haemodialysis and haemodiafiltration lead to similar changes in vascular stiffness during treatment

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ABSTRACT

Background: Haemodiafiltration (HDF) has been reported to cause less hypotension than haemodialysis (HD). We hypothesized that HDF causes less change in vascular tone, so reducing hypotension.

Methods: Aortic pulse wave velocity (PWVao) was measured in 284 patients, during a single dialysis session using cooled dialysate (117 HD, 177 HDF). Patient groups were matched for age, sex and cardiovascular co-morbidity.

Results: Systolic blood pressure (SBP) declined from 144±26 to 133±26 after 20 minutes, and to 131±26 mmHg post HD, and for HDF from 152±26 to 143±27 after 20 minutes, then to 138±27 mmHg post HDF. Net Ultrafiltration rates to achieve weight loss were similar; HD 0.13±0.06 vs HDF 0.12±0.05 ml/kg/min. PWVao did not change after 20 minutes HD 0.42(-0.7 to 1.3), HDF 0.5 (-0.6 to 1.8) or at the end of the session: HD -0.39 (1.5 to1.2), HDF -0.41(-2.0 to 1.3) m/s. Aortic augmentation index (AiAxo), assessment of vascular tone fell significantly with both HD; 20 min by 6.2 (-2.5 to 14), end 5.6 (-6.7 to 13.9), and HDF 20 min by 4.2 (-2.5 to 10), end 7.8 (-0.8 to 19.3), with no difference between HD and HDF. The ultrafiltration rate correlated with % change in aortic SBP (r=0.28 p=0.004), but not with changes in PWVao or augmentation indices.

Conclusion: Blood pressure declined during both HD and HDF treatments, as did augmentation indices, unrelated to weight loss, suggesting a reduction in vascular stiffness occurs independently of treatment modality. We did not observe an advantage for HDF.

INTRODUCTION

Although dialysis technology has evolved over the last fifty years [1] with more than 2 million patients with chronic kidney disease stage 5 (CKD5d) now treated worldwide, mortality remains high, with cardiovascular disease remaining the leading cause of death [2]. Haemodiafiltration, adding convective clearance to standard diffusional clearance has been recently suggested to improve patient survival [3], and in particular reducing cardiovascular mortality [4]. However the mechanism as to why haemodiafiltration may reduce cardiovascular risk remains to be elucidated. Several studies have reported that haemodiafiltration reduces the incidence of intra-dialytic hypotension compared to conventional haemodialysis [5-8], although not all studies observed an advantage for haemodiafiltration [9.10].

Hypotensive episodes during haemodialysis have been linked to intra-dialytic segmental myocardial contractile dysfunction, so called intra-dialytic “cardiac stunning” [11]. Repetitive episodes of intradialytic cardiac ischaemia could potentially lead to structural changes in the myocardium increasing intra-cardiac fibrosis, leading to diastolic dysfunction and predisposing to arrhythmias. Although predisposing factors including age, underlying ischaemic heart disease, diabetes and higher ultrafiltration rates have been identified, it was also noted that both falls in systemic blood pressure and cardiac stunning could occur shortly after the initiation of haemodialysis before any significant ultrafiltration had occurred [12]. This suggests that other mechanisms than ultrafiltration may be involved in determining haemodynamic instability during dialysis which could

exacerbate the effects of myocardial stunning [13]. For example, hypotension could occur due to a reduction in vascular tone, or failure to increase vascular tone to compensate for ultrafiltration. To investigate whether the greater cardiovascular stability reported with haemodiafiltration could be due to improved vascular tone we hypothesised that changes in arterial stiffness detected by pulse wave velocity would be different for patients treated by haemodiafiltration compared to haemodialysis shortly after initiating treatment before the effects of ultrafiltration occurred.

METHODS

Measurement of arterial stiffness

Arterial stiffness was measured non-invasively in recumbent patients using a validated brachial oscillometric device (Arteriograph™, TensioMed Ltd, Budapest, Hungary) [14] , in a standardized manner in a temperature controlled environment [15,16]. As this device requires a minimum of three sinus beats for analysis, patients with atrial fibrillation and other cardiac arrhythmias were excluded. We measured peripheral (brachial) blood pressure, central (aortic) blood pressure (SBPao), aortic pulse wave velocity (PWVao), aortic and brachial augmentation indices (Aix) and the diastolic reflection area (DRA). All results were adjusted for heart rate of 70 beats/min. The pressure profile in the aorta and brachial arteries has an early systolic pressure wave, followed by a diastolic fall, and then a later systolic wave, which is a reflection wave generated by the stiffness of the artery. Aortic and brachial augmentation indices (AixAo and

AixBo) are the ratios of the late and early systolic pressure waves The DRA is a dimensionless index derived from the area of the diastolic wave reflection and the duration of diastole and provides a measure of coronary artery perfusion during diastole. As blood flow to the heart itself depends upon diastolic pressure, then changes in DRA correspond to changes in myocardial perfusion. All measurements were performed according to the manufacturer's specification by two trained operators. Readings were taken at three time points: just prior to the initiation of dialysis then at 20 minutes into the dialysis session and finally within 5 minutes of conclusion of the HD session. Dialysis session parameters were recorded electronically, including episodes of symptomatic intradialytic hypotension requiring treatment (i.e. volume replacement, cessation of UF).

Dialysis treatment parameters

Patients were dialyzed thrice weekly using high-flux polysulfone haemodialyzers (Elisio-H™, Nipro Europe, Zaventem, Belgium) [17] and Braun Dialog machines (B. Braun Medical Inc., Bethlehem, PA, USA). Low-molecular weight heparin was used for dialysis circuit anticoagulation [18]. Dialysate water quality for all patients met current national bacteriological and chemical standards throughout the study period. All patients dialysed using a dialysate containing 0.5 mmol/l magnesium, 32 mmol/l bicarbonate and 3 mmol/l acetate. During the study period haemodialysis patients had their dialysis machines and the blood lines rinsed and primed with 0.9% saline, whereas the haemodiafiltration group used dialysate. Patients were connected directly to the

primed extracorporeal circuit at the start of dialysis, with no loss of volume and then treated as per centre protocol using a constant ultrafiltration rate designed to achieve target weight, which had been determined by the supervising clinicians based on clinical assessment.

Patients

Patient characteristics were recorded including age, gender, dialysis vintage, the presence of diabetes mellitus and other co-morbidities using the Stoke-Davies score [19]. No patient studied was documented to have autonomic neuropathy. In addition treatment details were recorded including dialysate composition and temperature, blood and dialysate flow rates, ultrafiltration (UF) volume estimated by the dialysis machine.

PVW was introduced into clinical practice as service development, and audited with local approval. Ethical approval was obtained from National Health Service ethics committee 12/LO/0976, LO/092, and registered ISRCTN 12870218/70556765, with appropriate informed consent in keeping with the Helsinki declaration.

Statistical analysis

Descriptive statistics were expressed as the mean ± standard deviation unless specified otherwise and the median with interquartile range (IQR) as appropriate. Continuous and categorical variables were compared using Student's t-test and the chi-square or Mann-Whitney U test, and intra-group

comparisons by ANOVA or Kruskal Wallis analysis with appropriate post-hoc correction, by Bonferroni, Tukey and Dunn's methods respectively. Spearman univariate analysis was used to analyse changes in PVW and ultrafiltration volumes. Analyses were performed using GraphPad Prism (version 4.0, GraphPad, San Diego, USA) and SPSS (SPSS version 21, University of Chicago, USA). Statistical significance was defined by $p<0.05$.

RESULTS

294 prevalent dialysis patients established on thrice weekly outpatient treatments, who had been established on dialysis for more than 3 months, were studied during a single haemodialysis or haemodiafiltration session (table 1). 69.7% patients were prescribed anti-hypertensive medications, and the median number of classes of antihypertensive agents prescribed was 1 (0-1); More haemodialysis patients were prescribed β blockers ($X2=7.4$, $p=0.007$) and either angiotensin converting enzyme inhibitors or angiotensin receptor blockers ($X2=4.2$, $p=0.04$) compared to those having haemodiafiltration. Centre policy was to advise patients not to take antihypertensive medications prior to dialysis. Pre-dialysis systolic blood pressure was higher in the haemodiafiltration group (table 2). Diastolic blood pressure was lower at 20 minutes and at the end of the dialysis session in the haemodiafiltration group, as was final heart rate compared to the haemodialysis group. During treatment there was a trend for both systolic and diastolic blood pressures to fall during both haemodialysis and haemodiafiltration treatments.

Aortic Pulse wave velocity and derived augmentation indices

Aortic pulse wave velocity did not change significantly during dialysis, or between haemodialysis and haemodiafiltration treatments (table 2). There was no difference in the absolute or percentage change in PWVao during treatments (table 3).

There was similarly no difference in brachial augmentation index (AixBo) between haemodialysis and haemodiafiltration treatments, as well as no differences in the absolute or percentage change in AixBo between the two dialysis modes (tables 2,3). However, for both haemodialysis and haemodiafiltration AixBo decreased significantly at 20 minutes ($p<0.05$), and at the end of the dialysis session ($p<0.01$).

Aortic augmentation index (AixAo) was greater at the start of haemodiafiltration and remained persistently higher compared to patients on haemodialysis (table 2). For both haemodialysis and haemodiafiltration AixAo was significantly lower after 20 minutes, and also at end of the dialysis session, $p<0.001$. The absolute change or percentage change in AixAo did not differ between dialysis modalities (table 3).

Aortic systolic blood pressure (SBPao) was not statistically different between the two cohorts, or during the dialysis session (table 2). The change and percentage change in SBPao again was not different between the two dialysis modalities (table 3). During both treatments SBPao was significantly lower at 20 minutes and at the end of the dialysis session, $p<0.05$ and <0.001 , respectively.

Cardiac DRA was similar at the start of dialysis for both groups, and there were no differences in DRA between the different modalities during treatment (tables 2,3). DRA increased significantly at the end of haemodialysis ($p<0.01$), and at 20 minutes ($p<0.05$), and the end of haemodiafiltration ($p<0.01$).

Ultrafiltration

To determine the effect of ultrafiltration losses, univariate Spearman correlation was used to determine whether there were any significant associations between changes in aortic pulse wave velocity, and the derived parameters both at 20 min and at the end of the haemodialysis session and also the absolute ultrafiltration rate, the ultrafiltration rate adjusted for weight, and the absolute ultrafiltration volume removed at 20 minutes. The only significant association was between the percentage change in SBPao at the end of haemodialysis and ultrafiltration rate ($r=0.28$ $p=0.004$). There was no association between ultrafiltration rates or ultrafiltration losses and change in PWVao or derived variables (data not shown).

Hypotension

Symptomatic hypotension requiring nursing intervention to reduce or stop the ultrafiltration rate, or administer intravenous fluids occurred during 3 haemodialysis sessions and 12 haemodiafiltration sessions ($p>0.05$).

DISCUSSION

Intra-dialytic hypotension remains the commonest complication of routine outpatient haemodialysis [20], despite the technological improvements in dialyzers and dialysis machines [21]. Pooling the individual patient data from recent multi-centre prospective trials has reported improved cardiovascular stability with haemofiltration and haemodiafiltration compared to standard haemodialysis [5,8], supporting the reports from previous observational studies [6,7]. However why haemodiafiltration may offer an advantage remains to be explained. Theories have included increased clearance of putative cardio-depressant factors [5], and enhanced thermal losses as cooling dialysate and increased thermal losses provide greater cardiovascular stability [22], and greater thermal cooling is achieved with haemofiltration and haemodiafiltration than haemodialysis [23]. Indeed haemodialysis treatments using cooled dialysate have been reported to provide greater cardiovascular stability compared to haemofiltration with warm replacement fluids [23].. This is supported by other studies which have tried to match conditions observing no differences in blood pressure during haemodialysis and haemodiafiltration treatments [9,10].

As falls in blood pressure during dialysis may be associated with reversible myocardial ischaemia, so called cardiac stunning [11], and that this has been reported to occur within the first 20 minutes of a dialysis session [12], when there has not been significant fluid removal we hypothesized that this could be due to a change in vascular tone, and that there may be differences between haemodialysis and haemodiafiltration.

To investigate this possibility we measured aortic pulse wave velocity and the changes in augmentation indices and cardiac diastolic reflection area as a marker of global cardiac blood flow. As expected blood pressure declined during the haemodialysis session, and there was a correlation between the fall in estimated aortic systolic blood pressure and the ultrafiltration rate. A similar pattern in SBPao was observed with haemodiafiltration. We found no difference in the magnitude of the absolute or relative change in brachial blood pressure or SBPao between the different modalities. However unlike many previous studies we compared haemodialysis with cooled dialysate and haemodiafiltration, both with a mean temperature of 35^{o}C. This cooling effect may have accounted for a failure to demonstrate any statistically significant difference in the incidence of intra-dialytic hypotension. We did not measure body temperature or directly assess thermal energy losses, but from previously published studies we would have expected greater thermal energy losses with haemodiafiltration [22,23].Although there were no changes in measured PWVao, both brachial and aortic augmentation indices deceased during haemodialysis and haemodiafiltration treatments, supporting a previous study which noted reduced carotid-femoral augmentation post-dialysis [24].The pressure profile in the aorta and major conduit arteries comprises an early systolic pressure wave, followed by a diastolic fall, and then a late systolic wave, which is caused by a reflection wave due to the stiffness of the artery. The aortic and brachial augmentation indices are ratios of the late systolic pressure wave compared to the early systolic pressure wave, and a fall in augmentation index is associated with a

reduction in vascular tone. Although these changes were greater at the end of the dialysis session, there were significant falls by 20 minutes. As such cooling of the dialysate in the haemodialysis cohort did not prevent these changes, nor did any additional thermal losses associated with post-dilutional haemodiafiltration exchanging an average additional 16 litres of warm plasma water for cooled infusate. Previous reports have suggested that vasodilatation during dialysis was associated with the removal of vasoconstrictors [25], or generation of vasodilatory prostanoids from lipid peroxidation [26]. Haemodiafiltration could potentially clear greater amounts of vasoactive mediators, including endothelin, nitric oxide or asymmetric dimethyl arginine [27]. As the pattern of change in augmentation indices was similar for both haemodialysis and haemodiafiltration this would argue against the clearance of a middle molecular weight peptide vasoconstrictor. Although dialysate composition was similar patients treated by haemodiafiltration would have received around an additional 48 mmol of acetate through the infusate. However this amount of acetate is well within the metabolic capacity of the liver, and recent studies have not shown that acetate free biofiltration has any discernable beneficial cardiac effects compared to standard haemodiafiltration with dialysate containing a low acetate concentration [28].

Coronary artery perfusion predominantly occurs during diastole, and depends upon diastolic blood pressure. We derived theDRA , which is determined from the area of the diastolic wave reflection and the duration of diastole and provides a measure predominantly of left coronary artery perfusion during diastole. Again there were no absolute or relative differences in the DRA

between haemodialysis and haemodiafiltration. However during both treatments there was a trend for the DRA to increase, with significant increases reported with both modalities at the end of the dialysis session. So although the fall in AixAo is associated with a lower diastolic blood pressure, and would suggest a potential mechanism for myocardial perfusion mismatch [11,12], the increase in DRA would be somewhat protective and may help to explain why if vasodilatation of conduit arteries develops during dialysis, cardiac stunning is more likely to occur in patients with ischaemic heart disease [29].

Previous studies have measured PVW pre and post dialysis [24,25,30]. However we now report an early and significant reduction in aortic and brachial Aix that occurred at a time point in the dialysis session when only a minimal amount of ultrafiltration had occurred. We did not find any statistical association between dialysis parameters, including ultrafiltration rate and volume and these changes in Aix. This is in keeping with previous studies comparing changes in pre and post PVW and ultrafiltration [25,2630]. This would suggest that fluid removal during dialysis alone cannot simply account for the changes observed. As these changes are common to both haemodialysis and haemodiafiltration this would suggest a common link to the dialysis process, for example an initial systemic inflammatory response with vasodilatation and reduction in Aix following exposure to the extracorporeal circuit [31]. Development of dialyzer membranes [32], may potentially reduce this inflammatory reaction [33], and further studies are required to elucidate the pathophysiology of this early response to dialysis with arterial conduit vessel vasodilatation. As dialysis then progresses the

effects of volume removal and uraemic toxin clearance with secondary modulation of endothelial function may result in further reductions in Aix and central SBPao.

As with any study there are a number of potential confounders. This was a cross sectional study, and although ideally patients would have acted as their own controls in prospective cross over design, we did study almost 300 patients, matching groups for cardiovascular history, but acknowledge that there were some differences between the groups. As with previous studies measuring PWV in dialysis and hypertensive patients, PWV was adjusted for heart rate to exclude effects of different antihypertensive medications [24,30]. Our centre policy was to omit anti-hypertensives prior to dialysis session, and as such this should have reduced the effects of antihypertensive medications. Although pre-dialysis systolic blood pressure and AiAxo were greater in the haemodiafiltration groups, changes during treatment mirrored those during haemodialysis treatments. There have been debates as to whether convective therapies lead to a greater sodium balance [34,35,36]. More recent modelling has also suggested that convective therapies may lead to a greater sodium balance [37]. However bioimpedance measurements have not been able to demonstrate differences in volume with haemodiafiltration compared to haemodialysis [38]. In this study we were unable to measure the gradient between serum and dialysate sodium. However previous studies have not been able to demonstrate that different gradients lead to different responses in terms of the changes in extracellular or intracellular volumes [39,40]. Similarly although the haemodiafiltration group dialysed using a

higher dialysate calcium, previous studies have not shown an increase in PVW over six months in patients using higher compared to lower dialysate calcium concentrations, and similarly no differences between patients treated by haemodialysis compared to haemodiafiltration [15,16].

There are a number of different types of PWV devices, which use planometry or oscillometry to measure PWV [41]. Some devices measure PWVao, whereas others measure a composite of conduit arteries (carotid and femoral) in addition to the aorta. Although absolute values of PWV may differ between studies, due to some measuring PWVao and others PWVcf, studies comparing devices using planometric and oscillometric techniques have reported a close association between both methods [41]. In addition, as the same pattern of changes has been reported with dialysis using different devices [24,30,41], it is most likely that our results would be reproduced by other PWV devices. .

Although studies using warmed dialysate have reported greater cardiovascular stability with haemodiafiltration compared to high flux haemodialysis, when using cooled dialysates for both haemodialysis and haemodiafiltration we were not able to demonstrate any advantage for haemodiafiltration treatments in terms of changes in PVW and derived variables.

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TABLE 1. Patient demographics and details of dialysis treatments. Data presented as absolute number or percentage, mean ± standard deviation or median with interquartile range (IQR). Percentage of patients prescribed drugs, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs). *p<0.05 , **p<0.01, ***p<0.001 vs haemodialysis.

	haemodialysis	haemodiafiltration
numbers	117	177
Age years	66.1±15.1	63.2±15.2
Weight kg	72.5±18.1	73.1±18.3
Body mass index kg/m^2	25.9±5.5	25.9±5.4
male	45 (38.5%)	76 (42.9%)
female	72 (61.5%)	101 (57.1%)
diabetic	58 (49.6%)	76 (42.9%)
History hypertension	88 (75.2%)	117 (66.1%)
History ischaemic heart disease	37 (31.6%)	57 (32.2%)
History cerebrovascular disease	13 (11.1%)	24 (13.6%)
History peripheral vascular disease	19 (16.2%)	31 (17.5%)
B blockers	33.8%	19.4%**
Calcium channel blockers	20.3%	22.6%
ACEI/ARBs	33.1%	21.9%*
Fistula access	77 (65.8%)	140 (79.0%)
Session time hours	4.0 (4.0-4.0)	4.0 (4.0-4.0)
Dialyzer surface area m^2	1.7 (1.7-2.1)	1.7 (1.7-2.1)
Blood flow ml/min	350 (300-360)	320 (300-350)***
Dialysate flow ml/min	500 (500-500)	500 (500-500)
Dialysate sodium mmol/l	137.3±1.0	137±1.3
Dialysate potassium mmol/l	2.0 (2-2)	2.0 (2-2)
Dialysate calcium mmol/l	1.25 (1.25-1.35)	1.35 (1.35-1.35)***
Dialysate temperature ^{o}C	35.3±0.3	35.3±0.3
Substitution volume L/session	0	16.2 ±4.0
Total ultrafiltration L	2.1±1.0	1.9±0.9
Ultrafiltration rate ml/min	9.2±3.9	8.1±3.5
Ultrafiltration rate ml/min/kg	0.13±0.06	0.12±0.05

TABLE 2. Brachial artery blood pressure and aortic pulse wave velocity (PWVa) measured during dialysis sessions, heart rate (HR) and PVWao derived central (aortic) blood pressure, (SBPao), aortic and brachial augmentation indices (AixAo, AixBo) and the diastolic reflection area (DRA). All results were obtained pre-dialysis, after 20 minutes and then after dialysis had been completed and PWV and derived variables were adjusted for heart rate of 70 beats/min. Brachial and systolic blood pressure (SBP, DBP) mmHg, PVWao m/s, and . AixAo, AixBo as %. Data presented as absolute number or percentage, mean ± standard deviation or median with interquartile range (IQR). *p<0.05 , ***p<0.001 vs haemodialysis after adjustment for multiple testing.

	HD-0	HD 20	HD end	HDF 0	HDF20	HDF end
SBP	144±26	133±26	131±26	152±26	143±27	138±27
DBP	78±14	72±14	71±16	82±14*	81±16*	81±16*
HR	72.8±14.5	70.5±14.5	71.2±12.9	75.4±14.5	73.7±13.9	78.1±15.6*
PWVao	9.5±2.1	10±2.0	9.7±2.2	10±2.0	10.0+2.0	10.1±2.3
AixBo	3.8 (-15.8 to 26.6)	0.9(-30 to 24.5)	-4.2(-29.1 to 24.0)	1.6(-20 to 28.5	-4.4(28.2 to 19.7	-11.1(41.4 to 17.7)
AixAo	33.7(14.3-48.6)	30.8 (14-46.9)	28.6(14.1-45.8)	38.4(27.5-52.0)***	35.4(25.1 - 47.6)***	32.0(16.7-46.6)***
SBPao	150.8±30.3	140.6±32.1	133.2±35.5	154.4±29.7	145.6±32	138.8±33.4
DRA	36.7(30.5-48.1)	41.0 (31.0-54.1)	44.5(34.9-55.2)	35.9(26.7-45.6)	41.9(33.4-53.8)	44.5(34.9-59.3)

Table 3. Absolute and percentage change in aortic pulse wave velocity (PWVao) measured during dialysis sessions, heart rate (HR) and PVWao derived central (aortic) blood pressure, (SBPao), aortic and brachial augmentation indices (AixAo, AixBo) and the diastolic reflection area (DRA). All results were obtained pre-dialysis, after 20 minutes and then after dialysis had been completed and PWV and derived variables were adjusted for heart rate of 70 beats/min. Change defined as difference from pre-dialysis value (positive change equates to a fall, and negative change a decrease). Brachial and systolic blood pressure (SBP, DBP) mmHg, PVWao m/s, and . AixAo, AixBo as %. Data presented as absolute number or percentage, mean ± standard deviation or median with interquartile range (IQR).

	HD pre to 20min	HD pre to post	HDF pre to 20 min	HDF pre to post
Δ PVWao	0.42 (-0.7 to 1.3)	-0.39 (-1.5 to 1.2)	0.5 (-0.6 to 1.8)	-0.41 (-2.0 to 1.3)
% Δ PVWao	3.7 (-6.3 to 15.4)	-4.3 (-18.4 to 13.4)	5.7 (-5.8 to 15.8)	-4.1 (-20.8 to 11.8)
Δ AixBo	6.1 (-5.6 to 17.5)	5.1 (-13.1 to 23)	5.5 (-8.3 to 22.9)	19.9 (-9.3 to 42.)
%Δ AixBo	13.5 (-58.1 to 71.9)	21.4 (-38.8 to 90.6)	21.4 (-38.8 to 90.6)	49.8 (-59.1 to 91.2)
Δ AiAxo	6.2 (-2.5 to 14)	5.6 (-6.7 to 13.9)	4.2 (-2.5 to 10)	7.8 (-0.8 to 19.3)
%Δ AiAxo	19.6 (-10.4 to 43.6)	11.0 (-7.2 to 25.3)	17.3 (-17.3 to 53)	20.3 (-1.9 to 50.9)
Δ SBPao	9.6 (-2.9 to 24.1)	6.0 (-2.7 to 19.7)	6.1 (-6.3 to 18.5)	4.1 (-3.9 to 13.1)
% Δ SBPao	7.4 (-2.1 to 15.8)	6.1 (-2.7 to 19.7)	17.4 (-8.2 to 35.4)	10.9 (-5.3 to 21.9)
Δ DRA	-3.2 (-11.3 to 5.8)	-7.4 (-21.3 to 3.4)	-5.8 (-12.8 to 2.4)	-11.6 (-23.4 to 2.1)
%Δ DRA	-8.1 (-34.6 to 14.9)	-25.6 (-54.6 to 8.9)	-14.5 (-38.7 to 5.6)	-35.4 (-66.8 to 4.6)