Horizon Scanning

TechScan

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BAROREFLEX ACTIVATION THERAPY FOR HYPERTENSION AND HEART FAILURE

Keywords: Barostim neo, Baroreflex Activation Therapy, resistant hypertension, heart failure, horizon scanning

SUMMARY OF TECHNOLOGY

Baroreflex activation therapy (BAT) is a new technology which was initially developed for treatment of resistant hypertension, and later evaluated for its potential usage in treating heart failure. The therapy is delivered by implanting a lead connected to a small device known as Barostim neo system on a carotid sinus where blood pressure sensor known as baroreceptor fibres are located.[1,2]

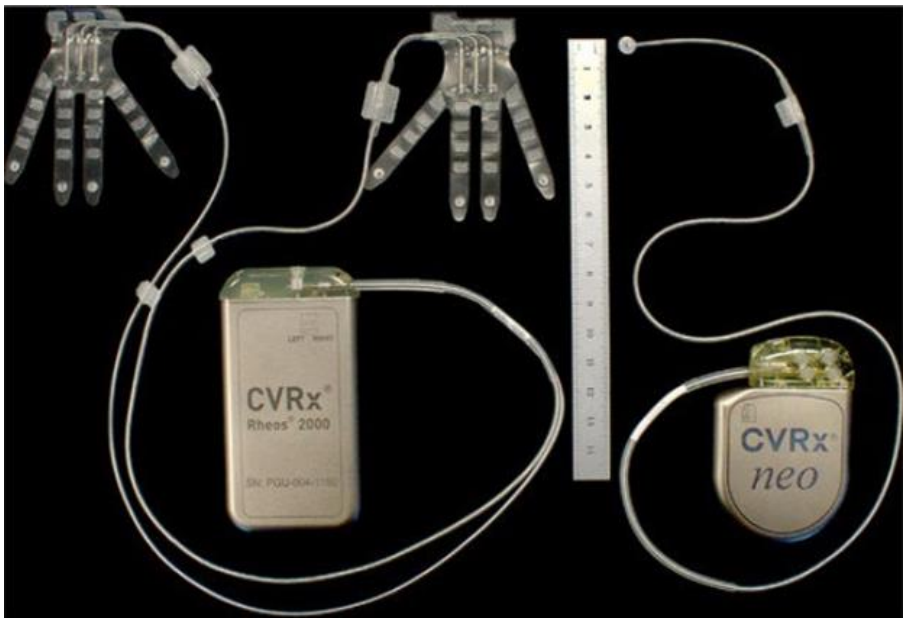

Figure 1: Rheos system (left) and Barostim neo system (right)
(Source: Gassler JP and Bisognano JD)

Baroreflex activation therapy acts by giving electrical stimulation continuously to these baroreceptors fibres. These receptors send signals via neural pathways to the brain. The brain works to counteract this perceived rise in blood pressure by sending signals to other parts of the body (heart, blood vessels, and kidneys) that relax the blood vessels resulting in reduction of systemic vascular resistance, reducing blood pressure, cardiac workload and heart rate. It also reduces fluid in the body by improving kidney function.[1,2]

Barostim neo system is a second-generation device replacing Rheos System which had become obsolete (Figure 1). It differs from the older generation in which it has smaller pulse generator, smaller lead and only one lead. The older generation is bigger and has two leads.[3] It is developed and patented by CVRx, a medical device company located at Minneapolis, Minnesota, USA.[4]

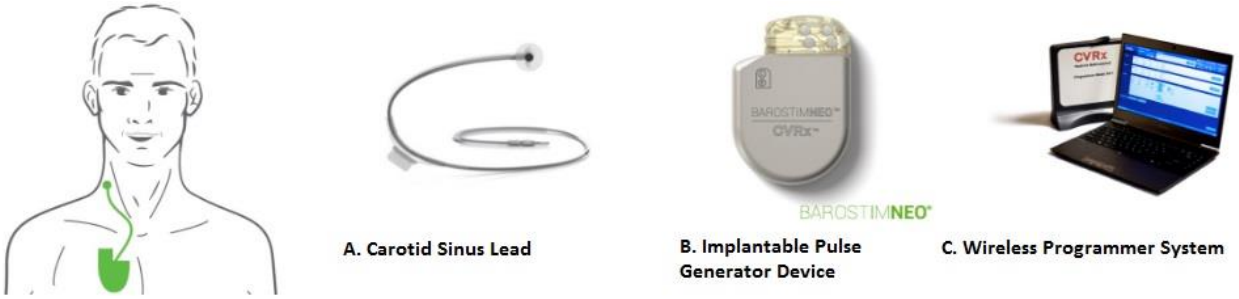

Figure 2: The Barostim neo System (Source: barostimtherapy.com)

The Barostim neo system consists of an implantable pulse generator (IPG) device, a carotid sinus lead and a wireless programmer system (Figure 2).[5] The carotid sinus lead is a 40 cm lead body that terminates in a 7 mm diameter circular backer. A 2 mm disc electrode made of iridium oxide-coated platinum-iridium centered on the backer is sutured to the carotid artery after mapping the sinus region. Then, the opposite end of the lead is connected to the IPG via a subcutaneous tunnel. The battery-powered IPG is implanted in a subcutaneous infraclavicular pocket made over a chest wall. Following implantation, patients need multiple follow ups for dose adjustment by up-titrating the dose until patients attain therapeutic effect without experiencing any side effects. The therapy can be turn on/off using the wireless programmer system.[6]

The device received CE Mark for the treatment of resistant hypertension in 2011 and heart failure in 2014. Hence, it is commercially available in Europe.[7,8] However, it is for investigational use in USA and Canada.[9]

Barostim neo legacy system was approved for Humanitarian Device Exemption (HDE) by the U.S. Food and Drug Administration (US FDA) in December 2014 for use in the treatment of resistant hypertension in patients previously implanted and responded with the Rheos System.[10,11] It received Expedited Access Pathway Designation by US FDA in November 2015 for the treatment of heart failure to speed up its market access.[12,13] The pulse generator which is battery-powered has an expected life span of three years.[14]

Hence, an early assessment was made to evaluate the potential impacts of BAT in treating resistant hypertension and heart failure.

POTENTIAL FOR IMPACT

RESISTANT HYPERTENSION

Resistant hypertension is defined as persistently elevated blood pressure (>140/90 mmHg) despite having good medication compliant with optimal doses of three groups of anti-hypertensive medication (including a diuretic). Treatment options include emphasised on therapeutic lifestyle modification, add more medications and some centres offer renal denervation therapy.[15]

Baroreflex activation therapy has been evaluated as one of the potential therapy for this group of patients. The therapy is delivered by bilateral Rheos System device before being replaced by the second-generation device unilateral Barostim neo System. Most evidence on the potential of BAT in reducing blood pressure were from Rheos system trials.[16,17,18,19,20,21,22] In subanalysis of Rheos Pivotal trial, unilateral lead stimulation in Rheos System particularly on right sided had been shown to have more profound effects than bilateral leads.[21] Later, unilateral Barostim neo system was used in subsequent trials replacing the first generation Rheos System.[14,23,24]

The Rheos Pivotal Trial was the only randomised controlled trial conducted for BAT. The study randomised (2:1), 265 resistant hypertension patients into Group A (immediate Rhoes system activation, n=181) and Group B (delayed Rheos system activation until after month 6, n=84).[19] The other six studies; three for Rheos and three for Barostim neo were non-randomised single arm trials involving small sample size with the longest follow up of six months.[16,17,18,14,23,24] Five studies reported BAT reduced blood pressure in patients with resistant hypertension. However, there were no control arm.[14,16,17,18,23] A study on the effect of Barostim neo therapy on ambulatory blood pressure showed a reduction of systolic blood pressure (SBP) from 148±17 mmHg to 140±23 mmHg, $p<0.01$ and diastolic blood pressure from 82±13 mmHg to 77±15 mmHg, $p<0.01$ on 24 hour ambulatory monitoring.[24]

The Rheos Pivotal Trial showed that there was no significant difference with the 20% superiority margin in percentage of responder who achieved at least 10 mmHg in SBP reduction in both groups (54% Group A versus 46% Group B, $p=0.97$) at six months follow up. The mean reduction of SBP at six months follow up was 16±29 mmHg for Group A compared with 9±29 mmHg for Group B ($p=0.08$). The SBP reduction was sustained in 88% of responders in Group A at 12 months assessment. At 12 months follow up, both groups had activated Rheos device. There was no different in mean reduction of SBP between two groups receiving activated Rheos for 12 months or six months duration (25±32 mmHg and 25±31 mmHg respectively).[19]

De Leeuw *et al.* reported the results of six years follow up of participants who were included in three studies; the US Rheos Feasibility Study, the DEBuT-HT trial and the Rheos Pivotal Trial. However, from a pooled of 383 patients implanted with Rheos

device, only 48 patients completed the six years follow up. Thus, the result of this study was not included.[22]

Hoppe *et al.* reported Barostim neo had comparable procedure related adverse event of pacemaker.[14] A study comparing both generation BAT device showed Barostim neo had better safety profile than Rheos system and longer lasting battery.[25] In Barostim neo, 90% of patients were free from immediate system or procedure related adverse events compared with 75% in Rheos trial.[14]

Among the reported adverse events of Barostim neo were device pocket haematoma, wound complication and intermittent pain near the device system.[14] While in Rheos trial, the complications were transient (4.8%) and permanent nerve injury (4.8%) occurred related to carotid sinus lead placement, general surgical complication (4.8%) which included respiratory or wound complication.[19]

In Germany, Barostim neo system priced €24,133 (RM120,464.27) for the lead and the replacement of battery costs were €21,000 (RM104,825.33). The incremental cost-effectiveness ratio in patients with resistant hypertension, presented in 2011 Euros was €7 797/QALY (RM38,920.15/QALY).[26] Currently, there are two ongoing studies evaluating the Barostim neo system in resistant hypertension patients.[27,28]

In conclusion, the potential efficacy of BAT in reducing blood pressure is comparable with current medical treatment for resistant hypertension based on one randomised trial. Hence, the results of the ongoing studies are anticipated to shed light on the potential of this therapy.

HEART FAILURE

Heart failure is a chronic progressive condition which contributed to 6.7% of acute medical admission in Malaysia.[29] Imbalance of neurohumoral response by excessive activation of sympathetic nervous system and renin-angiotensin-aldosterone system with inhibition of parasympathetic nervous system is the key factor contributing to progression of heart failure.[30]

Baroreflex activation therapy was investigated for its potential use in preventing progression of heart failure based on a concept of its ability to stimulate autonomic balance.[30] The studies conducted used the second generation of Barostim neo device.[31,32,33,34,35]

In the first randomised controlled trial by Abraham *et al*., a total of 146 heart failure patients with reduced ejection fraction were randomised into control group who received standard medical therapy (n=70) and treatment group with BAT plus standard medical therapy (n=76) and follow up for six months. Patients with Barostim neo activated therapy showed improvements in patients' symptoms and heart function measured by distance walked in six minutes (59.6±14m vs 1.5±13.2 m, p=0.004), quality of life score

(-17.4±2.8 points versus 2.1±3.1 points, p<0.001) and New York Heart Association (NYHA) class ranking (p=0.002).[34] The results were consistent with previous early small non-randomised studies.[31,32] Baroreflex Activation Therapy also significantly reduced N-terminal pro b-type natriuretic peptide (pro-BNP) level (p=0.02) and associated with trends toward fewer days hospitalisation for heart failure (p=0.08).[34]

The major adverse neurological and cardiovascular events free rate was 97.2% in BAT group. Two patients developed haematoma. However, no death, stroke, or cranial nerve injury was reported.[34] The event free rate was 85.9% for system and procedure related complication. The complications reported were urinary retention, urinary tract infection, pneumothorax, cervical neuralgia, bradycardia, hypotension and worsening heart failure in one patient each, and non-sustained atrial arrhythmias in two patients.[34]

Subgroup analysis of this study in patients with or without existing cardiac resynchronization therapy suggested that BAT was more effective in those without existing cardiac resynchronisation therapy.[35] Previous small study showed there was no device-device interaction of Barostim neo implanted in seven patients with pre-existing implantable cardiac defibrillator.[33]

In conclusion, the potential efficacy of BAT in improving symptoms and heart function in heart failure patients comes from small trials. There was some system and procedure related complications. However, in view of insufficient evidence, further study with proper randomisation, larger participants and longer follow up is needed. The results of three ongoing studies are much awaited.[36,37,38]

EVIDENCE

HYPERTENSION

- **PUBLISHED PAPERS**

<u>Rheos System</u>

Illig KA, Levy M, Sanchez L *et al.* An Implantable Carotid Sinus Stimulator for Drug-Resistant Hypertension: Surgical Technique and Short-Term Outcome from the Multicenter Phase II Rheos Feasibility Trial. J Vasc Surg. 2006;44(6):1213-1218.

Wustmann K, Kucera JP, Scheffers I *et al.* Effects of Chronic Baroreceptor Stimulation on the Autonomic Cardiovascular Regulation in Patients with Drug-Resistant Arterial Hypertension. Hypertension. 2009;54(3):530-536.

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Bisognano JD, Bakris G, Nadim MK *et al.* Baroreflex Activation Therapy Lowers Blood Pressure in Patients with Resistant Hypertension: Results from The Double-Blind, Randomized, Placebo-Controlled Rheos Pivotal Trial. J Am Coll Cardiol. 2011 Aug 9;58(7):765-773.

Bakris GL, Nadim MK, Haller H *et al.* Baroreflex Activation Therapy Provides Durable Benefit in Patients with Resistant Hypertension: Results of Long-term Follow-up in the Rheos Pivotal Trial. J Am Soc Hypertens. 2012;6(2):152-158.

de Leeuw PW, Alnima T, Lovett E *et al*. Bilateral or Unilateral Stimulation For Baroreflex Activation Therapy. Hypertension. 2015;65(1):187-192.

de Leeuw PW, Bisognano JD, Bakris GL *et al.* Sustained Reduction of Blood Pressure with Baroreceptor Activation Therapy. Results of the 6-Year Open Follow-Up. Hypertension. 2017;69:836-843.

Barostim neo System

Hoppe UC, Brandt MC, Wachter R *et al.* Minimally Invasive System for Baroreflex Activation Therapy Chronically Lowers Blood Pressure with Pacemaker-like Safety Profile: Results from the Barostim neo Trial. J Am Soc Hypertens. 2012 Jul-Aug;6(4):270-276.

Wallbach M, Lehnig LY, Schroer C *et al.* Impact of Baroreflex Activation Therapy on Renal Function – A Pilot Study. Am J Nephrol 2014;40:371–380.

Wallbach M, Lehnig LY, Schroer C *et al.* Effects of Baroreflex Activation Therapy on Ambulatory Blood Pressure in Patients with Resistant Hypertension. Hypertension. 2016;67:701-709.

- **ABSTRACTS**

Wachter R, Halbach M, Bakris G *et al.* Safety and Blood Pressure Effects of Second- Versus First- Generation System for Administering Baroreflex Activation Therapy. J Hypertens. 2016;34(2):e94.

- **ONGOING STUDIES**

BAROSTIM NEO HTN Pivotal Trial (NCT01679132). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT01679132.

Barostim Neo System in the Treatment of Resistant Hypertension (NCT01471834). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/ NCT01471834.

HEART FAILURE

- **PUBLISHED PAPERS**

Gronda E, Seravalle G, Brambilla G *et al.* Chronic Baroreflex Activation Effects on Sympathetic Nerve Traffic, Baroreflex Function, and Cardiac Haemodynamics in Heart Failure: A Proof-Of-Concept Study. Eur J Heart Fail. 2014;16(9):977-983.

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Abraham WT, Zile MR, Weaver FA *et al.* Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction. J Am Coll Cardiol HF. 2015;3(6):487-496.

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- **ONGOING STUDIES**

Barostim Therapy for Heart Failure (BeAT-HF) (NCT02627196). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT02627196.

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