Title

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Journal

Expert Review of Medical Devices, 17(7)

ISSN

1743-4440

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Publication Date

2020-07-02

DOI

10.1080/17434440.2020.1779054

Peer reviewed

HHS Public Access

Author manuscript

Expert Rev Med Devices. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Expert Rev Med Devices. 2020 July ; 17(7): 649–658. doi:10.1080/17434440.2020.1779054.

Device profile of the MobiusHD EVBA system for the treatment of resistant hypertension: overview of its mechanism of action, safety and efficacy

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Abstract

Introduction—Early promising results of renal nerve denervation awakened interest in developing medical device alternatives for patients with resistant hypertension. The subsequent sham-controlled renal nerve denervation randomized trials were disappointing leading researchers and innovators to explore alternative device and trial designs to address this significant unmet need. We describe the innovation process leading to the first endovascular carotid baroreflex amplification device currently undergoing clinical trials in the United States and Europe.

Areas covered—We provide a brief overview of carotid baroreceptor physiology and then couple this knowledge with the fundamental principles of strain pattern changes that led to the proposed innovation. The mechanism of blood pressure reduction via enhancing innate

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Declaration of interest

G Stone has received speaker or other honoraria from Cook, Terumo, QOOL Therapeutics and Orchestra Biomed; been a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme; and has equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix. M Bates is a past consultant for vascular dynamics and presently consultant for W.L. Gore and Associates. C Chen is a past consultant for Vascular Dynamics. W Spiering is a consultant for Vascular Dynamics.

GS: Speaker or other honoraria from Cook, Terumo, QOOL Therapeutics and Orchestra Biomed; Consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme; Equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix.
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WS: Consultant for Vascular Dynamics

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

physiologic carotid sinus baroreceptor signaling through changes in pulsatile focal carotid bulb strain is described alongside preclinical testing and early clinical results.

Expert opinion—The collective data to date suggest endovascular carotid baroreflex amplification may be an innovative alternative for resistant hypertension patients. However, well-controlled studies will be needed to assess efficacy, safety, durability, and risk: benefit of this permanent intravascular carotid implant.

Subject codes

high blood pressure; hypertension; treatment; physiology; Resistant Hypertension; carotid baroreceptor; baroreflex; barostimulation; device; MobiusHD; endovascular carotid baroreflex amplification

1. Introduction

Despite the remarkable efficacy of pharmacologic therapies for hypertension, the hypertension control rate has hit a plateau with a predictable noninvasive solution to resistant hypertension (RHTN) remaining elusive [1,2]. This has stimulated interest in device-based alternatives. To date, several non-pharmacologic approaches to modify sympathetic overdrive in hypertension have been proposed. These non-pharmacologic approaches tackle the sympathetic overdrive by either blocking efferent autonomic excitatory pathways (surgical sympathectomy [3,4], renal nerve denervation (RND) [5] and ureteral nerve denervation [6]) or modifying afferent inputs to change reflex outputs (carotid sinus stimulation [7] and carotid body ablation [8]). However, these early attempts to modify sympathetic outflow have been associated with significant morbidity [4,9], unpredictable and/or limited efficacy [10,11]. This is perhaps not surprising given the multi-factorial nature of hypertension, different hypertension phenotypes and susceptibility of RHTN cohorts to regression to the mean and Hawthorn effect. Recent off-HTN medication studies have suggested properly selected hypertension phenotypes may benefit from RND [12,13].

Among these approaches, carotid sinus stimulation appears to be most promising, albeit with limited efficacy [14]. One intriguing outcome from the first generation of carotid sinus stimulation devices is the significant reduction in blood pressure in the sham control group [7]. One potential explanation for this sham effect is that, by wrapping around the carotid sinus, the device may have altered the stretch pattern of the baroreceptor field. This un-anticipated sham effect raised the possibility of lowering blood pressure through enhancing baroreflex afferent signaling by altering the stretch pattern at the receptor field.

Based on the premise that favorable changes in stress-strain behavior can be predicted by changes in the shape of tubular structures, a hypothesis surfaced that alteration of carotid bulb geometry may enhance baroreceptor signaling without impacting physiologic flow and/or pulsatility. It was also believed that passively enhancing innate physiologic baroreceptor function may overcome some of the limitations of directly inhibiting activity, or severing feedback loops. This observation led to the development of a passive endovascular prosthesis designed primarily for augmenting baroreceptor activation, the MobiusHDR (Vascular Dynamics, Inc.; Mountain View, California, USA) Endovascular

Baroreflex Amplification (EVBA) device. This invited review is meant to complement previous MobiusHD device summaries by adding additional insight into the translational pathway of the idea into US and European Trials with emphasis on better understanding the mechanism of action [15–18]

2. Background

2.1. Baroreceptor physiology

Carotid baroreceptor physiology was first described in landmark animal studies by Hering in the 1920s and led to the discovery and mapping of the afferent nerve to a branch of the glossopharyngeal nerve (Hering's nerve, also termed the carotid sinus nerve [CSN]) [19]. In the simplified primary arc of the central baroreflex network in regulating sympathetic activities, an increase in systemic blood pressure (BP) results in increasing afferent signaling from carotid sinus (CS) baroreceptors and subsequent inhibition of sympathetic outflow to lower BP via inhibiting neurons in the rostral ventral lateral medulla [20]. Please note that an exhaustive overview baroreceptor physiology is beyond the scope of this review but can be found in the excellent expert summary authored by Manci G and Mark AL. in 1983 [21].

Through the years, since Hering's initial observations, we have now learned the following regarding baroreceptor anatomy, function, and pathophysiology: 1) the CSN action potential is triggered by pressure induced carotid bulb stretch rather than pressure alone [19]; 2) in response to sustained increases in static pressure (carotid sinus stretch) the baroreceptor afferent activities 'adapt' over time and this "resetting" of baroreceptors can be prevented or attenuated if the pressure is pulsatile [22]; and 3) pulsatile stretch (rather than static stretch) is required to obtain sustained effects on CSN activation (explaining why carotid stents don't impact BP long term) [23]. This phenomina is likely mediated by the preserved function of the unmyelinated C fibers that have higher pressure threshold and will not reset in response to acute pressure changes [24]. In systemic hypertension, it is believed that 1) both baroreceptor (peripheral) and central nervous system (central) 'resetting' take place in hypertension [22]; 2) the ability of the CS baroreceptor reflex to reduce BP is preserved in hypertension in-spite-of resetting [25]; 3) passively altering innate physiologic baroreceptor function (e.g. baroreceptor unloading) [26] may overcome the central resetting following severing the feedback loop (baroreceptor denervation) [19]; and 4) sustained BP reduction can be seen with CS electrical stimulation [7]. These key assumptions have been supported by 24-h intraarterial blood pressure recording alongside baroreflex sensitivity analysis with phenylephrine. Additionally, nitroglycerin and neck chamber induced changes in carotid transmural pressure provided important insight into how these different reflexes impact heart rate variability and interplay with other factors ('probably central in nature') in BP homeostasis [27].

2.2. Lessons from carotid baroreceptor stimulation devices for hypertension

Electrical stimulation of the CSN with a surgical implant to modulate carotid baroreceptor function as a treatment for hypertension dates back to animal studies in 1964 [28]. Subsequent human trials with follow-up to three years showed promising results in lowering arterial pressure [7]. Due to associated adverse events from this surgery as well as the

exponential growth of anti-hypertensive pharmaceutical discoveries in the 1980s, interventional carotid stimulation procedures were abandoned. Interest in baroreceptor stimulation resurfaced 10 years ago as promising results were obtained with improved technology and a well-defined unmet need of RHTN became better understood [7]. The success of BP reduction with the Barostem Neo device (CVRx Minisotta USA) provided needed insight into the potential of sustainable BP improvement with a contemporary stimulation device targeting the carotid baroreceptors. Last year Seravalle G. et al. provided an excellent comparison of carotid baroreceptor activation with the CVRx and the MobiusHD in this Journal [29]. Recently, clinical data have suggesting baroreceptor stimulation may uniquely benefit congestive heart failure patients as a countermeasure for the congestive heart failure associated altered baroreceptor function [30,31].

3. Preclinical development of carotid baroreceptor amplification

3.1. Concept

Observations from years of research on carotid baroreceptors led to exploration of alternative baroreceptor reflex activity enhancement by increasing carotid bulb stretch during the systolic phase of the cardiac cycle. Since stretch can be predicted by changes in strain, based on the strain equation (Figure 1), one would expect increased strain with increasing carotid bulb radius, decreasing wall thickness, and/or increasing pressure. It not possible to non-surgically decrease the carotid bulb wall thickness or to increase the blood pressure further to exploit these components of the strain equation to achieve an increased baroreceptor response. However, a non- surgical alternative of increasing stretch by reshaping the artery to a non-circular cross-section with an endovascular nitinol prosthesis would be expected to increase CS wall strain (increasing stretch) without impacting pulsatility and pressure (Figure 1). The decrease in pulsatility at the four corners created by the struts of the device is minimal compared to the significant increase in pulsatile strain and movement of the carotid bulb within the 4 EVBA device windows (between the struts) as shown in Figure 1

3.2. Testing of hypothesis

To better understand the stress–strain relationships and evaluate potential carotid flow changes, a fluid structure interaction simulation analysis with contact surface between the device and the arterial wall was conducted [32]. Results indicated that device deployment in the carotid sinus induces an increase of 2.5% and 7.5% in circumferential and longitudinal wall stretch, respectively. A maximum of 54% increase in von- Mises arterial stress at the sinus wall baroreceptor region was noted in this model [32]. In addition, device implantation had minimal effect on blood-flow patterns, indicating that it did not adversely affect carotid bifurcation hemodynamics in a physiologic model [32]. In fact, decreased internal carotid artery shear stress was predicted in this model. Based upon these fluid–structure interaction simulations, the device induces localized increases in wall stretch at the sinus (suggesting that this will activate baroreceptors) with no consequential deleterious effects on carotid sinus hemodynamics [32] (Figure 2(a–c)). The quantitative changes in stretch predicted in the computational models were confirmed in a benchtop pulsatile flow model using laser microscope measurements of wall excursion (Figure 2(d))

Unfortunately, very few animals have a carotid sinus/baroreceptor and this created challenges in developing an animal surrogate model to predict human outcomes [33,34]. A canine model was used to assess CSN firing patterns with the Mobius EVBA device as well as a carotid artery stent as the control (which, in contrast to the EVBA device, place a much higher constant outward pressure on the CSN receptor field) (not published). Angiography after implant showed preserved flow in all controls and device vessels, however, duplex imaging with adequate fidelity to quantify flow patterns was not available. CSN firing activity is linear to systolic BP between 110 and 200 mmHg, both in firing frequency (Figure 3(c), black line) and integrated activity (Figure 3(d), black line). As expected, the carotid artery stent shifted the CSN activity- systolic BP relationship upward for any given systolic BP. Also expected is that the slope of this relationship was flatter than the control (a blunted CSN response to increases in systolic BP), because the baroreceptors were operating at the upper limit of the full function curve. In contrast, the slope of the CSN activity-systolic BP relationship after implanting the EVBA device shifted upward without changing the slope (responsiveness). The results suggest the EVBA device reduces the pressure threshold for baroreceptor firing while maintaining reflex sensitivity. Subsequent acute animal studies involving hypertensive canines showed reductions in BP (~50 mmHg systolic and ~30 mmHg diastolic) that were sustained post-implant through 6 hours without resetting or extinguishing of the hemodynamic effect. The lack of tachycardic response to decreased BP seen in these studies suggested the EVBA can reset the reflex operating point to a lower BP. Durability assessment and evaluation of longer- term efficacy with this model was not possible because the canine CS is typically <1 mm in diameter, leading to difficulty in maintaining device patency for extended periods of time.

It was hypothesized that changes in carotid bulb architecture by placement of an external clip-like device could also enhance baroreceptor response (Figure 4(a)). After cadaver studies confirmed feasibility of an external clip-like device placement (Figure 4(b)), five patients undergoing carotid endarterectomy underwent temporary placement of an extravascular device meant to modulate carotid sinus architecture after endarterectomy [35]. There was an average of 22 mmHg drop in systolic BP while the device was in place but significant variability of response was noted [35]. The response variation, in part, may have been related to use of atropine and vasopressors in some patients during the carotid endarterectomy procedure. More importantly the baseline BP was 134/57 ± 14/10 mmHg, which is at the low end of expected baroreceptor response [35].

In the absence of a representative chronic pre-clinical model that replicates the human carotid baroreceptor nerve bed and related carotid sinus architecture, most of the study device survival animal studies were performed to confirm device safety and optimize design. Vascular Dynamics Inc. conducted several survival ovine carotid implant studies to allow the engineering team to confirm preclinical models for balancing radial force of the device to achieve desired geometric shape confirmation without migration through the basement membrane or impacting the architecture of the media and adventitia. While these studies were not a surrogate for long-term human carotid bulb healing, the MobiusHD healed in a favorable way. Specifically, unlike the diffuse neointimal response seen in the carotid stent controls, with associated circumferential vessel stiffening, the MobiusHD neointimal change was isolated to the four longitudinal device struts and did not impact the therapeutic

windows responsible for EVBA effect. These studies also compared carotid arterial healing of the EVBA device to stent controls, confirming similar healing patterns and inflammation scores. Additional finite element analysis and fatigue prediction analysis, fixtures were developed to challenge different designs for metal fatigue. The final intravascular EVBA device included three sizes that would accommodate various carotid bulb diameters. In addition, a low-profile monorail delivery system, compatible with a 0.014" guide wire, was developed that allowed for recapture after partial deployment, so repositioning is possible to ensure accuracy and safety. The final study product is housed in a 5.9 Fr monorail delivery system and has radiopaque markers at the apex of opposing proximal and distal interconnect crowns as seen in Figure 5.

4. Clinical findings to date

The sponsors of the clinical trials discussed the challenge of further development of this technology with the U.S. Food and Drug Administration in light of the absence of an ideal pre-clinical surrogate for human anatomy. The device was chosen as one of the first nine systems approved for the Early Feasibility Pilot Study Program – Controlling And Lowering Blood Pressure with the MobiusHD First in Man Study (CALM-FIM; clinicaltrials.gov NCT01831895). Since this is a carotid implant, with all the inherent risks of selective carotid angiography and instrumentation, an abundance of caution was used for patient selection. The rationale for including only RHTN patients in the trial was driven by the need to balance the risk of a carotid implant with the potential benefit in these patients. Specifically, patients with true RHTN have a significant increase in the risk of stroke and all-cause mortality (30% and 57% increased risk, respectively) and for every 10 mmHg reduction, systolic BP we see a 27% reduction in stroke and 13% decrease in all-cause mortality [36] [37]. Patients required imaging of the carotids and arch to exclude atherosclerotic disease and all the first cases underwent unique pre-procedure personalized patient anatomy analysis. Specifically, the patient's computed tomography angiography was used to construct a three-dimensional printed cast of their actual carotid allowing precise silicone molds to be generated for pre-procedure assessment by benchtop deployment (Figure 5(b)). The clinical trial sponsor limited interventional participation to those skilled in carotid procedures.

The CALM-FIM open-label study was performed at six European and seven US centers (ClinicalTrials.gov, number NCT01911897). Eligible patients were adults with RHTN (office systolic BP ≥160 mm Hg despite taking at least three antihypertensive agents, including a diuretic). MobiusHD devices were implanted unilaterally in the internal carotid artery at the site of the carotid bulb. The primary endpoint was the incidence of serious adverse events at 6 months. Secondary endpoints included changes in office and 24-hr ambulatory BP. Further details regarding patient enrollment characteristics and technique are detailed elsewhere [38]. The European arm enrolled 30 patients and their results were reported in 2017 [38]. The 30 patients reported in the CALM-FIM European study showed baseline office BP of 184/109 mmHg (SD 18/ 14), mean 24-hr ambulatory BP of 166/100 mmHg (SD 177/14), and mean number of antihypertensive medications 4.4 (SD 1.4). Mean office BP decreased by 24/11 mmHg (95%CI 12–35/4–18) at 3 months and 24/12 mmHg (95%CI 13–34/6–18) at 6 months. Mean 24-hr ambulatory BP decreased by 15/8 mmHg (95% CI 7–23/3–13) at 3 months and 21/12 mmHg (14–29/7–16) at 6 months. This decrease

was seen on top of reduction in the number of antihypertensive medication by 0.5 (IQR 1.3–0.0). There were five serious adverse events reported in four patients including: hypotension (n = 2), worsening hypertension (n = 1), intermittent claudication (n = 1) and access site wound infection (n = 1) [38]. Note the hypotension reported improved over time but does not exclude the possibility of seeing persistent low BP in future trials if the device is oversize. It should also be noted that two patients who had not taken their antihypertensive medications before implantation (both with periprocedural systolic BP greater than 200 mm Hg during the procedure) reported numbness and reduced strength in an arm and leg after the procedure. The trial independent data safety monitor board DSMB did not feel the residual symptoms were neurological and, because both patients' National Institutes of Health Stroke Scale scores were zero the day after implantation, these events were judged to be transient ischemic attacks not strokes.

The combined 6-month outcomes for the CALM-FIM US and European arms are illustrated in Table 1. The combined data set alongside 3-year follow-up results are presently undergoing peer review. Additional foundational research and clinical data have been reported by van Kleef et al. [18]. The CALM-2 study (Controlling And Lowering Blood Pressure with the MobiusHD) is an ongoing randomized, sham- controlled multicenter trial studying the effect of EVBA on BP and will study 300 patients enrolled at 40 centers throughout Europe and the US (ClinicalTrials.gov Identifier: NCT03179800). The primary effectiveness endpoint changes in mean 24-hr systolic BP from baseline to 180-day. The secondary endpoints are safety assessments measured at 90-day with a composite measure of death, myocardial infarction, stroke, device embolization, carotid occlusion, new ipsilateral carotid stenosis requiring surgical or percutaneous intervention, or Bleeding (Academic Research Consortium level 3 to 5 bleeding) events as adjudicated by trial clinical event committee from randomization through the 90-day visit.

5. Summary

The EVBA hypothesis is supported by known CSN action potential physiology and anatomy coupled with multidisciplinary clinical, biochemical, and engineering expertise in stress-strain fundamentals. EBVA associated changes in carotid sinus wall strain and resultant increased stretch result in amplification of endogenous physiological signals, allowing discriminatory discharge patterns of high- and low-threshold afferents at each phase of the cardiac cycle, while maintaining the 'pulsatile' phases in synchrony with other baroreceptor inputs [39]. These changes may reduce baroreflex resetting and augment the magnitude of output by way of central facilitation [40]. In addition, the MobiusHD device should selectively activate baroreceptors and spare CS chemoreceptors, translating into greater BP lowering efficacy [41]. Finally, the EVBA preserves the carotid baroreceptor reflex as a closed loop, allowing dynamic modification of feedback inputs to the CNS as BP continuously changes. Maintaining a closed reflex loop also facilitates differential regulation of sympathetic efferents to varying target organs in response to assorted internal changes [42]. Early human studies also support the potential for the MobiusHD to significantly reduce BP.

6. Expert opinion

Hemodynamic balance is maintained through a complex neurohumoral network of pressure, stretch, and volume sensing feedback loops (Figure 6). The signals impacting BP include local paracrine-driven changes in vessel tone and juxtaglomerular cell-mediated sodium retention, systemic modulation in enzymatic cascades including the renin-angiotensin system, and central – as well as peripheral-mediated changes in adrenergic tone. The complexity of these biochemical, neurologic, and cellular interactions, along with the heterogeneity of hypertensive patient phenotypes, may explain why no single feedback loop derangement has been consistently identified as the predominant cause of primary hypertension. It also may explain why the cure for hypertension has remained elusive.

Renal nerve denervation was heralded as one of the most important innovations of modern medical device research and brought hope to many patients with hypertension that was resistant to medical therapy. The unexpected failure of subsequent sham controlled RND randomized trials shocked researchers and informed ongoing hypertension device ideation. We now know RHTN cohorts are particularly prone to regression to the mean. Looking back, this may explain, in part, the irrational exuberance about renal stenting in the 1990s and early 2000s. We also, now categorize RHTN into phenotypes that may benefit from different medical device alternatives. For example, the elderly patient with longstanding hypertension and wide pulse pressure may have shifted away from an autonomic mediated hypertension to more of a structural cause. These ‘structural hypertension’ patients would seemingly be less likely to benefit from devices that modify adrenergic tone. There are many other variables that are difficult to control in RHTN trials including but not limited to; technical failures, noncompliance, Hawthorn effect, and Pseudo-hypertension. This detailed analysis of early failed sham-controlled RND trials led to successful subsequent studies showing benefit of RND in select hypertension phenotypes [12,13].

While the EVBA has the potential to reduce BP and thus avoid end-organ damage in patients with RHTN, many unanswered questions need to be addressed in future clinical trials. First and foremost is that of short-term and long-term device safety including but not limited ipsilateral stroke risk, unexpected carotid bulb remodeling, and impact on the future need of carotid endarterectomy. The occurrence of ipsilateral transient ischemic attacks that occurred in the CALM-FIM study heightened the need for strong safety data. The device success will depend on proven clinical RHTN benefit that outweighs any of the inherent risks for an ipsilateral hemispheric periprocedural event or long-term unexpected consequences from the carotid implant. These safety and efficacy questions are the principal aims of the ongoing CALM-2 studies. Regardless of the results of the ongoing EVBA trials, we anticipate this translational work will enhance the understanding of the CS contribution to hypertension and may contribute to the development of future device or pharmacologic RHTN solutions.

Acknowledgments

Funding

This invited review was not sponsored by Vascular Dynamics Inc. and the authors were not directly paid for their contribution to this manuscript. However, all four authors were remotely (MCB and C-Y C) or are presently (GWS and WS) consultants for Vascular Dynamics, inc and some of the company’s sponsored research was used to

construct the paper. Additionally, research done by one of the authors (MCB) is supported, in part, by the National Institutes of Health under Award Number 5U54GM104942-04. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Article highlights

1. Carotid baroreceptors play an important role in maintaining hemodynamic balance and are a potential therapeutic device target for blood pressure reduction.
2. The carotid baroreceptors are activated by pressure change induced carotid bulb stretch rather than pressure alone and pulsatile stretch is needed for sustained blood pressure response.
3. Sustained blood pressure reduction has been achieved with implantable electrical carotid baroreceptors stimulation devices.
4. The mechanism of action for blood pressure reduction with Endovascular Carotid Baroreflex Amplification is not intuitive and involves changes in pulsatile focal carotid bulb strain induced by implant induced geometric vessel changes.
5. Preclinical and early Endovascular Carotid Baroreflex Amplification clinical results in patients with resistant hypertension are promising but additional data is needed to confirm long-term safety and efficacy.

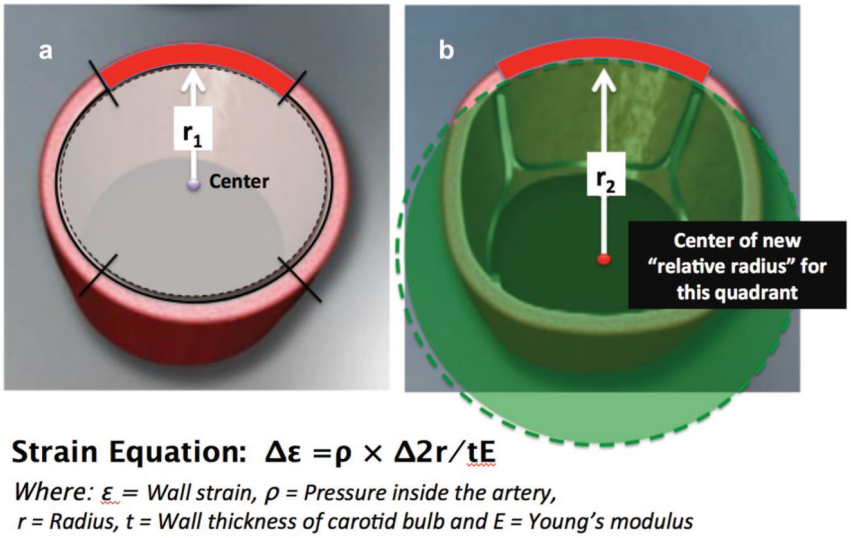

Figure 1.

To better understand the MobiusHD mechanism, a single quadrant of a carotid bulb prior to the implant (thick red line) is illustrated in A. The arc of that baseline quadrant projects a radius for the circle (r-1). The same quadrant is shown in B and note that the arc of the vessel in the window of the device after implant projects a circle that has a much larger radius (r-2). Based on the strain equation increased stretch would be expected in each quadrant of the device.

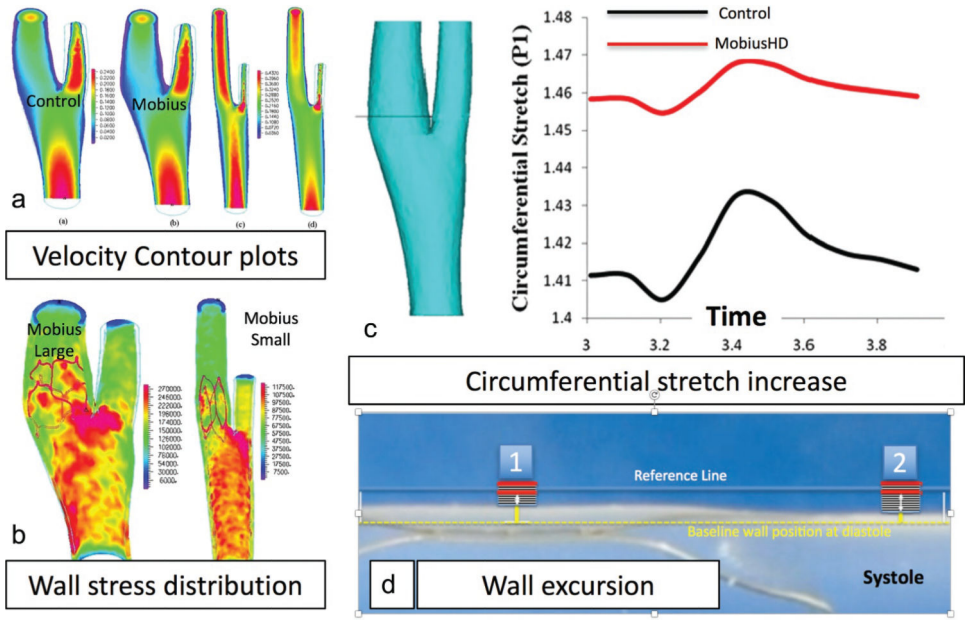

Figure 2.

Results of fluid-structure interaction (FSI) simulation analysis with contact surface between the device and the arterial wall findings are noted in A through C. Figure D shows the increase in systolic wall excursion within the windows of an implanted device (1) versus untreated segment utilizing a synthetic artery model (2).

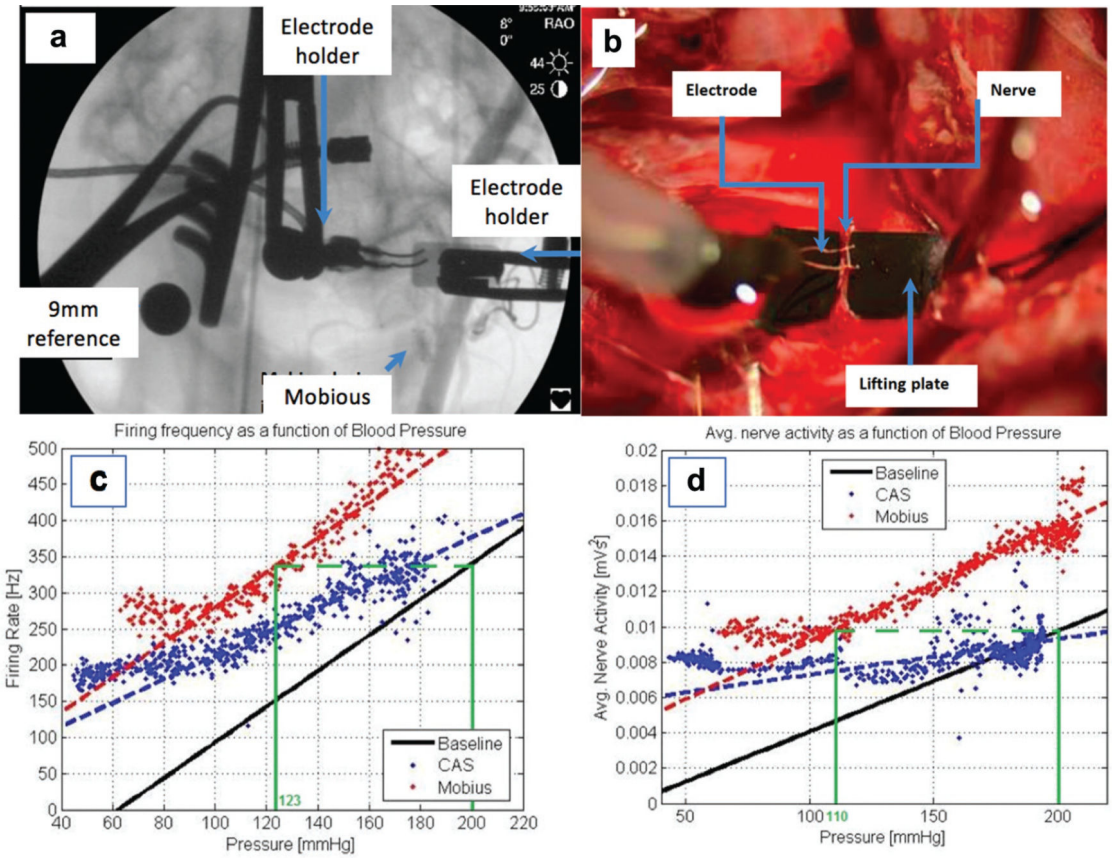

Figure 3.

A canine model was used to assess carotid sinus nerve (CSN) and firing patterns with the Mobius EVBA device were compared to responses after carotid artery stent (CAS) as the control. Figure A shows a fluoroscopic image of the experiment set-up and Figure B shows the electrodes attached to the CSN. Graphs C & D summerize the results. CSN firing activity is linear to systolic BP between 110 and 200 mmHg, both in firing frequency (Figure 3c, black line) and integrated activity (Figure 3d, black line). The red line illustrates the response after Mobius implant compared to the blue line which represents the carotid stent control.

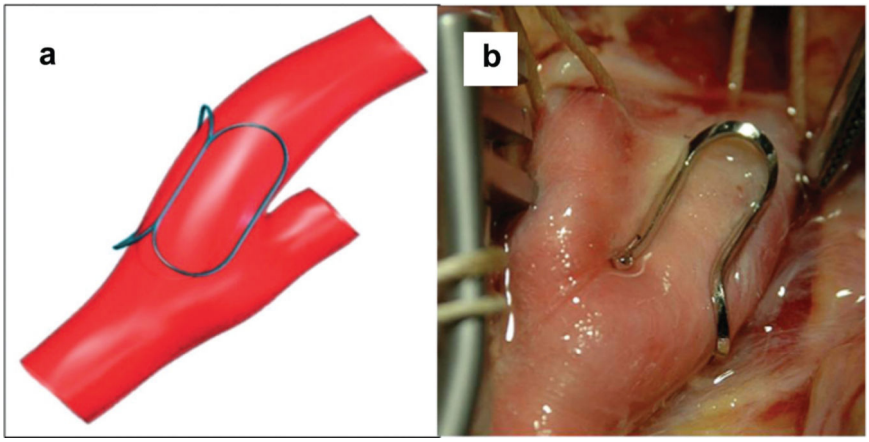

Figure 4.
The illustration on the left (A) shows the outer clip design and B pictured the original external Mobius clip following placement.

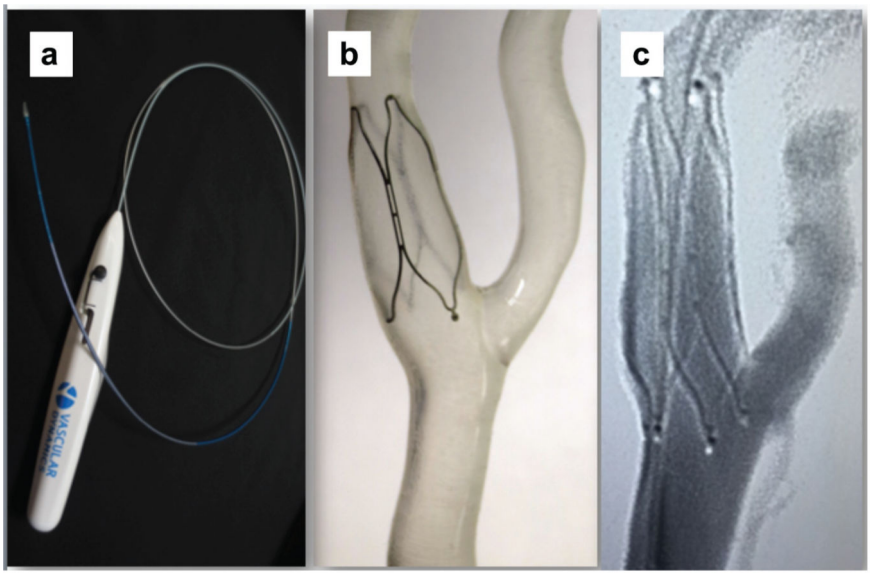

Figure 5.

A: the MobiusHD monorail delivery device. B: A mobiusHD device implanted in a synthetic carotid vessel that was built via 3-D printed molds from the patient's own CT angiogram. C: carotid angiogram after the procedure in the patient modeled in B.

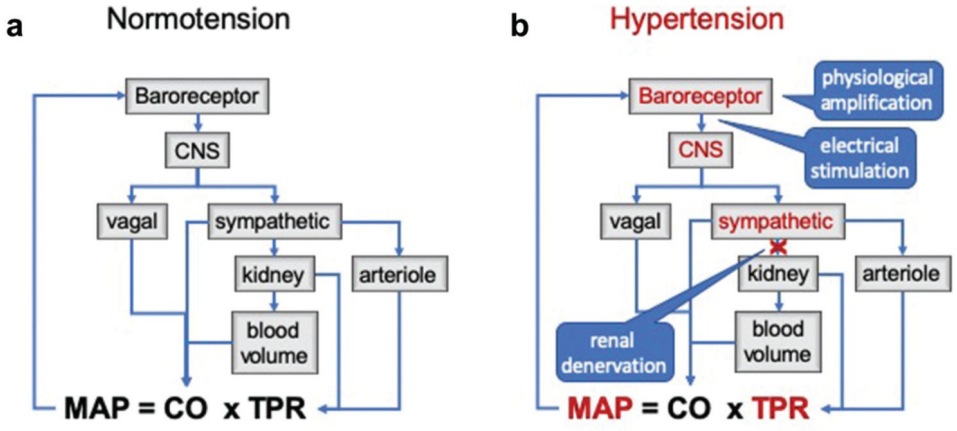

Figure 6.

Baroreceptor reflex control of blood pressure and anti-hypertensive treatment sites. A. Baroreceptor afferents send blood pressure information to the central nervous system (CNS) to regulate the sympathetic and vagal outflow to change cardiac output (CO) and total peripheral resistance (TPR). B. In hypertension, elevated blood pressure is associated with baroreceptor and central resetting to higher blood pressure, resulting in sympathetic overdrive and increased TPR with unchanged cardiac output. The three non-pharmacological anti-hypertensive approaches and their treatment sites are illustrated.

Table 1.

The combined 6-month outcomes for the CALM-FIM US and EU studies.

The “Baseline” column illustrates adjusted mean values for each outcome variable and subsequent columns show percent change over time. CI = confidence interval and “number of drugs” is the mean number of hypertension drugs patients are receiving (Drugs that included combined classes of medications were included separately). The “defined daily dose” is a statistical measure of drug consumption as defined by the World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology. Note that the change in SBP on 24-h BP monitor was significantly lower are 3 months (P < >001) and this difference was maintained at 6 months.

	Baseline		3 months		6 months	
Outcome Variable	***adjusted mean***	***95% CI***	***mean change***	***95% CI***	***mean change***	***95% CI***
Office BP (mmHg) Systolic	181	(173 – 188)	−24	(−31 – –16)	−25	(−33 – –17)
Office BP (mmHg) Diastolic	107	(102 – 111)	−11	(−15 – –7)	−12	(−17 – –8)
24-h ambulatory BP Systolic	166	(161 – 171)	−15	(−20 – –10)	−20	(−25 – –15)
24-h ambulatory BP Diastolic	98	(94 – 102)	−8	(−12 – –5)	−11	(−14 – –8)
Daytime ambulatory BP Systolic	168	(163 – 173)	−15	(−20 – –9)	−20	(−25 – –14)
Daytime ambultory BP Diastolic	100	(96 – 104)	−8	(−11 – –5)	−11	(−14 – –8)
Night-time ambulatory BP Systolic	157	(152 – 163)	−17	(−23 – –11)	−20	(−26 – –14)
Night-time ambulatory BP Diastolic	92	(88 – 96)	−12	(−15 – –8)	−12	(−16 – –9)
Office heart rate (bpm)	74	(70 – 78)	−2	(−5 – 1)	−1	(−4 – 3)
Daily defined dose	6.7	(5.3 – 8.2)	−1.3	(−2.2 – –0.4)	−1.1	(−2.3 – 0.0)
Number of drugs	4.2	(3.6 – 4.8)	−0.5	(−0.9 – –0.3)	−0.5	(−0.9 – –0.1)