Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease

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ABSTRACT

Background and objectives: Sympathetic activation is a hallmark of ESRD and adversely affects cardiovascular prognosis. Efferent sympathetic outflow and afferent neural signalling from the failing native kidneys are key mediators and can be targeted by renal denervation (RDN). Whether this is feasible and effective in ESRD is not known.

Design, setting, participants and measurements: In an initial safety and proof-of-concept study we attempted to perform RDN in 12 patients with ESRD and uncontrolled blood pressure (BP). Standardized BP measurements were obtained in all patients on dialysis free days at baseline and follow up. Measures of renal noradrenaline spillover and muscle sympathetic nerve activity were available from 5 patients at baseline and from 2 patients at 12month follow up and beyond.

Results: Average office BP was 170.8±16.9/89.2±12.1mmHg despite the use of 3.8±1.4 antihypertensive drugs. All 5 patients in whom muscle sympathetic nerve activity and noradrenaline spillover was assessed at baseline displayed substantially elevated levels. Three out of 12 patients could not undergo RDN due to atrophic renal arteries. Compared to baseline, office systolic BP was significantly reduced at 3, 6, and 12 months after RDN (from 166±16.0 to 148±11, 150±14, and138±17mmHg, respectively), whereas no change was evident in the 3 non-treated patients. Sympathetic nerve activity was substantially reduced in 2 patients who underwent repeat assessment.

Conclusions: RDN is feasible in patients with ESRD and associated with a sustained reduction in systolic office BP. Atrophic renal arteries may pose a problem for application of this technology in some patients with ESRD.

INTRODUCTION

The renal sympathetic nerves are major contributors to the complex pathophysiology of hypertension, both experimentally and in humans[1]. Renal sympathetic nerve activity is elevated in patients with various forms of hypertension as demonstrated by application of radiotracer dilution methodology to measure overflow of noradrenaline (NA) from the kidneys [2-4]. Augmentation of renin release[5], tubular sodium (Na^+) reabsorption[6], and renal vascular resistance[7, 8] are direct consequences of efferent renal sympathetic nerve stimulation and the major components of neural regulation of renal function. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in blood pressure control such as the heart and peripheral blood vessels, mainly by modulating posterior hypothalamic activity[9]. Abrogation of renal sensory afferent nerves has been demonstrated in various experimental models to have salutary effects, not only on blood pressure, but also on organ specific damage caused by chronic sympathetic over-activity, as reviewed previously[10, 11].

Sympathetic activation is a hallmark of end-stage renal disease and adversely affects cardiovascular prognosis[12]. Hypertension is present in the vast majority of these patients[13] and plays a key role in the progressive deterioration of renal function and in the exceedingly high rate of cardiovascular events, which represent the primary cause of morbidity and mortality in this patient group[14-16]. While successful renal transplantation can restore kidney function, sympathetic over-activity typically remains unaltered, most likely due to continued afferent signalling arising from the failing native kidneys[17, 18]. Indeed, compelling evidence from experimental models in conjunction with the demonstration of normalised central sympathetic outflow after bilateral nephrectomy in patients with end stage renal disease[18]

clearly indicate that afferent signalling via renal sensory nerves is a powerful modulator of sympathetic drive[19, 20].

The recent introduction of a catheter-based radiofrequency (RF) ablation approach to directly target both efferent and afferent renal nerves appears an obvious useful therapeutic approach in this context. Indeed, recent clinical trials in patients with resistant hypertension and normal renal function demonstrated the safety and efficacy of renal sympathetic denervation[21, 22]. Furthermore, there is accumulating evidence for additional beneficial effects of renal denervation on central sympathetic nerve activity[23] and insulin sensitivity [24, 25], both of which are of particular relevance in patients with end-stage renal disease.

Against this background we initiated a prospective pilot study to assess the feasibility and efficacy of catheter-based renal nerve ablation in patients with end-stage renal disease.

METHODS

The renal denervation studies in patients with ESRD were approved by the local Ethics committees at participating centres in accordance with the Declaration of Helsinki.

Patients were enrolled and treated in centres that already had experience with renal denervation from the previous Symplicity HTN-1 trial[21] in Melbourne, Minneapolis, Erlangen and Homburg, and continuously followed at 3, 6, and 12 months and then on a yearly basis. Systolic, diastolic and mean arterial blood pressure, as well as routine serum biochemistry were measured before and after treatment. All patients gave written informed consent.

Eligible patients were ≥18 years and had uncontrolled office blood pressure of >140/90 mmHg, despite being treated with ≥3 antihypertensive drugs with no changes in medication for a minimum of 4 weeks prior to enrolment. Patients were included if they had end-stage renal disease with concurrent haemodialysis treatment for at least 6 months prior to the study. All patients had a complete history and physical examination, assessment of vital signs, and review of medication. Patients were interviewed whether they had taken their complete medication at defined doses. Medications were not changed after the procedure unless blood pressure control was achieved or if medically required. Standardized office blood pressure readings were measured in a seated position after at least 5 minutes of rest by trained research personnel. Readings were performed on the arm contralateral to the arteriovenous fistula for dialysis access and were obtained on a mid week dialysis free day. Averages of the triplicate measures were calculated and used for analysis. Ambulatory blood pressure monitoring was performed with Spacelab® monitors on a mid week dialysis free day. Data were collected locally and statistical analysis of the entire data set was performed in Melbourne. Several measures such as noradrenaline spillover and microneurography to assess sympathetic nerve

activity were only available in the initiating centre in Melbourne, explaining the lower number of patients in whom these studies could be carried out.

Renal Denervation Procedure

The renal nerves, carrying both sympathetic efferent and sensory afferent nerve fibers, are circumferentially distributed in the adventitia around the renal artery. A radiofrequency ablation catheter (Symplicity®, Medtronic Ardian Inc, Mountain View, California, USA) was positioned in the lumen of the renal artery to allow ablation of renal nerves susceptible to this type of energy, as previously described in detail[21]. In 5 patients bilateral renal artery and vein sampling and selective renal angiography were performed prior to and 3 months after bilateral renal nerve ablation for assessment of regional NA kinetics.

Microneurography

Multiunit postganglionic sympathetic nerve activity (MSNA) was recorded using microneurography in the peroneal nerve, as described previously[3, 4].

Noradrenaline Kinetics

Assessment of noradrenaline kinetics were only performed at the Baker IDI Heart & Diabetes Institute, as described previously[3].

BNP assays

Brain natriuretic peptide was measured in plasma using the Abbott AxSYM MEIA Automated immunoassay (Abbott, Abbott Park, Ill) at the Alfred Hospital Pathology Department.

Statistical Analysis

Changes in blood pressure were analyzed from baseline to 3, 6, and 12 months by repeated measures analysis of variance with pair-wise comparison of significant values. A 2-tailed value of $P<0.05$ was regarded as statistically significant.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology[29].

RESULTS

Patient characteristics

A total of 12 patients with ESRD and uncontrolled hypertension were enrolled in this study. Confirmed (renal biopsy) or presumed (medical history and concomitant/underlying disease) causes of ESRD were hypertensive nephrosclerosis (n=4), glomerulopathies (n=5; specifically focal segmental glomerulosclerosis (n=1), fibrillary glomerulnephritis (n=1), membranous glomerulopathy (n=3)), IgA nephropathy (n=1), nephrolithiasis (n=1) and bilateral atrophic kidneys of unknown origin (n=1). Average duration of hemodialysis was 3.6±2.6 years. Pre-procedural renal artery Doppler ultrasound or alternative imaging did not reveal evidence for renal artery stenosis in any of the patients. Average office baseline BP was 170.8±16.9/89.2±12.1mmHg with a corresponding 24 hour ABPM of 164.8± 10.1/99.12±9.2mmHg (obtained only in n=10) (Table 1), despite the use of 3.8±1.4 antihypertensive drugs. None of the patients had signs or symptoms of hypervolemia, as assessed by physical examination including pulmonary auscultation, assessment of jugular vein distension and absence of peripheral pitting oedema. Their hemodialysis regimens (3 weekly sessions of 4-5 hours each) and dry weight were stable for at least the previous 3 months and unchanged during follow up to ascertain unaltered volume status. Application of radiotracer dilution methodology to measure renal and whole body NA spillover and microneurography to assess muscle sympathetic nerve activity could be obtained in 5 patients at baseline and revealed marked sympathetic activation in all 5 patients (Table 2).

Renal nerve ablation procedure

Prior to the introduction of the RF treatment catheter renal angiograms were performed via femoral access to confirm anatomic eligibility. One patient had dual renal arteries, which was a predefined exclusion criterion for RF treatment at the time. Consecutive patients 2 and 4

had bilateral renal artery diameters of <4mm, which was deemed too small to appropriately position the treatment catheter for adequate energy delivery and was predefined as an exclusion criterion in this particular study. The remaining 9 patients had suitable renal anatomy to allow for the treatment catheter to be introduced into each renal artery using an 8Fr guide catheter. On average, treated patients received a total of 10.2±3.0 ablation treatments of 2 minutes each which were delivered using a predetermined treatment protocol and algorithm.

Repeat assessment of renal NA spillover ~15 minutes after bilateral RDN in two treated patients who underwent sympathetic nerve activity assessment revealed an acute reduction of 55% and 34% (Figure 3b and 4), respectively.

Safety

The treatment was delivered without procedural complication in 8 of 9 patients. One treated patient and one non-treated patient developed a femoral pseudo-aneurysm both of which were treated conservatively without subsequent complications.

Follow up

Treated patients were scheduled for review at 3, 6, and 12 months after renal denervation, followed by 12 monthly review if available. Office systolic BP readings revealed a significant and sustained BP reduction over time, as depicted in Figure 1a/b. Office diastolic BP did not change significantly (Figure 1a). Office BP in the three untreated patients remained unchanged at 3month follow up (176±7/90±4 vs 172±6/89±3mmHg) Analysis of the limited number of ambulatory BP measurements obtained in 5 patients at 3 months and 5 patients at 6 months follow up revealed a significant reduction in systolic BP at 3 month, whereas diastolic BP did not change significantly at any time point (Figure 2a). Of note, 2 patients

refused to wear ABPM monitors at 6 months follow up, one patient due to discomfort during the previous ABPM monitoring period. However, if individual ambulatory BP recordings are analyzed, 6 out of 7 patients had systolic and diastolic BP reductions at the latest follow up compared to baseline. One patient experienced an increase in both systolic and diastolic BP (Figure 2b/c) which together with the small number of ABPM measurements available appeared to be the major driver of the inability to demonstrate a significant reduction in average ABPM.

In treated patients, the average number of antihypertensive drugs was reduced from 4.2±1.9 (n=9) at baseline to 4.0±1.9 (n=9), 3.7±2.3 (n=7), and 2.2±1.0 (n=5) at 3, 6, and 12 months follow up, respectively.

Patient 3 was of particular interest, since he received a kidney transplant 4 months after his bilateral renal denervation procedure. The patient refused ABPM measurements, so only standardized office BP readings were available. One month prior to his kidney transplantation, at the 3 months post-denervation follow up visit, his blood pressure had already improved substantially (Figure 3a), while his renal NA spillover at 3 months follow up demonstrated a reduction by only ~22% (Figure 3b), substantially less than the average reduction of ~47% previously observed in a larger scale renal denervation trial in patients with resistant hypertension and normal kidney function [21]. Whole body NA spillover was reduced by 15% from 761 to 646ng/min (normal range 200-500ng/min). However, the reduction in indices of central sympathetic outflow (MSNA) was much more pronounced, possibly indicating that a radiofrequency ablation related reduction in afferent signaling from the diseased kidneys contributed more to the blood pressure reduction than the interference with efferent renal sympathetic fibers. Indeed, at subsequent follow up visits MSNA was normalized at 12 months post-denervation and was sustained at normal levels at the last visit

for which the patient was available at 33 months post-denervation (Figure 3c). Interestingly, blood pressure control could be maintained throughout with less antihypertensive drugs and despite substantial weight gain post-transplantation (from 81.3 to 89.1kg) and the use of immunosuppressant drugs (corticosteroids, tacrolimus, mycophenolate mofetil) to avoid rejection of the kidney transplant. Of note, these immunosuppressant drugs are often associated with a blood pressure rise and renal vasoconstriction[26]. BNP levels were reduced from 2582 at baseline to 1031ng/L at 3 months follow up, possibly indicating improved volume homeostasis. The patient had minor residual urinary output of ~300mL/day which, according to the patient was unchanged after the renal denervation procedure, however this was not quantified by 24 urinary sampling.

Patient 5 was followed up at 3, 12 and 24 months with valid ABPM obtained at 3 and 24 months follow up, MSNA at 3 months and NA spillover (available only for the left kidney due to right renal vein inaccessibility) at 3 and 12 months follow up. This patient had no residual renal function. Sympathetic nerve activity was reduced at follow up, as assessed by repeat MSNA (Table 3) and renal NA spillover measurements (Figure 4). Whole body NA spillover was reduced by 21 % after 12 months from 638 to 504ng/min. Ambulatory blood pressure changes over time are summarized in Table 3. Interestingly, the reversed dipping pattern evident at baseline was reversed to a normal dipping pattern at 3 months which was sustained at 24 months. BNP was also reduced over time (Table 3).

DISCUSSION

End stage renal disease is associated with excess cardiovascular morbidity and mortality, with ventricular arrhythmias and sudden cardiac death representing the most common cause of death in this patient cohort[14-16]. Current recommended therapeutic efforts to reduce cardiovascular risk in these patients include optimal volume, electrolyte and calcium-phosphate balance, blockade of the renin-angiotensin-aldosterone system, and appropriate management of co-morbidities such as hypertension, dyslipidemia, heart failure[27,28], atherosclerotic vascular disease and others.

The sympathetic nervous system is commonly neglected as a therapeutic target in this context. This is somewhat surprising, given increased NA plasma levels predict both all cause and cardiac death in patients with ESRD.[12] Indeed, surgical removal of both kidneys typically results in normalization of sympathetic activation and improved blood pressure control, thereby supporting the essential role of afferent sensory renal nerves[17, 18].

We have recently demonstrated the safety and effectiveness of a catheter-based radiofrequency ablation approach to target both efferent sympathetic and afferent sensory renal nerves[21, 22]. In a parallel protocol to the first-in-man safety and proof-of concept study in patients with resistant hypertension but normal renal function[21], we initiated a similar pilot study in patients with ESRD. In contrast to the patients with resistant hypertension and normal renal function, we encountered several difficulties in our initial ESRD patients particularly relating to suboptimal anatomy of the renal arteries of these patients, resulting in the inability to treat 3 out of 10 patients. In addition, on 3 occasions in 2 patients the 2 minute ablation treatment periods were prematurely aborted due to rapidly rising temperature levels detected by the catheter tip thermistor, most likely owing to a lack of cooling consequent to

reduced renal blood flow in these patients. Nevertheless, an average of 10.2±3.0 ablation treatments could be completed in the renal arteries of each patient, which appeared to be sufficient to produce a substantial reduction of the sympathetic over-activity present at baseline, as assessed by serial NA spillover measurements and MSNA in selected patients.

Two patients developed a pseudo-aneurysm at the femoral vascular access site, both of which could be managed conservatively by pressure application without any sequelae, but may highlight an elevated susceptibility of ESRD patients for this complication of vascular access. Of note, at the time of this study 8F introducer sheaths were used, which are now commonly replaced with 6F sheaths, possibly reducing the risk of this complication.

It has previously been shown that restoration of renal function through a kidney transplant does not reduce muscle sympathetic nerve activity, as long as the native kidneys are still in situ[17, 18]. Only renal transplantation combined with bilateral nephrectomy can achieve this desirable state of normalized sympathetic nerve activity[17, 18]. Interestingly, one of the treated patients received a renal transplant 4 months after bilateral renal denervation. While the patient's renal function was restored through successful transplantation, the native kidneys remained in situ and MSNA would not be expected to be reduced solely as a consequence of renal transplantation. Although bilateral renal denervation only resulted in a modest reduction of renal NA spillover by 22%, the procedure was associated with a progressive reduction and normalization of central sympathetic outflow at 12 and 33 months follow up. This was accompanied by improved blood pressure on fewer medications over time, despite substantial weight gain and the requirement of immunosuppressant drugs, the use of which is often associated with a blood pressure rise. It could be speculated that the *functional nephrectomy* achieved via bilateral RF ablation of the renal nerves, particularly the reduction in afferent

signaling from the native diseased kidneys, was a substantial contributor to this series of events.

Several limitations and technical aspects that need to be considered and require further investigation: Our initial experience indicates that a certain proportion of patients with ESRD have renal artery anatomy that is at least suboptimal for this specific catheter-based radiofrequency nerve ablation approach. This technique requires the diameter of the renal arteries to be >4mm to allow adequate positioning of the treatment catheter to provide optimal contact between the tip of the catheter and the vessel wall. It appears that in several patients with ESRD the atrophy of the kidneys associated with several disease processes may also affect the renal arteries. It is therefore essential to adequately and accurately assess the renal artery anatomy and dimensions before renal nerve ablation is considered, perhaps ideally by CT- or renal angiogram. Aside from the mere diameter of the renal artery, the reduced renal blood flow commonly seen in patients with ESRD is also likely to be of relevance. Sufficient blood flow is required to cool the catheter tip at the contact site, and reduced blood flow may cause temperature rises within the renal arteries that trigger the RF ablation delivery to be aborted automatically for safety reasons, as was the case during some treatments in 2 of our patients. Alternatively, the inbuilt algorithm that responds to a rapid rise in temperature with automatic abortion of the energy delivery rather than the absolute temperature achieved locally may have led to the described errors. Accordingly, alterations of the treatment algorithm and adjustment to the specific circumstances encountered in patients with ESRD may help to overcome these issues. Practically, in renal arteries with borderline diameters (~3.5-4mm) intraarterial infusion of nitroglycerine to dilate the vessel may be useful and allow delivery of energy to various sites.

Further limitations include the small number of patients investigated in this initial proof-of concept study, the lack of an appropriate control group apart from the 3 patients that could not be treated, and the assessment of volume status by clinical parameters only. Further controlled and adequately sized randomized trials are required to substantiate our initial findings.

In summary, our initial experience with a catheter-based approach to target both efferent and afferent renal nerves applying radiofrequency energy through the lumen of the renal arteries demonstrates its feasibility and effectiveness in lowering blood pressure in selected patients with ESRD and suitable renal artery anatomy. Hard cardiovascular end-point studies will be required to demonstrate an improvement in cardiovascular outcomes with renal nerve ablation in this patient cohort.

DISCLOSURES

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Table 1: Baseline characteristics of the entire study cohort (n=12) (mean ± SD)

Age (years)	47.4 ± 13.0
Weight (kg)	68.3 ±12.2
Height (cm)	168.0 ± 11.0
BMI (kg/m2)	24.1 ± 2.7
Office Systolic BP (mmHg)	170.8 ± 16.9
Office Diastolic BP (mmHg)	89.2 ± 12.1
24 h ambulatory SBP (mmHg) (n=10)	164.8 ± 10.1
24 h ambulatory DBP (mmHg) (n=10)	99.2 ± 9.2
Heart Rate (beats/min)	81.5 ± 13.2
Number of antihypertensive drugs	3.8 ± 1.4
Drug classes used:	
ACE-inhibitors	6/12
Angiotensin receptor blockers	8/12
Beta-blockers	8/12
Calcium-channel blockers	8/12
α-blockers	5/12
Vasodilators	6/12
Centrally acting sympatholytic agents	5/12

Table 2: Baseline clinical and biochemical parameters, indices of sympathetic activation, and antihypertensive medication of 5 patients who underwent assessment of sympathetic nervous system activation (mean ± SD); MSNA: muscle sympathetic nerve activity; NA: noradrenaline.

Age (years)	52.8 ± 10.5
Weight (kg)	66.0 ±13.6
Height (cm)	163.0 ± 12.5
Office Systolic BP (mmHg)	174.6 ± 17.1
Office Diastolic BP (mmHg)	90.4 ± 4.3
ABPM 24 h (mmHg) (n=3)	163.7/88.7 ± 11.9/8.4
ABPM Day (mmHg) (n=3)	160.7/89.3 ± 16.7/9.1
ABPM Night (mmHg) (n=3)	170.3/87.3 ± 5.0/7.4
Heart Rate (beats/min)	78.4 ± 10.8
Sodium (mmol/L)	140.2 ± 2.9
Potassium (mmol/L)	4.9 ± 0.6
Creatinine (μmol/L)	740.2 ± 117.5
Urea (mmol/L)	21.4 ± 4.4
Plasma Glucose (mmol/L)	5.5 ± 1.4
MSNA (bursts/min)	50.8 ± 12.8
MSNA (burst/100 heatbeats)	69.4 ± 7.8
Whole body NA spillover (ng/min)	767.0 ± 199.8
Renal NA spillover (ng/min)	105.5 ± 20.9

Table 3: Ambulatory Blood Pressure Monitoring Results (ABPM) as 24 hour, day, and night averages obtained at baseline and 3 and 24 months after bilateral renal denervation in patient no 5. Brain natriuretic peptide (BNP) levels and muscle sympathetic nerve activity (MSNA) was obtained at same time points.

ABPM	**Baseline**	**3M**	**24 M**
Systolic BP 24h	150	136	131
Diastolic BP 24h	79	77	72
Pulse Pressure 24h	71	59	59
Heart Rate 24h	68	72	72
Systolic BP Day	142	146	139
Diastolic BP Day	79	84	78
Pulse Pressure Day	63	62	61
Heart Rate Day	71	76	73
Systolic BP Night	165	118	114
Diastolic BP Night	79	64	61
Pulse Pressure Night	86	55	53
Heart Rate Night	61	66	70
SBP Dipping	-16.1%	19.2%	18.0%
DBP Dipping	0.1%	23.9%	21.8%
BNP (ng/L)	1829	542	302
MSNA			
bursts per minute	36	19	-
bursts per 100hb	58	28	-
units per minute	1500	1219	-
units per 100hb	2459	1816	-

Figure Legends

Figure 1

a) Average systolic and diastolic *office* blood pressure (mmHg) at baseline and various time points of follow up in months (M); **b)** Individual office systolic BP changes (mmHg) at baseline and various time points of follow up in months (M). Data are expressed as mean ± SD, p-values refer to change in blood pressure compared with baseline.

Figure 2

a) Average systolic and diastolic *ambulatory* blood pressure (mmHg) at baseline and various time points of follow up in months (M). **b) and c)** Individual ambulatory systolic and diastolic BP changes (mmHg) at baseline and various time points of follow up in months (M). Data are expressed as mean ± SD,

Figure 3a

Graphic illustration of the blood pressure response to bilateral renal denervation (RDN) over time in a 37 year old male patient with ESRD, whose blood pressure was uncontrolled at baseline despite the use of 5 antihypertensive drugs at appropriate doses. Of note, this patient received a renal transplant (RTx) 4 months after his bilateral renal denervation procedure requiring standard immunosuppressant therapy including corticosteroids, tacrolimus and mycophenolat mofetil. Antihypertensive medications were altered during the peri-operative phase as clinically indicated. At routine follow up visits, blood pressure remained controlled and antihypertensive medication could be further reduced such that the patient was on single drug treatment at his last available follow up visit 33 months after renal denervation.

Figure 3b

Overflow of noradrenaline (NA) from the kidneys into the circulation (renal NA spillover) before (pre RDN), directly after (post RDN) and 3 months (3M FU) following bilateral renal denervation. Renal nerve ablation resulted in an acute and substantial reduction in renal NA spillover that is maintained at 3 months follow up, albeit on a lower level.

Figure 3c

Muscle sympathetic nerve activity (MSNA) as assessed by microneurography at baseline and various time points of available follow up after bilateral renal denervation in a 37 year old male patient with ESRD. Note the progressive reduction of sympathetic nerve activity over time resulting in normalization (as compared to healthy control subjects studied in our laboratory) at 12 months which was sustained at 33 months.

Figure 4

Overflow of noradrenaline (NA) from the kidneys into the circulation (renal NA spillover) before (pre RDN), directly after (post RDN) and at 3 and 12 months follow up (3M FU, 12M FU) from the left kidney only after bilateral renal denervation indicating that the reduction in renal NA spillover achieved with renal nerve ablation is maintained up to 12 months.

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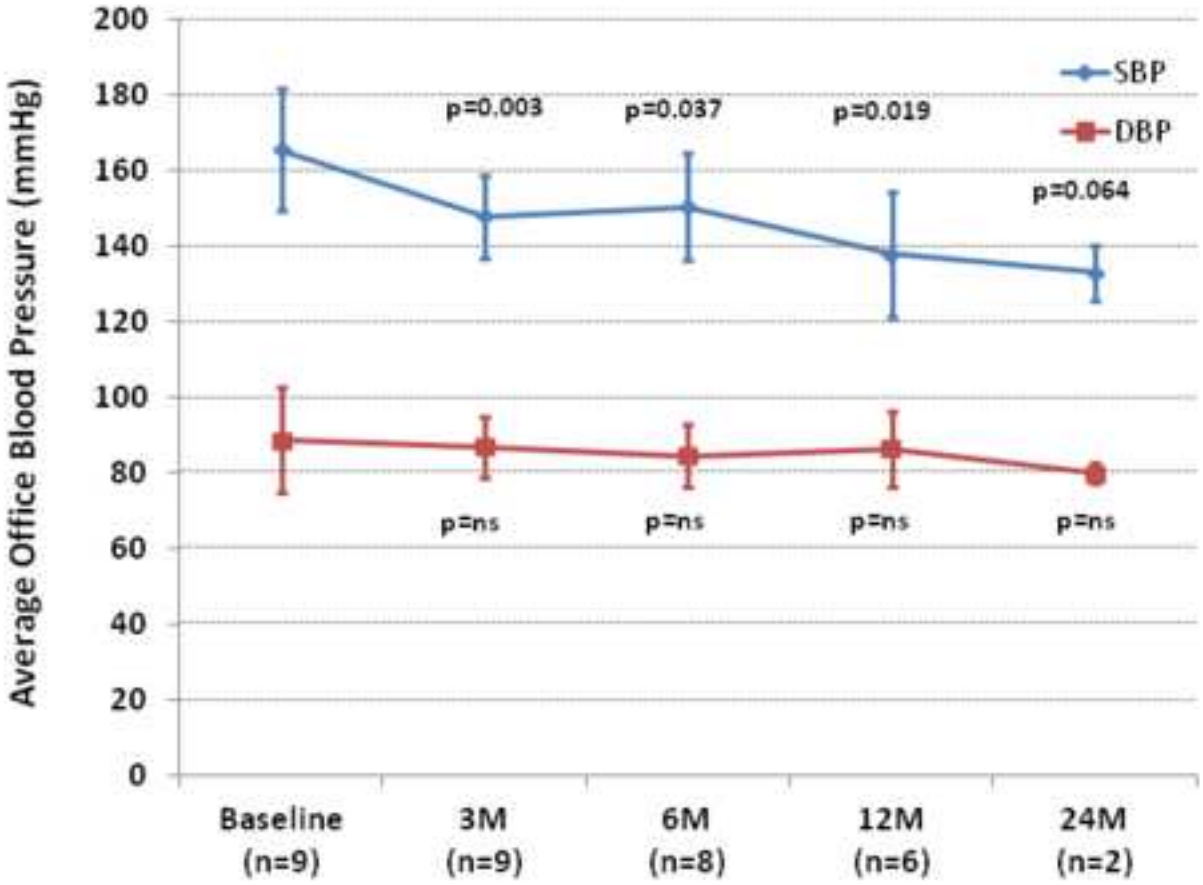
Figure 1a



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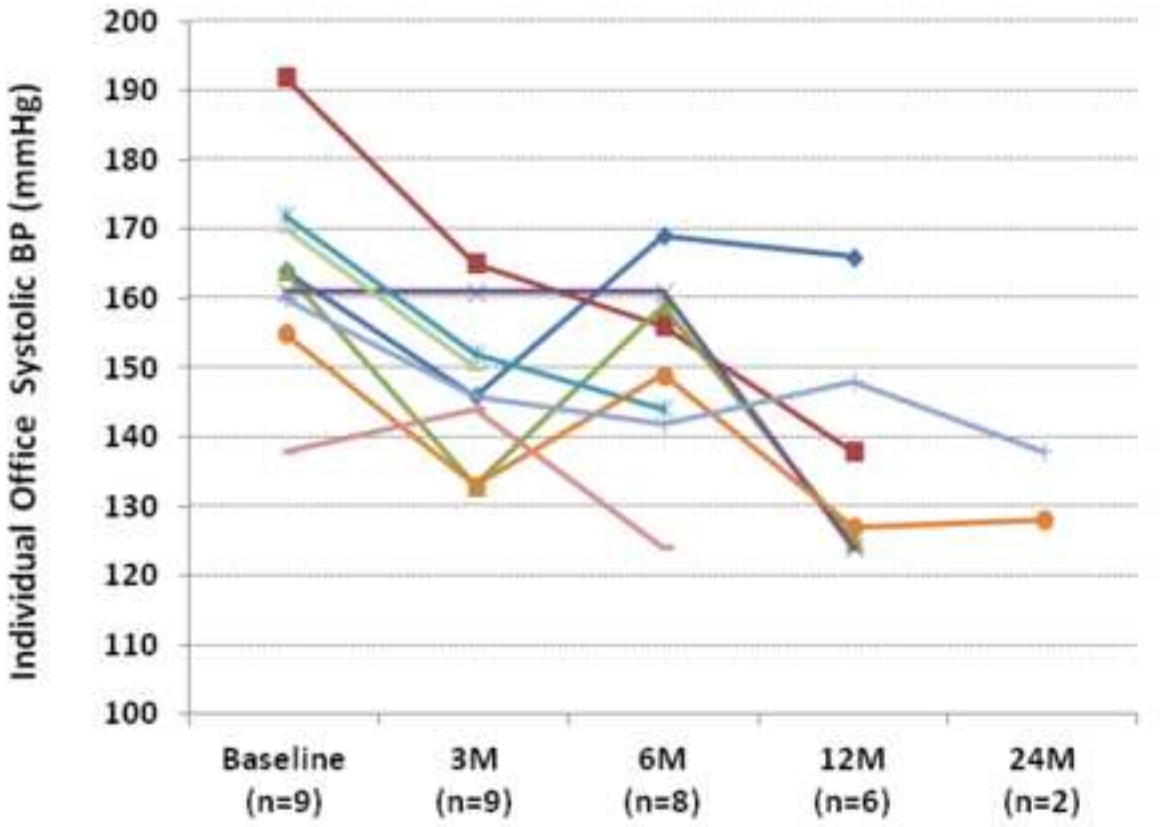

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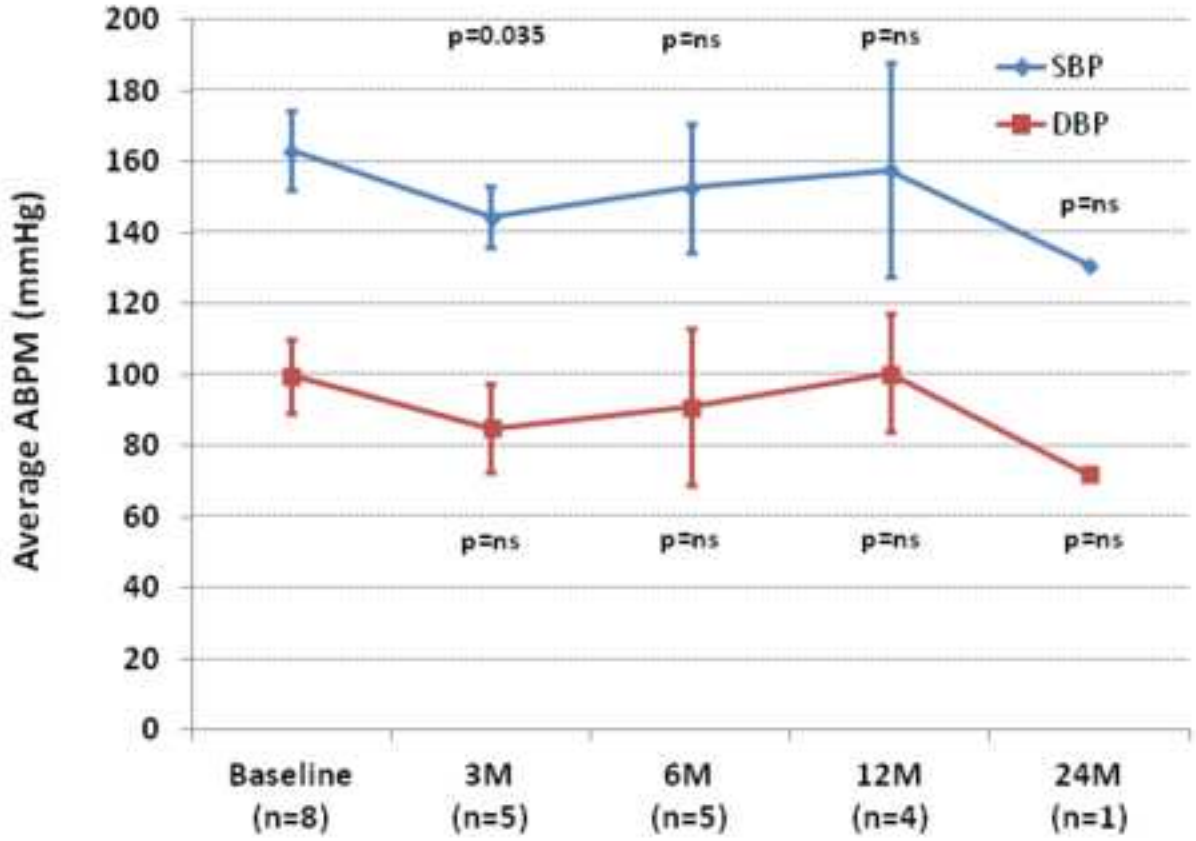
Figure 2a



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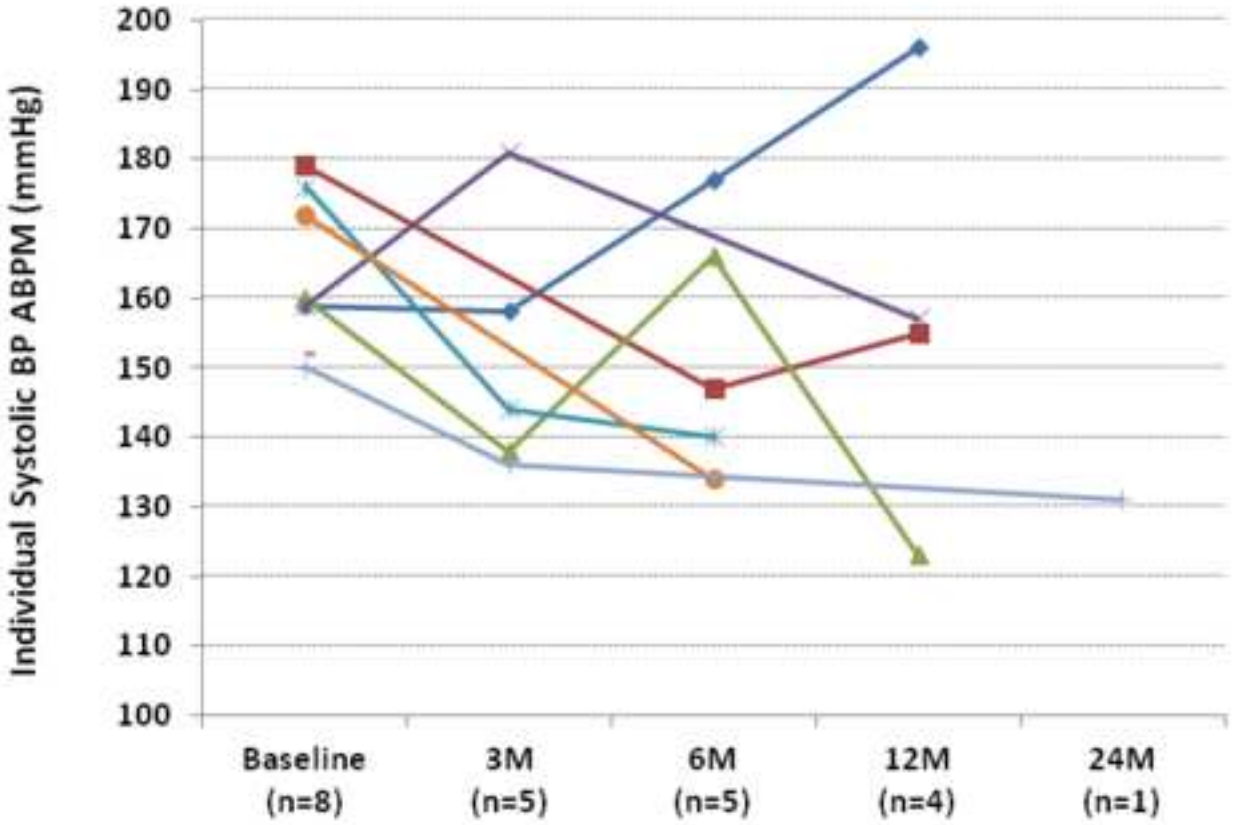

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Figure 2c

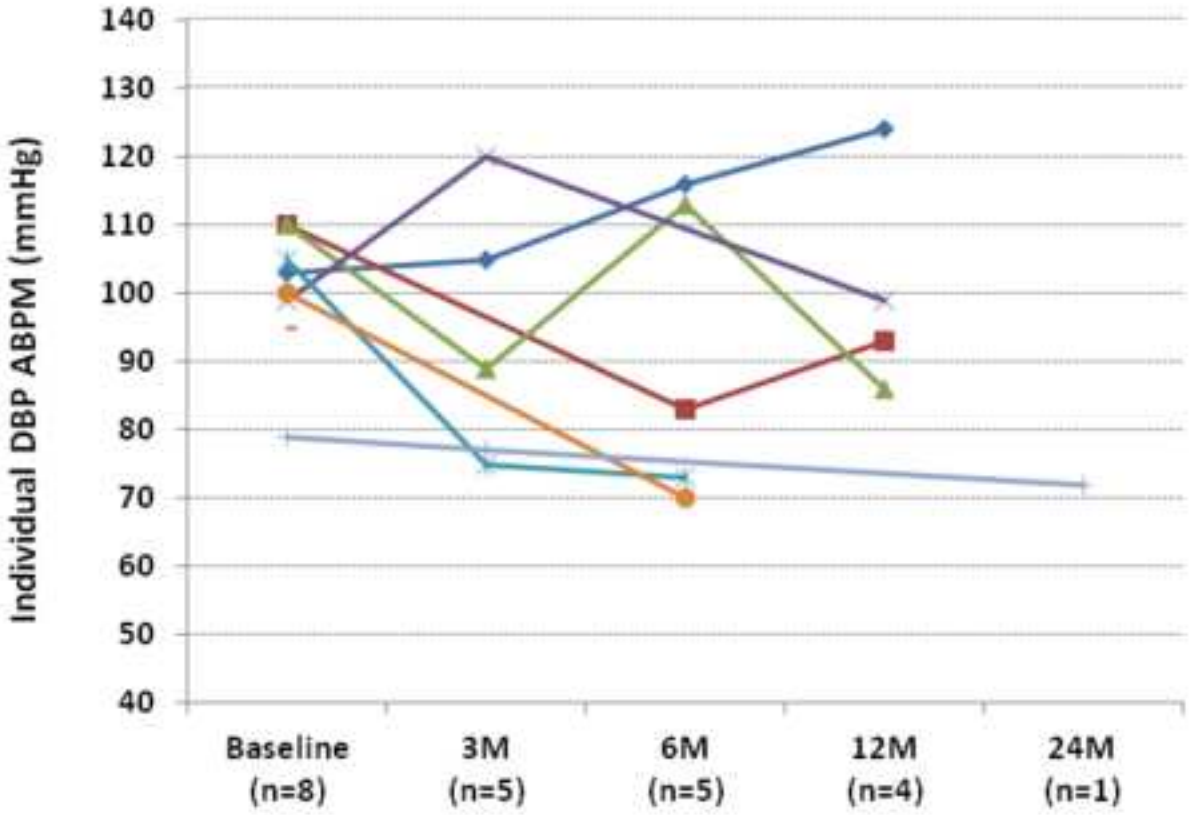

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Figure 3a

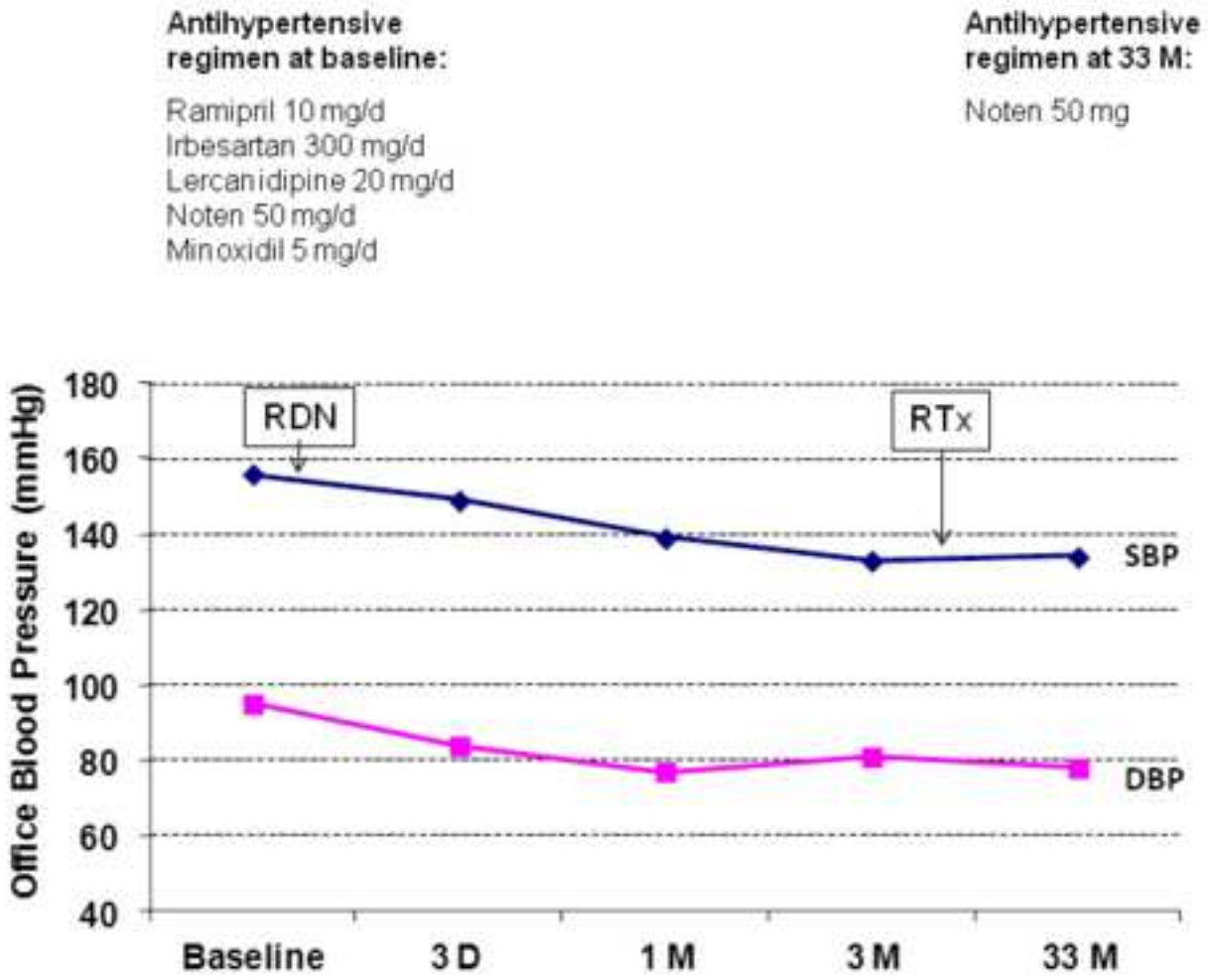

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Figure 3b

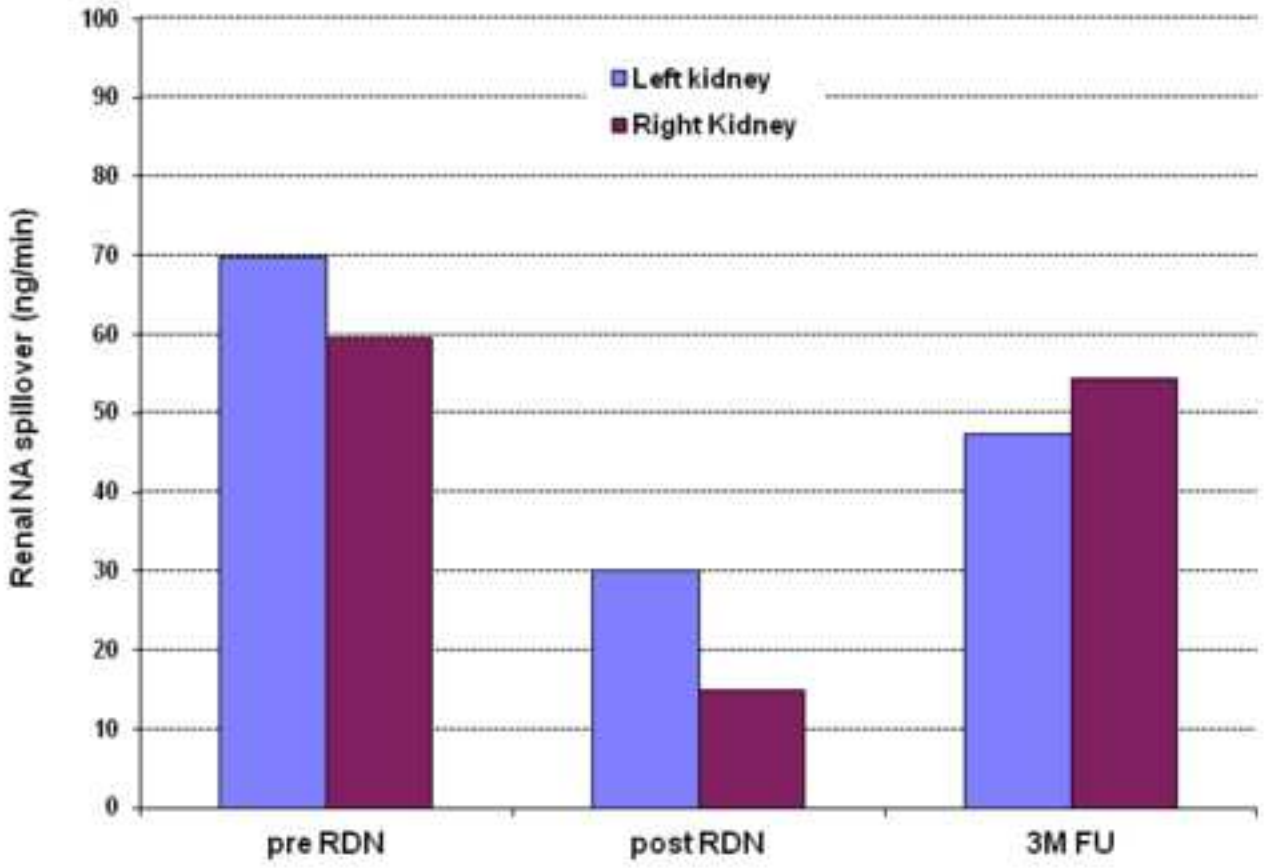

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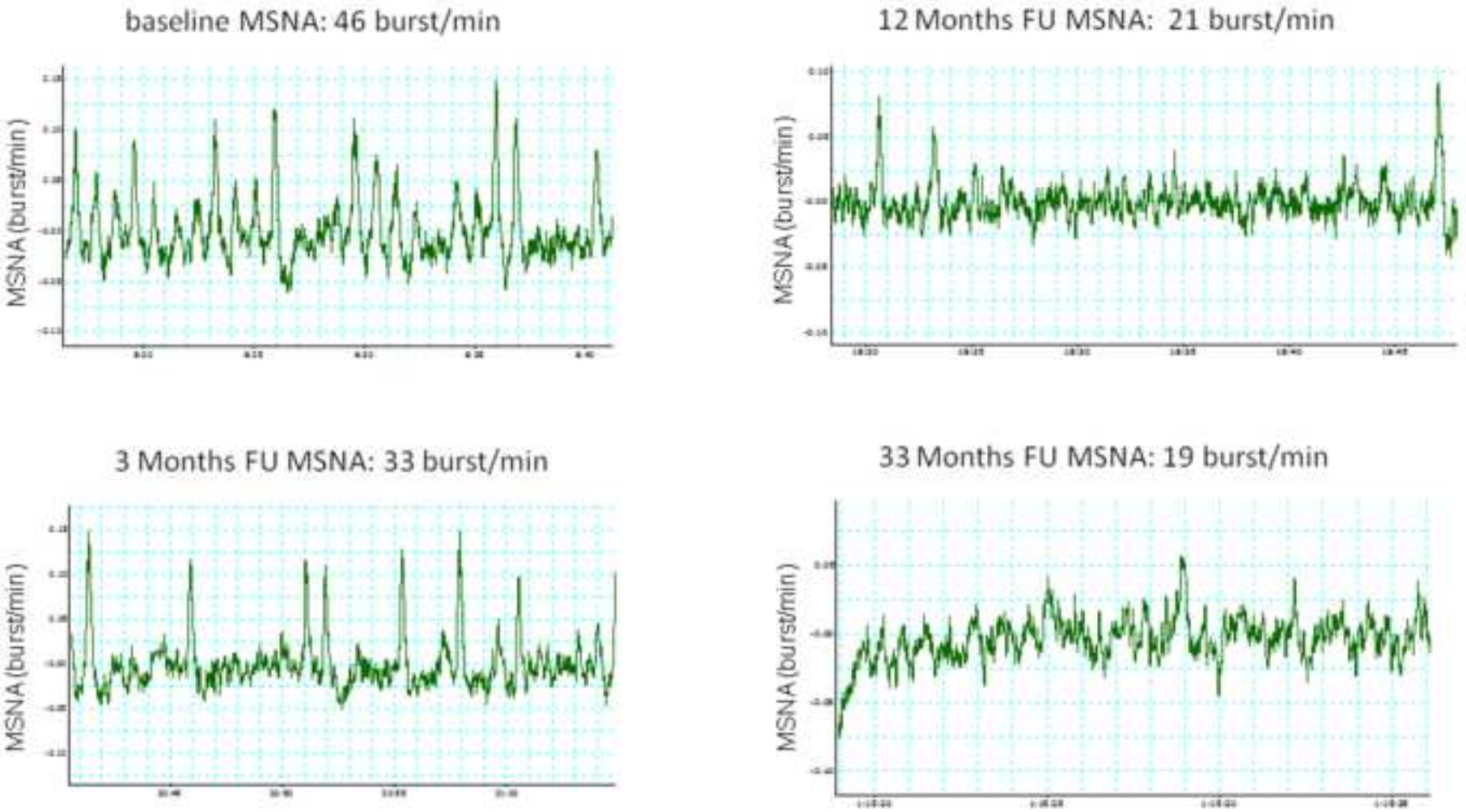
Figure 3c



Of note: MSNA typically between 15-20 bursts/min in young healthy subjects

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Figure 4