Modulation of Atrioventricular Conduction by Isometric Exercise in Human Subjects

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SUMMARY In humans, arterial baroreceptors depress atrioventricular (AV) conduction through vagal influences on the AV node but not on the His-Purkinje fibers. We investigated the influence on AV conduction of an excitatory neural influence, i.e., isometric exercise (handgrip). In subjects with normal AV conduction, blood pressure was measured by an intra-arterial catheter, R-R interval by an electrocardiogram, and A-H and H-V intervals (representing conduction, respectively, through the AV node and the His-Purkinje fibers) by His bundle recording. Handgrip raised blood pressure markedly, it shortened R-R interval, and caused no change in A-H and H-V intervals. Because prior studies had demonstrated that autonomic influences over AV conduction can be quantified accurately only when heart rate is constant, the subjects also were studied during atrial pacing. Under this condition, handgrip again caused a marked pressor response but also induced a marked shortening in the A-H interval (30%) whereas the H-V interval still was unaffected. The handgrip-induced shortening in the A-H interval was less pronounced after atropine but it was also impaired by propranolol. Thus AV conduction normally is modulated by inhibitory influences but also by powerful excitatory stimuli. Like the inhibitory influences, the excitatory ones are seen mainly at constant heart rate and are limited to the AV node with no effect on the His-Purkinje fibers. Unlike the inhibitory influences, however, the excitatory modulation is substantially mediated via the cardiac sympathetic nerves. Circ Res 49: 265-271, 1981

SEVERAL studies suggest that the autonomic nerves may have a large influence on atrioventricular conduction. First, a considerable number of vagal and sympathetic fibers impinge upon this structure along its entire course (Cohn and Lewis, 1913; Morison, 1912; Gesell et al, 1973; Levy and Martin, 1979). Second, when electrical stimulation of the cardiac branches of the vagus is performed in animals, there can be a marked depression of atrioventricular conduction (Levy and Zieske, 1969; Martin, 1977; West and Toda, 1967). Third, when the electrical stimulus is applied to the cardiac sympathetic branches, atrioventricular conduction can, conversely, be markedly accelerated (Gesell, 1916; Wallace and Sarnoff, 1964; Levy and Zieske, 1969; Priola, 1973; Spear and Moore, 1973). However, the above-mentioned studies only indicate a large potential ability of the vagal and sympathetic nerves to influence atrioventricular conduction and do not provide evidence concerning whether and to what extent this ability is used...
during physiological stimuli. We previously have addressed this problem in humans by inducing physiological alterations in arterial baroreceptor activity while recording His bundle potentials and have concluded that a powerful vagal influence on atrioventricular conduction does operate normally. We have also observed, however, that this influence is complex, because it is exerted on some but not all portions of the atrioventricular conduction system and is modified to a large extent by concomitant alterations in cardiac cycle length (Mancia et al., 1979).

The present study was planned to obtain further understanding of the physiological reflex control of atrioventricular conduction in humans, by examining its variations in response to a natural excitatory neural influence (i.e., that induced by isometric exercise). The study was conducted in subjects in sinus rhythm and after prevention of any heart rate changes by atrial pacing. This was done because prior studies have demonstrated that direct autonomic influences on AV conduction may be more evident and more easily quantified if cardiac cycle length is constant (Seidet et al., 1974; Martin, 1977; Mancia et al., 1979).

Methods

We studied 14 subjects of both sexes who had a mean age of 43.4 ± 5.6 years (mean ± SE) and a normal arterial blood pressure. The study was performed during cardiac catheterization necessitated by the possibility of heart disease; the criterion for being included in the study was that the presence of disease had been excluded by the examination. All subjects consented to the study after having had its nature and purpose fully explained.

Measurements

Arterial blood pressure was measured by a catheter introduced percutaneously into a femoral or a brachial artery and connected to a strain-gauge transducer (Statham P23Dc); the measuring system gave an optimal response up to 20 Hz. Mean arterial pressure was obtained by electric damping of the pulsatile pressure signal. Heart rate was evaluated by the R-R interval which was obtained from a conventional lead of a surface electrocardiogram. Pulsatile arterial pressure, mean arterial pressure, and R-R interval (shown as a beat-to-beat trace via a tachograph) were displayed at a lower speed (50 mm/min) on an ink-writing Grass polygraph. Pulsatile arterial pressure, mean arterial pressure, and R-R interval were recorded during cardiac catheterization necessitated by the possibility of heart disease; the criterion for being included in the study was that the presence of disease had been excluded by the examination. All subjects consented to the study after having had its nature and purpose fully explained.

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The atrioventricular conduction time was obtained in two different ways. In each subject the P-R interval during sinus rhythm and the St (stimulus artifact)-R interval during atrial pacing (see below) were measured using electrocardiographic leads in which the above-mentioned deflections were easily identifiable. In addition, in 10 of the 14 subjects, His bundle potentials were recorded via a bipolar electrode catheter introduced percutaneously into a femoral vein. His bundle electrograms allowed us to obtain the interval between the first atrial component of the low atrial electrogram and the onset of the His bundle deflection (the A-H interval), and the interval between the onset of the His bundle deflection and the earliest ventricular intracavitary activity (the H-V interval). In this way, both the nodal and the Purkinje-ventricular components (represented respectively by the A-H and H-V intervals) of the total atrioventricular conduction time were recorded (Narula, 1974). As in our previous study subjects in the present study had normal atrioventricular conduction as indicated by determining atrioventricular nodal refractory periods and by measuring the A-H and H-V intervals during both sinus rhythm and rapid atrial pacing. (For further details, see Mancia et al., 1979.)

In each subject, a catheter was introduced percutaneously (after local lidocaine anesthesia) into an antecubital vein, and guided under fluoroscopic control to lie in the right atrium near the superior vena cava. This catheter was used to pace the atria 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. Pulsatile arterial pressure, mean arterial pressure, and R-R interval (shown as a beat-to-beat trace via a tachograph) were displayed at a lower speed (50 mm/min) on an ink-writing Grass polygraph for a more immediate appreciation of the hemodynamic effects obtained by performing isometric exercise.

Isometric Exercise

Each subject performed isometric exercise by gripping a handle connected to a dynamometer with his left hand for 60 seconds. The strength of the handgrip was always limited to 40% of the subject’s maximal strength, which was determined by two or three short-lasting handgrips at the beginning of the study.

Protocol

Each subject lay supine throughout the study. After a suitable baseline interval, a handgrip was performed with the subject in sinus rhythm. Atrial pacing then was started with the pacing rate set at a level slightly higher than the peak rate observed during the handgrip performed at sinus rhythm. After another suitable baseline interval, a second handgrip was performed during atrial pacing.

After completion of the above maneuvers, a further step was undertaken. In seven subjects, this consisted of pharmacological blockade of β-adrenergic receptors with propranolol (0.2 mg/kg of body weight, iv), and in six subjects of cholinergic blockade with atropine (0.04 mg/kg of body weight, iv). Both drug administrations were followed at an interval of 10 minutes by two further handgrip trials, the first performed in sinus rhythm and the second during atrial pacing.
Data Analysis

Data were analyzed by averaging hemodynamic or electrophysiological values measured during the 10 seconds preceding the beginning of handgrip and comparing them with the average values measured during the last 10 seconds of handgrip.

Data obtained in single subjects were averaged to obtain means ± SE for the whole group of subjects. The t-test for paired observations was used to compare the data with reference either to the changes from control values induced by handgrip or to the differences in the effects of handgrip before and after administration of propranolol and atropine. A P value of 0.05 was taken as the limit of statistical significance. Values are presented as mean ± SE.

Results

Effects of Handgrip on Total Atrioventricular Conduction Time (14 Subjects)

The effects of handgrip on total atrioventricular conduction time are shown in Figure 1. When handgrip was performed with the subjects in sinus rhythm, there was a marked increase in mean arterial pressure, a marked shortening in R-R interval, but no alteration in P-R interval.

However, a different result was obtained when the shortening in R-R interval induced by handgrip was prevented by atrial pacing. This procedure did not modify resting mean arterial pressure but it caused a significant (P < 0.01) increase in the resting value of the P-R interval. Under this circumstance, handgrip was accompanied by an increase in mean arterial pressure which was similar to that obtained during sinus rhythm. However, the handgrip-induced rise in mean arterial pressure was accompanied by a marked shortening of the P-R interval.

Effects of Handgrip on A-H and H-V Conduction Times (10 Subjects)

The effects of handgrip on A-H and H-V conduction times are shown in Figure 2. When the subjects were in sinus rhythm, the rise in mean arterial pressure and the shortening in R-R interval induced by handgrip were not accompanied by any alteration in the A-H and H-V intervals. However, the results were different during atrial pacing as, under this circumstance, handgrip caused a marked reduction in A-H interval, although the H-V interval continued to remain unaffected. Thus, the increase in the total atrioventricular conduction rate induced by handgrip during atrial pacing was accounted for entirely by an effect on the nodal portion of the atrioventricular conduction system, with no apparent influence on its Purkinje-ventricular portion.

Effects of Propranolol on the Responses to Handgrip (Seven Subjects)

The effects of handgrip before and after administration of propranolol are shown in Figure 3 and

![Figure 1](image1.png)

![Figure 2](image2.png)

![Figure 3](image3.png)
Effects of Atropine on the Responses to Handgrip (Six Subjects)

The effects of handgrip before and after administration of atropine are shown in Figure 4 and in the lower panel of Figure 5. Figure 4 shows that atropine did not affect resting mean arterial pressure significantly. It caused a marked and significant shortening \((P < 0.001)\) in resting R-R interval, and it also caused a significant and appreciable shortening \((P < 0.01)\) in resting P-R interval, although this was evident mainly during atrial pacing. The rise in mean arterial pressure induced by handgrip was not affected by atropine. However, the handgrip-induced shortening in R-R interval was markedly reduced by administration of this drug. Furthermore, atropine caused a reduction in the handgrip-induced shortening of P-R interval in the circumstances in which this response could be observed, i.e., during atrial pacing.

The lower panel of Figure 5 shows how the effects of handgrip on A-H and H-V intervals during atrial pacing were modified by atropine in the five subjects in whom these observations were made. The

in the upper panel of Figure 5. Figure 3 shows that propranolol did not affect resting mean arterial pressure; it caused a significant \((P < 0.01)\) lengthening in the resting R-R interval, and it also lengthened \((P < 0.05)\) to a small degree resting P-R interval. The rise in mean arterial pressure and the shortening in R-R interval induced by handgrip were not affected by this drug. On the other hand, the shortening of the P-R interval (that could be observed in atrial pacing) was significantly reduced after administration of propranolol.

The upper panel of Figure 5 shows how the effects of handgrip on A-H and H-V intervals during atrial pacing were modified by propranolol in the five subjects in whom these observations were made. Resting A-H interval was not significantly modified by administration of this drug which, on the other hand, drastically reduced the amount of shortening of A-H interval induced by handgrip. Propranolol had no effect on resting H-V interval nor did it alter the absence of response that this variable showed during handgrip.

Effects of Atropine on the Responses to Handgrip (Six Subjects)

The effects of handgrip before and after administration of atropine are shown in Figure 4 and in the lower panel of Figure 5. Figure 4 shows that atropine did not affect resting mean arterial pressure significantly. It caused a marked and significant shortening \((P < 0.001)\) in resting R-R interval, and it also caused a significant and appreciable shortening \((P < 0.01)\) in resting P-R interval, although this was evident mainly during atrial pacing. The rise in mean arterial pressure induced by handgrip was not affected by atropine. However, the handgrip-induced shortening in R-R interval was markedly reduced by administration of this drug. Furthermore, atropine caused a reduction in the handgrip-induced shortening of P-R interval in the circumstances in which this response could be observed, i.e., during atrial pacing.

The lower panel of Figure 5 shows how the effects of handgrip on A-H and H-V intervals during atrial pacing were modified by atropine in the five subjects in whom these observations were made. The
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before and after propranolol (n = 5)

before and after atropine (n = 5)

MAP R-R interval A-H interval H-V interval

FIGURE 5 Effects of handgrip on MAP and on R-R, A-
H, and H-V intervals in five subjects who were studied
before and after propranolol and in five subjects who
were studied before and after atropine. Only data ob-
tained during atrial pacing are shown. Symbols as in
Figures 3 and 4.

resting A-H interval was significantly and markedly
reduced (P < 0.01) by administration of atropine,
which also reduced significantly the amount of
shortening of A-H interval induced by handgrip.
Atropine had no effect on the resting H-V interval,
nor did it alter the absence of response that this
variable showed during handgrip.

Discussion

The first result of our study is that atrioventric-
ular conduction time can be shortened considerably
during isometric exercise, due to both a withdrawal
of the vagal influence and an activation of the
sympathetic influence to the atrioventricular con-
duction system. This provides new information con-
erning how atrioventricular conduction is con-
trolled physiologically by the autonomic nervous
system in humans. We previously have shown that
this conduction is under the tonic restraint of a
depressor influence originating from the arterial
baroreceptors and that such restraint is exerted
exclusively through the vagus (Mancia et al., 1979).
We now can say that influences whose nature is not
only tonic and depressor but also phasic and excit-
atory participate in the control of this function, and
that the pathway that is used for this purpose is not
limited to the vagus but involves to an important
degree the sympathetic nerves.

There are several other important findings in our
study. First, atrioventricular conduction time was
shortened by isometric exercise when heart rate
was kept constant by atrial pacing, but it was not
altered when the tachycardiac effect of exercise was
allowed to develop. In this regard, it is important to
remember that a similar phenomenon has been
shown in studies of inhibitory rather than excitatory
neural effects on atrioventricular conduction (Levy
and Martin, 1979). For example Seides et al. (1974)
have shown that the reduction in atrioventricular
conduction that accompanies administration of a
β-blocking drug is more evident if the slowing of the
heart induced by the drug is prevented. Martin
(1977) and James et al. (1980) have found in dogs
that electrical or reflex vagal stimulation prolongs
atrioventricular conduction time under conditions
that allow a bradycardia to follow the vagal stimulus.
We have reported in humans (Mancia et al., 1979) that
activation of arterial baroreceptors by injection of phenylephrine
lengthens the atrioventricular conduction interval
during atrial pacing, but that this effect is lost when
the bradycardic response to the baroreceptor stim-
ulus is allowed to take place. Thus an antagonism
seems to exist between the effects on atrioventric-
ular conduction directly due to the neural influences
and those brought about indirectly by alterations
in the cardiac cycle length. The mechanism of this
antagonism is unexplained, although it may be hy-
pothesized that its functional meaning is related to
preservation of a constant atrioventricular conduc-
tion rate when excitatory or depressor neural stim-
uli act to increase or reduce heart rate. According
to this hypothesis, the neural influences that di-
rectly affect the atrioventricular conduction system

FIGURE 6 Modification of the effects of handgrip on
the R-R interval (left panel) and A-H interval (right
panel) by propranolol and atropine. Data are shown as
changes from control values. For each pair of histo-
grams, the one to the left represents the response ob-
tained before and the one to the right the response
obtained after administration of a drug. The effects
induced by handgrip on the R-R interval were studied
in subjects in sinus rhythm and those on A-H interval in
subjects during atrial pacing. Statistical symbols refer
to the difference in response to handgrip before and after
drug administration. NS = not significant.
may be viewed not as factors that tend to alter atrioventricular conduction time, but rather as an essential part of a homeostatic mechanism that prevents or limits the alterations of this function that would otherwise occur in daily life.

Another finding of our study is that the excitatory influence of isometric exercise on atrioventricular conduction can be explained entirely by a shortening of the conduction time through the atrioventricular node (represented by the A-H interval) and that no shortening whatsoever was observed with regard to the conduction time through the His-Purkinje structures (represented by the H-V interval) when the subjects were studied either in sinus rhythm or during atrial pacing. Interestingly, when we studied the depressor influence of the arterial baroreceptors, we similarly found that the effects on atrioventricular conduction could be explained entirely by an influence on the atrioventricular node, and that the His-Purkinje system was not affected (Mancia et al., 1979). A definite conclusion about this matter has to be drawn with caution, and attention has to be given to the anatomical finding obtained with histochemical techniques that the His-Purkinje fibers do possess both sympathetic and parasympathetic efferent innervation (Jacobowitz et al., 1967; Kent et al., 1974; Levy and Martin, 1979). However, on the basis of our present observations, it is at least possible to suggest that physiological modulation of the atrioventricular conduction system, be it excitatory or inhibitory in nature, does not make much use of this innervation and rather occurs through alterations of the functional properties of the atrioventricular node. That is, the His-Purkinje portion of the atrioventricular conduction system seems to remain relatively unaffected by ordinary neural influences.

The remaining aspects of our study to be discussed are: (1) the different pattern of the excitation provided by isometric exercise on the atrioventricular node as compared to the sinus node and (2) the interaction of this excitation with the inhibitory influence exerted by the arterial baroreceptors. The former point is raised by the observation that the efficacy of atropine and propranolol in blocking the effects of isometric exercise on R-R interval was different from their effects on the P-R and A-H intervals. In addition to the data shown in Figures 3, 4, and 5, an illustration of this phenomenon is given in Figure 6. It can be seen that the reduction in the R-R interval that was induced by isometric exercise was little affected by propranolol, whereas it showed a large impairment after administration of atropine. However, when the shortening of the A-H interval induced by exercise was considered (during atrial pacing), both drugs induced an approximately similar reduction of the original response. These findings suggest that isometric exercise may transmit its excitatory influence to the sinoatrial node more through engagement of the parasympathetic division, while using the parasympathetic and the sympathetic nerves to an approximately similar extent to excite the atrioventricular node. Both sympathetic and parasympathetic tonic influences on the human atrioventricular node (though not on His structures) have been shown in a recent study (Tonkin et al., 1960).

The last point, i.e., the interaction between isometric exercise and baroreceptors, will be discussed only briefly. In a previous study of subjects during atrial pacing, a pressure rise of 19 mm Hg induced by phenylephrine stimulated the arterial baroreceptors to prolong markedly atrioventricular conduction time (Mancia et al., 1979). In our present study of atrial pacing, isometric exercise increased arterial blood pressure to a greater extent (27 mm Hg). Yet a shortening and not a lengthening of the atrioventricular conduction time ensued. This indicates that the excitatory influence exerted by isometric exercise largely predominates over the inhibitory baroreceptor effect. The mechanism for this predominance has been ascribed to a central interaction which prevents the baroreceptors from influencing the sinoatrial node during exercise (Cunningham et al., 1972; Mancia et al., 1978). Our present data suggest that a similar phenomenon also exists for modulation of the atrioventricular node.

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