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 and poor response to accepted antihypertensive 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 approximately 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, an outpatient visit disclosed a blood pressure of 240/110 mm Hg (these and subsequent values are in the presented supine position). The drug doses were commensurate with the maximum-recommended doses given in the package inserts. Therefore, the patient was offered participation in the Device-Based Therapy of Hypertension Trial. This multicenter study is currently being conducted at 9 clinical centers in Switzerland, the Netherlands, Germany, Poland, and Latvia.

After written, informed consent was obtained following due approval from the ethics committee (internal review board), a device for stimulation of both carotid sinuses simultaneously was operatively placed in the patient under general anesthesia. Briefly, both carotid sinuses were surgically exposed and electrodes (Figure 1A) were placed around the carotid adventitial surface bilaterally. The electrode placement was tested in terms of adequate blood pressure and heart rate reductions after stimulation. The leads were subcutaneously tunneled and connected to the implantable stimulation device that was then placed in a subclavian subcutaneous position on the anterior chest wall as shown in the roentgenogram (Figure 1B). The patient recovered uneventfully and left the hospital.

According to the protocol, the device was not to be activated until 1 month postoperatively. One week after discharge, the patient presented with headache and a supine blood pressure of 260/160 mm Hg. She was admitted to the hospital, and the ethics committee was consulted to request premature activation of the device. After due approval, the blood pressure was monitored semiautomatically (Dynamap), and electrical baroreflex activation was initiated on both carotid sinuses simultaneously with incremental voltages as indicated (Figure 2). The stimulation was constantly kept on a continuous square-wave pattern at a frequency of 100 Hz and a pulse width of 480 μs; 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.

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peripheral resistance, per se, play essentially no role in the short-term regulation of arterial pressure. Nevertheless, the authors go on to state, "However, the nervous mechanisms can affect the long-term regulation of arterial pressure by autonomic reflexes, (2) control of arterial pressure by therapeutic modulation of the carotid baroreflex in the treatment of refractory hypertension and angina pectoris. These early reports were enthusiastic and clearly showed the potential of the technique. However, technical difficulties made the approach unattractive. For instance, the transistor had not even been introduced, printed circuits were rudimentary, chip technology was inconceivable, the electrode technology of the time was unreliable, and battery capacity was insufficient. These technical problems have been overcome, and the surgical implantation technique is now fully established. Those of us who grew up with systems analysis in terms of blood pressure regulation recall the teachings of Guyton et al. They emphasized that 3 main factors are extremely important in blood pressure regulation, namely: (1) control of pressure by autonomic reflexes, (2) control of arterial pressure by changes in body fluid volumes and electrolytes, and (3) control of arterial pressure by the renin-angiotensin-aldosterone mechanism. Guyton et al stated that, "The autonomic mechanisms seem to play their most significant role in short-term regulation of arterial pressure from second-to-second, minute-to-minute, and hour-to-hour, while other factors seem to play the primary role in long-term regulation of arterial pressure." Nevertheless, the authors go on to state, "However, the nervous mechanisms can affect the long-term also, as will be pointed out." The systems analysis of the Guytonians reveals 2 startling conclusions: changes in total peripheral resistance, per se, play essentially no role in the long-term regulation of arterial pressure, and it is impossible 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.

Guyton et al returned to neurogenic hypertension later in their presentation. They pointed out the importance of nervous stimuli to the kidney that can cause the necessary tendency for water and salt retention. In his Cannon lecture, DiBona discussed the important role of the renal sympathetic 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 impressive indeed. During prolonged baroreflex activation, heart rate decreased in parallel with blood pressure. Lohmeier et al also reported a mean blood pressure decreases to the previous stimulation level after baroreflex activation was discontinued, and blood pressure increased over 4 hours. Continuation of the stimulus resulted in blood pressure to decrease to the previous stimulation values. Voltage is indicated on the x axis. The stimulation was bilateral with a continuous square-wave pattern at a frequency of 100 Hz and a pulse width of 480 μs.

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 conventional pacemaker.

Discussion

Interestingly, attempts to lower blood pressure by means of carotid sinus afferent stimulation is not new. A rich literature from the 1960s and 1970s reflects the investigation into therapeutic modulation of the carotid baroreflex in the treatment of refractory hypertension and angina pectoris. These technical problems have been overcome, and the surgical implantation technique is now fully established. Those of us who grew up with systems analysis in terms of blood pressure regulation recall the teachings of Guyton et al. They emphasized that 3 main factors are extremely important in blood pressure regulation, namely: (1) control of pressure by autonomic reflexes, (2) control of arterial pressure by changes in body fluid volumes and electrolytes, and (3) control of arterial pressure by the renin-angiotensin-aldosterone mechanism. Guyton et al stated that, "The autonomic mechanisms seem to play their most significant role in short-term regulation of arterial pressure from second-to-second, minute-to-minute, and hour-to-hour, while other factors seem to play the primary role in long-term regulation of arterial pressure." Nevertheless, the authors go on to state, "However, the nervous mechanisms can affect the long-term also, as will be pointed out." The systems analysis of the Guytonians reveals 2 startling conclusions: changes in total peripheral resistance, per se, play essentially no role in the long-term regulation of arterial pressure, and it is impossible 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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Lohmeier et al. 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. The clinical implications of these data are uncertain and will have to be tested.

Lohmeier et al. next investigated the effects of renal innervation. The teachings of Guyton et al. and the detailed studies of DiBona 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. 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 sympathoexcitatory interactions 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. 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. 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. 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. 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. 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.
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 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.

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