Abstracts

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Successful ECMO treatment of acute cardiorespiratory failure due to shunt thrombosis after Norwood I procedure

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Introduction

Shunt thrombosis after correction of hypoplastic left heart syndrom leads to an acute hypoxemia and subsequently to cardiac failure. Implantation of extracorporeal life support (ECLS) remains the only therapeutic option for circulatory arrest in this situation. Establishment of ECLS requires a re-sternotomy or a potentially harmful cannulation of carotid artery. We report the first successful use of extracorporeal membrane oxygenation (ECMO) with a new bi-caval dual lumen catheter for treating an acute cardiorespiratory failure due to shunt thrombosis in a patient after Norwood I procedure.

Surgical technique

Two-week-old newborn developed profound hypoxemia and hypotension nine days following a Norwood I procedure with creation of a modified Blalock-Taussig-shunt. Emergency angiography showed a shunt thrombosis. Repeated balloon dilatation and local lysis were unsuccessful. During cardiopulmonary resuscitation, a new 13 Fr. bi-caval dual lumen catheter was implanted in the right jugular vein and ECMO was initiated. The ECMO system consisted of a diagonal pump DP3 and a newborn Hilte 800 LT ECMO Oxygenator. A surgical shunt revision was performed after 50 hours of ECMO support. Surgical revision was done using solely ECMO. Postoperatively weaning from ECMO was successful.

Discussion

Implantation of ECLS in cardiorespiratory failure due to shunt thrombosis after correction of hypoplastic left heart syndrome necessitates a re-sternotomy with a conventional thoracic cannulation or a cannulation of carotid artery and jugular vein. Re-sternotomy with a conventional thoracic cannulation is time consuming and associated with an increased risk of bleeding and infection. In addition cannulation of carotid artery may lead to neurological damage. In contrast, implantation of a bi-caval dual lumen catheter in the jugular vein is a fast and safe procedure. We show that ECMO support is a feasible emergency therapeutical option for an acute cardiorespiratory failure due to shunt thrombosis after correction of hypoplastic left heart syndrome.
Life Box experience with portable ECMO

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Background

For patients with cardiac failure, predictions are limited despite the progress made in emergency and intensive care. Increasingly, so-called miniaturized heart and lung support systems are used for patient stabilization. In addition, patients can be safely transported to special centers with these systems. In this case, the interhospital transport by ground or by air is not insignificant. With a portable miniaturized extracorporeal perfusion system, there is now the possibility to stabilize patients at an early stage and place.

Material and method

A fully portable perfusion system (Life Box, Sorin Group) has been developed, which can be used for cardiac and/or pulmonary stabilization, in Cardiology and ICU, or as support systems in a hybrid-OR as well as for the interhospital transport. The miniaturized system of a heart-lung machine is as light and compact that it can be easily carried and operated by one person.

Results

The system can be used by ground as well as by air patient transport. Thus there is a possibility to provide interhospital transfers of critically ill patients to hospitals of maximum level. The Life Box portable system was employed in early 2009 for the first time. Since then we provide emergency ground and air transport services in more than 30 cases.

The longest-duration emergency air transport service was from Guadeloupe to Germany (Frankfurt a. Main). Bad weather did not permit us to take the same route back as the outbound flight so we were forced to fly back to Germany via Halifax (Canada).

The flight was very bumpy and passed through numerous turbulent areas. Total flight time was roughly 15 hours and the transport took 18 hours in total.
Over the last decades the Middle East has undergone tremendous changes. And in the West, interest in that region has increased little by little. Nevertheless, specific information about countries in the Middle East was still largely based on storytelling and rumors. Since the beginning of the Arab spring nearly one year ago on Saturday, December 18, 2010, the region has gained further attention in the West and around the world. This presentation will focus on the United Arab Emirates and their special situation.

Founded 40 years ago, the UAE, consisting of the seven Emirates (princedoms) Abu Dhabi, Dubai, Ajman, Fujairah, Ras al-Khaimah, Sharjah and Umm al-Quwain, has seen unprecedented developments in numerous areas. In the early 1960s, oil was discovered in Abu Dhabi, an event that led to calls for quick unification by UAE sheikdoms. Zayed bin Sultan Al Nahyan became ruler of Abu Dhabi in 1966 and later on the first president of the UAE. The transition from ancient times – simple fishing communities and desert oases with Dubai being the old small trade town – to the 21st century was made in less than one generation. The population increased considerably, from 95,000 in 1963 to nearly 6 million in 2010. Today less than 20% of the people living in the UAE are UAE nationals or Emiratis. The majority are expatriates who immigrated to the UAE, resulting in the world’s highest immigration rate. Expatriates mainly come from India, Pakistan, other Arab countries and Iran; only about 10 percent of them are European, Asian or U.S. citizens.

Although the Emirates are unified, each Emirate still makes its own decisions. This includes regulations for practicing medicine as well as differences in law and justice.

The medical landscape is divided into the state and the private sector. In the Emirate of Abu Dhabi the HAAD, the Ministry of Health, acts as the regulatory body for both. Public hospitals are operated by Seha, a state-run organization.

To speed up development in the hospitals, international companies were charged with their management (John Hopkins, Bumrungrad, Cleveland Clinic) for a specific time period with clearly defined goals.

The major goal in the Emirates is to build up a health system of high quality. This goal is especially important due to the fact that Emiratis have the opportunity to apply to be sent abroad for treatment if the highest quality health care for their disease is not available in the country. This has become a significant burden on the Emirates’ budget. Social status – as much as the disease itself – determines whether a patient’s expenses will be covered. In some cases, the costs of sending an entire family with the patient will be covered. It has become a proof of status to receive treatment abroad, even if good treatment is available in the country.

Within the hospitals, the speed of change has been tremendous over the last five years. New recruitment and advanced quality standards have been put in place to enable these changes.

Hospital structures, as well as standards and qualifications in health care, show a strong orientation towards U.S. standards, but European influences are also present. This sometimes leads to conflicts but also creates opportunities for prioritizing the ones that work best in the local circumstances.

Within all Seha facilities a full electronic documentation system has been implemented, a Quality Management structure with international accreditation.
Anesthesia has been integrated into that framework with all the inherent advantages and challenges. The speed of change and the special and ongoing changes in regulations for recruitment have been constant challenges.

A department of Cardiac Services has been established in Mafraq Hospital combining Cardiology, Cardiac Surgery, Vascular Surgery and Cardiac Anesthesia including Cardiac Intensive Care. After consultation from a U.S. group, decisions have been made to make this the only adult public Cardiac surgery in the Emirate.

A new 800-bed hospital building is under construction within the present hospital site offering the great opportunity to build a structure for all modern needs, including a hybrid OT between the Cath lab and the regular Cardiac OT’s and good capacities of Cardiac Intensive care and Step down units.

Despite all the progress, the state hospitals are still operating at a financial loss with cost control and the entire insurance system still being under construction.

Taking into account from where this country started out 40 years ago, the current achievements are already impressive and it is likely that the huge investments in the field of health care will pay off in the future.
Treatment with anticoagulants and antiplatelet agents (alone or in combination) is widely performed to prevent or treat acute or chronic thromboembolic complications, such as in patients with atrial fibrillation or prosthetic heart valves, after myocardial infarction, percutaneous coronary interventions, or ischemic stroke, and in patients with venous thrombosis or pulmonary embolism. As a result, patients often present for surgery with an acquired hemostatic imbalance because of preexisting preoperative anticoagulation. During a 5-year follow-up, 26% of patients with percutaneous coronary intervention underwent at least 1 noncardiac surgical procedure and 8.6% had at least 1 bleeding episode either requiring or occurring during hospitalization. A previous bleeding admission and age were the strongest predictors of subsequent bleeding (1).

The most important complication of treatment with anticoagulants and antiplatelet agents is hemorrhage, which may cause long-term debilitating disease, or may even be life-threatening. In a very large series of 34,146 patients with acute ischemic coronary syndromes, anticoagulant-bleeding was associated with a fivefold increased risk of death during the first 30 days and a 1.5-fold higher mortality between 30 days and six months, whereby major bleeding was an independent predictor of mortality across all subgroups that were analysed (2). Also perioperative blood loss and re-exploration in patients with continued use of anticoagulants and antiplatelet therapy was augmented (3;4). For example, the likelihood of a bleeding complication after implantation of cardiac devices doubled in patients receiving aspirin therapy alone and more than quadrupled in those receiving dual antiplatelet therapy. In complex cardiac surgery Karkouti et al. found that blood loss is, among other factors, directly influenced by reduced thrombin generation rate before going on cardiopulmonary bypass (5).

Whenever severe bleeding occurs or a patient needs to undergo an urgent invasive procedure it may be required to reverse the anticoagulant effect of various agents (6). A reversal of the anticoagulant effect may take place in a few hours. However, in some cases immediate reversal is necessary. Furthermore, each reversal of anticoagulant or antiplatelet treatment needs to take into consideration the indication for the antithrombotic therapy. It requires a careful and balanced assessment of the benefits and risks of reversing and potential strategies to keep the period of reversal as short as possible, because withholding of antiplatelet and antithrombotic therapies that otherwise reduces the rate of death, stroke, or recurrent myocardial infarction may cause a high rate of adverse events. On the other hand, the additional risk of bleeding and blood transfusion in cardiac surgical patients receiving potent antiplatelet or antithrombotic therapy before surgery may also affect short- and long-term mortality.

The need for new anticoagulant and antiplatelet agents is quite obvious as the current agents are insufficiently effective. For example, 10 to 15% of patients undergoing major orthopedic surgery develop venous thromboembolism, despite prophylaxis with low-molecular-weight (LMW) heparin (7). Furthermore, the traditional anticoagulants are relatively unsafe, mostly due to the occurrence of bleeding. Lastly, they are often cum-
bersome with regards to their clinical use by requiring repeated laboratory control and frequent dose adjustments.

However, the advantages of the new anticoagulants (greater specificity toward activated clotting factors, predictable dose responses, fewer interactions with other drugs, dose adjustments not required, no lab monitoring necessary) and antiplatelet agents (less resistance, higher potency) over conventional ones might be disadvantageous for the perioperative period especially in case of severe bleeding. The most important limitation of the new class of anti-IIa and anti-Xa agents is the lack of an appropriate strategy to reverse their effect (Table 1). Whenever antiplatelet therapy cannot be stopped preoperatively e.g. in patients with a recently implanted drug eluting stents and high-risk characteristics for stent thrombosis needing urgent surgery, a bridging strategy using i.v. tirofiban may allow temporary withdrawal of oral clopidogrel without increasing the risk of bleeding (8).

### References

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### Table 1: Reversal of anticoagulation in case of severe bleeding (6). (PCC Prothromplex)

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Restoration after cessation of therapeutic dose</th>
<th>Antidote</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>3-4hrs.</td>
<td>Protamin (25-30mg) (immediate reversal)</td>
<td>1mg protamin per 100 anti Xa units given in the last 2-4 hrs.</td>
</tr>
<tr>
<td>LMW-Heparin</td>
<td>12-24hrs.</td>
<td>Protamin (25-30mg) (partially, immediate reversal)</td>
<td>1mg protamin per 100 anti Xa units given in the last 8 hrs.</td>
</tr>
<tr>
<td>Pentasaccharides</td>
<td>Fondaparinux 24-30hrs. Idraparinux 5-15days</td>
<td>Recombinant FVII (9)</td>
<td>No systematic experience in bleeding pts.</td>
</tr>
<tr>
<td>Vit. K Antagonists</td>
<td>Acenocoumarol 18-24hr Warfarin 60-80hr Phenprocoumin 8-10ds</td>
<td>Vit K i.v. 12-16h Vit K oral 24h PCC immediately</td>
<td>Dose dependent on INR and body weight</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>18 hrs.</td>
<td>Recombinant FXa PCC (4)</td>
<td>No systematic experience in bleeding pts.</td>
</tr>
<tr>
<td>Darbigatran</td>
<td>17hrs.</td>
<td>?</td>
<td>No systematic experience in bleeding pts.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5 - 10 days</td>
<td>DDAVP )(reversal in 15-30min), Platelets</td>
<td>Cessation not always required</td>
</tr>
<tr>
<td>Clopidogrel Prasugrel</td>
<td>5 -7days (10)</td>
<td>Platelets, DDAVP (reversal in 15-30min), Recombinant FVII(11)</td>
<td>Cessation not always desirable</td>
</tr>
</tbody>
</table>
11. Skolnick BE, Shenouda M, Khutoryansky NM, Pusateri AE, Gabriel D, Carr ME. Reversal of Clopidogrel-Induced Bleeding with rFVIIa in Healthy Subjects: A Randomized, Placebo-Controlled, Double-Blind, Exploratory Study. Anesthesia & Analgesia 2011; 113 (4): 703-10
Several experimental studies in small and large animals demonstrated functional and structural cardioprotective effects of xenon. Like volatile anesthetics pre- and postconditioning with xenon induced early window of protection (2-3 h). Up to now, late phase of protection, with an onset after 12-24 h after stimulus and a period of 72 h, has only been detected after preconditioning with xenon.

Xenon reduced extent (size) and severity (inflammation) of myocardial injury after transient left or right ventricular ischemia. Acute hemodynamic compromise (systolic and diastolic function) was reduced and recovery from myocardial stunning improved. Compared with isoflurane (0.9 Vol%) during xenon application (70 Vol%) higher levels of right and left ventricular afterload could be measured, whereas no different effects on myocardial contractility were observed. Xenon itself led to an impairment of active relaxation. Thus xenon was not superior to other anesthetics during the acute phase of cardiac compromise. Activation of known cardioprotective intracellular pathways demonstrated similarities with isoflurane (PKC, MAPK, ERK, PI3K, Akt) as well as differences (HSP27). This could be the reason why xenon inhibited cardiac remodeling after myocardial ischemia more than isoflurane. Less dilatation and fetal gene expression as well as better function could be detected in the rat 4 weeks after transient myocardial ischemia, although initial reduction of myocardial injury was comparable.

Thus even short term application of xenon seemed to provide long term cardioprotective effects, which seemed to be superior compared with volatile anesthetics. This begs the question if this effect could be detected in clinical settings.
Perioperative management and monitoring of the lung

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Patients undergoing cardiac surgical procedures are at risk of developing postoperative acute respiratory failure (1, 2). Many aspects leading to pulmonary insults have been identified during the past years, including inflammation following cardiopulmonary bypass, ischaemia/reperfusion injury, thoracotomy, hypothermia, medication and transfusion (1). In acute respiratory distress syndrome (ARDS) it has been established that mechanical ventilation itself may have an impact on outcome (3). Does perioperative ventilation in cardiac surgery have an impact on outcome, too?

In this review the following topics will be discussed:

- What is the current recommended way of ventilation during the perioperative care of cardiac surgery patients?
- Is there a difference whether the patients are healthy or have diseased lungs preoperatively?
- Should non-invasive ventilation be used routinely after extubation?
- What new monitoring techniques could help us guide the ventilatory therapy?

In acute lung injury (ALI) and ARDS it has been shown that a protective ventilatory strategy using small tidal volume ventilation with 6 ml/kg BW and an adequate positive end-expiratory pressure (PEEP) can reduce inflammation and improve outcome (3, 4). Should small tidal volume ventilation also be used during perioperative care in cardiac surgery patients with normal lung function? The evolution of lung injury due to injurious ventilation in animal models even with healthy lungs, has been clearly elaborated (5). However, the literature does not provide any strong evidence on outcome improvement in patients, and the risk for development of ventilator associated lung injury due to injurious mechanical ventilation in patients with previously healthy lungs is very low (6). Contrary, high tidal volume does not reduce the incidence ofatelectasis postoperatively (7). In addition, in a study in critically ill patients, ventilated due to extrapulmonary reasons, a prophylactic protective ventilation showed less patients with new ALI (8). As Pelosi stated in a recent editorial: It is better to prevent than to cure (9)! Thus, experts’ opinion is that tidal volumes between 6 and 8 ml/kg BW should also be considered in cardiac surgery patients (6). If patients with already diseased lungs are anaesthetized the use of small tidal volume ventilation is mandatory. Unfortunately, anaesthesiologists do not appear to use low tidal volume ventilation intraoperatively very often in this patient group (10).

Besides, the physiological tidal volume in healthy lungs of mammals is around 6.3 ml/kg BW (11). Thus, small tidal volume ventilation should better be named normal tidal volume ventilation.

The adequate level of PEEP is an aspect much debated on, not only during perioperative care. Post CPB patients seem to need much higher PEEP levels as compared to other anaesthetized patients. Reis Miranda et al. showed improved oxygenation up to 3 days postoperatively with an open lung approach starting directly after CPB (12). Their patients had PEEP levels of 14 to 15 cmH₂O, comparable to other studies (13, 14). But high PEEP levels may have profound negative side effects, including alveolar overdistension of already opened alveoli, right ventricular dysfunction, and haemodynamic compromise. More outcome studies are needed before generally high PEEP levels can be recommended. Thus, PEEP should be set on an individual basis.
Should the lung, if tolerated by the surgeon, be ventilated during cardio-pulmonary bypass, or should a continuous positive pressure (CPAP) be used? Most studies using CPAP up to 10 cmH2O could only find short term improvement in oxygenation variables, but no long standing advantages (15-19). Contrary, low frequency ventilation even without PEEP revealed reduced endothelial dysfunction and increased oxygenation in a swine model (20-22). In 50 patients undergoing continued ventilation during cardiopulmonary bypass lesser inflammatory and proteolytic responses and a better preserved pulmonary function could be found (22). More studies are needed before ventilation during CPB can be recommended.

Non-invasive ventilation (NIV) strategies have been used primarily for patients with exacerbated chronic obstructive pulmonary disease, cardiogenic pulmonary oedema and hypoxic respiratory failure. Few small studies have examined the value of NIV to prevent or treat postoperative pulmonary complications after cardiac surgery. In most of them increased oxygenation for a few hours compared to standard therapy was reported, but they showed no benefit in terms of atelectasis or spirometry (23). Recently, a large randomized trial including 500 patients could show that prophylactic nasal CPAP for at least 6 hours after extubation reduced the incidence of postoperative pulmonary complications (paO2 / FiO2 < 100mmHg, pneumonia, re-intubation) significantly. The readmission rate to the ICU was lower in the study group, while no differences in hospital length of stay could be shown. Of note, patients in the control group received nasal CPAP for 10 minutes every 4 hours (24).

Based on the available literature continuous nasal CPAP of at least 9 cmH2O can be recommended to prevent pulmonary complications and reduce the readmission rate to the ICU.

Commonly used parameters to monitor respiratory therapy perioperatively, namely oxygenation, respiratory mechanics, CO2 removal, or others, all have their limitations in terms of assessing the amount and distribution of ventilated alveoli. In the last years new monitoring techniques have been introduced in the clinical setting and are in part now commercially available. Hopefully, with the help of these modalities the ventilatory settings can be tailored to the patient’s individual needs. At present, these techniques are more suitable during ventilation in the ICU than intraoperatively during cardiac surgery.

Electrical impedance tomography (EIT) is a medical imaging technique in which an image of the conductivity of one part of the body is inferred from surface electrical measurements. The objective of thoracic EIT is to generate cross sectional images of the tissue impedance distribution within the thorax (25). The EIT allows a bedside, non-invasive radiation-free assessment of regional lung ventilation and dynamic evaluation of the lung status within each breath. The effects of perioperative ventilation therapy can be evaluated by dynamic real-time EIT monitoring (26). Calculations of distribution indices render the optimal ventilatory settings possible (25). The EIT has the potential to be used as a simple bedside technique for the measurement of pulmonary aeration and ventilation distribution.

Direct measurement of lung volume, i.e. functional residual capacity (FRC) has been recommended for monitoring during mechanical ventilation (27). Mostly due to technical reasons, FRC measurements have not become a routine monitoring tool, but promising techniques have been presented. The wash-in or wash-out of a tracer gas in a multiple breath maneuver seems to be best applicable at bedside, and promising techniques for nitrogen or oxygen wash-in/wash-out with reasonable accuracy and repeatability have been presented. Studies in ventilated patients demonstrate that FRC can easily be measured at bedside during various clinical settings, including positive end-expiratory pressure optimization, endotracheal suctioning, prone position, and the weaning from mechanical ventilation. Alveolar derecruitment can easily be monitored and improvements
of FRC without changes of the ventilatory setting could indicate alveolar recruitment. FRC seems to be insensitive to over-inflation of already inflated alveoli (28).

References


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During the last years concerns about the safe use of anesthetics in infants have been arisen. The significance of these concerns is even more emphasized since the US Food and Drug Administration (FDA) considers data on the potential risk of anesthesia use in infants and initiated with the International Anesthesia Research Society a program called Smart-Tots (1).

Several studies in rodents showed that anesthetics administered during the vulnerable phase of the developing brain can cause neuroapoptosis accompanied by neurocognitive deficits (2). Studies in primates confirmed these results and demonstrated cognitive and behavioral alterations after exposure to anesthesia persisting for at least one year (3).

In humans, the vulnerable phase of neurodevelopment lasts until the age of 4. Some retrospective studies demonstrated that anesthesia in early life can lead to cognitive problems and problems with language and speech in school. However, focusing on twins, cognitive development is comparable in twins discordant for anesthesia exposure, questioning a causal relationship between anesthesia and cognitive impairment (4). This study is confirmed by the results of Wilder et al who showed that the exposure to a single anesthesia in early life is not accompanied with cognitive or behavioral impairment, while multiple exposures cause cognitive dysfunction (5). However, children who need multiple procedures present with more comorbidities and are subjected to more pain, psychological and surgical stress, which can confound the results.

In summary, rodent and primate studies demonstrated a neurotoxic effect of anesthetics in the developing brain. Retrospective studies in humans however, showed no causal relationship between anesthesia and cognitive impairment, facing the problems of other confounding factors. Therefore, prospective studies are on the way like the PANDA and the GAS study, which might provide more answers to the significant question about potential neurotoxic effects of anesthetics in infants.

References

A simple method to assess the cardiac output of the native heart during the weaning phase from the heart lung machine

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Discontinuation of cardiopulmonary bypass is a critical time point in each heart or great vessel operation with the use of the heart lung machine. Many patients’ parameters and variables (for instance body temperature, heart rhythm, heart and lung function, metabolic and hematologic state, etc) should be monitored and checked (check list!), before the team tries to come off bypass. One of the most important parameters is the left ventricular function. One can try to assess it by visual observation of the contracting heart, one can analyze the arterial blood pressure curve, monitor end tidal CO₂ or one can use TEE to observe the contractility and the filling state of the heart chambers.

In this presentation the author proposes a simple method to assess the cardiac output of the native heart during each phase of coming off bypass. The method is based on the idea that the patient’s oxygen consumption during two time points: last minute of full cardiopulmonary bypass with empty beating heart and first minute of full ejecting heart and zero flow of the heart lung machine is the same. The author will show that, under some assumptions, the venous saturation measured in the heart lung machine reflects the patient’s cardiac output.

The limitations of the method will be discussed. Some clinical scenarios will be shown.
Guidelines SCA / STS Blood conservation

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Introduction

An analysis of the STS database 2008, data from nearly 800 hospitals with over 80,000 patients undergoing primary, isolated CABG surgery observed a wide variability in the rates of transfusion of red blood cell (RBCs) and other blood products. The rates of blood transfusion ranged from 8 to 93% for RBCs, from 0 to 98% for fresh-frozen plasma (FFP) and from 0 to 90% for platelets (1). This investigation confirms many previous studies (2,3). The aim of clinical practice guideline is to reduce this unacceptable variability in blood conservation and management.

In 2011 The Society of Cardiovascular Anesthesiologists (SCA) and The Society of Thoracic Surgeons (STS) have published an update (4) of the blood conservation and management clinical practice guideline first published in 2007. More than 400 references were included. The authors analyzed and evaluated 71 interventions in terms of blood conservation and the potential side effects in patients undergoing cardiac surgery. Of these 71 interventions 11 (15%) are classified as a Class I (should be done), 41 (70%) as a Class II (reasonable or not unreasonable) and 11 (15%) as a Class III recommendation (should not be performed, may be harmful). Only 18 (25%) of these interventions have a level of evidence grade A recommendation which are based on evidence from multiple randomized trials or meta-analyses, while 21 (30%) are based on expert opinion, case studies, or standards of care. Whether there is an indication for RBCs transfusion in patients with a hemoglobin level between 7 and 10 g/dL is still very questionable; in patients with a hemoglobin concentration greater than 10 g/dL, however, there is no indication for RBCs transfusion (Class III, Level C). In comparison to 2007 the revised guideline includes the preoperative discontinuation of clopidogrel 3 to 5 days before surgery (Level B) as well as the intraoperative use of tranexamic acid (Level A) as Class I recommendations. The use of a cell-saver and the need for a multidisciplinary approach were already stated as class I recommendations in the previous version of the guideline in 2007.

Conclusion

The revised recommendations for blood conservation and management 2011 show that the available evidence is still limited. At present, only some of the interventions described are based on evidence from multiple randomized trials or meta-analyses. This uncertainty might contribute to the wide variability in transfusion practice.

References

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Transcatheter Aortic Valve Implantation (TAVI)

Aortic stenosis is a disease with a long period without symptoms. At the time of onset of symptoms the mortality increases dramatically up to 50% in the first two years if untreated. But several patients in need of a surgical therapy are considered to be “inoperable”. By the invention of catheter based aortic valves, a new therapeutic option is available for these patients. Since the first in-man implantation by Alain Cribier in 2002 nearly 20,000 catheter valves were implanted worldwide. A study published in 2010 showed the equivalency of this therapy compared to standard therapy [1].

Anaesthesiologic considerations

TAVI is considered as an interventional procedure, but most of these procedures are performed in a Hybrid-OR (where available). The benefit of such an OR consists in the possibility to change to an open-chest operation if necessary. For this a pre-equipped extracorporeal circulation should be present during the whole procedure. The patients undergoing this procedure are usually of higher age and present multiple co-morbidities. As a result the anesthesiologic monitoring and techniques should be equivalent to those used in surgical aortic valve replacement. Although several publications showed their experience with sedation during the transfemoral approach of this procedure, there is no evidence that sedation is superior to general anesthesia. A recent study [2] showed that 17 of 100 patients undergoing sedation for TAVI needed a conversion to general anesthesia. This was mainly conditioned by interventional complications. Other sites of access like the subclavian artery, the ascending aorta or the apex of the left ventricle mandatorily need a general anesthesia for this patient. Using “modern” anesthetics like Remifentanil and Propofol/Sevoflurane general anesthesia can be performed in these patients with safety. Without interventional complications these patients can also safely be extubated at the end of the procedure. Continuance of catecholamine therapy is seldom necessary after the extubation. Prior to the valve implantation a balloon valvuloplasty is performed to enhance the implantation. During this valvuloplasty and the implantation of non-self expanding valves (e.g. Sapien©) a rapid ventricular pacing (RVP) is necessary to minimize the blood flow during this period of elevated afterload. An intense cooperation of cardiac anesthetists, cardiologists and cardiac surgeons is needed during this period, as well as during the whole procedure.

Nowadays the most experience is gained with the Medtronic CoreValve©, Edwards Sapien© and Sapien XT©. But new transcatheter valves are appearing at the horizon. Egager© and JenaValve© are only two of many new developments that will change the face of modern treatment of aortic valve disease. Cardiac anesthetists will have to face these new therapeutic options and have to take care of a higher proportion of “former inoperable” patients.
References


Cricoid pressure (CP) was introduced into anaesthetic practice in 1961 based on a single small case series that lacked essential information (1). The premise is that CP prevents regurgitation (and subsequently pulmonary aspiration) of gastric contents by occluding the oesophagus.

Does cricoid pressure occlude the oesophagus?

The claimed effectiveness of CP relies on direct compression of the oesophagus by the cricoid cartilage. However, in a retrospective review of 51 cervical CT scans, some degree of lateral displacement of the oesophagus was found in 49% of images (2). Furthermore, MRI images of the necks of 22 healthy awake volunteers revealed lateral displacement of the oesophagus relative to the midline of the vertebral body in 53% of subjects without CP and in 91% of subjects with two-handed CP (3). It has been argued that the location of the oesophagus is irrelevant to the efficiency of CP because hypopharynx and cricoid ring move together as an anatomic unit and CP results in compression of the postcricoid hypopharynx (4). However, the clinical relevance of this anatomical finding remains unknown.

Does cricoid pressure prevent reflux of gastric content from entering the pharynx?

Support for the effectiveness of CP in preventing regurgitation of gastric content into the pharynx is either limited because of a highly artificial methodology or purely anecdotal. Overall, there is no convincing evidence that CP reliably prevents reflux of gastric content from entering the pharynx.

Does cricoid pressure reduce the incidence of pulmonary aspiration?

While there is lack of convincing evidence for CP to reduce the incidence of pulmonary aspiration, numerous surveys, case reports, confidential enquiries, medico-legal reviews and epidemiological studies report aspirations despite the use of CP.

Is cricoid pressure harmless?

Numerous studies have reported airway obstruction during application of CP, resulting in difficult ventilation, difficult laryngoscopy, difficult intubation, decreased tidal volumes and increased inspiratory pressures (5-8). Overall evidence suggests that application of CP may cause significant distortion of upper airway anatomy which, in turn, may seriously interfere with optimal airway management. Obstruction of the upper airways during application of CP resulting in difficult ventilation and increased inspiratory pressures is of concern, considering the recommendation that CP be maintained during ventilation following failed intubation (9), and considering that CP most of times does not occlude the oesophagus (3), leaving the possibility that the increased inspiratory pressure causes gastric insufflation.

Cricoid pressure during rapid sequence induction: Effective measure or ritual?

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The oesophageal barrier pressure (the difference between lower oesophageal sphincter and intragastric pressure) is an important determinant of gastric regurgitation. CP consistently decreases oesophageal barrier pressure by lowering oesophageal sphincter tone (10-13). The decrease in lower oesophageal sphincter tone will facilitate gastric regurgitation and may explain observations of pulmonary aspiration during application of CP. Thus, CP predisposes to gastric regurgitation by lowering lower oesophageal sphincter tone.

Where does cricoid pressure stand in 2011?

Fifty years after Sellick’s publication, still no randomised controlled trial has been conducted to assess, let alone prove the effectiveness of CP in preventing pulmonary aspiration of gastric contents. Despite lack of proof of effectiveness, efficacy and safety of CP in clinical practice, documentation of considerable interference with airway management, decrease in lower oesophageal sphincter tone upon application of CP, uncertainty about the optimal mode of applying CP, and repeated documentation of lack of theoretical and practical knowledge of all aspects related to CP, there is continued widespread faith in the efficacy of CP in reducing the incidence of pulmonary aspiration, and CP is still considered by most anaesthetists standard of care during rapid sequence induction.

For anatomical as well as physical reasons, it is highly unlikely that it will ever be possible to define in the individual patient the appropriate externally applied force necessary to make the cricoid cartilage (a rigid tubular structure) compress the oesophagus (a semi-mobile, non-rigid tubular structure of varying thickness) against the vertebral body (a rigid structure with a curved surface) in the presence of potentially large variations in intraluminal oesophageal pressures (induced by regurgitation and vomiting). By using CP we may endanger more patients by interfering with optimal airway management than save lives through presumed prevention of aspiration of gastric contents. It is likely more important to avoid coughing, straining or retching during induction of anaesthesia by ensuring rapid onset of anaesthesia and muscle relaxation than applying CP. It may be dangerous to consider CP to be effective in most cases and become complacent about the many factors that contribute to regurgitation and aspiration. Although the use of CP seems to make intuitive sense, its scientific basis is weak at best and lacking at worst (14, 15). By today’s standards of evidence-based medicine, CP is more ritual than effective measure.

References

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Mechanical ventilation and organ dysfunction

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Cardiac surgery is associated with a pulmonary and systemic inflammatory response. The pulmonary effects of this inflammatory reaction are often modest: decreased lung compliance, pulmonary oedema, increased intrapulmonary shunt fraction and decreased functional residual capacity (FRC). While the respiratory system is known to be compromised after general anaesthesia, this effect is exaggerated after cardiac surgery. After cardiac surgery, FRC is reduced up to 40-50% during the first 24 hours after extubation and is still not fully recovered after 3 months. Hypoxemia (PaO2<60 Torr) is reported in 66% of the cardiac surgery patients within the first two days after extubation and hypoxemia at ICU discharge is an independent risk-factor for ICU readmission. Mechanical ventilation potentially causes pulmonary complications but also is able to cause distant organ failure. In experimental studies, injurious ventilation caused end-organ apoptosis and severe atelectasis can cause lethal right ventricular failure in rats.

The open lung concept, recruiting the lung and maintaining the lung open with sufficient amount of PEEP, significantly attenuates the FRC reduction after extubation in cardiac surgical patients. It subsequently also attenuates the occurrence of hypoxemia and reduces serum inflammation markers. Despite the use of high levels of PEEP during ventilation according to the open lung concept, right ventricular impedance is not increased. The use of ultra low tidal volumes and the resolution of hypoxic pulmonary vasoconstriction probably counterbalance the effects of high PEEP on right ventricular impedance. How to measure right ventricular impedance is difficult, lacking solid validation studies. In Fulda we will present new experimental results validating echocardiographic parameters for measuring right ventricular impedance.
Postoperative cardiac arrest has been reported to occur in 0.7 to 2.9% after cardiac surgical procedures and may be related to ventricular fibrillation, major bleeding, cardiac tamponade, (tension) pneumothorax, failure of epicardial pacemaker leads, and surgery specific complications. Recent experimental data show improved resuscitation efficiency (improved coronary blood flow, more effective defibrillation, lower complication and higher survival rates) during open chest conditions and that patients after cardiac surgery benefit from early rethoracotomy if the circulation cannot be restored immediately after a cardiac arrest.

Based on these findings, the latest guidelines for Cardiopulmonary Resuscitation published by the European Resuscitation Council (ERC) in 2010 [1] have included a detailed chapter on resuscitation of patients with cardiac arrest after cardiac surgery procedures and suggest that, if conventional basic and advanced cardiopulmonary life support measures fail to achieve hemodynamic stabilization within 5 minutes after arrest, a rethoracotomy shall be performed immediately by any intensive care specialist and that this shall not necessarily be performed in the operation theatre but may also be accomplished bedside on the intensive care unit. The guidelines recommend a dedicated set of surgical instruments for rethoracotomy and that personal treating patients after cardiac surgery needs to be instructed and trained to fulfil rethoracotomy successfully.

Intensive care units (ICU) that have adopted these guidelines as standard operating procedures are mostly led by cardiac surgeons. It is presently unknown whether ICUs driven by anaesthesiologists perform comparably when facing a cardiac arrest.

References

The implantation of coronary stents is an effective treatment option which is increasingly performed to treat stable coronary artery disease as well as acute coronary syndromes. Stent thrombosis can best be prevented by dual antiplatelet therapy using aspirin plus clopidogrel. Depending on the stent type and also the underlying disease there are different recommendations for dual antiplatelet therapy. In general, dual antiplatelet therapy is recommended for 12 months after an acute coronary syndrome and after implantation of drug-eluting stents whereas after bare-metal stent implantation in stable coronary artery disease the recommendation is only 4 weeks.

Newer oral antiplatelets such as prasugrel and ticagrelor can prevent stent thrombosis more efficiently than clopidogrel and these two drugs are approved for treatment after acute coronary syndromes.

Stent thrombosis is a disease with high mortality which can be up to 45% depending on the different studies. Therefore, stent thrombosis must be avoided in any case.

A problem occurs if patients with stents need surgery because in many cases this will lead to discontinuation of the dual antiplatelet therapy posing the patient at high risk for stent thrombosis.

Therefore, the decision to operate and also the decision to stop dual antiplatelet therapy should be based on the individual bleeding risk of the patient and the risk for stent thrombosis which is a little bit like being between Skylla and Charybdis. Another decision parameter should be the urgency to perform surgery. In many cases surgery might be delayed until stop of dual antiplatelet therapy and also in many cases surgery can be safely performed under dual antiplatelet therapy without imposing an increased risk on the patient.

There are several trials showing that patients undergoing coronary artery bypass grafting under dual antiplatelet therapy are at slightly higher bleeding risk, however, without an increase in mortality or even with lower mortality.

In the talk by Holger Thiele, MD all risks and also recommendations will be covered. Most of the recommendations will be based on the consensus recommendations from the German Cardiac Society.
Acidosis: How to prevent bleeding?

R. Zander
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Background
In severely injured patients aggressive management of the “lethal triad”, i.e. coagulopathy as a result of metabolic acidosis plus hypothermia, appears to have the greatest potential of reducing mortality. In about 8,200 multiple trauma patients, a strong correlation has been shown between mortality (%) and base excess (BE, mmol/l) on hospital admission: A base deficit (BD) of ~ 15 mmol/l predicts a mortality of ~ 50 %. Therefore, under clinical conditions, any kind of acidosis must be prevented as well.

Base excess and clotting
Experimental studies using three selected coagulation factors, have shown that in vitro, clotting factor activity is to a large extent determined by the pH: clotting factor activity was found to be halved at pH 7.20 (base deficit, 12.5 mmol/l) and doubled at pH 7.60 (base excess, 16.5 mmol/l). This observation has been corroborated in patients in vivo: A significant correlation between prothrombin level (%) and negative base excess was found in 4,066 out of a total of 20,815 severely injured (ISS ≥16) multiple trauma patients of the Trauma Registry of the German Society of Trauma Surgery receiving primary care. Apart from prothrombin time (PT), the partial thromboplastin time (PTT) can be correlated with the base deficit of trauma patients on hospital admission as well: a larger BD will substantially increase both parameters.

These bench and bedside findings therefore suggest that a base deficit of approx. 15 mmol/l primarily reduces clotting activity to approx. 50 %, which secondarily explains the reported mortality rate of approximately 50 % in multiple trauma patients.

Volume therapy
Haemodilution has general repercussions: Dilution means dilutional coagulopathy because the concentrations of coagulation factors are reduced. However, dilution also produces dilutional acidosis, which in turn may produce hypocoagulopathy.

During the management of haemorrhage, any acidosis must be prevented through the use of a balanced solution, and exacerbation of acidosis, in the form of dilutional coagulopathy or dilutional acidosis, must be avoided. Balanced solutions show a potential base excess of ~ 0 mmol/l, i.e. with no influence on the patient’s acid base status after infusion plus metabolism of the anions. Therefore, the use of conventional crystalloids, such as 0.9 % NaCl, should be minimised.

Coagulation and ionised calcium
The normal plasma calcium concentration is approx. 2.5 mmol/l, and about half of the plasma calcium is bound to proteins, mainly albumin. The calcium concentration (cCa²⁺) that has an important role in clotting is the concentration of ionised (free) Ca²⁺ (1.25 mmol/l). Ca²⁺ binding, or reduction in free calcium, has been described for lactate. The use of lactate-containing infusion fluids (Ringer’s lactate) and older packed red cell products should be avoided in acute haemorrhage because these are liable to produce or worsen hypocalcaemia. Balanced infusion fluids
should contain at least the physiological cCa²⁺ of 1.25 mmol/l.

**Haemotherapy using packed red cells or plasma**

The transfusion of erythrocytes in the form of packed red cells (PRCs) is being viewed with an increasingly critical eye. This view was condensed in the title of a 2008 NEJM editorial: “New blood, old blood, or no blood?”

The number of transfused PRC units shows a strong association with patient mortality, as has been demonstrated for almost 15,000 patients from 4 studies.

The age of transfused PRC units was also shown to be strongly associated with the mortality of cardiac surgery patients. A possible explanation might be the fact that even at the time of preparation, PRCs show a base deficit of about 20 mmol/l, increasing to 50 mmol/l at 6 weeks during storage. However, in both cases, no causal relationship can be deduced from this.

The transfusion of plasma alters the situation. The balance between the acidifying BD of red cells (production process and formation of lactic acid) and the potentially alkalis ing effect of citrate within the plasma produces the following result: PRC is an acidifying and plasma an alkalis ing product, because practically no alkalis ing citrate remains in the PRC unit.

In fact, in a retrospective study, it was demonstrated that the 30-day mortality of polytrauma patients after massive transfusion may be reduced from 46 to 24 % when the relation of PRCs to FFPs is reduced from > 1.1 to < 0.9. Therefore, the transfusion of red cells (PRCs), concerning the number and age, has significant drawbacks because PRCs are liable to increase acidosis and hence coagulopathy, thus causally maintaining and perpetuating bleeding. This may be avoided by the use of the alkalis ing plasma (FFP).

**Strategy of treating massive haemorrhage**

The currently accepted transfusion approach to major haemorrhage is as follows: First crystalloids, then colloids, then PRCs, and then plasma (FFP). This regimen merits revision and should be improved as follows:

1. Balanced colloids rather than crystalloids, e.g. HES 130/0.4 with BEpot ~ 0 mmol/l, acetate instead of lactate, including Ca²⁺: prevention or normalisation of any acidosis and thus coagulopathy.

2. Plasma for volume replacement plus clotting factors: e.g. fresh frozen (FFP) or lyophilised plasma, including prophylaxis of acidosis (citrate).

3. Coagulation therapy: Fibrinogen, coagulation factors, rFVIIa, aprotinin, tranexamic acid, etc., but only if no metabolic acidosis is present.

4. Transfusion of fresh PRCs (lactate) if at all possible once the cHb falls below a critical level and signs of hypoxia (ECG, BE, lactate) occur.

**References**

Adequate ventilation in hypothermic patients

R. Zander

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Background

In vitro diagnostics of e.g. coagulation, oxygen and acid-base status are commonly performed at a temperature of 37 °C in daily clinical routine, irrespective of the patient’s actual body temperature. If this body temperature is decreased in a situation of hypothermia, considerable problems occur in the acid-base balance, because the partial pressures of gases increase massively due to their reduced solubility associated with the warming up to 37 °C.

Unfortunately, the current discussion about optimal ventilation and management of the acid-base balance of a hypothermic patient, is still focused on two options:

1. Keeping uncorrected values in the normal range in hypothermic patients (a procedure known as alpha-stat regulation);
2. The measuring device performs an internal correction – using established known algorithms – of the values taken at 37 °C to the patient’s actual body temperature, which has previously been set in the device (a procedure known as pH-stat regulation).

The purpose of the following example is to demonstrate this issue for a patient with a body temperature of 25 °C, considering only the paCO₂, which is relevant for ventilation: The uncorrected paCO₂ value measured and displayed by the device at 37 °C is approx. 70 mmHg, which seems hardly plausible to the anaesthesiologist (alpha-stat); the paCO₂ value measured at 37 °C and corrected to 25 °C is 40 mmHg, a value the doctor is confident with and can be regarded as “correct” ventilation (pH-stat).

Question

Which endexpiratory and thus arterial paCO₂ is to be targeted in hypothermic patients and which pH value can then be expected in arterial blood in a status of normocapnia if the patient has a base excess of 0 mmol/l?

Experiments

The acid-base balance of a blood sample was simulated in vitro as follows: Equilibration of fresh blood in the tonometer at 37 °C and 25 °C to pCO₂ 40 mmHg and pO₂ 100 mmHg (gas mixtures of the gas mixing device adjusted to pH₂O values of 47.1 (37 °C) and 23.8 mmHg (25 °C), respectively). Measuring of the blood pH was made with a pH electrode after calibration with phosphate buffer using temperature-corrected target values [6.841 / 7.383 (37 °C) and 6.865 / 7.410 (25 °C), respectively]. Additionally, the pH and pCO₂ were measured using a BGA device (blood gas analyzer OMNI 9, Roche) with calculation of the base excess (BE, mmol/l). We analysed normal blood (expected BE ± 0 mmol/l) and blood with a quantitative addition of HCl in order to achieve a ΔBE of -10 mmol/l.

Results

Equilibration of a blood sample with a gas mixture of e.g. 40 mmHg pCO₂ can be defined in the alveolus as petCO₂ using a capnometer and then confirmed in the blood by blood gas analysis, maybe with minor deviations. This process is simulated in the tonometer with the same positive result as
long as the temperature remains constant for equilibration and measurement.

As expected, the values for pCO\textsubscript{2} (40) and pO\textsubscript{2} (100) were confirmed by the BGA device for both temperatures. The pH values determined for this blood sample with a presumed BE of 0 mmol/l using the two devices are close to the normal value of 7.40 at both 37 °C and 25 °C and thus resulted in a BE of almost 0 mmol/l. As expected, the addition of 10 mmol/l acid reduced the BE of the blood to approximately 10 mmol/l.

If a blood sample is now equilibrated at 25 °C but analysed at 37 °C in a device, this will yield an unusual result: A pCO\textsubscript{2} of approximately 70 mmHg will be measured instead of the expected 40 mmHg, similarly, a pO\textsubscript{2} of approx. 165 mmHg instead of 100 mmHg, which can be explained by the temperature increase in the closed system of the BGA device. The respiratory acidosis produced with a pCO\textsubscript{2} of 70 mmHg will generate a pH of approx. 7.25, but the BE calculated from pH and pCO\textsubscript{2} is still approx. 0 mmol/l, i.e. no change compared with the baseline value. The same holds true for a blood sample with a BE of -10 mmol/l, i.e. the BE remains constant even if an additional respiratory acidosis is mimicked with a pCO\textsubscript{2} of approx. 70 mmHg due to the temperature rise in the device.

If, however, the measurement is made with the BGA device at 37 °C, whilst a conversion to a body temperature of 25 °C is set, the baseline values will be retained, i.e. a normal pCO\textsubscript{2} and pH, so that the BE will be calculated correctly to be approx. 0 mmol/l. A similar result is found for a blood sample with a BE of approx. -10 mmol/l.

**Conclusion in vitro**

Under in vitro conditions, it can be demonstrated with a clinically sufficient precision that the BE is independent of the temperature: irrespective of the temperature, a blood sample with pCO\textsubscript{2} 40 mmHg and BE 0 mmol/l exhibits a pH of 7.40, and a blood sample with a BE -10 mmol/l exhibits a pH of 7.25. A common BGA device has been shown to be able to measure a sample at 37 °C, while that sample had been equilibrated at 25 °C, and to report a correct result after correction to 25 °C. This holds true for the parameters pCO\textsubscript{2}, pO\textsubscript{2} and pH and thus for the BE as well. What happens is that a fictitious respiratory acidosis (pCO\textsubscript{2} ↑, pH ↓) is imposed on the blood in the closed system of the analyzer due to the temperature rise to 37 °C leading to a decreased CO\textsubscript{2} solubility. By definition, this acidosis does not allow for any BE change. The analyzer will then be able to reverse this temperature increase mathematically.

**Clinical conclusion**

For the ventilation of a hypothermic patient, it is recommended to ventilate the patient with a target value of paCO\textsubscript{2} 40 ± 5 mmHg under capnometric monitoring (petCO\textsubscript{2}) and to correct the values obtained by invasive blood measurement at 37 °C to the patient’s body temperature to be entered in the BGA device using internal known validated algorithms (procedure known as pH-stat regulation). This will make sure that a physiological patient pH of 7.40 remains as long as the BE is 0 mmol/l. This procedure will keep you on the right track, because it is not necessary to learn „new normal values“ for pH (7.40), pCO\textsubscript{2} (40 mmHg), pO\textsubscript{2} (70 - 90 mmHg) and BE (± 0 mmol/l). The metabolism is diagnosed via a temperature-independent BE; the pH corrected for body temperature is used – if it is used at all – for the diagnostics of acidosis and alkalosis.

**References**

Postoperative effect of different lung protective strategies in patients during and after cardiopulmonary bypass – A systematic review and meta-analysis

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Background

Different lung protective techniques such as continuous positive airway pressure (CPAP) and vital capacity maneuvers (VCM) have been suggested as beneficial when applied during cardiopulmonary bypass (CPB). However, the evidence of the efficacy of these techniques seems to be weak. In order to better define the efficacy of these techniques a systematic review on different ventilation strategies during and after CPB was performed.

Methods

A full literature research in “MEDLINE”, “BIOSYS”, “EMBASE” and “Cochrane Clinical Trials” for randomized controlled trials was carried out until July 2011. A meta-analysis according to the PRISMA recommendation was implemented.

Results

16 trials with a total of 814 patients were included. Investigated techniques were CPAP and continuous positive pressure ventilation during CPB and VCM after weaning from CPB. A significant improvement of oxygenation parameters immediately after bypass was seen in VCM and CPAP, but none of these techniques had a sustained effect on oxygenation parameters or patients’ outcome.

Discussion

This meta-analysis shows that positive effects of the designated techniques are probably of short duration and have a questionable impact on the clinical outcome of treated patients. According to the literature available, it is currently impossible to recommend an optimal or best-evidence strategy of lung protection during CPB.
Sevoflurane-induced preconditioning in the isolated heart is abolished in Ecto-5’-nucleotidase- and A2B-adenosine receptor knockout mice

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Background

Extracellular adenosine is derived mainly via hydrolysis of extracellular adenosine monophosphate by the membrane bound ecto-5’-nucleotidase (CD73) and mediates signalling through adenosine receptors (AR). CD73 and A2B-adenosine receptors (A2B-AR) are involved in both ischemic preconditioning and anaesthetic-induced preconditioning [1; 2]. Application of sevoflurane (sevo) increases coronary flow. This study focused on sevo-induced preconditioning and sevo-induced coronary flow increase in isolated hearts of CD73 (CD73-KO) and A2B-AR (A2B-AR-KO) knockout mice.

Methods

Experiments were performed with isolated hearts from 12 (6-wk-old) male C57BL/6 (wild type = WT), 12 (6-wk-old) male CD73-KO and 12 (6-wk-old) male A2B-AR-KO mice. Instrumentation of the mouse heart was followed by constant-pressure perfusion using a crystalline buffer. In all three groups six control hearts were matched to six hearts subjected to 15 min of 2.8 vol. % sevo and a 10 min washout. Infarction was induced by 60 min of left coronary artery occlusion followed by 30 min reperfusion. Ventricular pressure, +dP/dt max, heart rate, coronary flow and coronary perfusion pressure were continuously measured. Arterial and venous perfusate samples were collected. The area at risk (AAR) and the infarct size were determined by microspheres and propidium iodide staining. The infarct size was calculated as percentage of the infarcted myocardium from the AAR. Data analysis was performed using Two-Way-ANOVA and post-hoc analysis by Bonferroni. Data are reported as means ± standard error of the means (SEM).

Results

After 60 min of ischemia infarct size in the WT-control group was 67.3 ± 2.3 % of AAR. Control hearts from CD73-KO (55.3 ± 2.3 % of AAR) and A2B-AR-KO (66.2 ± 1.8 % of AAR) showed similar infarct sizes. Application of sevo in WT reduced infarction significantly (33.6 ± 2.1 % vs. 67.3 ± 2.3 % of AAR; with sevo vs. without sevo; n=6 each; p ≤ 0.01). Sevo-induced preconditioning failed in CD73-KO (52.3 ± 3.6 % vs. 55.3 ± 2.3 % of AAR; CD73-KO with sevo vs. CD73-KO without sevo; n=6 each) and in A2B-AR-KO (70.3 ± 1.7 % vs. 66.2 ± 1.8 % of AAR; A2B-AR-KO with sevo vs. A2B-AR-KO without sevo; n=6 each) (Figure 1). Application of sevo significantly increased coronary flow in WT (19.8 ± 2.3 ml/min/gHW; p<0.01). This coronary flow increase was reduced in A2B-AR-KO (13.5 ± 3.2 ml/min/gHW; n.s.) and completely abolished in CD73-KO (7.7 ± 0.4 ml/min/gHW; p<0.05) (Figure 2).
Conclusion

The abolishment of sevo-induced preconditioning in CD73-KO and A2BAR-KO underscores the major role of CD73 and A2B-AR in sevo-induced preconditioning in the isolated mouse heart. CD73 and A2BAR seem to contribute for sevo-induced coronary flow increase in CD73-KO and A2BAR-KO.

Acknowledgements: CD73-KO and A2BAR-KO mice were kindly provided by Prof Triantafyllos Chavakis (Dresden) and Dr David Köhler (Tübingen). This study was supported by the ESA research grant.

References

Abstracts

Measurements based on 3D full volume data set are as accurate as in multiple 2D TOE standard views

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Introduction

A comprehensive intraoperative transoesophageal echocardiography (TOE) evaluation includes various measurements for chamber quantification based on multiple 2D standard views (1). Due to the lack of time most centres only perform a problem focused intraoperative examination (2) which does not allow all required measurements. Aim of our study was to investigate which measurements for chamber quantification could be performed with the acquisition of one Real Time 3D TOE full volume (RT 3D TOE FV) dataset. Secondly we compared these measurements with the measurements based on the 2D standard views.

Method

In patients undergoing elective surgical mitral valve repair a comprehensive 2D TOE examination according to ASE/SCA guidelines was performed after induction of anaesthesia. Additionally one RT 3D TOE FV data set based on the midesophageal 4 chamber view was recorded (iE 33, Philips, Netherlands). All measurements for chamber quantifications of the 2D examination and the 3D FV dataset (Qlab) were performed offline by two different echocardiographers, each blinded for the results of the other. Values are expressed as mean with standard deviation. Significant differences are indexed with an asterisk.

Results

After approval of the local ethic committee and written informed consent 45 patients (27m/18f) with a mean age of 59.4 ± 11.5 years were included in this study. All measurements recommended for chamber quantification could be done based on FV data set except the measurements of the sinuses of Valsalva and the sino-tubular junction (see table). There was a significant underestimation of the inner diameter of the left ventricle in systole and diastole and a significant underestimation of the inner diameter of the right ventricle in systole by RT 3D compared to 2D.

Conclusion

For the intraoperative problem focused TOE examination the acquisition of an additional 3D FV dataset allows accurate measurements of most of the recommended measurements for chamber quantification.
Table

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Significant differences are indexed with an asterisk.

References

Visualisation of the circumflex artery using Real Time 3D transoesophageal echocardiography in patients undergoing surgical mitral valve repair

S. Eibel, E. Hasheminejad, C. Mukherjee, M. Feussner, J. Ender

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Abstracts

Introduction

Distortion or damage of the circumflex coronary artery (CX) is a rare but well known complication of surgical mitral valve repair due to its proximity to the mitral valve annulus (1, 2). Aim of this study was to investigate the feasibility to describe the anatomical relationship between the CX and the mitral annulus with the help of Real Time (RT) 3D TOE.

Methods

After induction of anesthesia a 3D TOE probe (iE 33, Philips Amsterdam, The Netherlands) was introduced and a RT 3D TOE FV dataset was digitally stored in addition to comprehensive perioperative 2D TOE. This was performed pre and post operatively using midesophageal four chamber and long axis view.

By scrolling the sagittal and coronal planes between midesophageal long axis and mitral commissural view, we try to follow the CX course along the mitral annulus. The distance between the mitral annulus and the CX at P1 Segment was measured in y and x axes (see picture: green box represents y axes and blue box x axes) preoperatively and between the annuloplasty ring and the CX postoperatively. All measurements were performed offline using Qlab software® (Philips, Netherlands).

Values are expressed as mean with standard deviation.

Results

After approval of the local ethic committee and written informed consent 40 patients with a mean age of 65 ± 14 years undergoing elective minimally invasive mitral valve repair were included in this study. The measurements were possible in all patients preoperatively and in 38 patients postoperatively. The mean distance in x axis did not differ much between pre and postoperative (7.1 ± 2.1mm vs 7.7 ± 2.3mm) examination, ranging from 3 to 14 mm. The mean difference of the measured distance in y axis was 1.1 ± 1.5 mm preoperatively, ranging from -4 (below mitral annulus) to + 6 (above mitral annulus) mm. The distance in 16 patients could be measured at the level of mitral annulus, 3 below, and in 21 patients above the mitral annulus. Postoperatively the mean difference of the measured distance in y axis was 0.7 ± 2 mm. The distance in 17 patients could be measured at the level of annuloplasty ring, 5 below and 16 above the level of the ring.

Conclusions

It is possible to exactly localize the CX and its anatomical relationship to the mitral valve annulus preoperatively. It is also possible to determine the anatomical relationship of the CX and the implanted annuloplasty ring using RT 3D echocardiography. This information may be a guiding tool for the surgeon to prevent iatrogenic injury to the CX in patients undergoing mitral valve surgery.
Abstracts

References


Picture: Measurements of the distance from the circumflex artery in y axis (green box or left upper box) and in x axis (blue box or left lower box) using RT 3D echocardiography
Individual differences of perioperative granulocytes and monocytes release in patients undergoing cardiac surgery with extracorporeal circulation

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Objective

To investigate whether the CD62L (selectin) shedding assay can contribute to the analysis of the immunomodulation after extracorporeal circulation in cardiac surgery.

Methods

A total of 25 patients referred either to aorto-coronary bypass or for valve surgery were included in this prospective observational clinical study. Blood samples were taken before surgery (T1), immediately after surgery (T2) and at 24 hrs after anaesthesia induction (T3). CD62L shedding was quantified for granulocytes and monocytes after stimulation with lipoteichoic acid (LTA), endotoxin, Tumor necrosis factor (TNF), E. coli and bacteroides. The stimulation was performed with dilution series to provide an estimate of the cell activability. LC50 represented the concentration of the stimulant dose which caused the shedding of half of the CD62 molecules. A high LC50 indicated low activability and vice versa.

Results

Stimulation with LTA showed perioperative differences in the activability of granulocytes and monocytes (Kruskal-Wallis Test with Dunn’s Multiple Comparison Test p=0.0125, p<0.0001, figure 1). In contrast the stimulation with TNF (figure 1) or bacteria (data not shown) showed no significant changes (Kruskal-Wallis Test with Dunn’s Multiple Comparison Test p>0.05). The LTA induced activability of granulocytes was significantly reduced at T2 compared to T1 and T3. The monocyte CD62L loading decreased at T3 compared to T1 and T2 (figure 1).

Conclusion

This pilot study confirmed that the CD62L assay can be used to monitor immuno-modulation under cardiac surgery conditions with extracorporeal circulation. The interindividual differences especially at T2 may represent heterozygous patients, operation conditions or differences in the genetic background. Especially this question will be addressed in further studies.
Figure 1: * p<0.05
Cerebral embolic load during transcatheater aortic valve implantation

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Background

In high-risk patients transcatheter aortic valve implantation [TAVI] is an attractive alternative to surgical aortic valve replacement. For periprocedural stroke in TAVI, an incidence of 0-6.3% is reported (1,2). Clinically silent ischemic cerebral lesions have been documented by MRI in 66-84% (2-4). However, amount and pattern of cerebral embolic events as well as the relation to the procedural steps of TAVI is unclear.

Objective

Relating cerebral embolic load during TAVI to procedural steps. Comparing the transfemoral [TF] and the transapical [TA] access as well as the type of device deployment (balloon-expandable[BE] vs. self-expanding [SE].

Methods

In 44 patients (78±6y; log EuroScore 24±15%; n_TF=32; n_TA=12; n_BE=17; n_SE=27) transcranial Doppler ultrasound recordings were analyzed for high-intensity transient signals [HITS]. Procedural steps were defined as follows: instrumentation prior to valvuloplasty [IN], balloon valvuloplasty [BV], deployment of prosthesis [DP] and post-implantation [PI] including post-dilatation. Cerebral embolic load [CEL] was related to the duration of each procedural step comparing access route and method of device deployment. The Confusion Assessment Method [CAM](5) was used to identify periprocedural neurocognitive impairment. The CAM score was calculated prior and on POD 1, 4-6 after TAVI. Data are given as median (min, max), and comparisons used nonparametric testing (significance level, p<0.05).

Results

Deployment of prosthesis had the highest CEL (p<0.05). During instrumentation prior to valvuloplasty cumulative CEL was almost as large, however, HITS were recorded at a much lower time rate. Hemispheric CEL did not differ significantly. Cerebral embolic load was comparable between the routes of access. Only during post-implantation a larger CEL was released in TF than in TA. Self-expanding devices had a higher CEL due to increased HITS during deployment of prosthesis and post-implantation. The incidence of in-hospital death was 0/44, periprocedural stroke occurred in 2/44.

Conclusion

In TAVI, total embolic load detected by transcranial Doppler monitoring appears similar between routes of access. However, in the post-deployment phase, an increased HITS count is noted after TF implantation. This may be due to more frequent balloon dilatation post-deployment and/or delivery system retrieval through the aortic arch. With regard to deployment mechanism, SE devices ap-
pear to release more HITS during and after valve deployment. Beating heart deployment and aortic wall friction on retraction of the delivery system may play a role. Our results are in line with previous MRI findings of a substantial incidence of new ischemic brain lesions (2), which do however, not translate into clinical neurocognitive impairment.

References
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Increased Gq expression is associated with myocardial injury and survival after coronary artery bypass surgery

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Aims

Understanding gender differences in outcomes after coronary artery bypass grafting (CABG) is important for their public health implications. In CABG procedures recovery of contractile function is depressed during reperfusion. Moreover, Troponin I (cTnI) release is much more increased in hypertrophied hearts subjected to global ischemia, suggestive of greater susceptibility to ischemia/reperfusion injury. Chronic activation or overexpression of the heterotrimeric G-protein Gq is necessary and sufficient for myocardial hypertrophy. We recently identified a TT(-695/-694)GC polymorphism in the human GNAQ promoter. The GC allele evokes increased promoter activity and increased prevalence of cardiac hypertrophy compared to the TT allele, the effects being more pronounced in women.

We hypothesized, that the TT(-695/-694)GC polymorphism a) results in gender specific differences of myocardial Gq protein expression, b) influences myocardial damage after CABG; and c) is associated with altered one-year mortality.

Methods and results

Western Blot analysis from right atrial appendages (n=47) showed genotype dependent Gq expression in females (fold change GC/GC versus TT/TT, 2.13; p=0.023) but not in males. Perioperative myocardial injury was investigated in 227 consecutive patients undergoing CABG. Baseline characteristics between GNAQ genotypes were similar except of preoperative ejection fraction in females (GC/GC 58±11%, GC/TT 51±15%, TT/TT 47±15%; p=0.045).

While preoperative cTnl serum concentrations did not differ between genotypes, regardless of gender, postoperative analysis stratified to gender showed higher cTnl concentrations of female GC/GC patients followed by GC/TT and TT/TTs with a gene-dose effect (fig. 1; p=0.03) while the cTnl rise in male patients was unaffected of genotypes. In women, the cTnl AUC over 96 h after CABG was almost three times as high in GC/GC genotypes (643 ± 700 ng/mL x 96 h)
compared to GC/TG (280 ± 223 ng/mL x 96 h) and TT/TT genotypes (231 ± 191 ng/mL x 96 h; p=0.024). Peak postoperative cTnI concentrations in women were GC/GC 14.1 ± 13.6 ng/mL vs GC/TT 7.5 ± 5.0 ng/mL vs TT/TT 4.6 ± 2.0 ng/mL (p=0.016).

Moreover, one-year mortality was genotype dependent in women (GC/GC 22%, GC/TT 0% and TT/TT patients 0%; p=0.026).

Conclusions

Increased myocardial Gq expression due to the functionally relevant GNAQ TT(-695/-694)GC promoter polymorphism results in enhanced perioperative myocardial damage after CABG in women. Our data sheds new light on the pathophysiological role of increased Gq expression in ischemic cardiac disease and may help to identify patients at high risk for cardiac death after CABG in need for additional treatments.
miR-133a but not of miR-1 expression is associated with signs of heart failure in patients undergoing coronary bypass surgery

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Background

Coronary artery disease (CAD) is a multifactorial disorder and a major cause of morbidity and mortality. CAD associated ischaemic heart failure is characterized by dysregulated gene expression. Higher order mechanisms such as microRNA (miR) can alter gene expression control in cardiovascular disease, without involving any change in the underlying DNA sequence. While the muscle-specific miR-1 and miR-133 are involved in cardiac development and hypertrophy, their role in heart failure resulting from CAD is unknown.

Objective

In 86 patients undergoing coronary artery bypass grafting (CABG), we tested the hypothesis that cardiac miR-1 and miR-133 expression is associated perioperatively with signs of heart failure.

Methods

Medical history and venous NT-proBNP concentrations were determined prior to CABG. Cardiac index and vascular pressures were measured under general anesthesia and miR expression was quantified (RNase protection assay and real-time PCR) from samples of right atrial myocardium.

Results

miR-133 expression decreased significantly with increased severity of heart failure, as indicated by a greater NYHA functional class (p=0.0045) and increased pulmonary artery occlusion pressure (p=0.018). Furthermore, patients with NT-proBNP concentrations >1800 pg/ml showed a 60% decrease in miR-133 expression compared to patients with concentrations <300 pg/ml (p=0.0131). In contrast, no associations were detected for miR-1 expression.

Conclusions

In surgical CAD patients, decreased miR-133 expression is closely linked to variables characteristic of heart failure. This supports a role for miR-133 but not miR-1 in the adaption to and/or remodelling of the ischemic heart.
An association between duration of cardiopulmonary bypass and increased biomarkers of acute kidney injury in patients without postoperative renal dysfunction

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Background

Cardiac surgery associated acute kidney injury (CSA-AKI) is a major complication in patients undergoing cardiac surgery and associated with a poor short-term and long-term prognosis. Within the last years, various markers for early detection of CSA-AKI have been developed. The expression of several of these markers, among them Neutrophil-gelatinase associated lipocalin (NGAL), Kidney injury molecule -1 (KIM-1), L-Fatty acid binding protein (L-FABP), and Cystatin-C (CYS-C) is increased by renal ischemia-reperfusion injury and may thus be related to the duration of cardiopulmonary bypass (CPB-time). The present analysis focusses on patients not developing overt CSA-AKI according to Acute Kidney Injury Network (AKIN) criteria to determine the effects of CPB duration on putative biomarkers of AKI in a heterogeneous cohort of cardiac surgery patients.

Methods

As a part of a large, prospective observational study on the relationship between preoperative cerebral oxygen saturation and postoperative organ dysfunction, 131 consecutive patients undergoing cardiac surgery were studied. Plasma and urine for determination of biomarkers and creatinine were determined at baseline (t1) and at the end of surgery (t2). The incidence of CSA-AKI was derived from the cardiac surgery quality register. For analysis, duration of CPB was dichotomized and the plasma and urine concentration of biomarkers as well as renal outcomes were determined. Analysis was restricted to patients without postoperative renal dysfunction. Following Kolmogorov-Smirnov test showing that most variables were not normally distributed, analyses were performed non-parametrically by Mann-Whitney and Wilcoxon’s test, as appropriate.

Results

Median duration of cardiopulmonary bypass was 118 min (95%CI: 107 to 127 min). The incidence of AKI grade 1 to 3 was 14,5% (n = 19), 1,5% (n = 2), and 16% (n = 21), respectively. 89 patients (68 %) did not fulfill the AKI criteria and were used for analyses. The plasma and urinary levels of renal biomarkers and creatinine in patients without postoperative AKI is given in table 1, showing that – with the exception of cystatin-C – all biomarkers increased significantly in relation to baseline and were significantly higher in patients with a CPB-time above the median. In contrast, plasma cystatin-C and creatinine levels decreased significantly from t1 to t2. No significant differences in plasma creatinine levels were observed at t2.

Conclusions

Duration of CPB is a relevant factor for the expression of several biomarkers currently
under investigation as early markers for renal dysfunction after cardiac surgery. With respect to the fact that prolonged CPB is an important trigger for CSA-AKI, CPB-time has to be taken into account when defining cut-off levels for biomarkers for the early detection of renal dysfunction after cardiac surgery. Hereby our findings extend observations from recent reports on urinary NGAL excretion [1,2] to several other markers of AKI and support the concept of CPB induced subclinical renal injury and the need for new definitions beyond AKIN-criteria.

### References


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Aggravated myocardial damage in mice deficient for the lectin-like domain of thrombomodulin is mediated by HMGB1 through TLR2

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Introduction

Preservation of myocardial tissue is the most important therapeutic goal in patients suffering myocardial infarction. Thrombomodulin (TM) is an endothelial protein which inactivates thrombin and amplifies protein C activation. It has been demonstrated that TM, through its lectin-like domain (LLD), has anti-inflammatory effects as a result of HMGB1 scavenging. Using knock-in mice lacking the LLD of TM (TMLeD/LeD) and in vitro models of cardiomyocyte hypoxia, we examined the role of HMGB1 in myocardial ischemia and reperfusion.

Methods

Wildtype (WT), TMLeD/LeD, and WT-mice with systemic overexpression of the LLD by hydrodynamic transfection (HDTF) were subjected to transient LAD ligation and 24 h reperfusion after approval by the local government authority. Main measurements included infarct size, TNFα, IL-1β in tissue samples (RT-PCR), HMGB1 protein levels (ELISA, WB) Caspase 3 (WB) and the number of CD45-positive cells in the myocardium. Additional experiments were performed with the isolated mouse heart. The effect of HMGB1 on apoptosis in hypoxia was examined in isolated cardiomyocytes. The role of in vitro TLR2, TLR4 and RAGE for HMGB1 apoptosis signalling was assessed by si-RNA knockdown. The effects of in vivo TLR2 antibody application and LLD overexpression on infarct size was measured.

Results

Infarctions (24 h) were significantly larger and apoptosis was significantly increased in TMLeD/LeD compared to WT-mice. HMGB1 protein levels were increased. HMGB1 augmented hypoxia-induced apoptosis in rat neonatal cardiomyocytes. siRNA knockdown of TLR2 but not TLR4 or RAGE abolished the effect of HMGB1 on hypoxia-induced apoptosis. Administration of HMGB1- and TLR2-blocking antibodies in TMLeD/LeD-mice 60 min before MI/R diminished apoptosis levels in the infarct zone. Therapeutic systemic gene therapy using the LLD reduced the infarct size, HMGB1-protein levels and cardiomyocyte apoptosis 24 h after MI/R.
Conclusions
HMGB1 expression and cardiomyocyte apoptosis are increased in TM<sup>LeD/leD</sup>-mice. HMGB1 augments hypoxia-induced apoptosis in vitro and in vivo mediated by TLR2. HMGB1-antagonistic or LLD-agonistic strategies are therefore promising therapeutic strategies to prevent cardiomyocyte death.
Baseline shift of the Nyquist limit improves correlation between 2D and Real Time 3-D transoesophageal echocardiography for graduation of mitral valve regurgitation

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Introduction

Vena contracta (VC) and effective regurgitant orifice area (EROA) are well established methods for evaluation of mitral regurgitation (MR) using 2-dimensional (2D) transesophageal echocardiography (TEE). For these color-flow Doppler measurements (CF) a Nyquist limit of 50-60 cm/s is recommended (1). Both, VC and 2D TEE calculated EROA are indirect parameters for the anatomic EROA. CF Real time (RT) 3-dimensional (3D) TEE offers the possibility of direct planimetry of the EROA. Aim of the study was to investigate the usefulness of a baseline shift of the Nyquist limit in 2D TEE to compare VC and EROA with EROA planimetry using RT 3D TEE.

Methods

After induction of anesthesia a comprehensive 2D TEE examination was performed (iE33, Philips, Netherlands). The mitral regurgitation jet using CF was acquired with a Nyquist limit of 50 cm/s (NL50) as well as with a baseline shift to 37.5 cm/s (NL37.5) (see picture). Additionally a real time 3D color full volume dataset with a Nyquist limit of 50 cm/s was stored based on the ME 4 chamber view. Vena contracta (VC), Proximal Isovelocity Surface Area (PISA) and Effective Regurgitation Orifice Area (EROA) were measured based on 2D TEE and compared to planimetry of the EROA using Real Time 3D (RT). All measurements were performed offline by two independent examiners using Image Com® (TomTec, Germany) and Qlab software® (Philips, Netherlands). For statistical analysis the Pearson correlation was used with p<0.05 for significance and r >0.5 for good correlation. For inter and intraobserver-variability the Intraclass Correlation Coefficient (ICC) was used.

Results

After approval of the local ethics committee and written informed consent 50 patients with a mean age of 60.5 ± 14 years undergo-
ing elective surgical mitral valve repair were included in this prospective study. Correlation between VC NL37.5 and 3D Planimetry of EROA as well as correlation between 2D EROA NL37.5 and 3D Planimetry was better than the correlation of VC and 2D EROA with a Nyquist limit of 50 cm/s and 3D planimetry (Table 1). Intraobserver variability was lowest for 3D planimetry whereas interobserver variability was comparable for all measurements.

### Conclusion

Baseline shift of the NL to 37.5 cm/s from 50 cm/s leads to better correlation for VC and EROA in 2D TEE in comparison to RT 3D planimetry.

### References

Mortality in female rats after deep hypothermic circulatory arrest

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Abstracts

Background

Female gender is known as independent risk factor especially within the cardiopulmonary bypass (CPB) setting (1). Aim of the study was to investigate the role of gender and hormonal status on survival and histological outcome after CPB with 45 min of deep hypothermic circulatory arrest (DHCA) in normal and neutered female and male rats.

Methods

With institutional review board approval animals were assigned to 4 groups: female-normal, female-neutered, male-normal, male-neutered. At 12 weeks of age, animals were neutered or sham-neutered (female-normal, male-normal) according to group assignment. After 28 days to allow for elimination of sex hormones, rats were anesthetized, cannulated, connected to CPB, cooled down within 30 min (15-18°C) and exposed to 45 min of DHCA. Following reinstitution of flow and rewarming (40 min), animals were weaned from CPB at 35.5°C rectal temperature. 1 hour after DHCA, rats were allowed to recover from anesthesia. 14 days after DHCA, the surviving animals were sacrificed, serum 17β-Estradiol, Progesterone, and Testosterone levels were determined. Histological outcome was assessed with hematoxylin & eosin staining. Survival was analyzed with consecutive χ²-tests in a hierarchical model (p<0.05), histological data were analyzed using Kruskal-Wallis and post hoc Mann Whitney U (p<0.05).

Results

17β-Estradiol, Progesterone, and Testosterone differed between groups as expected (17β-Estradiol and Progesterone levels highest in the female-normal group, Testosterone present in the male-normal group only). The survival rate (table 1) after 45 min of DHCA in female rats was overall lower compared to the male animals (p<0.05). Within the female groups, female-normal rats showed a lower survival rate compared to female-neutered animals (p<0.05). There was no difference between the male-normal and male-neutered animals concerning survival rate. Histological outcome (figure 1) shows significantly less damaged neurons in both female groups compared to the male-normal group (p<0.05).

Conclusions

As expected, female gender reduced the overall survival rate after DHCA, with the highest mortality rate found in female rats.

Table 1: Mortality rate after 45 min of deep hypothermic circulatory arrest

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-Neutered</td>
<td>0/12</td>
<td>13/23</td>
<td>13/35</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>56%*</td>
<td>37%</td>
</tr>
<tr>
<td>Neutered</td>
<td>2/13</td>
<td>3/14</td>
<td>3/14</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>22%#</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>2/25</td>
<td>16/37§</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>43%</td>
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</tr>
</tbody>
</table>

* = p < 0.05 versus male-normal; # = p < 0.05 versus female-normal, § = p < 0.05 versus male
with normal sex hormone status. Combined with the histological outcome 14 days after 45 min of DHCA, our findings indicate that the male rat brain tolerates a more extensive neuronal damage. In addition, our results suggest that neuronal damage alone is likely not the main culprit for the reduced survival rate in the female groups. Further studies are needed to elucidate the mechanisms behind the gender-related mortality in this particular setting.

References

Intrathecal morphine is superior to intravenous PCA in patients undergoing minimally invasive cardiac surgery

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Introduction

Pain therapy in patients undergoing minimally invasive mitral and tricuspidal valve repair is challenging. Intrathecal morphine is of benefit but has the potential for postoperative apnoea. This effect is dose dependent. Aim of our study was to evaluate the potential benefit of low dose intrathecal morphine on postoperative analgesia in minimally invasive cardiac surgery using Fast Track anaesthesia.

Methods

In this prospective study patients undergoing minimally invasive mitral or tricuspidal valve repair were randomly assigned to receive either intravenous PCA with piritramide (Control group) or a single dose of intrathecal morphine (1,5 μg per kgBW) in combination with intravenous PCA (Morphine group). Primary endpoints were: time to extubation, pain score, sedation score, amount of piritramide in post anaesthesia care unit (PACU) and on first postoperative day. Values are expressed as mean with standard deviation.

Results

37 patients, at the age of 26 to 78 years (Control = 59 ± 9, Morphine =56 ±14) with a BMI between 18.87 and 30.90 (Control = 25.54 ± 2.96, Morphine =25.62 ± 2.87) were included. The morphine group showed significantly reduced pain scores on the day of operation and on first postoperative day. The demand for intravenous opioids in post anaesthesia care unit was significantly lower in morphine group, whereas sedation scores did not differ in both groups. Furthermore there was no significant increase of time to extubation in the morphine group. PaCO₂ values after extubation in the PACU showed no significant difference (47.8 ± 3.4 mmHg in the control group vs 49.8 ± 6.8 mmHg in the morphine group). For details see table.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Morphine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Score OP</td>
<td>4,31 ± 1,974</td>
<td>2,0 ± 1,541</td>
<td>0.01</td>
</tr>
<tr>
<td>Pain Score Post OP1</td>
<td>4,12 ± 1,867</td>
<td>2,25 ± 0,910</td>
<td>0.013</td>
</tr>
<tr>
<td>Sedation OP</td>
<td>3,06 ± 1,197</td>
<td>2,55 ± 1,050</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sedation Post OP</td>
<td>1,06 ± 0,659</td>
<td>1,10 ± 0,641</td>
<td>n.s.</td>
</tr>
<tr>
<td>Opioid PACU (mg)</td>
<td>13,88 ± 7,833</td>
<td>2,88 ± 4,195</td>
<td>0.002</td>
</tr>
<tr>
<td>Opioid Post OP1 (mg)</td>
<td>38,24 ± 31,590</td>
<td>24,30 ± 35,066</td>
<td>n.s.</td>
</tr>
<tr>
<td>Opioid Total (mg)</td>
<td>43,29 ± 25,602</td>
<td>30,55 ± 17,488</td>
<td>n.s.</td>
</tr>
<tr>
<td>Extub. Time (min)</td>
<td>106 ± 73</td>
<td>121 ± 102</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Conclusion

Low dose intrathecal morphine reduces the amount of opioids and increases postoperative analgesia. It does not prolong extubation time.

References

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Soluble guanylate cyclase stimulator BAY 41-8543 reduces pulmonary vascular resistance and increases cardiac output when inhaled or administered intravenously in porcine endotoxemic shock

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Background

Septic cardiomyopathy and increased pulmonary vascular resistance (PVR) can result in right heart failure. This study investigates whether a stimulator of soluble guanylate cyclase may be a possible treatment for reduction of PVR in septic shock.

Methoden

The study was ethnically approved by the local government. Septic shock (mean arterial pressure (MAP)<60) was induced in 32 pigs (25±3kg) by infusion of E. coli endotoxin (serotype O111:B4). Animals were then treated with fluids and vasopressor following a protocol according to the surviving sepsis campaign guidelines. Following randomization, either BAY 41-8543 inhalative (i.h.) (240mcg kg-1), intravenously (i.v.) (24mcg kg-1) or placebo was administered. Subsequently heat rate (HR (min-1)), MAP (mmHg), mean pulmonary artery pressure (MPAP (mmHg)), cardiac output (CO (l min-1)) and PVR (dyn sec cm-5) were registered every 15 minutes over one hour. After another 60 minutes, animals were subjected to either double dosage (D2) or a combination of BAY 41-8543 in single dose and nitric oxide (NO) (i.h.) 20 ppm. Hemodynamic measurements were taken once more every 15 minutes for the next hour. Results are displayed as mean ± standard deviation at shock and 30 minutes after treatment. Differences between groups were detected by a linear mixed effects model (R, version 2.12.0).

Results

Both i.h. and i.v. application of BAY 41-8543 resulted in a significant reduction of PVR compared to control, accompanied by an increase in CO (table 1). Increased dosage and

<table>
<thead>
<tr>
<th></th>
<th>shock (n=32)</th>
<th>i.h. (n=12)</th>
<th>i.v. (n=14)</th>
<th>con (n=6)</th>
<th>i.h. D2 (n=6)</th>
<th>i.h. no (n=5)</th>
<th>i.v. D2 (n=5)</th>
<th>i.v. no (n=5)</th>
<th>con no (n=5)</th>
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<tr>
<td>HR</td>
<td>127 (34)</td>
<td>150 (21)</td>
<td>163** (28)</td>
<td>123 (34)</td>
<td>140 (35)</td>
<td>146 (19)</td>
<td>171 (29)</td>
<td>148 (29)</td>
<td>113 (34)</td>
</tr>
<tr>
<td>MAP</td>
<td>58 (7)</td>
<td>71 (7)</td>
<td>68 (6)</td>
<td>73 (8)</td>
<td>75 (6)</td>
<td>69 (9)</td>
<td>68 (14)</td>
<td>73 (10)</td>
<td>73 (8)</td>
</tr>
<tr>
<td>MPAP</td>
<td>38 (7)</td>
<td>40 (7)</td>
<td>37 (8)</td>
<td>44 (6)</td>
<td>42 (10)</td>
<td>42 (9)</td>
<td>40 (16)</td>
<td>37** (9)</td>
<td>39** (9)</td>
</tr>
<tr>
<td>PVR</td>
<td>1246 (401)</td>
<td>491** (106)</td>
<td>469** (198)</td>
<td>497 (325)</td>
<td>691** (322)</td>
<td>573** (245)</td>
<td>849* (815)</td>
<td>460** (103)</td>
<td>887** (296)</td>
</tr>
<tr>
<td>CO</td>
<td>2.02 (0.51)</td>
<td>4.65** (0.76)</td>
<td>5.04** (1.43)</td>
<td>2.93 (0.89)</td>
<td>3.73 (1.71)</td>
<td>4.16* (1.44)</td>
<td>4.3** (2.85)</td>
<td>4.06** (0.78)</td>
<td>2.46 (0.67)</td>
</tr>
</tbody>
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*p<0.05, **p<0.01 vs. control group (con)
NO administration both reduced PVR effectively without differences in treatment.

Conclusion

The stimulator of soluble guanylate cyclase BAY 41-8543 appears to be a possible treatment option for pulmonary hypertension in septic shock. Both inhalative and intravenous administration of BAY 41-8543 reduces PVR and increases CO.
Low arterial compliance determined by applanation tonometry is not associated with postoperative morbidity and high-dependency unit stay in cardiac surgery patients – An observational pilot trial

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Background

Demographic changes have lead to an increasing number of older patients – often with substantial co-morbidities – undergoing cardiac surgery and an increasing scientific interest in measures for preoperative risk stratification [1, 2]. Structural and functional changes of the arterial vascular wall are a relevant aspect of cardiovascular morbidity and mortality [3]. Augmentation index (Alx) is considered to be an indirect measure of arterial stiffness. No data are available if arterial compliance may be used for risk stratification in patients undergoing cardiac surgery [4]. The present prospective, observational pilot study was designed to analyze an association between preoperative arterial stiffness, cardiovascular biomarkers and postoperative morbidity in cardiac surgery patients.

Methods

82 consecutive patients undergoing on-pump cardiac surgery participated in this study. Exclusion criteria were high-grade aortic insufficiency, permanent atrial fibrillation and nitroglycerin medication. Preoperative augmentation index was measured by applanation tonometry (SphygmoCor®, ATCOR Medical, Australia). In addition, preoperative N-terminal prohormone of brain natriuretic peptide (NT-proBNP), highly sensitive troponin T (hsTNT), placental growth factor (PIGF), soluble Fms-like tyrosine kinase 1 (sFlt-1), growth-differentiation Factor 15 (GDF-15), creatinine, cystatin C and cerebral oxygen saturation (ScO2), using infrared spectroscopy, were determined. In order to assign postoperative morbidity MAC-score (major adverse complication score; one point each for postoperative low-output syndrome, new kidney failure requiring dialysis, stroke, and reintubation) and HDU-time (high-dependency unit time; postoperative total length of stay on intensive care unit and intermediate care) were recorded. Alx was divided by median into two groups.

Results

No significant differences were observed in patients with a high vs. low Alx with respect to morbidity (MAC-score: Alx-high: 0.17 ± 0.49; Alx-low: 0.37 ± 0.73, p = 0.16) or HDU-time (Alx-high: 5.1d ± 2.6d; Alx-low: 6.3d ± 4.7d; p = 0.14). A significant correlation was observed between Alx and the plasma concentrations of sFlt-1 (r = 0.37, P <0.01) and hsTNT (r = 0.35, p <0.01). No correlations were observed between Alx and: NT-proBNP (r = 0.12, p <0.38), PIGF (r = 0.03, p = 0.84), GDF-15 (r = 0.09, p = 0.51), creatinine (r = 0.17, p = 0.22), cystatin C (r = 0.12, p = 0.36) and ScO2 (left: r = 0.15, p = 0.19, right: r = -0.11, p = 0.31).
Conclusion

No direct associations between preoperative arterial stiffness and postoperative morbidity were observed in this small pilot study in a heterogeneous population of cardiac surgical patients. A retrospectively performed power analysis suggests that more than 180 patients per group need to be analyzed to verify a possible association. Further studies are required to verify the relationship between arterial stiffness, the vascular marker sFlt-1 and the myocardial ischemia marker hsTNT.

References

Sevoflurane plasma concentration achieved with the constant application through the ventilator and the oxygenator membrane

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Background

Volatile anesthetics (VA) seem to have cardioprotective properties during cardiac surgery [1]. Sevoflurane is the most commonly used VA in studies showing these cardioprotective effects [2]. The Scientific Working Group in Cardiac Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI) recommends the application of VA during on-pump cardiopulmonary bypass (CPB) via the oxygenator since 2006 [3]. Until today there are no studies showing the in vivo uptake of sevoflurane across the microporous membrane oxygenators. Besides, there are no data showing the influence of the patient’s temperature, hematocrit and the plasma protein and albumin concentration on the sevoflurane plasma concentration (SPC) in vivo. In this prospective clinical study, the SPC is determined by gas chromatography during the constant application of sevoflurane through the ventilator and the membrane oxygenator.

Methods

After obtaining approval of the Ethics Committee (Hamburg, Germany) and with written informed consent, we included 30 patients undergoing elective on-pump cardiac surgery. Sevoflurane was constantly administered with 1.8 Vol% inspiratory through the respirator followed by the administration of 1.8 Vol% in the gas supply of the oxygenator. We derived the bispectral index (BIS) in order to quantify the depth of sedation. SPC was determined by gas chromatography before and to several defined points during CPB. Values were compared using the t-test for matched pairs. The correlation between the patient’s temperature, hematocrit, the plasma protein and albumin concentration and the SPC was determined univariate with the Pearson correlation test.

Results

The continuous application of inspiratory 1.8 Vol% sevoflurane through the ventilator led to a mean SPC of 56.95 (±15.61) µg/ml. After initiation of CPB the mean SPC declined to a minimum of 43.91 (±8.25) µg/ml (p<0.01). During the following CPB the SPC ranged between a mean of 47.16 (±8.59) µg/ml and 50.62 (±9.30) µg/ml. The BIS was measured under 60 in all patients throughout the study period and mean values ranged between 35.7 (±5.4) and 37.3 (±5.4). We could not find a correlation between the SPC and patient temperature (r = 0.54), hematocrit (r = 0.60), plasma protein concentration (r = 0.54) and plasma albumin concentration (r = 0.56).

Conclusion

Immediately after the onset of CPB, there was a significant decrease in SPC compared to the application through the ventilator before. However, this drop in SPC was not associated with an increase of BIS as a marker for the depth of sedation. We conclude that the
uptake of sevoflurane across the oxygenator membrane during CPB leads to a comparable SPC and equal safe level of sedation as during the application through the ventilator.

References
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BIS triggered Sevoflurane dosage during cardiac surgery and heart lung machine circulation

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Background

The Scientific Working Group in Cardiac Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI) recommends the continuous application of volatile anesthetics (VA) during on-pump cardiac surgery since 2006 [1]. Continuous application of VA in cardiac surgery procedures increased constantly within the last years. In most cases sevoflurane is the preferred VA in this setting. During cardiopulmonary bypass (CPB) VA are applied via the inlet air to the oxygenator membrane. Up to now detailed information about oxygenator transfer capacity, factors influencing diffusion of VA during routine use of the CPB and optimal VA dosage are not available. Increased risk of awareness during cardiac surgery can be reduced to normal levels by using Bispectral Index (BIS) for anesthesia monitoring. For sufficient depth of hypnosis a BIS value of 40-60 has to be maintained. Goal of this study was to define the sevoflurane plasma and inlet air concentration during BIS triggered sevoflurane dosage. These data were compared to a continuous application of 1.8 Vol% sevoflurane regarding plasma concentration, intraoperative need for vasoressors, blood lactate concentration at ICU admission and length of ICU stay.

Methods

After approval of the local ethics committee 61 patients scheduled for cardiac surgery were prospectively included and randomized in two groups. In group I 30 patients received 1.8 Vol% sevoflurane constantly via the ventilator or heart lung machine oxygenator. In group II in 31 patients sevoflurane dosage was titrated to maintain a BIS value of 40-60. In both groups sufentanil 0.7 µg/kg*h was applied for analgesia. For induction of anesthesia propofol or etomidate and a fix dose of 50 µg of sufentanil were administered. Plasma concentration of sevoflurane [Csev] was measured by gas-phase chromatography to fixed dates. Additionally cumulative dosage of norepinephrine, epinephrine, level of arterial blood lactate concentration at ICU admission duration of postoperative ventilation and length of ICU stay were monitored. For surveillance of explicit awareness Brice questionnaire was used postoperatively in all patients.

Results

For anesthesia induction 131.2 ± 25.2 mg of propofol and 16.9 ± 3 mg of etomidate in group I and 135.5 ± 33.6 mg of propofol and 14.7 ± 4.1 mg of etomidate in group II were applied. Csev in group I was higher in all measurements. In group I minimal Csev was 39.73 ± 7.88 µg/ml, maximal Csev 56.95 ± 15.61 µg/ml. In group II minimal Csev was 19.9 ± 10.45 µg/ml and maximal Csev 39.36 ± 16.34 µg/ml. BIS triggered inspiratory or inlet air sevoflurane dosage was between 0.56 ± 0.26 Vol% and 0.88 ± 0.43 Vol%. Regarding vasoactive and inotrope medication in group I patients received 1706 ± 1183 µg of norepinephrine and 91.3 ± 111.63 µg of epinephrine; in group II 796.4 ± 873 µg (p<0.01) and 78.1 ± 163.5 µg of epinephrine were ap-
plied (p=0.107). ICU admission blood lactate concentration was 2.85 ± 2.56 mmol/l in group I vs. 2.37 ± 1.54 mmol/l in group II. Postoperative ventilation lasted 7.63 ± 5.38 hrs in group I vs. 8.48 ± 4.77 hrs in group II. Length of ICU therapy was 60.4 ± 67.3 hrs in group I and 53.8 ± 30.4 hrs in group II. No indicator of awareness could be detected in any case.

**Conclusion**

BIS titrated application of sevoflurane during on pump cardiac surgery resulted in significantly reduced sevoflurane plasma concentration compared to continuous application of 1.8 Vol% inspiratory sevoflurane concentration. Mean inspiratory sevoflurane concentration in the BIS triggered patient collective was between 0.56 and 0.88 Vol%. Need for intraoperative norepinephrine was significantly reduced. A trend towards reduced length of ICU stay and lower ICU admission blood lactate concentrations may be discussed as sings of positive effects of a BIS triggered sevoflurane application during elective on pump cardiac surgery.
Objectives

Increasingly, transcardiopulmonary thermodilution (TCPTD) and arterial pulse contour analysis (PC) are promoted as less invasive technologies to measure cardiac output (CO) and stroke volume (SV) in critically ill patients. Transcatheter Aortic Valve Implantation (TAVI) is a therapeutic option in patients with severe aortic stenosis (AS) and high surgical risk. It is unknown, if measurement of SV by TCPTD or PC in its different applications is valid in AS or aortic insufficiency (AI).

Methods

With local ethics committee approval eighteen patients undergoing TAVI were included in this prospective study. Exclusion criteria were permanent arrhythmias, pacemaker dependency, intracardiac shunts and contraindications for catheterization of the brachial artery. We compared measurements of transoesophageal echocardiography (SVTEE), serving here as clinical gold standard during TAVI, with SV determined by TCPTD and PC. SV_{TCPTD} and calibrated PC (SV_{PC CAL}) were assessed by a central pressure signal via the brachial artery with the PiCCOplus™ system (Pulsion Medical Systems), while uncalibrated PC (SV_{PC UNCAL}) was simultaneously measured using a radial signal with the FlowTrac/Vigileo™ monitor (3rd generation, Edwards Lifesciences). Measurements were performed prior to intervention, when patients presented with severe AS, after aortic valvuloplasty with consecutive relevant AI and after TAVI with normal aortic valve function.

Results

A relevant systematic error of the bias has not been found at any time. Limits of Agreement (LoA) up to ± 30 % have been widely advocated as clinical acceptable values for hemodynamic measurement methods (1). The precision was satisfying for SV_{TCPTD} (normal valve function: LoA: -13.1 - 17.3 %, AS: LoA: -28.3 - 18.2 %; AI: LoA: -23.8 - 29.3 %) and for SV_{PC CAL} in normal valve function (LoA: -15.3 - 19.5 %) and AS (LoA: -28.7 - 20.3 %) but poor for SV_{PC CAL} in relevant AI (LoA: -56.6 - 65.8 %) compared with SV_{TEE}. The values for SV_{PC UNCAL} were out of the ± 30 % range during all conditions (normal valve function: LoA: -41.94 - 50.80 %, AS: LoA: -64.41 - 41.92 %, AI: LoA: -72.47 - 51.06 %).

Conclusions

Regarding accuracy and precision TCPTD has to be classified as a valid method of SV measurement in both, severe AS and AI. Calibrated PC via a central pulse signal allowed accurate and precise measurement of SV in
patients with normal aortic valve function and severe AS but failed by incidence of acute relevant AI. Uncalibrated PC via a peripheral pressure signal did not provide reliable data on SV at any time during the TAVI intervention.

Disclosure

AEG and DAR are members of the Medical Advisory Board of Pulsion Medical Systems, DAR received honoraria for lectures from Edwards Lifesciences. The study was solely financed by institutional sources.

References

Continues cardiac output monitoring (CCO): Response time and detection rate of monitors based on arterial pulse contour analysis

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Objectives

The aspects time delay and responsiveness separates a CCO-monitoring system from an intermittent CO-measurement method. However, CCO-monitors have been validated like snapshot tools not taking the specific dynamic impact of time into consideration (1). CCO-monitors based on thermodilution via pulmonary artery catheter (PAC) detect hemodynamic events with a delay of approximately 5-15 minutes (2, 3). Equivalent specific characteristics have not been described for calibrated (CCO_{PC \_CAL}) or uncalibrated (CCO_{PC \_UNCAL}) monitoring systems based on arterial pulse contour analysis (PC) yet.

Methods

With local ethics committee approval thirteen patients undergoing Transcatheter Aortic Valve Implantation (TAVI) were included in this prospective study. Exclusion criteria were permanent arrhythmias, pacemaker dependency, intracardiac shunts and contraindications for catheterization of the brachial artery. During TAVI a rapid ventricular pacing maneuver (RP, 184-227/min) with a transvenous pacemaker is used to enable a balloon-valvuloplasty. CCO_{PC \_CAL} assessed by a central pulse signal via the brachial artery (PiCCOplus™, Pulsion Medical Systems) and CCO_{PC \_UNCAL} determined using a radial signal (3rd generation FlowTrac/Vigileo™, Edwards Lifesciences) were recorded simultaneous during 37 episodes (≥ 10 seconds) of RP. A minor event was predefined as a 15% and a major event as a 25% decrease of the baseline CCO. The response time (t_{RES}) specifies the delay until detection of these cut-off values.

Results

Artificial cardiac low output induced by RP had a mean duration of 17.4 ± 6.8 sec including a episode of valvuloplasty and was registered by the mean arterial pressure (MAP) in 100% / 86.5% (minor / major event) with a response time of 9.5 ± 3.2 / 13.6 ± 5.2 seconds (minor / major event). In the same setting the detection rate of CCO_{PC \_CAL} was 100% / 91.9% with a response time of 9.9 ± 4.8 / 12.8 ± 7.0 seconds. Moreover the detection rate of CCO_{PC \_UNCAL} was 59.5% / 40.5% with a response time of 31.3 ± 14.8 / 35.6 ± 13.7 seconds.

Conclusions

Early recognition of relevant hemodynamic changes directs skillful therapeutic strategies. Taking the parameters response time and detection rate for a specific characterisation, CCO_{PC \_CAL} performed with a higher responsiveness to hemodynamic events than CCO_{PC \_UNCAL}. Moreover CCO_{PC \_CAL} was close to real-time conditions. Thus PC is more likely to fulfill the criteria of a monitoring method than
the semicontinues CCO-measurement via PAC (2, 3). These results underline the high impact of time and responsiveness to characterise the quality of CCO monitoring.

Disclosure

AEG and DAR are members of the Medical Advisory Board of Pulsion Medical Systems, DAR received honoraria for lectures from Edwards Lifesciences. The study was solely financed by institutional sources.

References


Influence of *Bairhugger 750* and *Allon* patient warming systems on core temperature and extubation times in patients undergoing offpump cardiac surgical interventions

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**Aim**

Fast-track procedures are becoming more and more important, especially due to the implementation of the DRG system. At the Heart Center Leipzig a special fast-track concept has been established [1]. In this fast-track concept, normothermia of the patient at the end of the surgical intervention is of special importance [2]. The present study aimed at comparing two patient warming systems as to their characteristics of patients’ core temperature and extubation times: *Bairhugger*, an Arizant system which is based on warm air, and an *Allon* system based on circulating warm water.

**Material and methods**

Design: retrospective study approved by the ethics committee. During cardiac surgical interventions without cardiopulmonary bypass patients were warmed from start until end of surgery either via *Bairhugger 750 System* (full access underbody blanket model 63500) produced by Arizant or via *Allon 2001 System* (Thermowrap MTRE 3363) produced by MTRE Advanced Technologies Ltd. The study included all patients undergoing fast-track procedures from August to October 2011 who were transferred to the post-anesthesia care unit postoperatively. Each operating theatre had their fixed patient warming system (4 theatres with Allon and 5 theatres with Bairhugger). The course of the core temperature, temperatures at start and end of surgery as well as extubation times were compared with single factor analysis of variance and examined by t-test for unrelated samples (one-sided, P < 0,05 significant).

**Results**

A total of 61 patients were included, with male preponderance. The groups did not differ as to sex and age. Core temperature of both groups did not vary significantly at the beginning (Allon 36,34 ± 0,505°C and Bairhugger 36,00 ± 0,468°C) and at the end of surgery (Allon 36,46 ± 0,46°C and Bairhugger 35,88 ± 0,57°C). Course of mean core temperature was significantly different between the Allon System 36,3 ± 0,45°C (n = 32) and the Bairhugger System 35,96 ± 0,55°C (n = 29) (p < 0,05; Fig.1). Extubation times (Fig. 2) did not show any significant differences: 3:08 ± 1:57h with Allon System and 3:56 ± 3:27h with Bairhugger System.

*Figure 1: Course of temperature*
Conclusions

The Allon System was capable to maintain the patient in a normotherm condition during the entire surgical procedure, whereas temperatures of Bairhugger-warmed patients dropped at the beginning (Fig. 1). This did not have any impact on extubation times as the Bairhugger patients also reached normothermia at the end of surgery.

References

eNOS mediates the first window of desflurane-induced preconditioning against myocardial infarction, whereas iNOS mediated the second window

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Aim

Nitric oxid synthases (NOS) are involved in the first window of desflurane-induced preconditioning (FWOP) against myocardial infarction (1). The role of the NOS isoforms for both windows of APC (=anesthetic-induced preconditioning) is ambiguous. We have tested the hypothesis that endothelial NOS (eNOS) mediates the first, whereas inducible NOS (iNOS) mediates the second (SWOP) window of APC.

Methods

Approval of the responsible animal protection authorities has been obtained. Male C57BL/6 mice, age: 8-12 weeks (wt, n=61), eNOS gene deleted (2) (eNOS+/−, n=21) and iNOS-gene deleted (3) (iNOS−/−, n=21) mice were randomised into 6 and 9 groups resp for the two trials. All animals were anesthetized with pentobarbital, endotracheally intubated, mechanically ventilated and equipped with instruments for measuring heart frequency and mean arterial blood pressure. Upon left lateral thoracotomy in the 4th ICR, proximal ligation of the LAD was performed. After 15 minutes of equilibration baseline values were measured. All animals had to undergo 45 minutes of coronary artery occlusion (CAO) and 3 hours of reperfusion. In order to characterize the SOWP (trial I) a 15-min. 1,0 MAC desflurane application was scheduled in the wt animals 30min, 12h, 24h, 48 h or 96 h before starting CAO.

In trial II, wt, eNOS+/− and iNOS−/− animals were administered 15 min. 1,0 MAC desflurane either 30min (FWOP) or 48h (SWOP) before starting CAO. The animals of the respective control group did not receive any further treatment before starting CAO. Size of myocardial infarction (IS=infarction area/ischemia area) was determined gravito-planimetrically after staining with evans blue and triphenyl tetrazolium chloride. Statistical analysis was performed by means of ANOVA and posthoc Duncan test, data are presented as means ± SEM, *p<0,05.

Results

Hemodynamic parameters after equilibration and ischemia area did not differ between the groups. In the control group I of wt animals, IS amounted to 48±6% and was significantly reduced (*p<0,05) when desflurane was applied 30min (9±2%*) or 48h (14±3%*) before starting CAO. In wt animals, application of desflurane 12h (42±8%), 24h (36±7%) or 96h (37±11%) before starting CAO did not result in any significant reduction of IS. There was no difference in IS between the eNOS−/− (52±5%) and iNOS−/− (46±4%) control groups and the wt control group II (50±4%). IS was significantly reduced when desflurane was applied in wt animals 30min (10±2%*) or 48h (16±3%*) before starting CAO, and in eNOS−/− animals 48h (21±5%*) and in iNOS−/− animals 30min (13±2%*) before starting CAO. Application of desflurane 30min before starting CAO in eNOS−/− animals
and 48h before starting CAO in iNOS−/− animals (48±8%) did not yield any significant reduction of IS in comparison to their respective control groups (see fig. 1).

Interpretation

The presented research is the first study to characterize the second window of APC in a murine model of acute myocardial infarction. This second window has been demonstrated 48h after preconditioning, but it could not be shown after 12h, 24h and 96h. The first window of APC was suppressed in eNOS gene deleted animals, but not in iNOS gene deleted animals, the second window of APC, however, was suppressed in iNOS gene deleted animals, but not in eNOS gene deleted animals. eNOS thus seems to play an important role in mediating the first, but not the second window of APC, whereas iNOS is necessary for mediating the second, but not the first window of APC.

References

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Case report series: Anaesthesiological management of four patients with left-ventricular assist device (LVAD) and non-cardiac surgery procedures


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Background

Due to an improved survival rate with second generation left-ventricular assist devices (LVAD) an increasing number of patients chronically treated with a LVAD needs to be treated for non-cardiac surgery. No guidelines for the perioperative anaesthesiological management of LVAD patients undergoing non-cardiac surgery procedures are available.

Here we present our anaesthesiological management of four LVAD patients undergoing non-cardiac surgery. All patients were supported by a Heart Mate II (Thoratec, Pleasanton, USA) for ischemic cardiomyopathy with severely depressed left ventricular ejection fraction.

Case 1

A 74-year old male patient was scheduled for emergency abdominal surgery for sigmoid colonic perforation. He received an open, discontinuous resection of the sigmoid colon (“Hartmann” procedure). During induction of general anaesthesia a short episode of severe bradycardia was encountered and successfully treated with epinephrine. Thereafter the patient was hemodynamically stable during moderate inotropic support. Endotracheal extubation of the patient was accomplished shortly after surgery. The patient was treated for two days on the intensive care unit (ICU).

Case 2

A 58-year old male patient was scheduled for an atypical resection of the left lung for pulmonary bleeding due to an overdose of phenprocoumon. A double lumen tube was inserted to facilitate one-lung ventilation. Hemodynamic monitoring was accomplished using a pulmonary artery catheter for continuous monitoring of pulmonary artery pressures, mixed venous oxygen saturation and cardiac index. The perioperative period was uneventful. The patient was extubated on the first post-operative day and discharged from ICU 4 days after surgery.

Case 3

Another 58 years-old male patient with a foreign body in his left lung was scheduled for atypical lung resection. As in case 2, a double lumen tube was inserted for one-lung ventilation. We also used a Swan-Ganz catheter in this case. Hemodynamic support by norepinephrine and dobutamine was necessary. The patient was transferred to the ICU with stable hemodynamic parameters, extubation was performed on the second post-operative day. Discharge to the normal ward was achieved five days after surgery.

Case 4

The fourth patient was a 68-years old male. He had a femur fracture and needed osteosynthetic stabilisation. Moderate doses of
dobutamine were required for hemodynamic support during anesthesia. The surgical procedure was uneventful. Endotracheal extubation was performed immediately after surgery and the patient was discharged to the normal ward thereafter.

**Anaesthesiological management**

All surgical procedures were performed during general anaesthesia. Perioperative prophylaxis with antibiotics was performed according to the recent guidelines of the ACA/AHA (2). In addition to the standard monitoring, arterial blood pressure and central venous pressure were monitored continuously and cerebral oxygen saturation (ScO2) by near infrared spectroscopy (NIRS) was used. Additionally, transesophageal echocardiography was performed in all patients.

**Conclusion**

Since an increasing number of patients is treated with a LVAD for “destination therapy”, many of these patients will also need non-cardiac surgical procedures and will sometimes be treated by anaesthesiologists without specific training in cardiac surgery.

We hereby suggest to monitor patients with LVAD undergoing non-cardiac surgery procedures with advanced hemodynamic monitoring, at least TEE. However, for successful treatment of these patients, special knowledge and skills are required that may ideally be acquired in centers implanting LVADs and permanently treating patients with this technology.

**References**

Feasibility and hemodynamic effects of xenon anesthesia compared to sevoflurane anesthesia in cardiac surgical patients – A randomized controlled pilot study

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Background

To date, only limited data exist about the performance of xenon as anesthetic agent in patients undergoing cardiac surgery. The favorable neuro- and cardioprotective properties of xenon could hypothetically attenuate postoperative complications and improve postoperative outcome. Therefore, we investigated the feasibility of general anesthesia in patients undergoing cardiac surgery. Furthermore, we evaluated the effects of xenon on intraoperative hemodynamics in comparison to patients with general anesthesia with sevoflurane.

Methods

Thirty patients undergoing elective cardiac surgery with the use of extracorporeal circulation were enrolled in this randomized, controlled, double-blind study (ClinicalTrials.gov: NCT01285271). After tracheal intubation, patients were randomly allocated to receive balanced general anesthesia with equipotent concentrations of either xenon (45-50 vol% MAC) or sevoflurane (1-1.4 vol% MAC). During anesthesia, BIS values were recorded for the assessment of hypnotic depth. At predefined time points, systemic and pulmonary hemodynamics were assessed by advanced hemodynamic monitoring including the use of a pulmonary artery catheter: tp1: after induction of anesthesia, tp2: after sternotomy, tp3: after weaning from cardiopulmonary bypass, tp4: after chest closure. Groups were statistically compared using the Mann-Whitney U test.

Results

Patients’ characteristics with respect to gender, age and weight did not differ between the groups. Throughout performance of anesthesia, patients in the xenon group did not show any adverse events or complications. The recorded BIS values were comparable between the two groups throughout anesthesia.

The comparison of hemodynamics between the groups showed higher values for cardiac output at tp₂, tp₃ and tp₄. Stroke volume increased intraoperatively and was significantly higher in the xenon group at tp₂ and tp₃. Pulmonary capillary wedge pressure was significantly higher in the sevoflurane group at tp₂ but did not differ between the groups throughout the further course [Fig 1-3] (see next page).

Conclusions

Xenon anesthesia is safe and feasible in patients undergoing cardiac surgery. Patients undergoing balanced anesthesia with xenon showed more favorable hemodynamics than patients receiving sevoflurane anesthesia.
Activation and nuclear translocation of transcription factor STAT3 mediate the second window of desflurane induced preconditioning against myocardial infarction

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Aim

„Signal Transducer and Activator of Transcription“ (STAT) 3 transcription factor mediates the second window of ischemic preconditioning, mainly through increase of transcription of cardioprotective proteins (1). In the cardiomyocyte, Pim-1 kinase exhibits an infarction size reducing activity (2) and is regulated via STAT3 (3). In the present study we have tested the hypothesis that the second window of desflurane-induced preconditioning (DES-SWOP) is mediated via STAT3 and Pim-1 kinase.

Methods

After approval of the relevant authorities, male C57BL/6 mice were anesthetized with pentobarbital, mechanically ventilated and equipped with instruments for measuring hemodynamic parameters. Upon left lateral thoracotomy LAD was entangled. In all animals 45 minutes of coronary artery occlusion (CAO) was performed which was followed by 3 hours of reperfusion. Control group animals did not receive any further intervention. SWOP was induced by 15 minutes of desflurane administration (1 MAC, 7.5 Vol-%) 48 hours prior to CAO (DES+48h). Desflurane was administered alone or in combination with the janus kinase (JAK)/STAT3-inhibitor AG490 (40 µg/g i.p.). Pim-1 kinase inhibitor II (PIM-Inh.II, 10 µg/g i.p.) was applied prior to CAO (PIM-Pre) either alone or in combination with desflurane (DES+48h+PIM-Pre). Infarction size (IS) and area at risk (AAR) were determined gravito-planimetrically. Additional experiments were performed to separate cytosolic and nuclear cell fractions; protein expression of STAT3 as well as activated phospho-STAT3Ser727 and phospho-STAT3Tyr705 were determined by means of Western-Immunoblot. Statistical analysis was performed with one-way and two-way ANOVA, respectively, and with posthoc Duncan test; data are presented as means ±SEM, p<0.05.

Results

IS was 47±2% in the control group (CON; n=7-8 per group). Desflurane was able to reduce IS to 23±4%* (*p<0.05 vs. CON). JAK/STAT3 inhibition via AG-490 did not have any influence on IS (44±7%), however, it completely suppressed DES-SWOP (44±4%). Inhibition of Pim-1 kinase did not inhibit protection through DES-SWOP (DES+48h+PIM-Pre: 34±4%*). Desfluran application led to reduced expression of phospho-STAT3Ser727 in the cytosolic fraction in association with an increased expression in the nuclear cell fraction.

Interpretation

These results point to the important role of activation and nuclear translocation of the transcription factor STAT3 in the context of DES-SWOP. However, unequivocal assessment of the importance of Pim-1 kinase for DES-SWOP is not possible.
References


β-adrenoceptor expression in an experimental model of cardiac insufficiency induced by aortocaval infrarenal shunt

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Aim

In this experimental model induced by aortocaval infrarenal shunt, chronic volume overload is leading to cardiac insufficiency and pulmonary congestion. However, there is still no consistency as to the expression of myocardial β1, β2 and β3 adrenoceptors (AR) in cardiac insufficiency. As a consequence, this experimental model was designed to identify specific adaptations in the expression of cardiac β3 AR as well as structural alterations in the subcellular myocardial structure.

Methods

In line with the relevant animal protection act, an aortocaval infrarenal shunt was placed in male Wistar rats using needle pucture technique (16G). After 28 ± 2 days hemodynamic characterization of the animals was performed through intraventricular pressure-volume catheter. Adaptive alterations in cardiac expression of β1, β2 and β3 AR mRNA were determined by PT PCR. Electron microscopic examination was used to detect compensatory subcellular modification processes of cardiac tissues.

Results

In animals with shunt there was a significant increase in cardiac index (3,84 ± 0,07 vs. 6,48 ± 0,22 mg/g BW) and in lung index (3,75 ± 0,14 vs. 6,75 ± 0,44 mg/g BW) accompanied by significantly increased right- and left ventricular filling pressures. LVEF (71,9 ± 2,2 vs. 39,8 ± 5,0 %) and maximum speed of increase in pressure were both significantly reduced. Furthermore, diastolic function was impaired as measured by lower maximum speed of decrease in pressure during relaxation and prolonged Tau value. Due to congestive heart failure β1 and β2 mRNA were down-regulated, whereas β3 mRNA was up-regulated in the left ventricle. A significant correlation has been shown between the respective β mRNA expression and decrease in LVEF (β1: r = 0,598; β2: r = 0,577; β3: r = -0,695). Electron microscopic examination yielded subcellular signs of cell nucleus fragmentation, mitochondrial swelling, loss of cell-cell contacts and evidence of phagocytic immune cells.

Conclusion

In the experimental model of aortocaval infrarenal shunt with subsequent decompen-sated congestive heart failure a significant impairment of systolic and diastolic function has been shown. This functional impairment was associated with down-regulation of β1 and β2 receptor and up-regulation of β3 receptor at ventricular level as well as with concomi-tant subcellular signs of myocardial degrada-tion.
Activation of cardiac delta opioid system during progression of congestive heart failure

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Aim

Despite increasing scientific interest in the protective function of the cardiac opioid system, there has still been no research focusing on the role of the cardiac opioid system in congestive heart failure. As a consequence, this experimental model of cardiac insufficiency aims at exploring adaptive modifications of the cardiac delta opioid receptor (DOR) and of the corresponding endogenous opioid peptide (PENK).

Methods

In line with the relevant animal protection act, congestive heart failure was induced in male Wistar rats by placing an aortocaval shunt using needle puncture technique (16G). After 28 ± 2 days hemodynamic characterization of the animals was performed through intraventricular pressure-volume catheter. Adaptive alterations of DOR and PENK were determined by RT PCR and Western blot in the left ventricle (LV) and in the atrium (LA). Anatomic localization of delta opioid receptors was intended to be identified by immunofluorescence microscopy.

Results

In animals with shunt there was a significant increase in cardiac index (3.84 ± 0.07 vs. 6.48 ± 0.22 mg/g BW) and in lung index (3.75 ± 0.14 vs. 6.75 ± 0.44 mg/g BW) accompanied by significantly increased right- and left ventricular filling pressures. Systolic function (LVEF: 71.9 ± 2.2 vs. 39.8 ± 5.0 %) and diastolic function were significantly reduced. Preliminary data have shown up-regulation of DOR mRNA in LA and LV as well as up-regulation of DOR in LV at protein level due to the congestive heart failure. A significant correlation has been observed between the increased DOR mRNA expression in LV and decrease in LVEF (r = -0.953, p < 0.01). Analogous to these findings, expression of PENK mRNA in the LV was significantly increased. Confocal immunofluorescence microscopy was able to identify anatomic localization of DOR immunoreactivity in the LV.

Conclusion

In the experimental model of aortocaval infrarenal shunt with subsequent decompensated congestive heart failure a significant impairment of systolic and diastolic function has been shown. This functional impairment was associated with up-regulation of DOR in the LV, on the level of both mRNA and proteins. Furthermore, expression of the endogenous delta opioid peptide PENK was increased in the LV. These preliminary results suggest activation of the cardiac opioid system in congestive heart failure.
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