Management of Uncontrollable Hypertension With a Carotid Sinus Stimulation Device

Markus G. Mohaupt, Jürg Schmidli, Friedrich C. Luft

Hypertensive crisis is a serious condition that results in target-organ damage, such as stroke, heart attack, or renal failure, if left untreated. Causes of acute increases in blood pressure in patients with primary essential hypertension include medication noncompliance and poorly controlled chronic hypertension. Treatment of a hypertensive crisis should be tailored to each individual based on the extent of target-organ injury and comorbid conditions. Prompt and rapid reduction of blood pressure under continuous surveillance is essential. We encountered a patient with target-organ damage and poor response to accepted antihypertensive regimens. Many terms are used to describe this degree of damage: severe, resistant, uncontrollable, or refractory hypertension; the term “uncontrollable” will be used here. After an 8-drug regimen was not successful, we elected a radical, controversial, but novel therapy. Only long-term clinical trials, perhaps above-and-beyond the trial in which we currently participate, will be necessary to answer the hypothesis that a device-based treatment can triumph over tablets alone.

The Patient

A 58-year-old woman with known primary hypertension for 40 years was referred to our clinic because of difficult-to-control “resistant or uncontrollable” hypertension. She did not have diabetes or known renal disease. However, she did have modest proteinuria at ≈500 mg/d. Her left ventricle wall thickness was moderately enlarged by echocardiography. Five or more different concomitantly prescribed medications failed to result in adequate blood pressure control. She had been diagnosed earlier with accelerated (malignant) hypertension on the basis of severe headaches, retinal hemorrhages, and macular edema. Secondary causes of hypertension were sought but not identified. Her medication consisted of furosemide, minoxidil, atenolol, metolazone irbesartan, amiloride, and glyceryl trinitrate. Amlodipine was added; however, no burst-like or further complex configurations were activated. Blood pressure progressively decreased with increasing stimulation. Systolic blood pressure fell more than diastolic blood pressure, whereas heart rate decreased from 125 to 100 bpm. To verify that the device activation was causal for the blood pressure responses, the stimulation was intermittently interrupted, which resulted in a prompt increase in blood pressure to 200/160 mm Hg. The device was then restarted, and blood pressure again decreased. During further “on-off” testing, the average decrease in systolic blood pressure was 19±7 mm Hg, and diastolic blood pressure decreased by 14±7 mm Hg. Complete control of blood pressure was achieved only with activation of the device and the entire palette of blood pressure medications.
long-term regulation of arterial pressure, and it is impossible
peripheral resistance, per se, play essentially no role in the
Guytonians reveals 2 startling conclusions: changes in total
"However, the nervous mechanisms can affect the long-term
"Nevertheless, the authors go on to state,
As an aside, the transistor had not
potential use of the technique. However, technical difficulties made
approach unattractive. For instance, the transistor had not
tendency for water and salt retention. In his Cannon
DiBona discussed the important role of the renal sympa-
their presentation. They pointed out the importance of ner-
Guyton et al returned to neurogenic hypertension later in
Lohmeier et al chronically implanted electrodes around
both carotid sinuses and used the same device reported here
to activate the carotid baroreflex in conscious dogs. Control
values for mean blood pressure and heart rate were 93 mm Hg
diastolic, and 13 mm Hg mean blood pressure, respectively, at the 3-month inspection. The resting heart rate had decreased by 13 bpm at that time.

Discussion
Interestingly, attempts to lower blood pressure by means of
carotid sinus afferent stimulation is not new. A rich literature
therapeutic modulation of the carotid baroreflex in the treat-
from the 1960s and 1970s reflects the investigation into
their presentation. They pointed out the importance of ner-
more insight into
Guyton et al. They emphasized that 3 main factors are extremely
important in blood pressure regulation, namely: (1) control of
by autonomic reflexes, (2) control of arterial pressure
by changes in body fluid volumes and electrolytes, and
level without either altering the function of the kidneys in
some way to change their output of water and electrolytes or
changing the intake of water and electrolytes. As an aside, the
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stimuli to the kidney that can cause the necessary
tendency for water and salt retention. In his Cannon
DiBona discussed the important role of the renal sympa-
thetic nerves to regulate various aspects of overall renal
function and blood pressure regulation. DiBona described
the renal nerves as "self-regulatory agencies, which operate to
preserve the constancy of the fluid matrix." More insight into
devices and blood pressure regulation can be gained by
examining the results of animal investigations.
Lohmeier et al chronically implanted electrodes around
both carotid sinuses and used the same device reported here
to activate the carotid baroreflex in conscious dogs. Control
values for mean blood pressure and heart rate were 93 mm Hg
and 64 bpm, respectively. After control measurements, the
carotid baroreflex was activated bilaterally for 7 days at a
level that produced a prompt and substantial reduction in
mean blood pressure to 75 mg for 7 days. When one considers
the fact that drugs do not generally reduce blood pressure in
nonhypertensive animals or humans, the results are impres-
sive indeed. During prolonged baroreflex activation, heart
rate decreased in parallel with blood pressure. Lohmeier et
al also reported ≈35% reduction in plasma norepinephrine
concentrations. After baroreflex activation was discontinued,
hemodynamic measures and plasma levels of norepinephrine
returned to control levels.

When the patient was noncompliant to the medication regi-
men, blood pressure increased in spite of the device. How-
ever, with the device and continued medications, the patient’s
24-hour blood pressure control was improved by 22 mm Hg
systolic, 9 mm Hg diastolic, and 13 mm Hg mean blood
pressure, respectively, at the 3-month inspection. The resting
heart rate had decreased by 13 bpm at that time.

Figure 1. A, Electrode system that is implanted on both carotid
sinuses is shown. The adventia is stimulated directly. Pacing
electrodes and suture pads of the electrodes are prepared to
accommodate placement close to the carotid bifurcation. B,
Chest roentgenogram after implantation showing the electrodes
in place and the stimulator that is somewhat larger than a con-
ventional pacemaker.

Figure 2. Dinamap blood pressure measurements of the patient
during a hypertensive crisis are shown. Systolic blood pressure
decreased ≈45 mm Hg, and diastolic blood pressure decreased
50 mm Hg. Thereafter, the device was shut off, and blood pres-
sure increased over 4 hours. Continuation of the stimulus
resulted in blood pressure decreases to the previous stimulation
values. Voltage is indicated on the x axis. The stimulation was
bilateral with on a continuous square-wave pattern at a fre-
cency of 100 Hz and a pulse width of 480 μs.

to change the arterial pressure chronically from its status quo
level without either altering the function of the kidneys in
some way to change their output of water and electrolytes or
changing the intake of water and electrolytes. As an aside, the
current introduction and “buzz word” of systems biology
would have bemused Guyton; he surely would have studied
this report carefully as well.

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returned to control levels.
Lohmeier et al\textsuperscript{14} next studied a model involving chronic angiotensin (Ang) II infusion in the dog. The animals were exposed to the same carotid stimulation protocol that decreased blood pressure by \(\approx 20\) mm Hg for a week without Ang II. However, with Ang II at an infusion rate (5 ng/kg per minute) and a mean blood pressure of 129 mm Hg, the carotid stimulation protocol decreased blood pressure by only \(\approx 5\) mm Hg. Thus, long-term baroreflex-mediated reductions in arterial blood pressure are markedly attenuated but not totally eliminated by chronic Ang II infusions. Conceivably, the actions of Ang II could have been central, because the peptide could have crossed the blood-brain barrier and influenced relevant brain regions.\textsuperscript{15} The clinical implications of these data are uncertain and will have to be tested.

Lohmeier et al\textsuperscript{16} next investigated the effects of renal innervation. The teachings of Guyton et al\textsuperscript{11} and the detailed studies of DiBona\textsuperscript{12} would make this notion an obvious hypothesis. Thus, 6 dogs underwent bilateral carotid baroreflex electrical activation for 7 days before and after bilateral renal denervation. Before renal denervation, control values for mean blood pressure and plasma norepinephrine concentration were 95 mm Hg and 96 pg/mL, respectively. During day 1 of carotid sinus stimulation, mean blood pressure decreased 13 mm Hg, and there was modest sodium retention. Daily sodium balance was subsequently restored, but reductions in mean blood pressure were sustained throughout the 7 days of baroreflex activation. Activation of the baroreflex was associated with decreases in plasma norepinephrine concentration and plasma renin activity. All of the values returned to control levels during a 7-day recovery period. Two weeks after renal denervation, control values for mean blood pressure, plasma norepinephrine concentration, plasma renin activity, and sodium excretion were similar to those measured when the renal nerves were intact. Moreover, after renal denervation, all of the responses to activation of the baroreflex were not different than those observed before renal denervation. Astonishingly, the renal nerves were not an obligate requirement for achieving long-term reductions in arterial pressure during prolonged activation of the baroreflex. Nonetheless, sympathetic innervation involves not only the kidneys but also all areas of the body. Conceivably, reduction in sympathetic tone to nonrenal areas was more important than most nephrologists would care to admit. Because circulating norepinephrine is a composite of total body release, clearance, and metabolism, its reduction is a further clue as to the significance of reduced sympathetic nerve activity to nonrenal areas. “Smart money” was lost on this one! The clinical implications are, at the moment, not interpretable, but will require novel studies along “translational” lines in animals and humans.

Lohmeier et al\textsuperscript{17} have also studied a dog model of obesity-related hypertension. After 4 weeks of a high-fat diet, the dogs gained weight from 25 to 39 kg. Their mean blood pressure increased from 97 to 110 mm Hg; their heart rates increased from 67 to 91 bpm and plasma norepinephrine concentration from 141 to 280 pg/mL. Plasma glucose and insulin concentrations were elevated, but increases in plasma renin activity during the initial weeks of the high-fat diet were not sustained. During week 5, baroreflex activation resulted in sustained reductions in mean blood pressure, heart rate, and plasma norepinephrine concentration; at the end of week 5, these values were 87 mm Hg, 77 bpm and 166 pg/mL, respectively. These suppressed values returned to week-4 levels during a 7-day recovery period after baroreflex activation. There were no changes in plasma glucose or insulin concentrations or plasma renin activity during prolonged carotid sinus stimulation. The findings indicate that baroreflex activation can chronically suppress the sympathoexcitation associated with obesity and abolish the attendant hypertension while having no effect on hyperinsulinemia or hyperglycemia.

These careful animal studies allow several important conclusions. Carotid sinus stimulation for a week lowers blood pressure reproducibly whereas decreasing norepinephrine levels. When the stimulation is discontinued, the basal state is reestablished. Ang II, at least when infused chronically, interferes with baroreflex activation-mediated blood pressure reduction. The renal nerves are not the prime mediators of the long-term effects of baroreflex activation, whereas circulating norepinephrine might be. A model of obesity-induced hypertension in the dog is amenable to baroreflex activation. Again, reduction in circulating norepinephrine levels is a prominent feature in this model.

The carotid sinus stimulator was first investigated in a proof-of-concept study.\textsuperscript{18} The Device-Based Therapy of Hypertension Trial was then initiated as a multicenter clinical trial of electrical carotid sinus stimulation in patients with uncontrollable or poorly controlled hypertension.\textsuperscript{19} In our department, these patients are invariably minoxidil treatment failures. In addition, although carefully considered as a prerequisite of study inclusion, patient compliance is an ongoing concern in uncontrollable hypertension. The objective means to improve therapy adherence, as has been demonstrated for electronic drug monitors.\textsuperscript{20} Device-based blood pressure control could provide an advantage, because device programming is independent of patient behavior. The device does not forget.

There are numerous unanswered questions that this study and subsequent investigations must answer. Does this device effectively lower blood pressure in humans long term? If so, by what mechanism does the baroreflex activation work? We could imagine that sympathetic tone is diminished. However, because renal nerve activity was apparently not a prerequisite, nerve traffic to the kidney may not be the only mechanism. Renal denervation reduced renal nerve traffic to 0 in the study by Lohmeier et al.\textsuperscript{16} For this reason, muscle sympathetic nerve activity should and can be readily measured in humans. The notion underscores the possible importance of nonrenal sympathetically regulated areas. We plan such measurements in device-treated patients. However, in patients with autonomic failure and with autosomal-dominant hypertension with brachydactyly, muscle sympathetic nerve activity was actually reduced, although baroreflex blood pressure buffering was almost absent.\textsuperscript{21} In any event, some answers will be forthcoming to a variety of fascinating clinical questions regarding the baroreflex. Perhaps the pioneers in device-related antihypertensive strategies will be vindicated at long last.\textsuperscript{2–9}
Perspectives
Finally, what does device-related medicine mean for most of our patients? The data regarding Life After the Multicenter Automatic Defibrillator Implantation Trial suggest, at least to the senior author, that the chances of exiting this life without a “lump on the chest” are slim. The cost-effectiveness of internal cardiac defibrillators appears to be given if we compare the quality-adjusted life years with the disability-adjusted life years.22 We are possibly being too restrictive in our thinking about carotid sinus stimulators. Persons with severe vascular injury and target-organ damage represent the cohort that we would like to protect from such an outcome in the first place. Conceivably, device-related blood pressure treatment could be introduced much earlier in the treatment chain. Failure of nocturnal “dipping” could be an example of an early indication.

Disclosures
M.G.M., J.S., and F.C.L. participate in the Device-Based Therapy of Hypertension Trial, which manufactures this device. The manufacturer had no input into this presentation and did not provide sanction or approval. F.C.L. is an advisor to Novartis, Boehringer-Ingelheim, and Cadbury, all of whom have nothing to do with this project.

References
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