Effects of Intravenous Dexmedetomidine in Humans

II. Hemodynamic Changes

Byron C. Bloor, Ph.D.,* Denham S. Ward, M.D., Ph.D.,† Jon P. Belleville, M.D.,‡ Mervyn Maze, M.B., Ch.B.§

Dexmedetomidine (DMED) is a novel clonidine-like compound known to have sedative, analgesic, and cardiovascular stabilizing qualities. DMED is a more highly selective α₂-adrenergic agonist than clonidine. This investigation examined the hemodynamic effects of four selected iv doses in consenting healthy male volunteers. In a randomized, double-blind, placebo-controlled trial subjects received 0 (n = 9), 0.25 (n = 6), 0.5 (n = 6), 1.0 (n = 6), or 2.0 (n = 10) μg/kg of DMED by infusion (2 min). ECG, heart rate (HR), arterial blood pressure (MABP), bioimpedance cardiac output (CO), and plasma catecholamines concentrations (CA) were monitored from 90 min before to 360 min after infusion. Plasma DMED concentrations were measured. DMED produced a maximum decrease in MABP at 60 min of 14%, 16%, 23%, and 27% for the 0.25, 0.5, 1.0, and 2.0 μg/kg groups, respectively (P < .05). At 330 min MABP remained below baseline by 8% and 17% at the two largest doses (P < .05). Both HR and CO decreased maximally by both 17% at 105 min. The two largest doses produced a transient (peak at 3 min lasting < 11 min) increase in MABP (16 ± 2.5 and 24 ± 10 mmHg, respectively; P < .05) with a concomitantly reduced CO (41%, 2 μg/kg; P < .05) and HR (22%, 2 μg/kg; P < .05), whereas systemic vascular resistance doubled. Even the lowest dose decreased CA immediately to values close to 20 pg/ml for 5 h. A 2-min iv infusion of DMED produced a transient increase in MABP and a longer lasting decrease in MABP and CA. These DMED doses were well tolerated in the healthy volunteers. (Key words: Hemodynamics. Pharmacology: dexmedetomidine. Receptors: α₂-adrenergic. Sympathetic nervous system: α₂-adrenergic agonist; dexmedetomidine.)

CLONIDINE AND OTHER α₂-adrenergic agonists have been shown to have beneficial properties in the anesthetic setting including sedation,1,2 analgesia,3,4 anxiolysis,5 improved hemodynamic stability,1,6,7 and muscle flaccidity.6,9 Dexmedetomidine (DMED) is a novel α₂-adrenergic agonist that may have different clinical properties than clonidine for the following reasons: 1) DMED is seven times more selective than clonidine for the α₂-adrenergic receptor10,11; 2) DMED is a full agonist at the α₂-adrenoceptor, whereas clonidine is only a partial agonist12; and 3) the maximum reduction in inhalational anesthetic requirement to maintain 1 MAC provided by clonidine is 50%,13 whereas DMED has been shown to result in approximately a 90% reduction.14,15 These differences in DMED’s pharmacologic characteristics may lead to therapeutically beneficial properties.

The α₂-adrenergic compounds were first developed for use as a vasoconstrictor to diminish nasal congestion but were subsequently found to be more useful as antihypertensive agents.16 The known cardiovascular properties of these compounds include a biphasic response (pressor followed by a depressor) when these compounds are administered intravenously (iv).

While hemodynamic effects of α₂-adrenoceptor agonists have been extensively studied in dogs,15,17-19 there is evidence to suggest that dog may not be the most appropriate model to study human α₂-adrenoceptor mediated hemodynamic responses15 (see Discussion). The purpose of this study was to examine the hemodynamic effects of four incremental iv doses of DMED—0.25, 0.5, 1.0, and 2.0 μg/kg—in healthy adult human male volunteers. The ventilatory and metabolic rate data taken simultaneously from this study population are reported in an companion paper.20

Methods

SUBJECTS

The UCLA Human Subjects Protection Committee approved the protocol. All subjects gave written informed consent and DMED was supplied under FDA Investigational New Drug Approval. Thirty-seven consenting healthy male volunteers between the ages of 18 and 45 years, weighing less than 100 kg were used for this study. Their health was documented by history and physical examinations and laboratory tests, which included a CBC, serum chemistry panel, urinalysis, urine drug screen, and ECG. Subjects evidencing acute or chronic disease, drug use, or routine use of medications were excluded from the study. All subjects were asked and agreed to refrain from all medications, tobacco, and ethanol for at least 24

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h prior to the study day and to eat nothing after midnight prior to the experiment.

Dexmedetomidine was administered iv at four dose levels. All subjects in a dose group were studied before proceeding to the next higher dose. Placebo-treated subjects were interspersed within each dose group. In each of the 0.25, 0.5, and 1.0 μg/kg dose groups, 6 subjects received dexmedetomidine and 2 received placebo. In the 2.0 μg/kg dose group, 10 subjects received dexmedetomidine and 8 received placebo. Thus, a total of 37 subjects were studied, of whom 9 received placebo. Each subject participated in only one experiment.

**Hemodynamic Monitoring**

The subject arrived at the testing facility at approximately 8 AM. An iv cannula (20-G) was placed into a large forearm vein for fluid and drug administration. The radial artery was cannulated with a 20- or 22-G catheter for continuous blood pressure monitoring (Abbott disposable transducer, North Chicago, IL) and blood sampling. Electrodes for the measurement of cardiac output by thoracic bioimpedance were positioned on each subject according to the methods described by the manufacturer (Bo-Med). Intravenous fluids were given as follows: normal saline was infused during the first hour to replenish one half the subject’s fluid deficit and then at a maintenance rate of 2.5 ml ⋅ kg⁻¹ ⋅ hr⁻¹ for the remainder of the study. Subjects were studied in a semireclining position. While hemodynamic measurements were monitored continuously throughout the study period, 4-min epochs were tabulated every 45 min to match the time of other measurements (1-min epochs were used where indicated in certain tables). Two baseline measurements were made at 90 and 45 min prior to the start of the drug infusion. Data was recorded on a polygraph (Hewlett Packard 7754A, Waltham, MA) and collected and processed, online, by computer. Hypercapnic ventilatory response measurements were determined in these same subjects and reported in the accompanying manuscript. Hemodynamic parameters reported herein were taken prior to the hypercapnic challenges to avoid confounding the hemodynamic parameters.

**Blood Samples**

The arterial blood samples were collected at the same intervals in an EDTA tube and immediately centrifuged and the plasma frozen at −80°C. Catecholamines were assayed by high performance liquid chromatography. The lower limit of epinephrine and norepinephrine detection by this assay is 20 pg/ml. Dexmedetomidine concentrations were assayed by gas chromatography-mass spectrometry.

**Statistical Analysis**

The comparability of data from the pooled placebo, 0.25, 0.5, 1.0, and 2.0 μg/kg dose groups with regard to age, weight, and height was examined using a one-way general linear model analysis of variance for unbalanced parallel designs. Comparability of data from the treatment groups with regard to racial distribution, baseline physical exam, medical history, and substance consumption (nicotine, caffeine, alcohol) was performed using the likelihood ratio statistic. Hemodynamic measurements were analyzed using two-way analysis of variance with a post hoc Newman-Keuls tests (SAS, BMDP, Los Angeles, CA). Comparisons within a dose group were made to the individual subject’s control measurements. Comparison across the dose groups at a given time were made by comparing different subjects. Thus, more statistical power is available for detecting differences from baseline within a dose group than differences from placebo across dose groups. All data are reported as mean ± SD.

**Results**

There were no significant differences among the treatment groups with regard to age, weight, height, race, baseline physical examination, medical history, substance consumption, laboratory test results, or ECG. There were no significant differences in the baseline periods taken at 90 and 45 min prior to the start of the drug infusion. These two sample measurements were averaged and used as a single baseline measurement. There were no significant differences in the baseline between treatment groups and no discernible time effect in the placebo group. As

**Fig. 1.** Mean systolic and diastolic blood pressure are shown 4 min before, during (2 min), and for 10 min after the drug infusion for the placebo and 0.25, 0.5, 1.0, and 2.0 μg/kg treatment groups. Table 2 contains mean ± SD for selected time points at MABP.
### Table 1. Mean Arterial Blood Pressure after Four Doses of Dexmedetomidine

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>−90 and −45 min</th>
<th>1 min Preinfusion</th>
<th>0–1 min</th>
<th>10 min</th>
<th>60 min</th>
<th>105 min</th>
<th>150 min</th>
<th>195 min</th>
<th>240 min</th>
<th>285 min</th>
<th>330 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>98 ± 11</td>
<td>96 ± 10</td>
<td>96 ± 11</td>
<td>96 ± 10</td>
<td>93 ± 9</td>
<td>95 ± 10</td>
<td>95 ± 11</td>
<td>95 ± 11</td>
<td>96 ± 10</td>
<td>96 ± 9</td>
<td>97 ± 9</td>
</tr>
<tr>
<td>0.25</td>
<td>97 ± 12</td>
<td>91 ± 7</td>
<td>90 ± 5</td>
<td>85 ± 15*</td>
<td>84 ± 8*</td>
<td>84 ± 4*</td>
<td>88 ± 8*</td>
<td>90 ± 10</td>
<td>91 ± 9</td>
<td>92 ± 9</td>
<td>92 ± 10</td>
</tr>
<tr>
<td>0.5</td>
<td>98 ± 4</td>
<td>98 ± 5</td>
<td>103 ± 10</td>
<td>85 ± 6*</td>
<td>83 ± 7*</td>
<td>86 ± 8*</td>
<td>87 ± 8*</td>
<td>90 ± 6*</td>
<td>91 ± 6*</td>
<td>95 ± 6</td>
<td>97 ± 6</td>
</tr>
<tr>
<td>1.0</td>
<td>102 ± 7</td>
<td>100 ± 7</td>
<td>115 ± 6*</td>
<td>94 ± 6*</td>
<td>79 ± 6*</td>
<td>81 ± 7*</td>
<td>83 ± 5*</td>
<td>85 ± 6*</td>
<td>88 ± 8*</td>
<td>91 ± 7*</td>
<td>94 ± 9*</td>
</tr>
<tr>
<td>2.0</td>
<td>99 ± 11</td>
<td>95 ± 11</td>
<td>118 ± 12*</td>
<td>103 ± 9</td>
<td>72 ± 8*</td>
<td>72 ± 6*</td>
<td>74 ± 7*</td>
<td>78 ± 7*</td>
<td>78 ± 8*</td>
<td>82 ± 8*</td>
<td>82 ± 8*</td>
</tr>
</tbody>
</table>

Values are mean ± SD (mmHg).

*P < .05 versus baseline.

† P < .05 versus placebo.

### Table 2. Heart Rate after Four Doses of Dexmedetomidine

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>−90 and −45 min</th>
<th>1 min Preinfusion</th>
<th>0–1 min</th>
<th>10 min</th>
<th>60 min</th>
<th>105 min</th>
<th>150 min</th>
<th>195 min</th>
<th>240 min</th>
<th>285 min</th>
<th>330/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>57 ± 9</td>
<td>57 ± 9</td>
<td>56 ± 8</td>
<td>56 ± 8</td>
<td>58 ± 8</td>
<td>58 ± 6</td>
<td>58 ± 6</td>
<td>57 ± 6</td>
<td>57 ± 6</td>
<td>58 ± 6</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>0.25</td>
<td>56 ± 7</td>
<td>55 ± 8</td>
<td>49 ± 5*</td>
<td>58 ± 10</td>
<td>52 ± 7</td>
<td>52 ± 7</td>
<td>52 ± 6</td>
<td>52 ± 6</td>
<td>53 ± 8</td>
<td>53 ± 7</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>0.5</td>
<td>58 ± 9</td>
<td>57 ± 9</td>
<td>53 ± 8*</td>
<td>62 ± 8*</td>
<td>55 ± 9</td>
<td>53 ± 8*</td>
<td>53 ± 9*</td>
<td>53 ± 9*</td>
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<td>55 ± 10</td>
<td>56 ± 11</td>
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<tr>
<td>1.0</td>
<td>62 ± 9</td>
<td>62 ± 9</td>
<td>49 ± 14*</td>
<td>57 ± 10*</td>
<td>55 ± 6*</td>
<td>50 ± 7*</td>
<td>51 ± 7*</td>
<td>53 ± 8*</td>
<td>54 ± 9*</td>
<td>56 ± 8*</td>
<td>56 ± 9*</td>
</tr>
<tr>
<td>2.0</td>
<td>66 ± 7</td>
<td>57 ± 9</td>
<td>44 ± 11*</td>
<td>54 ± 11*</td>
<td>53 ± 9*</td>
<td>50 ± 9*</td>
<td>50 ± 9*</td>
<td>51 ± 8*</td>
<td>51 ± 9*</td>
<td>52 ± 8*</td>
<td>53 ± 10*</td>
</tr>
</tbody>
</table>

Values are mean ± SD (beats/min).

*P < .05 versus baseline.
there was no time effect in the placebo group, statistical comparisons were made to the baseline periods for each individual.

**BLOOD PRESSURE**

A biphasic effect on blood pressure was seen in the two largest DMED dose groups (1 and 2 µg/kg), which was characterized by an initial increase (fig. 1 and table 1) followed by a decrease (table 1). The largest dose of DMED increased systolic, mean, and diastolic blood pressure by 11%, 24%, and 29%, respectively. Blood pressure returned to baseline within 11 ± 3 min. One µg/kg increased systolic, mean, and diastolic blood pressure by 7, 16, and 20%, respectively, and all passed through baseline within 7 ± 2 min. This transient increase in pressure peaked at about 3 min after the start of the DMED infusion (fig. 1).

A decline in blood pressure (depressor phase) occurred in all treatment groups, reaching its maximum near 60 min. Diastolic blood pressure decreased by 13%, 13%, 20%, and 26% (P < .05 all groups) from baseline, reaching 68 ± 8, 66 ± 5, 63 ± 5, and 57 ± 6 mmHg in the 0.25, 0.5, 1.0, and 2.0 µg/kg dose groups, respectively. Mean arterial blood pressure (MABP) remained significantly reduced in all the 0.25, 0.5, 1.0, and 2.0 µg/kg treated groups through 150, 240, 330, and 330 min, respectively (table 2).

**HEART RATE**

Baseline heart rate (HR) in these healthy subjects was 59 ± 1.3 bpm across all groups (fig. 2 and table 2). HR was decreased after DMED at two different points in time.

**ESTIMATED CARDIAC OUTPUT AND SYSTEMIC VASCULAR RESISTANCE**

Cardiac output (CO) was significantly decreased by the infusion of DMED in the 0.5, 1.0, and 2.0 µg/kg groups (fig. 3 and table 3). The dose-dependent decrease in CO reached its maximum at about 3 min after the start of the 2 min DMED infusion (fig. 3). Systemic vascular resistance was found to double during the peak increase in MABP.

The cardiac output was much less reduced during the depressor phase. It remained significantly depressed for 195, 330, and 150 min following the 0.5, 1.0, and 2.0 µg/kg doses, respectively (table 4). Maximal reductions of 19%, 12%, and 18% occurred 95, 150, and 105 min
### TABLE 3. Cardiac Output after Four Doses of Dexmedetomidine

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>Baseline Data</th>
<th>Time Post Drug Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-90 and -45 min</td>
<td>1 min Preinfusion</td>
</tr>
<tr>
<td>Placebo</td>
<td>100 ± 17</td>
<td>98 ± 18</td>
</tr>
<tr>
<td>0.25</td>
<td>100 ± 19</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>0.5</td>
<td>100 ± 36</td>
<td>97 ± 34</td>
</tr>
<tr>
<td>1.0</td>
<td>100 ± 21</td>
<td>98 ± 21</td>
</tr>
<tr>
<td>2.0</td>
<td>100 ± 24</td>
<td>98 ± 21</td>
</tr>
</tbody>
</table>

Values are mean ± SD (percent of control).  
* P < .05 versus baseline.  
† P < .05 versus placebo.

### TABLE 4. Plasma Norepinephrine Levels after Four Doses of Dexmedetomidine

<table>
<thead>
<tr>
<th>DMED Dose (µg/kg)</th>
<th>Baseline</th>
<th>10 min</th>
<th>60 min</th>
<th>105 min</th>
<th>150 min</th>
<th>195 min</th>
<th>240 min</th>
<th>285 min</th>
<th>330 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>140 ± 50</td>
<td>150 ± 30</td>
<td>150 ± 30</td>
<td>140 ± 50</td>
<td>140 ± 40</td>
<td>130 ± 60</td>
<td>130 ± 50</td>
<td>140 ± 60</td>
<td>130 ± 40</td>
</tr>
<tr>
<td>0.25</td>
<td>110 ± 40</td>
<td>60 ± 40†</td>
<td>70 ± 30†</td>
<td>70 ± 20†</td>
<td>80 ± 30†</td>
<td>90 ± 40†</td>
<td>100 ± 50*</td>
<td>80 ± 30*</td>
<td>100 ± 50*</td>
</tr>
<tr>
<td>0.5</td>
<td>140 ± 90</td>
<td>30 ± 20†</td>
<td>40 ± 30†</td>
<td>50 ± 30†</td>
<td>60 ± 50†</td>
<td>70 ± 50†</td>
<td>80 ± 40†</td>
<td>100 ± 90*</td>
<td>100 ± 60*</td>
</tr>
<tr>
<td>1.0</td>
<td>120 ± 30</td>
<td>±20*†</td>
<td>20 ± 10*†</td>
<td>20 ± 10*†</td>
<td>30 ± 10*†</td>
<td>40 ± 10*†</td>
<td>50 ± 50*†</td>
<td>50 ± 40*†</td>
<td>50 ± 40*†</td>
</tr>
<tr>
<td>2.0</td>
<td>120 ± 70</td>
<td>±20*†</td>
<td>±20*†</td>
<td>±20*†</td>
<td>±20*†</td>
<td>±20*†</td>
<td>±20*†</td>
<td>±20*†</td>
<td>±20*†</td>
</tr>
</tbody>
</table>

Values are mean ± SD (pg/ml).  
* P < .05 versus baseline.  
† P < .05 versus placebo.
following the 0.5, 1.0, and 2.0 μg/kg treatment groups, respectively (table 3).

**CATECHOLAMINES**

The lowest level of detection for the assay used for norepinephrine and epinephrine was 20 pg/ml. Levels below this have no known physiologic significance (tables 4 and 5). Under the conditions of this study (unstimulated subjects in the semireclining position) plasma catecholamine levels were often found to be indistinguishable from 20 pg/ml. For reporting purposes a value of 20 pg/ml was used whenever this occurred.

Plasma norepinephrine levels (140 ± 50 pg/ml) were low in the placebo group and did not change over time. Even so, the plasma norepinephrine concentrations were reduced in all dose groups following DMED infusion through 285 min (table 4). Baseline plasma epinephrine levels were 40 ± 20 pg/ml. Few changes in plasma epinephrine levels were found (table 5).

**ECG ABNORMALITIES**

There were four episodes of alterations in ECG rhythm noted in these studies. Three episodes occurred in the 2.0 μg/kg group and one in the placebo group. In the 2.0 μg/kg group there was one event of a R-R interval lasting 2.4 s and two episodes of junctional escape rhythm. These events occurred within minutes of the drug infusion and required no medical intervention. In the placebo group a single premature ventricular contraction was noted in one subject 24 min after infusion.

**PLASMA DMED LEVELS**

The first DMED plasma levels were obtained at 10 min after the DMED infusion (i.e., after the pressor effect; table 6). The mean dexmedetomidine concentrations, at 10 min after injection, were 200 ± 110, 350 ± 60, 940 ± 180, and 2,350 ± 450 pg/ml in the four groups. At 330 min, subjects in the 2.0 μg/kg dose group still had a concentration of 130 ± 40 pg/ml (table 6).

**Discussion**

Clonidine, the prototypical α₂-adrenoceptor agonist, has been widely studied in humans. When given by rapid iv administration in humans, clonidine exerts a biphasic effect on arterial blood pressure starting with transient hypotension followed by a longer lasting reduction in blood pressure. The increase in blood pressure is mediated by an α₂-adrenoceptor-induced vasoconstrictive response in the peripheral vasculature. The blood-pressure-lowering effects of clonidine are largely mediated by centrally located receptors both of the α₂-adrenergic and the imidazole receptor classes. This hypotensive effect is consistent with a resetting of the baroreceptor system to maintain a lower blood pressure. The result is a marked reduction in sympathetic tone and an enhanced parasympathetic outflow. Clonidine’s ability to reduce blood pressure is limited to these effects on the autonomic nervous system (e.g., clonidine is not a vasodilator). Clonidine reduces HR by reduced sympathetic tone and the increased vagal tone. Additionally, increased blood pressure (e.g., by a rapid iv injection) will result in a baroreflex-mediated reduction in heart rate.

Dexmedetomidine’s hemodynamic profile was found to be similar to that previously reported for clonidine. While the lower two doses of DMED (0.25 and 0.5 μg/kg) resulted in only a reduction in blood pressure, the two larger doses produced a biphasic effect on blood pressure. An initial transient increase in blood pressure, presumably mediated by peripheral vasoconstriction, was followed by a reduction in blood pressure presumably due to both a centrally and peripherally mediated sympatholytic action. The reduction in circulating catecholamines is consistent with the long-lasting reduction in sympathetic tone by these compounds.

Schmeling et al. reported a 39% and a 160% increase in MABP and systemic vascular resistance (SVR), respec-

**Table 5. Plasma Epinephrine Levels after Four Doses of Dexmedetomidine**

<table>
<thead>
<tr>
<th>DMED Dose (μg/kg)</th>
<th>Baseline</th>
<th>10 min</th>
<th>60 min</th>
<th>105 min</th>
<th>150 min</th>
<th>195 min</th>
<th>240 min</th>
<th>285 min</th>
<th>330 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>40 ± 20</td>
<td>40 ± 30</td>
<td>50 ± 10</td>
<td>40 ± 30</td>
<td>40 ± 30</td>
<td>50 ± 30</td>
<td>50 ± 30</td>
<td>50 ± 30</td>
<td>58 ± 58</td>
</tr>
<tr>
<td>0.25</td>
<td>50 ± 20</td>
<td>40 ± 20</td>
<td>20 ± 10*</td>
<td>30 ± 30</td>
<td>40 ± 30</td>
<td>50 ± 30</td>
<td>50 ± 30</td>
<td>71 ± 44</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>70 ± 50</td>
<td>40 ± 30</td>
<td>50 ± 20*</td>
<td>40 ± 50</td>
<td>60 ± 60</td>
<td>50 ± 40</td>
<td>66 ± 54</td>
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<td>1.0</td>
<td>80 ± 50</td>
<td>±20*</td>
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<td>51 ± 22</td>
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<td>20 ± 10</td>
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<td>±20</td>
<td>±20</td>
<td>±20</td>
<td>20 ± 10</td>
<td>23 ± 12</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD (pg/ml). *P < .05 versus baseline.
tively, following a 10-min infusion of 2.5 μg/kg DMED in awake dogs. This was followed by a modest 8% reduction in blood pressure at 60 min. In our study a slightly lower dose (2.0 vs. 2.5 μg/kg DMED) infused faster (2 min vs. 10 min) resulted in a 20% and 110% increase in MABP and SVR, respectively (vs. 39% and 160% Schmeling et al.), and a subsequent 27% reduction in blood pressure (vs. 8% Schmeling et al.). It is evident that dogs exhibit a more profound vasoconstrictive response to α2 agonists than that seen in humans in this study. There is much evidence to suggest a species-dependent heterogeneity of the α2-adrenergic receptor (see Nichols et al. for a review).

As such, dog may not be an appropriate model for studying cardiovascular properties of this class of agent with reference to humans.

Kallio et al. reported an initial brief increase in BP (8 mmHg, MABP) associated with marked, but transient reduction in heart rate 2 min after a 75-μg iv dose of DMED in humans. In the present study there were two nadirs in the heart rate. The first and most marked was during the hypertensive peak just after the drug infusion. The 2.0 μg/kg DMED dose produced the largest increase in blood pressure and resulted in the lowest heart rates (44 ± 10 bpm). As this decrease in heart rate was associated with an increase in systemic blood pressure it is probably mediated by the baroreceptor reflex. A reduced infusion rate of DMED may decrease the hypertensive and thereby reduce the associated bradycardia. The second and less prominent nadir in heart rate, which occurred between 60 and 120 min, is probably caused by both an increased parasympathetic tone and a reduction in sympathetic tone.

In this group of healthy young subjects with low resting heart rates, three vagally mediated dysrhythmias were observed in the 2.0 μg/kg DMED-treated dose group. These events occurred within minutes of the drug infusion and required no medical intervention. These events were associated with an increase in blood pressure and a reflex-mediated decrease in HR. It is probable that the dysrhythmias may be avoided by minimizing the pressor response by slowing the rate of DMED infusion. In all likelihood, atropine pretreatment (or any other atropine-like drug) would have prevented these dysrhythmias.

α2-Adrenergic agonists are known to increase the gain of the baroreceptor system. The low resting HR of the subjects in this study (55 ± 8 to 62 ± 9 bpm) implies a higher vagal tone in these individuals than subjects with more “normal” (i.e., closer to 80 bpm) heart rates. Less well conditioned individuals with higher heart rates and lower vagal tone should be less susceptible to bradycardia mediated by increased gain in the baroreceptor system.

Caution must be exercised in the interpretation of the cardiac output data. A bio-impedance method was used that may limit its validity. The results of this study are consistent with other studies using different methodologies. Maze et al. using a flow-directed pulmonary artery thermal dilution catheter, have shown comparable reductions in CO at similar DMED plasma levels. Kallio et al., using a two-dimension Doppler-echocardiographic method, reported a 23% reduction in CO 60 min after a single 100-μg dose of medetomidine. These findings are also consistent with those reported by others after clonidine. The CO data obtained during and shortly after the DMED infusion from the present study indicates a marked reduction during the early transient increase in blood pressure. Similar reductions in CO shortly after or during DMED infusion have been found in awake and anesthetized dogs. Our data showing a marked transient reduction in CO merit further study and should be corroborated by studies in humans with invasive CO techniques. If these effects are substantiated, this is further reason to avoid the initial transient effect by using a lower infusion rate or different route of administration.

There was an approximate doubling of the SVR during the period of increased arterial blood pressure (initial transient pressor effect) and reduced CO. This marked increase in SVR was short-lived (less than 2 min). The combined reduction in sympathetic activity and the apparent increased SVR would be undesirable in patients.

\[\text{VALUES ARE MEAN ± SD (PM/ML).}\]

\[
\begin{array}{|c|c|c|c|c|c|c|c|c|c|}
\hline
\text{DMED Dose (μg/kg)} & \text{Baseline} & \text{10 min} & \text{60 min} & \text{105 min} & \text{150 min} & \text{195 min} & \text{240 min} & \text{285 min} & \text{330 min} \\
\hline
\text{Placebo} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0.25 & 0 & 200 ± 110 & 90 ± 40 & 90 ± 20 & 70 ± 20 & 50 ± 30 & 50 ± 30 & 40 ± 20 & 40 ± 20 \\
0.5 & 0 & 350 ± 60 & 150 ± 50 & 120 ± 30 & 110 ± 30 & 80 ± 30 & 60 ± 30 & 70 ± 40 & 50 ± 30 \\
1.0 & 0 & 940 ± 180 & 290 ± 40 & 200 ± 40 & 180 ± 30 & 110 ± 50 & 100 ± 40 & 80 ± 30 & 40 ± 30 \\
2.0 & 0 & 2,350 ± 450 & 600 ± 110 & 470 ± 100 & 350 ± 60 & 260 ± 50 & 190 ± 40 & 160 ± 4 & 120 ± 40 \\
\hline
\end{array}
\]

Footnote: Unpublished data.

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with impaired cardiac function. The reduction in sympathetic tone, evidenced by decreased circulating plasma catecholamines (tables 5 and 6), would result in decreased β-adrenergic inotropic support for the myocardium contractility commensurate with the reduction in sympathetic support. The approximate doubling in systemic vascular resistance could result in a supply/demand imbalance in patients with low cardiac reserve. Thus DMED should not be given by an iv infusion at a rate which produces a marked increase in SVR except in healthy patients.

A maximum reduction in MABP of 27% following the transient pressor effect occurred between 60 and 150 min after DMED infusion (i.e., the depressor phase of the biphasic response). The maximum reductions in HR and CO for this same period of time (60–150 min) were 12% and 17%, respectively. (This corresponds to the same period of time when there was a 16% reduction in O₂ consumption.) Since MABP and CO decreased proportionally, the reduction in MABP was due to the reduction in CO, not SVR. As no direct myocardial depressant effects of clonidine or DMED have been found this reduction in CO would be consistent with reduced metabolic demands.

The major source of circulating epinephrine are the adrenal glands, while circulating norepinephrine “spills over” into the circulation from its site of release at the neuroeffector junction. DMED activates peripheral presynaptic α₂ autoreceptors which serve to reduce the release of catecholamines. In addition there is a reduction in the central sympathetic outflow through action on the regulatory centers in the brainstem. Both the central and peripheral effects contribute to the reduction in catecholamines. Clonidine, when given pre- and intraoperatively, has been shown to reduce postoperative norepinephrine and epinephrine levels in patients undergoing CABG, aortic or major abdominal surgery. In our unstimulated subjects, DMED suppressed norepinephrine but epinephrine levels were indistinguishable from the low baseline values. Perioperative stress (in which increased catecholamines is a hallmark) can result in undesirable myocardial ischemia. Anesthetic regimens that minimize this could prove beneficial. DMED may serve to mitigate this response as even the lowest dose resulted in over a 4-h reduction in circulating norepinephrine levels.

The first DMED plasma levels were determined 10 min after the DMED infusion when MABP had returned to a baseline level. At that time DMED plasma levels were 2,350 ± 450 pg/ml. A significant level of sedation was found at a DMED level of 260 ± 50 pg/ml, MABP, HR, and plasma norepinephrine levels were significantly reduced at DMED plasma of 40 ± 30 pg/ml. From this it is evident that higher plasma DMED concentrations are required to result in increased MABP. Individuals who need a high level of sympathetic tone to maintain blood pressure may not tolerate even low doses of DMED.

In summary, when DMED was given by a 2-min iv infusion in healthy volunteers a similar hemodynamic profile to that reported for clonidine was found. The lower doses (0.25 and 0.5 μg/kg) result in a monophasic ± 10% reduction in MABP. The two largest doses resulted in a biphasic MABP response. The maximal early transient pressor effect (MABP increased 20%) was associated with a doubling of SVR and a reduction in CO (41%). The increase in blood pressure in the 2 μg/kg dose group was associated with a reduction in HR of between 12% and 25% and was presumably mediated by enhanced baroreceptor reflexes. The transient pressor phase is unimportant to anesthesia and should probably be avoided by using either a slower infusion rate or a different route of administration, particularly in patients with impaired cardiac function. The second of the biphasic pressure effects was a longer lasting reduction in MABP (15–27%), with a concomitant decrease in HR (10–20%) and CO (11–16%). DMED reduced plasma norepinephrine levels at all doses for more than 4 h. DMED was well tolerated by all subjects.

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