Head-up tilt rapidly compromises hemodynamics in healthy anesthetized swine

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Short title: Head up tilt compromises hemodynamics in anesthetized swine

Summary.

Aims: to explore the effect of head-up tilt (HUT) to 30 and 60 degrees on hemodynamics and tissue oxygenation in anesthetized healthy swine. The data serve as a reference for a study of resuscitation efficacy at HUT such as during transport.

Methods: 9 healthy swine (49 +/- 4 kg) were anesthetized and multiple sensors including myocardial PV loops catheter, carotid flow probe, blood pressure catheters, NIRS tissue oximetry and mixed venous

oximetry (SvO2) catheter were introduced and parameters continuously recorded. Experimental protocol: baseline in supine position (15 minutes), 30 degrees HUT (15 min), recovery at supine position (15 min) and 60 degrees HUT (5 min). Vacuum mattress was used for body fixation during tilts.

Results: 30 and 60 degrees inclination led to significant immediate reduction in hemodynamic and oximetry parameters. Mean arterial pressure (mmHg) decreased from 98 at baseline to 53 and 39, respectively. Carotid blood flow dropped to 47% and 22% of baseline values, end diastolic volume to 49% and 53% and stroke volume to 47% and 45% of baseline. SVO2 and tissue oximetry decreased by 17 and 21 percentage points. The values are means.

Conclusion: Within minutes, both 30 and 60 degrees head-up tilting is poorly tolerated in anesthetized swine. Significant differences among individual animals exist.

Key words: Head-Up Tilt, Hemodynamics, Pressure-Volume Loop / Cardiac Output, Swine, Oximetry,

Abbreviations

HUT – head up tilt, MAP – mean arterial pressure, EF - ejection fraction, S_VO_2 - mixed venous blood saturation, rSO2 - regional tissue saturation, HR – heart rate, EDV - end diastolic volume, CVP – central venous pressure, CPR – cardiopulmonary resuscitation

Introduction

Maintaining adequate perfusion during cardiopulmonary resuscitation (CPR) effort remains a challenge. Furthermore, during CPR it is sometimes necessary to transport the patient in head-up tilted position such as inside the buildings (climbing the stairs or transport in space-restricted elevators). At present it is not known how harmful such tilting is or conversely, whether it can be beneficial as recently suggested by Debaty (Debaty *et al.* 2015).

Head up tilting is a challenge to hemodynamics even in healthy subjects. Full power of several compensatory mechanisms needs to be engaged to maintain peripheral blood flow (Rowel LB 1993). These include vasoconstriction - both arterial and venous, increased myocardial contractility, baroreceptor reflex and its orthostatic adjustment, muscular and diaphragmatic pump (Miller *et al.* 2005) local myogenic reactions and more (Stewart 2012). Normal blood volume, normal oxygen carrying capacity and intact intrinsic vascular structure are other prerequisites of orthostatic tolerance.

Under the conditions of cardiac arrest, hypoxia, acidosis and subsequent CPR with multiple drugs administration including general anesthetics many of the abovementioned mechanism can be seriously compromised. Nevertheless, available knowledge regarding tilting during CPR is scarce. Recently, an interesting results were reported by Debaty. In a porcine CPR at 30 degrees HUT an increased cerebral perfusion was observed despite a decrease in systemic arterial pressure and carotid blood flow by about half compared to horizontal position (Debaty, et al. 2015).

In the present study, the effect of head up tilting to 30 and 60 degrees in healthy anesthetized swine fixed in vacuum mattress was explored in the setup similar to that of ongoing resuscitation. In order to differentiate between the effects of tilting and the effects that are secondary to cardiac arrest and subsequent CPR healthy animals with spontaneous rhythm were observed in this study. Swine is a commonly used biomodel in biomedical research including resuscitation studies. While there are

similarities with human, the concern also exists that there could be differences in the response to orthostatic stress. Based on published data it was expected that 30DEG tilt would be tolerated and 60 DEG would severely compromise hemodynamics.

Methods:

Preparation and Anesthesia

The study was approved by institutional care and use committee and was performed an accordance with European Guidelines on Laboratory Animal Care. Nine healthy swine m=48 +/- 4.2 kg were used. Following the premedication with midazolam 0.3 mg/kg and ketamine 20 mg/kg i.m. the marginal ear vein access was secured and animal transported to the lab. Here, initial propofol bolus (2 mg/kg) was administered and animal was orotrachealy intubated and connected to mechanical ventilator. Tidal volume (VT) was set to 8 ml/kg and respiratory rate (RR) was adjusted to keep end-tidal CO2 (ETCO2) beween 38-24 mmHg. Anesthesia was maintained with continuous i.v. propofol (6-8 mg/kg.h) midazolam (0.1-0.2 mg/kg.h) and morphin (0.1-0.2 mg/kg.h). Heparin bolus (100 IU/kg) was given initially followed by continuous administration of 50 IU/kg.h so that activated clotting time (ACT) was maintained over 200 s. Normal saline was administered at 500 ml/h until central venous pressure (CVP) was 5-6 mm Hg. Saline drip was then continued at 5 ml/kg.h to maintain fluids balance. Multiple intravascular sheaths were inserted percutaneously for later placement of measurement catheters.

Monitored parameters

ECG, pulse oximetry (SPO2), rectal temperature and etCO2 were monitored noninvasively by patient monitor (LifeScope TR, Nihon Kohden, Japan). Regional tissue oximetry (rSO2) was monitored by NIRS oximetry (INVOS Oximeter, Covidien, USA) in forehead and right thigh. Pulmonary artery catheter (CCO V, Edwards Lifesciences, USA) was placed into pulmonary artery via femoral vein. It provided continuous cardiac output (CCO), mixed venous saturation (SVO2) and pulmonary artery pressure measurement.

High fidelity pressure-volume catheter (type 7F VSL, Scisense-Transonic, USA) was inserted via the left carotid artery into the left ventricle under fluoroscopy control and pressure-volume data were obtained by admittance method (Raghavan *et al.* 2004). Blood pressure was measured directly via catheters placed in right femoral artery, carotid artery, pulmonary artery and superior vena cava by means of fluid-filled transducers (Truwave, Edwards Lifesciences, USA) placed at the heart level. Transient ultrasound flow probe (PSB, Transonic, USA) was implanted around right carotid artery to provide continuous volumetric flow measurement. Intracranial pressure sensor (Neurovent-P, Raumedic, Germany) was inserted into parietal cortex via a burr hole 2 cm laterally from the midline. Measured parameters were sampled at 400 Hz by Powerlab A/D converter and continuously recorded to PC running Labchart Pro software (AD Instruments, USA).

Positioning

After all the systems were in place, animals were immobilized in resuscitation vacuum mattress that was shaped around the body and fixed to the motorized tilting bed. Additionally, the front legs were stretched above head and tied to the tilting bed. Care was taken that flushed pressure sensors were placed so that they would remain at the heart level during the whole protocol including tilting.

The Protocol

The protocol is summarized in Figure 1. After minimum of 15 minutes' stabilization the baseline values were recorded and the animals were tilted to 30 degrees (head up) for 15 minutes. Then the position was resumed to horizontal and 15 minutes hemodynamic stabilization followed. Subsequent 60 degrees tilt lasted for 5 minutes. The time to position was 40 and 60 seconds, respectively. The tilt was interrupted prematurely in case of hemodynamic intolerance defined as a decline in MAP below 40 mmHg or rSO2 below 40% or carotid flow below 50 ml/min for longer than 2 minutes.

Statistics.

Shapiro –Wilk normality test proven the normal distribution of analyzed parameters. Thus statistical

analysis was performed by analysis of variance (ANOVA) for repeated measurements and paired t-test.

Results:

Baseline.

After anesthesia induction and stabilization, the baseline physiological parameters attained normal

values that are summarized in table 1. Significant interindividual variation was observed in carotid blood

flow that ranged from 207 to 510 ml/min. This variability correlated neither with body size nor with

cardiac output.

Head up tilting.

The results are summarized in the Table 1 and Figure 2. Tilting to 30 degrees rapidly compromised

hemodynamics and tissue oxygenation. Arterial pressure, carotid blood flow, LV stroke volume and end

diastolic volume fell to about 50% of respective baseline values. Intracranial pressure decreased by 16

mmHg, however after eliminating the effect of hydrostatic pressure drop secondary to sensor elevation,

the ICP reduction was 4.5 mmHg. Hydrostatic pressure was calculated as sin(30 deg) x 30 cm (distance

between right atrium and ICP sensor), that is 15 cm or H_2O or 11.5 mm Hg. Then, the calculated cerebral

perfusion pressure (MAP-ICP) decreased from 79.3 (+/-12.8) at horizontal position to 37.6 (+/- 19.6) at

HUT 30. Central venous pressure changed from 6.8 to 1.8 mmHg suggesting reduced preload. At the

same time the ejection fraction remained unchanged. Tissue oxygenation and mixed venous

oxygenation decreased to 46.5% and 31.5%, respectively (i.e. 74% and 64 % of their baseline values)

demonstrating an increased O2 extraction partially compensating reduced oxygen delivery.

Tilting to 60 degrees compared to 30 degrees resulted in dramatically reduced carotid blood flow 90 +/-109 ml/min vs. 404 +/-164 ml/min (22% of baseline), further reduced CVP (-5.6 mmHg) and mean arterial pressure 39 mmHg (40% of resting values). However, other parameters (EDV, SV, SVO2, rSO2) did not differ significantly between 30 and 60 degrees tilt. Left ventricular ejection fraction again remained unchanged.

A representative time course of hemodynamic parameters changes after both tilts is presented in Figure 3. The time to the position was 40 sec and 60 sec and already during this period the monitored parameters rapidly decreased near to the minimal values in each position. Then, in most animals, the hemodynamics stabilized throughout the rest of HUT period and little hemodynamic compensation was observed if any. Oximetry parameters declined less rapidly than hemodynamic ones. With the return to horizontal position, all the parameters recovered promptly excluding stroke volume that required more than 10 minutes to return to the baseline.

Intolerance. Two and four animals did not tolerate tilting to 30 and 60 degrees, respectively and thus the HUT maneuver was interrupted.

Complications. All the animals survived the study and there were no complications. However, tilting to 60 degrees represented a challenge to securing all the monitoring systems in place so that the data recording was reliable. Despite the effort to prevent sensors misplacement some signals had to be excluded from further processing for poor recording quality.

Discussion

While it was expected that head up tilting to 60 degrees will compromise and possibly collapse hemodynamics, it was surprising to find that already 30 degrees elevation has an immediate significant

adverse effect that was even not tolerated by some animals. Hemodynamic destabilization in our setup

was thus greater than in other studies exploring head up tilting in pigs. In our study the 30 degrees HUT

in anesthetized swine resulted in about 50% decrease in mean arterial pressure, carotid blood flow, end

diastolic volume and stroke volume immediately during tilting (see Fig. 3). Peripheral NIRS oximetry

(rSO2) dropped to saturation values at around 40% which indicated tissue hypoperfusion while normal

values are near 60%. In a study by Klopfenstein a 20 degrees head-up tilt resulted only in moderate

decrease in cardiac output (-20% of baseline) and mean arterial pressure (-10% of baseline)

(Klopfenstein *et al.* 1998). In 30 degrees tilt with capnoperitoneum, Junghans reported similar changes

in hemodynamics to Klopfenstein study: cardiac output was reduced by 24%, mean arterial pressure by

6% and stroke volume by 30% (Junghans, et al. 2006). Our results are more similar the resuscitation

study reported by Debaty et al. In 30 deg tilt during cardiac arrest treated by automated chest

compressions they found considerable decrease in arterial pressure (roughly 50%) and carotid flow

(more than 50%). Despite this they have seen improved brain tissue perfusion at 30 degrees HUT

compared horizontal position, presumably due to improved venous return from brain circulation.

There could be several reasons for markedly compromised hemodynamics in our study compared to

others. i) General anesthesia. Propofol, an i.v. anesthetic used in the study, is known to inhibit

hemodynamics by various effects (contractility, arterial vasoconstriction, venous tone). It has been

suggested that in clinically relevant doses venous depression might be the most pronounced effect of

propofol (Muzi *et al.* 1992). This would be in line with our results of reduced EDV but preserved EF and

increased arterial resistance. In other studies inhalation anesthetics are commonly administered, but

these would certainly not be used during CPR.

ii) Venous return restriction. The animal fixation by means of vacuum mattress could interfere with the

venous return. Though rather homogenous pressure is expected, it cannot be excluded that the amount

of pressure the mattress exerts on the body and the location of this pressure could result in variable

chest and abdominal compression. The effect could then range from beneficiary centralization of venous blood or an "autotransfusion" effect to adverse blood pooling in subdiaphragmatic region, specifically if combined with tilting. In laparoscopic patients it has been reported, that intra-abdominal pressure increase by 12 mmHg combined with 30 degrees HUT reduces CO by 35% and SV by 25% (Junghans, et al. 2006). In present study, there were no signs of consistent changes in CVP and/or airway pressure following the mattress inflation. However, no direct information was recorded concerning the pressure or flow in subdiaphragmatic region.

iii) Animal species. It can be argued that swine posture is naturally horizontal resulting in poor tolerance to more vertical position, however we consider this a less likely reason. The results of other studies demonstrate reasonable tolerance of anesthetized pigs to tilting. Also, the elevation to 30 degrees represents a position that in swine can physiologically occur during daily life activities.

iv) Fluid depletion. Hypovolemia was unlikely in the current study since enough infusions were administered so that CVP was always above 6 mmHg prior to baseline measurement. However, in human medicine some degree of hypovolemia can be rather common.

Several hypotheses/conclusions can be drawn from our observations.

Even in the absence of cardiac arrest hence in the absence of severe metabolic disbalance, head-up tilting of anesthetized swine in vacuum mattress can result in a critical reduction of hemodynamic parameters. This seems to be a consequence of reduced preload since ventricular filling and central venous pressure were markedly reduced while vascular resistance increased. Despite hemodynamic changes, myocardial perfusion remained preserved or well compensated since ejection fraction changed neither at 30 nor at 60 degrees tilt. Regarding the brain, decreased cerebral perfusion pressure and regional tissue oxygenation in forehead would suggest limited cerebral perfusion. However it is still possible that preserved autoregulation in cerebral bloodstream and improved venous return could keep cerebral microcirculation preserved.

Whether similar effects can be seen in humans during standard out-of-hospital CPR remains to be elucidated. In fully conscious healthy human volunteers a rapid passive tilting to 30 degrees provokes almost 20% decrease in stroke volume that is explained by blood pooling in dependent body regions (Toska and Walloe 2002). Thus it is quite likely that under CPR conditions preload restriction will be a very important determinant of hemodynamics and any situation limiting venous return such as hypovolemia, blood pooling and impeded vasoreactivity should be addressed promptly.

Limitations

There are several limitations that deserve attention and further investigation. First, no robust markers of cerebral tissue perfusion adequacy such as electrophysiology were employed. Second, the need for global anesthesia in the doses relevant for miniivasive procedures did introduce effects that may not apply to typical clinical scenarios. Particularly the use of propofol might have influenced the results, specifically via vascular reactivity. Another anesthetic such as midazolam might provide more relevant data. Additionally, despite a great care the tilting did interfere with the accuracy of data recording since some moves such those of internal organs within body cavities could not have been avoided. This might result in greater data variability than expected. Finally, significant interindividual variability was noticed with some animals not tolerating the tilt. This might confound some of the observations. The study was neither aimed nor powerful enough for any subgroup analysis.

Conclusions

Head up position significantly compromises hemodynamics in healthy anesthetized swine restrained in vacuum mattress, probably due to preload limitation. Some of the findings might apply to human resuscitation pathophysiology.

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Table 1

Averaged hemodynamic and oximetry results for baseline (0 DEG), 30 and 60 degrees head up tilt (HUT 30 and HUT 60). MAP – mean arterial pressure, CAR– carotic blood flow, SV – stroke volume left ventricle, EDV – end-diastolic volume left ventricle, EF – ejection fraction left ventricle, CVP – central venous pressure, ICP – intracranial pressure, SVO2 – mixed venous blood saturation, rSO2 – regional oxygen saturation (forehead), n – number of samples.

Fig 1.

Study protocol outline. Sequence of protocol phases. Horizontal represents sequence and duration of individual phases in minutes. HUT30, HUT 60 – head up tilt to 30 (60) degrees. Vertical axis represents degree of head-up inclination (deg).

Fig2.

Hemodynamic and oximetry parameters at baseline (0 DEG) 30 and 60 degrees head-up tilt. (HUT 30, HUT 60).). MAP – mean arterial pressure, CAR– carotid blood flow, SV – stroke volume left ventricle (gray), EDV – end-diastolic volume left ventricle(white), SVO2 – mixed venous blood saturation (white), rSO2 – regional oxygen saturation (grey). Asterisk - p <0.001 vs. 0 deg. Hash - p< 0.015 vs. HUT 30. Box plots: inside the box there are 50% of values, thick line represents median. Top (bottom) 25% of values are above (below) the box as indicated by vertical lines.

Fig 3

Sampe continuous data traces from one animal. Horisontlal axis is the protocol timeline. 0 DEG – baseline, HUT30 and HUT 60 - 30 and 60 degrees head-up tilt. LVV left ventricular volume, AoP - Aortic blood pressure, SVO2 mixed venous blood saturation, CO – cardiac output, CAR – carotid bood flow, HR – heart rate.

Table 1

parameter (unit)	0 DEG mean	SD	HUT 30 mean	SD	HUT 60 mean	SD	p values 0 vs 30	30 vs 60	n
MAP (mmHg)	98.22	13.52	52.67	18.81	38.88	9.28	0.001	0.015	9
CAR (ml/min)	358.86	108.58	140.29	55.08	53.29	33.27	0.001	0.015	7
SV (ml)	88.88	22.36	41.75	14.59	40.00	16.53	0.001	n.s.	8
EDV (ml)	157.38	33.00	76.38	33.87	82.63	53.25	0.001	n.s.	8
EF (%)	56.75	9.72	57.63	16.04	56.50	17.80	n.s.	n.s.	8
CVP (mmHg)	6.89	1.54	1.83	2.00	-5.63	4.84	0.001	0.001	9
ICP (mmHg)	18.29	7.20	2.29	7.52	-7.43	8.10	0.001	0.001	7
SVO2 (%)	49.71	7.06	31.57	12.27	26.57	10.03	0.001	n.s.	7
rSO2 (%)	64.00	11.10	46.52	7.82	44.00	7.18	0.013	n.s.	6

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