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The Effect of Convective Dialytic Modalities on Arterial Stiffness in End-Stage Renal Disease Patients

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Abstract

Among end-stage renal disease (ESRD) patients receiving hemodialysis, increased arterial stiffness is an independent cardiovascular risk predictor. Over the past few years, arterial stiffness attenuation has been increasingly recognized as a novel therapeutic target toward cardiovascular risk reduction in the dialysis population. Structural alterations related to the long-term arteriosclerotic process are difficult to modify; with the exception of blood pressure (BP)-lowering, there are no other therapeutic interventions with well-documented benefits in delaying the progression of arteriosclerosis among dialysis patients. Enhanced clearance of middle-to-high molecular weight solutes by combining convective and diffusive transport through hemodiafiltration and the associated benefits on microvascular endothelial function have generated the hypothesis that convective dialytic modalities may be advantageous in improving large-artery stiffness. This notion is supported by some clinical studies showing that switching ESRD patients from low-flux hemodialysis to high-efficiency on-line hemodiafiltration was associated with significant reduction in arterial stiffness. These beneficial effects, however, were not confirmed in a recent subanalysis of the CONvective TRANsport STudy (CONTRAST) trial. In this chapter, we summarize the currently available evidence on the effect of hemodiafiltration versus hemodialysis on arterial stiffness, discussing also the potential clinical implications of this effect.

Keywords: arterial stiffness, hemodiafiltration, hemodialysis, pulse wave velocity, vascular calcification

1. Introduction

Patients with end-stage-renal-disease (ESRD) receiving maintenance hemodialysis have one of the highest rates of cardiovascular morbidity and mortality [1, 2]. Although classical atheromatosis of middle-sized arteries is an important contributor to this elevated cardiovascular risk, atherosclerotic cardiovascular events (i.e., myocardial infarction and stroke) can only partially explain the huge burden of cardiovascular mortality in ESRD. Among these patients, serious arrhythmias and sudden cardiac deaths related to the high prevalence of left ventricular (LV) hypertrophy and disturbances in electrolyte balance represent another major cause of cardiovascular death [3]. This phenomenon is explained by the fact that the spectrum of arterial remodeling in ESRD is much broader, including also long-term structural alterations in the visco-elastic properties of the biomaterial constituting the wall of the aorta and large conduit arteries [4, 5]. The so-called “arteriosclerotic process” is accompanied by substantial hemodynamic alterations and is considered one of the most important pathogenic mechanisms of isolated systolic hypertension, LV hypertrophy, and subendocardial hypoperfusion [4, 5]. It is therefore unsurprising that among ESRD patients, increased arterial stiffness is a strong and powerful predictor of cardiovascular morbidity and mortality [6, 7].

Given the strong prognostic association of arterial stiffness with cardiovascular outcomes, regression of the arteriosclerotic process is increasingly recognized as a novel therapeutic target toward cardiovascular risk reduction in dialysis patients. However, whether arterial stiffness in this particular population is modifiable and if so, which therapeutic interventions are effective in delaying the progression of arteriosclerosis are aspects that remain unclear [5, 8]. Observational evidence and a few randomized studies suggested that blood pressure (BP)-lowering and use of agents blocking the renin-angiotensin-aldosterone-system (RAAS) may be of some benefit [5, 8, 9]. The modality of renal replacement therapy is suggested to be another factor possibly determining the progression of arteriosclerosis in dialysis patients. In this regard, higher clearance of middle-to-large molecular weight solutes by combining diffusive and convective transport and the associated improvement in phosphate control, endothelial dysfunction, and circulating inflammatory biomarkers [10–14] is proposed to be translated into a beneficial impact of hemodiafiltration on large-artery structure and function in dialysis patients.

The aim of this chapter was to review the currently available evidence on the effect of hemodiafiltration versus hemodialysis on the long-term progression of the arteriosclerotic process and discuss the potential implications that this effect may have in the choice of the most appropriate dialytic modality for ESRD patients.

2. Arterial stiffness in dialysis patients

Acceleration of the arteriosclerotic process is the typical feature of arterial remodeling in ESRD. Aortic and carotid-artery stiffness is significantly higher in ESRD patients than in

age-, sex-, and BP-matched controls with normal renal function [15]. Among dialysis patients, arteriosclerotic process is a pathophysiological continuum of structural alterations that begin from the early stages of renal impairment, with several studies showing a step-wise increase in arterial stiffness with advancing stage of chronic kidney disease (CKD) [16, 17]. Structural alterations related to arterial stiffening in ESRD include fibro-elastic intimal thickening, calcification of elastic lamellae, increased extracellular matrix deposition, elastinolysis and inflammation, increased collagen, and decreased elastic fiber content [4, 18, 19]. The mechanistic background of these arterial wall alterations is complex and not yet fully elucidated. Apart from the contribution of accumulated traditional cardiovascular risk factors, it is suggested that specific mechanistic pathways related to the ESRD status and renal replacement therapy may play a particular role in the progression of arteriosclerosis in this population. Some of the most important ESRD-specific mechanisms involved in the pathogenesis of arteriosclerosis include impaired mineral metabolism and elevated calcium-phosphate product, vascular calcification, excessive activation of the RAAS, endothelial dysfunction, inflammation, oxidative stress, and chronic volume overload [4, 18, 19]. Compared with traditional cardiovascular risk factors, these ESRD-specific pathways were shown to be stronger determinants of the progression of arteriosclerosis over time [20].

The main physiological role of the aorta and large conduit arteries is (i) to dampen the high-pressure oscillations generated from the intermittent LV ejection and (ii) to transform the cyclic blood flow in the aorta into a continuous capillary flow pattern required for perfusion of organs and tissues [4, 19, 21]. During systole, the stroke volume ejected by the left ventricle interacts with the elastic properties of the aorta to generate a pulse wave (incident or forward-traveling) that is propagated at a pulse wave velocity (PWV) that progressively increases across the arterial tree. Structure of the arterial system is normally characterized by progressive increase in arterial wall stiffness from the ascending aorta to the peripheral muscular-type arteries (so-called stiffness gradient) [4, 19, 21]. Impedance mismatches at the transition between these segments generate pulse wave reflections. These reflected waves travel from the periphery back to the ascending aorta (backward-traveling reflected wave), opposing pulsatile energy transmission downstream to microcirculation. In young subjects with elastic central arteries, this process is coupled with slower pulse wave propagation and the overlap of the incident and reflected waves in the ascending aorta occurs in late systole or early diastole. This phenomenon results in rise of diastolic aortic pressure, favoring coronary perfusion during diastole. Arteriosclerotic process, however, affects preferentially the wall of the aorta and large central arteries, reversing the normal stiffness gradient between central and peripheral arterial segments [22]. In conditions of accelerated arterial stiffness, such as ESRD, there is premature arrival of reflected waves back to the ascending aorta, during systole rather than diastole [4, 19, 21]. This results in augmentation of central aortic systolic pressure, thereby increasing cardiac after load and promoting adverse myocardial remodeling toward fibrosis and hypertrophy. In addition, greater pulsatile energy transmission from macro- to microcirculation promotes microvascular damage in peripheral organs and tissues (**Figure 1**) [4, 19, 21].

ARTERIAL STIFFNESS

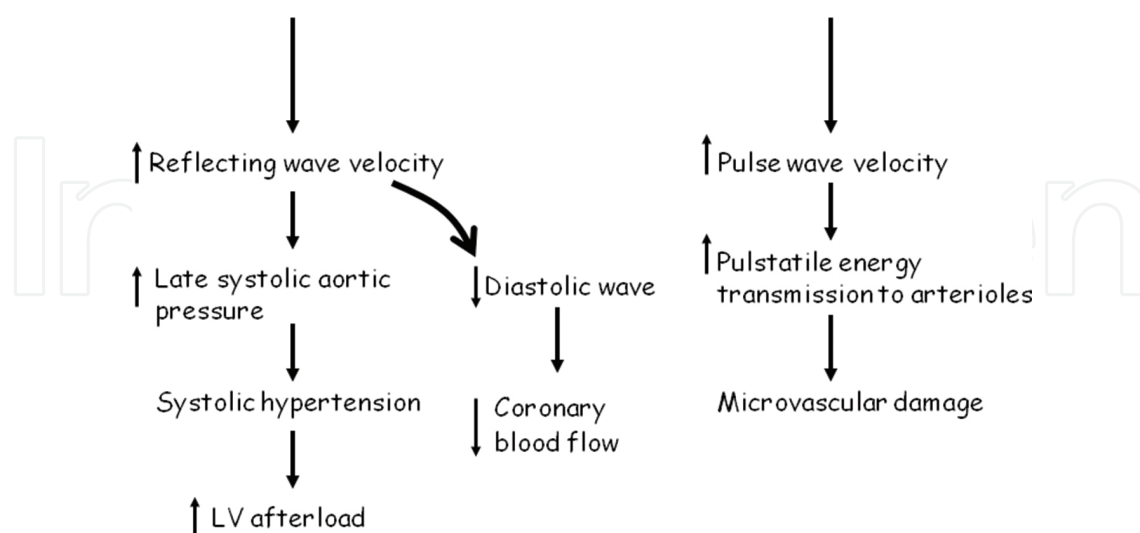


Figure 1. Pathophysiological role of increased arterial stiffness in ESRD.

The close pathophysiological association of arterial stiffness with promotion of end-organ damage is in line with a strong epidemiological association of increased arterial stiffness with worse cardiovascular outcomes. Among dialysis patients, prospective observational studies have for long-connected higher aortic PWV with increased risk of all-cause and cardiovascular mortality independently from other cardiovascular risk factors [7]. In the first study conducted in the late 1990s in a cohort of 241 hemodialysis patients prospectively followed for a mean period of 6 years, Blacher et al. [6] showed that the fully adjusted odds ratio (OR) for aortic PWV > 12.0 versus PWV < 9.4 m/s was 5.4 [95% confidence intervals (CIs): 2.4–11.9] for all-cause mortality and 5.9 (95% CI: 2.3–15.5) for cardiovascular mortality [6]. The strong prognostic association between aortic PWV and cardiovascular outcomes was confirmed in several subsequent cohorts of hemodialysis patients [15, 23]. Similarly to patients receiving hemodialysis, more recent observational studies have demonstrated the strong and independent prognostic significance of arterial stiffness in the whole spectrum of CKD, showing that aortic PWV is an independent predictor of mortality in patients receiving peritoneal dialysis [24] in renal transplant recipients [25] and in patients with CKD not yet on dialysis [26]. Most importantly, regression of arterial stiffness in response to BP-lowering was shown to be associated with improvement in survival [9], providing evidence that arterial stiffness is not simply a risk predictor, but a true cardiovascular risk factor in the dialysis population.

3. Studies comparing the effect of hemodiafiltration versus hemodialysis on arterial stiffness

Uremic toxin accumulation, particularly retention of protein-bound solutes and middle-weight molecules as a result of their inadequate clearance through conservative dialytic

modalities, is proposed to play a prominent role in promoting vascular atherosclerosis and pathogenesis of cardiovascular disease among dialysis patients. In support of this notion, background and clinical studies have shown that accumulation of *p*-cresol and indoxyl sulfate, two protein-bound uremic toxins, acts as a triggering factor for the expression of pro-inflammatory cytokines and adhesion molecules, induces shedding of endothelial microparticles, and disrupts the nitric oxide signaling pathway [27–29]. Importantly, in recent prospective observational studies, high concentrations of both *p*-cresol and indoxyl sulfate in hemodialysis patients have been associated with increased risk of cardiovascular morbidity and mortality independently from other traditional cardiovascular risk factors [30–32].

Hemodiafiltration is a dialytic modality that uses a combination of convective transport and diffusion to enhance the removal of middle-to-high molecular weight solutes in comparison with standard hemodialysis [33, 34]. In some clinical studies, enhanced middle-molecule clearance achieved through convective dialytic modalities was shown to be associated with improvement in phosphate control, better preservation of intradialytic hemodynamic stability, as well as, with a number of beneficial actions on vasculature, such as reduction in circulating markers of vascular inflammation and oxidative stress and improvement in flow-mediated endothelium-dependent vasodilatation [11–14, 35]. These beneficial effects of hemodiafiltration on the vasculature have generated the hypothesis that switching ESRD patients from conventional hemodialysis to high-efficiency hemodiafiltration may be a therapeutic maneuver with potential advantages in causing regression of arterial stiffness. This hypothesis was tested in a number of clinical studies summarized in **Table 1** and discussed in detail below.

Author	Year	n	Patient characteristics	Design	Intervention	Follow-up (months)	Change in arterial stiffness over time	Overall effect
Beerenhout et al. [35]	2005	40	ESRD patients treated with thrice-weekly low-flux HD	RCT	Pre-dilution on-line HDF versus low-flux HD	12	Aortic PWV increased similarly over time in both dialytic modalities (HDF: 12 ± 5 versus 13 ± 5 m/s; HD: 12 ± 3 versus 13 ± 5 m/s)	Neutral
Bellien et al. [37]	2014	42	ESRD patients treated with thrice-weekly high-flux HD	RCT	Post-dilution on-line HDF versus high-flux HD	4	Carotid artery distensibility was increased in the on-line HDF group, but not in the HD group (between group difference: $-6.7 \text{ kPa}^{-1} \times 10^{-3}$, 95% CI: -9.9 to $-3.5 \text{ kPa}^{-1} \times 10^{-3}$, $P = 0.048$)	Better

Author	Year	n	Patient characteristics	Design	Intervention	Follow-up (months)	Change in arterial stiffness over time	Overall effect
Mostovaya et al. [39]	2014	189	ESRD patients participating in the CONTRAST trial	RCT	Post-dilution on-line HDF versus low-flux HD	36	Aortic PWV remained unchanged over time with both dialytic modalities (annual rate of PWV change: HDF group: -0.01 , 95% CI: -0.41 to 0.40 m/s/year; HD group: -0.04 , 95% CI: -0.31 to 0.23 m/s/year; p value HDF versus HD: 0.89)	Neutral
Charitaki et al. [38]	2014	289	ESRD patients on maintenance HD	Observational	69 patients on low-flux HD versus 78 patients switched from low-flux HD to HDF versus 142 patients on HDF	6	Aortic PWV increased over time in the low-flux HD group (9.5 ± 1.9 versus 10.2 ± 2.2 m/s, $p < 0.01$) as well as in the HD to HDF group (9.4 ± 1.9 versus 10.1 ± 2.2 m/s, $p < 0.01$), but remained constant in the HDF group (9.9 ± 2.1 versus 10.1 ± 2.2 m/s)	Better
Georgianos et al. [36]	2014	48	ESRD patients on maintenance HD	Observational	HDF versus low-flux HD	Single dialysis session	Aortic PWV remained unchanged from pre- to postdialysis either with HDF or with low-flux HD (HDF: 9.3 ± 0.5 versus 9.4 ± 0.5 m/s, $p = 0.686$ low-flux HD: 9.1 ± 0.4 versus 8.9 ± 0.4 m/s, $p = 0.396$)	Neutral

HD, hemodialysis; RCT, randomized controlled trial.

Table 1. Prospective studies comparing the effect of hemodiafiltration versus standard hemodialysis on arterial stiffness.

3.1. Acute effects of hemodiafiltration on arterial stiffness

In a nested case-control design, Georgianos et al. [36] compared the acute changes in aortic PWV from pre- to postdialysis in 24 ESRD patients receiving hemodiafiltration and in 24 age-

and sex-matched controls receiving low-flux hemodialysis. Aortic PWV was not significantly changed from pre- to postdialysis during both the first and second weekly dialysis sessions. These modest acute changes in aortic PWV from pre- to postdialysis were no different between the hemodiafiltration and low-flux hemodialysis groups in both dialysis sessions studied [36]. With regards to wave reflections, augmentation index and related parameters were significantly reduced from pre- to postdialysis in both dialysis sessions and patient groups. Similarly to aortic PWV, intradialytic reduction in wave reflection indices was no different between patients treated with hemodiafiltration and standard low-flux hemodialysis [36]. These findings suggest an acute intradialytic improvement in wave reflections from the periphery but not in aortic stiffness, an effect that was independent of the mode of dialysis. However, these comparable acute alterations in large-artery cushioning function do not necessarily prespecify the pattern of long-term progression of the arterial stiffness in patients treated with different dialytic modalities.

3.2. Long-term effects of hemodiafiltration on arterial stiffness

Studies evaluating the long-term effects of hemodiafiltration relative to hemodialysis on arterial structure and function provided contradictory results. Beerenhout et al. [35] randomized 40 ESRD patients treated with conventional low-flux hemodialysis to switch to high-efficiency pre-dilution on-line hemodiafiltration or to continue on the same dialytic modality. After 12 months of follow-up, aortic PWV increased similarly in both low-flux hemodialysis (12 ± 3 versus 13 ± 5 m/s) and on-line hemodiafiltration groups (12 ± 3 versus 13 ± 5 m/s). Notably, change in 48-h ambulatory systolic and diastolic BP and in LV mass index over time were also no difference between the two dialytic modalities [35]. Furthermore, on-line hemodiafiltration was not superior to low-flux hemodialysis in inhibiting the formation of advanced glycation end-products and reducing the circulating levels of asymmetric dimethylarginine (ADMA) and markers of oxidative stress or total anti-oxidant capacity. In a subsequent study, 42 ESRD patients were randomly assigned to switch from high-flux conventional hemodialysis to high-efficiency post-dilution on-line hemodiafiltration or to remain on high-flux hemodialysis for a mean follow-up period of 4 months [37]. Arterial stiffness assessed with the use of the distensibility co-efficient of the common carotid artery was improved in the on-line hemodiafiltration group, but not in the high-flux conventional hemodialysis group (between-group difference: $-6.7 \text{ kPa}^{-1} \times 10^{-3}$, 95% CI: -9.9 to $-3.5 \text{ kPa}^{-1} \times 10^{-3}$, $p = 0.048$) [37]. Improvement in carotid artery distensibility was accompanied by a significant improvement in Kt/V urea, predialysis levels of β 2-microglobulin, circulating levels of ADMA and tumor necrosis factor (TNF)- α , and brachial artery flow-mediated endothelium-dependent vasodilation. In a multiple regression analysis model, hemodiafiltration-induced improvement in conduit artery endothelial dysfunction and stiffness was associated with the changes in Kt/V urea and predialysis levels of β 2-microglobulin, suggesting that enhanced clearance of middle-to-high molecular weight solutes is one factor potentially contributing to the beneficial effect of hemodiafiltration on large-artery stiffness.

A beneficial effect of hemodiafiltration on arterial stiffness is supported by another observational study, in which aortic PWV measurements were performed 6 months apart in three different groups of ESRD patients [38]. The first group consisted of 69 ESRD patients receiving conventional low-flux hemodialysis, the second group consisted of 78 ESRD patients who were switched from low-flux hemodialysis to on-line hemodiafiltration, and the third group included 142 ESRD patients receiving long-term renal replacement therapy with on-line hemodiafiltration. Over the 6-month observational period, a significant increase in aortic PWV was noted in those patients treated with hemodialysis (9.5 ± 1.9 versus 10.2 ± 2.2 m/s, $p < 0.01$) as well as in those switched from hemodialysis to hemodiafiltration (9.4 ± 1.9 versus 10.1 ± 2.2 m/s, $p < 0.01$); in contrast, aortic PWV remained unchanged in the group of hemodiafiltration (9.9 ± 2.1 versus 10.1 ± 2.2 m/s) [38]. The most important finding of this study was that aortic PWV remained constant during follow-up only in those patients receiving long-term treatment with hemodiafiltration, whereas aortic PWV increased in patients who were switched from hemodialysis to hemodiafiltration. This observation could be interpreted in two different ways: either the 6-month-long therapy with hemodiafiltration might be inadequate in order to modify the arterial wall structure and stiffness, or aortic PWV increased in those patients switched to hemodiafiltration due to a carry-on effect of previous long-term therapy with conventional hemodialysis.

The above beneficial impact of hemodiafiltration in causing regression of arterial stiffness was not confirmed in a recent subanalysis of 189 prevalent dialysis patients participating in the CONvective TRANsport STudy (CONTRAST) trial [39]. In this study, ESRD patients receiving conventional low-flux hemodialysis were randomly assigned in a 1:1 ratio for treatment with on-line hemodiafiltration or continuation of low-flux hemodialysis for a mean follow-up period of 36 months. Median aortic PWV at baseline was 9.8 m/s (interquartile range: 7.5–12.0 m/s). Aortic PWV was not significantly changed over time, and the annual rate of PWV change had no difference between the on-line hemodiafiltration and hemodialysis groups (hemodiafiltration group: -0.01 m/s/year, 95% CIs: -0.41 to 0.40 m/s/year; hemodialysis group: -0.04 m/s/year, 95% CI: -0.31 to 0.23 m/s/year; p value for the between-group comparison: 0.89) [39]. The absence of difference between the two dialytic modalities in the rate of PWV change was consistent across subgroups of age, sex, residual renal function, dialysis vintage, diabetes, and history of pre-existing cardiovascular disease. Of note, the annual rate of PWV change had once again no difference between the two dialytic modalities regardless of the convection volume used for on-line hemodiafiltration (convection volume <18.9 L/session: 0.37 m/s/year; 95% CIs: -0.25 to 0.98 m/s/year, $p = 0.23$; convection volume >18.9 L/session: -0.01 m/s/year; 95% CIs: -0.59 to 0.57 , $p = 0.99$) [39].

4. Studies comparing the effect of hemodiafiltration versus hemodialysis on mortality

The above contradictory results of clinical studies that evaluated the comparative effectiveness of hemodiafiltration versus standard hemodialysis in causing regression of arterial stiffness

are in line with the uncertain superiority of hemodiafiltration on mortality across large-scaled randomized controlled trials that included “hard” cardiovascular outcomes as primary endpoints. For example, in the primary analysis of the aforementioned CONTRAST study [40], 714 ESRD patients were randomly assigned to switch from low-flux hemodialysis to on-line hemodiafiltration or continue renal replacement therapy with low-flux hemodialysis. After a mean follow-up period of 3 years, incidence of all-cause mortality [Hazard Ratio (HR): 0.95; 95% CIs: 0.75–1.20] and occurrence of fatal and non-fatal cardiovascular events (HR: 1.07; 95% CIs: 0.83–1.39) were not different between the two dialytic modalities [40]. The subsequent Turkish on-line hemodiafiltration (OL-HDF) study enrolled 782 ESRD patients receiving standard thrice-weekly hemodialysis who were randomly assigned in a 1:1 ratio to post-dilution on-line hemodiafiltration or high-flux conventional hemodialysis [41]. Over a mean follow-up period of 22.7 ± 10.9 months, the occurrence of the composite primary outcome of all-cause mortality and non-fatal cardiovascular event was identical in both study arms (event-free survival of 77.6% in hemodiafiltration versus 74.8% in the high-flux group, $P = 0.28$) [41]. Contrary to the above results, the Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL) study supports the notion that on-line hemodiafiltration is superior over hemodialysis in reducing all-cause and cardiovascular mortality [42]. In this open-label, randomized controlled trial, 906 prevalent hemodialysis patients were randomly assigned either to switch to high-efficiency post-dilution on-line hemodiafiltration or to remain on standard low-flux hemodialysis. Switching from low-flux hemodialysis to on-line hemodiafiltration was associated with a 30% risk reduction for all-cause mortality (HR: 0.70; 95% CI: 0.53–0.92), 33% risk reduction for cardiovascular mortality (HR: 0.67; 95% CIs: 0.44–1.02) and 55% risk reduction for infection-related mortality (HR: 0.45; 95% CIs: 0.21–0.96) [42].

5. Conclusion

In summary, the currently available evidence from observational and randomized clinical studies does not conclusively support a clear superiority of hemodiafiltration versus standard hemodialysis in improving arterial compliance. The contradictory results of clinical studies with respect to PWV, a surrogate cardiovascular risk factor, are in line with the uncertain survival benefit of convective dialytic modalities in large-scaled clinical trials evaluating “hard” cardiovascular outcomes. Additional research efforts are urgently warranted to fully elucidate the comparative effectiveness of hemodiafiltration versus conventional hemodialysis on arterial stiffness attenuation. In the meantime, we believe that dialysis treatment optimization is undoubtedly one useful tool toward cardiovascular risk reduction for patients receiving maintenance hemodialysis.

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