OBSTETRICS

Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during Caesarean section

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Background. ECG changes, similar to those seen during myocardial ischaemia, together with symptoms of chest pain, are common during Caesarean section (CS). We hypothesized that oxytocin administration has cardiovascular effects leading to these symptoms and ECG changes.

Methods. Forty women undergoing elective CS under spinal anaesthesia were given an i.v. bolus of either 10 IU of oxytocin (Group OXY-CS, n=20) or 0.2 mg of methylergometrine (Group MET-CS, n=20), in a double-blind, randomized fashion after delivery. Ten healthy, non-pregnant, non-anaesthetized women were used as normal controls (Group OXY-NC, n=10) and were given 10 IU of oxytocin i.v. Twelve-lead ECG, on-line, computerized vectorcardiography (VCG), and invasive arterial pressure were recorded.

Results. Oxytocin produced a significant increase in heart rate, +28 (SD 4) and +52 (3) beats min⁻¹ [mean (SEM); P<0.001], decreases in mean arterial pressure, −33 (2) and −30 (3) mm Hg (P<0.001), and increases in the spatial ST-change vector magnitude (STC-VM), +77 (12) and +114 (8) µV (P<0.001), in CS patients and controls, respectively. Symptoms of chest pain and subjective discomfort were simultaneously present. Methylergometrine produced mild hypertension and no significant ECG changes.

Conclusions. Oxytocin administered as an i.v. bolus of 10 IU induces chest pain, transient profound tachycardia, hypotension, and concomitant signs of myocardial ischaemia according to marked ECG and STC-VM changes. The effects are related to oxytocin administration and not to pregnancy, surgical procedure, delivery, or sympathetic block from spinal anaesthesia.

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Transient ECG changes, such as ST-segment depression and T-wave abnormalities, can be observed in healthy women undergoing Caesarean section (CS) under regional anaesthesia.1–3 The ECG changes appear to occur during and immediately after delivery and have been associated with systemic hypotension and tachycardia. Subjective symptoms, such as chest discomfort or pain, headache, and dyspnoea, are also described. Air emboli, pain from retroperitoneal traction, cardiac sympathetic block, and hyperventilation are some of the suggested explanations.1–6 Case reports of myocardial infarction and cardiac complications in the parturient and reports of a significant increase in serum levels of cardiospecific troponin T after CS6–8 have increased our interest in evaluating this in more detail.

I.V. oxytocin produces hypotension and tachycardia and has been associated with ECG changes suggestive for myocardial ischaemia.5–9 The present study was designed
to determine whether or not the cardiovascular effects, ECG changes, and subjective symptoms during CS are related to oxytocin or whether they are associated with pregnancy, sympathetic block, surgery, or the profound physiological changes during delivery. The aim was also to evaluate the relevance of ECG changes as a sign of myocardial ischaemia using computerized vectorcardiography (VCG).

Methods

After approval by the ethics committee at the University of Umeå, informed consent was obtained from all included women.

Forty healthy women, pregnant at full term and undergoing elective CS with spinal anaesthesia, were randomised into two subgroups: Group OXY-CS (n=20), oxytocin (Syntocinon®, Novartis, Täby, Sweden) after delivery and Group MET-CS (n=20), methylergometrine (Methergin®, Novartis, Täby, Sweden) after delivery.

Ten healthy, non-pregnant, non-anaesthetized women received oxytocin in an open fashion, as normal controls: Group OXY-NC.

Oxytocin and Caesarean section and methylergometrine and Caesarean section

No premedication was given. Upon arrival at the operating room, i.v. access was established and a catheter was inserted into the right radial artery under local anaesthesia. Conventional 12-lead ECG and VCG were recorded in each patient. Baseline measurements were made in the left lateral tilt position and an i.v. infusion of 500 ml of dextran 70 in Ringer’s acetate was given. Spinal anaesthesia was then induced in the sitting position with 12.5–13.75 mg of hyperbaric bupivacaine. The women were placed in a supine position, with a left lateral tilt of the operating table to avoid vena cava compression by the uterus, and supplementary nasal oxygen (2 litre min⁻¹) was administered. Five milligrams of ephedrine were given as an i.v. bolus when the systolic arterial pressure (SAP) decreased below 95 mm Hg. Surgery began when the increase was more than 50 mm Hg. Right radial SAP, diastolic arterial pressure (DAP), and heart rate (HR) were measured continuously for 15 min. Subjective symptoms were systematically documented.

Oxytocin and non-pregnant controls

Measurements were performed in 10 healthy, non-pregnant, non-anaesthetized women using the same protocol as that used for the OXY-CS and MET-CS groups. After measurements ‘before drug’ at rest in the horizontal position, 10 IU of oxytocin were injected as an i.v. bolus within 30 s and the effects on STC-VM, ECG, arterial pressure, and HR were recorded continuously for 15 min. Subjective symptoms were systematically documented.

Measurements

Scalar 12-lead ECG signals, with an amplifier bandwidth of 0.05–500 Hz, were recorded (Mingograph 7, Siemens-Elema AB, Solna, Sweden). ST-segment depressions in the ECG chest leads were measured at 60 ms after the J-point and were considered abnormal if they were horizontal or sloped downwards and had a change of more than 0.1 mV from baseline. The sum of the ST changes for all chest leads was calculated at the point of peak change. The ECGs were assessed by a cardiologist blinded to the drug the subjects had been given. The ECGs were classified according to changes in voltage, increases in HR, ST-segment depression, changes in T-waves, and the development of positive U-waves.

Spatial ST-change vector magnitude (STC-VM) was recorded with a computerized system for VCG (MIDA 1000, Orivitus Medical AB, Täby, Sweden) using a measurement sensitivity of 1.0 μV for averaged complexes, a sampling frequency of 500 Hz, and an amplifier bandwidth of 0.03–500 Hz. Electrodes were placed in the standardized fashion described by Frank[10] and the signals were sampled and averaged in periods of 15 s. Changes in STC-VM were considered significant as a sign of ischaemia if the increase was more than 50 μV.[11 12]

Right radial SAP, diastolic arterial pressure (DAP), and mean arterial pressure (MAP) were measured using a fluid-filled catheter system (1.0 mm cannula, Ohmeda transducer DT-XX 992523A, Singapore) and was recorded on a polygraph (Mingograph 7). HR was derived from the VCG recordings.

Intervals of 15 s between measurements included for analysis were chosen, based on previous reports of the rapid onset and time course of oxytocin effects. Absolute values for all variables were taken immediately before drug administration and at the time of peak STC-VM for each patient. Furthermore, the mean difference compared with values before drug was calculated for each group.
Signs of myocardial ischaemia after injection of oxytocin

Statistics
Absolute values for variables were expressed as mean values (SEM). Differences between the groups were tested using one-way ANOVA. When a significant difference between groups was found, post hoc tests for differences were performed using Tukey’s HSD test.

Results
The three groups were similar in terms of age [OXY-CS: 31 (1.3); MET-CS: 31 (1.2); and OXY-NC: 33 (2.2) yr] and height [OXY-CS: 166 (1.4); MET-CS: 163 (1.3); and OXY-NC: 169 (1.7) cm]. The pregnant women were significantly heavier than the women in the control group [OXY-CS: 79.4 (3.2); MET-CS: 79.4 (2.7); and OXY-NC: 63.6 (1.8) kg]. The spinal blocks in the OXY-CS and MET-CS groups had a sensory level of Th 4 or higher in all but one woman in each group, who reached a level of Th 6. All included patients and controls fulfilled the study protocol and no one was lost to analysis.

At baseline ‘before spinal’ and interventions, the HR was significantly higher in the pregnant women than in the non-pregnant controls ‘before drug’. This was probably due to the normal physiological increase in cardiac output at full term. The higher SAP, MAP, and DAP in pregnant women compared with controls may be an effect of anxiety before spinal anaesthesia and surgery. The STC-VM values did not differ between the groups (Table 1).

Table 1 Haemodynamic and vectorcardiographic data in the two groups of Caesarean section (OXY-CS and MET-CS) and in non-pregnant controls (OXY-NC). Measurements were performed before spinal (OXY-CS and MET-CS), before drug (OXY-NC), and before drug but after spinal and delivery (OXY-CS and MET-CS) and at the time of maximum ST changes. Values are HR (beats min\(^{-1}\)), SAP, MAP, and DAP (mm Hg), and STC-VM (μV). Data are presented as mean ± SEM. One-way repeated measures ANOVA was used to test for differences within groups. *P<0.05 vs before drug; †P<0.05 vs before spinal

<table>
<thead>
<tr>
<th></th>
<th>OXY-NC (n=10)</th>
<th>OXY-CS (n=20)</th>
<th>MET-CS (n=20)</th>
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<tr>
<td>HR (beats min(^{-1}))</td>
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<tr>
<td>Before spinal</td>
<td>89 (3)</td>
<td>82 (3)</td>
<td>82 (3)</td>
</tr>
<tr>
<td>Before drug</td>
<td>64 (2)</td>
<td>89 (3)</td>
<td>83 (3)</td>
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<tr>
<td>At max. STC-VM</td>
<td>116 (5)*</td>
<td>117 (3)*</td>
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<tr>
<td>SAP (mm Hg)</td>
<td></td>
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<tr>
<td>Before spinal</td>
<td>146 (5)</td>
<td>143 (4)</td>
<td>87 (3)</td>
</tr>
<tr>
<td>Before drug</td>
<td>139 (3)</td>
<td>131 (3)*</td>
<td>136 (6)</td>
</tr>
<tr>
<td>At max. STC-VM</td>
<td>107 (4)*</td>
<td>85 (4)*</td>
<td>150 (6)*</td>
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<td>DAP (mm Hg)</td>
<td></td>
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<tr>
<td>Before spinal</td>
<td>79 (2)</td>
<td>76 (2)</td>
<td>76 (2)</td>
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<tr>
<td>Before drug</td>
<td>73 (2)</td>
<td>70 (2)*</td>
<td>69 (3)*</td>
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<td>45 (3)*</td>
<td>43 (2)*</td>
<td>78 (2)*</td>
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<td>MAP (mm Hg)</td>
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<tr>
<td>Before spinal</td>
<td>101 (3)</td>
<td>98 (3)</td>
<td>98 (3)</td>
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<tr>
<td>Before drug</td>
<td>95 (2)</td>
<td>91 (3)*</td>
<td>91 (4)*</td>
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<tr>
<td>At max. STC-VM</td>
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<td>57 (2)*</td>
<td>102 (3)*</td>
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<tr>
<td>STC-VM (μV)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Before spinal</td>
<td>10 (1)</td>
<td>10 (1)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Before drug</td>
<td>6 (1)</td>
<td>37 (5)*</td>
<td>43 (6)*</td>
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<tr>
<td>At max. STC-VM</td>
<td>120 (8)*</td>
<td>114 (13)*</td>
<td>54 (5)</td>
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Oxytocin and Caesarean section
After the spinal anaesthesia and delivery, the HR did not change compared with baseline, although there was a small yet significant decrease in arterial pressure to levels similar to the controls and a small yet significant increase in STC-VM to 37 (5) μV ‘before drug’ (Table 1). Within a few seconds after the bolus of oxytocin, there was an additional significant increase in STC-VM up to 114 (13) μV, concomitant with a significant decrease in arterial pressure and an increase in HR to up to 117 (3) beats min\(^{-1}\) (Table 1). The temporal relationship between the VCG and haemodynamic changes is shown in Figure 1. The peak values for all parameters were reached within 1 min after oxytocin administration and returned to baseline within 5 min.

An analysis of the scalar ECG revealed an increase in HR of more than 25 beats min\(^{-1}\) in 10/20 OXY-CS women and more than 30 beats min\(^{-1}\) in 7/20. Eleven of 20 women developed transient ST-segment depression and 7/20 had T-wave changes. The mean sum of ST depressions (at the point of maximum change) in all chest leads was 5.3 (0.6) mV (Fig. 2).

An example of the ECG and VCG response to oxytocin in one woman undergoing a section is shown in Figure 3.

Methylergometrine and Caesarean section
Like the OXY-CS group, HR was unchanged, arterial pressure decreased, and STC-VM increased significantly to 43 (6) μV after ‘spinal’ and delivery ‘before drug’ (Table 1). After the injection of methylergometrine, STC-VM and HR did not change, whereas arterial pressure increased significantly (Fig. 1, Tables 1 and 2).

An analysis of the scalar ECG changes revealed no increase in HR. Six of 20 women in the MET-CS group developed a transient ST-segment depression and 3/20 had T-wave changes. The mean sum of ST depressions (at the point of maximum change) in all chest leads 60 m s after the J-point was 1.8 (0.3) mV (Fig. 2).

Oxytocin and non-pregnant controls
HR and arterial pressure were normal at rest before drug and lower compared with the pregnant women at baseline before spinal. STC-VM was normal and similar to the values before spinal in the women undergoing CS. Oxytocin produced a significant reduction in arterial pressure and an increase in HR up to 116 (5) beats min\(^{-1}\) and STC-VM up to 120 (8) μV that was of the same magnitude as that seen in the women receiving oxytocin during CS. The peak changes occurred within 1 min after oxytocin administration and returned to baseline within 5 min (Fig. 1 and Tables 1 and 2).

An analysis of the scalar ECG revealed a HR increase of more than 30 beats min\(^{-1}\) in all the control women. Five of 10 developed a transient ST-segment depression.
and 6/10 had T-wave changes. The mean sum of ST depressions (at the point of maximum STC-VM change) in all chest leads was 3.73 (0.44) mV, which did not differ from the women given oxytocin during CS but was significantly higher than the women receiving methylergometrine during CS (Fig. 2).

Subjective symptoms in the 10 control women included headache (n=9), flushing (n=8), palpitations (n=6), chest pressure (n=3), and hyperventilation with dyspnoea and nausea (n=1). These symptoms were reported during the minutes after the injection of oxytocin and were concurrent with the ECG, VCG, and peak haemodynamic changes. The symptoms ceased in parallel with the resolution of the ECG changes.

Heart rate and vectorcardiography

The controls (OXY-NC) displayed a greater increase in HR and STC-VM after oxytocin administration than the women undergoing a section (OXY-CS) (Table 2). Paired observations for HR and STC-VM showed increases in STC-VM, with increasing HR in both groups receiving oxytocin (Fig. 4). The linear regression of HR and STC-VM in the control group immediately after oxytocin injection until the maximum STC-VM level showed a 4.6 (3.1) μV per beat increase in STC-VM.

Discussion

An i.v. bolus of 10 IU of oxytocin produced a transient hypotension, tachycardia, ECG ST-T depression, and the elevation of STC-VM in women during CS under spinal anaesthesia and in healthy non-pregnant, non-anaesthetized controls. Methylergometrine produced a significant increase in arterial pressure but had no effect on HR and STC-VM. The results demonstrate that the cardiovascular and ECG changes often observed during CS are related to the administration of oxytocin and not to pregnancy, spinal anaesthesia, surgical procedure, or delivery. Oxytocin induced striking ECG changes and subjective symptoms that were typical of myocardial ischaemia. The symptoms of flush, chest pain, and dyspnoea were closely related to the injection of oxytocin and the cardiovascular effects. They were typical of the complaints commonly described in women undergoing CS under spinal anaesthesia.
In spite of many investigations, there is still a question of whether or not the ECG changes and subjective symptoms observed during CS are important and relevant as signs of myocardial ischaemia. Most previous studies of this topic have used Holter ECG with averaging periods of 30–60 s and intermittent non-invasive arterial pressure measurements. With continuous monitoring and short averaging periods of 15 s, we could demonstrate that the short-lasting cardiovascular and ECG changes were related to the injection of oxytocin and could easily have been missed with intermittent monitoring.

McLintic and colleagues and Mathew and colleagues were unable to demonstrate myocardial ventricular wall motion abnormalities as a sign of myocardial ischaemia using echocardiography during CS. The method is, however, difficult to perform during this procedure. Moran and colleagues demonstrated frequent episodes of ST-segment depression by continuous Holter monitoring both perioperatively and up to 12 h after delivery. They also found a release of cardiосpecific troponin T as a biochemical marker of myocardial ischaemia in two of the patients with ST-T depression.

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Table 2 Haemodynamic and VCG changes from controls before the injection of the drug to the peak STC-VM. The data are expressed as mean values of peak differences in HR, SAP, MAP, DAP, and STC-VM. Data are presented as mean (SEM). One-way ANOVA was used to compare groups. When significant ANOVA was found, post hoc tests were conducted using Tukey’s HSD test. *P<0.05 vs MET-CS; †P<0.05 vs OXY-CS

<table>
<thead>
<tr>
<th></th>
<th>OXY-NC</th>
<th>OXY-CS</th>
<th>MET-CS</th>
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<tbody>
<tr>
<td>ST changes (s)</td>
<td>91 (18)</td>
<td>58 (5)</td>
<td>70 (8)</td>
</tr>
<tr>
<td>ΔHR (beats min⁻¹)</td>
<td>52 (3)*</td>
<td>28 (4)*</td>
<td>+4 (3)</td>
</tr>
<tr>
<td>ΔSAP (mm Hg)</td>
<td>-35 (6)*</td>
<td>-46 (3)*</td>
<td>+15 (2)</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>-28 (2)*</td>
<td>-27 (2)*</td>
<td>+9 (2)</td>
</tr>
<tr>
<td>ΔSTC-VM (μV)</td>
<td>114 (8)*</td>
<td>77 (12)*</td>
<td>+11 (4)</td>
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</table>

We used both continuous 12-lead ECG and computerized VCG that has the advantage to provide both a magnitude and direction of a spatial vector reflecting changes in myocardial electrical activity in three dimensions (STC-VM). An increase in STC-VM of more than 50 μV is considered to be a more sensitive and specific sign of myocardial ischaemia than conventional ECG.

The spatial vector is sensitive to postural changes of the heart. The first small increase in STC-VM from the zero point to the value ‘before drug’ in both pregnant groups was probably due to change in position of the operation table and reduction of abdominal content at delivery. The second large increase in STC-VM from the level ‘before drug’ to levels far above the limit for myocardial ischaemia after oxytocin injection was not biased by postural...

Fig 3 Recordings of scalar ECG and VCG in one OXY-CS woman after 10 IU of oxytocin i.v. Note the pronounced peak in STC-VM in the VCG trend curve and the ST-segment depression in the scalar ECG.

Fig 4 Paired observations of STC-VM and HR in women receiving oxytocin during Caesarean section and controls.
changes and reflect true changes in cardiac electrical activity.

One of the limitations of ECG methods when it comes to detecting myocardial ischaemia is the influence of tachycardia on ST changes. Recently, Häggmark and colleagues demonstrated that STC-VM increased by approximately 2 μV per paced heart beat over 100 beats min⁻¹ without metabolic signs of myocardial ischaemia in patients without cardiac disease and suggested a correction factor for the ischaemic threshold at HR above 100 beats min⁻¹. Patients with coronary artery disease had a more prominent increase of STC-VM at similar paced HR along with lactate-verified myocardial ischaemia. In our women, the STC-VM increased with 4.6 μV per beat along with subjective symptoms, a pattern that was similar to the patients with coronary disease.

Oxytocin is an ‘old’ vasoactive peptide with a complex hormonal activity. Specific receptors for oxytocin have been described in all kinds of tissue such as the myocardi

The oxytocic cardiovascular effects appear to be transient and persistent myocardial damage seems to be unusual.

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**References**


6 Bolton TJ, Randall K, Yentis SM. Effect on the confidential enquiries into maternal deaths on the use of syntocinon at caesarean section in the UK. *Anaesthesia* 2003; 58: 277–9
15 Hagmark S. Detection of myocardial ischemia. Clinical and experimental studies with focus on vectrocardiography, heart rate and perioperative conditions. Umeå University Medical Dissertations 2005; VI: 1–25 ISBN 91-7305-942-0. ISSN: 0346-6612; N.S., 982
26 Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. Br J Anaesth 2007; 98: 116–9