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The Chronotropic Effect of Isoproterenol is Reduced in Term Pregnant Women

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Parturients appear to have a decreased chronotropic response to epinephrine. Epinephrine 15 μg iv in non-pregnant volunteers causes a significant tachycardia lasting greater than 3 min.[1] In contrast, epinephrine 15 μg produces only a mild tachycardia lasting less than 90 s in laboring term parturients.[2] An animal study, wherein pregnant rats were resistant to the chronotropic effects of isoproterenol, suggests that pregnancy-induced changes in the sensitivity of the cardiac beta receptor may explain at least part of this difference.¶

We therefore designed this isoproterenol dose response study to determine if pregnant women are more resistant than non-pregnant women to the chronotropic effect of isoproterenol.

MATERIALS AND METHODS

After receiving approval from our institutional review board, we obtained written informed consent from five healthy, non-laboring, term pregnant patients and from five non-pregnant women. Pre-injection continuous fetal heart rate tracings by external monitoring were normal (fetal heart rate >120 and <160 beat/minute with long term variability present, 5–10 beats/minute short-term variability and no decelerations). We explained the procedure to the participants and the likely subjective effects. We informed the participants that they might feel an intense desire to inhale after the isoproterenol injection and that they should continue to relax and breath normally to prevent the added effect of hyperventilation on the heart rate.[3]

After inserting an intravenous catheter, a continuous infusion of .9% normal saline was begun. With all participants resting quietly in a supine position, blood pressure was recorded every minute using an automated blood pressure cuff, and maternal heart rate, fetal heart rate, and uterine contractions were continuously recorded using a Hewlett Packard® HP8040A. Left uterine displacement was maintained in the pregnant patients throughout the study.

After recording baseline measurements for 5 min, incremental bolus iv injections of isoproterenol (0, 0.1, 0.25, 0.5, 1, 2, 4, and 8 μg) were administered until the patient's heart rate responded with an acute increase of 25 beats per minute above the heart rate at the time of the drug injection. The chronotropic dose 25 (CD_{25}) was the dose of isoproterenol which increased the participant's heart rate 25 beats above their baseline heart rate. Each incremental injection was administered either 5 min after the previous injection if there was no change in heart rate, or 5 min after the patient's heart rate had returned to baseline in response to the previous injection. The patient's blood pressure, heart rate, fetal heart rate, and uterine contractions along with any subjective effects were recorded until the patient's heart rate returned to baseline or for at least 5 min. The study was terminated if the systolic blood pressure fell below 100 mmHg, if the fetal heart rate pattern showed any evidence of fetal distress, or if the patient requested we discontinue the procedure.

An obstetrician analyzed the fetal heart rate tracings for evidence of any changes. We estimated each patient's CD_{25} by log interpolating between the two neighboring isoproterenol doses. The difference between the group geometric mean CD_{25} was analyzed by Student's t test with log transformation. Three way analysis of variance determined the difference in blood pressure between the groups. $P < 0.05$ indicated significance.

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¶ Auclair MC, Carli A, Lechat P, Leperlier M, Verminmen C: Diminution de l'effet tachycardisant de l'isoprenaline chez les rattes gravides. Role d'un facteur serique. C. R. Acad Science Paris 289:205, 1979.

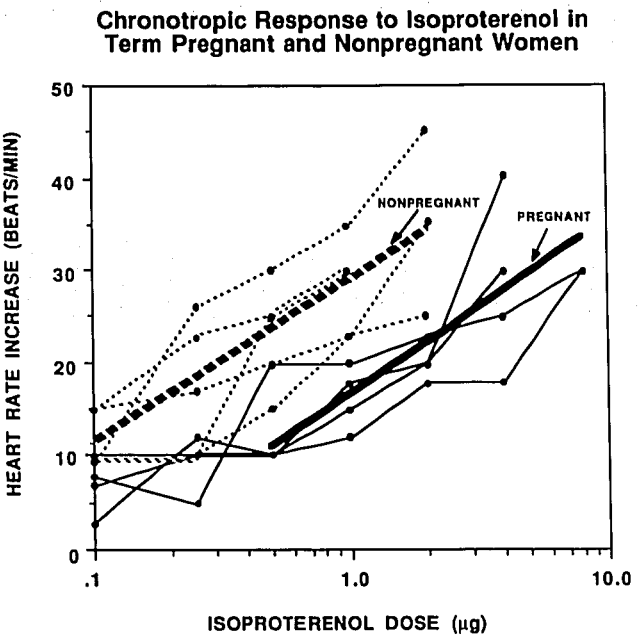

FIG. 1. The chronotropic response to isoproterenol in term pregnant and non-pregnant women. Shown are individual dose-response results in pregnant and non-pregnant women. Mean regression lines for pregnant and non-pregnant women were interpolated from the individual dose-response curves. The CD_{25} in term pregnant patients (3.6 μg) was significantly greater than the CD_{25} (0.7 μg) in non-pregnant patients; the slopes of the mean regression lines did not differ significantly.

RESULTS

Age, height, and weight did not differ significantly between pregnant and non-pregnant women.

One term pregnant patient became anxious and asked that we terminate the study. She experienced a 20 beat/minute increase in heart rate after receiving 2 μg of isoproterenol. Her results were not used to calculate the CD_{25}.

The mean CD_{25} in term pregnant patients (3.6 μg with a coefficient of variation of 51%) was significantly different from that in non-pregnant patients (0.7 μg with a coefficient of variation of 130%) ($P < 0.01$). The slopes of the mean regression lines for term pregnant and non-pregnant patients did not differ (fig. 1).

Blood pressure response was the same in both groups of women. Systolic blood pressure and mean arterial pressure did not change throughout the study. Diastolic blood pressure decreased by 4 mmHg between the two doses of isoproterenol surrounding the CD_{25} ($P < 0.05$).

After completion of the study it was noted that one fetus had an isolated 5 beat/minute late deceleration (associated with a Braxton-Hicks contraction) 2 min after the mother received isoproterenol 0.25 μg.

DISCUSSION

We found that an increased dose of isoproterenol is needed to produce a 25-beat-per-minute heart rate increase in term pregnant patients. Pregnancy appears to shift the isoproterenol dose-response curve to the right without changing its slope. The CD_{25} increases with increasing age and with pharmacologic beta receptor blockade.[3] As in the beta-blocked patient, we found that the CD_{25} increased but the slope of the dose response line was unchanged. Pregnancy, therefore, is one of the few factors which increases the CD_{25}, whereas sex, weight, previous atropine administration, and differences in resting heart rate do not change the CD_{25}.[3]

In pregnancy at term there is about a 35–40% expansion of the maternal blood volume from 1000 to 1500 ml compared to the non-pregnant state.[4] If the differences in the CD_{25} between non-pregnant and pregnant patients was attributed to changes in pharmacokinetics secondary to the increasing blood and plasma volume at term, we would expect the CD_{25} to increase by 35–40%. Our results showed greater than fivefold increase in the CD_{25} in pregnant patients as compared to non-pregnant patients. This greater than fivefold increase in the CD_{25} for isoproterenol at term cannot be explained by changes in the volume of distribution.

Both animal and human studies suggest that pregnancy may decrease responsiveness of the sympathetic nervous system. When rat myocardial cells are stimulated by isoproterenol, the contraction rate increases less when they are bathed in sera from pregnant women than when they are bathed in sera from non-pregnant women or from men. Neither estrogen nor progesterone, when added to the sera of non-pregnant rats, inhibit the chronotropic response to isoproterenol.[5] This work suggests that a circulating inhibitor to beta sympathomimetic response develops during pregnancy.

Other animal work suggests a change in alpha and beta receptor sensitivity during pregnancy. *In vitro* studies on isolated segments of intra- and extracranial arteries from pregnant and non-pregnant rabbits and cats have found altered responses of vessels to sympathomimetics in pregnancy. Arteries from pregnant animals require more isoproterenol to dilate maximally, and the maximal dilation achieved is less intense in the arteries from pregnant than from non-pregnant animals. Similarly, the vasoconstrictive response to norepinephrine is also attenuated.[6]

Pregnancy in humans is associated with an altered cardiovascular response to catecholamines. Healthy pregnant and non-pregnant patients were compared with regard to cardiovascular response to iv infusion of norepinephrine (0.10, 0.20, and 0.40 $nmol \cdot kg^{-1} \cdot min^{-1}$) and epi-

nephrine (0.05, 0.10, and 0.30 nmol · kg^{-1} · min^{-1}) administered in a stepwise fashion. Both non-pregnant and pregnant women responded to the stepwise infusion of norepinephrine with a concentration-dependent increase in blood pressure and decrease in heart rate. Non-pregnant women responded to norepinephrine with increase in blood pressure which was the result of an increase in systemic vascular resistance caused by peripheral vasoconstriction. Pregnant women responded to norepinephrine with a similar increase in blood pressure, but this was due to a stroke volume-dependent increase in cardiac output with no change in peripheral vasoconstriction. Following epinephrine, non-pregnant women responded with a concentration-dependent decrease in diastolic blood pressure and systemic vascular resistance and an increase in cardiac output and heart rate. However, pregnant women responded with little to no concentration-dependent decrease in diastolic blood pressure, a significantly smaller decrease in systemic vascular resistance as compared to non-pregnant patients, and only a mild increase in cardiac output and heart rate.[7] These results suggest that pregnancy is associated with an attenuated vascular response to circulating catecholamines; pregnancy may diminish both alpha adrenergic vasoconstriction and beta adrenergic vasodilation.

The decreased sensitivity of pregnant women to beta adrenergic stimulation may explain the limited usefulness of epinephrine 15 μg as a marker of iv injection in laboring women. Epinephrine 15 μg iv causes a significant tachycardia lasting greater than 3 min in non-pregnant volunteers.[1] In contrast, epinephrine 15 μg iv produces only a mild tachycardia lasting less than 90 s in laboring term pregnant women.[2]

In summary, we found a decreased response to the chronotropic effect of isoproterenol in pregnant women. The cardiovascular response to sympathomimetics in pregnant women cannot be assumed from results in non-pregnant women.

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