

Despite the supporting evidence for the hemodynamic benefits of exercise in other clinical populations, very limited information is available on hemodynamic responses to a bout of IDEX

in HD patients. Investigating the therapeutic value of exercise as a non-pharmacological approach to ameliorate hemodynamic instability during HD is important, especially considering the heavy usage of vasoactive medications to treat co-morbidities in many HD patients.

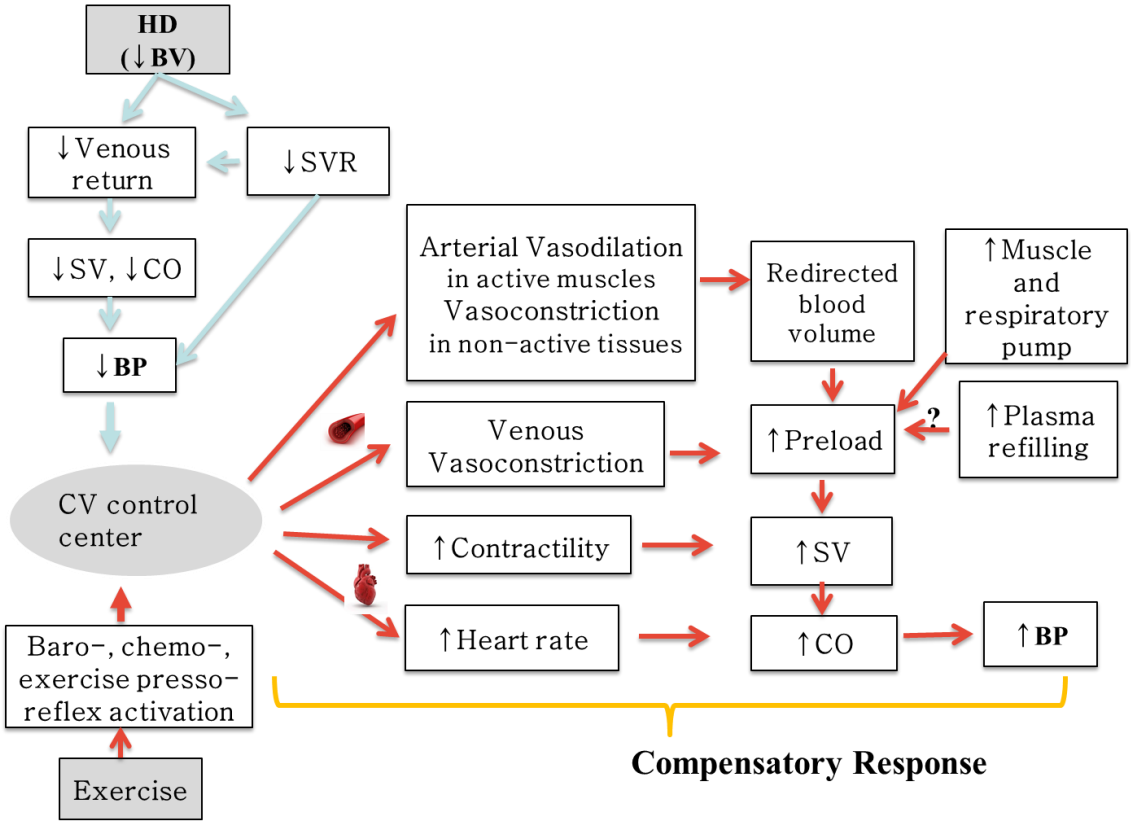

Figure 3. ***Potential CV compensatory responses to IDEX in patients with IDH***
HD: hemodialysis, **BV**: blood volume, **SM**: skeletal muscle, **SM VR**: skeletal muscle vascular resistance, **SV**: stroke volume, **CO**: cardiac output, **SVR**: systemic vascular resistance, **CV**: cardiovascular, **BP**: blood pressure

2-9. Previous Studies on Acute CV Responses to IDEX and Limitation

Currently, very little information is available regarding which factors influence the CV safety of IDEX, and only one study has investigated the safety aspect of CV responses to IDEX. 8 HD patients cycled for 5 minutes at 60% of VO2 peak at every hour into HD treatment[21]. No significant effect of IDEX on CO, SV and BP were observed until 2hours into HD treatment, but the hemodynamic parameters dropped with exercise during the 3rd hour. The hemodynamic instability was driven partly by decreased heart rate despite fluid loss, which indicates blunted CV compensatory response. Leung et. al., reported no changes in mean arterial BP, heart rate and uremic clearance rates with a 30-minutes of cycling 2 hours into HD treatment[113]. In contrast, Banerjee et al., implemented transcutaneous muscle stimulation and passive cycling movement, with both eliciting an increase in systolic/diastolic BP from 121/64 to 125/66 and to 132/69 mmHg, respectively, without a change in heart rate[182]. IDEX also resulted in normal physiological responses such as increased oxygen uptake and heart rate[183] and decreased total peripheral vascular resistance and increased cardiac output[184] without significant changes in mean arterial BP. By contrast, Dungey showed that, compared to on a non-dialysis day, BP levels were higher immediately after 1-hour of IDEX (112±20 vs. 125±18 mm Hg), lower 1-hour post exercise period (117±25 vs. 106±22 mm Hg) and not different at the end of HD session. However these BP fluctuation occurred without change in plasma markers of cardiac injury,

systemic inflammation and neutrophil degranulation[185]. In summary, IDEX was generally well tolerated, not eliciting abnormal hemodynamic responses except a possible increased risk of IDEX during the 3rd hour of treatment (**Table 1**).

However, the previous investigations were not sufficiently powered to address the safety of IDEX in an appropriate way. Most studies did not include a control group, and the primary outcome examined in many was HD efficiency, an indicator of the amount of solutes removed during treatment. The current proposed study will be controlled within patients adding a normal HD session day to be compared with the day receiving IDEX. The impact of the timing of exercise (1- vs 3-hr into HD) will be examined as well. Among possible confounding factors, fluid overload status may have a significant impact on CV response to HD. Additionally, we will evaluate whether pre-existing CV complications that may predispose patients to abnormal hemodynamic responses during HD may also impact the response to IDEX. Therefore, it is important to understand how the CV system regulates hemodynamic changes in response to concomitant exercise during HD in patients with VO and/or different underlying CV conditions. The current proposed study includes measures of hydration, as well as an integrated set of CV measures, including functional and structural measures of heart, arteries, and autonomic function. Thus, the proposed study is innovative given the novel information we will obtain

regarding the interaction between VO status and IDEX on CV responses, and the inclusion of various CV measures, allowing deeper mechanistic understanding of CV physiology with IDEX.

Table 1. Summary of Studies of Effects of Acute IDEX on Hemodynamic Parameters

Authors, year	***Aim***	***Sample Size, n***	***Exercise modality***	***Timing of exercise***	***Outcomes***	***Main findings***
Moore et.al.,1998[21]	Effects of acute IDEX on hemodynamic parameters	8 (6 males, 46.9 yr)	Cycling for 5 min at 60% of VO2peak ,	0,1-,2-,3-hr into HD	BP, SV, CO, TPR	No difference in hemodynamic variables until 2-hr. Exercise Intolerance at 3-hr for 5 patients due to ↓HR, ↓BP, ↓CO at rest
Leung, 2004[113]	Effects of acute IDEX on HD efficiency	15 (8 males, 58.6 yr)	Cycling for 30min at moderate intensity on RPE	2~2.5hr into HD	Urea removal, post-HD urea rebound, HR, BP	No difference in urea removal and rebound. BP, HR were maintained during IDEX
Farese et.al., 2008[182]	Effects of acute transcutaneous muscle stimulation (TEMS), passive cycling (PC) on BP and HD efficiency	10 (6 males, 58.1 yr)	15 min of TEMS and 20min of passive cycling	2 into HD	BP, HR, serum urea, nitrogen, phosphorous	Both TEMS& PC ➔ ↑MBP, ↑urea and phosphorous removal

Table 1 (cont.)

Authors, year	***Aim***	***Sample Size, n***	***Exercise modality***	***Timing of exercise***	***Outcomes***	***Main findings***
Banerjee et.al. 2004[184]	Effects of acute IDEX on the fall RBV during isovolaemic HD	10 (4males , 37yr)	Cycling for 10min at 20% greater than $HR_{pre\text{-}HD}$	In the beginning HD before starting UF	RBV, hemodynamic parameters	IDEX ➔ ↓RBV, ↓TPR , ↑CO, ↑SV,
Rosales et. al., 1998[183]	Effects of acute IDEX and cool dialysate on hemodynamic parameters	4 (49.9 yr)	Cycling up to 1 hr at 20-25W and 60-80 rpm	1hr into HD	Thermal, hemodynamic and energy expenditure parameters	IDEX ➔ ↔MBP, ↓RBV%change but reversed in the end of HD, ↑O_2 uptake/HR
Dungey et. atl., 2015[185]	Effect of acute IDEX on	15 (9 males, 57.9 yr)	Cycling for 30min at moderate intensity on RPE	1 hr into HD	BP, HR, cardiac injury markers, inflammation , neutrophil degranulation	IDEX ➔↓ BP at 1-hr post EX. No difference in plasma markers of cardiac injury and inflammation

IDEX: interdialytic exercise, **HD**: hemodialysis, **BP**: blood pressure, **SV**, stroke volume, **CO**, cardiac output, **TPR**: total peripheral resistance, **HR**: heart rate, **MBP:** mean arterial blood pressure, **RBV**: relative blood volume, **TEMS**: transcutaneous muscle stimulation, **PC**: passive cycling

2-10. Significance

The annual mortality rate is excessively high in patients with HD treatment, despite advances in HD techniques and pharmacological therapies. Only half of patients survive 3 years after the initiation of HD[25]. This indicates additional therapeutic strategies are needed in this population[25].

From a public policy perspective, IDEX training represents a low-cost, easy to administer treatment strategy that could potentially reduce the burden of CV disease, the leading cause of death in HD patients, and other uremic symptoms including muscle wasting, anemia and elevated inflammation in this population. The recent National Kidney Foundation recommendations include an exercise prescription[186], but nephrologists rarely counsel their patients to increase their physical activity levels or to exercise during HD treatment, in part due to safety concerns[4].

The proposed study is significant because it will improve our understanding of the safety of CV responses to IDEX, especially in relation to VO status and the normal CV response to HD. Results from this study will enable nephrologists to make more informed decisions regarding the timing and the selection of a group of patients who should/should not be encouraged to engage in IDEX. Such understanding will significantly advance the field and lead to improved therapeutic

approaches, including exercise training, that will prevent or minimize the deleterious effect of renal failure, as well as the HD process itself.

CHAPTER 3

PRELIMINARY DATA

The only previous research that examined the safety of IDEX in regards to hemodynamic responses was a small pilot study that used 5-min of IDEX[21]. This timeframe is too short to draw robust conclusions from the data, especially given that most protocols require patients to cycle for 30-45 minutes per session. We are currently conducting a project examining the effects of IDEX training on physical function and CV disease risk factors. Furthermore, we recently conducted a pilot study to examine hemodynamic responses to a bout of 30min IDEX. 8 HD patients without CHF and COPD (4 males, 4 with diabetes, age 47±13 years) were recruited from a local HD clinic. Patients received each of two treatments in a random order: 1) normal dialysis session with no intervention and 2) 30 minutes of intradialytic cycling (RPE 11) starting 30 minutes into dialysis. Brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) on the non-dialyzing arm were measured every 15 minutes using an automated cuff built-in to the dialyzer. We found that IDEX helped maintain BP levels from dropping during HD session (**Figure 4-6***)*. In addition to preliminary data from these studies, previous work by our lab demonstrates our experience with the proposed measurement techniques (**Figure 7 and 8**).

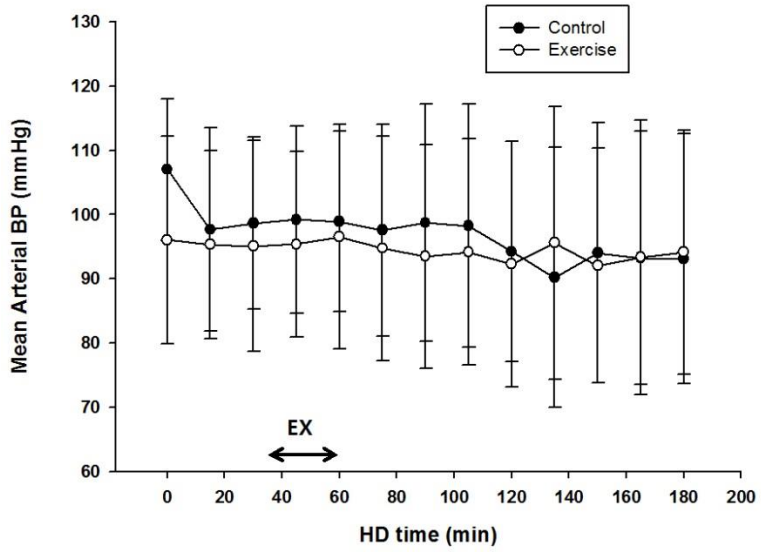

Figure 4. BP responses with IDEX in HD patients.

In a pilot study with 8 HD patients, mean arterial BP decreased over the course of a single HD session ($p=0.029$). However, the decreased trend was blunted with 30 min of IDEX implemented during 1st hour during HD treatment ($p>0.05$). The higher initial BP values on CON day may partly explain the higher magnitude of BP change on CON day than the day with exercise. Based on mixed model of repeated measures with a random effect of patients, there were no significant interactions between Time and Treatment (CON vs EX) in changes in BP, heart rate and relative blood volume indicating a bout of IDEX during 1st hour did not cause greater hemodynamic fluctuation than normal intradialytic hemodynamic response to HD.

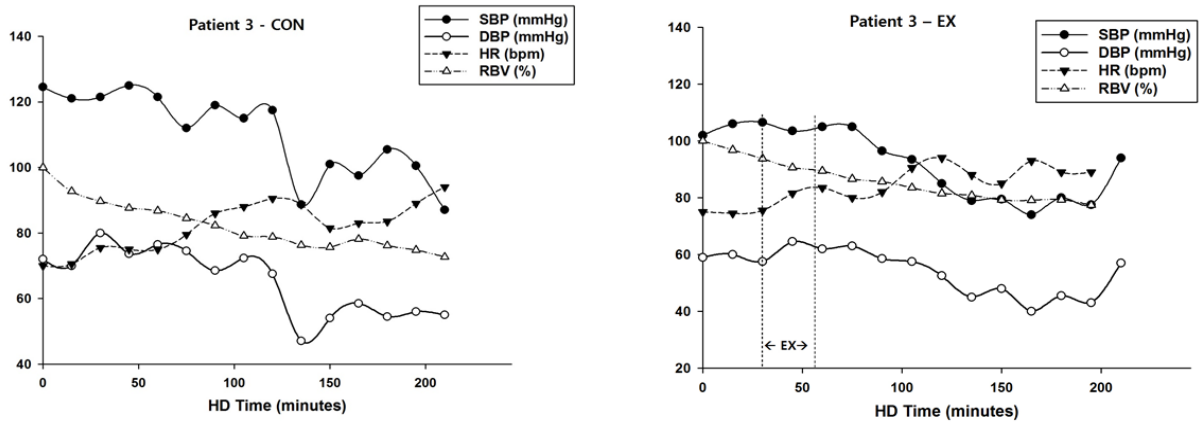

Figure 5. Hemodynamic responses with and without IDEX in a patient with intradialytic hypotension (IDH)

Intradialytic responses of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and relative blood volume (RBV) in a patient who had IDH (SBP <90mmHg during HD) on the normal HD day (CON). The fluctuation of BP responses was reduced on the day received a 30 min of IDEX (EX). Of note, the low initial BP values on EX day may partly explain the blunted BP change. The similar trends were shown in two other patients with IDH (a decrease in SBP >25% from the pre-HD measure) (figures not shown).

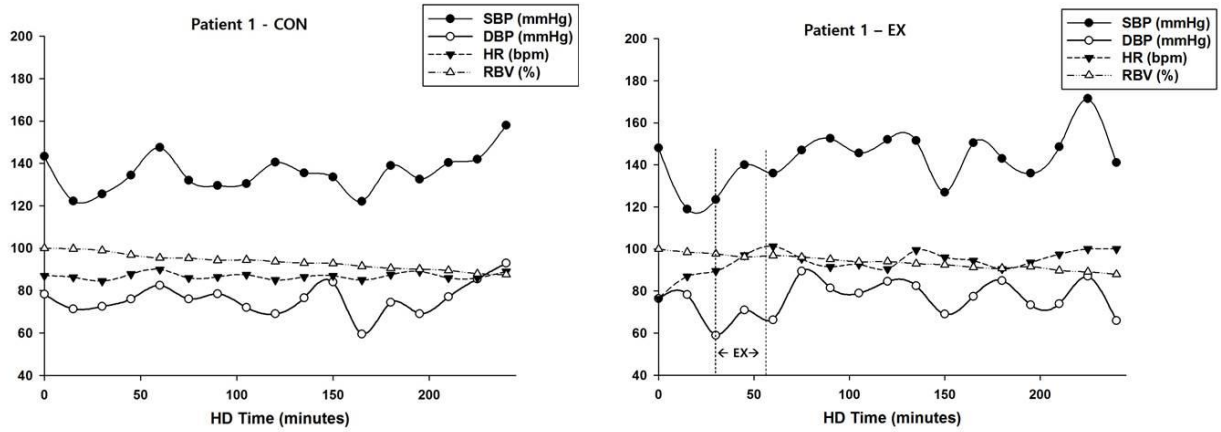

Figure 6. Hemodynamic responses with and without IDEX in a patient with intradialytic hypertension (IDHTN)

Intradialytic responses of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and relative blood volume (RBV) in a patient who had IDHTN (an increase in mean arterial BP >15mmHg during and/or immediately after HD) on the normal HD day (CON) and

on the day received a 30 min of IDEX (EX). The final intradialytic BP was dropped to the initial BP value on the day with IDEX.

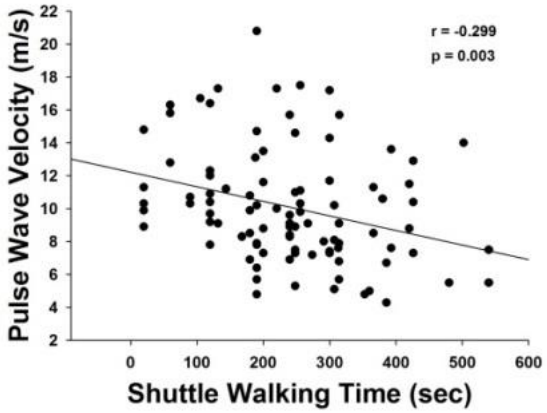

Figure 7. Arterial and Cardiac Relationship to Exercise Intolerance in HD patients. We conducted a cross sectional analysis of CV variables and physical function in 81 HD patients (mean age: 55.4 yr). Walking performance was more closely associated with arterial function (pulse wave velocity) measures than cardiac structure (left ventricular mass) or function (ejection fraction) in HD patients[187].

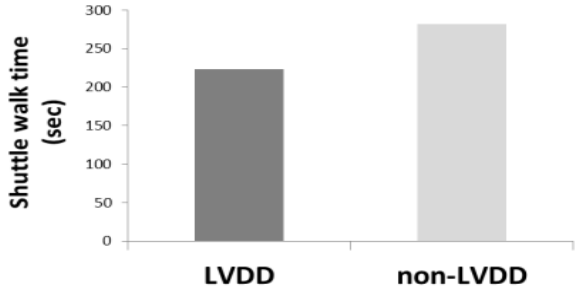

Figure 8. Relationship between left ventricular diastolic function and physical function in HD patients. Subclinical LVDD (left ventricular diastolic dysfunction) was identified in 50% of the patients undergoing HD and had a significant impact on physical function, regardless of age in 86 HD patients (mean age: 52.9 yr). After adjusting for age, shuttle walk distance was longer in the group without LVDD than with LVDD (p=0.031)[188].

CHAPTER 4

PREVIOUS STUDIES

Previously Published: J Nephrol. 2015 Dec;28(6):739-47[189]

THE PRESENCE AND IMPACT OF DIASTOLIC DYSFUNCTION ON PHYSICAL FUNCTION AND BODY COMPOSITION IN HEMODIALYSIS PATIENTS

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Key words: maintenance hemodialysis patients, cardiac abnormalities, diastolic dysfunction, physical function, body composition

Acknowledgements

The authors of this study have no conflict of interests to report. This study was funded the National Institute of Health, NIH (RO1 DK084016-01 to KR. Wilund).

4-1. Abstract

Background: Cardiovascular (CV) diseases are the main cause of death in maintenance hemodialysis (MHD) patients. Muscle wasting and declines in physical function are common in MHD patients, which significantly impair their quality of life. This can result from abnormalities in cardiac function, which can be further worsened by physical deconditioning. Left ventricular diastolic function parameters were recently shown to be a better predictor of exercise capacity than systolic measures in patients with CV complications. Little is known about the relationship between cardiac function and physical function in MHD patients.

Methods: In 82 MHD patients using echocardiography, left ventricular systolic dysfunction (LVSD) was assessed by ejection fraction and fractional shortening, and left ventricular diastolic dysfunction (LVDD) was assessed by pulse wave and tissue Doppler indices. Physical function was assessed by gait speed, performance on a shuttle walk test, and leg muscle strength. DXA was used to measure whole body lean mass (WBLM).

Results: The prevalence of LVDD and LVSD were 48.8% and 12.2% respectively. Gait speed, shuttle walk time, leg strength, and WBLM% were significantly higher in the group without LVDD than with LVDD ($p < 0.05$ for all). However, there was no significant difference in any measure of physical function or body composition between patients with and without LVSD.

Conclusion: This data suggests that LVDD is more closely related to physical function and body composition than LVSD in MHD patients, and suggests that LVDD may be an important therapeutic target.

Key words: maintenance hemodialysis patients, cardiac abnormalities, diastolic dysfunction, physical function, body composition

4-2. Introduction

The prevalence of cardiovascular (CV) disease and CV mortality are excessively high in patients undergoing maintenance hemodialysis (MHD) therapy [190]. Cardiac abnormalities such as left ventricular (LV) hypertrophy, and systolic and diastolic dysfunction are present in up to 80% of MHD patients [85]. These cardiac abnormalities independently predict adverse cardiac events, and are the strongest predictor of mortality in this population [88].

Cardiac abnormalities adversely impact physical function and also can be exacerbated by reduced physical function; however, the relationship between cardiac and physical function in MHD patients is not well established. Decrements in physical function are common in MHD patients and significantly impair their quality of life (QOL) [191]. A variety of non-cardiac factors, such as decreased muscle mass [192], abnormal muscle metabolism [193], and inflammation, are known to contribute to low physical function in MHD patients [1]. However, the evidence linking cardiac abnormalities and physical impairment is limited.

LV diastolic function measures have been proposed to provide better prognostic value in this population because they are less sensitive to blood volume changes than systolic function measures [194]. Furthermore, LV diastolic dysfunction (LVDD), characterized by impaired LV dilation, is strongly associated with poor exercise capacity in other clinical populations including cardiac patients [195] . While inadequate cardiac output and exertional dyspnea may contribute to

poor exercise capacity during LVDD, the exact mechanism is unclear [196]. However, no studies to date have examined the relationship between LVDD and reduced physical functioning in MHD patients. Increasing our understanding of this relationship may help identify novel therapeutic approaches to improve overall health in MHD patients.

Therefore, the purpose of this study was to evaluate 1) the prevalence of LVDD in MHD and 2) the relationship between LVDD and physical function in patients undergoing MHD. We hypothesized that LV diastolic function will be associated with declines in physical function in MHD patients.

4-3. Research Design and Methods

4-3-1. Study population

Eighty two patients receiving MHD therapy were recruited from hemodialysis clinics in Champaign and Oak Park, IL. Patients were screened for eligibility with a health and medical history questionnaire. Inclusion criteria for participation in this study included the following: 1) >3 months of MHD treatment; 2) 30-80 years old; 3) at least 3 days of MHD treatments per week, and,4) medical clearance from a nephrologist to determine patient' eligibility for the study. Subjects were excluded if they had chronic obstructive pulmonary disease (COPD), decompensated congestive heart failure (CHF), or cardiovascular surgery (e.g., coronary bypass

or valve replacement) in the past 6 months. All participants provided written informed consent. All patients were treated using bicarbonate dialysis with blood flow rates between 400 and 600 ml/min and dialysate flow rates between 500 and 800 ml/min with treatment times between 3 and 4 hour/session. Patient clinical information was available only from participants who provided a HIPPA release form. This study was approved by University of Illinois at Urbana-Champaign and at Chicago Institutional Review Boards.

4-3-2. Echocardiography

The transthoracic echocardiographic examinations were performed using a high resolution ultrasound system (ProSound SSD-α7, Aloka, Japan) by two experienced sonographers blinded to all other data and analyzed by a single sonographer. The measurement sessions occurred within 24 hours after a MHD session on a non-dialysis day to minimize the effect of fluid overload. Two-dimensional images were obtained and analyzed according to the recommendations of the American Society of Echocardiography (ASE) [197]. At least 3 consecutive heartbeats in parasternal long and short axis views were acquired. LV volumes and LV mass were measured in M-mode. LV volume parameters were indexed by body surface area (BSA (m^2) = $0.007184 \times \text{weight(kg)}^{0.425} \times \text{height(cm)}^{0.725}$). LVSD was defined as LV EF < 40% using the Teicholz method. Left ventricular mass index (LVMI) was calculated as

LVM/height$^{2.7}$. Left ventricular hypertrophy (LVH) was defined as LVMI > 45 (g/m$^{2.7}$) for females and LVMI > 50 (g/m$^{2.7}$) for males. LV diastolic function was assessed by standard Doppler echocardiographic indices [198]. LV diastolic filling patterns were assessed by placing the pulsed Doppler sample volume between the tips of the mitral valve leaflets. Based on the mitral inflow velocity curve, peak early (E) and late (A) diastolic velocities, E-wave deceleration time (DT), and E/A ratio were assessed. Peak early-diastolic mitral annulus velocity (E') was measured using tissue Doppler imaging of mitral annulus movement. LVDD stages were graded according to ASE guidelines using an integrated evaluation of LV filling patterns by an experienced sonographer blinded to all other data [199] : 1) mild LVDD (E/A < 0.8 , E' <8 cm/s, E/E' < 8 and DT > 200ms), 2) moderate LVDD (0.8< E/A< 2, E' <8 , E/E'<9, and DT <200) and, 3) severe LVDD (E/A>2, E'<8, E/E' >9, and DT <200). The combination of moderate and severe LVDD was classified as 'advanced LVDD'.

4-3-3. Shuttle Walk Test and Gait Speed Assessment

An incremental shuttle walk test (ISWT) was conducted to estimate cardiorespiratory performance[200]. ISWT is a progressive test in which patients walk back and forth continuously over a 10 meter course. The walking speed is paced by a series of auditory signals for the

termination of the 10 meter walk. The test was terminated when the subject was unable to complete the 10m course before the subsequent beep.

Normal gait speed was measured prior to the start of the ISWT while patients walked at a self-selected speed along a 10-meter walkway. Average gait speed was calculated based on 3 trials.

4-3-4. Muscle Strength

Bilateral quadriceps femoris and hamstring muscle strength was evaluated using isokinetic testing modes. Following dynamometer calibration, knee extension and flexion isokinetic peak muscle torque (Nm) was evaluated at a speed of 60 degrees per second on a dynamometer (Biodex Medical Systems, Shirley, NY). Peak torque was recorded for analysis. For all tests, participants were verbally encouraged to perform as vigorously as possible.

4-3-5. Body Composition

Whole body fat, lean and bone mass were measured by dual emission x-ray absorptiometry (DXA, Hologic QDR 4500A, Bedford, MA). Whole body lean mass (WBLM) and regional mineral free lean mass (LM) was calculated by subtracting the bone mineral content

from the LM quantity of the whole body or region of interest. Whole body bone mineral density (BMD) was also measured. Precision for DXA measurements of interest are 1.0 – 2.0% in our laboratory.

4-3-6. Statistics Analysis

Continuous data was compared using one-way analysis of variance testing. Categorical data were compared using χ^2 tests or Fisher exact tests as appropriate. Univariate regression analysis was performed to identify correlates of physical performance and muscle strength. Significant associations indicated by univariate regression analysis were included in the multivariable linear regression models and tested using a stepwise method with the entry and removal criteria of $p<0.05$ and <0.10 respectively. Model 1 adjusted for basic demographic (age) and anthropometric (BMI) measures. Model 2 included additional adjustment for other variables correlated with ISWT. Model 3 and 4 were performed for the relationship between LVDD and leg strength. The strength of the model was expressed using adjusted R-square and p-values. Standardized ß coefficient (ß) was reported to assess its relative independent effect on the outcome variable. A p-value less than 0.05 was considered statistically significant in two-sided tests using SPSS 22.0 (IBM, Armonk, NY).

4-4. Results

4-4-1. Subject Characteristics and Prevalence of LV Diastolic and Systolic Dysfunction

Patient demographics are shown in **Table 1**. The mean dialysis vintage available from fifty nine patients was 42.9 ± 37.9 months. Races were African American (76.8%) and Caucasian (22.0%). The primary causes of ESRD were hypertension (55.7%), diabetes (29.2%), polycystic kidney (10.1%) and nephritis/nephropathy (5.0%). There was no difference in race and primary ESRD causes between groups with and without LVDD. The prevalence of LVDD was 48.7% (34.1% with advanced LVDD and 14.6% with mild LVDD). LVSD was identified in 10 patients (12.2%).

4-4-2. Body composition and LVDD

WBLM % and leg LM % were significantly lower in the group with LVDD than without LVDD (**Table 1**).

4-4-3. Physical function and LVDD

Patients with LVDD had a significantly slower gait speed and poorer performance on the ISWT and leg maximal extension and flexion than the group without LVDD (**Figure 1**).

4-4-4. CV parameters and LVDD

There was no difference in CV parameters, with the exception of E' and E/E', between groups with and without LVDD (**Table 2**). Due to the body size difference (BMI) between groups with and without LVDD, stroke volume index (SVI) and cardiac output index (COI) were compared.

4-4-5. Predictors of Physical Performance (ISWT and Leg Strength)

LVDD, age, BMI, WBLM% and diabetes status were each significantly correlated with ISWT by univariate analysis, so were included in the multivariable linear regression models. In Model 1, both age and LVDD, but not BMI, significantly predicted ISWT performance. In Model 2, age, WBLM% and diabetes status, but not LVDD and BMI, significantly predicted ISWT performance (**Table 3**). Similar relationships were found between gait speed and LVDD (data not shown).

LVDD and WBLM% were significantly correlated with leg extension strength by univariate regression. LVDD remained significant in the multivariable Model 3 when age and BMI were entered together, but was not a significant predictor when WBLM was entered into the multivariable Model 4 (**Table 3**).

LVDD, BMI and diabetes were each significantly correlated with WBLM by univariate regression. LVDD remained a significant predictor of WBLM when age and diabetes were entered together into a multivariable regression model (R^2 =.10 and p=0.002).

4-4-6. LVSD and physical function and body composition parameters

There was no difference in all demographic, body composition, physical function performance and cardiac parameters except systolic function measures (SVI, COI, EF and FS) between groups with and without LVSD in our study population (**Table 4**).

4-5. Discussion

This study examined the relationship between cardiac function, physical function and performance, and body composition in MHD patients without overt CHF. The primary findings included the following: 1) the prevalence of LVDD was significantly higher than LVSD; 2) physical function (gait speed) and physical performance (ISWT and leg muscle strength) were reduced in those with LVDD; and 3) those with LVDD had a reduced whole body and leg LM%. By contrast, no differences in physical function and body composition were seen in MHD patients with and without LVSD. Our findings suggest that LVDD is associated with declines in physical performance and body composition in MHD patients. To our knowledge, this is the first

study to analyze the relationship between LVDD, physical performance and body composition in MHD patients.

Our echocardiographic data showed that approximately half of MHD patients had LVDD while the prevalence of LVSD was much lower (12%). Other studies reported a similar incidence of LVDD (50-75%) and LVSD (10~40 %) in MHD patients including those with CHF [201]. It should be noted that this present study excluded patients with decompensated CHF. CHF can be caused by LVSD, LVDD or both, but LVSD identified by a decreased EF is commonly used as an echocardiographic diagnostic for CHF [202]. Moreover, a lack of diagnostic knowledge in diastolic CHF has challenged early and accurate diastolic CHF diagnosis [203]. This may explain the relatively low LVSD and the high LVDD prevalence in our findings.

LVH was identified in 83.7% of patients in our analysis, which is consistent with previous findings in MHD patients [204]. This high LVH prevalence suggests that LV structural remodeling may precede development of cardiac dysfunction regardless of the presence of decompensated CHF in MHD patients. Indeed, LVH is known to initiate a vicious cycle of cardiac maladaptation in MHD patients [205]. Together with accompanying interstitial fibrosis and myocardial ischemia, increases in LV mass contributes to impaired LV diastolic distensibility, a main feature of LVDD. As LVDD progresses, LV end-diastolic pressure increases as a

consequence of inadequate LV filling in response to a given change in blood volume. Therefore, patients with LVDD may suffer from CV complications due to an inability to adjust LV volume for a given change in pressure. This results in either 1) pulmonary congestion with an increased blood volume or 2) hypotension with a decreased blood volume. This has significant clinical implications for MHD patients who experience frequent blood volume shifts between MHD treatments and during a MHD treatment. Therefore, identification of LVDD would provide important information for therapeutic strategies to prevent adverse CV events in MHD patients.

One interesting observation was a higher percentage of females in the LVDD group than in the non-LVDD group (57.5% vs 26.2% respectively, p=0.004). Although not accounted for in this study, hormonal factors may have contributed to the high prevalence of LVDD in female dialysis patients. Female MHD patients have female-hormone related symptoms and accelerated rates of CVD and mortality compared to the general female population [206] . Further investigation is needed to confirm the relationship between female hormonal abnormalities and cardiac dysfunction in this population.

Growing evidence suggests that MHD patients experience reduced physical functioning, which is associated with a poor prognosis and impaired QOL [57]. Exercise capacity has been shown to be approximately 50% of the level of healthy sedentary controls [58]. Physiologically,

exercise capacity is affected by the efficiency of oxygen delivery (central factors) and oxygen utilization (peripheral factors). The peripheral contributors such as decreased muscle mass [192] and muscle metabolism [193] have been reported in MHD patients. However, few studies have examined cardiac mechanisms underlying declines in physical function, and the data that exist mostly used LV systolic function measures that are volume dependent in MHD patients [66].

In this present study, patients with LVDD had significantly slower gait speed, poorer performance on shuttle walk test, and reduced hamstring and quadriceps strength. Regression analysis revealed that LVDD was an independent predictor of walking performance and muscle strength even after adjusting for age, but not when additionally adjusting for WBLM and diabetes in our study population.

A possible pathophysiological explanation for this association is that LVDD leads to limited LV filling and decreased cardiac output even with preserved systolic function. Especially, during exercise, the failure to increase cardiac output in response to the increased oxygen demand may significantly limit exercise performance [207]. Additionally, an increased LV filling pressure, a hallmark of LVDD, frequently coincides with an augmented left atrial pressure and consequently leads to ventilation-perfusion abnormalities. This can limit exercise capacity as well [196]. Respiratory muscle weakness, a cause for dyspnea and tachypnea, has also been shown to be closely related to LVDD [208]. Regarding strength, abnormal skeletal muscle metabolism,

including impaired mitochondrial energy transfer and ATP production have been found in heart failure models, and may also partially explain the strength decline in patients with LVDD [209].

In MHD patients, it has been suggested that LV diastolic performance may reflect CV fitness more than systolic function due to the volume dependence of LV systolic function measures [201]. Although the contribution of LV systolic function to physical performance has been studied widely, recent studies reported echocardiographic LV systolic function parameters were poor predictors of exercise capacity in patients with mild and severe cardiac disorders [207]. Studies demonstrated that LV diastolic function surrogates such as E', E/E' and left atrial volume were strongly associated with exercise capacity in cardiac patients [210]. This present study found that only LVDD, not LVSD, was significantly related to physical function and body composition in MHD patients.

We also found correlations between body composition (LM%) and body size (BMI) and cardiac function in MHD patients. Previous studies demonstrated an unfavorable effect of high BMI on mortality when body sizes were assessed separately as LM and fat mass (FM) to further stratify wasting symptoms. For example, a high BMI with a low ratio of LM to FM, called sarcopenic obesity, was associated with increased systemic inflammation and high

mortality rates in MHD patients [211]. Apart from mortality data, little is known about the contribution of increased body size, and even less with FM or LM, on cardiac function in MHD patients. In the present study, patients with LVDD had a higher BMI and lower WBLM% than the group without LVDD. Also, decreasing WBLM% was significantly correlated with impaired walking capacity ($p < 0.001$, data not shown), but this trend was not significant after controlling for body weight in our analysis. Indeed, LM predicts exercise capacity better than total body weight in the general population [212]. Furthermore, whole body FM was associated with unfavorable CV adaptations such as increased blood pressure, impaired LV contractility and LVH, whereas increased WBLM was primarily related to preload determinants such as CO and SV, perhaps due to the increased metabolic needs of skeletal muscle [213]. Taken together, our findings suggest body FM and LM should be used to further refine stratification of CV risk in relation to cardiac dysfunction in clinical settings in MHD patients.

4-6. Strengths and Limitations

To our knowledge, this is the first study that assessed the correlation between LV diastolic function and functional capacity in MHD patients. This present study excluded patients with CV complications that are known to limit physical function. Therefore, the impact of LVDD on physical performance was not confounded by other common CV complications in our

analysis. However, these exclusions resulted in our study population being younger and fitter than the general dialysis population, thus our results may not be valid for older and less fit MHD patients. The low prevalence of LVSD may limit the statistical power to detect significant difference between groups with and without LVSD. It is possible that use of other criteria to identify LVSD such as tissue Doppler S-wave velocity and global strain by speckle tracking could have added more precision to our determination of LVSD. However, because there are no clinically accepted cut points for defining LVSD using these methodologies, we did not include them in this analysis. The most validated technique to estimate LV filling pressures, invasive catheters, was not used, and other possible contributors that affect LV diastolic function such as left atrial volume and filling profiles and arterial stiffness parameters were not available in this study. However, integrated indices using echocardiographic pulsed and tissue Doppler assessments that our study used are widely validated to estimate LV filling pressure for LVDD classification, and their subclinical prognostic values have been well confirmed in patients with ESRD [201]. Body composition measures by DXA are fluid dependent, but the measurement sessions in our study occurred 24 hours after a dialysis session on a non-dialysis day to minimize the effect of fluid overload. Additionally, the design was cross-sectional, making a causal relationship impossible.

4-7. Conclusion

The prevalence of LVDD was higher than LVSD in MHD patients without major CV complications such as CHF. The severity of LVDD was related to physical functional capacity and body composition in this population. Furthermore, our data suggests that distinguishing between body fat and lean mass may improve CV risk stratification in relation to cardiac dysfunction. Further investigation is needed to confirm these findings, including in MHD patients with diagnosed CV comorbidities.

Table 2. Subject Characteristics

	Total (n=82)[a]	Patients with LVDD (n=40)[a]	Patients without LVDD (n=42)[a]	p-value[b]
Gender (male,%)	48 (58.5%)	17 (42.5%)	31 (73.8%)	**0.004**
Age (y)	54.5 ± 12.0	53.7 ± 12.4	55.2 ± 11.8	0.559
BMI (kg/m^2)	31.5 ± 7.2	33.5 ± 7.6	29.5 ± 6.3	**0.011**
WBLM (%)	66.2 ± 10.5	62.6 ± 9.0	69.6 ± 10.8	**0.002**
BMD (g/cm^2)	1.1± 0.2	1.1 ±0.2	1.1 ± 0.2	0.834
SBP (mmHg)	134.0 ± 28.0	133.2 ± 32.1	134.7 ± 23.9	0.825
DBP (mmHg)	75.0 ± 16.8	74.4 ± 19	75.8 ± 14.6	0.729
Smoking status (n, %)	23 (34.2%)	8 (20%)	15 (35.7%)	0.113
Diabetes (n, %)	40 (48.7%)	21(52.5%)	19 (45.2%)	0.511

a: Data expressed as mean ± SD for continuous variables and numbers for countable variables
b: p-value for group difference between patients with and without LVDD
BMI = body mass index, **WBLM** = whole body lean mass, **LM** = lean mass, **BMD** = whole body bone mineral density, **SBP** = resting brachial systolic blood pressure, **DBP**= resting brachial diastolic blood pressure.

Table 3. Cardiac Function Parameters in Patients With and Without LVDD

	Total[a]	Patients with LVDD (N=40)[a]	Patients without LVDD (N=42)[a]	p-value[b]
SVI(mL/m^2)	28.3 ± 14.6	25.8 ± 13.2	30.7 ± 15.7	0.144
COI (L/m^2)	2.2 ± 21.3	2.1 ± 1.1	2.2 ± 1.5	0.910
EF (%)	58.8 ± 18.4	58.4 ± 19.7	59.2 ± 17.3	0.857
FS (%)	31.3 ± 14.3	30.5 ± 15.2	32.1 ±13.5	0.648
LVMI (g/$m^{2.7}$)	74.9 ± 40.5	75.8 ± 40.8	73.9 ± 40.6	0.829
LVH (n, %)	62 (87%)	32 (80%)	30 (71.4%)	0.096
E/A	1.1 ± 0.4	1.1 ± 0.5	1.0 ± 0.3	0.336
E' (cm/s)	11.0 ± 5.0	8.8 ± 3.9	13.0 ±5.0	**< 0.001**
A'(cm/s)	11.7 ± 4.8	10.5 ± 4	12.7 ± 5.1	**0.039**
E/E'	7.6 ± 4.3	10.1 ± 4.8	5.5 ± 2.3	**< 0.001**
DT of E (ms)	164.4 ± 75.0	157.1 ± 63.0	171.4 ± 85.1	0.390
LVSD (n)	10	5	5	0.868

a: Data expressed as mean ± SD for continuous values and a number for countable values.

b: p-value for group differences between patients with and without LV DD, , **SVI**= stroke volume indexed by BSA, **COI**= cardiac output indexed by BSA **, EF**= ejection fraction, **FS**= fractional shortening, **LVMI**: left ventricular mass index; LVM/height$^{2.7}$, **LVH**= left ventricular hypertrophy, **E/A**= the ratio of early / late diastolic mitral valve flow velocity, **E'**= peak early diastolic mitral annulus velocity, **A'**= peak late diastolic mitral annulus velocity, **DT of E**= deceleration time of early diastolic mitral valve flow (E), **LVSD**: left ventricular systolic dysfunction.

Table 4. Univariate and Multivariate Predictors of Physical Performance in ISWT and Leg Strength

ISWT	Univariate model		Multivariable model 1 Adjusted R^2 = 0.203, p < 0.001		Multivariable model 2 Adjusted R^2 = 0.338, p < 0.001	
	β	p	β	p	β	P
LVDD	-.303	**0.007**	-.307	**0.004**	-.187	0.116
Age	-.359	**0.001**	-.361	**0.001**	-.335	**0.001**
BMI	-.254	**0.025**	-.226	0.051	.023	0.850
WBLM%	.435	**<0.001**			.328	**0.001**
Diabetes	-.369	**< 0.001**			-.290	**0.004**

Leg Strength	Univariate model		Multivariable model 3 Adjusted R^2 = 0.044, p = 0.039		Multivariable model 4 Adjusted R^2 = 0.098, p = 0.004	
	β	p	β	p	β	P
LVDD	-.238	**0.039**	-.238	**0.039**	-.159	0.179
Age	-.180	0.119	-.194	0.087	-.152	0.174
BMI	-.108	0.355	-.047	0.694	.240	0.135
WBLM%	.332	**0.004**			.332	**0.004**
Diabetes	-.008	0.944			-.084	0.469

The relationship between LVDD presence and ISWT and leg strength performance and potential confounders (age, BMI, WBLM, diabetes status) of these associations were tested in univariate regression analysis. Multivariable Model 1 and 3 tested multivariable prediction of LVDD, age and BMI on ISWT and leg strength respectively. Multivariable Model 2 and 4 added WBLM and diabetes status into Model 1 and 3.

Table 5. Demographic, Physical and Cardiac Function Parameters in Patients With and Without LVSD

	Patients with LVSD (N=10)[a]	Patients without LVSD (N=71)[a]	p-value[b]
Age (y)	54.9 ± 11.3	54.4 ± 12.2	0.905
BMI (kg/m^2)	32.5 ± 8.0	31.3 ± 7.1	0.631
WBLM (%)	64.4 ± 10.3	66.7 ± 10.6	0.520
Physical Function			
ISWT (sec)	188.0 ± 102.1	261.4 ± 117.7	0.066
Gait speed (m/sec)	0.7 ± 0.2	0.9 ± 0.3	0.125
Peak torque extension (Nm)	87.1 ± 34.1	80.3 ± 39.9	0.627
Peak torque flexion (Nm)	41.2 ± 13.8	39.1 ± 21.5	0.780
Cardiac Function			
SBP (mmHg)	125.8 ± 26.2	135.6 ± 28.2	0.327
DBP (mmHg)	77.3 ± 18.1	74.9 ± 16.9	0.690
SVI(mL/m^2)	11.6 ± 5.3	30.8 ± 13.9	**< 0.001**
COI (L/m^2)	0.9 ± 0.5	2.4 ± 1.3	**< 0.001**
FS (%)	10.5 ± 5.0	34.7 ± 12.2	**< 0.001**
LVMI (g/m$^{2.7}$)	66.4± 13.5	77.1 ± 42.1	0.111
LVH (n, %)	3 (30%)	55 (77.5%)	0.108
E/A	1.1 ± 0.5	1.0 ± 0.3	0.336
S' (cm/s)	10.8 ± 4.0	8.9 ±3.7	0.170
E'(cm/s)	13.2± 6.0	10.7 ± 4.8	0.160
E/E'	5.9 ± 3.3	7.9 ± 4.4	0.225
LVDD (n)	5	35	0.615

a: Data expressed as mean ± SD for continuous values and a number for countable values.
b: p-value for group differences between patients with and without LVSD, **BMI** = body mass index, **WBLM** = whole body lean mass, **ISWT** = incremental shuttle walk test, **SBP** = resting brachial systolic blood pressure, **DBP**= resting brachial diastolic blood pressure, **SVI**= stroke volume indexed by BSA, **COI**= cardiac output indexed by BSA **, EF**= ejection fraction, **FS**= fractional shortening, **LVMI**: left ventricular mass index; LVM/height$^{2.7}$, **LVH**= left ventricular hypertrophy, **E/A**= the ratio of early / late diastolic mitral valve flow velocity, **S'**= peak systolic mitral annulus velocity, **E'**= peak early diastolic mitral annulus velocity.

Table 6. Abbreviation Table

Abbreviations	Definitions
BMD	Bone mineral density
BMI	Body mass index
BSA	Body Surface Area
CHF	Congestive Heart Failure
COI	Cardiac output index
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
DBP	Diastolic blood pressure
DT of E	Deceleration time of E’
DXA	Dual emission x-ray absorptiometry
E/A	Diastolic early to late mitral flow velocity ratio
E’, A’	Peak early / late diastolic mitral annulus velocity
EF	Ejection fraction
ESRD	End-stage renal disease
FM	Fat mass
FS	Fractional shortening
ISWT	Incremental shuttle walk test
LM	Lean mass
LV	Left ventricular
LVDD	Left ventricular diastolic dysfunction
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
LVSD	Left ventricular systolic dysfunction
MHD	Maintenance Hemodialysis Patients
SBP	Systolic blood pressure
SVI	Stroke volume index
WBLM	Whole body lean mass

CHAPTER 5

RESEARCH DESIGN AND METHODS

5-1. Study Overview

This study was a cross-over design with 3 randomized conditions. Twenty-eight HD patients from local dialysis clinics in Champaign, IL were approached, and 12 agreed to participate. Reasons for exclusion were no interest (n=7), not eligible (n=6), transplant (n=1) and switching to peritoneal dialysis (n=2). Inclusion/exclusion criteria included the following: 1) receive HD treatment at least three days per week; 2) 30-70 years of age; 3) on HD treatment for > three months, due to physiological changes that typically occur at the onset of dialysis; 4) be physically able to exercise (e.g., no orthopedic problems that would preclude them from cycling during dialysis); 5) no chronic obstructive pulmonary disease or decompensated congestive heart failure, due to limitations in exercise capacity; 6) receive medical clearance from their Nephrologist to participate; 7) have no changes in antihypertensive therapy in the 4 weeks before enrollment, and unchanged dose and timing of antihypertensive drug intake during the trial. All patients provided informed consent and the trial was registered at Clinicaltrials.gov NCT02753868.

5-2. Intervention

Following the initial screening, patients were assigned to receive *each of three treatments* in a random order during their normally scheduled HD session at the Champaign-Urbana Dialysis Clinics. All interventions were administered on the mid-week dialysis session one week apart. The interventions included: 1) no intervention control (normal dialysis session), 2) exercise on a stationary cycle for 30 minutes starting 30 minutes after the start of ultrafiltration, 3) exercise on a stationary cycle for 30 minutes starting 3 hours after the start of ultrafiltration. On days patients were asked to exercise, a stationary cycle (Monark Rehab Trainer 881E) was placed in front of the dialysis chair and patients were asked to cycle at a self-selected pace and resistance that coincides with a subjective exertion between 11 and 13 on the rating of perceived exertion (RPE) scale. A series of CV measures were collected before, during, and after each HD session (**Figure 9**).

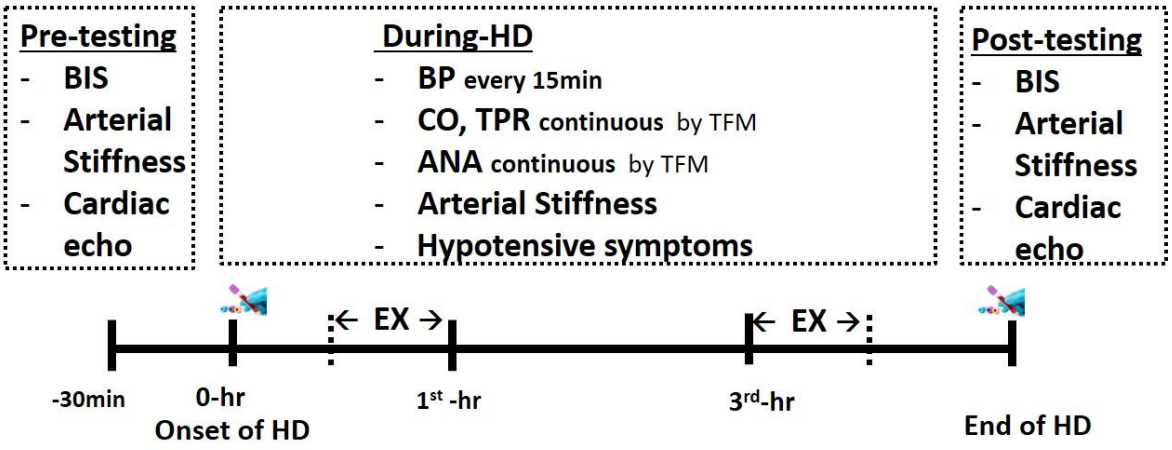


Figure 9. Study Overview

BIS: Bioimpedence Spectroscopy (for hydration status), **Cardiac Echo**: Cardiac Echocardiography, **BP**: Blood Pressure, **CO**: Cardiac Output, **TPR**: Total Peripheral Resistance, **ANA**: Autonomic Nerve System Activity, **TFM**: Task Force Monitor (thoracic bioimpedance), **EX**: Exercise, **HD**: Hemodialysis

5-3. Measurements

5-3-1. Pre- and Post- HD Testing

A battery of measurements (described below) were collected on each patient immediately prior to, and immediately following their HD sessions on each of the three intervention days. For the pre-HD measurements, patients were asked to lay in a supine position for up to 30min before the start of HD treatment, during which cardiac and arterial measures and hydration status were collected. The same procedures were conducted immediately after the end of their HD treatments.

- Cardiac Function: Transthoracic echocardiography was performed (*ProSound α-7, Aloka*) according to the recommendations of the American Society of Echocardiography[214]. In short, the parasternal short-axis view was used to determine left ventricular volumes using the Teichholz equation. In the 4-chamber view, early (E) and late (A) flow in to the left ventricle and tissue movement (S', E' and A') were measured by Doppler.

- **Arterial Function:** Arterial function was measured using an automated BP cuff (*Mobil-O-Graph*) that was placed on the non-dialyzing arm of the patient. In addition to standard brachial BP measurement, the cuff remained inflated at DBP for 10-15 additional seconds to measure pressure wave reflection to calculate augmented pressure (Aix). This technique also allowed us to obtain estimates of central BP at the level of the aorta and arterial stiffness (pulse wave velocity).

- **Hydration Status:** Whole body hydration status was measured by multi-frequency bioimpedence spectroscopy (BIS) (*SFB7, Impedimed Inc.,CA,USA*). Three measures were collected and averaged for analysis. Electrodes and recording pads were placed on the non-access side of ankle and wrist and connected to the device that utilizes low and high frequency currents to estimate extracellular water (ECW), intracellular water (ICW) and total body water (TBW). Based on these terms, hydration status, represented as fluid overload (FO) was defined using the following variables:

Absolute FO: FO (L) = 1.136 * ECW(liter) - 0.430 * ICW (liter) - 0.114 * Body weight(kg)[215]

Relative FO: FO% = Absolute FO / ECW) *100 [216]

Hyperhydration is defined as: $FO\%_{Pre\text{-}HD} > 15\%$[216]

Underhydration is defined as: $FO\%_{Pre\text{-}HD} < 6.8\%$[216]

5-3-2. Testing ***during*** HD sessions

The following testing measures were conducted during all three intervention days.

- **Blood Pressure:** Brachial BP was measured on the non-dialyzing arm every 15 minutes throughout the HD session using an automated BP cuff integrated into the dialysis unit. Aortic BP and pulse wave reflection were also obtained every hour using a second automated BP cuff (*Mobil-O-Graph*).

- Hemodynamics and Autonomic Monitoring: Stroke volume (SV) was continuously estimated by transthoracic impedance and used to calculate cardiac output (CO) along with ECG-driven heart rate (HR) (*Task Force Monitor, CNSystems*). Beat-to-beat peripheral BP was derived via finger plethysmography and was used to calculate total peripheral resistance (TPR). Finger BP measurements were collected for 10 minutes, at 30 minute intervals throughout the treatment, using a finger cuff placed on the index and middle fingers of the arm not containing

the vascular access. Intermittent finger cuff measurements (as opposed to continuous) were done so as not to interfere with clinic BP measurements and also to minimize patient burden.

Measures of autonomic function was measured by heart rate variability (HRV) with the intervals between successive heart beats and blood pressure variability (BPV) with the beat-to-beat peripheral BP. Frequency domain analysis using Fast Fourier transformation generates low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.40 Hz) components by an autoregressive model, from which the LF/HF ratio is calculated. The LF band of HRV has been shown to be associated with baroreceptor-mediated regulation of BP and suggests a mixed modulation of sympathetic and parasympathetic activities. The HF component of HRV reflects vagal modulation of the sinoatrial node and is thus used a surrogate marker of parasympathetic modulation. LF/HF ratio is suggested to be an index of sympathovagal balance, with high values suggesting sympathetic predominance. Normalized units of LF and HF to the total power (LFnu and HFnu, respectively) were also calculated. BPV analysis provides information related to sympathetic modulation through the LF component measures.

Baroreflex sensitivity (BRS), an index of arterial baroreflex function, was estimated using the spontaneous sequence method. Time series of R-R intervals and SBP were analyzed to identify sequences in which SBP and R-R interval increased or decreased concurrently over at least 3 cardiac cycles. The average value of the individual slopes was taken as the measure of

BRS. Data are reported as the average of all beats in each measured time segment to represent every 30 minutes throughout an HD treatment. Beats that were greater than 20% different from the previous beat were excluded under the assumption that this was an artifact due to patient movement.

- **Blood Chemistry:** 5mL of blood were drawn from each patient before the start of HD and 30 seconds after the end of HD session with the help of clinic nursing staff. The blood samples were used to measure changes in serum albumin, glucose, calcium and phosphorus using an auto analyzer (Piccolo Xpress®, POCT Ltd) and Piccolo® Renal Panels.

- Intradialytic CV-adverse Events and Symptoms Assessment

Hypotension-related intradialytic adverse events were defined as one or both of the following conditions recorded during a HD session: (i) a fall of SBP to less than 90 mmHg during HD, and/or (ii) a fall of SBP of more than 25% from the start of dialysis associated with symptoms related to hypotension, including dizziness, vomiting, nausea, and muscle cramps, and may require an intervention to be corrected (modifying dialysate temperature, stopping ultrafiltration, or saline solution boluses to increase SBP to 100-110 mm Hg)[217]. Hypertension-related intradialytic adverse events were defined as an increase in mean BP over 15mmHg during or after a HD session[218].

Intradialytic symptoms were subjectively assessed by asking patients to complete a questionnaire immediately following HD to describe the nature and severity of symptoms experienced during the preceding treatment. The questionnaire was created based on the previous literature reported detailed methodologies of collection of intradialytic symptoms. The questionnaire included symptoms of nausea, dizziness and cramps, stratified severity of none, trivial, mild, moderate, and severe and scored 0, 1, 2, 3, or 4, respectively. Post-HD symptoms were collected using the same questionnaire and the Fatigue Severity Scale (FSS) questionnaire by contacting patients over the phone 5-hours after the preceding HD treatment was ended[219]. FSS questionnaire measures levels of fatigue with stratified scales from 0 being worse to 10 being normal and includes nine statements designed to evaluate different dimensions of fatigue: general fatigue, physical fatigue, motivation, interfering with work, family or social life[220].

5-3-3. Clinical factors

A variety of information from clinic records related to the patient's treatment were collected. This includes intradialytic BP changes for the last two weeks prior to the intervention to monitor the typical BP response to HD, the participant's interdialytic weight gain (IDWG) since the previous treatment, the volume of fluid removed during the treatment, the composition of the dialysate used during the treatment, and the rate of flow of both the blood and dialysate through

the hemodialysis machine during the treatment. Monthly standard blood chemistry values were collected from each participant from the month prior to their enrollment. These values included serum albumin, phosphorus, and calcium.

The participants were asked to refrain from using non-steroidal anti-inflammatory (NSAID) medications for 7 days prior to the study, as this may affect the results from this study. Additionally, on the day of testing the participant were asked to refrain from drinking caffeinated beverages.

5-4. Statistical Analysis

Variables collected at pre- and post-HD were compared by paired t-tests and also tested for difference between three intervention days by one-way analysis of variance (ANOVA). As a primary analysis, the changes in hemodynamic variables during HD were analyzed by Mixed Model Analysis with Repeated Measures with fixed effects of Exercise (CON, 1st-hour EX and 3rd-hour EX) and Time and a random effect of patients to control for their associated intraclass correlation. This analysis was conducted both in the pool of all participating patients (n=12) and in the subset of patients who completed all three intervention sessions (n=8). This model also tolerates the necessarily unequal number of response variables. To examine the influence of hydration status on intradialytic hemodynamic changes, markers of hydration status

(ultrafiltration goal volume, IDWG and FO) were additionally entered into the same models. Furthermore, between group comparisons were conducted to examine the difference among three intervention days at each measured time point (i.e.,15-minute interval for BP and 30-minute interval for cardiac and autonomic data) throughout HD. For example for SBP, both the absolute ($SBP_{i\text{-}min}$, the level of SBP at i-minutes into HD) and the difference ("delta") values between the beginning and i-minutes of HD ($\Delta SBP_{i-0\text{-}min} = SBP_{i\text{-}min} - SBP_{0\text{-}min}$) were compared between three intervention days by one-way ANOVA. For the cardiac and autonomic data, their time annotations in delta values reflect an end time of a 30-minutes interval (i.e., $\Delta SV_{60\text{-}30min} = SV_{30\sim60min} - SV_{0\sim30min}$). When a significance was presented by ANOVA, LSD post-hoc analysis was used to further elucidate the difference between two groups. Primary outcomes include intradialytic changes in BP, CO and TPR. Secondary outcomes include intradialytic changes in markers of arterial stiffness and autonomic activity. LF and HF measures in HRV and BPV data were not normally distributed by Shapiro-Wilks tests, and thus the log transformed variables of LF and HF were used for analysis.

Secondary analysis was performed to enhance our understanding of the factors influencing BP regulation during HD. Independent determinants of SBP changes during HD were explored by entering each target variable (CO, SV, HR, TPR, LFnu and LF/HF) into the Mixed Model with Repeated Measures as a covariate. Correlation between the delta values of different

hemodynamic variables were also examined by Pearson Correlation tests. Clinical and hemodynamic factors were compared between HD sessions with and without IDH or IDHPT. SAS version 9.4 (SAS Inc.) and SPSS version 22.0 SPSS Inc.) were utilized for data analysis, with $P < 0.05$ considered statistically significant.

CHAPTER 6

RESULTS

6-1. Patient characteristics

Descriptive characteristics of study participants are presented in **Table 7**. Patients were predominantly African American and all except one patient had hypertension. Three patients completed two intervention days (CON and 1st-hr EX but not 3rd-hr EX) because they no longer wanted to participate, and one patient only finished the CON day due to an ankle injury not related to the study. Thus, the number of patients completing CON, 1st-hr EX, and 3rd-hr EX was 12, 11, and 8, respectively.

Table 7. **Patient Characteristics**

Characteristics (n=12)	**Mean ± SD**
Age (yr)	55.9 ± 8.6
Height (cm)	171.5 ± 10.0
Body Weight at pre-HD (kg)	83.3 ± 20.2
BMI (kg/m^2)	48.5 ± 14.6
Gender (male/female)	7 / 5
Race	
African American (n, %)	10 (83.3%)
Caucasian (n, %)	2 (16.7%)
Diabetes (n, %)	4 (33.3%)
Hypertension (n, %)	11 (91.7%)
Smoking (n, %)	8 (66.7%)
Albumin (g/dL)	3.9 ± 0.3
Hemoglobin (g/dL)	32.0 ± 7.2
iPTH (pg/mL)	583.6 ± 394.9
Calcium (mg/dL)	8.5 ± 0.8
Phosphorus (g/dL)	5.3 ± 1.7
Potassium (mEq/L)	4.7 ± 0.5
Bicarbonate (g/dL)	23.2 ± 2.6
BUN-to-creatinine	4.9 ± 1.6
Neutrophil:lymphocyte ratio	2.8 ± 0.9

BMI: body mass index, **PTH**: parathyroid hormone, **BUN**: blood urea nitrogen, **iPTH:** intact parathyroid hormone, **BUN**: blood urea nitrogen

6-2. Comparison of treatment-related parameters at Pre- and Post-HD

A comparison of HD treatment-related parameters across the three treatment days, including weights, hydration status, blood chemistries, and intradialytic symptoms are presented

in **Table 8**. While a number of variables related to fluid status and solute concentration changed in expected directions between the pre- and post-HD measurements, there were no significant differences in these variables across the different treatment days.

Out of the thirty-one HD sessions, ten and five sessions were identified as HD sessions with IDH and IDHTP, respectively. Seven sessions with IDH were symptomatic. In sessions with and without IDH, pre-HD and delta values from the beginning to end of HD were compared for selected CV characteristics, including SV, CO, TPR, LFnu, and BRS. No difference was found between the sessions with and without IDH (data no shown).

Table 8. Treatment-related parameters, Hydration Status, and Blood Parameters at Pre- and Post-HD

Variables	Total	CON	1st-hr EX	3rd-hr EX
IDWG (kg)	2.3 ± 1.1	2.2 ± 1.1	2.4 ± 1.1	2.3 ± 1.1
Ultrafiltration Goal (L)	2.83 ± 1.09	2.94 ± 0.84	2.74 ± 1.14	2.77 ± 1.44
Body Weight at pre-HD (kg)	83.3 ± 20.2	84.0 ± 20.8	85.0 ± 22.9	80.0 ± 17.4
Body Weight at post-HD (kg)	82.1 ± 21.3*	83.1 ± 22.2	84.6 ± 24.1	77.5 ± 18.4
Hydration Status Parameters				
TBW at pre-HD (L)	49.5 ± 9.4	49.9 ± 9.4	50.6 ± 11.3	47.4 ± 6.8
TBW at post-HD (L)	46.0 ± 6.9*	45.7 ± 6.9	46.6 ± 7.6	45.6± 6.6
TBW at pre-HD (%)	61.0 ± 11.5	61.3 ±14.3	60.7 ± 10.1	61.0 ± 10.0
TBW at post-HD (%)	58.6 ± 11.6*	58.4 ±11.8	57.7 ± 12.9	60.1 ± 11.2
ECW at pre-HD (L)	21.7 ± 2.8	21.8 ± 2.6	22.1 ± 3.6	21.0 ± 1.9
ECW at post-HD (L)	19.7 ± 2.2*	19.6 ± 2.3	20.0 ± 2.7	19.4 ± 1.5
ECW at pre-HD (%)	44.3 ± 3.5	44.3 ± 4.3	44.2 ± 3.4	44.6 ± 2.7
ECW at post-HD (%)	42.3 ± 4.3*	41.6 ± 5.3	43.4 ± 3.4	43.0 ± 3.9
ICW at pre-HD (L)	27.8 ± 7.1	28.1 ± 7.6	28.5 ± 8.1	26.4 ± 5.1
ICW at post-HD (L)	26.5 ± 5.4*	26.7 ± 5.8	26.6 ± 5.5	26.2 ± 5.7
ICW at pre-HD (%)	55.7 ± 3.5	55.7 ± 4.3	55.8 ± 3.4	55.4 ± 2.7
ICW at post-HD (%)	56.8 ± 3.5*	57.4 ± 3.3	56.0 ± 3.6	57.0 ± 3.9
FO at pre-HD (L)	10.7 ± 4.6	10.4 ± 5.4	11.5 ± 3.8	10.0 ± 4.9
FO at post-HD (L)	8.9 ± 4.4*	8.3 ± 4.6	10.0 ± 4.0	8.3 ± 4.8
FO at pre-HD (%)	48.9 ± 19.8	47.2 ± 22.7	52.0 ± 15.0	47.1 ± 22.9
FO at post-HD (%)	44.5 ± 21.0*	42.09 ± 22.9	48.5 ± 17.5	42.8 ± 24.4
Blood Markers				
Glucose at pre-HD (mg/dL)	99.9 ± 25	104.7 ± 37	99.2 ± 17	92.9 ± 6
Glucose at post-HD (mg/dL)	108 ± 29*	104 ± 32	114 ± 35	106 ± 15
BUN at pre-HD (mg/dL)	47.2 ± 11.0	43.2 ± 8.8	47.1 ± 9.7	54.1 ± 14.0
BUN at post-HD (mg/dL)	11.4 ± 4.0*	10.1 ± 2.8	12.1 ± 4.4	12.6 ± 4.6
Calcium at pre-HD (mg/dL)	8.6 ± 0.9	8.5 ± 0.9	8.6 ± 0.9	8.7 ± 1.0
Calcium at post-HD (mg/dL)	8.5 ± 0.4*	8.5 ± 0.4	8.5 ± 0.4	8.6 ± 0.5

Table 8 (cont.)

Variables	Total	CON	1st-hr EX	3rd-hr EX
Creatinine at pre-HD (mg/dL)	9.9 ± 2.6	9.9 ± 2.3	10.0 ± 2.5	10.0 ± 3.5
Creatinine at post-HD (mg/dL)	3.0 ± 1.1*	3.0 ± 1.1	3.2 ± 1.0	3.0 ± 1.3
Albumin at pre-HD (g/dL)	3.2 ± 0.3	3.2 ± 0.3	3.2 ± 0.3	3.1 ± 0.3
Albumin at post-HD(g/dL)	3.6 ± 0.5*	3.6 ± 0.4	3.5 ± 0.5	3.7 ± 0.7
Phosphorus at pre-HD (mg/dL)	5.8 ± 1.5	5.6 ± 1.4	6.0 ± 1.6	6.1 ± 1.7
Phosphorus at post-HD (mg/dL)	2.0 ± 0.5*	2.0 ± 0.5	2.1 ± 0.6	2.0 ± 0.5
Na at pre-HD (mmol/L)	140.5 ± 4.4	140.8 ± 4.7	139.3 ± 4.4	141.4 ± 4.1
Na at post-HD (mmol/L)	140.5 ± 4.4	140.8 ± 4.7	139.3 ± 4.4	141.0 ± 1.6
K at pre-HD (mmol/L)	5.9 ± 0.6	5.9 ± 0.6	6.1 ± 0.6	5.6 ± 0.5
K at post-HD (mmol/L)	3.6 ± 0.3*	3.6 ± 0.3	3.6 ± 0.3	3.6 ± 0.4
*Physical Symptoms*ǂ				
Nausea during HD (0~4)	0.5 ± 1.0	0.3 ± 0.7	0.8 ± 1.5	0.4 ± 0.7
Dizziness during HD (0~4)	0.4 ± 1.0	0.3 ± 0.7	0.6 ± 1.2	0.4 ± 1.1
Cramping during HD (0~4)	1.0 ± 1.1	0.9 ± 1.0	1.1 ± 1.4	1.0 ± 1.2
Nausea at 5hr-post-HD (0~4)	0.5 ± 1.3	0.0 ± 0.0	0.6 ± 1.5	0.8 ± 1.6
Dizziness at 5hr-post-HD (0~4)	0.5 ± 1.3	0.0 ± 0.0	0.4 ± 1.1	1.0 ± 2.0
Cramping at 5hr-post-HD (0~4)	0.9 ± 1.4	0.8 ± 1.8	0.7 ± 1.3	1.3 ± 1.5
Fatigue at 5hr-post-HD (0~10)	5.2 ± 2.9	4.8 ± 2.6	5.3 ± 3.4	5.7 ± 3.8
*IDH & IDHPT*ǂ				
IDH (HD session, n)	8	2	2	4
IDHPT(HD session, n)	3	1	1	1

IDWG: interdialytic weight gain, **HD**: hemodialysis, **TBW**: total body water, **ECW**: extracellular water, **ICW**: intracellular water, **FO**: fluid overload, **BUN**: blood urea nitrogen, **Na**: Natrium, **K**: potassium, **IDH**: intradialytic hypotension, **IDHPT**: intradialytic hypertension

*: indicates a significant difference between pre- and post-HD levels by paired t-test.

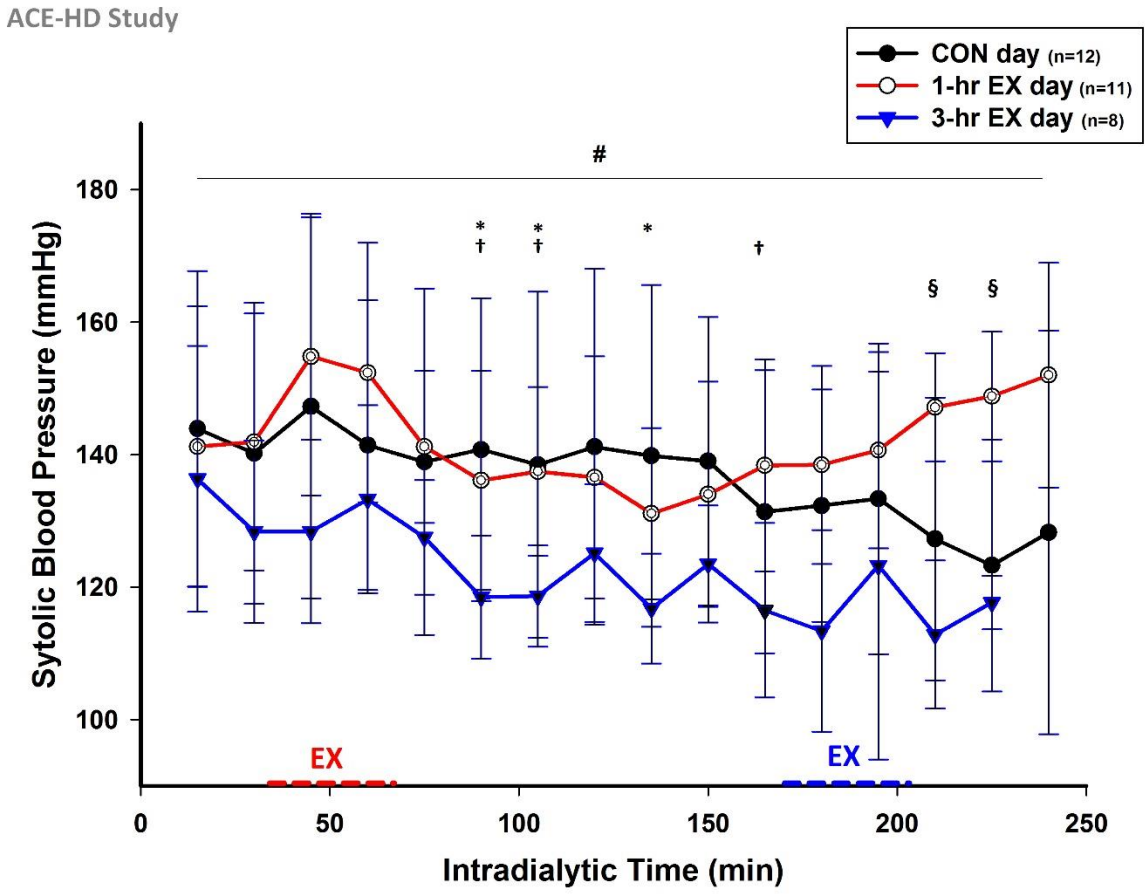
ǂ : Represents an analysis of data from patients who completed all the three interventions (N = 8).

6-3. Change in brachial hemodynamics during HD (Figure 10 A~G)

There was no significant *Time* * *Exercise* interaction for any of the brachial hemodynamic parameters including brachial SBP ($F_{2,28}$ = 0.9, p = 0.4176), MAP ($F_{2,28}$ = 0.53, p = 0.5942) and PP ($F_{2,28}$ = 1.16, p = 0.3276). The analysis including only the patients who completed all three interventions demonstrated the similar results for brachial SBP ($F_{2,21}$ = 0.=76, p = 0.479), MAP ($F_{2,21}$ = 0.33, p = 0.720 and PP ($F_{2,21}$ = 1.63, p = 0.219). This indicates that brachial hemodynamic changes during HD were similar between treatment days, regardless of if or when the patients exercised. However, there was a significant effect of *Time* with a decreasing trend in the overall population in brachial SBP ($F_{1,28}$ = 20.06 for all patients and $F_{1,21}$ = 12.22 for patients who completed the three interventions, p < 0.001 for all), MAP ($F_{1,28}$ = 17.35, $F_{1,21}$ = 11.06 for patients who completed the three interventions, p < 0.001 for all) and PP ($F_{1,28}$ = 16.34, $F_{1,21}$ = 10.79 for patients who completed the three interventions, p < 0.001 for all). Similar trends were seen when the influence of fluid status (IDWG, UF goal and FO%) was added as a covariate in the model. Between group-comparisons demonstrated no difference in SBP at 0- and 30-minutes into HD, but a significant difference was found after 60-minutes into HD between the three intervention days. Post-hoc analysis showed that the SBP during 3rd-hr EX day were lower than CON day at 90, 105, and 135 minutes, and lower than 1st-hr EX day at both 90 and 165-minutes into HD (p <0.05 for all). Interestingly, SBP on the 1st-hr EX day was significantly

higher than the other two days in the later hours of HD (at 210 and 225 minutes), $p < 0.05$ for all). No significant difference between intervention days were found for the delta values ($\Delta SBP_{i-0\text{-}min}$). Despite the numerical increases in $\Delta SBP_{60-0min}$ and $\Delta SBP_{60-30min}$ during the 1st-hr EX day compared to other intervention days, the difference did not reach the statistical significance, partly due to the large variability between patients. The data on MAP showed similar trends to the results for SBP.

Figure 10-A. Changes in brachial systolic blood pressure during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

§: indicates a significant difference between 1st-hour IDEX and CON and 3rd-hour IDEX.

***:** indicates a significant difference between 3rd-hour IDEX and CON.

†: indicates a significant difference between 3rd-hour IDEX and 1st-hour IDEX.

Figure 10-B. Changes in brachial diastolic blood pressure during a standard HD treatment with and without exercise.

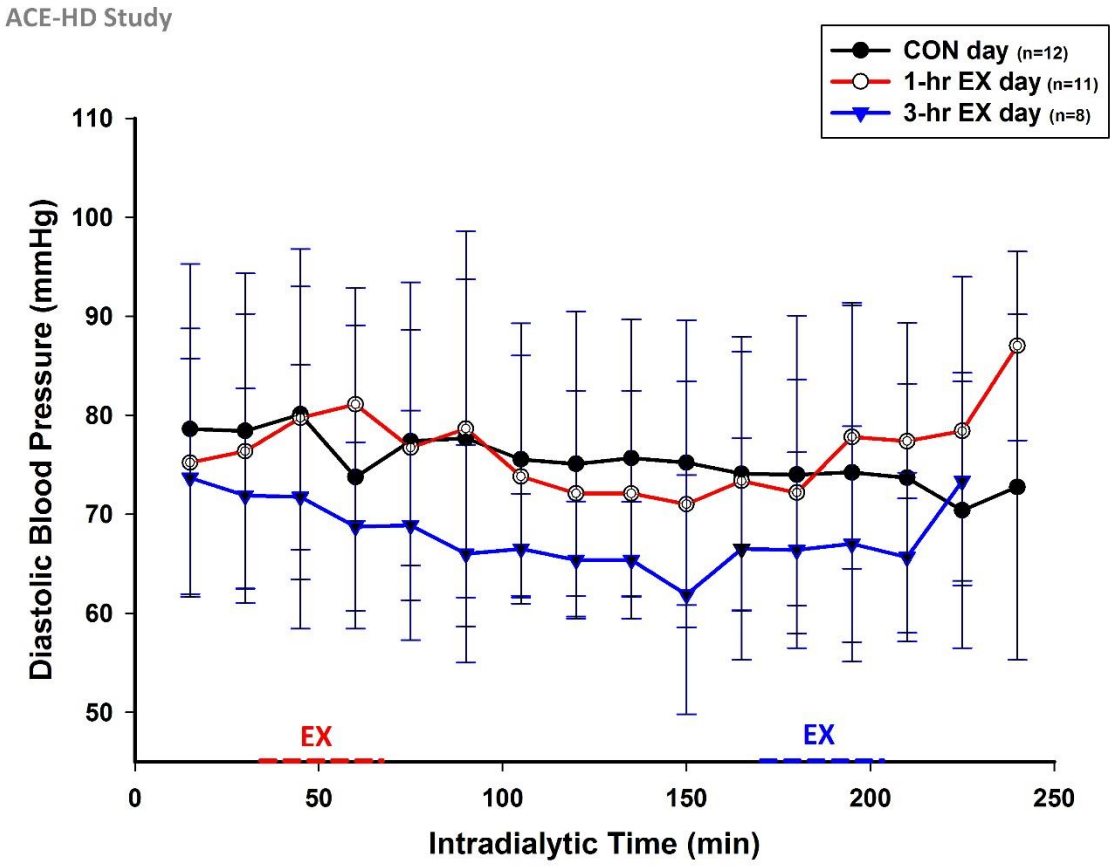
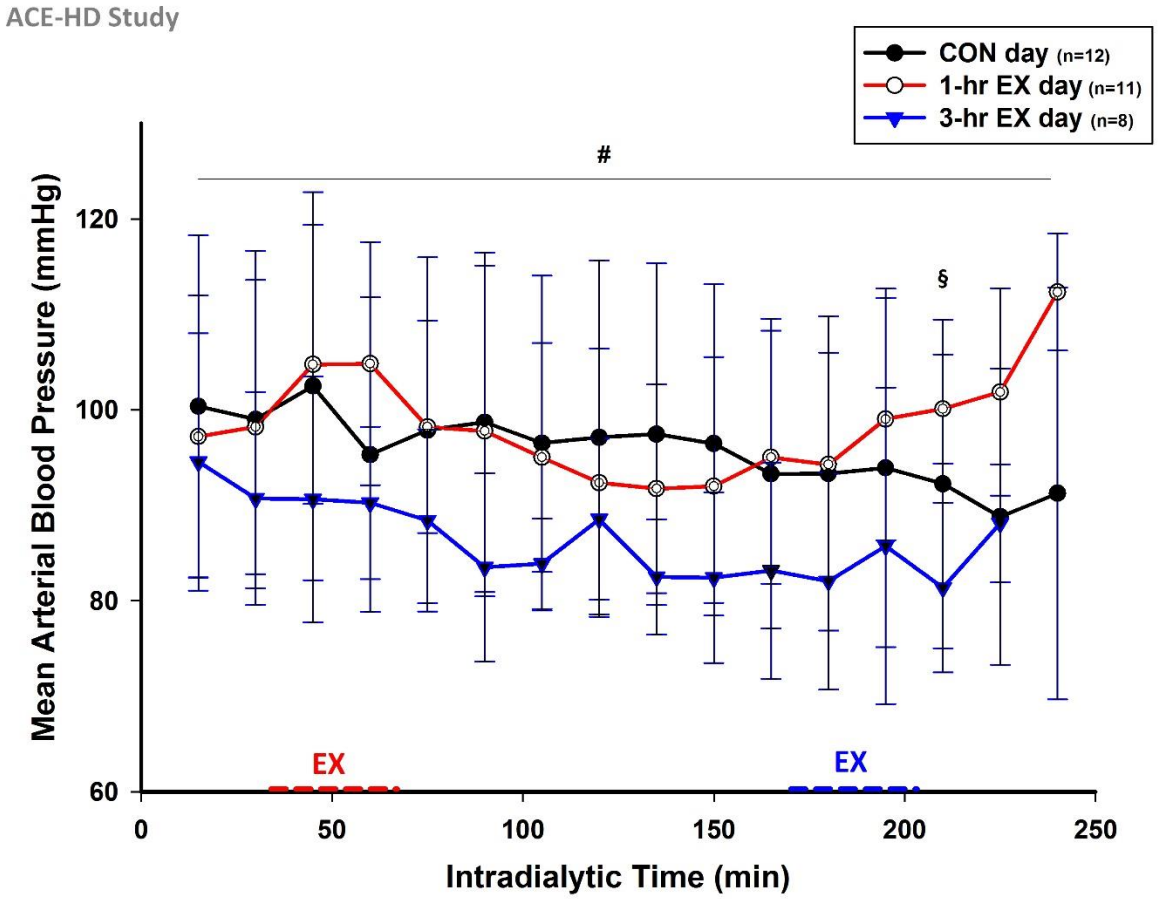


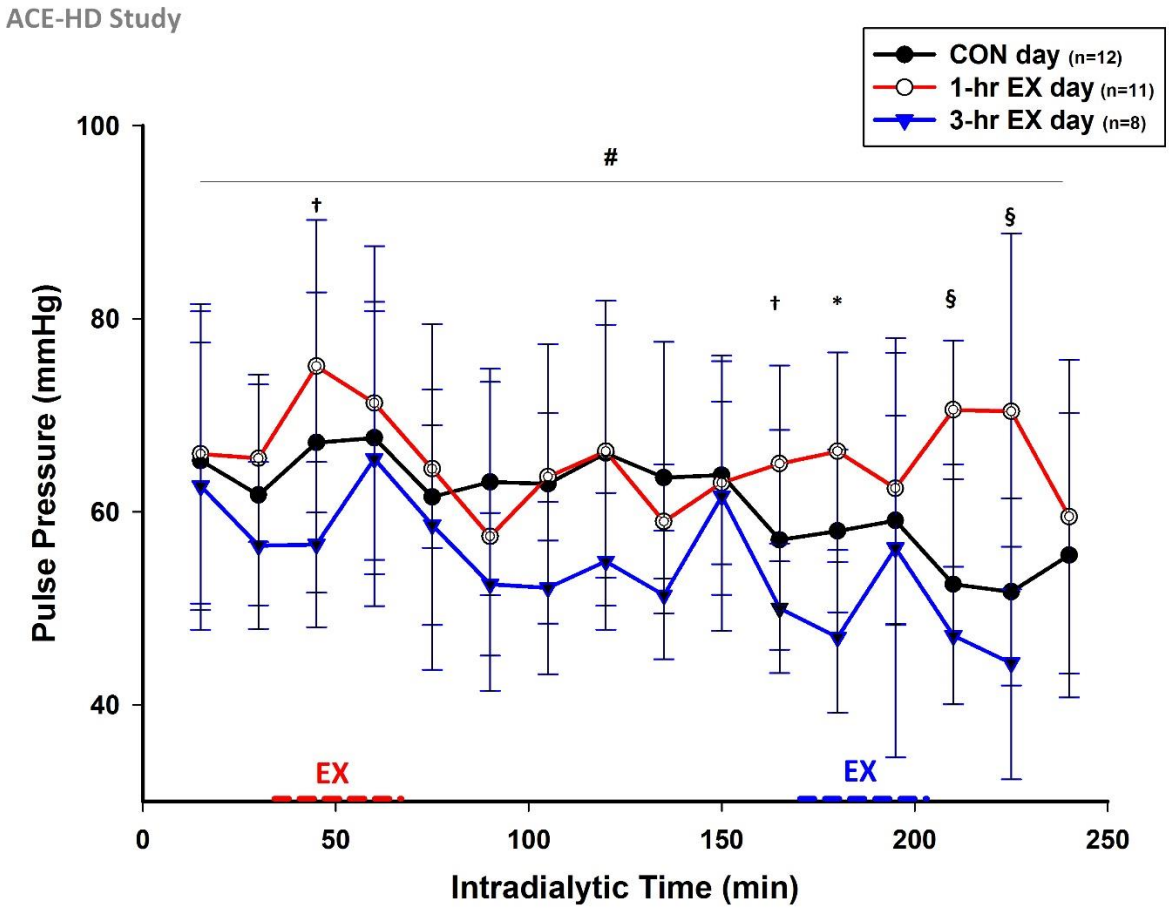
Figure 10-C. Changes in mean arterial blood pressure during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

§: indicates a significant difference between 1st-hour IDEX and CON and 3rd-hour IDEX.

Figure 10-D. Changes in brachial pulse pressure during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

§: indicates a significant difference between 1st-hour IDEX and CON and 3rd-hour IDEX.

***:** indicates a significant difference between 3rd-hour IDEX and CON and 1st-hour IDEX.

†: indicates a significant difference between 3rd-hour IDEX and 1st-hour IDEX.

Figure 10-E. Individual changes in brachial blood pressure during a standard HD treatment without IDEX.

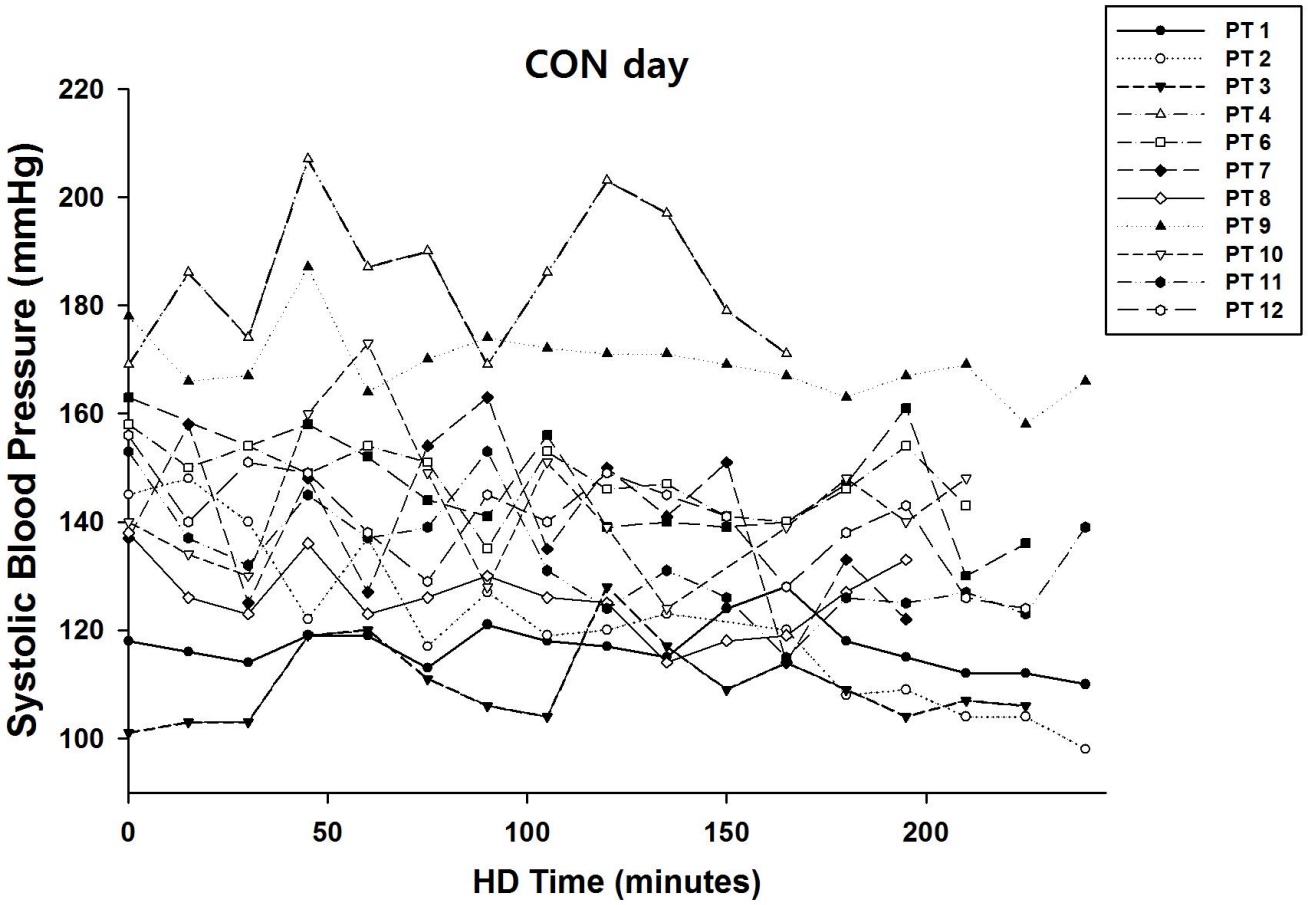


Figure 10-F. Individual changes in brachial blood pressure during a standard HD treatment with exercise during the 1st hour of treatment .

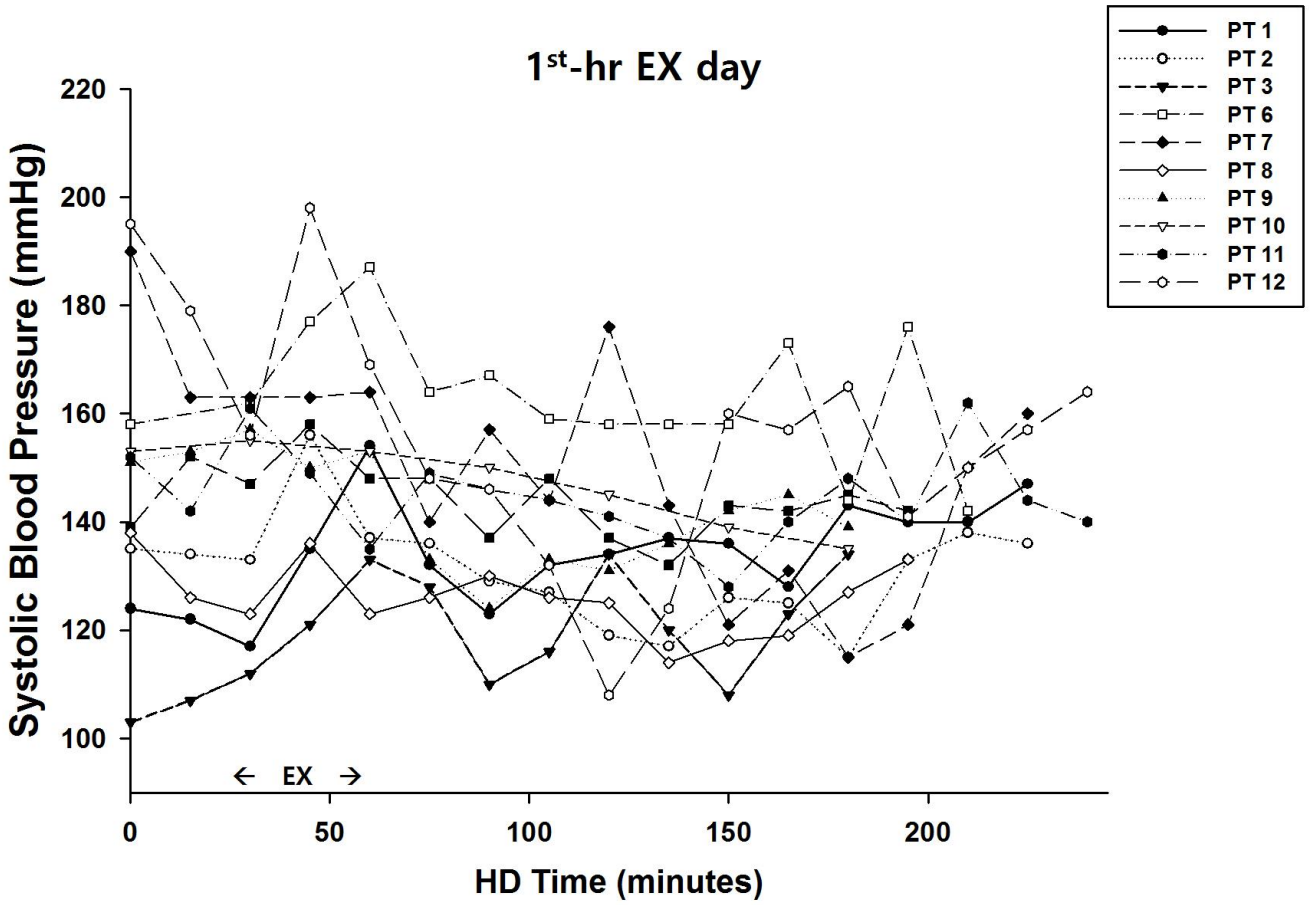
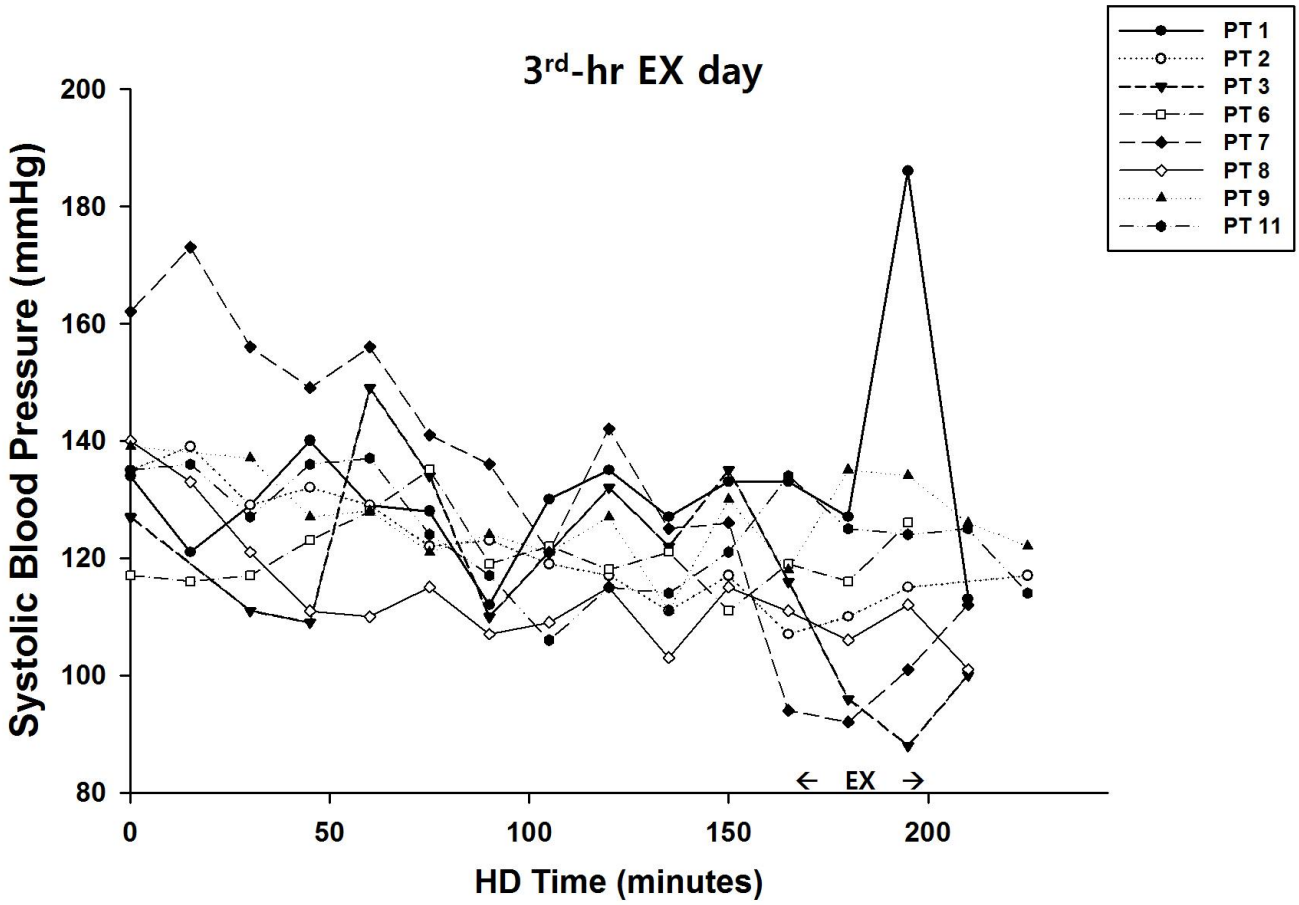


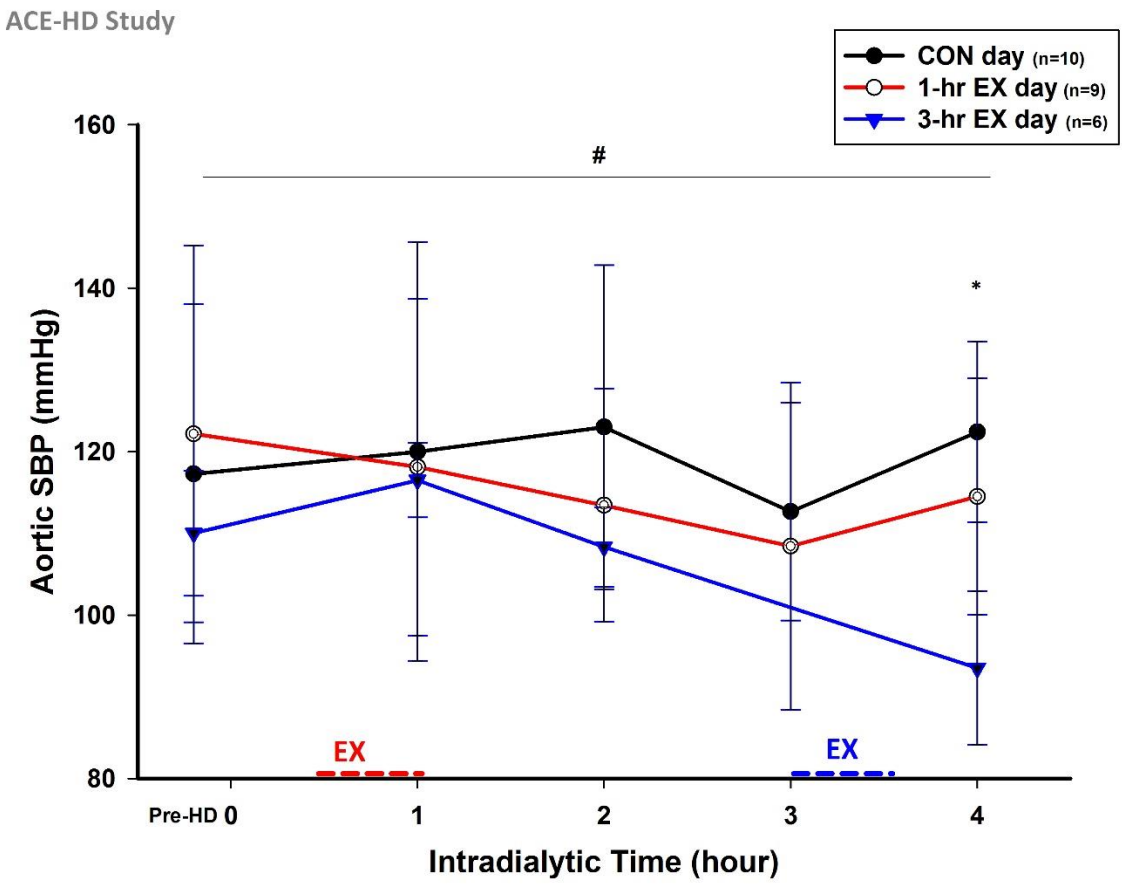
Figure 10-G. Individual changes in brachial blood pressure during a standard HD treatment with exercise during the 3rd hour of treatment.



6-4. Change in aortic hemodynamics during HD (Figure 11 A~E)

Aortic hemodynamics were measured every hour during HD and the measurement at pre-HD was included in the Mixed Model with Repeated Measures. There was no significant *Time* * *Exercise* interaction for any aortic hemodynamic parameter including aortic SBP ($F_{2,22}$ = 2.44, p = 0.110), PP ($F_{2,22}$ = 1.47, p = 0.252), AugP ($F_{2,22}$ = 0.27, p = 0.763), Aix75 ($F_{2,22}$ = 0.92, p = 0.414) and PWV ($F_{2,22}$ = 2.65, p = 0.093). This indicates that changes in hemodynamic variables across a dialysis session did not differ between treatment days. There was a significant main effect of *Time*, with a decreasing trend in the overall population in aortic SBP ($F_{1,22}$ = 8.45, p = 0.0082) and PWV ($F_{1,22}$ = 5.59, p =0.027) but not in aortic PP ($F_{1,22}$ = 2.09, p = 0.162), AugP ($F_{1,22}$ = 0.2, p = 0.662) and Aix75 ($F_{1,22}$ = 0.4, p = 0.533). Similar trends were seen when the influence of fluid status (IDWG, UF goal and FO%) were added as a covariate in the model.

Figure 11-A. Changes in aortic systolic blood pressure (SBP) during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

***:** indicates a significant difference between 3rd-hour IDEX and CON.

Figure 11-B. Changes in aortic diastolic blood pressure (DBP) during a standard HD treatment with and without exercise.

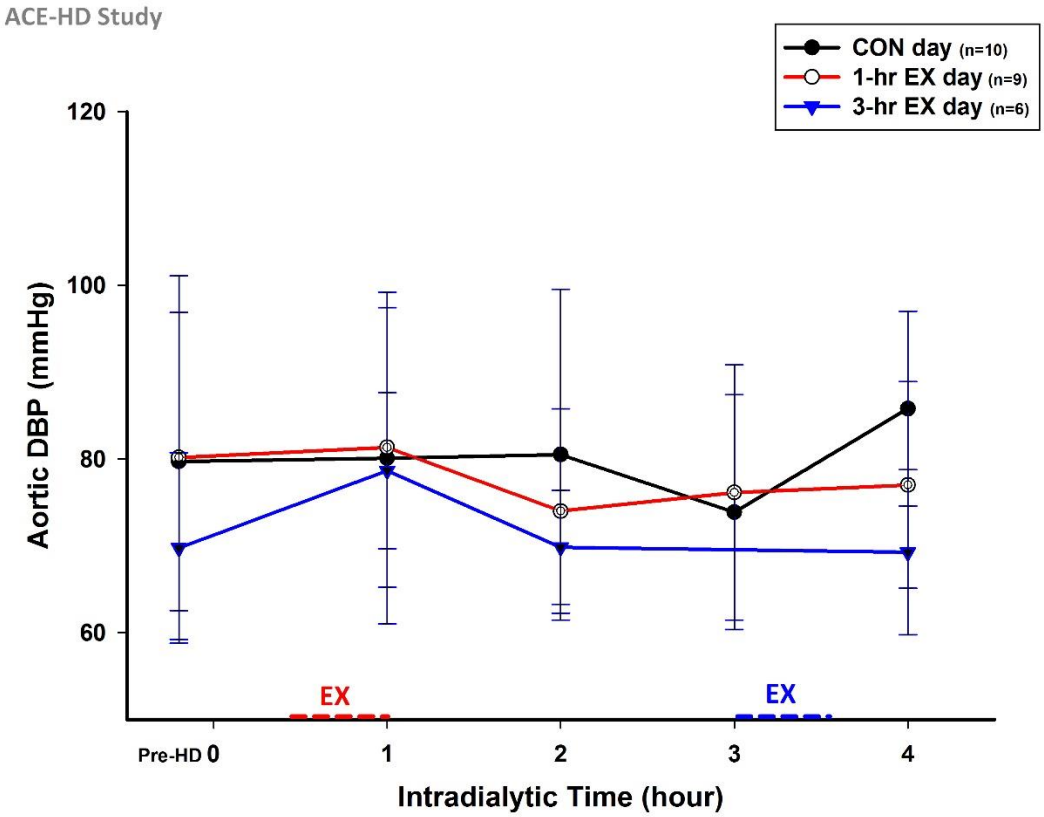
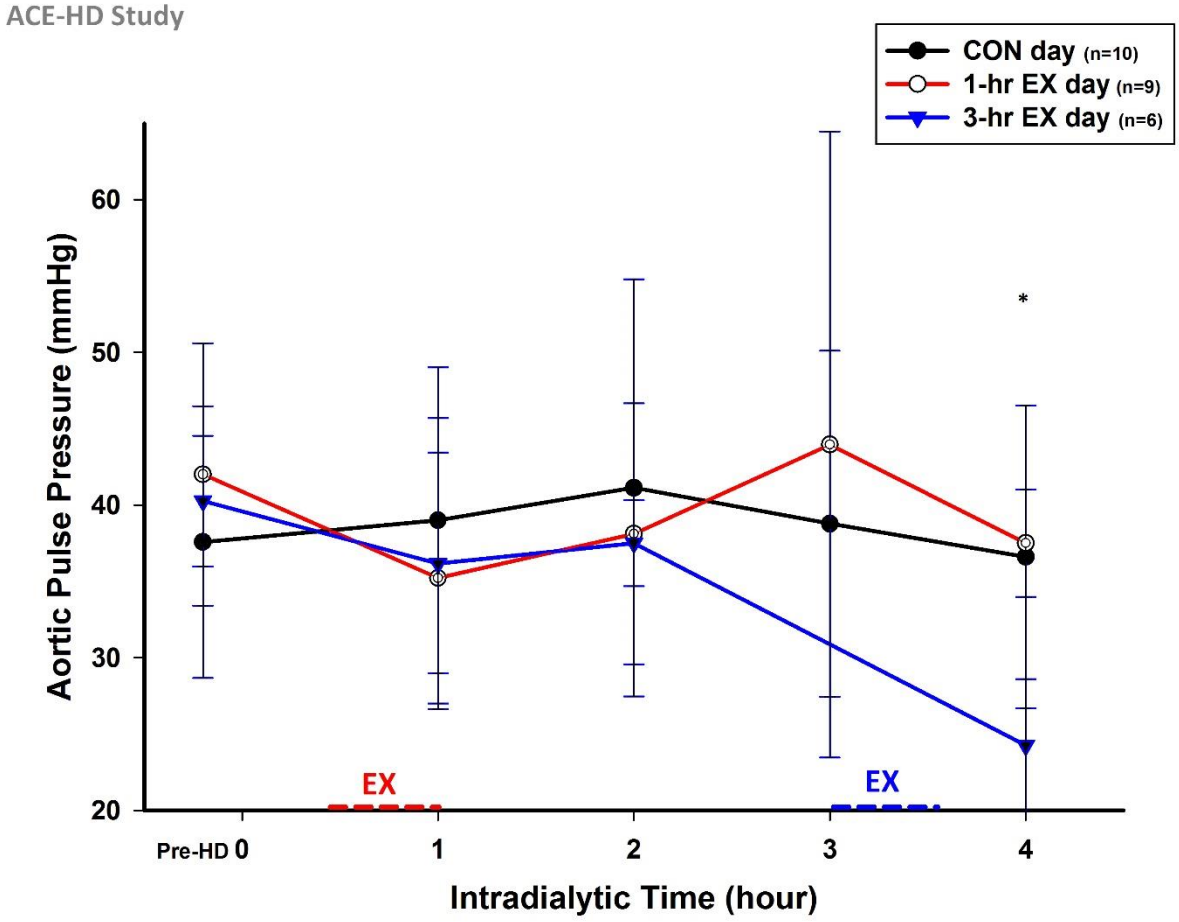


Figure 11-C. Changes in aortic pulse pressure during a standard HD treatment with and without exercise.



*: indicates a significant difference between 3rd-hour IDEX and CON.

Figure 11-D. Changes in augmentation index at heart rate75 (Aix HR@75) during a standard HD treatment with and without exercise.

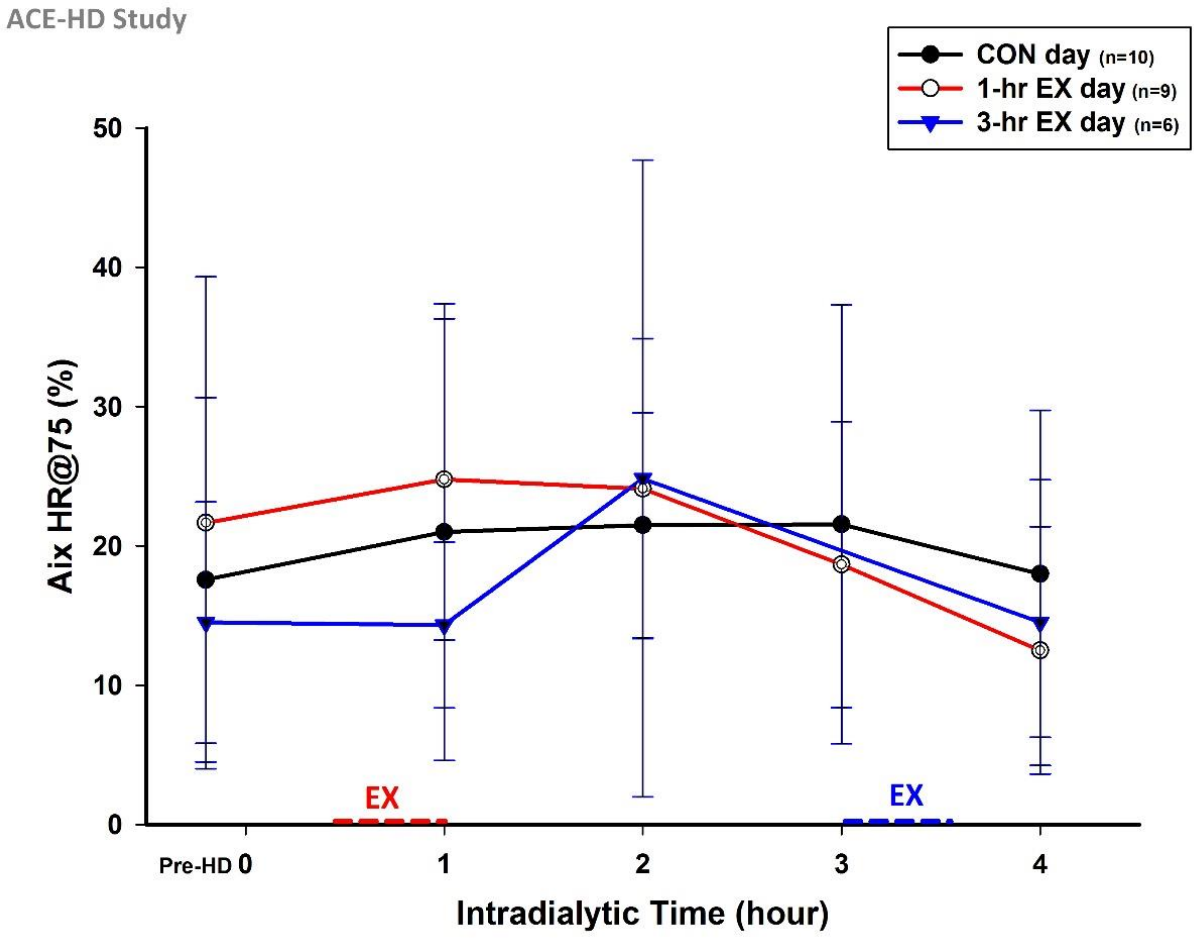
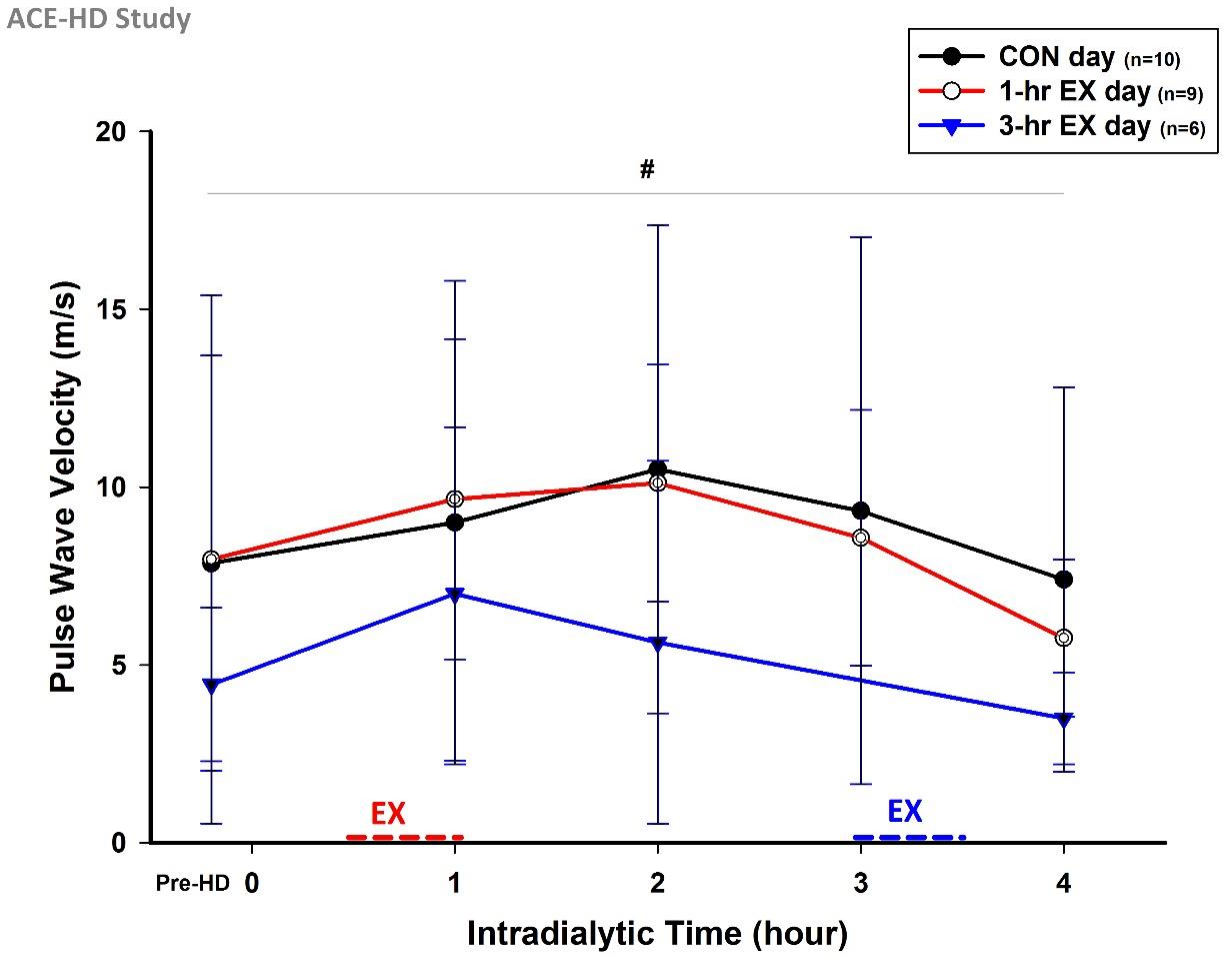


Figure 11-E. Changes in pulse wave velocity during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

6-5. Change in cardiac hemodynamics and peripheral vascular resistance during HD (Figure 12 A~K)

SV, HR, CO and TPR were continuously measured during HD, and the beat-to-beat values were averaged every 30 minutes for analysis. There was no significant *Time * Exercise* interaction for any cardiac hemodynamic parameter including SV ($F_{2,28}$ = 1.25, p = 0.303), SI ($F_{2,28}$ = 1.26, p = 0.298), CO ($F_{2,28}$ = 3, p = 0.066) and CI ($F_{2,28}$ = 3.01, p =0.065) and TPR ($F_{2,22}$ = 2.65, p = 0.093). The analysis including only the patients who completed all three interventions demonstrated similar results in brachial SV ($F_{2,21}$ = 1.09, p = 0.354), CO ($F_{2,21}$ = 3.22, p = 0.062 and TPR ($F_{2,21}$ = 0.93, p = 0.412). This indicates that changes in cardiac hemodynamics and vascular resistance during HD were similar across the treatment days. Similar trends were seen when the influence of fluid status (IDWG, UF goal and FO%) were added as covariates in the model.

Between-group comparisons at each measured time point demonstrated a significant difference in CO, CI and left ventricular ejection time between the intervention days 30 to 60 minutes into HD during which the 1st-hour IDEX was performed. Post-hoc analysis showed that 1st-hr EX day had higher CO, CI and HR, and shorter left ventricular ejection time compared to the other two treatment days at these time points. ($p < 0.05$ for all). On the 3rd-hr EX day, there was a higher SV, CO and CI at 150- and 180-minutes into HD during which the 3rd-hour IDEX

was performed, compared to the other intervention days ($p < 0.05$ for all). Using the cardiac delta values, similar trends for exercise-induced increases in SV and CO were seen during the time intervals when IDEX was performed: increased ΔSV_{60-30} and ΔCO_{60-30} in 1st-hr EX day; and increased ΔSV_{120-30} and ΔCO_{120-30} in 3rd-hr EX day ($p < 0.05$ for all). There was a numerical decrease in TPR before and after the 3rd-hour IDEX (mean $\Delta TPR_{240-180} = -222.87$, CI: (-627.79, 178.03), $p = 0.174$). When compared to 1st-hour IDEX, there was a trend for a difference in $\Delta TPR_{240-180}$ in 3rd-hour IDEX (mean difference= -386.48, CI= (-804.97, 31.99) and p=0.068).

Figure 12-A. Changes in stroke volume during a standard HD treatment with and without exercise.

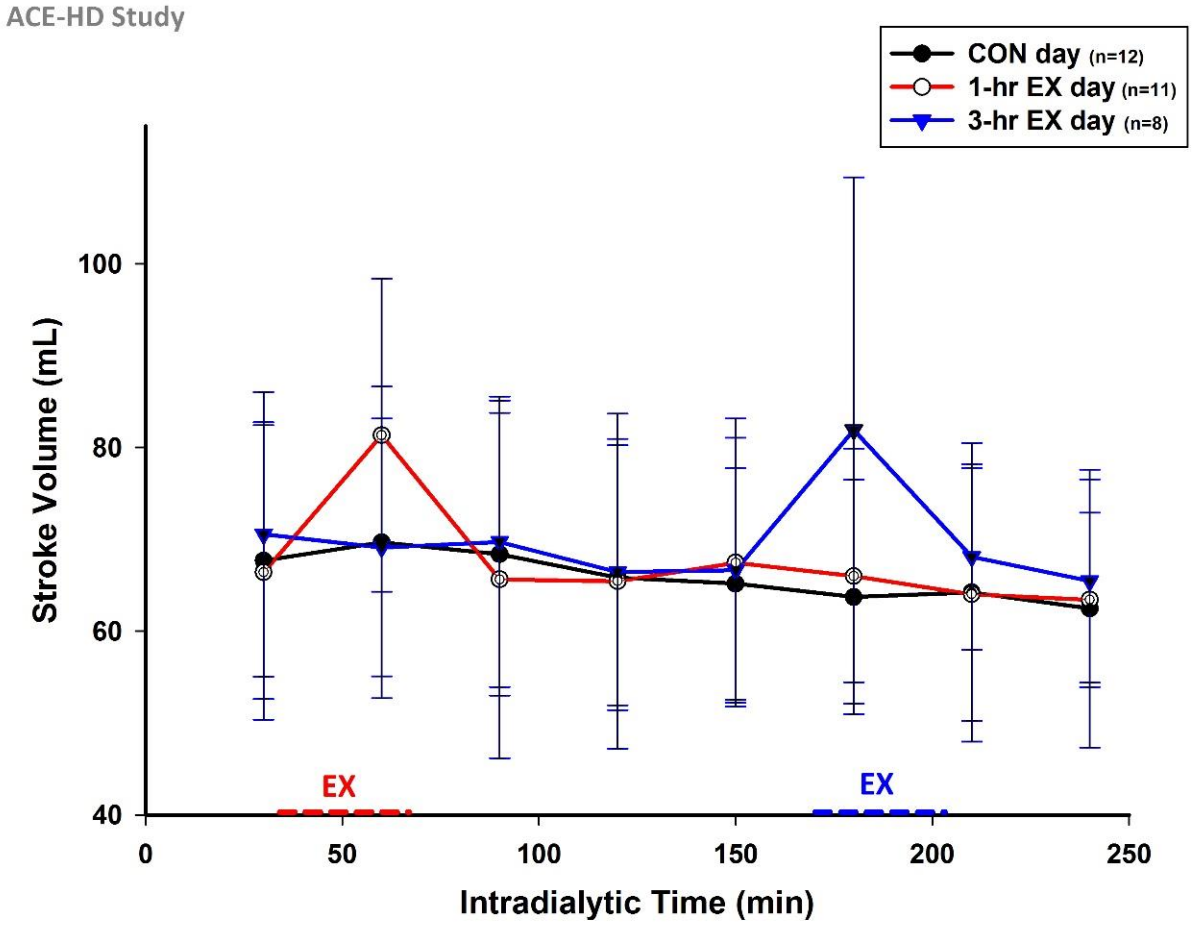
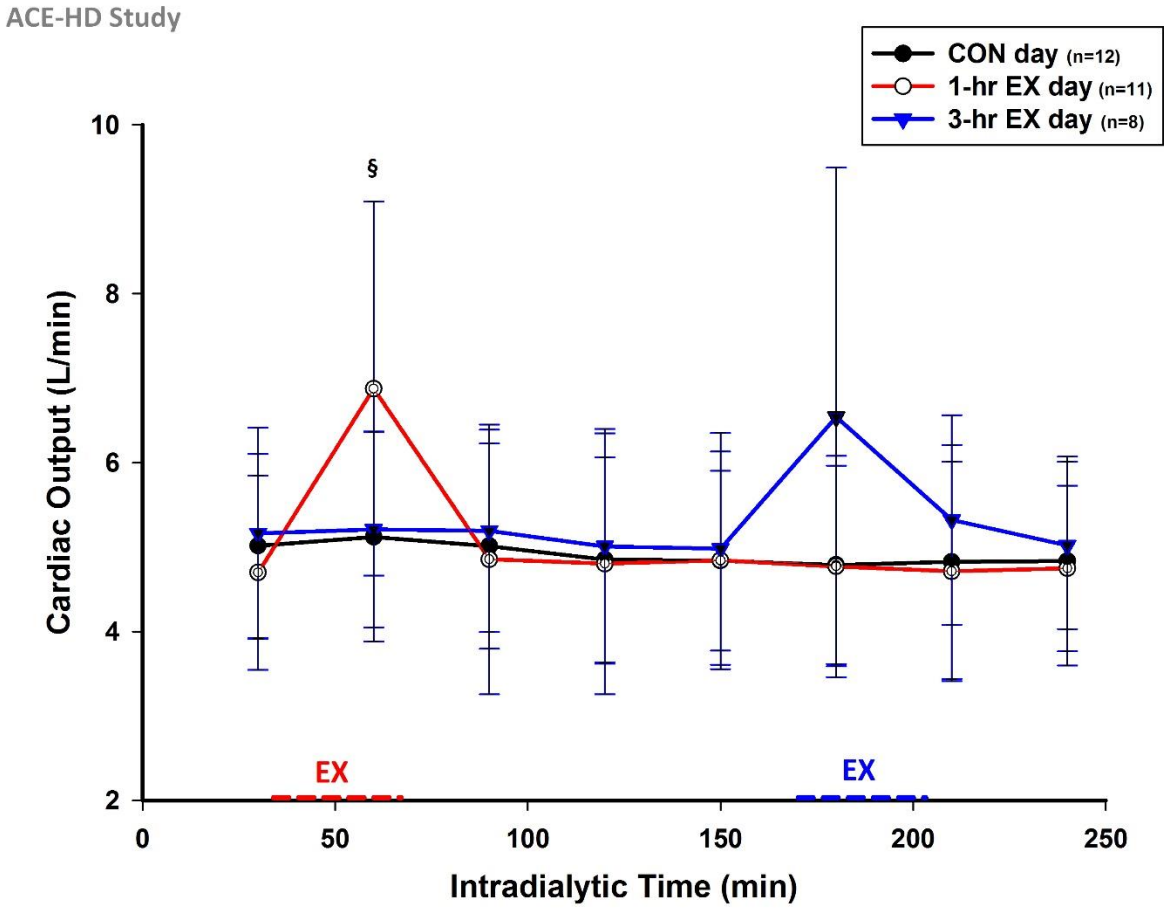
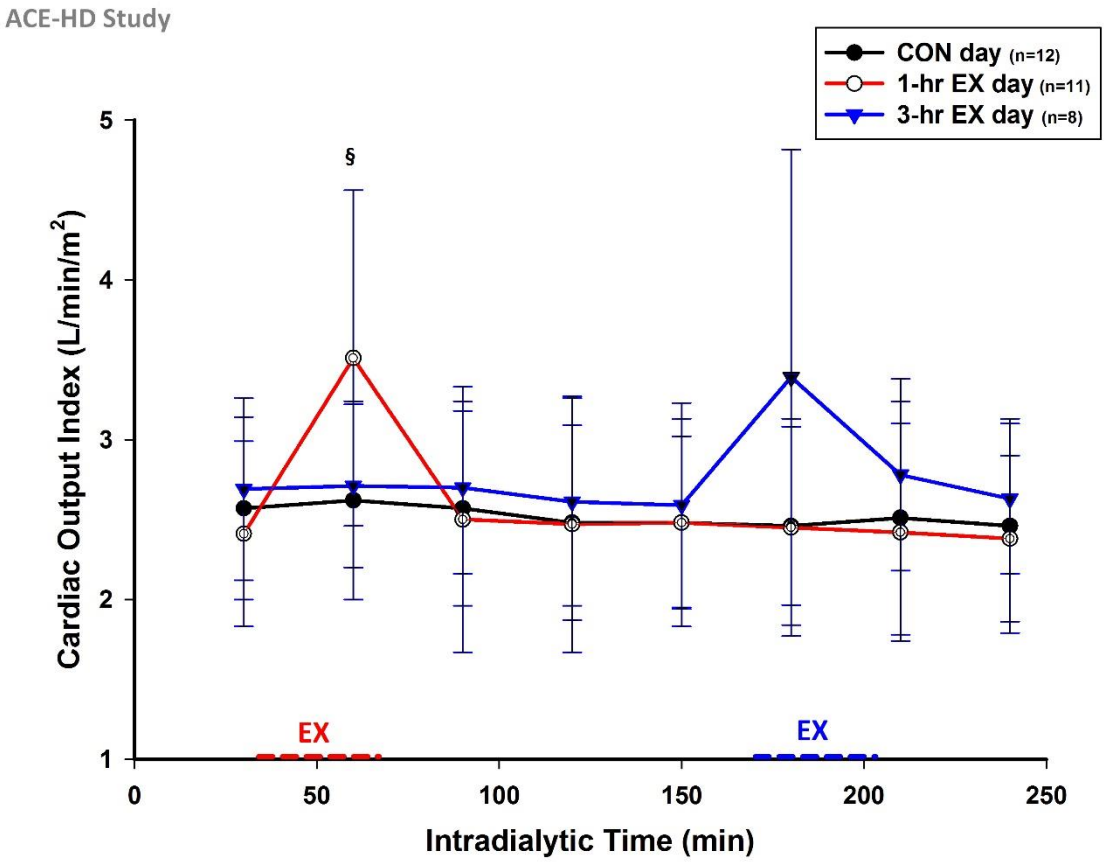


Figure 12-B. Changes in cardiac output during a standard HD treatment with and without exercise.



§: indicates a significant difference between 1st-hour IDEX and CON and 3rd-hour IDEX.

Figure 12-C. Changes in cardiac output index during a standard HD treatment with and without exercise.



§: indicates a significant difference between 1st-hour IDEX and CON and 3rd-hour IDEX.

Figure 12-D. Changes in total peripheral resistance during a standard HD treatment with and without exercise.

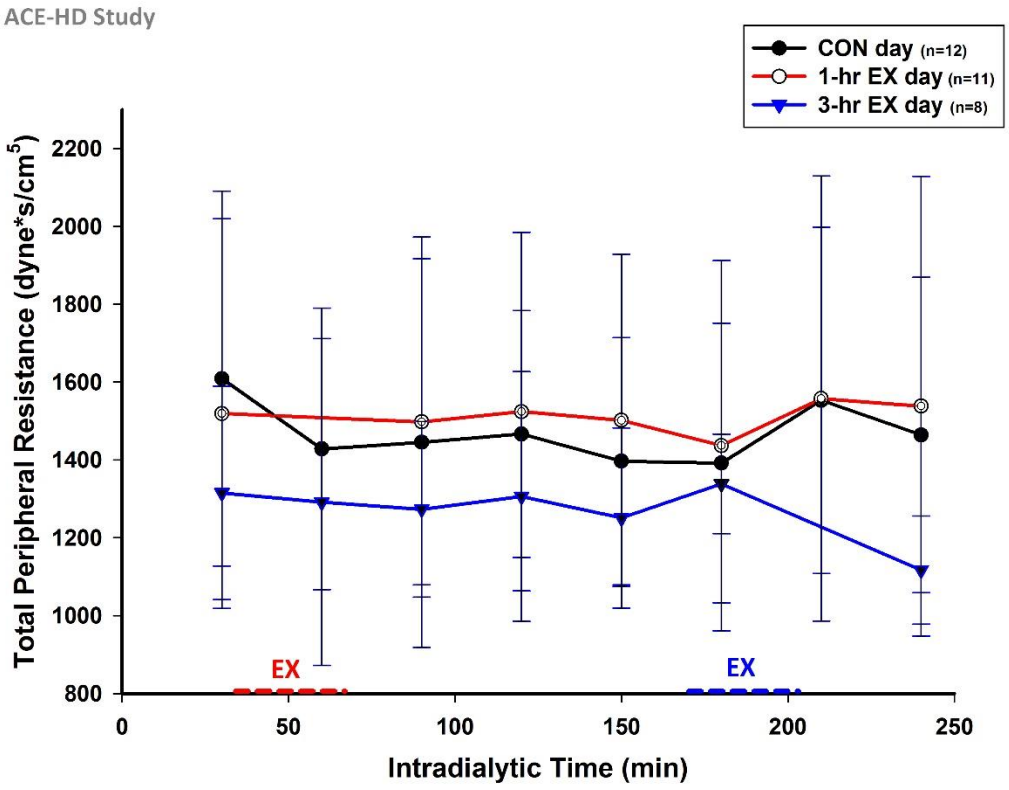


Figure 12-E. Changes in heart rate during a standard HD treatment with and without exercise.

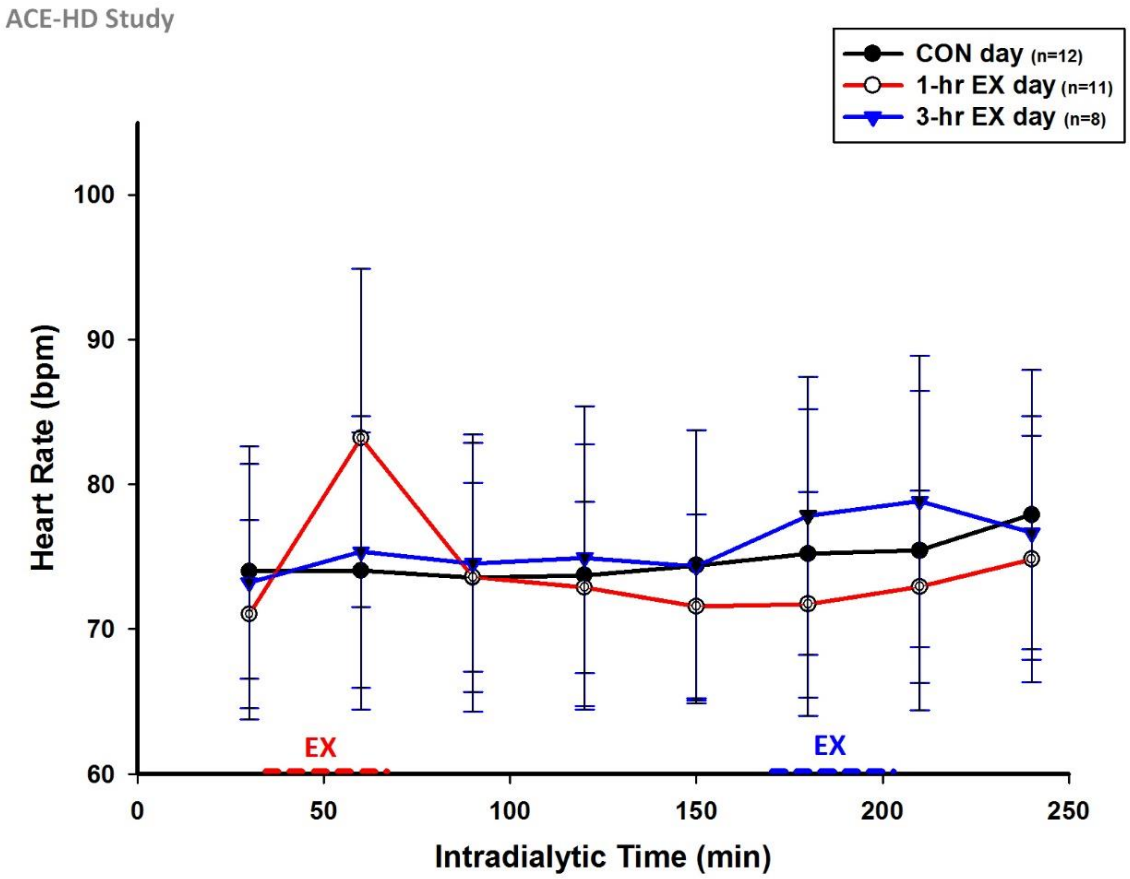


Figure 12-F. Individual changes in stroke volume during a standard HD treatment without exercise.

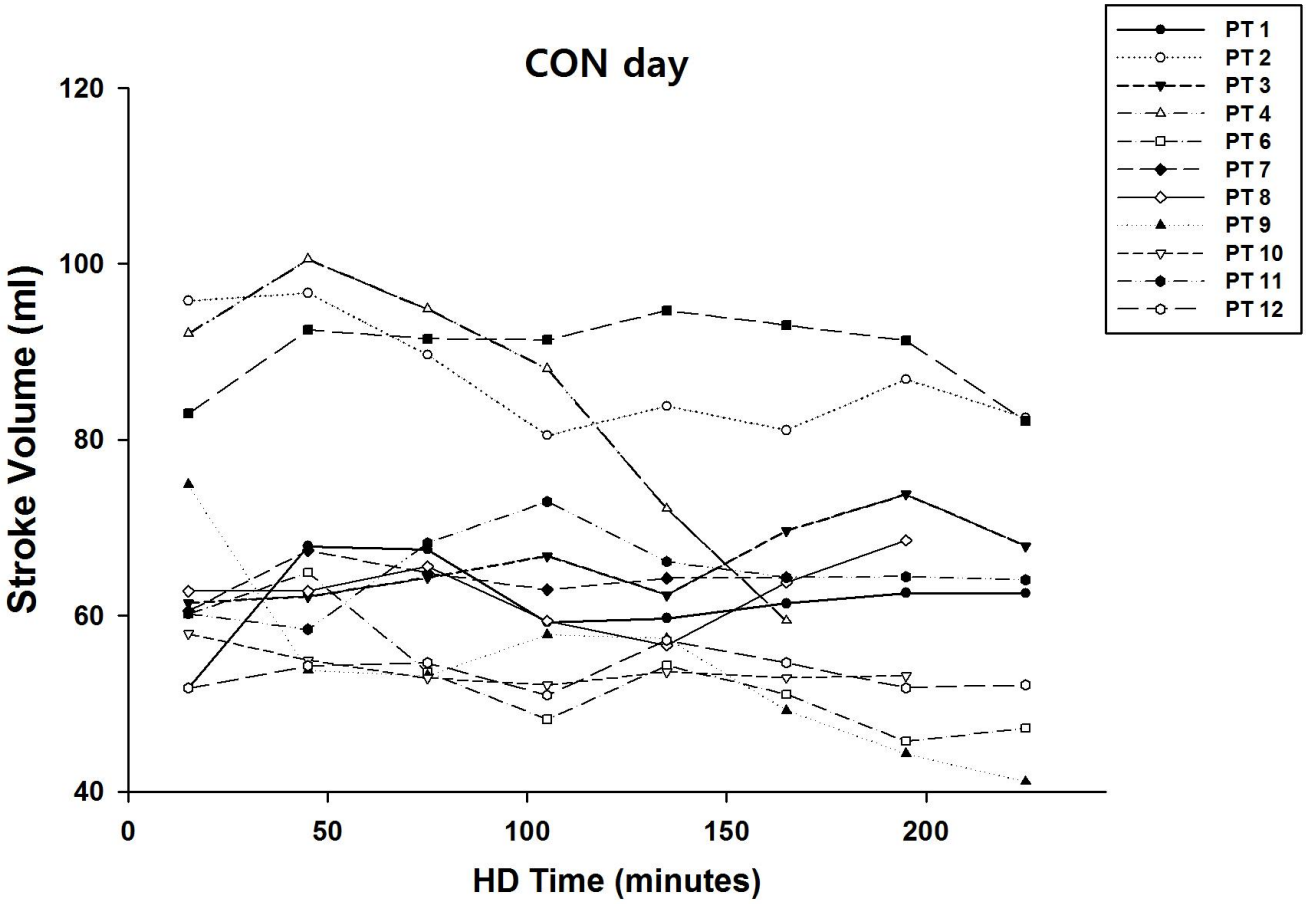


Figure 12-G. Individual changes in stroke volume during a standard HD treatment with exercise during the 1st hour of treatment.

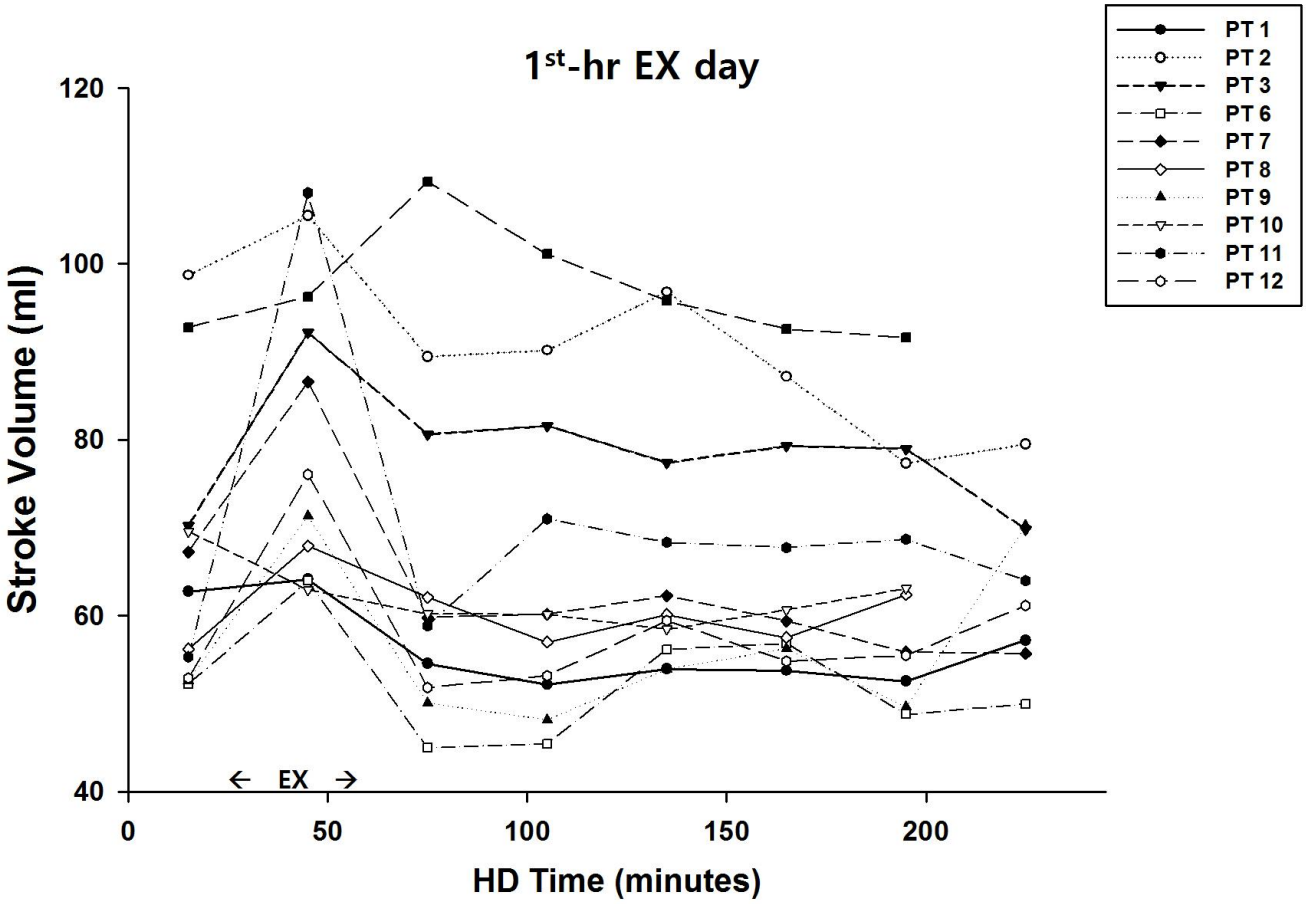


Figure 12-H. Individual changes in stroke volume during a standard HD treatment with exercise during the 3rd hour of treatment.

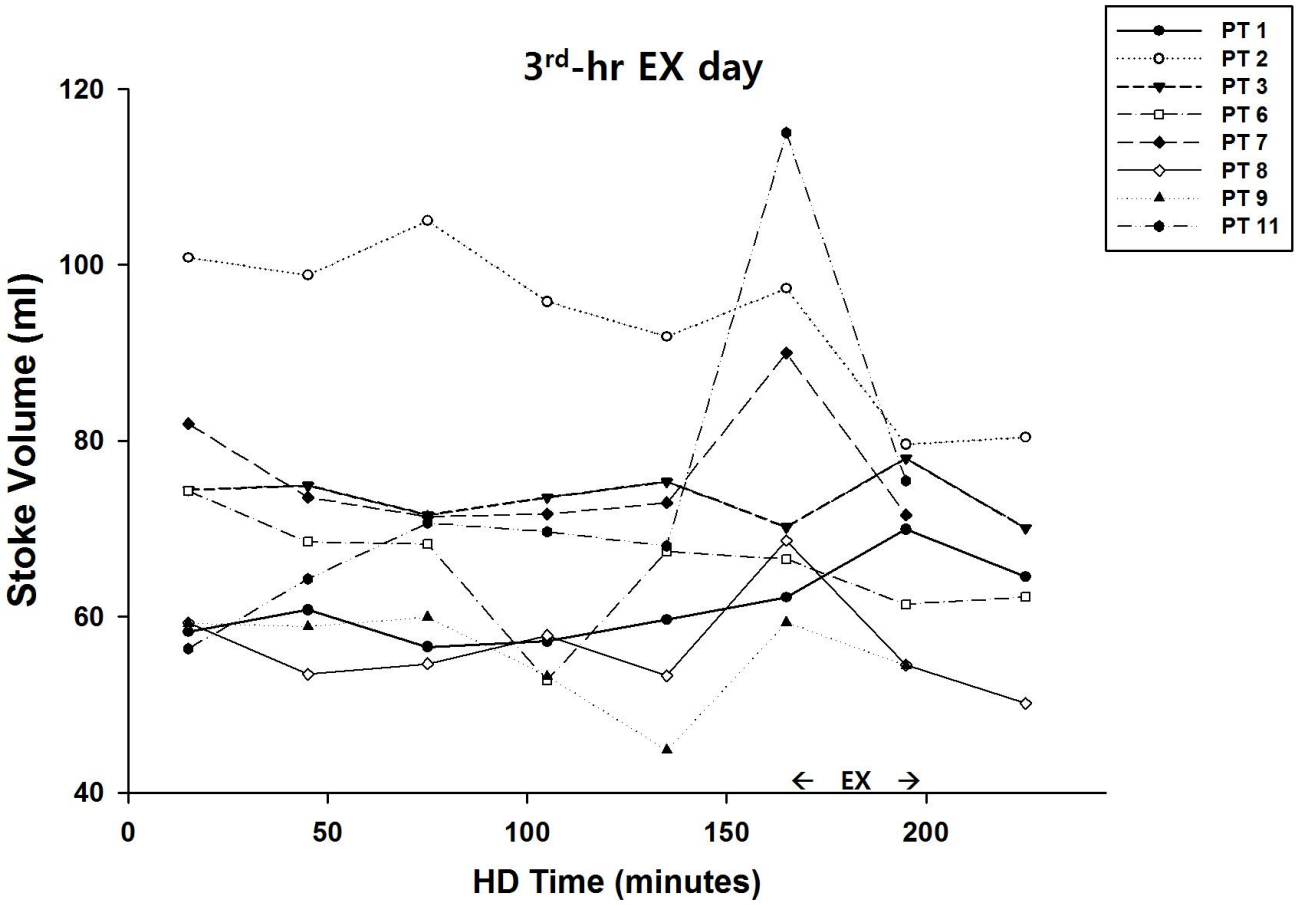


Figure 12-I. Individual changes in cardiac output during a standard HD treatment without exercise.

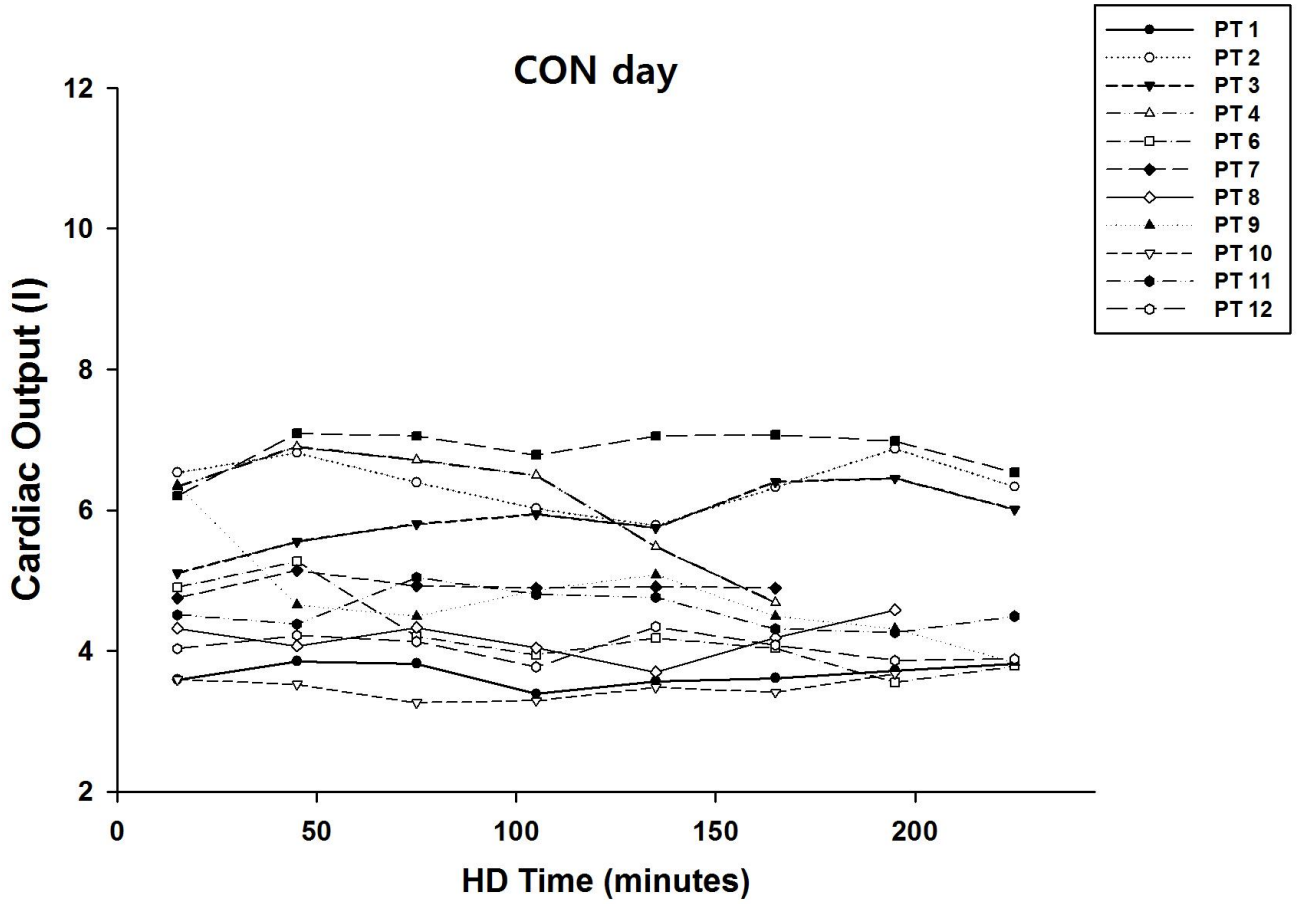


Figure 12-J. Individual changes in stroke volume during a standard HD treatment with exercise during the 1st hour of treatment.

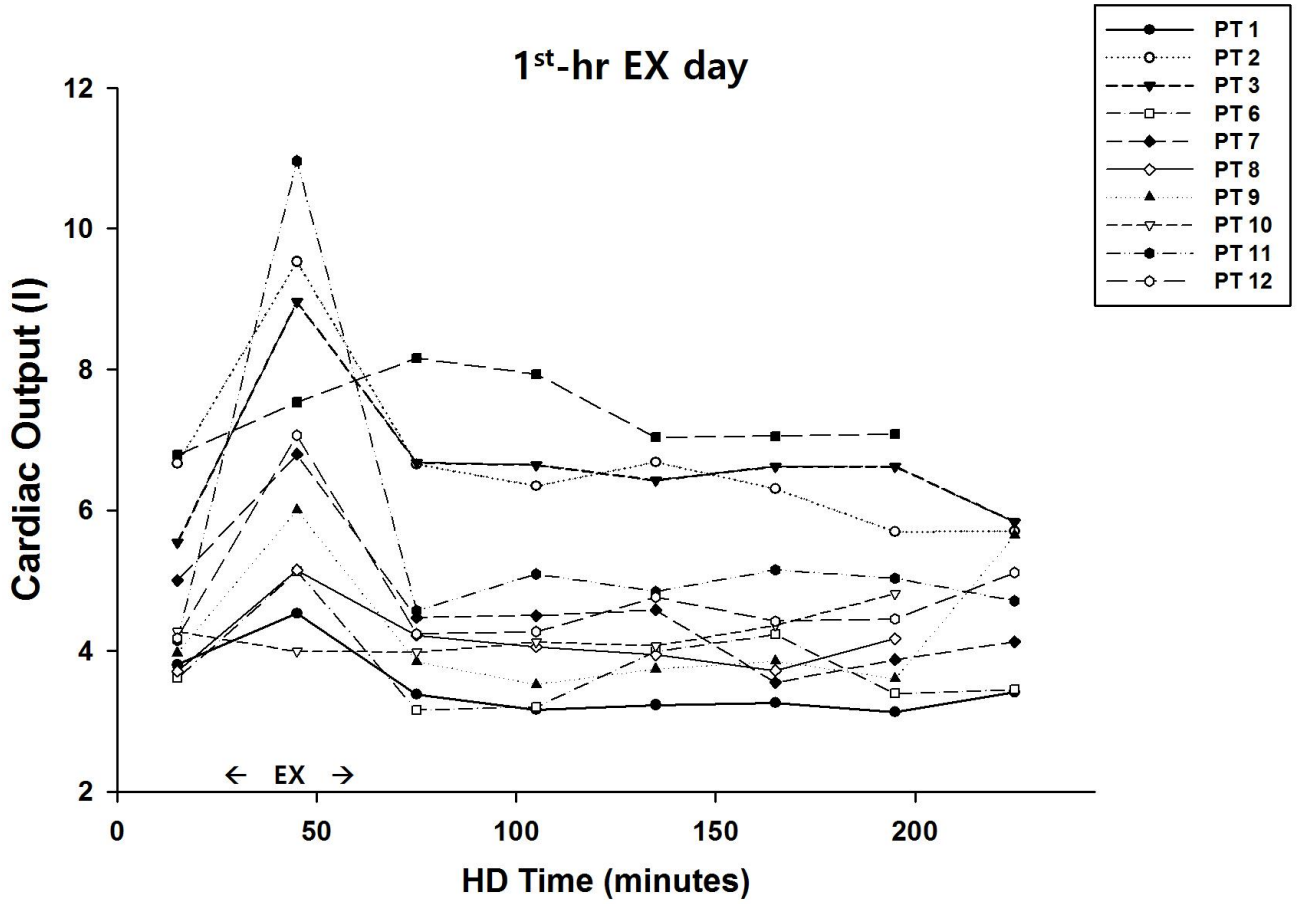
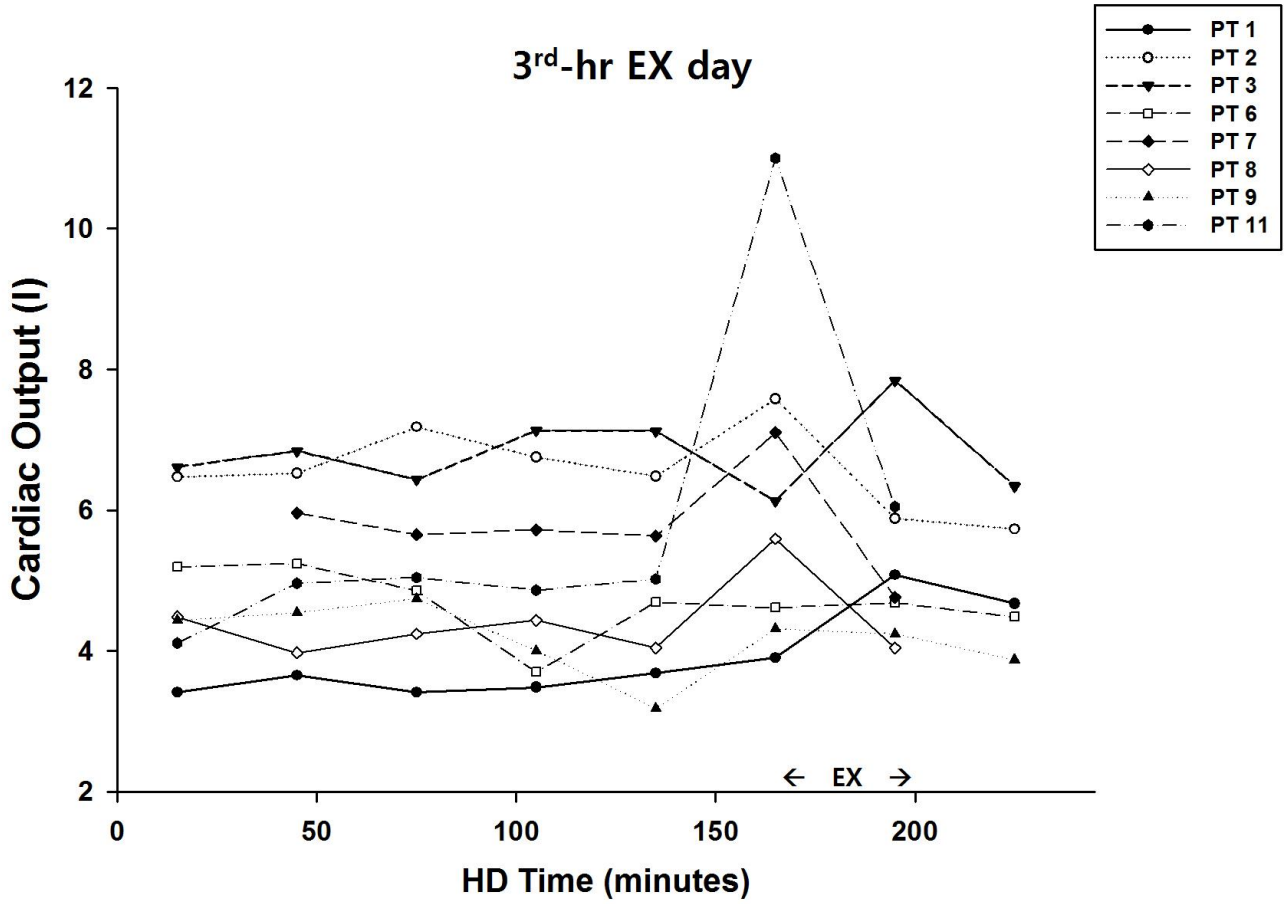


Figure 12-K. Individual changes in stroke volume during a standard HD treatment with exercise during the 3rd hour of treatment.

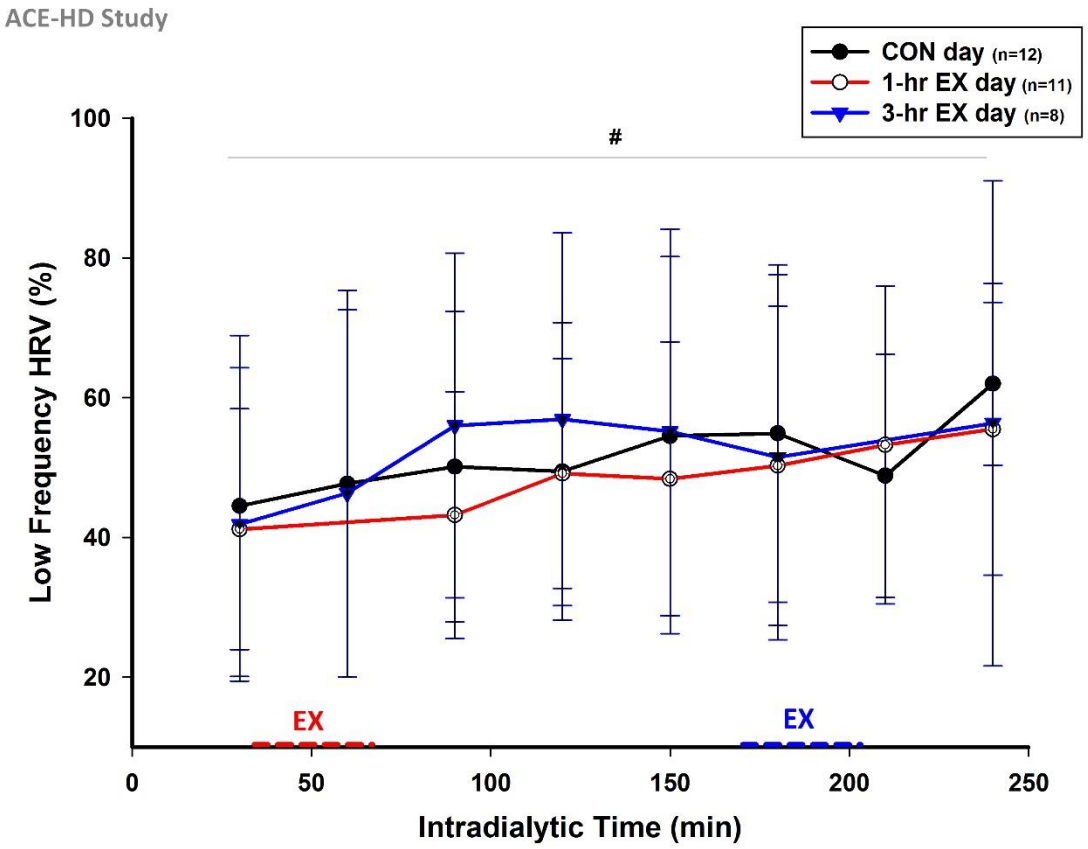


6-6. Change in autonomic function by heart rate variability and blood pressure variability during HD (Figure 13 A~D)

LF, HF, LFnu, HFnu and LF/HF by HRV and BPV were continuously measured and averaged every 30 minutes throughout HD for analysis. There was no significant interaction effect of *Time * Exercise* for any autonomic function parameters including LF by HRV ($F_{2,28}$ = 0.36, p = 0.701), HF by HRV ($F_{2,28}$ = 0.08, p = 0.946), LFnu by HRV ($F_{2,28}$ = 0.54, p = 0.587), HFnu by HRV ($F_{2,28}$ = 0.43, p = 0.653), LF/HF by HRV ($F_{2,28}$ = 1.32, p = 0.282), PSD ($F_{2,25}$ = 0.07, p =0.930), LF by BPV ($F_{2,27}$ = 0.65, p = 0.531), HF by BPV ($F_{2,27}$ = 0.08, p = 0.925), LFnu by BPV ($F_{2,27}$ = 0.2, p = 0.823), HFnu by BPV ($F_{2,27}$ = 0.95, p = 0.399), LF/HF by BPV ($F_{2,27}$ = 0.54, p = 0.588), BRS ($F_{2,24}$ = 0.76, p =0.477) and BEI ($F_{2,24}$ = 0.12, p =0.884). This indicates that autonomic function changes during HD did not behave differently between intervention days. However, there was a significant effect of *Time* with an increasing trend in LFnu by HRV ($F_{1,28}$ = 6.85, p = 0.014) and a decreasing trend in HF by HRV ($F_{1,28}$ = 4.58, p = 0.041) and HFnu by HRV ($F_{1,28}$ = 6.88, p = 0.013) in the overall population. The ratio of LF/HF by HRV ratio showed a borderline significant increasing trend ($F_{1,28}$ = 3.92, p = 0.057). Similar trends for changes in autonomic variables were seen in the analysis including only the subset of patients who completed all three interventions, or when the influence of fluid status (IDWG, UF goal and FO%) was added as a covariate in the model. Between-group comparisons by ANOVA showed

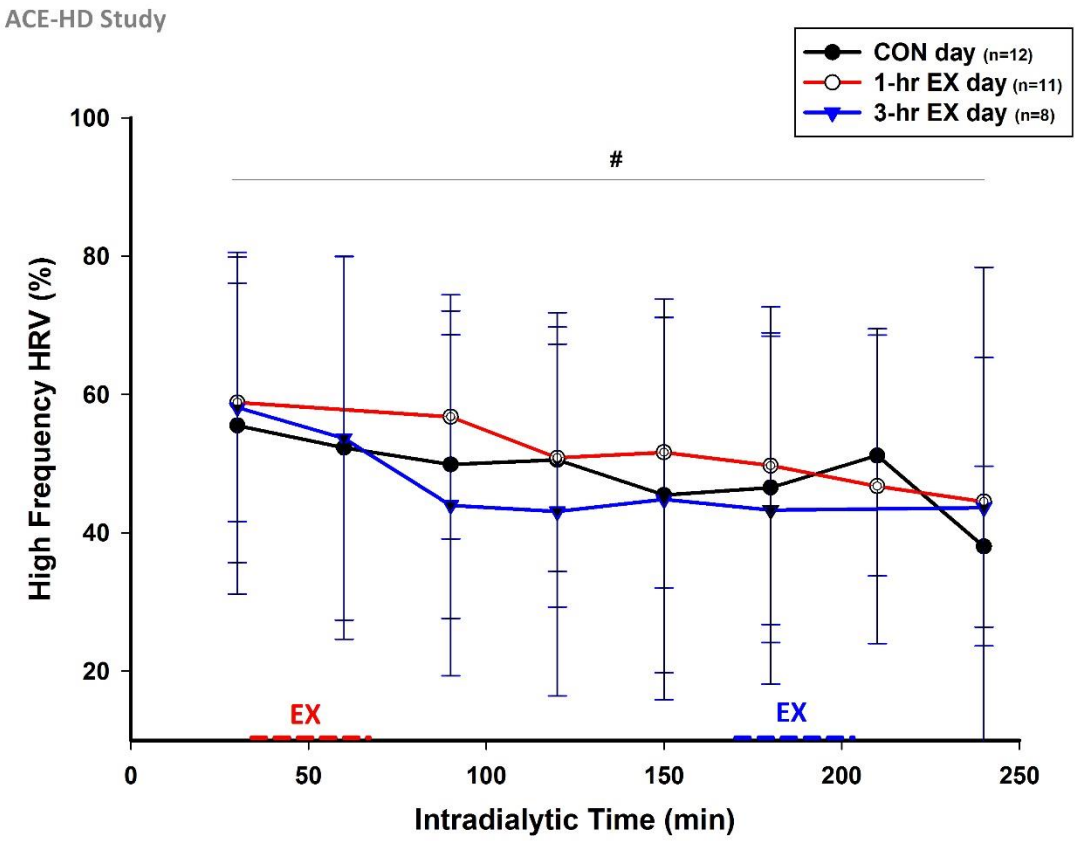
no difference at each measured time point in the absolute and the delta values of autonomic parameters.

Figure 13-A. Changes in normalized low frequency component of heart rate variability (HRV) during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

Figure 13-B. Changes in normalized high frequency component of heart rate variability (HRV) during a standard HD treatment with and without exercise.



#: indicates a significant effect of *Time* in the overall group ($p<0.05$).

Figure 13-C. Changes in low to high frequency ratio of heart rate variability (HRV) during a standard HD treatment with and without exercise.

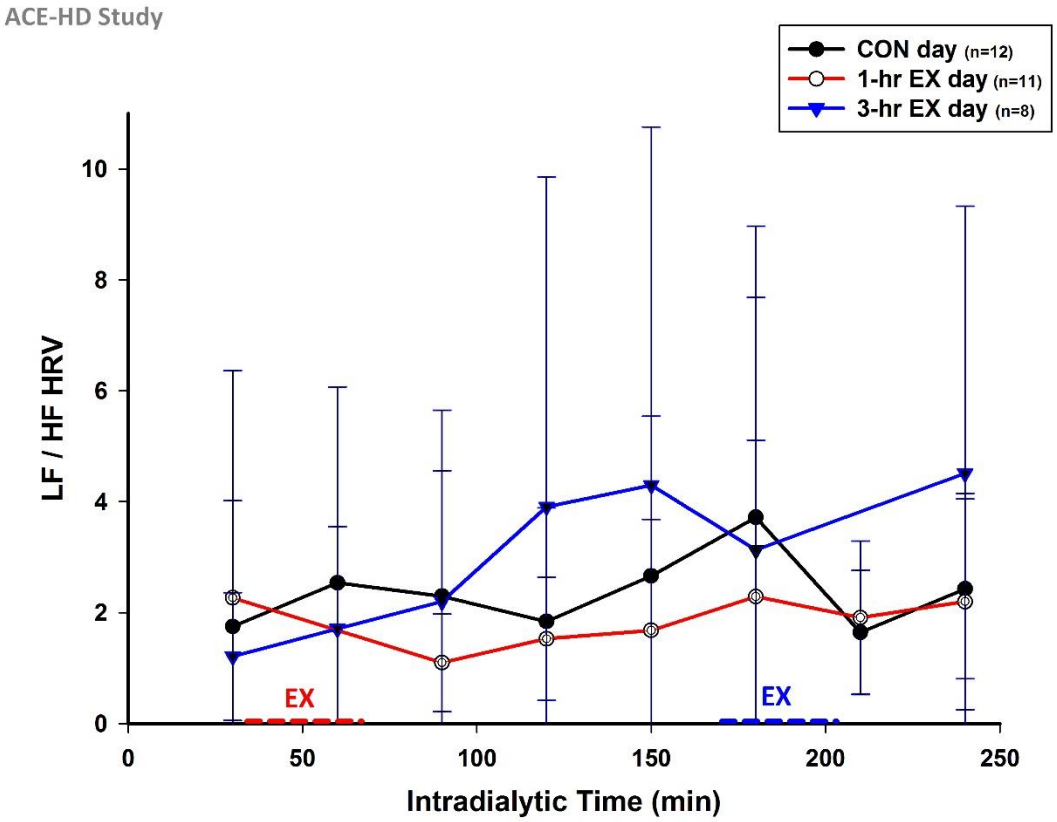
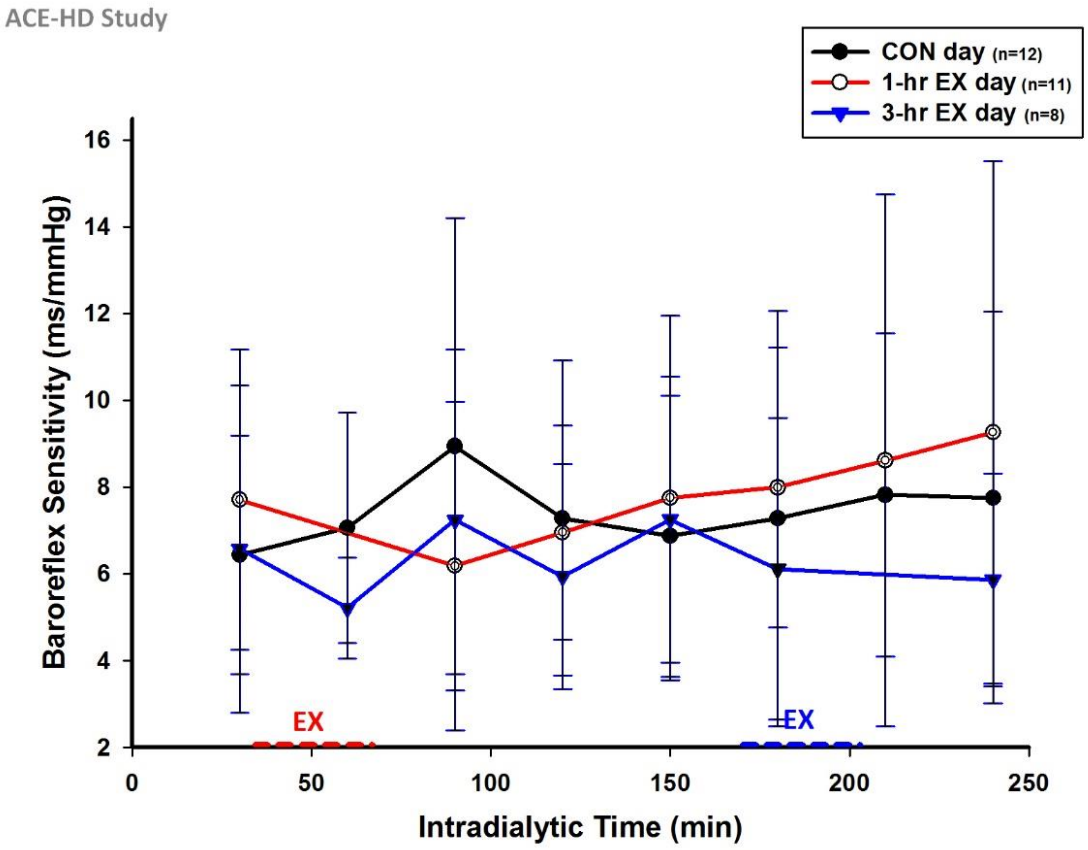


Figure 13-D. Changes in baroreflex sensitivity during a standard HD treatment with and without exercise.



6-7. Comparison of cardiac and arterial parameters at Pre- and Post-HD

Cardiac and arterial parameters before and after HD on the three treatment days were obtained in a subset of participants and are summarized in **Table 9**. Due to patient's time constraints before or after treatment, this data was only collected on 8, 6, and 3 patients on the CON, 1st-hour IDEX, and 3rd-hou IDEX days, respectively. There was no difference between three intervention days in all parameters measured at pre- and post-HD with the exception of AugP and Aix75. Post-hoc analysis indicated that AugP and Aix75 at post-HD in the 3rd-hr EX was significantly lower than those in 1st-hr IDEX ($p<0.05$ for both). Body weight and all hydration related variables at post-HD were significantly lower than pre-HD values. Among cardiac and arterial variables, only E/E' at post-HD was significantly different from the pre-HD value when all data was combined.

Table 9. Cardiac and Arterial Parameters at Pre- and Post-HD

Variables	Total	CON	1st-hr EX	3rd-hr EX
Cardiac Parameters		(n=8)	(n=6)	(n=3)
SV at pre-HD (mL)	73.2 ± 23.4	74.5 ± 24.9	74.2 ± 24.5	67.7 ± 25.7
SV at pre-HD (mL)	67.5 ± 30.3	81.2 ± 41.6	58.7 ± 15.8	53.0 ± 2.8
CO at pre-HD (L)	5.4 ± 1.7	5.7 ± 1.6	5.5 ± 1.9	4.4 ± 1.6
CO at post-HD (L)	5.1 ± 2.7	6.4 ±3.5	4.5 ± 1.8	3.4 ± 0.6
EF at pre-HD (%)	57.8 ± 18.7	63.0 ± 18.5	55.2 ± 20.0	49.2 ± 19.0
EF at post-HD (%)	59.7 ± 17.6	64.2 ± 8.2	57.1 ± 22.4	54.1 ± 30.8
E/A at pre-HD	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	1.0 ± 0.0
E/A at post-HD	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.1	1.0 ± 0.2
S' at pre-HD	8.7 ± 1.9	8.9 ± 2.6	8.9 ± 1.6	8.1 ± 1.2
S' at post-HD	8.8 ± 2.1	9.6 ± 1.9	8.5 ± 2.5	7.6 ± 1.1
E' at pre-HD	10.5 ± 3.4	9.8 ± 3.0	11.4 ± 4.8	10.4 ± 1.6
E' at post-HD	9.2 ± 2.3	9.1 ± 1.7	9.8 ± 2.8	8.3 ± 2.9
A' at pre-HD	9.6 ± 3.2	10.0 ± 4.4	9.5 ± 2.6	8.9 ± 1.6
A' at post-HD	8.9 ± 2.0	8.6 ± 1.1	9.7 ± 2.9	8.0 ± 1.9
DecT at pre-HD	168 ± 111	175 ± 126	173 ± 103	144 ± 128
DecT at post-HD	180 ± 110	196 ± 103	152 ± 91	188 ± 180
E/E' at pre-HD	9.6 ± 5.9	10.8 ± 6.4	9.4 ± 7.6	7.5 ± 0.6
E/E' at post-HD	7.5 ± 3.8*	7.5 ± 4.1	7.7 ± 4.7	7.2 ± 2.8
LVM at post-HD (g)	327.8 ± 96.4			
Arterial Parameters		(n=7)	(n=6)	(n=4)
bSBP at pre-HD (mmHg)	126.2 ± 19.3	127.6 ± 20.7	130.7 ± 23.8	117.2 ± 6.1
bSBP at post-HD (mmHg)	132.1 ± 20.6	130.0 ± 17.7	142.7 ± 23.9	116.0 ± 5.0
bDBP at pre-HD (mmHg)	76.5 ± 17.1	78.4 ± 17.0	79.0 ± 21.5	69.2 ± 11.2
bDBP at post-HD (mmHg)	77.5 ± 13.5	75.0 ± 9.8	82.8 ± 17.5	71.7 ± 10.7
aSBP at pre-HD (mmHg)	117.3 ± 19.0	117.3 ± 20.8	122.2 ± 23.0	110.0 ± 7.7
aSBP at post-HD (mmHg)	120.6 ± 19.6	118.8 ± 17.4	129.5 ± 22.4	106.3 ± 11.2
aDBP at pre-HD (mmHg)	77.5 ± 17.0	79.7 ± 17.2	80.2 ± 20.9	69.8 ± 11.0

Table 9 (cont.)

Variables	Total	CON	1st-hr EX	3rd-hr EX
aDBP at post-HD (mmHg)	78.9 ± 13.5	76.2 ± 10.1	84.7 ± 17.0	72.7 ± 10.7
AugP at post-HD (mmHg)	8.5 ± 6.0	6.7 ± 4.2	12.8 ± 6.2	3.3 ± 1.5#
Aix75 at pre-HD (mmHg)	18.3 ± 13.6	17.6 ±13.1	21.7 ± 17.7	14.5 ± 8.7
Aix75 at post-HD (mmHg)	16.1 ± 12.5	13.5 ± 9.7	24.8 ± 12.4	4.0 ± 3.5#
PWV at pre-HD (m/s)	8.2 ± 0.7	8.2 ± 0.8	8.1 ± 0.6	8.2 ± 0.6
PWV at post-HD (m/s)	8.3 ± 0.9	8.3 ± 1.0	8.7 ± 0.5	7.8 ± 0.9

SV: stroke volume, **CO**: cardiac output, **EF**: ejection fraction, **E/A**: the ratio of early to late diastolic filling pressures, **S'**: peak systolic annular velocity, **E'**: peak early diastolic annular velocity, **A'**: peak late diastolic annular velocity, **DecT**: deceleration time of E', **E/E'**: the ratio of early diastolic filling pressure to tissue velocity, **LVM**: left ventricular mass, **bSBP**: brachial systolic blood pressure, **bDBP**: brachial diastolic blood pressure, **aSBP**: aortic systolic blood pressure, **aDBP**: aortic diastolic blood pressure , **AugP**: augmentation pressure, **Aix75**: Augmentation pressure at heart rate 75, **PWV**: pulse wave velocity

*: indicates a significant difference between pre- and post-HD levels by paired t-test.

#: indicates a significant difference between three intervention days by ANOVA and a significant difference from 1st-hr EX by LSD-post-hoc analysis.

6-8. Relationship between hemodynamic changes during HD: Potential determinants of BP changes during HD

The relationship between changes in brachial BP and other hemodynamic variables that potentially influence BP levels, including SV, HR, CO, TPR and LFnu were examined by two different methods; 1) covariance slope comparison in a Mixed Model with Repeated Measures to examine the overall contribution of the potential candidates to BP fluctuation; and 2) correlation between delta values to examine the short-term fluctuation.

- *Mixed repeated models with covariance slopes*

In this analysis, SBP was used as a dependent variable with potential hemodynamic determinants of SBP fluctuation (SV, HR, CO, TPR and LFnu) added as covariates. When the slope of the *covariate * Time* is not significantly different from the slope of *SBP * Time*, it can be interpreted that the intradialytic change of the covariate is similar to the intradialytic change of SBP and thus, potentially has influenced the SBP changes during HD. The results from this analysis showed that the slopes of each of hemodynamic parameters except TPR were significantly different from the slope of SBP fluctuation during HD; CO ($F_{1,404}$= 11.99, β-difference: 1.23, SE: 0.35, p = <0.001), SV ($F_{1,404}$= 11.99, β-difference: 1.23, SE: 0.35, p = <0.001), HR ($F_{1,442}$= 5.65, β-difference: 1.96, SE: 0.83, p = 0.018) and LFnu ($F_{1,404}$= 11.99, β-difference: 1.23, SE: 0.35, p < 0.001). This indicates that intradialytic fluctuations in CO, SV,

HR and LFnu were not similar to the change in SBP over the course of a HD treatment. On the other hand, the slope of *TPR * Time* was not significantly different than the slope of *SBP * Time* during HD ($F_{1,414}$= 0.01, β-difference: -0.675, SE:5.6, p = 0.90), indicating a potential relationship between intradialytic changes in TPR and SBP.

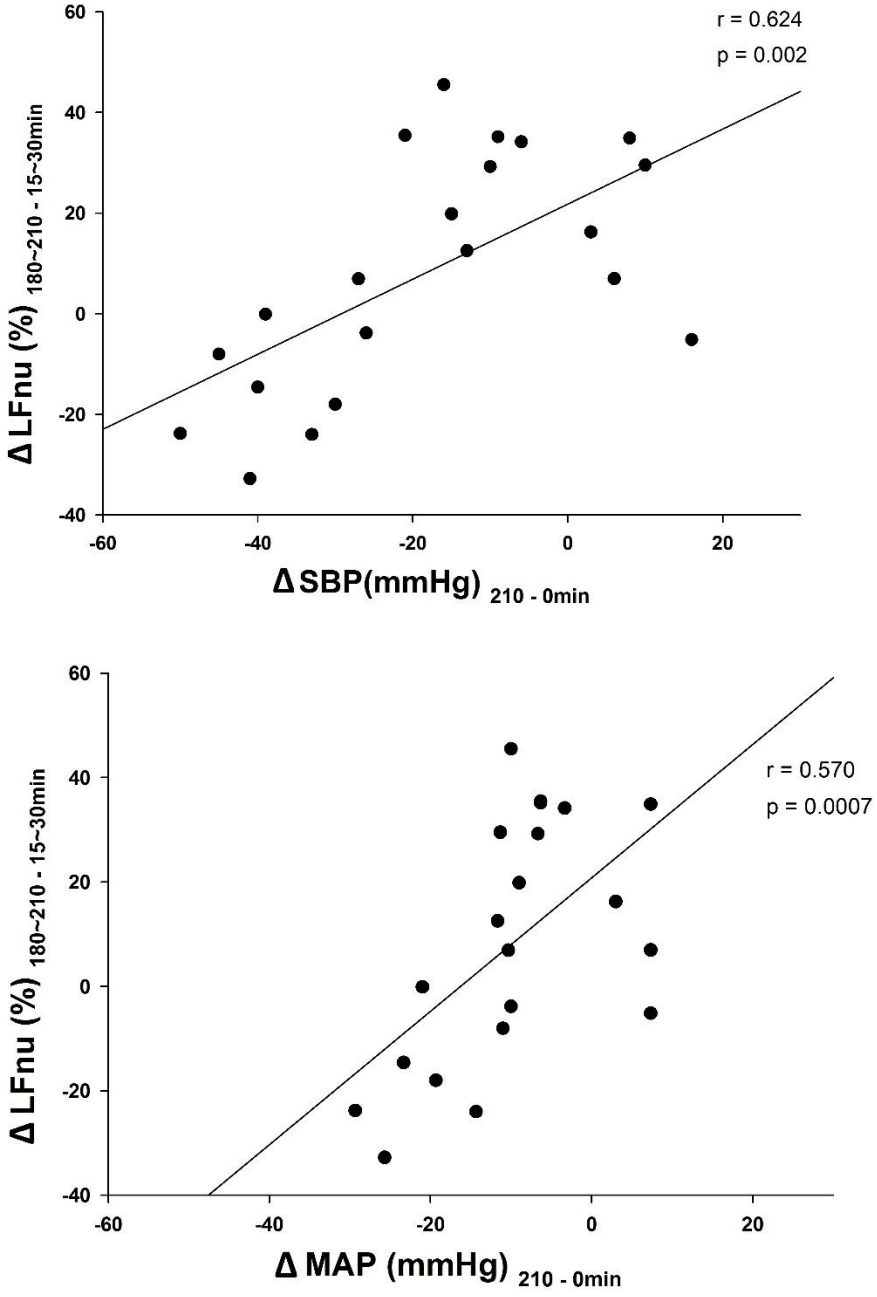
A similar analysis was done to assess factor associated with the change in MAP during HD. The slope of *MAP * Time* was not significantly different from either *SV * Time* ($F_{1,422}$= 0.91, β-difference: 0.30, SE: 0.32, p = 0.342) or *TPR *Time* ($F_{1,399}$ = 0.02, β-difference: -0.938, SE: 6.02, p < 0.8764). However, there was a significant slope difference between *MAP*Time* and *CO * Time* ($F_{1,421}$ = 8.31, β-difference: 0.63, SE: 0.22, p = <0.004), *HR*Time* ($F_{1,426}$ = 3.21, β-difference: 1.55, SE: 0.87, p = 0.074) and *LFnu *Time* ($F_{1,390}$= 8.68, β-difference: 0.862, SE: 0.3, p < 0.003). These results indicate that intradialytic changes in MAP were similar to intradialytic changes in SV and TPR, but not with CO, HR and LFnu.

- *Correlation analysis between intradialytic change values*

Correlation analysis was performed to assess the relationship between intradialytic changes in BP and other hemodynamic variables. There were positive associations between ΔSBP_{210-0} and $\Delta LFnu_{210-30}$ (r = 0.624, p = 0.002) and ΔSBP_{240-30} and $\Delta LFnu_{240-30}$ (r = 0.928, p = 0.008), indicating the magnitude of attenuation in sympathetic activity was related with the magnitude of drop in SBP at 210 and 240 minutes from the beginning of HD. Similarly, a significant

association between ΔMAP_{210-0} and $\Delta LFnu_{210-30}$ ($r = 0.570$, $p = 0.0007$) was noted. ΔSV_{60-30} was negatively associated with ΔTPR_{60-30} ($r = 0.672$, $p = 0.001$) and ΔSV_{120-30} was positively associated with $\Delta LFnu_{120-30}$ ($r = 0.400$, $p = 0.026$). This may indicate a coordinated regulation of SV and TPR in the early phase of HD, and SV and autonomic function in the later phase of HD. Furthermore, the bigger drop in LFnu from the beginning to the end of HD ($\Delta LFnu_{240-30}$) was associated with higher scales of nausea, dizziness and cramping during HD. Lower aortic SBP ($r = -0.585$, $p = 0.022$), DBP ($r = -0.555$, $p = 0.012$) and PP ($r = -0.685$, $p = 0.0021$) at post-HD were associated with higher cramping during HD.

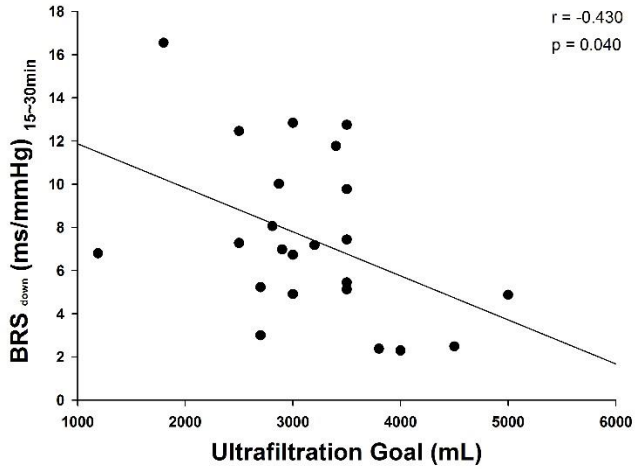
Figure 14-A and B. Association between the changes in systolic blood pressure (A) and mean arterial blood pressure (B) and the corresponding changes in normalized unit of low frequency from the beginning to 210-minutes into HD.

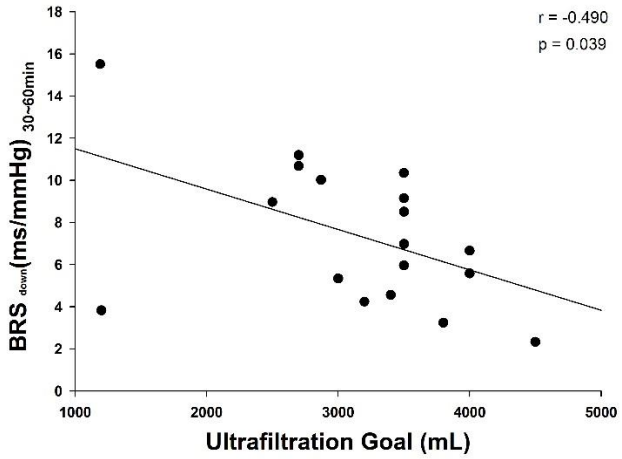


6-9. Association between hydration status and CV characteristics

Higher UF levels were associated with greater drops in SBP, CO and SV in the later hours during HD (ΔSBP_{180-0} : r = -0.428, p = 0.046, ΔSBP_{210-0} : r = -0.440, p = 0.046, ΔSBP_{240-0} : r = -0.846, p = 0.034, ΔCO_{210-30} : r = -0.454, p = 0.013, ΔSV_{210-30} : r = -0.436, p = 0.018). Furthermore, higher UF goal was linked to lower BRS levels throughout HD (**Figure 15 A~E**). Increased TBW%, ECW (L) and FO (L) at post-HD were associated with higher magnitude of EEm, an indicator of diastolic dysfunction. Increased TBW (L), ECW(L) and FO (%) were associated with increased aortic SBP levels at post-HD.

Figure 15-A~E. Association between ultrafiltration goal and baroreflex sensitivity throughout HD.





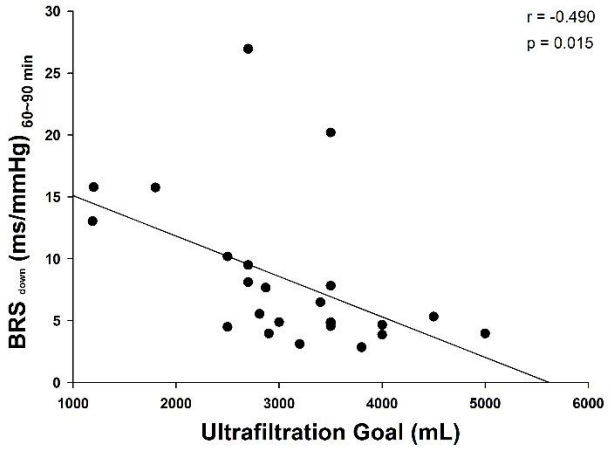
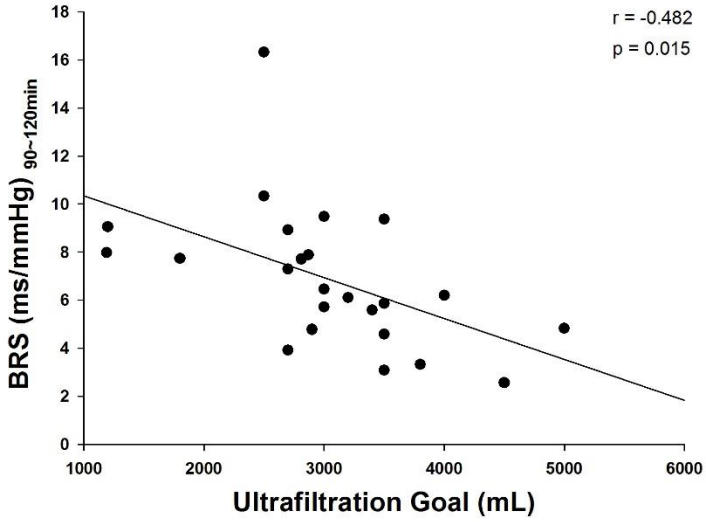
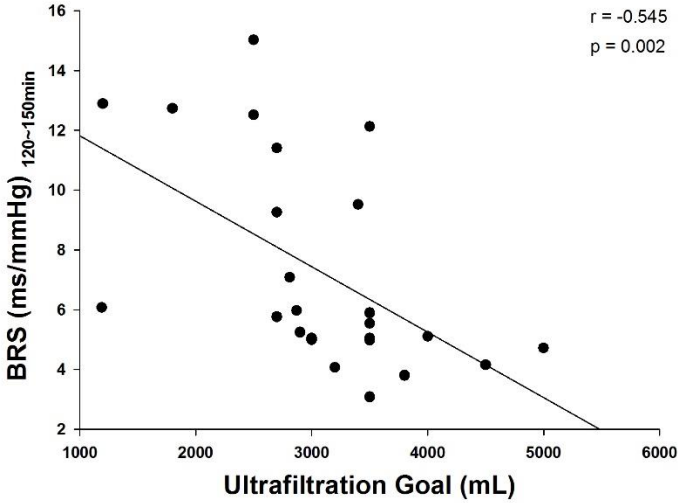


Figure 15 A~E (cont.)





CHAPTER 7

DISCUSSION

The primary purpose of this study was to evaluate the safety of IDEX by examining its effect on intradialytic CV hemodynamics. Specifically, intradialytic changes in brachial, aortic and cardiac hemodynamics and autonomic function were examined during a normal HD session without exercise, or when 30-minutes of cycling exercise was performed during the 1st- or 3rd-hour into HD. The primary finding from this study was that IDEX performed during either the 1st- or 3rd- hour does not appear to exacerbate hemodynamic instability during HD. While there were transient increases in SV, CO and HR during IDEX, the intradialytic changes in brachial and aortic BP parameters, cardiac hemodynamics and autonomic function were similar on days with and without IDEX. This null effect of IDEX on hemodynamic parameters during HD was demonstrated regardless of the timing of exercise and patients' underlying CV characteristics. Patient hydration status was correlated with the magnitude of BP drop and autonomic dysfunction, and increasing sympathetic activity was also correlated with drops in BP during HD. This data suggests potential mechanisms that may contribute to intradialytic hypotension.

7-1. Brachial Hemodynamic Response during HD with and without IDEX

Previous studies have demonstrated that IDEX can improve important health-related outcomes including CV function, physical function, and quality of life[1-3]. Exercise during HD has been advocated for its convenience as a time-efficient strategy to increase physical activity during a forced sedentary period. However, concerns regarding its potential impact on hemodynamic instability has been a cause for concern for clinicians, despite a lack of evidence for these effects. HD imparts a significant CV stress mainly due to the progressive loss of blood volume during treatment, and exercise may in theory exacerbate these effects. In particular, post exercise hypotension (PEH) may increase the risk of ischemic adverse events, particularly during the latter phase of HD when the total blood volume is already low. Despite this theoretical concern, the present study demonstrated that intradialytic changes in brachial BP parameters were not different between HD sessions with and without IDEX performed during either the 1st-hour or the 3rd-hour of treatment. This finding is consistent with previous studies in which IDEX was well tolerated and did not elicit abnormal hemodynamic responses[21, 113, 183, 184], though much of the previous data examining the impact of IDEX on hemodynamic variables came from small pilot studies lacking a control group. The only previous study that systematically investigated the CV safety of IDEX used a short submaximal exercise bout (5-minutes of cycling at 60% of VO2peak) that was repeated every hour during an HD treatment. Stable hemodynamic responses

to IDEX were demonstrated through the 2nd-hour of HD, but 5 out of 8 patients were unable to perform cycling during the 3rd-hour due to hypotension that was accompanied by reductions in HR and CO. One potential explanation for this is that the patients that were unable to exercise in the 3rd hour due to hypotensive symptoms had a higher ultrafiltration volume compared to the patients who were able to exercise in the 3rd-hour (4596±1339 ml vs 3170±1092 ml respectively)[21]. This suggests that exercise may indeed be well tolerated in the 3rd hour of treatment in the absence of excessive ultrafiltration requirements, thus does not need to be contraindicated in all patients.

There was a trend for a reduction in both brachial and aortic BP throughout HD across all groups. This is a well-known phenomenon likely resulting from the loss of plasma volume during HD. The reduction in plasma volume reduces venous return, and if this is not compensated by an increase in HR or TPR, there will be a gradual decrease in BP during HD.

The typical reduction in SBP during HD is around 10~15mmHg, though the reduction is often more rapid in the first hour compared to the later hours of treatment[221]. The average intradialytic SBP drop in this study was 18 mmHg, which is comparable to other data in the literature. CO and TPR are mutual determinants of mean arterial BP and are expected to behave reciprocally to maintain mean arterial BP. In the present study, both CO and TPR were numerically reduced

over the course of HD, but these changes were not statistically significant. This may indicate suboptimal compensatory CV responses that are insufficient to maintain BP during HD.

7-2. Cardiac Hemodynamic Response during HD with and without IDEX

During exercise, peripheral vasodilation occurs to meet the increased metabolic demands in exercising muscles. At the same time, local signals integrated from baroreflex, chemoreflex and skeletal muscle receptors help to augment sympathetic outflow in the heart, the adrenal gland and the splanchnic vasculatures, with the final result of maintained or increased systemic BP levels during exercise. In the present study, increases in SV, CO and HR observed during the IDEX period indicate that most patients appeared to have a normal CV response to the moderate intensity exercise bout. However, we did not observe a reduction in BP following the cessation of exercise, a phenomenon known as post-exercise hypotension (PEH). This is normally caused by a post-exercise reduction in TPR. This lack of an effect may have been due to autonomic dysfunction, though it could also have been due to the relatively modest intensity of the exercise bouts that were conducted. It is also possible that the removal of fluid by ultrafiltration prevents the signals that are normally responsible for PEH. The magnitude of local vasodilation in active tissues, despite an increased systemic sympathetic outflow, is termed "functional sympatholosis", and normally becomes greater as exercise intensity increases[168, 169].

Vasoconstriction is one of the important compensatory responses to the progressive hypovolemia and thus presumably occurred to some extent in our patients. Furthermore, decreased levels of systemic nitric oxide concentration have been reported after HD treatment, suggesting a partial reduction in vasodilatory capacity[222]. Thus, it can be speculated that the effect of mild to moderate intensity IDEX on the CV system might be offset by the profound impact of HD, resulting in the absence of PEH. Although beyond the scope of the present study, pre-existing ESRD-comorbidities, such as autonomic dysfunction, impaired vasoreactive capacity, and HD-driven increases in systemic inflammation cannot be ruled out as factors responsible for the blunted post-exercise responses in HD patients.

7-3. Autonomic Response during HD with and without IDEX

HRV is a measure of autonomic regulation of heart rate, reflecting the ability of the sinoatrial node to modify HR in response to sympathetic and parasympathetic signals. The beat-to-beat BPV provides information regarding the relative contribution of neuro-humoral systems in BP regulation, including baroreceptor reflex, the renin-angiotensin system, the vascular myogenic response, and the endothelial response to nitric oxide[223]. Spectral analysis provides an analysis of HR and BP oscillations at different frequencies. In HRV analysis, oscillations within HF ranges and HFnu (normalized HF component over total power) are considered to be a marker of

parasympathetic and respiratory modulations. LF oscillations are attributed to the interaction of slow sympathetic and fast vagal actions, and LFnu is often accepted as a measure of sympathetic nerve activity. BPV at LF domain is modulated by sympathetic vascular activity while BPV at HF has shown to be largely influenced by CO[224]. HD patients are characterized by suppressed HRV and BPV and enhanced sympatho-excitation[38, 142] and decreased baroreflex sensitivity, a measure of HR response to BP fluctuations[225].

In the present study, there was a significant increasing trend in LFnu and decreasing trends in HF and HFnu by HRV throughout HD sessions in the overall population, indicating a shift of sympathovagal balance toward a sympathetic predominance during HD. While BPV was not altered, the HRV data are consistent with previous findings demonstrating increased sympathetic activity during a HD treatment[41, 130]. This trend toward sympathetic activation was inversely associated with intradialytic BP in the present study, and helps describe the integrative CV regulation in response to HD. HD-driven blood volume depletion causes drops in systemic BP and systemic vascular resistance, signaling arterial baroreceptors to augment sympathetic activity. Sympathetic outflow is likely to be discharged continuously or at increasing manner when the subsequent arterial BP levels do not recover to normal levels. Despite the increasing sympathetic and decreasing parasympathetic stimulation, there was no corresponding change in HR and TPR throughout HD in the present study. These blunted responses in the heart and the

vasculature to the autonomic modulation reflect an impaired CV regulatory capacity and are likely to be partly responsible for the failure to maintain BP during HD. In support of this, previous studies have demonstrated a high prevalence of autonomic neuropathy[226], an impaired vascular adrenoceptor number and function[227], and decreased vascular response to Ang II[228] in patients with intradialytic hypotension.

There is no previous study investigating the acute effect of IDEX on autonomic function, though several studies examined the autonomic control during dynamic exercise in HD patients on non-HD days. Compromised autonomic regulation in response to exercise has been consistently shown, particularly in related to abnormal BP responses[142 157 39]. In the present study, there was no significant effect of IDEX on intradialytic change in autonomic activity, including LFnu, HFnu, LF/HF and BRS. The explanation for this is likely to be multifactorial and the influence of HD is likely to create disturbances in autonomic modulation. A patient's hydration status[229, 230], the composition[231] and temperature of the dialysate[232], and PTH levels[233] can also influence HRV. Despite the methodological challenges, further investigation of autonomic regulation during IDEX is warranted.

7-4. Change in Arterial Compliance during HD with and without IDEX

Given the high CV disease burden in HD patients, measurements of aortic hemodynamics provide pathophysiologically important information because central BP reflects the volume and pressure load imposed on the left ventricle more accurately than peripheral BP. Apart from volume change, arterial stiffness and the magnitude of arterial wave reflection significantly influences aortic BP and PP. Accordingly, PWV and Aix have been consistently related to CV morbidity and mortality in HD patients[88, 234]. However, there are conflicting data regarding the acute effect of HD treatment on arterial compliance. Decreased Aix[235, 236] and aortic PWV[237] and increased aortic and brachial PWV[236, 238] have been shown after HD, though other studies indicate no effect of HD on aortic PWV[239, 240] and markers of large artery compliance[241, 242]. These inconsistent results might be attributed to methodological and population discrepancies between studies, as well as the acute effects of HD on the CV system. In theory, volume overload increases arterial distension and consequently augments arterial stiffness according to Laplace's law *(*$T = P \cdot D/2$, T: circumferential wall tension, P: internal pressure, D: internal diameter). However, with decreasing blood volume as a result of ultrafiltration, the renin angiotensin aldosterone (RAA) system is activated and Ang II levels are increased. This results in vasoconstriction and arterial stiffness. Furthermore, HD not only creates a huge volume fluctuation but also changes levels of some vasoactive molecules that may affect the arterial

properties such as endothelin NO and Ang II[222]. The timing and amplitude of the reflected waves from the peripheral vasculatures to the aorta have been shown to be attenuated following a submaximal exercise, which in turn decreases aortic pulse amplification, aortic PP and PWV[243]. While the present study showed no significant effect of IDEX on any aortic hemodynamics, there was a significant effect of HD, with decreasing trends in aortic BP and PWV over the course of a treatment. However, it should be noted that only a limited number of aortic measurements were available from a subgroup of participants in this study, thus limiting the validity of the results.

7-5. The Potential Protective Effect of IDEX for IDH

In the present study, brachial BP levels were elevated in the last hour of HD after performing the 1st-hour IDEX. This was in contrast to the progressive decreasing trend in the HD sessions either without IDEX or with 3rd-hour IDEX. The challenge of maintaining hemodynamic stability during HD, particularly in the later hours, arises mainly from inadequate CV compensatory responses to hypovolemia. Although speculative, when total blood volume is critically low and the expected compensatory responses are suboptimal, the acute stimulation of the CV system by exercise may help maintain CV homeostasis. Exercise engages a wide range of mechanisms to increase central blood volume. During exercise, plasma volume diffuses from the

intravascular compartment to interstitial space around skeletal muscles. This reduction in plasma volume activates autonomic peripheral afferent receptors such as baroreflex, chemoreflex and skeletal muscle receptors to increase sympathetic outflow. The efferent responses to the sympathetic activation include increased HR and myocardial contractility in the heart, and vasoconstriction in non-active organ vasculatures. This sympathetic modulation in the CV system as a whole helps increase central blood circulation. Previous studies demonstrate that IDEX indeed produces a transient reduction in plasma volume at the onset of exercise[184, 244]. However, when monitored until the end of HD, the change in relative blood volume was gradually increased, compared to during HD without IDEX where there was a gradual decreasing trend[244]. The authors speculated that IDEX has the potential to promote plasma refilling during the post-exercise period. Exercise-induced fluid shifts from the intravascular space to the active tissues can lead to an increased plasma hematocrit concentration during exercise. This facilitates plasma refilling from the extravascular to intravascular compartment due to an increased intravascular colloid osmotic pressure after exercise. Furthermore, exercise is proposed to induce increased capillary membrane pore sizes to allow efficient nutrient delivery for exercising tissues in HD patents[109, 245]. This decreased inter-compartment resistance may boost the influx of interstitial fluid to the intravascular space, at least shortly after exercise is ended, although it is unclear how long this effect may last in HD patients. In addition, the local contribution from the

muscle pump can accelerate CV refilling via increased venous return and mobilization of interstitial fluid. Micromechanical stimulation of calf muscle pump increased CV refilling, as evidenced by an initial rapid rise and a longer slow rise in BP, via improved interstitial fluid recovery from low extremities in HD patients[246]. Further studies are needed to examine the protective effect of IDEX from the standpoint of development and understanding of non-pharmacological treatment modalities for HD patients prone to hypotensive events.

7.6 Interplay between Intradialytic Hemodynamic Parameters; Determinants of BP changes during HD

Hemodynamic instability is one of the biggest clinical challenges in HD patients. Thus, determining what CV factors influence BP regulation during HD are clinically important. The present study examined the relationship between BP and other hemodynamic indices by two methods in regard to different time frames: 1) comparison of the slopes of CV indices throughout HD and 2) correlation between intradialytic changes between different CV variables during specific time frames. The slope-based analysis suggested a contribution of SV to MAP intradialytic changes. This supports a dominant role for blood volume changes in determining systemic BP levels during HD. The correlation analysis showed that a significant relation between the changes in SBP and LFnu from the beginning to the end of HD. This indicates that

the degree of attenuation in sympathetic activity was related to the magnitude of drop in SBP in the last hour of HD. Likewise, a larger drop in LFnu from the beginning to the end of HD was associated with increased incidence of intradialytic symptoms including nausea, dizziness and cramping. Lower aortic BP at post-HD was also associated with higher cramping during HD. Additionally, a negative correlation between SV and TPR changes during the first-hour and a positive association between SV and LFnu changes in the third hour of HD were found. These results indicate reduced venous return, as indicated by decreased SV, is compensated by increased vascular constriction during the early hour, whereas autonomic regulation plays an increasing role to maintain arterial BP in the later hours of HD when circulating blood volume is low. However, it should be noted that this analysis included all available HD sessions, irrespective of whether or when exercise was conducted. This was done to increase the power of the analysis, though may complicate the interpretation of the results. Nevertheless, exercise-induced hemodynamic fluctuation was only observed during the period of exercise, and all primary analysis indicate that the exercise had little impact on most hemodynamic variables.

7.7 Influence of Hydration Status on Intradialytic Hemodynamic Changes

The magnitude of hydration status, as measured by IDWG, ultrafiltration volume, and FO% at pre-HD, did not significantly influence the intradialytic changes of hemodynamic parameters

between HD sessions with and without IDEX. The high variability in hydration state within and between patients and the heterogeneous intradialytic hemodynamic responses may have limited the power to detect an influence of hydration status on intradialytic hemodynamic changes with and without IDEX. However, the correlation between hydration status and hemodynamic indices revealed that higher ultrafiltration volume was associated with larger drops in SBP, CO and SV in the later hours during HD, and lower BRS throughout HD sessions. These results may confirm the notion that high IDWG and the consequent high target volume removal during HD is likely to increase the risk of HD-intolerance in the later hours of HD. The finding of the dampened BRS levels with increased ultrafiltration volume is in line with other data showing a correlation between FO and HRV[247]. As incomplete volume correction during HD contributes to the development of chronic FO, our results supports the hypothesis that FO may alter autonomic control. Furthermore, the increased levels of hydration status were associated with higher levels of EE', a marker of LV diastolic dysfunction, at post-HD. Chronic FO has been associated with pathological myocardial dilation, and our results add to the evidence for myocardial functional impairment in overhydrated HD patients.

7.8 Adverse Events

In this study, 32.3% of HD sessions were associated with IDH and 16.1% with IDHTP. The sessions with IDH were mostly accompanied with physical symptoms, and half of the sessions with IDH required saline infusion and/or adjustments to the ultrafiltration volume and/or flow rates. No effect of IDEX was found in the presence of IDH and IDHPT, and the history of IDH and IDHPT also did not have a significant effect on our main outcomes. As such, no IDEX-driven serious adverse events were observed throughout the study period. However, two patients developed severe hypotensive symptoms (cramping and nausea) accompanied by a rapid drop in SBP immediately after performing the 3rd-hr exercise. The symptoms remained until a few hours after the HD sessions. It might be argued that the hypotensive symptoms were in part driven by the 3rd-hour exercise during HD. However, the first patient with the adverse event had a post-HD weight on that day that was 1 kg below their prescribed dry weight, suggesting the patient may have been under-hydrated. The second patient had an exceptionally high ultrafiltration volume (4500ml) considering their body size (152 cm in height and 120kg in body weight) on their 3rd hour exercise day. Thus, it is not clear whether the late-hour exercise, excessive ultrafiltration, or both, contributed to the development of the hypotensive symptoms. It also should be recognized that brachial and aortic BP were lower throughout the 3rd-hour IDEX day compared to other intervention days during the mid-hours of HD. Although the reason for this is

unclear, the suppressed BP before performing the 3rd-hour IDEX indicates that the last-hour exercise was unlikely to be the reason for the hypotensive events. For the sake of maximal safety, it should be advised to examine potential factors that may increase the risk of HD-intolerance such as abnormal hydration status at pre-HD, as well as recent illness, when considering IDEX in the 3rd hour of treatment.

7.9 Limitations

This study has several limitations. First, exercise intensity and workload were not objectively measured. Different levels of exercise intensity cause different physiological responses and the results from the self-selected intensity exercise may limit the generalizability of the results to all HD patients. Similarly, the blunted CV response, as indicted by no significant increases in HR, CO and BP, during the 3rd-hour exercise may also be attributed to the subjectivity of exercise intensity. Patients may be less motivated to exercise during the last hour than the earlier hours during HD sessions due to the HD-driven physical and mental exhaustion. As such, the intensity of exercise during the 3rd-hour may have been decreased compared to the levels that patients would exercise during 1st-hour into HD. However, we chose this approach (RPE-based) because it was the most practical approach, and it is similar to how exercise is normally prescribed in IDEX programs in the United States. Furthermore, the gold standard method (HR-based) remain

invalid due to the high prevalence of autonomic dysfunction in HD patients. Calibration to estimate the total workload was unfortunately not possible with the ergometers used in our study.

Second, patient's IDWG and the subsequent ultrafiltration volume were not controlled between intervention sessions, although patients were advised to maintain the typical eating patterns during the study period. HD patients are recognized to be heterogeneous in their hemodynamic response to HD, particularly related to ultrafiltration volumes. Environmental factors as well as HD prescriptions should be considered as potential confounding factors for hemodynamic changes during HD in future studies. Third, only a subset of patients was available for cardiac and arterial measures at pre- and post-HD. Thus, the impact of CV comorbidities on the intradialytic hemodynamic responses were not adequately powered to examine as confounding factors.

7-10. Conclusion

From a public policy perspective, IDEX training represents a low-cost, easy to administer treatment strategy that could potentially reduce the burden of CV disease and other uremic symptoms in this population. Our data suggests that IDEX does not exacerbate hemodynamic instability during HD regardless of hydration status and the timing of the exercise. Despite the gradual decreases in brachial and aortic BP throughout HD, IDEX did not cause further

hemodynamic instability. We also observed the potential roles of overhydration and autonomic dysfunction on hemodynamic regulation during HD. These results should help to improve our understanding regarding the CV safety of IDEX. Such understating will lead to improve therapeutic approaches, including exercise training, that will prevent or minimize the deleterious effect of renal failure, as well as the HD process itself.

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