Effects of Clonidine on Heart Rate Variability

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SUMMARY

We compared the effects of intravenous infusions of clonidine and placebo on heart rate variability in 10 healthy male controls. Clonidine produced a significant decrease in blood pressure and significantly decreased the heart rate variability during quiet standing.

Key Words:
Clonidine  Antimuscarinic  Posture  Heart rate  Heart rate variability

ClONIDINE is an antihypertensive agent that is widely used in clinical practice. Clonidine is an alpha-2 adrenergic agonist and presumably exerts its effect by stimulating alpha adrenoceptors in the brain stem. Recent evidence suggests that clonidine decreases heart rate (HR) variability both in experimental animals and in patients with hypertension. Clonidine produced a significant decrease of both mid frequency (MF) and high frequency (HF) power in subjects with essential hypertension in sitting posture. These studies used spectral analysis of HR and blood pressure (BP). Several reports suggest that vagal activity influences HR variability at all frequencies up to 0.5 Hz, while the sympathetic nervous system affects HR variability below 0.15 Hz. Thus, the high frequency (HF: 0.2–0.5 Hz) power is specifically related to vagal activity and the mid frequency (MF: 0.07–0.15 Hz) power is dually influenced by cholinergic and beta-adrenergic activity. The relative influence of the two limbs of the autonomic nervous system on HR variability is shifted from vagal to sympathetic predominance during the change from supine to standing posture.

We have been conducting studies on HR variability in normal controls and patients with anxiety and depression. Our previous studies found that panic disorder patients have a decreased HR variability as measured by the standard deviation (SD), mean consecutive difference (MCD) and the SD
of the MCD compared to normal controls, especially in standing posture.\textsuperscript{7,8} Patients with panic disorder experience symptoms of panic attacks, when challenged with the alpha-2 adrenergic antagonist, yohimbine, which is known to increase the firing of locus coeruleus.\textsuperscript{9} Panic disorder patients have also been reported to have exaggerated hypotensive responses to clonidine, an alpha-2 adrenergic agonist.\textsuperscript{10} In this pilot study, we examined the effect of intravenous clonidine on HR variability in healthy controls both in supine and standing postures using time domain measures of HR variability to understand the influence of the alpha-2 adrenergic effects on HR variability. To our knowledge, this is the first study to examine the effects of clonidine on HR variability in healthy controls.

**Materials and Methods**

**Subjects**

Ten male volunteers participated in this study. Their age was 32.6±6.8 years (mean±SD). All subjects were nonsmokers. They were healthy and routine blood chemistry tests and the electrocardiogram were within normal ranges. All subjects signed an informed consent prior to their participation in the study.

**Procedure**

The experiment was performed in the morning and the subjects were on an empty stomach. There was a gap of at least 3 days between the infusions of clonidine and placebo. Prior to the infusion, they were seated in a chair for 10 min. The infusion of placebo (20 ml of normal saline) or clonidine (2 mcg of clonidine per kg body weight in 20 ml of normal saline) were given under double-blind conditions while the subjects were seated. BP and HR were monitored at regular intervals using a Hewlett Packard 78352 A Patient Monitor using limb leads and a brachial artery cuff attached to one arm and a 78173 A ECG Monitor (Palo Alto, California, USA). The ECG was recorded at a paper velocity of 50 mm per second.

At the end of the infusion, the patients assumed a supine posture. After 45 min of supine posture, the subjects were asked to stand up actively. The ECG was recorded continuously for 1 min prior to standing-up and for 1 min during and after the change of posture. They remained in quiet standing posture for 15 min and the ECG was continuously recorded for 5 min. Then, they assumed a supine posture and were supine until the end of the experiment. While supine (about an hour before the conclusion of the experiment), they were also asked to breath deeply at a rate of six breaths per
minute. The ECG was continuously recorded for 1 min prior to deep breathing and for 1 min during deep breathing. No mechanical techniques were used to monitor the rate of respiration during that period.

R-R intervals reported in this study were measured in millimeters from the ECG strips manually. The following variables were used in the analyses. R-R variability was calculated for 150 consecutive beats during the standing posture after 10 min of quiet standing. This method has been used previously.7),11),12) R-R variability was also calculated for the R-R intervals during 1 min of resting supine posture and 1 min of deep breathing.

The following measures of variability were used.7),11),12) Standard deviation (SD) of the R-R intervals, which measures the long-term variance, the mean consecutive difference of successive R-R intervals (MCD) and the standard deviation of the MCD (MCSD), which measure the short-term variance of the R-R intervals. The SD, MCD and MCSD were all corrected for heart rate by dividing each of these measures by the mean R-R interval and multiplying it by 1,000.7),12) This was done because heart rate can influence the variance. These new measures are referred to in this paper as SDC, MCDC and MCSDDC.

Supine HR is the average of five heart rate values before standing up and standing HR is the average of values at 1 and 2 min after standing up. Supine SBP and DBP are the averages of two values before standing up and standing SBP and DBP are the values 2 min after standing up.

Statistical analysis

BMDP statistical software (Berkeley, California, USA) was used for the analyses. Paired 't' tests were used to compare different variables between placebo and clonidine conditions. Two-tailed tests with a probability value of <0.05 were accepted as significant.

Results

Heart rate and blood pressure

Table I shows the values of HR and BP during placebo and clonidine conditions. Although there was no significant change in supine HR between placebo and clonidine conditions, standing HR was significantly higher for the clonidine condition. The supine and standing SBPs and DBPs were significantly lower during clonidine condition.

R-R variability

There was no significant difference in any of the measures (SDC, MCDC
Table I. Heart Rate, Blood Pressure, and Heart Rate Variability Measures

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Clonidine</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>58±8</td>
<td>58±7</td>
<td>0.4</td>
<td>9</td>
<td>ns</td>
</tr>
<tr>
<td>Standing</td>
<td>76±9</td>
<td>87±9</td>
<td>3.38</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>118±8</td>
<td>109±5</td>
<td>3.01</td>
<td>9</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Standing</td>
<td>123±10</td>
<td>107±9</td>
<td>4.24</td>
<td>9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>64±9</td>
<td>51±11</td>
<td>6.71</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standing</td>
<td>74±10</td>
<td>62±12</td>
<td>4.23</td>
<td>9</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

- **R-R Variability**
  - **Standing**
    - SDC: 69.3±32.1 vs. 59.6±25.2, t = 0.91, df = 9, p = ns
    - MCDC: 27.3±8.4 vs. 17.7±6.2, t = 4.15, df = 9, p < 0.005
    - MCSDC: 29.8±20.6 vs. 17.4±8.2, t = 4.23, df = 9, p < 0.005
  - **Supine**
    - SDC: 72.7±18.0 vs. 63.3±23.7, t = 1.24, df = 9, p = ns
    - MCDC: 44.2±19.0 vs. 47.5±28.4, t = 0.66, df = 9, p = ns
    - MCSDC: 35.6±11.9 vs. 34.5±15.4, t = 0.31, df = 9, p = ns
  - **Supine Deep Breathing**
    - SDC: 112.8±28.5 vs. 108.0±29.3, t = 1.13, df = 9, p = ns
    - MCDC: 63.3±28.1 vs. 66.7±34.5, t = 0.57, df = 9, p = ns
    - MCSDC: 61.1±30.2 vs. 66.3±27.0, t = 0.74, df = 9, p = ns

SDC, MCDC, and MCSDC are in values corrected for mean R-R interval.

or MCSDC) of R-R variability between the two conditions during supine or supine deep breathing conditions (Table I). After quiet standing for 10 min, the R-R variability was significantly lower during clonidine condition compared to the placebo condition as measured by MCDC and MCSDC. Though the SDC was lower after clonidine administration, this was not significantly different from the placebo condition.

**DISCUSSION**

This pilot study examined the effects of clonidine on HR variability. Since we did not have access to computerized techniques to record and analyze the data, the interpretation of our findings is very limited. The significant increase in HR upon standing after clonidine infusions is probably due to a reflex tachycardia due to a decrease in peripheral vascular resistance. There was a significant decrease of the standing HR variability measures, MCDC and MCSDC. It should be noted that the HR variability measures were corrected for the mean HR. Previous studies suggest that the MCD is a more statistically effective measure of short-term HR variability. There is also evidence suggesting that there is a high degree of correlation between the MCD and the 0.25 Hz respiratory peak of the R-R
interval power spectrum. These findings suggest an atropine-like effect for clonidine. However, due to the lack of information on the mid frequency HR variability from our analyses, it is difficult to attribute the decrease in MCD to exclusively an atropine-like effect on respiratory-related HR variability.

There is evidence to suggest that stimulation of presynaptic alpha adrenergic receptors, which are localized on peripheral cholinergic nerve terminals, can inhibit the release of acetylcholine. Thus it is possible that clonidine alters HR variability measures by stimulating M1 receptors, thereby decreasing the release of acetylcholine. The possible antimuscarinic effect of clonidine is of interest because of the hypothesis that the antimuscarinic effects of clonidine may contribute to its antihypertensive effects. Muscarinic agents that cross the blood brain barrier and cholinesterase inhibitors given intravenously or intracerebrally can produce an increase in BP. Cholinergic pathways in the central nervous system also appear to be involved in certain models of hypertension in experimental animals. However, the possible antimuscarinic effect of clonidine should be interpreted with caution as there was no significant difference in the HR variability measures after clonidine during supine posture. There are several methodological limitations to this study in that we did not use computerized techniques to record and analyze the data and also we do not have continuous BP recordings. However, to our knowledge, this is the first report on the effects of clonidine on HR variability in normal subjects.

REFERENCES