Results of renal denervation in clinical practice. Differences between the Flex and Spiral radiofrequency catheters

Resultados de la denervación renal en la práctica clínica. Diferencias entre los catéteres de rediofrecuencia Flex y Spiral

Alessia Gambaro, Flavio Ribichini

ABSTRACT

Background: renal sympathetic denervation (RSD) is emerging as a new therapeutic option for patients with severe hypertension refractory to medical therapy. However, results regarding the efficacy of RSD are contradictory. Recently, a new radiofrequency tetrapolar catheter (Symplicity Spiral) has been introduced into clinical practice with the potential for better results. We aimed to compare the results obtained with the first radiofrequency catheter (Symplicity Flex) and the new Symplicity Spiral catheter.

Methods: from April 2013 to February 2014, 5 patients were treated with the Flex monopolar catheter (group 1) and from February 2015 to October 2015, 11 patients were treated with the new Spiral tetrapolar catheter.

Results: none of the 16 patients treated suffered a complication or adverse event related to the procedure. The blood pressure (BP) reduction in the Flex group was 5 mmHg systolic, and 5 mmHg diastolic BP at 3 months follow-up. In the Spiral group, the systolic BP reduction was 29 mmHg and the diastolic BP 4 mmHg. At three months follow-up, the systolic values were significantly lower compared to baseline (p=0.05).

Conclusions: the results obtained in our study with the Symplicity Flex catheter closely reproduce those expected according to the results reported in the HTN III trial in terms of both safety and efficacy. The introduction of the new tetrapolar Symplicity Spiral catheter yielded a significant reduction in systolic BP without adverse events at three months.

Keywords: *resistant hypertension, sympathetic renal denervation, radiofrequency.*

RESUMEN

Antecedentes: La denervación simpática renal (DSR) está surgiendo como una nueva opción terapéutica para pacientes con hipertensión severa refractaria a la terapia médica. Sin embargo, los resultados respecto a la eficacia de la DSR son contradictorios. Recientemente un nuevo catéter tetrapolar de radiofrecuencia (Symplicity Spiral) se introdujo en la práctica clínica con mejores resultados potenciales. Nuestro objetivo fue comparar los resultados obtenidos con el primer catéter de radiofrecuencia (Symplicity Flex) y el nuevo catéter Symplicity Spiral.

Métodos. Desde abril de 2013 a febrero de 2014, 5 pacientes fueron tratados con el catéter Flex Monopolar (grupo 1) y desde febrero de 2015 a octubre de 2015, 11 pacientes fueron tratados con el nuevo catéter tetrapolar Spiral.

Resultados. Ninguno de los 16 pacientes tratados sufrieron complicaciones o eventos adversos relacionados con el procedimiento. La reducción de presión arterial (PA) en el grupo Flex fue de 5 mm Hg de sistólica y de 5 mm Hg de diastólica a los 3 meses de seguimiento. En el grupo Spiral, la reducción de PA sistólica fue de 29 mmHg y la diastólica de 4 mmHg. A los 3 meses de seguimiento los valores sistólicos fueron significativamente menores comparados con los basales (p=0,05).

Conclusión. Los resultados obtenidos en nuestro estudio con el catéter Symplicity Flex reproducen de forma similar aquellos esperados de acuerdo con los resultados del estudio HTN III en términos de seguridad y eficacia. La introducción del nuevo catéter Symplicity Spiral produjo una reducción de la PA sistólica significativa sin eventos adversos a los 3 meses.

Palabras clave: *hipertensión resistente, denervación simpática renal, radiofrecuencia.*

Revista Argentina de Cardioangiología Intervencionista 2015;6(4):176-179

INTRODUCTION

Sympathetic renal denervation (SRD) has emerged as a therapeutic alternative for patients with resistant hypertension[1,2].

Resistant hypertension is defined as a systolic blood pressure of 140 mmHg or higher despite the adherence to at least three maximally tolerated doses of antihypertensive medication from complementary classes, including a diuretic at an appropriate dose[3], after the exclusion of any possible cause of secondary hypertension[4].

The promising results of SRD performed with radiofrequency in initial clinical experiences could not be replicated when the treatment was compared to a sham procedure and optimized medical treatment, as designed in the Hypertension III study (HTN III)[5]. Indeed, the initial HTN I[6] and HTN II[7,8] studies revealed a significant reduction of the systolic and diastolic office blood pressure of 22 mmHg and 10.2 mmHg respectively at 6 months for HTN I and of 32 mmHg and 12 mmHg respectively at 6 months for HTN II with the use of the Medtronic Symplicity Flex radiofrequency catheter

1. Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy.

✉ Correspondence: *Flavio Ribichini | Professor of Cardiovascular Medicine, Director Cardiovascular Interventional Unit, University of Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy | Phone: +39 045 812 2039 | flavio.ribichini@univr.it*

Los autores declaran no tener conflictos de intereses.

Recibido: 09/11/2015 | Aceptado: 26/11/2015

TABLE 1. Clinical characteristics of the Flex catheter and the Spiral catheter population.

	Flex catheter	Spiral catheter
Age (average)	69.8	56.3
Sex	5 male	4 male
Diabetes mellitus (n)	5	1
Coronary artery disease (n)	2	1
eGFR average at baseline (ml/min/1.73m^2)	36.6	32.8
		41.3 (patient in haemodyalisis excluded)
eGFR ≤35 ml/min/1.73m^2 (n)	3	2
Number of drugs at baseline	6,4	5

eGFR: estimated glomerular filtration rate.

(Medtronic Inc, Santa Rosa,CA, USA). Unlike these results, the double blind, randomized HTN III trial did not confirm such a substantial blood pressure reduction with the same catheter. As a consequence, the anti-hypertensive effect of the SRD catheter was not significantly different as compared to the results of the medically treated group. Indeed, although a significant change from baseline to 6 months office systolic blood pressure and ambulatory blood pressure was observed in sham and denervation group, the group difference did not meet a test of superiority with a margin of 5 mmHg for office blood pressure (–2.39 mmHg, p=0.98) and 2 mmHg for ambulatory blood pressure (–1.96 mmHg, p=0.98)[5]. Although the trial confirmed the safety endpoint, the lack of efficacy casted serious doubts on the real value of the SRD treatment, and the therapy was almost abandoned in 2014 after the publication of the HTN III trial on March 29th 2014 in the *New England Journal of Medicine*[5].

Several interpretations have been speculated to analyze the possible causes of the negative results of HTNIII[9]. Based on some anatomical observations related to the innervation of the renal arteries, a different pattern of radiofrequency delivery in the artery with a new SRD tetrapolar Spiral catheter has reopened the interest on the technique.

This article reports on the clinical experience of a single center activity performed in 2013 with the Flex catheter, and in 2015 with the new Spiral catheter, and compares the results obtained with the two different radiofrequency systems.

MATERIAL AND METHODS

The SRD clinical program was approved by the Department of Health of the Veneto Region, Italy, in September 2012 that authorized the clinical use of the Symplicity Flex radiofrequency catheter in two University Hospitals of the Region, Verona and Padova. The clinical use of the SRD catheter was conditioned however, to the presence of a specialized multi-disciplinary group dedicated to the treatment of hypertension and vascular pathologies, including nephrologists, cardiologists, interventionalists and vascular surgeons. The clinical outcomes, as well as any adverse event related to the SRD procedureafter the first year of activity were reported to a dedicated committee of the Departmentof Health as *"efficacy"* and *"safety"* endpoints respectively. According to the declared findings, the committee would have considered the extension of the therapy to other, non-academic institutions in the Veneto Region.

TABLE 2. Pressure trend during follow up after renal denervation.

Symplicity cathether		Baseline	1 month	3 months
Flex	Psyst (mmHg)	154 (150-170)	147 (130-185)	149 (130-185)
	Pdiast (mmHg)	79 (70-83)	75 (55-85)	74 (65-85)
Spiral	Psyst (mmHg)	174 (150-215)	149 (130-168)	145 (125-171)
	Pdiast (mmHg)	92 (65-105)	78 (68-80)	88 (75-100)
* p <0.05 baseline-follow up 1-3 months			ANOVA for repeated measures	

Psyst: systolic pressure. Pdiast: diastolic pressure.

Inclusion criteria of patients were office systolic blood pressure ≥160 mmHg (≥150 mmHg for patients affected by diabetes mellitus) with three antihypertensive medications from complementary classes, including a diuretic, all at the maximum tolerated doses. Age ≥18 years old.

Exclusion criteria were secondary form of hypertension other than those secondary to renal parenchymal disease or dialysis associated, pregnancy, significant valvular heart disease, recent coronary artery syndrome (atypical angina, NSTEMI, STEMI) or recent severe cardiovascular events (stroke, myocardial infarction or pulmonary embolism in the last three months); and hemodynamically significant renal artery stenosis (diameter stenosis >50%).

Safety endpoints: death, embolic events, worsening of renal disease (decrease of eGFR higher than 25% in 2 consecutive determinations), embolic events resulting in end-organ damage, nephro-vascular complications, hypertensive crisis after 1 month or new renal-artery stenosis of more than 70% diameter stenosis at 3 months.

*Efficacy endpoint:*change in office blood pressure at 3 months.

*Follow-up:*patients were followed up at 1 and 3 months for the assessment of eventual adverse events and drug regimen, as well as the the measurements of office blood pressure and serum creatinine concentration.

Statistical methods

Patients treated with Flex catheter (group 1) and patients treated with Spiral catheter (group 2) were compared. Furthermore patients were also analyzed according to eGFR ≤35 ml/min/1.73m^2 or higher.Systolic and diastolic BP at baseline, 1 month and 3 months were analyzed with ANOVA for repeated measures.

RESULTS

In the first year of SRD activity, from April 2013 to February 2014, 5 patients were treated with the Symplicity Flex unipolar catheter (group 1). After the publication of the results of HTN III, the Regional com-

TABLE 3. Pressure trend during follow up after renal denervation.

eGFR		Baseline	1 month	3 months
eGFR >35 ml/min/1,73 m^2	Psyst (mmHg)	160 (150-170)	147 (141-152)	140 (125-150)
	Pdiast (mmHg)	80 (65-83)	70 (55-80)	80 (65-100)
eGFR ≤35 ml/min/1,73 m^2	Psyst (mmHg)	165 (150-215)	153 (130-185)	153 (130-185)
	Pdiast (mmHg)	89 (80-105)	81 (70-85)	80 (65-95)
eGFR ≤35 ml/min/1,73 m^2 haemodialysis patient excluded	Psyst (mmHg)	153 (150-160)	149 (130-185)	148 (130-285)
	Pdiast (mmHg)	85 (80-100)	80 (70-85)	80 (65-95)

eGFR: estimated glomerular filtration rate. Psyst: systolic pressure. Pdiast: diastolic pressure.

mittee left the decision whether to continue or suspend the SRD activity to the SRD multi-disciplinary group of the Verona University Hospital. In any case, referral of patients following HTN III disclosure dropped dramatically.

By the end of 2014, the new Symplicity tetrapolar Spiral catheter become available at our center and a new recruitment of cases was agreed within members of the SRD multi-disciplinary group.

So far, 11 patients have been treated with the Spiral catheter, and 5 of them have reached the 3-months follow-up assessment (group 2).

The clinical characteristics of the two groups are reported in **Table 1.**

*Safety endpoints:*None of the 16patients treated in the two different periods had complications as defined by protocol. Only one patient treated with the Flex catheter (group 1) had a contrast-induced nephropathy.

Efficacy endpoints: The effect on the office blood pressure values at 1 and 3 months in the two groups are shown in **Table 2.**

As a secondary analysis, the effect of denervation on blood pressure was evaluated in patients classified according to their renal function as measured by the eGFR calculated with the MDRD formula. Whether an eGFR ≤35 ml/min/1.73m^2 affects trends in blood pressure after denervation was analyzed. Unlike Symplicity HTN I, II, III, an eGFR <45 ml/min/1.73m^2 was not an exclusion criterion in our study. Results are summarized in **Table 3.**

According to our very preliminary findings, and with the obvious limitation of the low number of treated subjects, renal function does not seem to influence the denervation effect on blood pressure, and vice-versa, the SRD procedure does not impact negatively the renal function in this population.

DISCUSSION

The advent of SRD in clinical practice created enormous expectations in the medical community. Indeed, the possibility of reducing BP further on top of medical therapy in patients with uncontrolled BP values would have a tremendous impact in terms of life saved and reduction of severe disabilities secondary to major cardiovascular events[10,11]. Furthermore, the acquisition of a relatively simple interventional technique in the armamentarium of cardiologists was perceived as a further enlargement of the fields of interest in the interventional medical community.

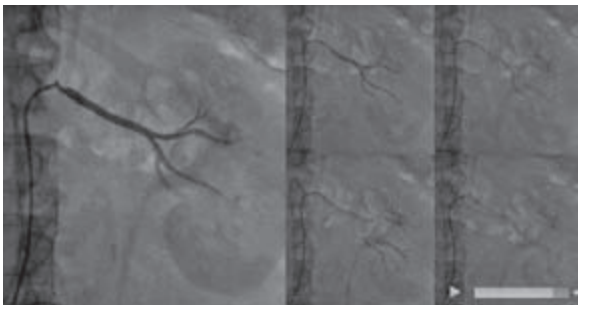

Figure 1. *SRD with the Symplicity Flex catheter. Delivery of radiofrequency was perfomred at single points, generaly 3 or 4 points in each renal artery for a mean of 6 to 8 per patient.*

The overwhelming results obtained in the initial trials[7] were likely biased by the small number of patients, the weak endpoint of single BP office measurements, and the lack of a blinded research model. As a consequence, when a large and well-designed SRD trial denied such initial positive results, serious doubts on the real value of SRD were advanced[12].

However the negative findings of the HTN III study have been the object of intense debate and analysis of possible explanations[12]. Among these, the effective action of the radiofrequency catheter has been identified as one of the main drivers of a limited efficacy of the technique as applied in the HTN III trial. Indeed, although both systems run into a 6 Fr guiding catheter, the former Flex radiofrequency catheter navigates within the renal artery as a monopolar catheter guided from the external grip (**Figure 1**) while the tetrapolar Spiral catheter follows a conventional 0.014" coronary guide-wire, allowing a better control and a more distal positioning of the catheter (**Figure 2**). The Flex catheter, having a single electrode, delivers the radiofrequency energy at one point at a time, making the procedure much longer, while the Spiral catheter delivers at four different points each time. Apart from the duration of the procedure, the spatial orientation of the 4 electrodes of the Spiral catheter allows a more homogeneous distribution of the radiofrequency energy along the four quadrants of the artery wall, a technical detail that has been implied as a main driver in the efficacy of the SRD procedure with radiofrequency[13,14]. Furthermore, the application of the radiofrequency in more distal segments of the renal artery branches enabled by the smaller diameter and the guided navigation of the device on a guide-wire, may be better than the ablation of proximal

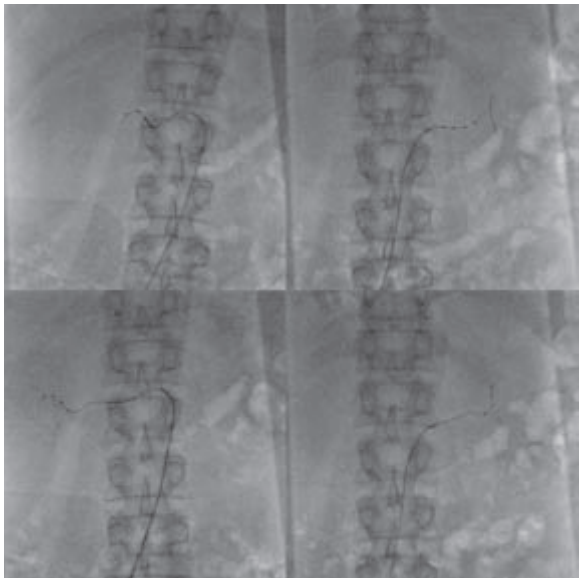

Figure 2. *SRD with the Symplicity Spiral catheter. Delivery of radiofrequency is perfomred at four different points simultaneously, allowing a minimum of 8 points per artery and a mean of 18 ablations per patient. The number and the spacial orientation of the ablation points have been identified as importan technical variables that dictate the efficacy of SRD with radiofrequency.*

tracts that are far more distant to the sympathetic nerves, reducing the capability of the radiofrequency energy to damage the nervous fibers[15].

Our experience is limited to a small number of cases, however, it is relative to cases of real resistant hypertension as diagnosed by the nephrologist and discussed by a multi-disciplinary team. Furthermore, it represents the largest series of SRD cases perfomred in Italy so far.

The clinical findings of our preliminary experience in terms of efficacy confirm a significant difference between the two catheters, and support the use of SRD in clinical practice with the new Spiral catheter. Using this catheter the change in systolic office blood pressure at 3 monthswas ~ 30 mmHg, much more than that detected in HTN III, and in line with the HTNI[6] and HTNII studies[7,8] (HTNI: 21 mmHg and 26 mmHg at 1 and 6 months respectively, HTNII: 20 mmHg and 24 mmHg at 1 and 3 months respectively). Furthermore comparing the efficacy of Flex and Spiral catheters in our series, the latter is significantly more effective in lowering systolic blood pressure at one (25 mmH) and 3 months (30 mmHg) compared to 7 and 5 mmHg with the Flex system.

It is noteworthy that the use of the new Spiral tetrapolar ablation catheter did not affect the safety profile of the SRD procedure in our experience. Indeed, despite its much higher efficacy no adverse event was noted among the patients treated with the new device.

CONCLUSION

Technical advancements in the development of new radiofrequency catheters for SRD seem to improve the clinical outcome of SRD without impairing the safety of the procedure. The results of a large number of patients treated with the new Spiral catheter are being collected in the Worldwide Global Symplicity Registry[16]. Furthermore, other important trials (on/off therapy) are underway and will provide conclusive information regarding the real value of this innovative therapeutic option. Other systems of SRD are also under study and results obtained with different forms of energy for ablation of the renal nervous system are expected in the near future.

Until more data in terms of efficacy of SRD will be available, the Spiral radiofrequency system should be used in the context of clinical trials, or controlled internal protocols.

REFERENCES

1. *Persu A, Renkin J, Thijs L, Staessen JA. Renal denervation: ultima ratio or standard in treatment-resistant hypertension. Hypertension. 2012;60(3):596-606.*
2. *Thukkani AK, Bhatt DL. Renal denervation therapy for hypertension. Circulation. 2013;128(20):2251-4.*
3. *Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension--its identification and epidemiology. Nat Rev Nephrol. 2013;9(1):51-8.*
4. *Sperati CJ, Whaley-Connell A. Secondary hypertension: beginnings and transitions. Adv Chronic Kidney Dis. 2015;22(3):177-8.*
5. *Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393-401.*
6. *Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014;383(9917):622-9.*
7. *Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376(9756):1903-9.*
8. *Esler MD, Böhm M, Sievert H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J. 2014;35(26):1752-9.*
9. *Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J. 2015;36(4):219-27.*
10. *Perkovic V, Huxley R, Wu Y, Prabhakaran D, MacMahon S. The burden of blood pressure-related disease: a neglected priority for global health. Hypertension. 2007;50(6):991-7.*
11. *Dorenkamp M, Bonaventura K, Leber AW, et al. Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. Eur Heart J. 2013;34(6):451-61.*
12. *Epstein M, de Marchena E. Is the failure of SYMPLICITY HTN-3 trial to meet its efficacy endpoint the "end of the road" for renal denervation? J Am Soc Hypertens. 2014.*
13. *Mahfoud F, Edelman ER, Böhm M, et al.Catheter-based renal denervation is no simple matter: lessons to be learned from our anatomy? J Am Coll Cardiol. 2014 Aug 19;64(7):644-6.*
14. *Sakakura K, Ladich E, Cheng Q, et al.Anatomic assessment of sympathetic peri-arterial renal nerves in man.J Am Coll Cardiol. 2014 Aug 19;64(7):635-43.*
15. *Tzafriri AR, Mahfoud F, Keating JH,et al.Innervation patterns may limit response to endovascular renal denervation. J Am Coll Cardiol. 2014 Sep 16;64(11):1079-87.*
16. *Böhm M, Mahfoud F, Ukena C, et al. Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry. EuroIntervention. 2013;9(4):484-92.*