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THE IMBALANCE BETWEEN VASOCONSTRICTORS AND VASODILATORS IN SERUM FROM PRE-ECLAMPTIC WOMEN: RESULTS FROM PERFUSED SWINE UTERI USING A COMPLETE DIGITAL MEASUREMENT AND DATA RECORDING SYSTEM

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ABSTRACT. OBJECTIVE: To compare the effects of serum from pre-eclamptic (PE) and healthy pregnant (HP) women to the effects of serum from healthy non-pregnant (HNP) women on intra-arterial pressure (IAP) and intra uterine pressure (IUP) in the perfusion swine uteri model using a complete digital measurement and data recording system. METHODS: Thirty-six swine uteri were perfused with the aim to preserve a viable organ. Serum from PE, HP and HNP women (N = 12 per group) were administered. IAP and IUP were continuously monitored using a complete digital data recording system. RESULTS: The greatest increase in IUP was caused by serum from HNP women, followed by serum fro PE and serum from HP ($P < 0.05$). IAP following the administration of serum from PE women was higher compared to the effect of serum from HNP women, but the difference was not statistically significant. The increase of IAP caused by serum from HP women was significant lower ($P = 0.002$) compared to serum from HNP women. CONCLUSION: The findings show that serum from PE women has significant vasoconstrictive and oxytocic effects in comparison with serum from HP women. In pre-eclampsia, the balance between vasorelaxing and vasoactive substances may be disturbed. The complete digital data monitoring and recording system was feasible, reliable and simplified the data measurement and recording procedure extensively while it enabled a higher sensitivity.

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1. INTRODUCTION

Pre-eclampsia is a multi-system disorder that is unique to human pregnancy. It is a major causes of maternal and fetal mortality and morbidity worldwide [1,2]. The vascular endothelium plays a key role in the regulation of vascular tone, coagulation and blood pressure by synthesizing and releasing potent vasoactive substances such as vasoconstrictors as well as vasodilators [3]. Hypertension, proteinuria and oedema are the most common and well-known clinical features in the mothers affected [4]. On the other side a fetal syndrome with growth restriction, reduced amniotic fluid and abnormal oxygenation may be present. The appearance of the disorder is heterogeneous and the pathogenesis can differ in women with various possible risk factors, while the real cause of pre-eclampsia remain still unknown [5]. Pre-eclampsia is caused by the presence of the placenta or the maternal response to placentation. One possible theory on the cause of pre-eclampsia is that ischaemia-reperfusion leads to oxidative stress and results in a vascular disease [5]. It has been hypothesized that endothelial cell dysfunction may be a major pathophysiological mechanism, leading to the complications observed in women with pre-eclampsia [3]. Many endothelial studies have focused on the importance of thromboxane A2 and prostacyclin imbalance in women with pre-eclampsia [6]. The pathway mediating endothelial cell dysfunction is still unknown, despite the fact that this maternal inflammatory response may also be a feature of healthy pregnancy in the third trimester [5,7]. In addition, many women with preterm births have similar implantation abnormalities to those seen in pre-eclamptic patients [8,9].

In pre-eclampsia, endothelial dysfunction may decrease the production and/or activity of vasodilators, resulting in an imbalance of vasoconstrictors.

Nowadays only cell culture experiments and *in vivo* vessel models involving the incubation of pre-eclamptic serum or plasma have been carried out in an effort to identify the substances involved in these processes [10,11]. *In vitro* experiments on vascular and uterine reactivity, with isolated arterial rings from various arteries or uterine stripes or rings, have been performed using vasoactive components, rather than serum from pre-eclamptic women [12]. The primary site of the pre-eclamptic disorder is the uterus, but the uterus itself has never been examined as a complete organ with intact anatomical structures in relation to this question.

We have previously demonstrated that the swine uterus perfusion model is capable of keeping the swine uterus in a functional condition for up to at least 7 hours and that it is appropriate for the study of physiological questions [13]. The experimental system detects electrical and mechanical activities in the whole organ, as it maintains the architecture and intercellular relations of the uterus [14,15]. Using this model we are able to characterize oxytocic or tocolytic properties of different test substances [13,16]. Furthermore the assessments of vascular tone changes [intra-arterial pressure (IAP)] are possible. In the present study the changes in intrauterine pressure (IUP) and intra-arterial pressure (IAP) after administration of serum from pre-eclamptic (PE) women, healthy pregnant (HP) women and healthy non-pregnant (HNP) women (serving as controls) were compared using the previously described perfusion swine uterus model. For the first time we used a complete digital IUP and IAP measurement system with microchip catheters connected with a digital datalogger and a computer assisted data recording system, which makes it possible to monitor IUP and IAP continuously. Perfusion models of various organs have been of great interest, particularly in the field of transplantation medicine and in studies of the physiology and metabolism of tissues. The aim of our study was to test the hypothesis that serum from PE women has more oxytocic and/or vasoconstrictive potential compared with serum from HP women, as a raised ratio of vasoconstrictors to vasodilators is expected to reduce uteroplacental blood flow in pre-eclamptic women [5]. This complete digital system may be feasible and reliable, and easy to handle because no calibration or maintenance is necessary.

2. METHODS

2.1. SWINE UTERUS

Swine (*Sus scrofa domestica*) are widely used in

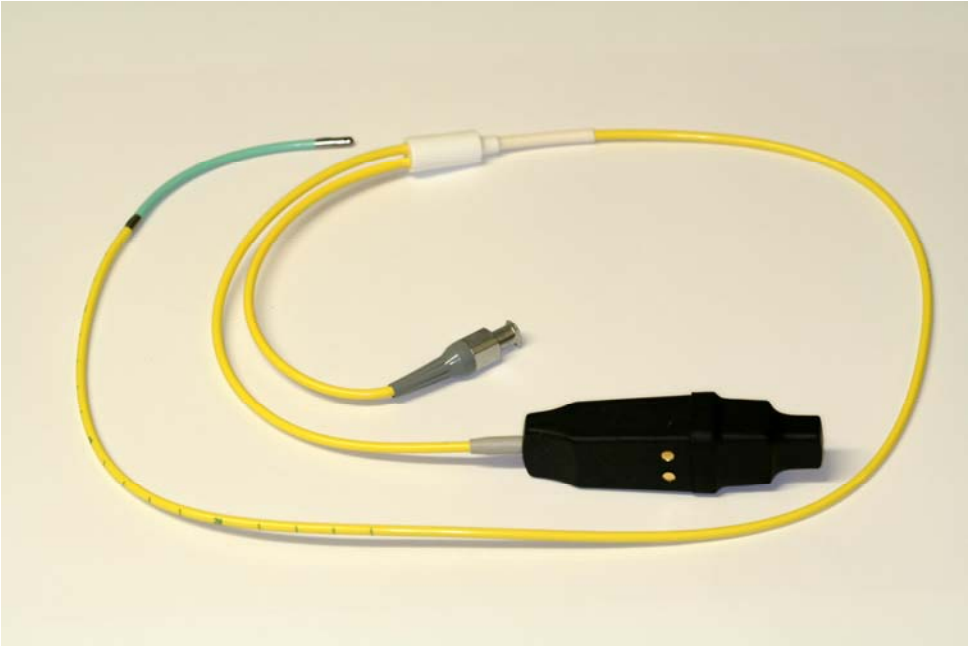

FIGURE 1. THE DIGITAL INTRAUTERINE MICROCHIP-CATHETER, UROBAR-DL 8, RAUMEDIC, ERLANGEN, GERMANY.

research. The female reproductive system in the swine has a bicornate uterus with tortuous fallopian tubes. The fallopian tubes in an adult female swine have the same diameter as those in the human, but they are much longer. The sow has an oestrous cycle of 20–21 days.

Thirty-six swine uteri were obtained from the local slaughterhouse. They were selected on the basis of their size, overall condition and the condition of the uterine arterial stumps. The mean weight of the swine uteri was 117.27 g (68.5–185.8 g). They all came from healthy animals aged 5 months to 1.5 years. On the basis of previous observations involving perfusion experiments [13,16], it was decided that the ideal size of uteri for the experiments would be approximately 90–100 g. The swine uteri were very easily separated from the rest of the body in approximately 2 minutes shortly after the animal had been killed by electric shock (1.5 A, 400 V, 4 s).

2.2. PERFUSION SYSTEM

After cannulation of both uterine arteries with 16–24-gauge needles (Abbocath-T, Abbott, Ireland) depending on the size of the uterus, the organ was placed in a controlled-temperature perfusion chamber (Karl Lettenbauer, Erlangen, Germany) filled with the perfusion medium. The uterus was then connected bilaterally to two reservoirs containing the perfusion buffer (Krebs–Ringer bicarbonate-glucose buffer, Sigma, Deisenhofen, Germany).

The perfusion medium was oxygenated with carbogen gas (a mixture of 95% oxygen and 5% carbon dioxide) and then pumped into the uterine arterial catheters with two roller pumps. The flow rates of the perfusion medium and oxygenation were constantly monitored and kept at 15 ml/min and 0.05 bars, respectively, with an ideal pressure rate of 100 mmHg being maintained throughout the duration of the experiments. Oxytocin was purchased (Syntocinon) from Novartis (Nuremberg, Germany).

Serum samples (1 ml) were administered at intervals of 30 minutes. The contractility of the perfused uterus was checked between serum administrations by administering a bolus of oxytocin

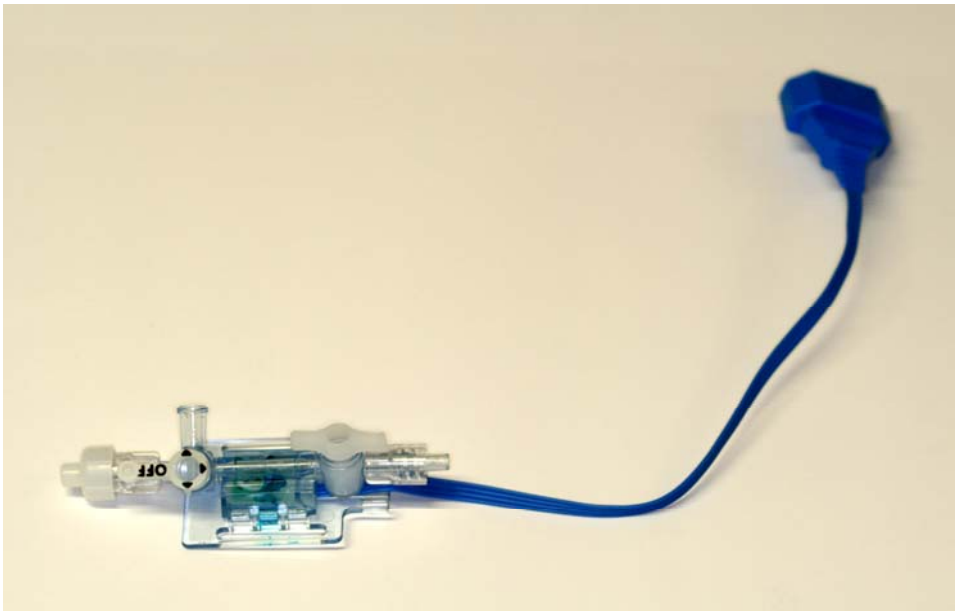

FIGURE 2. THE DIGITAL ELECTRONIC SEMICONDUCTOR PRESSURE SENSOR SPS 1, RAUMEDIC, ERLANGEN, GERMANY.

(0.5 IU/ml) for intrauterine pressure measurements and uterine arterial pressure measurements. The uterus was used for further experiments only when the pressure increases after the application of oxytocin was within an acceptable range (median 15.5 mmHg, maximum 25.3 mmHg, minimum 9.0 mmHg).

2.3. VITALITY PARAMETERS

Samples of the perfusate were taken at 1-hr intervals after collecting the medium for measurements of pH, PO_2, PCO_2, HCO_3, lactate and oxygen saturation (for details, see [13]).

2.4. INTRAUTERINE AND INTRA-ARTERIAL PRESSURE MEASUREMENT

Intrauterine pressure was recorded with a digital intrauterine microchip-catheter (Urobar-DL 8, Raumedic, Erlangen, Germany, FIG. 1). Intra-arterial pressure was recorded directly by connecting the arterial cannula to a digital electronic semiconductor pressure sensor (SPS 1, Raumedic, Erlangen, Germany, FIG. 2). The digital intrauterine microchip-catheter and the digital electronic semicondurctor pressure sensor were then connected to a digital Datalogger (MPR 1, Raumedic, Erlangen, Germany, FIG. 3), which was connected to a personal computer. Continuous monitoring and recording of IUP and IAP was performed automatically.

2.5. STUDY SUBJECTS

Twelve pre-eclamptic and twelve normotensive pregnant women were recruited from the perinatal and labour ward at the University of Erlangen-Nuremberg and included in the study. Twelve healthy non-pregnant women from the hospital staff were asked to volunteer. All of the study patients were of Caucasian ethnicity. Only women with singleton pregnancies and with no history of diabetes mellitus, angiopathy, or autoimmune disease were included in the study. The study was approved by the ethics committee at the University of Erlangen-Nuremberg, and informed written consent was obtained from all of the women included. Blood was collected on admission to the labour and delivery ward and before the administration of any medications, centrifuged, and serum was stored at –40 °C.

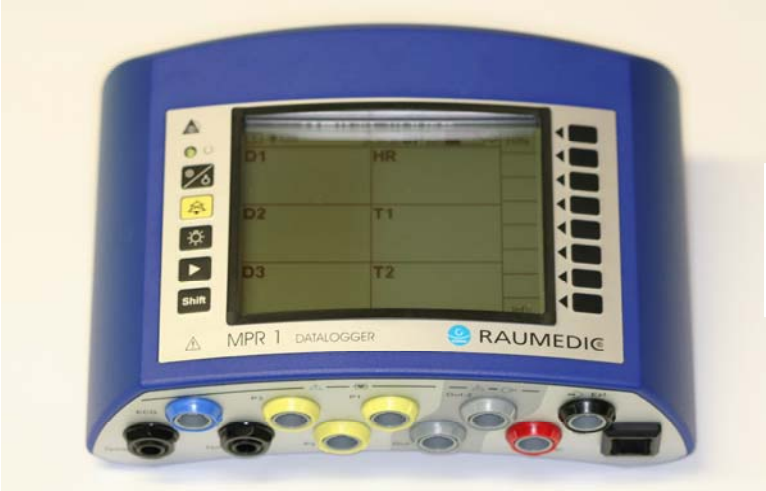

FIGURE 3. THE DIGITAL DATALOGGER, MPR 1, RAUMEDIC, ERLANGEN, GERMANY.

Pre-eclampsia was assessed on the basis of increased blood pressure (> 140/90 mmHg) occurring in a pregnant woman after 20 weeks' amenorrhoea, accompanied by proteinuria (> 0.3 g/24 h), as defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [4]. Women in the control group were considered to be normotensive if their blood pressure was < 140/90 mmHg. None of the control patients had proteinuria.

2.6. STATISTICAL ANALYSIS

The changes in IUP and IAP after administration of serum from PE women and HP women were compared to the effects caused by serum from HNP women (serving as controls) using unpaired Student's *t*-test using the Statistical Package for the Social Sciences, version 10.1 for Windows (SPSS, Inc., Chicago, Illinois, USA). A *P* value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. EFFECT OF SERUM BOLUS ADMINISTRATION

Each administration of serum (1 mL) led to a general pressure rises in both the uterus (IUP) and the uterine arteries (IAP).

3.2. INTRAUTERINE PRESSURE

Serum from HNP women showed the greatest effect in increasing IUP (21.3 ± 4.2 mmHg), followed by serum from PE women (15.6 ± 4.9 mmHg) (FIG. 4). The lowest pressure increases were induced by serum from HP women (10.2 ± 4.1 mmHg). The differences between HP and HNP ($P < 0.001$) and PE and HNP ($P = 0.04$) were statistically significant (FIG. 4).

3.3. INTRA-ARTERIAL PERFUSION PRESSURE

Serum from PE women caused the greatest increases in intra-arterial perfusion pressure (47.4 ± 7.8 mmHg), followed by serum from HNP women (44.3 ± 9.6 mmHg) (FIG. 5). The lowest pressure increases were caused by the use of serum from HP women (26.3 ± 9.7 mmHg). The differences between HP and HNP ($P = 0.002$) were statistically significant, while the differences between PE and HNP ($P = 0.3$) were not statistically significant (FIG. 5).

4. DISCUSSION

Pre-eclampsia is the most common disease specific to pregnancy, causing fetal growth restriction, and is therefore a major cause of perinatal mortality

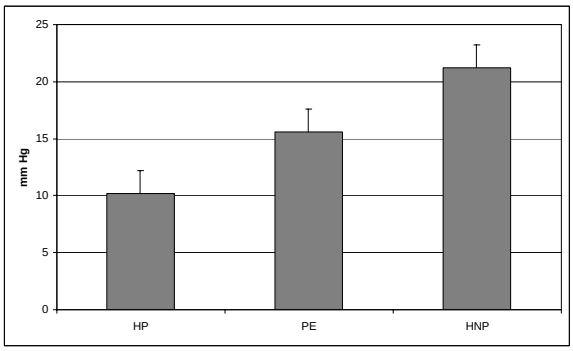

FIGURE 4. INCREASE IN INTRAUTERINE PRESSURE (IUP) AFTER APPLICATION OF SERUM (1 ML BOLUS) FROM HEALTHY PREGNANT (HP) WOMEN, PRE-ECLAMPTIC (PE) WOMEN AND HEALTHY NON-PREGNANT (HNP) WOMEN. Values are means ± SD, N = 12 in each group.

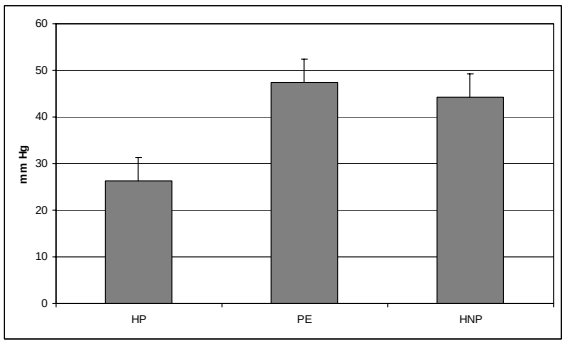

FIGURE 5. INCREASE IN INTRA-ARTERIAL PRESSURE (IAP) AFTER APPLICATION OF SERUM (1 ML BOLUS) FROM HEALTHY PREGNANT (HP) WOMEN, PRE-ECLAMPTIC (PE) WOMEN AND HEALTHY NON-PREGNANT (HNP) WOMEN. Values are means ± SD, N = 12 in each group.

and morbidity. It complicates 6–8% of all pregnancies longer than 20 weeks, but the etiology is still unknown [2,4,7].

Theories on the cause of pre-eclampsia were often depicted as two opposing schools of thoughts [5]. One theory (the vascularists) for the pathophysiology involved a ischemia-reperfusion model leading to oxidative stress and endothelial damages. Another theory (the immunologists) suggested a maternal-paternal immune maladaption, leading to pathological cytokine release [5]. Some studies have also suggested a genetic defect in endothelial NO-synthetase in the renin–angiotensin system. Mitochondrial defects might also explain the incomplete invasion of cytotrophoblasts into the maternal endometrium [7].

The proposed model is that a reduced blood supply to the placenta results in the production of unknown factors, which are released into the maternal circulation and act on endothelial cells, leading to endothelial dysfunction [17-19]. Several endothelial markers have been found to be elevated in pre-eclampsia, such as cellular fibronectin, von Willebrand factor, tissue plasminogen activator and plasminogen activator and inhibitor [20,21]. In addition, enhanced endothelial expression of adhesion molecules has been reported in pre-eclampsia [22].

Pre-eclampsia is also associated with increased levels of plasma ET-1 [23–25], and a causative role for ET-1 in pre-eclampsia has been suggested by the observation that raised levels of plasma ET-1 in pregnant sheep, produced by continuous systemic infusion of ET-1, resulted in cardiovascular and haemodynamic changes that in many ways resemble the human disease of pre-eclampsia [26,27].

In addition to their actions as vasoconstrictors, endothelins also produce a variety of other biological effects. These include stimulation of cardiac contraction, regulation of the release of vasoactive substances and stimulation of smooth-muscle mitogenesis. Endothelins also stimulate contraction of most smooth muscles and stimulate secretion by tissues such as the kidney, liver and adrenals [28].

Many studies gives evidence that in serum or plasma from pre-eclamptic women a imbalance between vasoconstrictors and vasodilators may exist in comparison with normal pregnant women [5,17,19,29].

The aim of the present study was to verify this hypothesis. In addition, the intention was to test the intrauterine contractile effect of the serum, since it is known that vasoactive substances such as prostaglandins are also oxytocic [13]. Vasoactive drugs have been investigated by various research groups in human and animal organ perfusion models in recent decades [30,31]. In the present study, a swine uterus perfusion model was used to overcome the problems arising from the small numbers

and the poor condition of the human uteri that can be obtained for experimental purposes [13].

Swine have been increasingly used as biomedical research models during the last 20 years, as they are recognized as a suitable animal model for human disease on the basis of comparable anatomy and physiology [30,32]. In order to avoid *in vivo* animal experiments, it was decided to use uteri from freshly killed animals from the slaughterhouse. Logistically, this had the advantage that obtaining a large number of uteri every day only took a matter of minutes, and in addition, approval from an ethics committee or animal experimentation board was not needed, since no animals were killed for experimental purposes. Moreover, the uteri were derived from healthy young animals in their reproductive years.

Normally, the uterus would rapidly degenerate without constant perfusion. A complex perfusion system was therefore established that provided the uteri with a steady flow rate of circulation, a constant temperature and continuous oxygenation of the perfusion medium, simulating physiological conditions in every way possible.

Using this perfusion model with a full electronically pressure recording system, it was possible to demonstrate that serum from all of the women included in the study had a vasoconstrictive effect. The most potent effect was observed in serum from PE women, followed by serum from HNP and HP women. The difference between serum from HP women and serum from HNP women was statistically significant, whereas the difference in the perfusion pressure increase between serum from PE women and from HNP women did not reach significance. This might be explained by the presence of either increased circulating concentrations of vasodilators or decreased concentrations of contractile factors in healthy pregnancy, whereas this balance is massively disturbed in pre-eclamptic patients. In healthy pregnancy placenta may be considered to balance increased oxidative stress and vascular disease [33]. These findings are in accordance with those of Neal et al., who demonstrated in an *in vivo* animal experimental model that plasma from patients with mild pre-eclampsia and normotensive women did not increase vascular permeability whereas, plasma from patients with severe pre-eclampsia induced a statistically significant increase in vascular permeability [34]. Furthermore, serum from HP women produced intrauterine contractions with lower amplitude in comparison with serum from HNP and PE women.

In general, serum from HP women showed the lowest increase in IAP and IUP suggesting the conclusion that serum from HP women contains more vasodilators and mediators with tocolytic effects. This balance may be disturbed in PE women and is comparable near to HNP women.

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5. CONCLUSION

In a novel set of experiments, the intra-arterial and intrauterine effects of serum from PE, HP and HNP women on an isolated swine uterus were examined. The findings show that serum from PE women has significant vasoconstrictive and oxytocic effects and confirm former results obtained with a delicately measuring device [35]. These experiments demonstrate that there is an imbalance between vasoconstrictors and vasodilators observed in the perfusion swine uteri model that require further examination. The examination of this imbalance remains a topic for further studies. The swine perfusion model is an appropriate experimental model for the study of vascular reactivity and uterine contractility, especially in disorders such as preeclampsia. The used complete digital data monitoring and recording system was feasible, reliable and simplified the data measurement and recording procedure extensively while it enabled a higher sensitivity.

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