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[54] APPARATUS FOR INFLUENCING THE SYSTEMIC BLOOD PRESSURE IN A PATIENT BY CAROTID SINUS NERVE STIMULATION

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Feb. 4, 1969 Sweden..................................2528/69

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[51] **Int. Cl.** **A61n 1/36**
[58] **Field of Search** ....128/418, 419 R, 421, 422, 423, 128/2.05 A, 2.05 P, 2.05 E, 2.05 M, 2.05 B, 2.05 R, 2.06 A, 2.06 R, 2.1 B, 2.1 R

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[57] **ABSTRACT**

A system for reducing and controlling the blood pressure of a hypertensive patient has electrical pulse stimulation of the carotid-sinus nerves controlled by the arterial blood pressure of the patient in such a manner that the number of stimulation pulses within each heart cycle is determined by the arterial means blood pressure whereas the distribution of stimulation pulses over the heart cycle is a function of the arterial pulse wave shape with the pulse frequency being greater during the first portion of the heart cycle.

6 Claims, 6 Drawing Figures

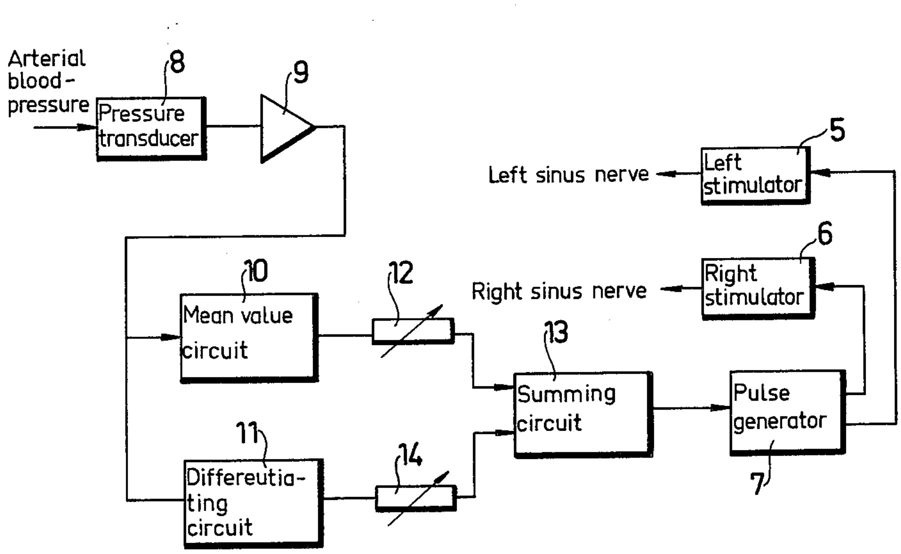


Fig.1

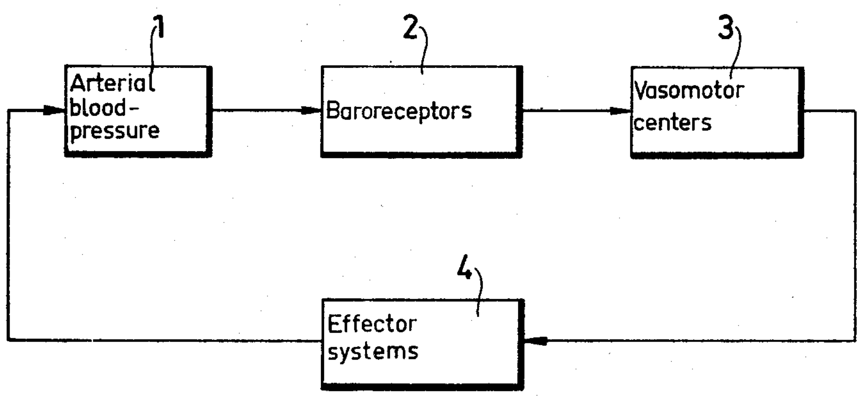

1
Arterial blood-pressure
2
Baroreceptors
3
Vasomotor centers
4
Effector systems

Fig.2

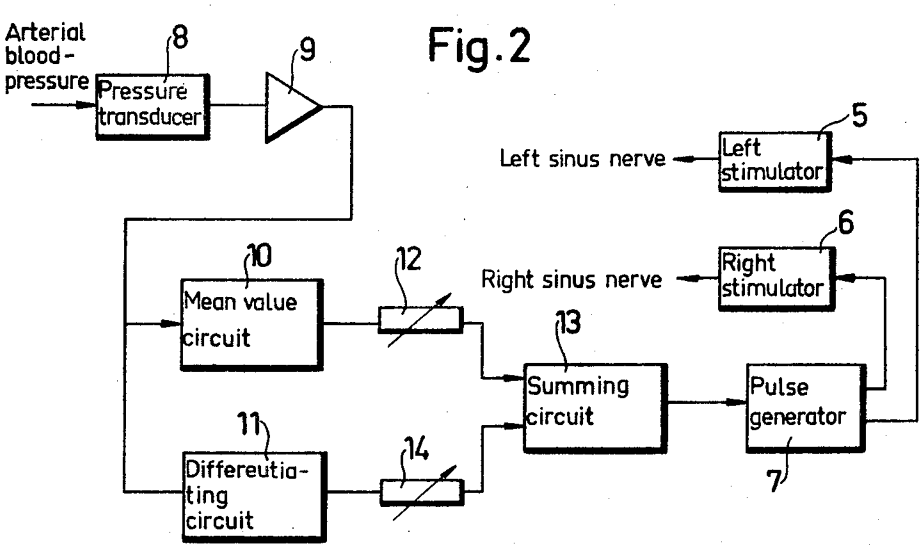

Arterial blood-pressure
8
Pressure transducer
9
5
Left sinus nerve
Left stimulator
6
Right sinus nerve
Right stimulator
10
Mean value circuit
12
13
Summing circuit
Pulse generator
11
Differeutiating circuit
14
7

Fig. 3

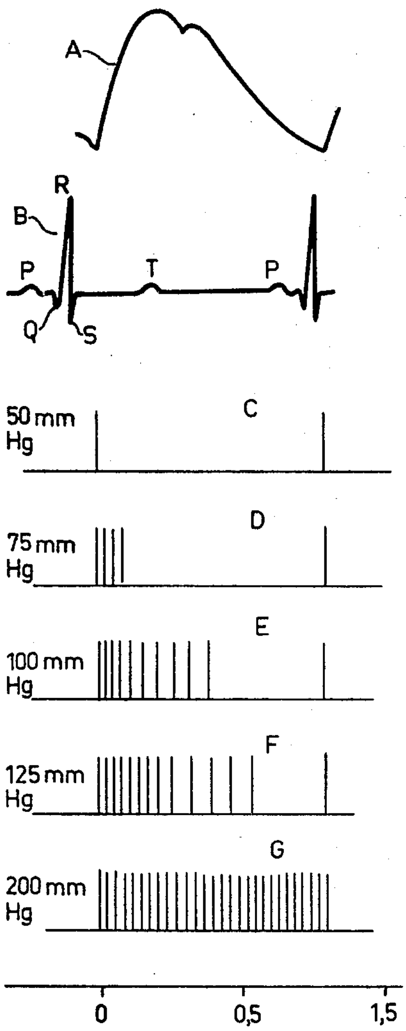


Fig. 4

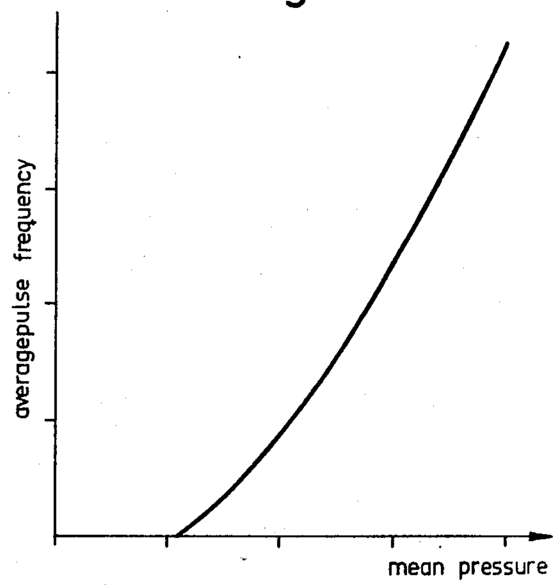


Fig. 5

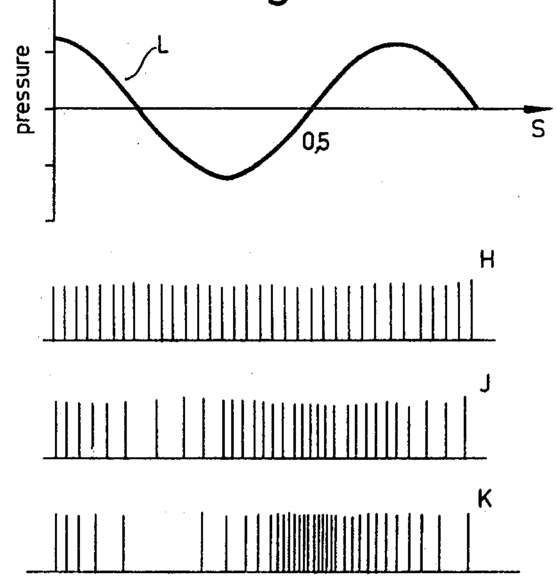
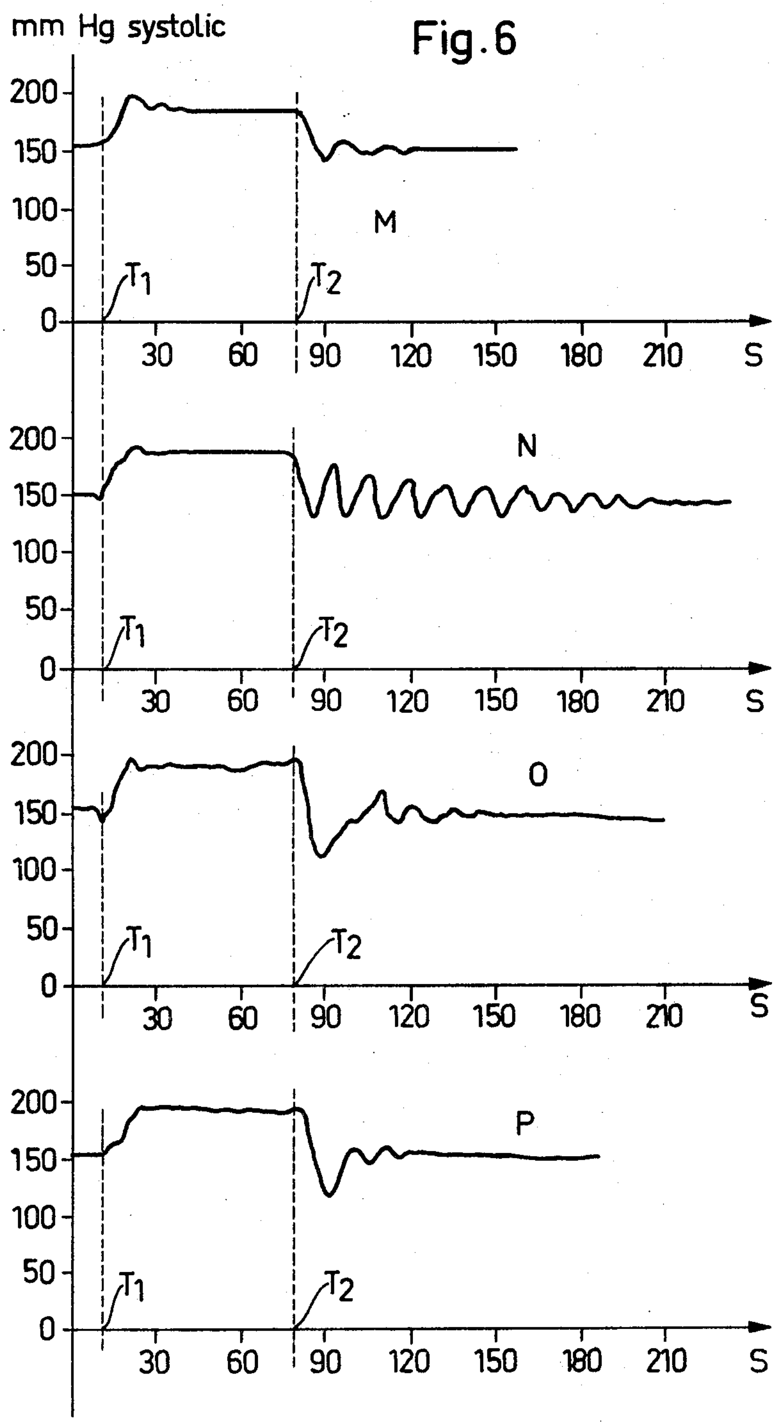


Fig. 6


mm Hg systolic
200
150
100
50
0
30
60
90
120
150
180
210
S
M
N
O
P
T_1
T_2

APPARATUS FOR INFLUENCING THE SYSTEMIC BLOOD PRESSURE IN A PATIENT BY CAROTID SINUS NERVE STIMULATION

The present invention is related to an apparatus for influencing the systemic blood pressure in human beings and more particularly for reducing and controlling the blood pressure in hypertensive patients.

The blood pressure regulatory system of higher mammals and man is preferably described and studied as a closed-loop control system. FIG. 1 in the enclosed drawing illustrates a lay-out of this control system. The arterial systemic blood pressure is sensed by baroreceptors 2 in the body, which can be regarded as pressure-signal-transducers to convey information on the actual arterial blood pressure through afferent nerve paths to the vasomotor center 3. Man has several such baroreceptor areas, the most important ones being located at the aorta arch and in the two carotid-sinus regions. As components in a closed-loop control system these baroreceptors may be regarded as parameter sensors conveying information to the vasomotor center of the actual arterial blood pressure. With reference to a closed-loop control system, the vasomotor center can be regarded as a comparator and regulator which compares the information about the actual blood pressure received from the baroreceptors with information about the desired blood pressure received from other cardio-vascular centers and other receptors in the body and which in response to this comparison influences those effector systems 4 in the body directly determining the systemic arterial blood pressure. These effectors are primarily the heart, the volume rate of which is an important factor determining the systemic blood pressure, and the peripheral-vascular system, in particular the arterial system but also the venous system, the contraction and dilation of which affect the blood pressure. For the treatment of hypertensive patients one uses at the present in most cases various types of drugs which either affect the effectors, primarily the peripheral-vascular system for reduction of the blood volume, or have an inhibiting effect upon the nerve activity from the vasomotor center to the effectors. These drugs have, however, the very serious disadvantage that they impair considerably the capacity of the natural biological blood pressure regulatory system for producing the natural and desired adjustment of the blood pressure to the activity of the patient and other factors, which would normally cause changes in the blood pressure.

Therefore one has in the last years become interested in the possibility of influencing the blood pressure through the nerve activity on the afferent nerve paths from the baroreceptors to the vasomotor center by artificial stimulation of these nerves by means of electric pulses so that the natural nerve activity is supplemented or replaced with an artificially increased nerve activity, in response to which the vasomotor center is caused to reduce the blood pressure. In this way it is possible to obtain a reduced pressure level while maintaining the biological blood pressure regulatory system unaffected so that this can provide a natural control of the blood pressure at the reduced level. This method should of course be particularly advantageous in those cases where the hypertension is caused by an abnormally low sensitivity of the baroreceptors so that for a given arterial blood pressure the baroreceptors produce a substantially lower nerve activity than would be the case in a normotensive patient. Nerves suitable for such an electrical stimulation are primarily the sinus nerves from the baroreceptors in the two carotid-sinus areas, as these nerves are comparatively easily accessible. Experiments carried out with electrical stimulation of the sinus nerves or the carotid-sinus areas with electric pulse series have also verified that such a stimulation has a certain reducing effect on the blood pressure. However, the practical results obtained have been comparatively limited, which seems primarily to have been due to the fact that the artificial electrical stimulation has not been sufficiently similar to the natural nerve activity from the baroreceptors, wherefore the vasomotor center has not responded to the artificially stimulated nerve activity in the intended manner.

The object of the present invention is therefore to provide an improved apparatus for influencing the blood pressure in a patient, in particular for reducing the blood pressure of a hypertensive patient, by electrical stimulation of afferent nerve paths from the baroreceptors of the patient, in particular the sinus nerves from the carotid-sinus areas. The device according to the invention comprises as already suggested in the prior art an electrode or stimulator assembly which can be applied on or close to an afferent nerve for stimulation thereof with short electric pulses and a pulse generator connected to said stimulator assembly for supplying stimulating pulses thereto. Preferably one uses two electrode or stimulator assemblies to be applied to each one of the sinus nerves of the patients in which case the pulse generator is provided with two pulse outputs connected to said two stimulator assemblies respectively. The device according to the invention is characterized in that it comprises a signal generator for producing a control signal for the pulse generator dependent on the heart activity of the patient and that the pulse generator produces in response to said control signal during each heart cycle a pulse series of limited length, which starts at the beginning of the heart cycle and in which the majority of pulses appear during the first portion of the heart cycle.

The device according to the invention satisfies two essential conditions for a true-to-nature stimulation of the afferent nerve activity on the sinus nerves, namely on the one hand that the stimulation is synchronized to the heart activity of the patient and consists of a limited pulse series during each heart cycle and on the other hand that this pulse series has the majority of its pulses concentrated to the first portion of the heart cycle.

In a more refined embodiment of the invention, the signal generator responsive to the heart activity of the patient may consist of a pressure transducer which is connected to an artery of the patient and produces an electric output signal substantially representing the instantaneous arterial blood pressure of the patient. Such a pressure transducer may for instance consist of a strain gauge device coupled to the artery through a catheter inserted therein. It is also possible to mount the pressure transducer externally on the artery so as to be affected by the stresses in the wall of the vessel, which stresses are dependent on the blood pressure in the vessel. It is of course also possible to use other types of pressure sensitive electrical transducers, as for instance piezoelectric crystals. The electric output signal which is obtained from the pressure transducer and which varies with the instantaneous arterial blood pressure of the patient is supplied to signal transforming circuits which produce a first signal representative of the arterial mean blood pressure of the patient and a second signal representative of the derivative or rate of change of the arterial blood pressure of the patient and which sum said first and second signals and produces a signal corresponding to said sum, said last-mentioned signal being connected to the pulse generator as a control signal therefor and the pulse generator being adapted to produce pulses having a pulse frequency corresponding to the amplitude of the control signal supplied to the generator. Thus, also in this embodiment of the invention a stimulation is obtained which is synchronized with the heart activity of the patient in that a limited pulse series is produced during each arterial pulse cycle so as to start at the beginning of the pulse cycle. However, each such pulse series will contain a number of pulses determined by the prevailing arterial means blood pressure and display a pulse frequency modulation determined by the shape of the arterial pulse wave during the current pulse cycle. As the arterial pulse wave has a large positive derivative of comparatively short duration at the beginning of the pulse cycle and thereafter during the remaining, substantially longer portion of the pulse cycle a smaller negative derivative, each pulse series will display a pulse frequency which after an initial and rapid increase in pulse frequency decreases continuously from its maximum value at the beginning of the pulse series. With such a design of the device according to the invention the artificially stimulated nerve activity will duplicate the natural biological nerve activity from the baroreceptors with a much higher fidelity. As, furthermore, the artificial stimulation of the nerve activity is dependent on the mean blood pressure of the patient as well as the derivative of the blood pressure, that is the shape of the arterial pulse wave, the device according to the invention will form an integral part of the natural biological blood pressure regulator system. Related to this regulator system the device according to the invention can be regarded as a parameter sensor which supplements the natural biological parameter sensors in the blood pressure regulatory system formed by the baroreceptors of the patient.

In the following the invention will be further described with reference to the accompanying drawing, in which

FIG. 1 is the schematic and very simplified block diagram described in the foregoing for the natural biological blood pressure regulator system;

FIG. 2 shows by way of example the block diagram for an embodiment of a device according to the invention, in which the artificial stimulation of the nerve activity is dependent on the arterial mean blood pressure as well as the derivative of the arterial blood pressure;

FIG. 3 is a diagram schematically illustrating the natural afferent nerve activity from a baroreceptor during an arterial pulse cycle for different arterial mean blood pressures;

FIG. 4 is a diagram of the mean pulse frequency of the stimulating pulses as a function of the mean pressure for the device according to the invention illustrated in FIG. 2;

FIG. 5 is a diagram illustrating schematically the pulse series produced by the device according to the invention illustrated in FIG. 2 for a sinusoidally varying pressure and for different settings of the device; and

FIG. 6 shows a number of blood pressure curves illustrating the blood pressure regulation obtained in experiments on dogs with a device according to FIG. 2 as compared with the blood pressure regulation caused by the natural baroreceptors in the carotid-sinus areas.

In FIG. 3 curve A illustrates schematically the shape of the normal arterial pulse wave during an arterial pulse cycle, whereas curve B illustrates the corresponding ECG-signal. The diagrams C, D, E, F and G respectively illustrate the nature of the afferent nerve activity on the sinus nerve during the heart pulse cycle for different arterial mean blood pressures. As illustrated by these diagrams this nerve activity consists of pulse series. A characteristic property of this nerve activity is that it is synchronized with the arterial pulse cycle so that the nerve activity consists of a pulse series for each arterial pulse cycle starting at the beginning of the arterial pulse cycle and having its pulses primarily concentrated in the first portion of the arterial pulse cycle. The number of pulses in each pulse series, that is the mean pulse frequency of the pulse series, is dependent on the arterial mean blood pressure in such a manner that the number of pulses increases with increasing arterial mean blood pressure. There is a lower threshold level at about 40–50 mm. Hg. below which no nerve activity exists and an upper saturation level at about 200–250 mm. Hg. above which the nerve activity is "saturated" and each pulse series comprises a maximum number of pulses which is not additionally increased for increasing arterial means blood pressure. Another characteristic property of the afferent pressure responsive nerve activity is that each pulse series is modulated with respect to its pulse frequency, generally speaking in such a manner that the pulse frequency decreases continuously during the duration of the pulse series from a maximum frequency at the beginning of the pulse series.

In a device according to the invention for electrical stimulation of the afferent nerve activity for instance on the sinus nerve, in order to influence the blood pressure the aim must consequently be to compose this stimulation in such a manner that it copies or resembles as closely as possible the natural nerve activity illustrated in FIG. 3 and described above.

For this purpose the device according to the invention may in the most simple case comprise a pulse generator having a pulse output connected to a stimulator or electrode assembly applied on or close to a selected nerve or nerves and designed to produce in response to a starting signal a pulse series having a predetermined number of pulses and a predetermined pulse frequency. For the synchronization of the pulse generator and thus the nerve stimulation with the heart cycle of the patient one may preferably use an electrode located at or close to the heart of the patient for picking up an ECG-signal which is supplied to the pulse generator as a control signal therefor, in which case the pulse generator is designed to start a pulse series in response to the readily detectable R-wave in the ECG-signal at the beginning of each a heart cycle. By adjustment of the length, the pulse frequency and possibly also the pulse frequency modulation of the pulse series produced by the pulse generator to the natural biological regulatory response of the patient in question it is possible to achieve a desired reduction of the blood pressure level of the patient. However, it is appreciated that in such a simple device according to the invention the artificial stimulation of the nerve activity will not adapt itself automatically to the prevailing arterial mean blood pressure of the patient as the natural nerve activity does (FIG. 3) and neither will it be affected by any variations in the shape of the arterial pulse wave. Although such a simple device has produced good results in experiments that have been made, it is more advantageous to make also the artificial stimulation on the nerve activity dependent of the arterial mean blood pressure on the patient and also of the shape of the arterial pulse wave.

FIG. 2 illustrates the fundamental block diagram for such a more sophisticated device according to the invention. This device includes two identical electrode or stimulator assemblies **5** and **6** adapted to be applied on or close to the sinus nerves of the patient for electrical stimulation of the nerve activity therein. Each such stimulator or electrode assembly may for instance include two loop-shaped electrodes arranged to enclose the nerve at spaced positions. Also other types and locations of the stimulator assemblies may of course be used. The two stimulator assemblies **5** and **6** are connected to separate pulse outputs from a controlled pulse generator **7** of any suitable design, which on its two outputs produces pulses having a pulse frequency determined by a control signal, as for instance a direct voltage signal, applied to the control input of the pulse generator. Consequently the two stimulators **5** and **6** are supplied with identical pulse series from the pulse generator **7**. However, the one output of the pulse generator is provided with a delay circuit **15** so that the pulse series on this output is delayed relative to the pulse series on the other output by a delay time which is shorter than the shortest interval between two successive pulses in the pulse series. In this way cross-stimulation between the two stimulators **5** and **6**, that is between the left side and the right side of the patient, is prevented. The device includes also a pressure transducer **8** of suitable type, which can be connected or applied to an artery of the patient and which produces an electric output signal which is substantially proportional to the instantaneous arterial blood pressure of the patient. As mentioned in the foregoing, such a pressure sensitive signal transducer may consist of a strain gauge transducer which is connected to the artery through a catheter inserted into the artery or is mounted externally on the artery so as to be affected by the mechanical stresses in the wall of the artery.

The output signal from the pressure transducer **8**, representing the instantaneous arterial blood pressure, is through an amplifier **9** supplied to two signal transforming circuits **10** and **11**. The circuit **10** is designed to calculate on the basis of the input signal the arterial mean blood pressure and to produce an output signal proportional thereto. The calculation of the arterial mean blood pressure may be carried out in various manners. For instance the circuit **10** may consists of a mean value rectifying circuit having a suitable time constant. In a practical device according to the invention, however, the circuit **10** includes two peak detecting amplifiers which are connected to the signal from the pressure transducer **8** with opposite polarities so that the one amplifier produces an output signal representing the systolic blood pressure, whereas the other amplifier produces an output signal representing the diastolic blood pressure. These two output signals are supplied to an analog summing circuit which sums the two signals according to the equation

$$P_{mean} = P_{diastolic} + 1/\sqrt{2}\,(P_{systolic} - P_{diastolic})$$

This is an approximative expression for the arterial mean blood pressure P_{mean} based upon a substitution of a triangular curve for the arterial pulse wave. The output signal from the circuit **10**, proportional to the calculated arterial mean blood pressure, is connected through a variable circuit element **12**, as for instance a potentiometer, to the one input of a signal adding amplifier **13**. By means of the potentiometer **12** it is possible to vary the proportionality factor for the signal representing the mean blood pressure.

The second signal transforming circuit **11** is a differentiating circuit which produces an output signal having an amplitude proportional to the derivative or rate of change of the arterial blood pressure and a polarity corresponding to the sign of this derivative. The output signal from the differentiating circuit **11** is supplied through a variable circuit element **14**, for instance a potentiometer, to the second input of the signal adding amplifier **13**. By means of the potentiometer **14** it is consequently possible to vary the proportionality factor for the signal from the differentiating circuit **11** representating the derivative of the blood pressure. The signal adding amplifier **13** sums the two input signals and produces an output signal proportional to the sum. This output signal is connected to the pulse generator **7** as a control signal therefor. Consequently the pulse generator will generate pulses having a frequency proportional to the sum of the prevailing arterial mean blood pressure, as calculated by the circuit **10**, and the instantaneous derivative of the arterial blood pressure, as determined by the circuit **11**. However, the pulse generator **7** is designed to have a lower threshold level for the input signal below which threshold value no pulses are generated. This lower threshold level for the input signal corresponds preferably to a constant non-varying blood pressure of about 40–50 mm. Hg. Further the pulse generator has preferably an upper "saturation" frequency of for instance about **300** Hz., which is reached for an input signal corresponding to a constant non-varying blood pressure of for instance about 250–300 mm. Hg. It is appreciated that the pulse series generated by the pulse generator **7** will have a mean pulse frequency determined by the magnitude of the calculated arterial mean blood pressure and the setting of the potentiometer **12** and a pulse frequency modulation determined by the derivative of the arterial blood pressure, that is the shape of the arterial pulse wave, and the setting of the potentiometer **14**.

FIG. **4** is a diagram illustrating the relationship between the mean pulse frequency of the pulse series produced by the pulse generator **7** and the mean pressure sensed by the pressure transducer **8** for a pressure which varies sinusoidally about the mean pressure with the frequency 2 Hz. This relationship is substantially linear and substantially independent of the setting of the potentiometer **14**, that is of the magnitude of the component of the control signal for the pulse generator **7** corresponding to the derivative of the pressure. This is also what one would expect, as for a signal varying periodically about a constant value, the time integral of the positive derivative of the signal is always equal to the time integral of the negative derivative of the signal.

In FIG. **5** the diagrams H, J and K illustrate the pulse series produced by the pulse generator **7** for different settings of the potentiometer **14**, when the pressure transducer **8** is affected by a pressure which varies sinusoidally about a given mean pressure with the frequency 2 Hz. as illustrated by the curve L. The pulse series illustrated by the diagram H is obtained when the potentiometer **14** has such a setting that the signal supplied to the signal adding amplifier **13** from the differentiating circuit **11** is zero, that is when the pulse generator **7** is controlled only by the signal representing the mean pressure from the circuit **10**. As expected one obtains in this case a constant pulse frequency, the magnitude of which is determined by the mean pressure. The diagrams J and K respectively illustrate pulse series obtained when the potentiometer **14** has such a setting that a certain signal proportional to the derivative of the pressure is supplied from the circuit **11** to the adder amplifier **13**, this derivative representing signal component being larger in the case illustrated by the curve K than in the case illustrated by the diagram J. As can be seen these two pulse series contain substantially the same number of pulses during each period of the varying pressure (curve L), whereas the pulses are distributed differentially over the period dependent on the relative magnitude of the derivative representing signal component from the circuit **11**.

Experiments have been carried out on animals in order to compare on the one hand the blood pressure reducing and regulating effects that can be obtained by artificial stimulation of the nerve activity in the sinus nerves by means of a device according to the invention designed as illustrated in FIG. **2** as against the natural blood pressure regulating effect caused by the natural afferent nerve activity on the sinus nerves in response to the baroreceptors in the carotid-sinus areas. For these experiments dogs have been used, as the vascular system in dogs is very similar to that in man and as anesthetic techniques are developed for dogs which do not give cause to any disturbance in the blood pressure regularoty system.

The experiments were carried out in the following manner: The two carotid-sinus regions of the animal were dissected free. The common carotid artery on each side was provided with a device by means of which the artery could be clamped for a desired time interval and thereafter reopened. On each side of a catheter was inserted into the carotid-sinus and fixed by a ligature as close as possible to the bifurcation between the external and the internal carotid arteries. These two catheters were connected through polyethene catheters and a valve to a catheter inserted into the femoral vein. By means of the valve it was possible to open or close the communication between the two sinuses and the femoral vein. By clamping the two common carotid arteries and simultaneously opening the communication between the two sinuses and the femoral vein it was possible to produce such a low and pulsation-free blood pressure in the sinuses that the normal nerve activity from the baroreceptors in the two carotid-sinus areas was completely interrupted. Consequently, this corresponded to a complete disconnection of the natural baroreceptors from the natural biological blood pressure regulatory system of the experimental animal.

The sinus nerves from the carotid-sinus areas were also dissected free and on these nerves the two stimulators **5** and **6** of the device according to the invention (FIG. **2**) were applied near to the origin of the nerves in the sinuses. The pressure transducer **8** of the device according to the invention (FIG. **2**) was connected to a catheter inserted in the femoral artery. The output signal from the pressure transducer **8** was connected not only to the two signal transforming circuits **10** and **11** in the device according to the invention but also to a recorder for recording the arterial blood pressure of the animal during the experiment.

At the experiments the two common carotid arteries were clamped at the same time as the two sinuses were connected to the femoral vein through the catheters inserted in the sinuses and the valve device. This caused a pronounced rise in the arterial blood pressure of the experimental animal, which was exactly what could be expected, as the normal nerve activity from the baroreceptors in the two carotid-sinus areas was interrupted, as explained in the foregoing. This state was maintained until it was certain that a stable arterial blood pressure (at the higher level) had been obtained. Thereafter the two common carotid arteries were reopened instantaneously and at the same time the communication between the catheters inserted in the sinuses and the femoral vein respectively was interrupted. In this way a very rapid transient rise in the intrasinusal blood pressure was produced and thus a stepfunction activation of the baroreceptors in the carotid-sinus areas. The arterial blood pressure of the experimental animal returned then to its original value under the influence of the reappearing normal afferent nerve activity in the sinus nerves from the baroreceptors. This natural regulatory response of the natural biological blood pressure regulatory system under the influence of the operation of the natural baroreceptors was studied by means of the recording of the arterial blood pressure of the animal made by the recorder. The curve M in FIG. **6** illustrates the typical variation of the systolic pressure of an experimental animal during such an experiment. The experiments showed that the variations in the systolic pressure and the diastolic pressure respectively were so similar that it was only necessary to record one of them. In the experiment corresponding to curve M in FIG. **6** the common carotid arteries were clamped at the time T_1 and reopened at the time T_2. As can be seen, a well damped regulatory response is obtained on the momentary stepwise rise in the intrasinusal pressure and the systemic blood pressure is returned comparatively rapidly to a constant value equal to the value before the experiment, which shows also that the natural biological blood pressure regulatory system has not been permanently affected by the experiment.

The experiment described above was thereafter repeated but with the difference that at the time T_2 the common carotid arteries were not opened and neither was the communication between the catheters inserted in the sinuses and the femoral vein respectively interrupted. Consequently the natural baroreceptors in the two carotid-sinus areas remain inoperative. Instead at the time T_2 an artificial stimulation of the sinus nerves was started by means of the device according to the invention (FIG. **2**). The curves N, O and *P* in FIG. **6** illustrate typical regulatory responses in the systolic pressure of the experimental animal under the influence of such an electric stimulation of the sinus nerves for different settings of the potentiometer **14** in the device (FIG. **2**), that is for different magnitudes of the control signal component of the pulse generator dependent on the derivative of the blood pressure. At the experiment illustrated by curve N the potentiometer **14** had such a setting that no signal component from the circuit **11** dependent on the derivative of the blood pressure was supplied to the adder amplifier **13** and thus to the pulse generator **7**. Consequently, in this case the stimulation was carried out with a constant pulse frequency during the entire cardial cycle, the magnitude of this pulse frequency being determined by the arterial mean blood pressure of the animal. As can be seen this artificial stimulation of the sinus nerves caused the blood pressure to return to a level substantially equal to the value before the clamping of the carotid arteries. However, the blood pressure returned to its original value through very pronounced oscillations, remaining for a considerable time, and the regulatory response has consequently in this case a very low damping.

In the experiment illustrated by curve **0** the potentiometer **14** had such a setting that a certain but comparatively small signal component representing the derivative of the blood pressure was supplied to the pulse generator **7**. In this case a considerably more damped response was obtained, but still the amplitude and the duration of the oscillations were considerably larger than in the natural biological regulatory response illustrated by curve M.

In the experiment illustrated by curve *P* the potentiometer **14** had such a setting that a substantially larger signal component representative of the derivative of the blood pressure was supplied to the pulse generator than in the experiment illustrated by curve **0**. As can be seen, in this case a well damped regulatory response was obtained which was very similar to the natural biological regulatory response illustrated by curve M.

Consequently, the experiments show that it is essential that the artificial stimulation of the afferent nerve activity has a pulse frequency which is modulated in such a way, preferably in dependence of the derivative of the arterial blood pressure, that the majority of the stimulation pulses appear during the first portion of the hear cycle, if a regulatory response is to be achieved which is similar to the natural regulatory response caused by the natural nerve activity from the baroreceptors.

Between the different experiments which artificial stimulation of the nerve activity with a device according to the invention the natural regulatory response was checked repeatedly in that the clamping of the carotid arteries was removed as described above in connection with curve M in FIG. **6**. The purpose of this was to check that the artificial stimulation of the sinus nerves did not have any permanently remaining effect upon the natural blood pressure regulatory system. No such remaining changes could be found.

As it is known that the biological baroreceptors have different sensitivities for the positive and the negative derivative of the blood pressure respectively, experiments have also been made with a device according to the invention as shown in FIG. **2**, in which, however, the differentiating circuit **11** was so designed that it could be set to have unequally large amplifications for the positive derivative and the negative derivative respectively. Comparative experiments were made on the one hand with unequally large amplifications for the positive and the negative derivatives and on the other hand with equally large amplification for both derivatives. The regulatory responses obtained at these experiments did not, however, shown any marked fundamental differences. Just as described in the foregoing, however, it was observed that a large signal component dependent on the derivative of the blood pressure supplied to the pulse generator **7** produces a more damped response than a small signal component dependent on the derivative. Further experiments have shown that a relatively large signal component, dependent on the mean blood pressure from the circuit **10** (set by means of the potentiometer **12**) to the pulse generator **7**, i.e., a higher mean pulse frequency for the stimulation, gives a lower blood pressure level than a smaller static signal component from the circuit **10** to the pulse generator **7**, i.e., a lower mean pulse frequency for the stimulation.

It is appreciated that in the practical use of a device according to the invention it may be necessary to adjust the relative magnitude of the mean pulse frequency of the stimulation, which is dependent on the arterial mean blood pressure of the patient, and the pulse frequency modulation which is dependent on the blood pressure derivative of the patient as well as to adjust the lower threshold level for the pulse generation and the maximum saturation pulse frequency respectively to the patient concerned if optimum results are to be obtained.

In the experiments on dogs the stimulation was made with square wave pulses having an amplitude of 2 v. and a pulse length of 0.1 msec. However, it is appreciated that the pulse amplitude as well as the pulse length must be adjusted to the actual design of the stimulator assemblies and their location relative to the nerves to be stimulated so that the desired nerve activity is achieved in the nerves. However, it seems that a pulse amplitude within the range 1–5 v. and a pulse length within the range 0.1–2 msec. should be suitable.

In a device according to the invention the two stimulator assemblies and the pressure transducer sensing the arterial blood pressure may be permanently implanted in the body and connected through wire conductors to a unit located outside the said external unit including the pulse generator, the signal transforming circuits and the necessary power source. Alternatively the stimulator assemblies and the pressure transducer may be coupled inductively to said external unit. It is also possible to miniaturize the device so that the complete device can be subcutaneously implanted, in which case it is preferably provided with inductively rechargeable batteries so that the device does not have to be removed for replacement of the batteries.

What is claimed is:

1. A system for influencing the natural biological blood pressure regulatory system in an individual, in particular for reducing and controlling the blood pressure in a hypertensive individual, by electrical pulse stimulation of an afferent nerve from a baroreceptor in the individual, said system comprising:

1. pressure sensitive transducer means adapted to be connected to the arterial system of the individual for sensing the arterial blood pressure and producing an electric output signal substantially representing the instantaneous arterial blood pressure in the individual;
2. signal transforming means receiving the transducer output signal and including (a) a first signal transforming circuit providing an output signal substantially proportional to the mean value of the transducer output signal, and (b) a second signal transforming circuit providing an output signal whose amplitude is proportional to the derivative of the transducer output signal and whose polarity corresponds to the algebraic sign of said derivative;
3. signal combining means for additively combining the output signals of said first and second signal transforming circuits and providing an output signal whose amplitude is a function of said combined signals;
4. a frequency controlled pulse generator receiving the output signal of said signal combining means as a frequency control signal for generating output pulses having a frequency proportional to the amplitude of the output signal of said signal combining means; and
5. stimulator means connecting to receive the output pulses of said pulse generator and including at least one electrode means adapted for connection to an afferent nerve from a baroreceptor in the individual.

2. A system according to claim **1**, wherein said pulse generator has a minimum threshold signal value for its frequency control signal to initiate operation of the generator.

3. A system according to claim **1**, comprising variable signal attenuating means connected between the outputs of said first and second signal transforming circuits and the input of said signal combining means for variation of the relative magnitudes of the signals combined by said signal combining means.

4. A system according to claim **1**, wherein said second signal transforming circuit has unequally large proportionality factors for the positive and negative derivatives respectively of the transducer output signal.

5. A system according to claim **1**, wherein said pulse generator has a pulse frequency range up to about 300 Hz.

6. A system for influencing the natural biological blood pressure regulatory system in an individual, in particular for reducing and controlling the blood pressure in a hypertensive individual, by electric pulse stimulation of an afferent nerve from a baroreceptor in the individual, said system comprising:

1. pressure responsive transducer means adapted to be connected to the arterial system in the individual for sensing the arterial blood pressure and producing an output signal substantially representing the instantaneous arterial blood pressure in the individual;
2. signal transforming means responsive to the transducer output signal and including (a) a first signal transforming circuit providing an output signal substantially proportional to the mean value of the transducer output signal, and (b) a second signal transforming circuit providing an output signal whose amplitude is substantially proportional to the derivative of the transducer output signal and whose polarity corresponds to the algebraic sign of said derivative;
3. signal combining means for additively combining the output signals of said first and second signal transforming circuits to provide an output signal whose amplitude is a function of said combined signals;
4. a frequency controlled pulse generator connected to receive the output signal of said signal combining means as a frequency control signal to generate output pulses having a pulse frequency proportional to the amplitude of the output signal of said signal combining means; said pulse generator having two outputs for said output pulses;
5. stimulator means including right and left electrode means connected to receive the output pulses from the two outputs respectively of the pulse generator and adapted for connection to the right and left carotid-sinus nerves respectively in the individual; and
6. a pulse delay circuit in the one generator output connection for providing a time delay shorter than the shortest interval between two successive output pulses from the generator to prevent cross-stimulation between the right and left carotid-sinus nerves in the individual.

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