Baroreceptor Control of Atrioventricular Conduction in Man

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SUMMARY   Although human baroreflexes are known to exert a powerful physiological control on heart rate, little information exists on the physiological control they exert on the atrioventricular conduction system. In 11 normotensive subjects with normal atrioventricular conduction, we altered baroreceptor activity by injection of pressor and depressor drugs (phenylephrine and trinitroglycerin) and recorded mean arterial pressure (MAP, catheter measurements), R-R interval, and pre-His and post-His intervals (A-H and H-V, His bundle recording). With the subjects in sinus rhythm, increasing MAP by 21 ± 1 mm Hg caused a marked lengthening (250 ± 28 msec), and decreasing MAP by 17 ± 2 mm Hg a marked shortening (142 ± 16 msec) of the R-R interval. There was little change in the A-H interval and no change at all in the H-V interval. However, when the R-R interval was kept constant in these subjects by atrial pacing, a similar increase and decrease in MAP caused, respectively, a marked lengthening (49 ± 6 msec) and shortening (19 ± 3 msec) of the A-H interval, although the H-V interval remained unaffected. Thus physiological ranges of baroreceptor activation have a marked influence on the atrioventricular node but apparently not on the ventricular portion of the atrioventricular conduction system. This influence is unmasked when pacing prevents the baroreceptor influence on the sinoatrial node. *Circ Res 44: 752-758, 1979*

SEVERAL STUDIES in man have reported that physiological alterations in baroreceptor activity induced by changing arterial blood pressure with pressor and depressor drugs free of direct cardiac action are accompanied, respectively, by bradycardia and tachycardia. These studies have therefore demonstrated that heart rate ordinarily is influenced strongly by baroreceptors (Robinson et al., 1966; Gribbin et al., 1971; Pickering et al., 1972b; Korner et al., 1974; Mancia et al., 1977).

In contrast, little information is available for man concerning the baroreflex controls normally exerted on atrioventricular conduction. The only finding in this regard is the description of the effects of massive activation of baroreceptors by carotid sinus massage (Castellanos et al., 1974; Glasser et al., 1974; Rizzon and Di Biase, 1976). We have investigated baroreflex control of atrioventricular conduction in normotensive subjects by injecting pressor and depressor drugs while recording His bundle potentials from the right cardiac chambers. This allowed us to assess baroreceptor effects not only on total atrioventricular conduction but also on the atrioventricular node and the left and right bundle branch systems (Narula, 1974). Observations were made during sinus rhythm and during atrial pacing to investigate the influence of the baroreceptors on atrioventricular conduction without the simultane-

ous effects of changing cardiac cycle length (Hoffman and Cranefield, 1960).

Methods

We studied 11 subjects during a diagnostic cardiac catheterization required to exclude the existance of organic heart disease. The subjects were of both sexes (five male, six female), had a mean age of 36 ± 5 years, and had normal arterial blood pressures. They all gave informed consent for performance of the study after being told of its aim and methods.

Measurements

Recording of His bundle potentials was made by standard techniques (Narula, 1974). A bipolar recording catheter (U.S.C.I., no. 6) was introduced percutaneously into the right femoral vein after administration of local anesthesia with 2% lidocaine and guided under fluoroscopic control to the intracardiac septum at approximately the level of the triscupid valve. While bipolar recordings between two electrodes were displayed on an oscilloscope, the tip of the catheter was manipulated until bi- or triphasic potentials indicating depolarization of the His bundle became clearly visible between those indicating atrial and those indicating ventricular depolarization. This allowed monitoring of the two main parts of the total atrioventricular conduction time: that between the first atrial component of the low atrial electrogram and the onset of the His bundle deflection (the A-H interval), and that between the onset of the His bundle deflection and the earliest ventricular intracavitary activity (the

H-V interval). It is believed that the A-H interval is an indirect measure of atrioventricular nodal conduction, whereas the H-V interval represents an absolute measure of Purkinje-ventricular conduction (Narula, 1974).

Arterial pressure was measured by a catheter introduced percutaneously into the left femoral artery and connected to a strain gauge transducer (Statham P23Dc). Mean arterial pressure was obtained either by electronic damping of the pulsatile signal or by integration of the area beneath the pulsatile trace over consecutive periods of 10 seconds. Measurement also was made of the R-R interval which was derived from two leads, II and V1, of a surface electrocardiogram.

In each subject, a stimulating catheter was introduced percutaneously into an antecubital vein. This catheter was guided under fluoroscopic control to lie in the right atrium near the origin of the superior vena cava, and was used to pace the atrium from a site close to the anatomical location of the sinoatrial node.

All measurements were displayed at high speed (100 mm/sec) on an ultraviolet Hewlett-Packard polygraph, which allowed satisfactory recording of the atrial, His bundle, and ventricular potentials, as well as precise calculations of the intervals between them. Pulsatile arterial blood pressure, mean arterial pressure, and R-R interval (tachograph trace) also were simultaneously displayed at lower speed (50 mm/min) on an ink-writing Grass polygraph for more immediate evaluation of the hemodynamic effects obtained with the administration of the vasoactive drugs.

Drug Administration

To increase and decrease arterial blood pressure (and therefore baroreceptor activity) from the control level, we used phenylephrine and trinitroglycerin, drugs which have minimal or no direct effect on impulse initiation or conduction in the heart (Gribbin et al., 1971; Pickering et al., 1972b; Korner et al., 1974; Varma et al., 1960; Beck et al., 1969; Mancia et al., 1978). The drugs were injected into an antecubital vein in doses of 25–150 μg (phenylephrine) and 100–150 μg (trinitroglycerin) diluted in 2–5 ml of saline. The speed of injection was adjusted so that the entire dose was delivered in 5–10 seconds, because Korner et al. (1974) and we ourselves (Mancia et al., 1977, 1978) have shown that in this way arterial blood pressure changes rapidly to reach a plateau which is maintained for 10–15 seconds. We thought that such relatively stable and prolonged stimuli would be better suited to induce and analyze alterations in the atrioventricular conduction times.

In a few subjects atropine was given intravenously in a dose of 0.04 mg/kg of body weight. This dose was selected because of evidence that it can block completely the influence of the parasympathetic nervous system upon the heart (Jose and Taylor, 1969).

Evaluation of Atrioventricular Conduction

The following points demonstrated that atrioventricular conduction in our subjects was normal. (1) Basal values of A-H and H-V intervals were within the normal range. (2) Pacing rates of up to 140 beats/min did not induce a Wenckebach phenomenon. (3) The refractory periods of the atrioventricular node (measured by the extrastimulus technique in five subjects) were within the normal range. (4) Pacing rates of up to 160 beats/min did not increase H-V intervals (see Damato et al., 1969, and Krikler and Goodwin, 1974).

Protocol and Data Analysis

All subjects were studied supine. The study initially was performed with the subjects in sinus rhythm. We began with the injection of a large dose of phenylephrine, followed at 6-minute intervals by three progressively smaller doses of the same drug and by one large dose of trinitroglycerin. Multiple doses of phenylephrine were used because it was evident from the initial observations that the changes in atrioventricular conduction induced by this drug were so marked that stimulus-response curves relating doses to effects could be obtained.

The study continued with the subject receiving atrial pacing. The vasoactive drugs were injected according to the doses and the sequence adopted when the subject was in sinus rhythm. When phenylephrine was injected, the rate of pacing was adjusted to be higher than that observed during sinus rhythm in the control periods *between* the drug injections. When trinitroglycerin was injected, the rate of pacing was adjusted to be higher than that observed during sinus rhythm *during* the effect of the drug. In this way, reflex changes in heart rate due to the drug-induced increase and decrease in blood pressure could be totally eliminated.

In a few cases a third sequence of drug injections was performed after administration of atropine, both with the subject in sinus rhythm and during atrial pacing. Also, in this case, pacing rates were adjusted to be higher than those naturally present before or during the effects of the vasoactive drugs.

Data were analyzed by averaging values measured during the 10 seconds preceding the drug injection and the 10 seconds during the plateau alterations in blood pressure that followed drug injection. Effects of injecting trinitroglycerin and the maximal dose of phenylephrine were evaluated in each subject. The mean values (± standard errors) were calculated for the entire group, and the *t*-test for paired observations was used to assess the statistical significance of the differences. Effects of injecting multiple doses of phenylephrine were evaluated in each subject by calculating the linear regressions between the drug-induced increase in

mean arterial pressure and the resulting changes in the R-R, A-H, and H-V intervals. Statistical significance was given by the r value of the regression. Single regression coefficients were averaged to obtain mean (± standard errors) regression coefficients for the group.

Results

Phenylephrine (11 Subjects)

When the subjects were in sinus rhythm, the maximal dose of phenylephrine caused an increase in mean arterial pressure of 21 ± 1 mm Hg ($P <$ 0.001; Fig. 1, top). This increase was accompanied by a marked lengthening of the R-R interval (250 ± 28 msec, $P < 0.001$) but only a slight increase in the A-H interval (4 ± 2 msec, $P < 0.05$), and no effect was seen in the H-V interval. When, in the same subjects, the alterations in R-R interval were prevented by atrial pacing (Fig. 1, bottom), the same dose of phenylephrine caused an increase in mean arterial pressure of 28 ± 2 mm Hg ($P < 0.001$). This increase had no effect on the H-V interval, but it now induced a marked lengthening of the A-H interval (49 ± 6 msec, $P < 0.001$). This lengthening followed the increase in blood pressure induced by phenylephrine, beginning when blood pressure began to rise and achieving a plateau when blood pressure did.
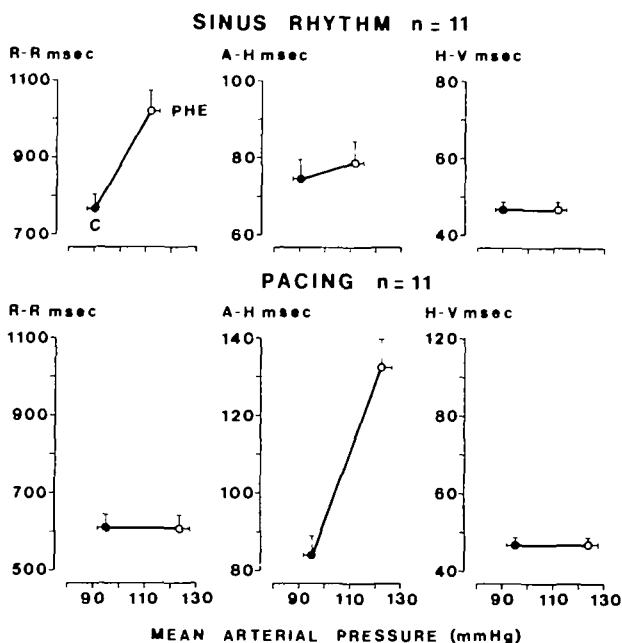
The results described were confirmed by testing the effects of injecting multiple doses of phenylephrine, thereby inducing increases in blood pressure of different magnitudes (Fig. 2). When the subjects were in sinus rhythm, the increase in mean arterial pressure showed a steep linear relationship with the lengthening of the R-R interval (the relationship was significant at $P < 0.01$ in each individual subject), a less steep linear relationship with the lengthening of the A-H interval (significant at $P < 0.05$ in only three subjects), and no relationship at all with the H-V interval. When the subjects were paced atrially, the increase in mean arterial pressure developed a much steeper linear relationship with the lengthening of the A-H interval (the relationship was now significant in each subject), whereas no relationship was observed with the H-V interval.

In a limited number of cases, injecting the maximal dose of phenylephrine during atrial pacing caused a second-degree atrioventricular block of a Wenckebach type (Fig. 3). Because of the difficulty in calculating the lengthening of the A-H interval induced by phenylephrine in these cases, these results were not included in Figure 1. Instead, injection of phenylephrine was repeated at slightly lower doses which caused marked A-H lengthening. This lengthening, however, was not associated with dropped ventricular beats.

Trinitroglycerin (Nine Subjects)

As shown in Figure 4, when the subjects were in sinus rhythm, trinitroglycerin caused a decrease in mean arterial pressure of 17 ± 2 mm Hg ($P < 0.001$). This decrease was accompanied by a marked re-

SINUS RHYTHM n = 11

PACING n = 11

MEAN ARTERIAL PRESSURE (mmHg)

FIGURE 1   *Effects of phenylephrine-induced increases in mean arterial pressure on R-R, A-H, and H-V intervals. Data are means ± standard errors of 11 subjects studied in sinus rhythm and during atrial pacing. C refers to control values and PHE to values during the plateau increase in mean arterial pressure induced by phenylephrine. Atrial pacing was performed to produce R-R intervals shorter than those present in sinus rhythm during the control period.*

n = 11
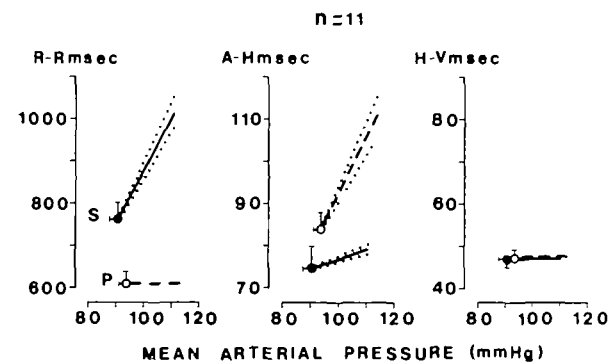
MEAN ARTERIAL PRESSURE (mmHg)

FIGURE 2   *Effects on R-R, A-H, and H-V intervals of variable increases in mean arterial pressure induced by different doses of phenylephrine. Data are shown as regression lines which represent means ± standard errors of the regression lines obtained in each of the 11 subjects studied. Observations were made in sinus rhythm (S: control values indicated by the filled circles, mean regression coefficients by the solid lines, and standard errors of the mean regression coefficients by the dotted lines) and during atrial pacing (P: control values indicated by the unfilled circles, mean regression coefficients by the broken line, and standard errors by the dotted lines).*
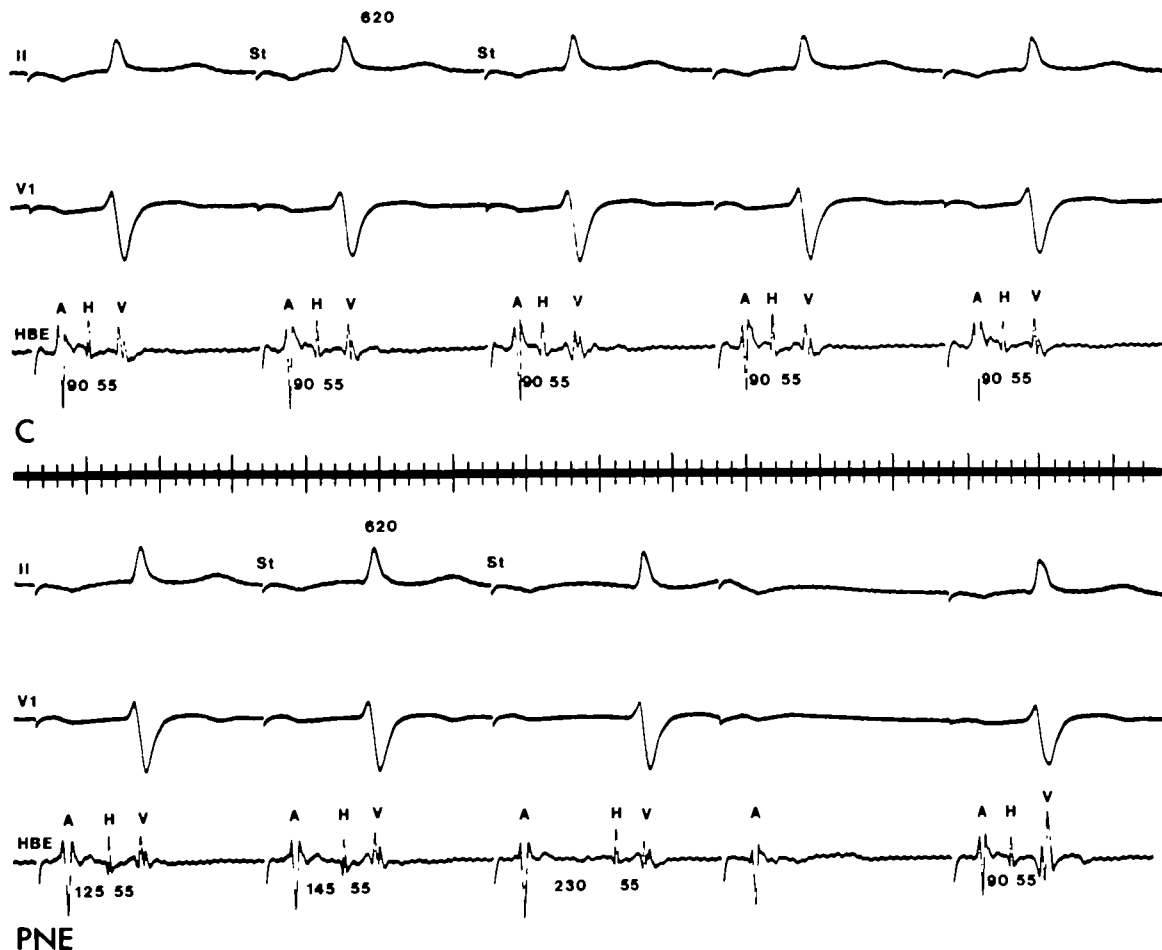
FIGURE 3 *Alterations in the A-H interval induced by injection of 150 μg of phenylephrine into one subject. C represents the control condition before drug injection and PNE the plateau increase in arterial blood pressure induced by drug injection. II and V1 are surface ECG leads, and HBR is the recording of the His bundle potentials (H) between the atrial (A) and the ventricular (V) potentials. The numbers below this trace refer to A-H and H-V intervals in msec. Notice that during phenylephrine administration the A-H interval lengthens progressively until a dropped ventricular beat ensues. Time shown is between the three control traces (above) and the three traces obtained during phenylephrine (below). Each small division represents 40 msec.*

duction in the R-R interval (142 ± 16 msec, $P < 0.001$) but caused only a slight decrease in the A-H interval (2 ± 1 msec, $P > 0.05$). The decrease had no effect on the H-V interval. When in the same subjects the alterations in R-R interval were prevented by atrial pacing (Fig. 4), the same dose of trinitroglycerin caused a reduction in mean arterial pressure of 19 ± 2 mm Hg ($P < 0.001$). This reduction had no effect on the H-V interval, but it now induced a considerable shortening of the A-H interval (19 ± 3 msec, $P < 0.001$). As occurred for the lengthening induced by phenylephrine, the shortening in A-H interval tended to parallel the alteration in blood pressure.

In seven of the nine subjects mentioned above, trinitroglycerin was injected also when the atria were paced at a faster rate, the basal R-R value being thus lower (Fig. 5). Although at this faster rate of pacing the basal value of the A-H interval was increased, the shortening of the A-H interval

caused by the trinitroglycerin-induced hypotension was not modified. The faster rate of pacing did not alter the basal value of the H-V interval, nor did it unmask any effect of the trinitroglycerin injection.

Atropine (Three Subjects)

As shown in Figure 6, when the subjects were in sinus rhythm, administration of atropine shortened the basal R-R intervals and virtually abolished both the lengthening induced by phenylephrine and the shortening induced by trinitroglycerin. Atropine administration also was followed by disappearance of both the lengthening and the shortening of the A-H interval caused by the injection of the vasoactive drugs when the subjects were paced atrially (Fig. 6, right panel).

Discussion

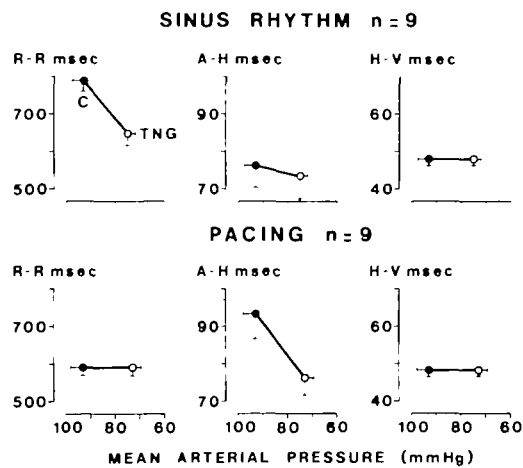Our results give the first demonstration in man of the following points. First, increases in arterial

FIGURE 4   *Effects of trinitroglycerin-induced decreases in mean arterial pressure on R-R, A-H, and H-V intervals. Data are shown as means ± standard errors from nine subjects studied in sinus rhythm and during atrial pacing. C refers to control values and TNG to values during the plateau decrease in mean arterial pressure induced by trinitroglycerin. Atrial pacing was performed to produce R-R intervals shorter than those present in sinus rhythm during the tachycardia induced by the drug.*

blood pressure induced by phenylephrine can lengthen the A-H interval, indicating that physiological activation of the baroreceptors exerts an inhibitory influence on conduction through the atrioventricular node. Second, the effects of baroreceptor activation on the atrioventricular node are very marked, provided that alterations in heart rate are prevented by atrial pacing. Indeed, under these circumstances, blood pressure increases cause not only marked lengthening of the A-H interval but even in a few cases cause second-degree atrioventricular block. Third, reduction of blood pressure
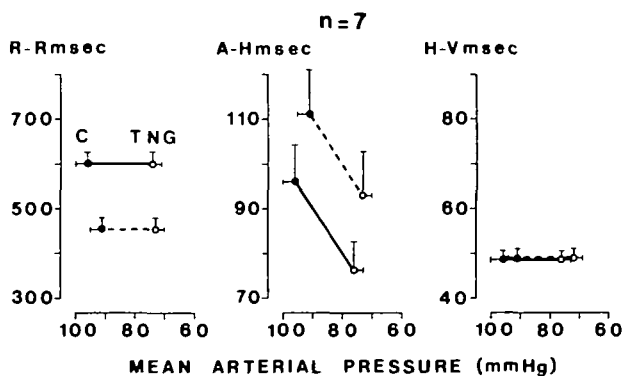

FIGURE 5   *Effects of trinitroglycerine-induced decreases in mean arterial pressure on R-R, A-H, and H-V intervals at slower (continuous line) and faster rates (dashed lines) of atrial pacing. Data are shown as means ± standard error from the seven subjects in whom the two different pacing rates were used. Symbols are as in Figure 4.*
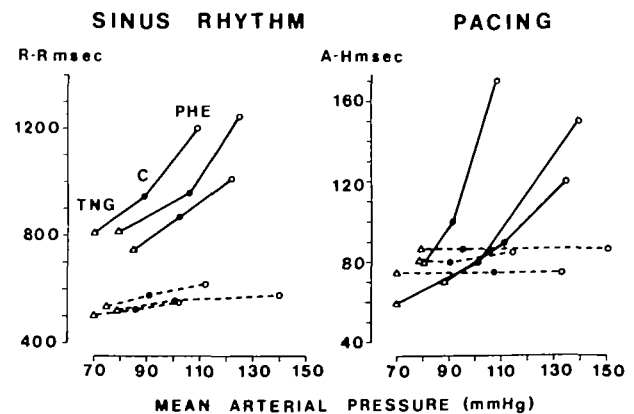

FIGURE 6   *Effects of atropine on the alterations in R-R interval induced by phenylephrine and trinitroglycerin in sinus rhythm, and on alterations in A-H interval induced by the same vasoactive drugs on atrial pacing. Individual data from three subjects are shown. The solid lines refer to the results obtained before, and the broken lines to those obtained after atropine administration. Symbols are as in the preceding figures.*

by trinitroglycerin can shorten the A-H interval, an effect which also is more marked during atrial pacing. This means that at normal blood pressures the baroreceptor influence on the atrioventricular node has a "tonic" nature, and that the baroreflexes lengthen nodal conduction time if blood pressure increases above normal, but can also shorten this variable if blood pressure decreases below normal. Foruth, the baroreceptor effects on the A-H interval are virtually abolished by atropine, indicating that, at least when steady state responses in supine subjects are considered, they occur almost exclusively through modulation of the efferent vagal activity.

In our study the pre-His conduction time was markedly increased or decreased by the baroreflexes only during atrial pacing, and only small effects were observed when heart rate was allowed to decrease and increase as a result of the baroreceptor manipulation. This finding reproduces in man a phenomenon obtained in experimental animals, in which the direct effects of vagal stimulation on the atrioventricular node were largely masked by simultaneous changes in cardiac cycle (Martin, 1977; Beer et al., 1977), and raises an obvious question: is the direct baroreceptor influence on this structure an unimportant component of the reflex in ordinary life, or does it represent a physiologically meaningful effect? If we consider that baroreflexes markedly alter the cardiac cycle (Robinson et al., 1966; Gribbin et al., 1971; Pickering et al., 1972b; Korner et al., 1974; Mancia et al., 1977), and that this alteration profoundly affects atrioventricular nodal conduction (Damato et al., 1969), then the influence of the baroreceptors on the nodal tissue appears as a homeostatic mechanism that counteracts the effects of alterations in cardiac cycle length

to maintain atrioventricular conduction values close to normal despite large changes in heart rate. Of course this homeostatic mechanism may work properly only over a limited range, the balance breaking when either variable largely predominates. There is evidence that the massive baroreceptor stimulation obtained with carotid sinus massage also induces marked lengthening of the A-H interval with simultaneous marked bradycardia (Rizzon and Di Biase, 1976).

In contrast to pre-His conduction, baroreceptor effects could not be demonstrated on post-His conduction time, either when the observations were made during sinus rhythm or during atrial pacing. This is a surprising result, because the post-His conduction time represents the rate of conduction through ventricular structures that are innervated by parasympathetic as well as sympathetic fibers (Kent et al., 1974; Bailey et al., 1972). Also, recent evidence suggests that a phenylephrine-induced activation of the baroreceptors can terminate ventricular tachycardia through an increase in vagal efferent drive (Waxman and Wald, 1977). It is true that in our study the alterations in the pre-His conduction time that occurred with alterations in baroreceptor activity during pacing might have directly affected these ventricular structures so as to offset and mask any direct neural effect. An alternative explanation, however, is that baroreceptors do not have a major influence on the His and bundle branch portion of the atrioventricular conduction system, their control being limited to the nodal portion. This explanation would of course leave open the question of what reflex and central influences make use of the innervation that impinges upon these ventricular structures.

Three other aspects of our study should be commented on briefly. The first is that our data describe steady state more than transient changes following alterations in baroreceptor activity. This suggests that caution be used when considering the applicability of our findings to mechanisms involved in rapidly occurring events such as arrhythmias. The second aspect is that, during atrial pacing, reduction in baroreceptor activity sped A-H conduction to a similar extent when the baseline A-H interval was normal and when it was prolonged by increasing the rate of pacing. This suggests that baroreceptor effects on the A-H interval are evident within a wide range of nodal conduction characteristics. The third aspect refers to two analogies that appear to exist between the baroreceptor influence on the atrioventricular and sinoatrial nodes. One is that both these structures are influenced by the baroreceptors largely through the vagi (Eckberg et al., 1972; Pickering et al., 1972a; Eckberg et al., 1976; Leon et al., 1970), although either of them possesses a pronounced sympathetic innervation (Stoler and McMahon, 1947). The other analogy, which is illustrated in Figure 7, shows that the shortening in A-H interval obtained with reduction in baroreceptor
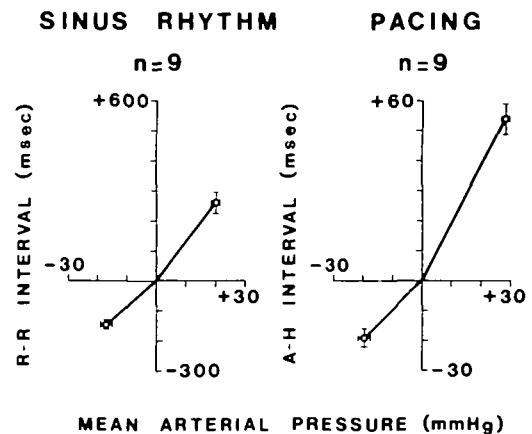

SINUS RHYTHM   **PACING**

FIGURE 7 *Effects of increasing and decreasing mean arterial pressure by phenylephrine and trinitroglycerin on R-R interval (observations performed in sinus rhythm) and on A-H interval (observations performed during atrial pacing). Data are shown as mean changes (± standard errors) from control values in the group of nine subjects in whom both drugs were injected.*

activity below the existing level is less than the lengthening obtained with an increase in baroreceptor activity above the existing level, an asymmetry that can be clearly demonstrated also for the baroreceptor effects on the R-R interval (see also Pickering et al., 1972b; Mancia et al., 1977). Thus baroreceptors affect the sinoatrial and atrioventricular nodes not only through the same autonomic pathway but also in a quantitatively similar pattern.

Acknowledgments

References

Bailey J, Greenspan K, Elizari MY, Anderson GJ, Fisch C: The effects of acetylcholine on automaticity and conduction within the proximal His-Purkinje specialized conduction system. Circ Res 30: 210–216, 1972

Beck W, Barnard CN, Schrire V: Heart rate after cardiac transplantation. Circulation 40: 437–445, 1969

Beer EL, Boom HBK, Naafs B: The combined influence of the stimulus frequency of the vagal nerves and the atrial stimulus interval on the atrioventricular conduction time. Cardiovasc Res 11: 47–54, 1977

Castellanos A, Sung RJ, Cunha D, Myerburg RJ: His bundle recordings in paroxysmal atrio-ventricular block produced by carotid sinus massage. Br Heart J 36: 487–491, 1974

Damato AN, Sun HL, Helfant RH, Stein E, Berkowitz WD, Cohen S: Study of atrioventricular conduction in man using electrode catheter recordings of His bundle activity. Circulation 39: 287–296, 1969

Eckberg DL, Fletcher GF, Braunwald E: Mechanism of prolongation of the R-R interval with electrical stimulation of the carotid sinus nerves in man. Circ Res 30: 131–138, 1972

Eckberg DL, Abboud FM, Mark AL: Modulation of carotid baroreflex responsiveness in man: Effects of posture and propranolol. J Appl Physiol 41: 383–387, 1976

Glasser SP, McCarty RJ, Iannone LA: Hyperactive carotid sinus reflex and His bundle electrocardiography. J Electrocardiol 7: 71–74, 1974

Gribbin B, Pickering TG, Sleight P, Peto R: Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 29: 424–431, 1971

Hoffman BF, Cranefield PF: Electrophysiology of the Heart. New York, McGraw-Hill, 1960

Jose AD, Taylor RR: Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. J Clin Invest 48: 2019–2031, 1969

Kent KM, Epstein SE, Cooper T, Jacobowitz DM: Cholinergic innervation of the canine and human ventricular conducting system. Circulation 50: 948–955, 1974

Korner PI, West MJ, Shaw J, Uther JB: "Steady-state" properties of the baroreceptor-heart-rate reflex in essential hypertension in man. Clin Exp Pharmacol Physiol 1: 65–76, 1974

Krikler DM, Goodwin JF: Cardiac Arrhythmias. London, Sanders, 1974

Leon DF, Sharer JA, Leonard JJ: Reflex heart rate control in man. Am Heart J 80: 729–739, 1970

Mancia G, Ferrari A, Gregorini L, Valentini R, Ludbrook J, Zanchetti A: Circulatory reflexes from carotid and extracarotid baroreceptor areas in man. Circ Res 41: 309–315, 1977

Mancia G, Ludbrook J, Ferrari A, Gregorini L, Zanchetti A: Baroreceptor reflexes in human hypertension. Circ Res 43: 170–177, 1978

Martin P: Paradoxical dynamic interaction of heart period and

vagal activity on atrioventricular conduction in the dog. Circ Res 40: 81–89, 1977

Narula OS (ed): His bundle electrocardiography and clinical electrophysiology. Philadelphia, FA Davis, 1974

Pickering TG, Gribbin B, Petersen ES, Cunningham DJC, Sleight P: Effects of autonomic blockade on the baroreflex in man at rest and during exercise. Circ Res 30: 177–185, 1972a

Pickering TG, Gribbin B, Sleight P: Comparison of reflex heart rate response to rising and falling arterial pressure in man. Cardiovasc Res 6: 277–283, 1972b

Rizzon P, Di Biase M: Modificazioni elettrofisiologiche indotte dalla compressione dei seni carotidei. Boll Soc Ital Cardiol 10: 1835–1842, 1976

Robinson BF, Epstein SE, Beiser GD, Braunwald E: Control of heart rate by the autonomic nervous system. Circ Res 19: 400–411, 1966

Stoler WA, McMahon RA: The innervations and structure of the conductive system of the human heart. J Comp Neurol 87: 57–72, 1947

Varma S, Johnsen SD, Sherman DE, Youmans WB: Mechanisms of inhibition of heart rate by phenylephrine. Circ Res 8: 1182–1186, 1960

Waxman MB, Wald RW: Termination of ventricular tachycardia by an increase in cardiac vagal drive. Circulation 56: 385–391, 1977

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