Cardiopulmonary Effects of the α₂-Adrenoceptor Agonists Medetomidine and ST-91 in Anesthetized Sheep

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ABSTRACT

To test the hypothesis that pulmonary alterations are more important than hemodynamic changes in α₂-agonist-induced hypoxemia in ruminants, the cardiopulmonary effects of incremental doses of (4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole) hydrochloride (medetomidine; 0.5, 1.0, 2.0, and 4 μg/kg) and 2-(2,6-diethylphenylamino)-2-imidazol (ST-91; 1.5, 3.0, 6.0, and 12 μg/kg) were compared in five halothane-anesthetized, ventilated sheep using a placebo-controlled randomized crossover design. Pulmonary resistance (Rl), dynamic compliance, and tidal volume changes in transpulmonary pressure (ΔPpl) were determined by pneumotachography, whereas cardiac index (CI), mean pulmonary artery pressure (Ppa), and pulmonary artery wedge pressure (Ppaw) were determined using thermodilution and a Swan-Ganz catheter. The most important finding was the fall in partial pressure of oxygen in arterial blood (PaO₂) after administration of medetomidine at a dose (0.5 μg/kg) 20 times less than the sedative dose. The PaO₂ levels decreased to 214 mm Hg as compared with 510 mm Hg in the placebo-treated group. This decrease in PaO₂ was associated with a decrease in dynamic compliance and an increase in Rl, ΔPpl, and the intrapulmonary shunt fraction without changes in heart rate, CI, mean arterial pressure, pulmonary vascular resistance, Ppa, or Ppaw. On the other hand, ST-91 only produced significant changes in PaO₂ at the highest dose. After this dose of ST-91, the decrease in PaO₂ was accompanied by a 50% decrease in CI and an increase in mean arterial pressure, Ppa, Ppaw, and the intrapulmonary shunt fraction without significant alterations of Rl and ΔPpl. The study suggests that the mechanism(s) by which medetomidine and ST-91 produce lower PaO₂ are different and that drug-induced alterations in the pulmonary system are mainly responsible for the oxygen-lowering effect of medetomidine.

The α₂-adrenoceptor agonists (α₂-agonists) are becoming increasingly popular in veterinary and human medicine for use as anxiolytics, analgesics, and preanesthetic sedatives (Maze and Tranquilli, 1991). In veterinary practice, the relatively new α₂-agonist, (4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole) hydrochloride (medetomidine), is widely used in Europe and Australia for sedation and to reduce the general anesthetic requirement (Cullen, 1996). This drug is 7 times more selective for α₂-adrenergic receptors than the prototype α₂-agonist, clonidine (Virtanen, 1989). The dextroisomer of medetomidine, dexmedetomidine, is being developed for use in human anesthetic practice. Dexmedetomidine has been used in the perioperative period to provide sedation and anxiolysis (Aantaa et al., 1990a), to reduce opioid, thiopental, and inhalation anesthetic requirements (Aantaa et al., 1990b), and to reduce hemodynamic instability in humans (Aantaa et al., 1990b).

It has been known for some time that the α₂-agonist xylazine decreases partial pressure of oxygen in arterial blood (PaO₂) in cattle (DeMoor and Desmet, 1971), goats (Kumar and Thurmon, 1979), and sheep (Doherty et al., 1986; Nolan et al., 1986). The degree of hypoxemia in sheep after sedation with clonidine (Eisenach, 1988) or xylazine (Nolan et al., 1986; Doherty et al., 1986) is quite severe. We recently reported that three newer α₂-agonists (detomidine, medetomidine, and romifidine) also produce severe hypoxemia when administered i.v. at equipotent sedative doses in conscious sheep (Celly et al., 1997a,b). The level of hypoxemia was similar with the five α₂-agonists studied, irrespective of their differences in selectivity for α₂- versus α₁-adrenoceptors.

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ABBREVIATIONS: medetomidine, (4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole) hydrochloride; ST-91, (2-(2,6-diethylphenylamino)-2-imidazol); α₂-agonist, α₂-adrenoceptor agonist; CI, dynamic compliance; CI, cardiac index; ΔPpl, maximum change in transpulmonary pressure; IPPV, intermittent positive pressure ventilation; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood; PVO₂, partial pressure of oxygen in mixed venous blood; P(Al-a)O₂, alveolar oxygen tension; P(A-a)O₂, alveolar to arterial oxygen tension gradient; Ppa, pulmonary artery pressure; Ppaw, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; Rl, pulmonary resistance; SV, stroke volume; SVR, systemic vascular resistance; TXB₂, thromboxane-B₂; V̇̇, tidal volume; Q̇̇̇̇̇̇̇, shunt fraction; HR, heart rate; TPP, total plasma protein.
(Celly et al., 1997a). A selective α2-agonist that does not cross the blood brain barrier, 2-(2,6-diethylphenylamino)-2-imidazol (ST-91), also induced a comparable level of hypoxemia, suggesting involvement of a peripheral component in the development of hypoxemia (Eisenach, 1988; Celly et al., 1997b). The hypoxemia was not caused by hypoventilation and was not due to postural changes after drug administration (Celly et al., 1997a). It was accompanied by significant changes in respiratory frequency and in the maximum change in transpulmonary pressure (ΔPppl) required for tidal volume (VT) breathing; heart rate (HR) and mean arterial pressure (MAP) were less affected. Others have reported that the development of hypoxemia occurs even when the animal is ventilated artificially (Nolan et al., 1986; Eisenach, 1988). Although these studies suggest a drug-induced increase in the proportion of blood flow going through the lungs without becoming oxygenated, i.e., intrapulmonary shunt fraction (Qs/Qt), as one possible mechanism underlying α2-agonist-induced hypoxemia, the origin of this increase in shunt fraction remains unclear.

From the studies reported to date, it is not possible to separate the relative contribution of pulmonary and cardiovascular alterations with respect to the development of hypoxemia in sheep. The doses used were clinically useful sedative doses, and these doses produce significant circulatory alterations (Campbell et al., 1979; Cullen, 1996). It is quite possible that a fall in cardiac output (Qt) and mixed venous oxygen saturation magnified the apparent degree of venous admixture associated with any ventilation/perfusion mismatch (McDonell, 1996).

The present study was conducted to investigate the relative contribution of the cardiovascular and respiratory systems to α2-agonist-induced hypoxemia in ruminants. To test the hypothesis that the pulmonary alterations are paramount and that these effects can occur without central α2-receptor involvement, the effect of incremental doses of the central and peripheral acting α2-agonist, medetomidine, the peripherally acting α2-agonist, ST-91, and a saline placebo were studied in halothane anesthetized, ventilated sheep.

Materials and Methods

Experimental Animals. Five adult female Arcot sheep weighing 80 to 90 kg [mean body weight 84 ± 1.7 S.E.] were used in the study. Each animal was used on three different occasions to study the cardiopulmonary effects of placebo (physiological saline), medetomidine, and ST-91. A minimum of 7 days separated each experiment and the order of treatment was randomized. The study was approved by the institutional Animal Care Committee and followed the guidelines of the Canadian Council on Animal Care.

At least 1 month before experimentation, the carotid artery was relocated under halothane anesthesia to a s.c. position in all animals. Health status was established on the basis of physical examination, a complete blood count, arterial blood gas analysis, and chest radiography. Water was available ad libitum but feed was withheld 20 to 24 h before each experiment.

Instrumentation. The sheep were positioned in a custom designed restraint device that served to minimize the positional effects of anesthesia on pulmonary function. The base of the wooden stock had four holes cut to permit the animal’s legs to protrude such that the sheep rested comfortably on its sternum and abdomen on a pad of foam 15 cm thick. Sternal recumbency is associated with less interference of gas exchange in anesthetized large mammals than lateral or dorsal recumbency (McDonell, 1996). Anesthesia was induced with pentobarbital sodium (20 mg/kg i.v.), a cuffed endotracheal tube (diameter 9.5–10.5 mm) was inserted, and halothane/O2 was used for maintenance of anesthesia with intermittent positive pressure ventilation (IPPV) to maintain eucapnia. Muscle paralysis was induced with 0.2 mg/kg atracurium (Tracrium, Burroughs Wellcome, Research Triangle Park, NC) administered i.v., and the level of muscle relaxation was monitored with a peripheral nerve stimulator (Innervator, Fisher & Paykel Electronics Ltd., Auckland, NZ) using electrodes applied to the ulnar nerve. Total absence of muscle response to a train of four 20-mA stimuli was maintained throughout the study by the supplemental administration of atracurium (usually 0.1 mg/kg i.v.) as needed. Airway gas concentrations (inspired O2 and end-tidal halothane and CO2) were monitored on a breath-to-breath basis using a rapid response monitor (Criticare 1100 Patient Monitor, Criticare System Inc., Waukesha, WI). The gas analyzer was calibrated at the beginning of each experiment using known concentrations of halothane, O2, and CO2 (Anesthesia calibration gas, Criticare System Inc., Waukesha, WI). A constant volume, electronically cycled, sinusoidal airflow ventilator (Harvard pump, Harvard Apparatus Co., Inc., Dover, MA) was inserted into the inspiratory side of the anesthetic rebreathing circuit to produce constant volume IPPV. The pump was set to deliver a constant VT (700 ml) with respiratory frequency at approximately 8/min. Breathing frequency was adjusted as needed to maintain eucapnia [partial pressure of carbon dioxide in arterial blood (PaCO2) ranging between 40–45 mm Hg], whereas VT was kept constant.

A 14-gauge, 10-cm long catheter (Angiocath, Becton Dickinson, Sandy, UT) was inserted in the rumen to provide a means of venting for any gas production in the rumen. A 20-gauge, 8-cm long catheter (Becton Dickinson) was introduced percutaneously into the relocated carotid artery to measure MAP and to collect arterial blood samples. The scapulohumeral joint was used as the zero reference point for MAP measurements. A base apex lead system of electrocardiography (ECG) was used for recording HR and rhythm. Copper alligator clip leads were attached to stainless steel wire loops placed s.c. An 8.5-F introducer catheter (Arrow International Inc., Reading, PA) was placed in the jugular vein to permit insertion of a 130-cm thermistor catheter (Swan Ganz, American Edwards Laboratories, Irvine, CA) into the pulmonary artery. This catheter was used to record mean pulmonary artery pressure (Ppa), pulmonary artery wedge pressure (Ppaw), and Qt using thermodilution and a computer system (Com-2, Edwards Critical Care, Irvine, CA), which provided a visual display of the thermal curve. Iced 5% dextrose solution (10 ml) was used as the thermal indicator and the mean of three Qt determinations made in rapid succession was taken as the representative Qt for that sampling interval. To minimize the effect of ventilation on Qt measurements, estimation of Qt was done by timing each injection to start at the same point in the ventilatory cycle. Likewise, Ppaw was recorded at the end of expiration. A five-channel monitor (Criticare 1100 patient monitor, Criticare System Inc., Waukesha, WI) was used to record MAP, Ppa, Ppaw, and ECG continuously. The blood pressure measurement system was calibrated before and after completion of each experiment with a mercury manometer. From recorded variables, the cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and Qs/Qt were derived using standard equations (Martin, 1987).

Three-milliliter arterial and mixed venous blood samples were drawn simultaneously into heparinized air tight glass syringes containing washers to facilitate thorough mixing of the specimen before analysis. Blood samples were stored on ice for not more than 30 min before blood gas and acid base analysis using an automated blood gas analyzer (Stat Profile Plus 9, Nova Biomedical, Waltham, MA). The packed cell volume and total plasma protein (TPP) levels were estimated by microhematorcit and refractometry methods, respectively. Blood gas and acid base values were corrected to body temperature. The alveolar oxygen tension (PAO2) was calculated using the alveolar gas equation (Martin, 1987). The PaO2 value was subtracted from
the calculated value of PAO2 to estimate the alveolar-to-arterial oxygen tension gradient [P(A-a)O2]. The blood gas analyzer was calibrated daily with known serum equivalents (Nova Stat Profile Control, Nova Biomedical, Waltham, MA) and between samples with precision gas mixtures. Paired arterial and mixed venous blood samples were collected in tubes containing EDTA and indomethacin to measure thromboxane B2 (TXB2) levels. The samples were spun to collect plasma, which was stored at −80°C until analyzed using a radioimmunoassay (Vinnikka and Ylikorkala, 1980) with a radioimmunoassay kit (Thromboxane B2 [800] assay system, Amersham International PLC, Buckinghamshire, UK).

Air flow was measured with a screen pneumotachograph (Gould Electronics, Bilthoven, the Netherlands) positioned between the endotracheal tube and anesthetic Y piece and connected to a differential pressure transducer (Validyne, #6-14, range ± 2.5 cm of H2O, Validyne Engineering Corp., Northridge, CA). Tidal volume was derived through integration of the measured flow signals (Pulmonary Mechanics Analyzer, model 6, Buxco Electronics, Inc., Sharon, CT). Transpulmonary pressure was the difference between the pressure at the airway opening (endotracheal tube) and the pleural pressure, as estimated with a thin latex esophageal balloon (7 cm long) affixed to the end of a 130-cm polyethylene catheter (2 mm i.d. and 3 mm O.D.) passed to the mid-thorax (Wanner and Reinhart, 1978). A volume of 1.5 ml of air was maintained in the balloon; this volume was within the high compliance range of the pressure recording system, and was close to the minimal relaxed volume of the balloon. The two pressure ports were connected to a differential pressure transducer (Validyne, #6-32, range ± 140 cm of H2O, Validyne Engineering Corp., Northridge, CA) to measure change in pressure. The flow, volume, and pressure signals were processed through an analyzer (Pulmonary Mechanics Analyzer, model 6) and stored on a computer for subsequent breath-by-breath analysis using software from Buxco Electronics. Dynamic compliance (Cdyn), total stored on a computer for subsequent breath-by-breath analysis using Validyne Engineering Corp., Northridge, CA) to measure change in volume using a 1-l calibration syringe (Collins, model #5540, Hans was calibrated for pressure using a water manometer, and for vol-

respiratory variable at each sampling period. Breaths were analyzed and used to provide the mean value for the volume loop analysis (Tesarowski et al., 1996). A minimum of nine pulses were collected in tubes containing EDTA and indomethacin to collect plasma, which was stored at −80°C until analyzed using a radioimmunoassay (Vinnikka and Ylikorkala, 1980) with a radioimmunoassay kit (Thromboxane B2 [800] assay system, Amersham International PLC, Buckinghamshire, UK).

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The frequency response of the transducer/catheter system was tested as described elsewhere (Young and Tesarowski, 1994), and was linear up to 6 Hz. Before and after each experiment, the system was calibrated for pressure using a water manometer, and for volume using a 1-l calibration syringe (Collins, model #5540, Hans Rudolph Inc., Kansas City, MO). The volume calibration of the pneumotachograph was performed using a gas mixture (1% halothane in O2) similar to the gas mixture inspired during the experiment (Horbes, 1967).

Drugs. The drugs tested were the relatively selective α2-adrenoceptor agonists medetomidine (molecular weight = 236.7) and ST-91 (molecular weight = 253.8). Medetomidine was available as a 1 mg/ml solution (Domitor, Orion Corporation, Farmos, Turku, Finland), whereas ST-91 (Boehringer Ingelheim, Ridgefield, CT) was dissolved in 0.9% saline to make a final concentration of 1 mg/ml. All doses have been expressed as saline.

Experimental Protocol. After the onset of anesthesia and instrumentation, more than 1 h had been provided as a stabilization period. Any gas accumulation in the rumen was expressed and then the lungs were “sighed” as follows to ensure a previous volume history for pulmonary mechanics measurements (Wheeler et al., 1990). The animal was disconnected from the pneumotachograph and anesthetic machine/ventilator at the level of the endotracheal tube and any secretions in the upper airways were suctioned out. The endotracheal tube was then attached to a second anesthetic circuit containing 1% halothane in oxygen and a 3-l rebreathing bag. Using this circuit, the sheep’s lungs were expanded to an inflation pressure of 30 cm of H2O over 3 to 5 s, after which passive exhalation to functional residual capacity (FRC) was permitted. This maneuver was repeated three times before the animal was reconnected to the pneumotachograph and primary anesthetic circuit. A 2-min period of constant volume IPPV was permitted to provide for stabilization of cardiovascular, respiratory, and end-tidal gas measurement before baseline (pretreatment) measurements of respiratory data, vascular pressures, and Qt were obtained. At this time, arterial and mixed venous blood samples were collected simultaneously for subsequent blood gas analysis and TXB2 determination. After baseline sampling, the first dose of the test drug (0.5 µg/kg for medetomidine, 1.5 µg/kg for ST-91, or 2.0 ml saline) was then given i.v. diluted to a 2.0 ml volume. Thereafter, cardiovascular measurements were made at 3, 10, and 20 min, and respiratory measurements were made at 2, 5, 10, and 20 min.

After the 20-min post-treatment sampling period for the first dose of drugs, the catheters were flushed with saline, and the anesthetic concentration and IPPV rate was adjusted if needed to ensure conditions of eucapnia and a stable end-tidal halothane concentration (1.2%). There was some variation among sheep in the time required to achieve this degree of stability; usually 20 to 25 min was required after the last measurements were made.

Before administration of the second dose of drugs (1.0 µg/kg medetomidine, 3.0 µg/kg ST-91, 2.0 ml saline), suction of upper airway secretions and suctioning of the lungs was carried out as described above. A 2-min stabilization postsigh period was again utilized, followed by administration of the second drug dose and post-treatment sampling at the same time intervals as for the first dose of the drugs. The same sequence of events was repeated for the third dose (2.0 µg/kg medetomidine, 6.0 µg/kg ST-91, or 2.0 ml saline) and fourth dose (4 µg/kg medetomidine, 12 µg/kg ST-91, or 2.0 ml saline) of each drug. Mean elapsed times between the end of recordings after one dose and the administration of the next dose was similar: 24.4 ± 17 min between the first and second dose; 30.8 ± 13.3 min between the second and third doses; and 28.5 ± 12.4 min between doses III and IV.

Statistical Analysis. A general survey of the data showed that, after administration of each dose, the peak drug effect for the variables in individual animals was either 3 or 5 min postdrug administration, irrespective of the variable. The effects tended to decrease in intensity by 20 min. To represent the overall response of a variable after each dose administration, a weighted mean was calculated from the values at 3, 10, and 20 min postdrug administration for cardiovascular variables and from values calculated at 2, 5, 10, and 20 min postdrug administration for respiratory variables. This resulted in five sampling interval values; i.e., pretreatment baseline values and weighted mean values after dose I, II, III, and IV. The data were then subjected to two-way ANOVA for repeated measures to test for significance (p ≤ .05) of treatment over time, as well as for differences between treatments and the placebo (Dawson-Saunders and Trapp, 1990). When a significant effect of treatment was observed, comparisons were performed between treatments using one-way ANOVA and a post hoc least significant difference (LSD) test. To account for repeated measures in the experimental design, the LSD was calculated using α values corrected by Bonferroni’s method to control the overall level of significance (p ≤ .05; Dawson-Saunders and Trapp, 1990). The results have been presented as the average of weighted mean ± S.E.

Results

Placebo-Treated Group. No significant changes were observed in any of the variables throughout the length of the experiment in the placebo group; however, Cdyn tended to decrease, whereas Rl tended to increase over the period of the experiment (Fig. 1).

Medetomidine-Treated Group. A significant decrease in Cdyn was seen within 2 min of dose I; this response was repeated after doses II, III, and IV (Fig. 1). An increase in ΔPpl and Rl occurred with dose I and subsequent doses (Fig. 1). A significant decrease in PaO2 was observed with all doses
The decrease in PaO₂ was accompanied by a significant increase in PaCO₂ after doses I, II, and III, with a maximum increase to 50.3 mm Hg after dose I (Fig. 2). A significant increase in P(A-a)O₂ was present after all doses (Fig. 2). No significant changes were seen in PVR, Ppa, and Ppaw after any dose of medetomidine (Fig. 3). There was a significant decrease in MAP after doses I and II, but not after doses III and IV (Fig. 4), whereas HR did not change. Cardiac index and SV did not change, whereas SVR decreased after doses I and II, but was unchanged after doses III and IV (Fig. 4). Shunt fraction was increased after each dose of medetomidine; however, the greatest increase (27%) occurred after dose I (Fig. 4). No changes were seen in arterial pH, packed cell volume, TPP, and base excess. Similarly, PVO₂ did not change after medetomidine, and there were no significant changes in arterial and mixed venous blood concentrations of TXB₂ when compared with the placebo-treated animals.

ST-91-Treated Group. Treatment with ST-91 produced similar but smaller alterations of pulmonary mechanical variables than observed after medetomidine. A significant decrease in Cdyn occurred after doses III and IV, whereas RT and ΔPpl values were not significantly different from the placebo treatment at any dose (Fig. 1). A trend toward lower PaO₂ levels and elevated P(A-a)O₂ gradients was noticed after all doses; however, this decrease was only significant...
after dose IV (Fig. 2). The lowest level of PaO₂ after the fourth dose of ST-91 was 271 mm Hg, whereas it was 487 mm Hg in placebo-treated animals. The drop in PaO₂ was not accompanied by any change in PaCO₂ (Fig. 2) or P(\text{A-a})O₂.

The changes in cardiovascular variables were more pronounced with ST-91 than with medetomidine, and they occurred at smaller doses than were required to produce pulmonary changes. Increases were seen in Ppa, PVR, Ppaw, MAP, and SUR after doses II, III, and IV (Figs. 3 and 4). An increase in Qs/Qt was seen only after dose IV (Fig. 4), along with a decrease in CI and SV. Shunt fraction increased to 20% after the fourth dose, compared with 9% with placebo treatment. No changes were seen in the arterial pH, TPP, or base excess after ST-91, and no changes occurred in arterial and mixed venous blood TXB₂ concentrations compared with the saline-treated animals.

**Discussion**

The most important finding of the study was the fall in PaO₂ and increase in P(A-a)O₂ after i.v. medetomidine at a dose (0.5 μg/kg) that is 1/20 the sedative dose. This decrease in PaO₂ was associated with rapid onset of changes in R_L, Cdyn, and ΔPpl, without changes in CI, MAP, HR, PVR, Ppa,
or Ppaw. On the other hand, ST-91 only produced significant changes in PaO₂ at the highest dose. After ST-91, the decrease in PaO₂ was accompanied by a decrease in CI and an increase in MAP, Ppa, and Ppaw, without significant alterations of R_l and ΔPpl. These findings suggest that the mechanism(s) by which medetomidine and ST-91 produced lower PaO₂ levels were different.

Baseline cardiovascular and blood gas values were similar to normal sheep anesthetized with halothane (Fujimoto and Leuchan, 1985). Pretreatment PaO₂ levels were above 450 mm Hg, and mean Q_s/Q_t values were between 6 and 11%. Breath-by-breath repeatability of pressure-volume loops, C_dyn, R_L, and ΔPpl was excellent and the values were similar to measurements previously reported for conscious, standing sheep with a nasal endotracheal tube (Wanner and Reinhart, 1978; Wheeler et al., 1990). No significant changes were observed with the placebo treatment, although C_dyn tended to decrease and R_L and CI to increase. The temporal increase in CI during constant depth halothane anesthesia was expected, probably due to a gradual increase in blood volume over time (Dunlop et al., 1987).

The complexity of the animal model and ethical consideration of animal numbers prevented doing a classic dose-response study. The elimination half-life of medetomidine is 37.9 ± 6.2 min in sheep (Muge et al., 1996) and there undoubtedly was only partial metabolism of the first dose by the time the fourth dose was administered. In our previous studies with medetomidine in conscious sheep (Celly et al.,

Fig. 3. The effect of four doses of saline (●), medetomidine (○), and ST-91 (▼) on mean Ppa (A), PVR (B), and Ppaw (C). Baseline measurements were obtained in the halothane-anesthetized ventilated sheep (n = 5) before administration of dose I. Doses I to IV for medetomidine were 0.5, 1.0, 2.0, and 4.0 μg/kg; for ST-91 were 1.5, 3.0, 6.0, and 12 μg/kg; and for the placebo treatment were 2.0 ml saline. Significant differences (*) between values obtained with placebo treatment and either medetomidine or ST-91 treatment at each dose level are shown (p ≤ .05; two-way repeated measures ANOVA followed by LSD test with Bonferroni’s correction).
an i.v. dose of 10 µg/kg produced sedation for 30 to 45 min and bradycardia for 30 min with no significant change in blood pressure. The effects of prior metabolism might be different for ST-91 because less is known about its elimination kinetics. However, the fractionated doses we used produce variations in threshold for respiratory and circulatory changes that we hoped to achieve.

Medetomidine Group. Medetomidine produced a significant decrease in PaO₂, a marked increase in R₄ and ΔPpl, and a 3-fold reduction in Cdyn at the lowest dose. Although the results are presented as a weighted mean of the 20-min interval, actual onset of changes in pulmonary mechanics

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Fig. 4. The effect of four doses of saline (○), medetomidine (◇), and ST-91 (▼) on MAP (A), SVR (B), and Q_S/Q_T (C). Baseline measurements were obtained in the halothane-anesthetized ventilated sheep (n = 5) before administration of dose I. Doses I to IV for medetomidine were 0.5, 1.0, 2.0, and 4.0 µg/kg; for ST-91 were 1.5, 3.0, 6.0, and 12 µg/kg; and for the placebo treatment were 2.0 ml saline. Significant differences (*) between values obtained with placebo treatment and either medetomidine or ST-91 treatment at each dose level are shown (p < .05; two-way repeated measures ANOVA followed by LSD test with Bonferroni’s correction).
were evident at 2 min and reached a peak by 5 min in all cases. The magnitude of the changes in ΔPpl produced by 0.5 μg/kg medetomidine was similar to those observed in conscious sheep using a sedative dose, i.e., 10 μg/kg (Celly et al., 1997a). A subdose of xylazine (20 μg/kg) produced a 3-fold increase in airway pressure in halothane anesthetized, ventilated sheep (Nolan et al., 1986), whereas Gustin et al. (1989) observed a dose-related increase in respiratory resistance and ΔPpl after non sedative doses of xylazine in conscious calves.

Papazoglou et al. (1995) showed that xylazine produced a concentration-dependent contractile effect on isolated sheep trachea, suggesting the presence of postsynaptic α2-adrenoceptors. In contrast, clonidine and medetomidine did not produce this response with bovine tracheal smooth muscle (Manning and Broadstone, 1995). These α2-agonists actually attenuated the response to electrical field stimulation, but only with supratherapeutic doses. Besides a direct effect of α2-agonists on airway smooth muscles, a decrease in Cdyn and an increase in Rl could occur in response to pulmonary edema, edema of the airway wall, or mucus accumulation (McDonell, 1996). It is possible that some of the respiratory mechanics alterations occurred secondary to development of interstitial and alveolar edema as seen in another study within 10 min of sedative doses of medetomidine in sheep (Celly et al., 1997c).

The initial low dose of medetomidine produced significant alterations in gas exchange, without a reduction of CI or PVO2, confirming a respiratory origin. The alterations in gas exchange were maintained, but not intensified by increasing doses of medetomidine, suggesting that conventional drug/response kinetics did not prevail. The maximum decrease in PaO2 was less than previously observed with 20 μg/kg i.v. xylazine in halothane-anesthetized sheep (Waterman et al., 1987). It was also less than we observed after a full sedative dose of xylazine (150 μg/kg) during halothane anesthesia (C.S.C. and W.N.M., unpublished observation).

It is evident that the fall in PaO2 was primarily due to an increase in PA-aO2 as a result of an increase in Q/Ql. An increase in the shunt fraction could occur because of the development of segmental airway obstruction, pulmonary edema or atelectasis, or the opening up of previously closed vascular connections between the right and left sides of the circulation. The rapid increase in Rl suggests there is an airway obstruction component, probably in conjunction with the development of pulmonary edema (Celly et al., 1999). No change was noticed in PVR, Ppa, and Ppaw; therefore, it is very unlikely that left atrial failure or an alteration of pulmonary circulation contributed to the hypoxemia. In anesthetized, ventilated sheep, clonidine did not alter Ppa or Ppaw (Eisenach, 1988).

No significant change was recorded in TXB2 concentrations after any dose of medetomidine, whereas Raptopoulos et al. (1995) reported a significant increase in venous plasma TXB2 2 and 5 min after i.v. xylazine (0.1 mg/kg). Possibly the response to xylazine differs from medetomidine as suggested in a study on platelet aggregation (Papazoglou et al., 1993) or we may have drawn our samples too late.

**ST-91-Treated Group.** Respiratory responses to ST-91 tended to be biphasic with increasing doses, whereas changes in vascular pressures, PVR, and SVR were dose-related. With the initial low dose, Cdyn decreased by 50% whereas RL ΔPpl, and P(A-a)O2 doubled and Q/Ql tripled. These changes were not significant due at least in part to interanimal variability. The decrease in PaO2 was less pronounced (509 mm Hg with placebo; 349 mm Hg with ST-91). Cardiac index remained stable until dose IV, whereas PVO2 was not altered at any dose. The pulmonary changes were sustained, but not increased, by increasing ST-91 doses, and only the fall in Cdyn was statistically significant. The fall in PaO2 and increase in P(A-a)O2 and Q/Ql became significant with the fourth dose; at this dose, Ppa, PVR, Ppaw, MAP, and SVR were markedly elevated.

The usual response after an i.v. α2-agonist includes an initial transient pressor response mediated by α2β-adrenoceptor subtypes (Link et al., 1996). This is followed by hypertension and bradycardia caused by stimulation of central α2-adrenoceptors (Timmermans et al., 1983; Ruffolo et al., 1993). Because ST-91 cannot cross the blood-brain barrier and stimulate central α2-adrenoceptors, peripheral effects dominate and produce the long-lasting hypertension seen in the present study (Scriabine et al., 1977; Eisenach, 1988; Celly et al., 1997b).

In the present study, mean Ppaw values reached 35.5 mm Hg after the fourth dose, which, on a cumulative basis, added up to 22.5 μg/kg. A Ppaw value greater than 25 mm Hg has been associated with pulmonary edema (Martin, 1987). It is possible that acute pulmonary edema developed in these animals after dose IV as indicated by the concomitant decrease in Cdyn and PaO2, and the increased Q/Ql. It is worth mentioning that, in another study, we observed severe pulmonary edema within 3 min of i.v. ST-91 at a similar dose (Celly et al., 1999).

The present study suggests important differences in the hypoxemic response of medetomidine and ST-91. Low dose medetomidine-induced hypoxemia was associated with significant changes in respiratory variables and no hemodynamic changes, whereas ST-91 induced significant decreases in PaO2 only at higher doses when peak alterations were seen in systemic and pulmonary hemodynamics. Despite these differences in dose and the systems affected, an increase in Q/Ql seems to appear to be the common underlying mechanism producing hypoxemia. It appears that the increase in Q/Ql was related entirely to pulmonary dysfunction in the case of medetomidine, whereas ST-91 produced less pulmonary dysfunction and an increase in Ppaw and pulmonary edema of cardiac origin at higher doses.

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