EFFECT OF RITODRINE AND BETAMETHASONE ON METABOLISM, RESPIRATION, AND CIRCULATION

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ABSTRACT

In order to obtain information on pharmacologic side effects of the most commonly used betamimetic in obstetrics, ritodrine (R) was infused under standardized, controlled conditions in one male and four nonpregnant female volunteers in increasing doses from 0.9 to 7.2 μg/kg/min. In second series, the same was done after premedication with 12 mg betamethasone (B), intravenously, 30 minutes before the start of the R infusion. Ritodrine caused increases in cardiac and respiratory work that were associated with rises in energy requirements and impaired efficiency of breathing. Premedication with betamethasone potentiated all side effects with the exception of diffusion capacity.

Beta-sympathomimetics have been used successfully to treat premature labor, their use has systemic and particularly cardiovascular side effects. Frequently observed symptoms consist of maternal tachycardia and tremor. Less often fatal complications as a result of pulmonary edema were described as early as 1977 by Bender and co-workers.[1] Elliott[2] reported the same complication when ritodrine was used in conjunction with betamethasone. Glucocorticoids reduce the incidence of respiratory distress syndrome, thus are frequently given in conjunction with beta-agonists. Previous discussions on the pathogenesis of side effects have focused on exaggerated metabolic and cardiovascular responses during pregnancy. Systematic dose-response investigations of cardiac and pulmonary function do not exist for pregnant patients because they would certainly be ethically objectionable. Our opinion is that study of nonpregnant individuals may contribute to the understanding of these side effects. For this reason we performed studies on nonpregnant volunteers to investigate the effects of betamimetics alone, or in combination with betamethasone at clinically used dosage levels.

MATERIAL AND METHODS

One male and four nonpregnant female volunteers between the ages of 26 and 36 years had intravenous infusions of the beta-2-agonist ritodrine (R) and the glucocorticoid betamethasone (B). In the first experiment, the subjects received R at a starting dose of 0.9 μg/kg/min by continuous infusion. Ritodrine was increased every 30 minutes in eight equal steps over a period of 4 hours until a final dose of 7.2 μg/kg/min was reached. The intravenous carrier solution was 5% glucose and water infused at rates of 15 to 150 ml/hr. In a second experiment 2 weeks later, the same subjects were given B, 12 mg intravenously, by bolus injection. This was followed by R infusion 30 minutes later in the same manner described in the first experiment. In the following, the dose of 1.8 μg/kg/min is labeled Step 1, 3.6 μg/kg/min A Step 2, and 7.2 μg/kg/min as Step 3. The tests were begun at 9 AM after breakfast, with the subject sitting relaxed in a reclining chair. During the experiment, oral intake of fluid was allowed ad libitum. A snack was given for lunch. Music was played and light reading material was offered for entertainment.

The following cardiopulmonary variables were measured: the diffusion capacity of the lung using the single-breath method for carbon monoxide (DLCO), heart rate (HR), respiratory frequency (RF), tidal volume (VT), oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$). The following values were calculated from the previous measurements: minute volume of respiration (MV), respiratory equivalents for oxygen ($\dot{V}EO_2$) and carbon di-

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oxide ($\dot{V}ECO_2$), the respiratory quotient (RQ), and the caloric consumption.

Measurements were performed using a computerized cardiopulmonary function module (Fenyves & Gut, Basel, Switzerland) and a cardiorespirograph (Hewlett Packard, Widen, Switzerland). Systolic and diastolic blood pressures (with calculated mean arterial pressure) were measured with a DINAMAP (Applied Medical Research Corporation, Tampa, Florida). All apparatus was calibrated before and after measurement. Reproducibility and precision of results were determined before beginning the study.

The tests were performed before, at each increase of dose, and 60 minutes after stopping infusion. All variables were determined between the 15th and 30th minute after each dose increase. Subjective sensations and objective symptoms were protocoled. The statistical analysis was performed using the Student's t-test for paired values. Values are calculated with standard deviations.

The study was performed in the laboratories of the division of Perinatal Physiology at the Department of Obstetrics, University of Zurich, Switzerland.

RESULTS

Diffusion Capacity of the Lung

There was a slight increase in DLCO upon R infusion initially, then a significant decrease was found from Step 1 to Step 2 ($P < 0.01$). A further decrease occurred after infusion was stopped (Fig. 1). Premedication with 12 mg of betamethasone intravenously caused no significant change in DLCO. During the entire course of infusion, the mean DLCO was 5.2 and decreased to 5.0 mmol/min/kPa/m^2 30 minutes after the infusion. This value was significantly lower ($P < 0.005$) than the baseline measurement taken before start of the infusion (1 kPa = 7.5 mm Hg; 1 mmol gas = 22.4 ml STPD).

Heart Rate

The heart rate already showed a significant increase at Step 1 levels ($P < 0.05$), and further increased during Step 2. It remained significantly elevated 30 minutes after intravenous infusion (Fig. 2). A maximal value of 115 beats/min was found during infusion of R; with R plus B medication, 130 beats/min was noted. After the infusion, there was a significant decrease ($P < 0.001$). The HR was significantly higher during R plus B than under during R infusion alone ($P < 0.05$). The heart rate increased 56% with R, with R plus B it increased by 68% (Table 1).

Respiratory Rate

In the first experiment, respiratory rate was almost 14 before infusion and increased to nearly 17 at Step 2 (Fig. 2). No significant increase occurred from Step 2 to Step 3. Sixty minutes after infusion, RF was still significantly above baseline ($P < 0.002$). In the second experiment (R plus B), RF was significantly higher than in the first at Step 3 and 60 minutes after stopping infusion.

Tidal Volume

There was a highly significant increase in VT in the second experiment ($P < 0.005$). Sixty minutes after infusion, VT was still significantly above the baseline (Fig. 3). Because of large standard deviations, these values did not reach statistical significance in first experiment, but do indicate the same trend as found in the second.

Table 1. Change in Respiratory Parameters and Heart Rate (HR) in Percent Compared to at Rest) During Maximal Ritodrine (R) and Ritodrine with Betamethasone (R + B) Medication. Change in Respiratory Parameters and HR (in Percent Compared to at Rest) 60 Minutes After Stopping Infusion of R and R + B

	During		*After*	
	Ritodrine 7.2 µg/kg/min	*Ritodrine 7.2 µg/kg/min plus Betamethasone 12 mg*	*Ritodrine 7.2 µg/kg/min*	*Ritodrine 7.2 µg/kg/min plus Betamethasone 12 mg*
HR	56	68	35	37
DLCO	0	−2	−6	0
RF	20	22	15	12
MV	44	55	42	46
VT	20	27	23	30
$\dot{V}O_2$	26	50	27	32
$\dot{V}CO_2$	36	59	42	45
RQ	8	6	12	12
$\dot{V}EO_2$	17	5	12	13
$\dot{V}ECO_2$	3	−2	−3	−1
kcal/day	28	52	30	35

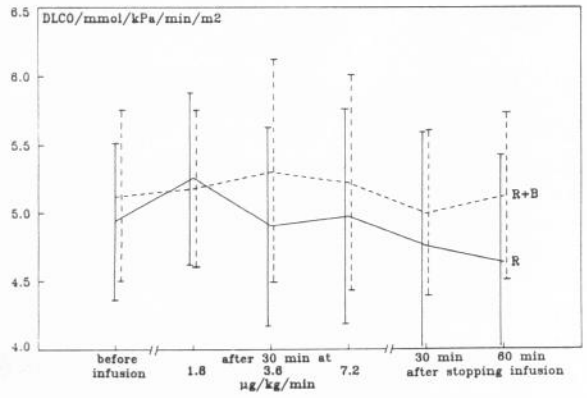

Figure 1. Diffusion capacity of the lung using the single-breath technique with carbon monoxide (DLCO) (expressed as 1 mmol gas = 22.4 ml STPD, 1 kPa = 7.5 mmHg) before, during, and after infusion of ritodrine (R) or ritodrine and betamethasone (R plus B). Infusion rates of R are in µg/kg/min. Bars represent ± SD.

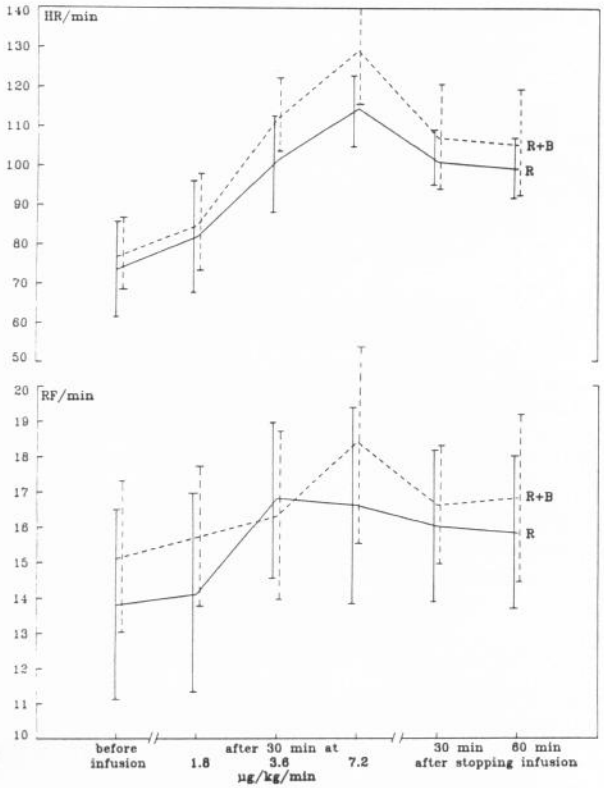

Figure 2. Heart rate (HR) and respiratory frequency (RF) before, during, and after infusion of R or R plus B. Bars represent ± SD.

Minute Volume

There was a significant increase in MV up to Step 3 ($P < 0.01$). This increase was more pronounced in the second experiment ($P < 0.005$) than in the first (Fig. 3). It was also evident that 60 minutes after the infusion, MV was still higher during experiment two than during experiment one. An interesting observation was made when MV was found to be lower at 30 minutes than at 60 minutes after stopping infusion.

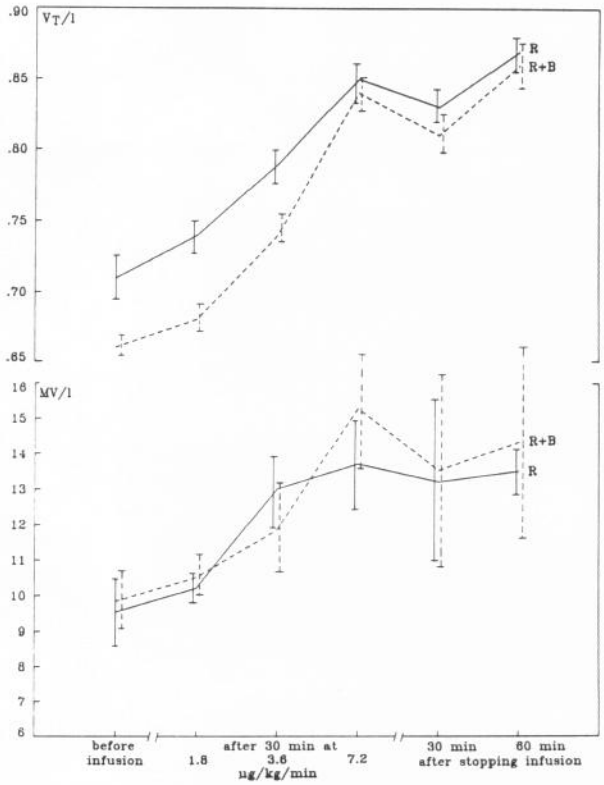

Figure 3. Tidal volume (VT) in liters and minute volume of respiration (MV) in L min before, during, and after infusion of R or R plus B. Bars represent ± SD.

Oxygen Uptake

Oxygen consumption increased until Step 2 in experiment one and until Step 3 in experiment two ($P < 0.01$) (Fig. 4). Even 60 minutes after infusion, oxygen consumption was still 27% higher than baseline in experiment one, it was 32% higher in experiment two (Table 1).

Carbon Dioxide Production

There was a significant increase in carbon dioxide production until Step 3, both in experiment one ($P < 0.01$) and two ($P < 0.005$). Under R plus B infusion, there was a further significant increase from Step 2 to Step 3 (Fig. 4).

Respiratory Quotient

There was an increase in the RQ from 0.83 to 0.90 with R ($P < 0.05$), and from 0.82 to 0.87 with

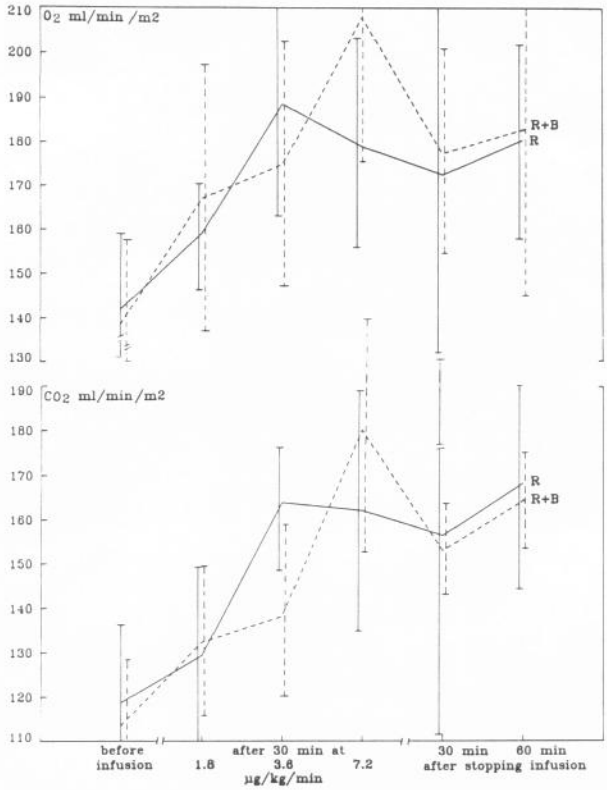

Figure 4. Oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) in ml/min/m^2 before, during, and after infusion of R or R plus B. Bars represent ± SD.

R plus B (Fig. 5). Therefore carbon dioxide production increased more than oxygen uptake. Sixty minutes after the end of infusion, the RQ persisted at approximately the same level as during Step 3.

Ventilatory Equivalents for Oxygen and Carbon Dioxide

The ventilatory equivalents are indexes to describe efficiency of breathing. The $\dot{V}EO_2$ and $\dot{V}ECO_2$ are the volumes of inspired or expired air in liters necessary for oxygen uptake of 1 L or carbon dioxide elimination of 1 L, respectively. The $\dot{V}EO_2$ fell during R infusion from 39 L at rest to 36 L at low dose, Step 1. The $\dot{V}ECO_2$ also fell from 48 to 45 L. The corresponding measurements for R plus B were from 41 to 37 L for $\dot{V}EO_2$ and from 50 to 46 L for $\dot{V}ECO_2$. This trend indicated an increase in efficiency of breathing at low-dose R infusion. However, at higher doses (Step 3), breathing became less efficient compared to preinfusion measurements. This is expressed by a rise in $\dot{V}EO_2$ to 45 L, in $\dot{V}ECO_2$ to 49 L during R infusion, during R plus B infusion, $\dot{V}EO_2$=43 L and $\dot{V}ECO_2$ = 49 L.

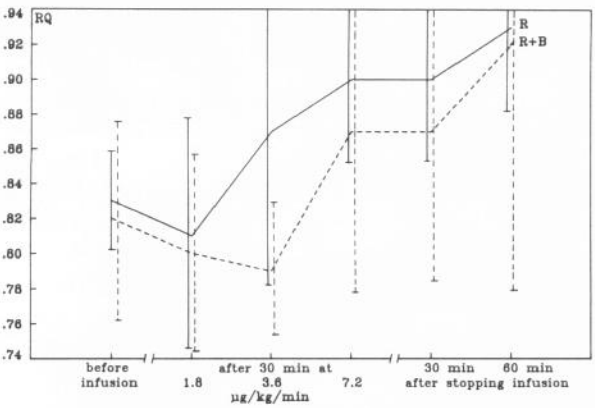

Figure 5. Respiratory quotient (RQ) before, during, and after infusion of R or R plus B. Bars represent ± SD.

Blood Pressure

During R infusion, there was a 7% increase in systolic pressure from 119 ± 5 to 127 ± 9 mm Hg, and a significant decrease ($P < 0.05$) in diastolic pressure from 73 ± 3 to 68 ± 5 mm Hg (7%). The mean arterial pressure was maintained constant at 86 mm Hg. After premedication with B, there was a significant increase in systolic blood pressure from 123 ± 4 to 132 ± 4 mm Hg ($P < 0.05$, 7%) and a significant decrease in diastolic blood pressure from 76 ± 8 to 69 ± 3 mm Hg ($P < 0.05$, 9%). In this group, mean arterial pressure decreased from 91 ± 11 to 85 ± 4 mm Hg (7%). This fall was not statistically significant, however.

Subjective Symptoms

The most common subjective symptoms were palpitation, flushes, and nausea at higher doses. One of the volunteers experienced a hypotensive syncope at the maximal infusion rate. One volunteer noted dyspnea. All subjects reported a sensation they described as a waxy feeling upon such movements as getting up from the chair. In addition, the following side effects were noted: head pressure, headache, dizziness, heartburn, chills, paresthesias, nose bleeds on the following day, and singultus lasting for 2 days. The investigators also detected extrapyramidal symptoms such as robot-like movements which could explain the feeling of altered muscle tonus.

DISCUSSION

This study revealed that the betamimetic ritodrine caused profound changes in cardiopulmonary function and metabolic requirements. The catecholamine-initiated stimulation of metabolism caused an enormous increase in cardiac and pulmonary work at dosages used in obstetric practice. Tachycardia, well-known to every physician who uses ritodrine, is demonstrated in our results (Fig. 1). A 60% increase in heart rate above baseline was noted. The tachycardia was significantly more pronounced

when steroids were added to ritodrine, a phenomenon we also observed with fenoterol, the most widely used tocolytic in Europe.[5] One explanation for this phenomenon is the increase of beta-receptors observed when glucocorticoids were used in the treatment of patients with bronchial asthma.[6,7]

Cardiac output was not measured in our study. An increase in cardiac output by betamimetics is probably based on the known positive inotropic and positive chronotropic effect of the drugs. The latter was seen in our volunteers. Cardiac output measurements were performed in humans receiving ritodrine by Biennarz and others in 1974.[8] These investigators showed that heart rate and cardiac output increased in parallel at low dosages. At doses of 150 μg/min and higher, which correspond to our Step 2 infusion rate, (3.6 μg/kg/min), there was a divergence of these two variables—stroke volumes declined, but heart rate rose further.

The accelerated respiratory workload was more pronounced with combination therapy than with ritodrine alone. The minute volume, the product of respiratory rate and tidal volume, rose 55% above baseline with combination therapy, compared to 44% with single-drug therapy. Tidal volume and respiratory rate participated evenly in the observed increase of minute volume during both modes of medication. As a consequence of larger minute volumes, O_2 uptake and CO_2 elimination were increased as well. It is apparent that neither, particularly oxygen uptake, kept pace with increased minute volumes. The maximal increase in oxygen uptake was 26% with R infusion and 50% with R plus B infusion. As a consequence, there was an increase in ventilatory equivalents for oxygen and carbon dioxide which are expressions of a fall in efficiency of breathing. A likely explanation for these results is to be found in the measurements of the diffusion capacity of the lungs. Determination of this variable was performed with the hypothesis that changes in lung function leading to pulmonary edema might be diagnosed in its early stages.

Unfortunately, diffusion capacity of the lung (DL) is not solely a measure of diffusion of gases from alveolus across the interstitial space to the pulmonary capillaries, but is also influenced by pulmonary blood flow and ventilation. In this study, ventilation was clearly increased. It can only be surmised from these data that pulmonary perfusion was increased because of an increase in cardiac output, at least at low infusion rates. Consequently, one would expect an increase in DL. The absence of an increase (Fig. 1) can be interpreted as a consequence of impaired alveolar-capillary diffusion. The decrease in oxygen uptake per volume of inspired air further supports this point. The extent of impairment in diffusion cannot be assessed from the data because DL is a global measure that depends on many subvariables. Apparently, a change in diffusion occurs at low doses of infused ritodrine. The influence on diffusion can be explained by interstitial water uptake leading to an alveolar-capillary block, as was demonstrated in animal experiments by Grospietsch and others in 1980[3,4] and Hauth and others in 1983.[10]

Case reports on pulmonary edema with betamimetics are more often found to be associated with glucocorticoid medication,[11] even though it is known that these steroids have a membrane-stabilizing effect and, therefore, should counteract the development of pulmonary edema. Our results point in this latter direction. The discrepancy between the theoretically expected increase in DL as a consequence of increased cardiac output and pulmonary blood flow and the measured trend in DL is more pronounced with ritodrine alone (Fig. 1). A discrepant effect between R and R plus B was also documented in the measurements of ventilatory equivalents for oxygen and carbon dioxide.

Naturally, the catecholamine-induced augmentation of cellular metabolism, as well as the increased cardiac and respiratory work, will necessarily lead to an accelerated metabolic rate. From oxygen uptake we calculated that caloric requirements were increased by 586 kcal per 24 hours with R and were increased 884 kcal per day with R plus B. This corresponds to increases of 28 and 52% above baseline values, respectively.

Our calculations of initially falling RQs and subsequent rises were similar to observations made by Unbehaun in 1974.[13] This effect is apparently the result of initial lipolysis followed by glycolysis which then becomes the preponderant source for energy.

The directly observed symptoms of our volunteers should be emphasized. Some of the subjects reported these to be so severe that they only agreed to tolerate them for the sake of a successful experiment. For clinicians, this demonstrates the need to reduce ritodrine in patients as soon as the desired effect in suppression of uterine activity is reached, and not to prolong high-dose medication for long periods of time without bonafide indications.

Our results are hampered by the fact that they were not conducted in pregnant women. It is possible, on the one hand, that pregnant women can better tolerate these medications because their organisms have already adapted to the state of pregnancy by increasing cardiopulmonary capacity. On the other hand, the opposite could be true: perhaps women already under such a pregnancy-induced cardiopulmonary burden cannot tolerate further increases as readily. Even with these limitations, we can say that R alone, or in combination with steroids, leads to considerable changes in homeostatis of the organism. As our measurements show, these changes persist for at least 60 minutes and probably longer after discontinuation of ritodrine. Therefore, a potentiating effect may exist with any subsequent course of treatment instituted for breakthrough labor. These medications cause a definite increase in cardiac and pulmonary workloads, as well as increased energy requirements. Our results also document an impairment in diffusion capacity of the lung, but we cannot conclude that these changes explain the

occurrence of fatal pulmonary edema as reported in the literature. Betamethasone potentiates the effect on heart and lung function, but not the effect on diffusion capacity of the lung.

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