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Maternal and preterm fetal sheep responses to dexmedetomidine

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Abstract

Background—The α_2 adrenergic receptor agonist dexmedetomidine has some unique pharmacologic properties that could benefit pregnant patients (and their fetuses) when they require sedation, analgesia, and/or anesthesia during pregnancy. The purpose of the present study was to delineate maternal and fetal responses to an intravenous infusion of dexmedetomidine.

Methods—This study was conducted on surgically-recovered preterm sheep instrumented for physiologic recording and blood sampling. Maternal and fetal cardiovascular and blood gas parameters and fetal cerebral oxygenation levels were recorded before, during, and after 3 h of dexmedetomidine infusion to the ewe at a rate of 1 $\mu\text{g/kg/h}$.

Results—Drug infusion produced overt sedation but no apparent respiratory depression as evidenced by stable maternal arterial blood gases; fetal blood gases were also stable. The one blood parameter to change was serum glucose. By the end of the 3 h infusion, glucose increased from 49 ± 10 to 104 ± 33 mg/dL in the ewe and from 22 ± 3 to 48 ± 16 mg/dL in the fetus; it declined post-drug exposure but remained elevated compared to the starting levels (maternal, 63 ± 12 mg/dL, $P = 0.0497$; and fetal, 24 ± 4 mg/dL, $P = 0.012$). With respect to cardiovascular status, dexmedetomidine produced a fall in maternal blood pressure and heart rate with fluctuations in uterine blood flow but had no discernable effect on fetal heart rate or mean arterial pressure. Likewise, maternal drug infusion had no effect on fetal cerebral oxygenation, as measured by *in utero* near-infrared spectroscopy.

Conclusions—Using a clinically-relevant dosing regimen, intravenous infusion of dexmedetomidine produced significant maternal sedation without altering fetal physiologic status.

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Results from this initial acute assessment support the conduct of further studies to determine if dexmedetomidine has clinical utility for sedation and pain control during pregnancy.

Keywords

Dexmedetomidine; Fetus; Near-Infrared Spectroscopy; Obstetrical Anesthesia; Precedex; Pregnant Sheep

Introduction

The need for non-obstetric related invasive therapeutic or diagnostic intervention can occur at any point during gestation.^{1,2} For instance, women have a higher incidence of abdominal disorders than men and amongst females of child-bearing age the incidence of emergent corrective surgery such as appendectomy is unaffected by pregnancy status.³ Pregnancy may also necessitate the use of invasive diagnostic procedures because non-invasive alternatives are contraindicated to avoid fetal exposure to radiation.⁴ As a result, almost 100 000 women per year in the USA receive agents for sedation, anesthesia and pain control at some point during their pregnancy for non-obstetric related care.⁵ Interest remains high in identifying drug regimens that optimize maternal comfort with minimal fetal impact.⁶

The α_2 adrenergic receptor (α_2 AR) agonist dexmedetomidine was approved in 1999 by the Food and Drug Administration for sedation and pain control of intensive care patients. Reports continue to indicate the drug is efficacious in this setting.^{7,8} From this initial indication, dexmedetomidine has also been used to provide intraoperative sedation.⁹ Some research groups have identified inappropriate applications¹⁰ or questioned its analgesic potency,¹¹ while others have even utilized dexmedetomidine to provide surgical anesthesia to select patient populations.¹²

In addition to its sedative, anxiolytic, and analgesic actions, dexmedetomidine (similar to other α_2 AR agonists) can reduce the need for other procedural medications through synergistic effects on opioid and benzodiazepine-based agents.¹³ These effects are all produced with minimal respiratory depression. Collectively, this profile of activity continues to prompt evaluation of additional clinical applications,^{14,15} ranging from facilitation of awake intubation,¹⁶ to supplementation of sedation and pain control during craniotomy,¹⁷ and sedation of pediatric patients.¹⁸ As of now, these investigations have not included significant cohorts of pregnant patients outside of women who were terminating their pregnancies¹⁹ or single case reports^{20–22} and pregnancy is an exclusion criteria for most currently active dexmedetomidine clinical trials (<http://www.clinicaltrials.gov>-accessed 8th April 2012). Nonetheless, a number of dexmedetomidine's actions could be of potential benefit to fetuses of parturients requiring heavy sedation, anesthesia, and/or analgesia during pregnancy.²³

One intriguing aspect is the potential for decreased dexmedetomidine-mediated cardiovascular depression in the mother and fetus because of the pregnancy-related decline in systemic maternal α_2 AR sensitivity²⁴ even as the fetus has increasing numbers of α_2 AR both systemically²⁵ and centrally.²⁶ Another intriguing aspect is the possibility that dexmedetomidine can protect the developing brain from excitotoxic injury.²⁷

With this background, the goal of the present study was to delineate maternal and fetal physiologic responses to dexmedetomidine. The studies were conducted on preterm pregnant sheep at gestational day 92, a time point approximately equivalent to the end of the second trimester in humans. The effects of dexmedetomidine on the preterm fetus are not known, yet this is a relevant developmental stage applicable to pregnant patients requiring

sedation for nonobstetric related procedures. The ewes and fetuses were instrumented for recording cardiovascular activity and for monitoring arterial blood gas status. Because other α_2 AR agonists have been reported to decrease uterine blood flow and fetal blood pO₂ levels,²⁸ and since the developing brain is arguably the most sensitive organ to a decline in oxygen availability, the fetuses were also instrumented with near-infrared spectroscopy (NIRS) probes to assess changes in fetal cerebral oxygenation during and after maternal drug administration.²⁹

Methods

All aspects of the surgical and experimental protocols were approved by the Duke University Institutional Animal Care and Use Committee. Mix-breed time-dated Q-fever-negative preterm pregnant ewes were obtained from a commercial supplier. Upon arrival at the Duke University, each ewe received an intramuscular injection of procaine penicillin G (1 200 000 IU). This penicillin regimen was repeated at 48 h intervals for the duration of the study. Sheep were housed individually and were allowed *ad libitum* access to food and water except for a 12–14 h fasting period before the surgical procedure; food was not withheld before the dexmedetomidine exposure.

Instrumentation and catheterization of the ewe and fetus were performed at a mean gestational age of 90±1 days. Surgery was conducted using a sterile technique and all components were cold-gas sterilized before installation. Following pre-sedation with subcutaneous midazolam 1 mg/kg, surgical anesthesia was induced with intravenous sodium thiopental 7 mg/kg and the trachea intubated. Surgical anesthesia was maintained with 1–2% isoflurane in oxygen delivered by a Narkomed 2B ventilation system (North American Dräger, Telford, PA, USA). To prevent aortocaval compression, ewes were placed (tilted) in the left lateral position.³⁰ Using standard surgical techniques, catheters were inserted into the left maternal femoral artery and left jugular vein and both the right and left fetal femoral arteries. Next, an electronic flow probe (Transonic Systems Incorporated, Ithaca, NY, USA) was secured around the left uterine artery for recording uterine blood flow (UBF). The fetal head was then exteriorized and the skull was revealed following a midline scalp incision.

To install the NIRS fiberoptic bundle, a burr hole was drilled along the midline of the head, approximately 7.5 mm posterior to the coronal suture. The laser light source was gently inserted through this hole onto the dura and secured with the use of a custom-made 2 cm diameter metal plate and a series of small self-tapping screws. A second metal plate was used to secure the detector to the skull, 15 mm anterior to the light source. The fetus was then returned to the uterus. As the incisions were closed, a catheter was installed inside the amniotic cavity. The catheters, the flow probe lead, and the fiberoptic bundle were tunneled subcutaneously and then exteriorized through a small incision in the left flank of the ewe.

Upon completion of the surgery (3–4 h), bupivacaine 0.25 % w/v was infused subcutaneously around the incision sites and the animal returned to its pen. Nalbuphine hydrochloride, up to 1.0 mg/kg (or similar opioid) was administered intramuscularly to the ewe as needed to control postoperative pain. In addition to penicillin, prophylactic antibiotic therapy included two doses of gentamicin (ewe 80 mg intravenously; fetus 40 mg via the amniotic catheter) and daily maternal intravenous infusions of sulfamethoxazole 800 mg and trimethoprim 160 mg in 5% glucose. All animals were allowed 48 h to recover from instrumentation before conducting the dexmedetomidine exposure experiment.

On the day of experimentation, the ewe was placed in a support harness (Munks Livestock Sling Manufacturing Company, Anacortes, WA, USA) within a transportation cart. The arterial catheters were flushed with heparinized saline and then attached to force transducers

(Transpac®; Abbott Laboratories, North Chicago, IL, USA); maternal and fetal cardiovascular data along with uterine blood flow (UBF) were recorded using a 16-channel PowerLab system (ADInstruments, Colorado Springs, CO, USA). Fetal arterial pressure measurements were corrected for variations in intrauterine pressure by subtracting simultaneously-measured amniotic fluid pressure. Fetal cerebral oxygenation, as measured by changes in oxygenated, deoxygenated, and total hemoglobin (oxyHb, deoxyHb, and totalHb, respectively), was quantitated using a NIRS monitor (CAS Medical Systems, Branford, CT, USA) adapted for fetal sheep use.

Drug exposure was initiated after a baseline recording period of 30–60 min. Since we had no *a priori* knowledge of a species-specific drug regimen for pregnant sheep, we followed the human dosing guidelines. Each ewe received an intravenous bolus injection of dexmedetomidine 1.0 µg/kg (Precedex®; Hospira, Inc. Lake Forest, IL, USA), given over 10 min, followed by a constant intravenous infusion at 1.0 µg/kg/h. The infusion was discontinued after 3 h and the experiment terminated 2 h later. During the study, hemodynamic and fetal cerebral oxygenation data were continuously recorded while maternal and fetal arterial blood samples were obtained at 30-min intervals; blood gas status was determined using a Gem Premier 3000 blood gas analyzer (Instrumentation Laboratory, Lexington, MA, USA).

Statistical analysis

Arterial blood gas data are presented as group mean $\pm$ SD. For the NIRS data, baseline values of fetal cerebral oxyHb, deoxyHb, and totalHb were calculated for each animal by averaging measurements taken during the pre-infusion period. Measurements taken during and after dexmedetomidine infusion were divided by these values and expressed as percent of baseline. Similar calculations were performed on the UBF data. With respect to the other cardiovascular parameters, maternal and fetal heart rate and mean arterial pressure (MAP) were averaged at 1-min intervals for each animal and presented as group mean.

Since this was an exploratory characterization study, i.e. the study did not seek to test a predetermined hypothesis, the results, including *P* values, are presented descriptively. In addition there was no applicable information on which to base a power estimate because *a priori* the effects of dexmedetomidine on the preterm fetus were unknown. The statistical analyses focused on the three primary end-points, *viz.* changes in fetal cerebral oxygenation, maternal and fetal cardiovascular status, and arterial blood gas status. All analyses were conducted using SAS® version 9.1 software (SAS Institute Inc. Cary, NC, USA). For cerebral oxygenation, changes in oxyHb, deoxyHb, and totalHb during and after anesthesia were assessed by calculating the duration above or below baseline as well as the average change from baseline (change was calculated as the difference between each minute's measure minus baseline). For each animal, the average of these minute-by-minute changes was taken as a summary measure representing how far above or below baseline the measure was and for how long. Mean change during and after drug infusion (along with 95% confidence intervals) were calculated and compared to baseline using *t*-tests. A similar methodology was employed to test for differences in maternal and fetal heart rate and MAP.

To assess changes in maternal and fetal blood gas status, a mixed-model repeated-measures analysis of variance was employed. Measurement times were treated categorically to allow post-hoc comparisons to baseline with Dunnett's test adjusting as needed for multiple comparisons. With the maternal and fetal glucose values follow-on testing (paired *t*-test) was conducted to determine if levels were different between the start and end of the study. For all end-points, *P* values of <0.05 were considered significant.

Results

Nine preterm sheep were utilized for this study. All animals tolerated the infusion well with no intra- or post-drug exposure complications. Technical problems (detachment of the fiber optic bundle from the fetal skull) prevented us from obtaining complete fetal cerebral oxygenation data from four subjects.

Profound sedation was observed within minutes of initiating the dexmedetomidine infusion with sentience returning between 30 and 60 min after the infusion was terminated. During drug infusion, animals were unresponsive to painful stimuli (skin pinch). No standardized metrics were used to score sedation or stimuli response. Qualitative observations indicated that the ewes maintained a normal respiratory pattern throughout the exposure period; this was corroborated by the measured arterial blood parameters, which remained constant during the study (Fig. 1; normal blood gas values are similar between sheep and human fetuses^{31, 32}). The one exception was blood glucose: in both the ewe (baseline of 49 ± 10 mg/dL; 95% CI 41–56 mg/dL) and fetus (22 ± 3 mg/dL; 95% CI 20–24 mg/dL), blood glucose continued to rise during dexmedetomidine infusion peaking at 104 ± 33 and 48 ± 16 mg/dL, respectively, at the 180 min point (i.e. immediately before terminating drug exposure). During the post-exposure period, glucose levels declined but still remained modestly elevated 2 h later compared with starting levels: maternal, 63 ± 12 mg/dL (95% CI 54–72; $P = 0.0497$) and fetal 24 ± 4 mg/dL (95% CI 21–27 mg/dL, $P = 0.012$).

Maternal and fetal cardiovascular responses to dexmedetomidine are presented in Figures 2 and 3, respectively. Before drug infusion, maternal heart rate and blood pressure were within the normative range for pregnant sheep³³ (these ranges along with UBF match well with values for humans at a similar gestational stage³⁴). Baseline fetal heart rate also matched published reports³⁵ but the values (>160 beats/min) would be defined as tachycardia for a human fetus.³⁶

Intravenous infusion of the loading dose did not produce an abrupt alteration in cardiovascular status; there was no initial maternal hypertension nor was there an acute rise in blood pressure after the infusion was terminated. Rather, dexmedetomidine produced a progressive decline in the ewes' heart rates from approximately 90 beats/min to a nadir of 70 beats/min during the first 30 min of drug exposure. Heart rate remained at this level until it started to return to baseline at the 240 min point, 60 min after stopping drug administration. Maternal MAP exhibited a similar rate of decline from a baseline level of 110 mmHg to a nadir of 97 mmHg; MAP ranged between 97–102 mmHg during infusion and then gradually increased towards (but did not return to) baseline (peak 105 mmHg). From a mean starting flow rate of 183 ± 63 mL/min, UBF fluctuated between 85 and 115% of baseline (~ 155 –210 mL/min) during dexmedetomidine exposure. This level of variability was maintained during the 2 h post-infusion period.

In contrast to the maternal responses, dexmedetomidine had minimal effects on fetal cardiovascular status (Fig. 3): throughout the study, fetal heart rate and MAP remained within normal limits for this gestation. Consistent with the absence of a fetal systemic response, there were minimal dexmedetomidine-induced changes in cerebral oxygenation within the mid-term brain (Fig. 4). All three measures (oxyHb, deoxyHb, and totalHb), remained within 5% of baseline during and after drug exposure. Change from baseline and time spent above and below baseline were used as a summary measure of the actions of dexmedetomidine (Table 1). While each Hb component trended below baseline during and after maternal drug infusion, the actual amount of change in fetal cerebral oxygenation was nominal.

Discussion

Dexmedetomidine has been used successfully in a variety of clinical settings to produce sedation, analgesia, and anesthesia.^{15, 37} The present preclinical assessment suggests that the drug could also be used during pregnancy. Infusion of the standard human dose to preterm pregnant sheep induced significant maternal sedation without respiratory depression and sentience returned quickly after termination of drug exposure. Despite producing a graded decline in maternal heart rate and blood pressure, dexmedetomidine did not alter fetal systemic or central physiologic status. This is in contrast to maternal general anesthesia in preterm ewes where we observed progressive declines in both fetal heart rate and blood pressure.³⁸ As such, even though the current reported clinical use of dexmedetomidine in parturients is limited to case reports,^{20–22} there would seem to be considerable clinical utility for an agent that is capable of producing profound maternal sedation with minimal fetal effects.

The one statistically-significant effect observed was a rise in plasma glucose concentration, which would be consistent with a dexmedetomidine-mediated inhibition of insulin release.³⁹ Dexmedetomidine has been reported to increase glucose levels in some patients such as females undergoing gynecologic laparoscopic procedures,⁴⁰ but larger reviews have not identified hyperglycemia as a concern.⁸ As such, the clinical significance and impact upon maternal or fetal well-being of a relatively brief period of hyperglycemia is unclear. For humans, modestly elevated glucose levels during pregnancy are associated with a higher future risk of diabetes even in the absence of gestational diabetes mellitus.⁴¹ At the same time, clinical studies and reviews on the chronic use of other α_2 AR agonists, notably clonidine and α -methyldopa for blood pressure control during pregnancy, have not identified hyperglycemia as a specific concern,^{42, 43} and some early assessments of clonidine reported occasional occurrence of neonatal hypoglycemia immediately after delivery.⁴⁴

The main route of dexmedetomidine inactivation is through cytochrome P450 metabolism in the liver, specifically through isoenzyme CYP2A6.³⁷ CYP2A6 levels are known to increase significantly during pregnancy,⁴⁵ which may have contributed to the ewes' relatively rapid return to sentience after drug infusion was terminated. Elevated CYP2A6 levels presumably also allow for the prompt return of insulin secretion and regulation of blood glucose levels although we do note that the maternal and fetal glucose concentrations, while off their peaks, were still elevated 2 h post-infusion. In any event, additional tracking of serum glucose during and after administration dexmedetomidine appears warranted independent of pregnancy status, especially in the setting of reduced liver function and/or impaired glucose regulation.

Similar to the other adrenergic receptor sub-types, α_2 ARs are widely distributed throughout the body. In the periphery, they are located on blood vessels where direct activation produces vessel constriction; the α_2 AR can also be found in various organ systems including the liver, pancreas, and kidneys.¹³ Within the central nervous system, pre-synaptic and post-synaptic α_2 ARs primarily regulate (inhibit) norepinephrine release. Stimulation of α_2 ARs in the locus coeruleus produces sedation whereas α_2 AR activation in the medullary dorsal motor complex leads to a centrally-mediated suppression of cardiac activity.¹³ It is the α_2 ARs located within the spinal cord that appear to mediate pain perception.⁴⁶ Collectively, administration of an α_2 AR agonist activates these areas to produce the desired analgesic, anxiolytic, and sedative effects.

As a group, the α_2 AR agonists might offer benefits to pregnant patients. In addition to their direct pharmacologic effects, their ability to enhance the actions of opioids and

benzodiazepines¹³ would result in less maternal use and thus reduced fetal exposure. Starting with clonidine (followed by xylazine and medetomidine amongst others) the α_2 AR agonists have been used by physicians and veterinarians to sedate and to provide pain control. Dexmedetomidine is in the same pharmacologic class but has more therapeutic uses due to its greater affinity for the α_2 AR over the α_1 subtype. There is also the possibility of less fetal exposure to dexmedetomidine as *ex vivo* human placenta studies have demonstrated an increased uptake (as opposed to passage) of this agent compared with clonidine.⁴⁷ Countering these benefits is the concern that α_2 AR stimulation of uterine tissue could induce contractions. Notable in this regard is that *in vitro* testing identified dexmedetomidine as been a much more potent inducer of uterine contractions than clonidine.⁴⁸

Reduced fetal drug exposure and/or the decreased response of the fetus to adrenergic stimulation^{26,27} would certainly account for the absence of any observed change in the fetal systemic and central physiologic parameters that we monitored. However, this interpretation is hampered by the absence of plasma dexmedetomidine concentrations. During the course of the study we did collect maternal and fetal blood samples for determination of drug levels but our group lacked the equipment to develop and validate the gas chromatography-mass spectrometry methods described in the literature^{49, 50} (funding limitations prevented us from contracting with a commercial analytical firm to conduct the analyses, a limitation reported by another group studying dexmedetomidine²¹). Finally, the stored samples were lost during the laboratory's move from North Carolina to Ohio. As a result, while physiologic data suggest minimal placental passage of dexmedetomidine, fetal plasma drug levels are needed for confirmation. With this caveat, the NIRS results are nonetheless informative. Dexmedetomidine decreases cerebral blood flow⁵¹ and cerebral metabolic rate⁵² in the adult brain. With the fetal brain well-populated with α_2 AR (at least at near-term in the fetal sheep),⁵³ if a pharmacologically-relevant amount of dexmedetomidine had entered the fetal circulation one would anticipate reductions in fetal cerebral blood flow and oxygenation. Instead, the three parameters we monitored, namely oxyHb, deoxyHb, and totalHb, did not change during or after maternal infusion.

A positive control was not included in the present study because during device development we previously validated the ability of our NIRS system to rapidly track changes in fetal brain oxy-, deoxy-, and totalHb.²⁹ Validation employed fetal sheep with the fiberoptic bundle installed on their skulls along with inflatable vascular occluders placed around the umbilical cords. This allowed us to use umbilical cord occlusion to reduce fetal systemic and central oxygen levels in a controlled manner. Inflation of the occluder produced a rapid decline in oxyHb and a corresponding increase in deoxyHb and totalHb, the latter reflecting centralization of blood flow by the fetus in response to a decrease in blood oxygen content. Changes in the NIRS readings tracked with reductions in fetal arterial oxygen saturation and they were enhanced with increasing magnitude of insult i.e. by increasing the degree and/or duration of occluder inflation.²⁹ We have since gone on to use our NIRS system to characterize the preterm³⁸ and the near-term⁵⁴ fetal cerebral oxygenation responses to maternal general anesthesia and we have found it a useful technique for assessing the fetal responses to maternal manipulation, now including dexmedetomidine.

In conclusion, we have determined that infusion of dexmedetomidine into pregnant sheep at gestational day 92, a time point approximately equivalent to the end of the second trimester in humans, produces profound maternal sedation and modest cardiovascular changes in the absence of any significant fetal response except for a rise in blood glucose concentration. The present findings, in combination with other related publications, support conducting additional studies, including maternal administration at different gestational time points, to

determine if dexmedetomidine has clinical utility for sedation and pain control during pregnancy.

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Fig. 1.

Mean $\pm$ SD measurements of maternal (triangles, $\blacktriangle$) and fetal (squares, $\blacksquare$) arterial blood pH (panel A), oxygen saturation (SaO₂; panel B), carbon dioxide (PCO₂; panel C), standard base excess (SBE; panel D), and glucose (panel E). Arterial blood glucose levels in the ewe and fetus were the only parameters to change in response to agent administration; from 30 min onward, glucose values are significantly different ($P < 0.05$) from their respective baseline (experimental time 0) levels as indicated by the line and asterisk.

Fig. 2.

Mean $\pm$ SD measurements of maternal heart rate (panel A), mean arterial pressure (MAP; panel B), and uterine blood flow (UBF; panel C). Data are presented as 1 min averages with the SD (error bars) marked every 5 min for clarity. Maternal heart rate and MAP data points identified by the line and asterisk are significantly different from their respective baselines ($P < 0.05$).

Fig. 3. Mean $\pm$ SD measurements of fetal heart rate (panel A), and mean arterial pressure (MAP; panel B). Data are presented as 1 min averages with the SD (error bars) marked every 5 min for clarity. Fetal heart rate and MAP did not significantly change during the experiment.

Fig. 4. Median (black lines) and 1st and 3rd quartile deviations (gray lines) measurements of fetal cerebral oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb), and total hemoglobin (totalHb). All are expressed as percent of baseline with data presented at 1 min intervals. Results of the statistical analyses are detailed in Table 1

Table 1
Fetal cerebral near-infrared spectroscopy summary data during and after dexmedetomidine infusion

	oxyHb (n=5)		deoxyHb (n=5)		totalHb (n=5)	
	During	After	During	After	During	After
Time spent below/above baseline						
min	471/434	424/176	384/521	162/438	526/379	428/172
percent	52/48	70/30	42/58	27/73	58/42	71/29
AUC (%min)						
Mean $\pm$ SD	-92 $\pm$ 112	-39 $\pm$ 82	-103 $\pm$ 95	-147 $\pm$ 136	-69 $\pm$ 49	-65 $\pm$ 52
Median (95% CI)	-14 (-230-47)	-3 (-140-63)	-90 (-221-15)	-167 (-316-22)	-57 (-130-8)	-49 (-130-0)
P-value	0.063	0.13	0.063	0.063	0.063	0.63

AUC, area under the curve. Calculations in percent minutes are relative to baseline where a negative value is below and a positive value is above baseline. P-values for sum rank comparisons conducted to determine if the distance from baseline of each variable was significant.