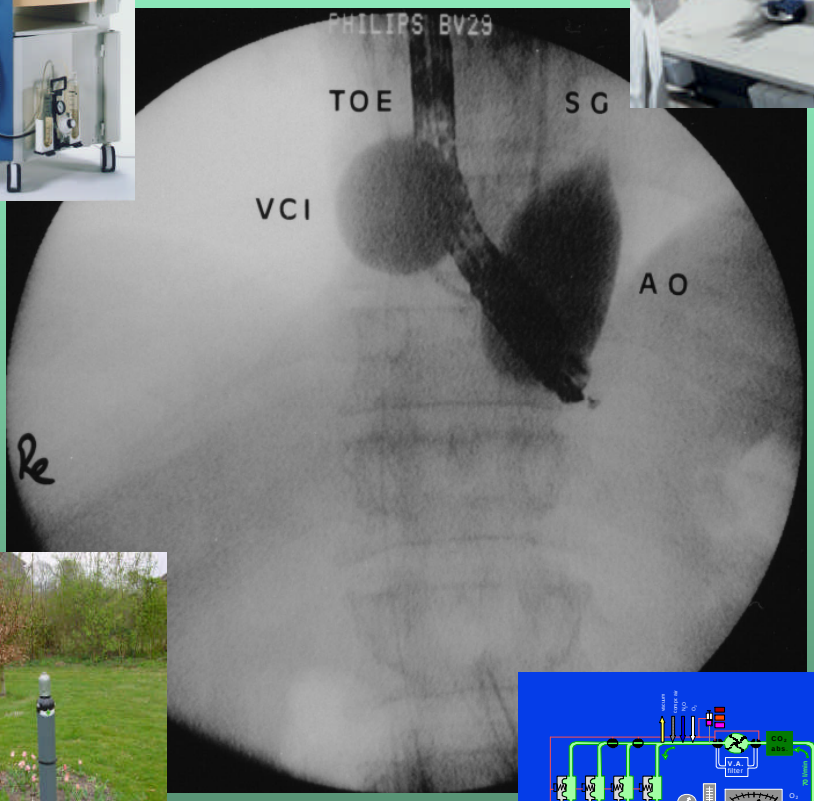
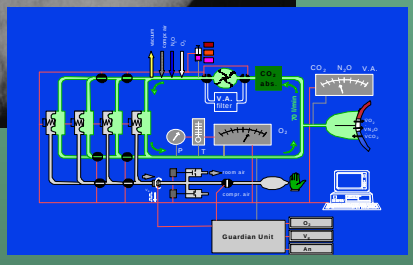
Anaesthetic Aspects of Simultaneous Aortocaval Occlusion





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ANAESTHETIC ASPECTS OF SIMULTANEOUS AORTOCAVAL OCCLUSION

ANESTHESIOLOGISCHE ASPECTEN VAN SIMULTANE AORTOCAVALE OCCLUSIE

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus

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Alle vorsten moeten zich gezamenlijk inspannen
om oorlogen niet te laten plaatsvinden in plaats van ze te winnen,
om legers overbodig te maken in plaats van ze op de been te brengen,
en allen moeten proberen hun grootheid te ontlenen aan hun vredesinspanningen,
die gedragen worden door wijs beleid en geesteskracht.

(Brief van Erasmus van Rotterdam aan de hertogen Frederik en Georg van Saksen, Antwerpen, 5 juni 1517)

Aan Eline en Rik

Contents

PREFACE

Saturday 22 July 2000.
Chicago, ANP.
"Scientists have shown the existence of the last sub-atomic particle that was not proved yet, the tau-neutrino. They announced this yesterday. The particle itself cannot be seen. Shooting the tau-neutrino on a nuclear centre is the only way to proof its existence. The tau-neutrino then turns into a tau-lepton particle." [1]

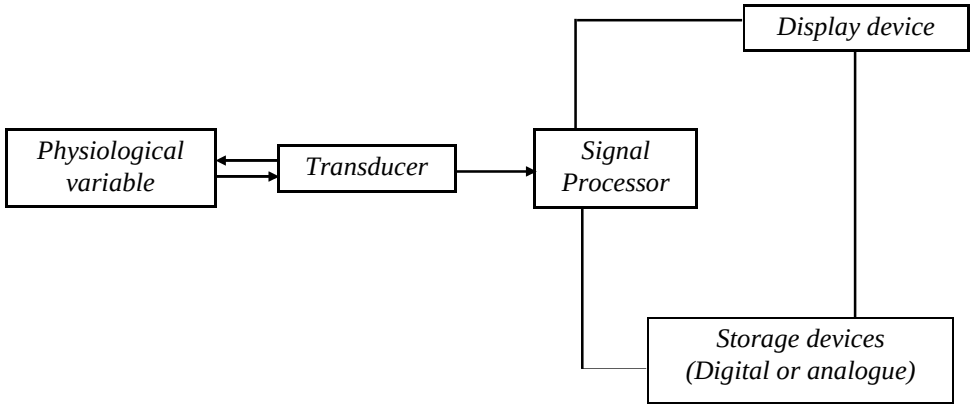
Monitoring; some aspects

Patient monitoring has been a key aspect of anaesthesiology since its beginning as a medical specialty. As the specialty has grown more sophisticated and complex, so have the measurement devices and the data they present. Anaesthesiologists must be able to understand and interpret the data from their measurement devices and also to anticipate and recognize errors associated with their use. They cannot accomplish this without understanding how these devices work [2].

Figure 1 shows a schematic representation of a measurement process. At first an interaction between a physiological variable and a transducer is shown. It must be realised that choosing a particular measurement device may induce data reduction by its own. The physicist Heisenberg said: "What we observe is not nature itself, but nature that is subjected by our way of observation" [3]. Measuring interferes with the isolated development of the observed system [4]. If we disturb this isolated development, we in fact make a subject of one of the possibilities that were part of the observed system when it was still in isolation. This is known as the "*wave function collapse*".

A second element of the monitoring process, only implicitly shown in Figure 1, is the time elapsed before storage or display of data occurred. This elapsed time become important when we want to analyse data that are collected by two different measurement devices. Synchronisation of the devices for time is then essential and the 'time unit' must therefore be equally defined. Time, however, is a remarkable variable, without a good definition; "We still cannot say what time is; we cannot agree whether there is one time or many times, cannot even agree whether time is an essential ingredient of the universe or whether it is the grand illusion of the human intellect." Davis and Hersh said [5]. Time synchronisation in the world community has yet to be established. Calendars are for instance still different between different cultural communities. Time synchronisation in our community has only recently been established. Large Dutch cities had their own different 'clock time', based on 'local sunrise', during the entire nineteenth and part of the twentieth century. Thus, clock time at Arnhem was 10 min later then clock time at The Hague.

Figure 1: *Schematic representation of a measurement process*



Therefore, making a national time schedule for a train service was therefore hardly possible. It was not until 1956, that the Dutch government decided to introduce 'Middle European Time' as 'the standard time' to be used in the Netherlands [6].

A third element of the monitoring process already mentioned above is the necessity that the observer understands the variation of the physiological variable that is displayed by his monitoring device [2]. Knowledge of the physiological system itself by the observer is therefore essential. Although humanity is blessed that anaesthesia can safely be induced by anaesthesiologists, the far bigger blessing of understanding the mechanism, has yet not come for granted [7]. The absence of knowledge about 'how the anaesthetics work' has implications for e.g. monitoring the depth of anaesthesia. Bispectral index (BIS) and spectral edge frequency (SEF) are nowadays used to measure depth of anaesthesia and sedation [8]. Although BIS and SEF decreases with increasing sleep depth, the distribution of values at each sleep depth was shown considerable, with overlap between each sleep stage [8]. The response of BIS was slow and patients could arouse with low BIS values, which then took some time to increase [8]. Furthermore, inhalation of 70% nitrous oxide induces loss of responsiveness to voice commands, but BIS does not change [9]. BIS also does not predict responsiveness to verbal commands in patients emerging from xenon anaesthesia [10]. It must therefore be concluded, that the BIS

concept cannot be used for monitoring depth of anaesthesia regardless the kind of anaesthetics that is used.

If we want to improve this monitoring tool, the site of action of anaesthetics must be elucidated. It is, however, not obvious how this type of research will proceed today [11]. Historical analysis of published reports seems to reveal that the search for the mechanism of anaesthetics is going to descend to the smallest elements of nature [12-15]. The lipid bilayer theory has already been replaced by the theory of actions on proteins [12]. However, it is not clear why some proteins are sensitive to anaesthetics whereas others are not [12]. One theory postulates that coordination of functional protein conformational changes (ion channel conductance, receptor activation, cytoskeletal function etc.) depends on electron mobility and coherent dipole oscillation within protein hydrophobic regions [13]. It was shown that potent anaesthetics are indeed able to inhibit electron mobility, perhaps by "van der Waals" interaction between the mobile electrons and the electron clouds of anaesthetic molecules [14]. This has led to a "two part unitary quantum hypothesis" suggesting that:

1) Consciousness depends on quantum states in hydrophobic pockets of certain brain proteins,
2) Anaesthetics act by preventing quantum states in these hydrophobic pockets [15].

If this hypothesis can be confirmed, it may perhaps explain why very different entities like nitrous oxide, ether derivates, propofol, xenon and electric current can all induce unconsciousness. If the quantum theory indeed can explain how anaesthetics work, perhaps necessarily even considering effects playing a role on a subatomic level, then it may be hard to develop a generally usable monitoring system for monitoring depth of anaesthesia regardless the kind of anaesthetics being used, because in such a system the time, mass, energy relationship, as considered by the "uncertainty principle of Heisenberg" may raise considerable problems in the development of it. When, however, we are able to understand the mechanism of action of anaesthetics, the whole monitoring process will become more physiological based rather than empirical based as it is at present, which will improve the monitoring process anyhow.

A fourth relevant element of the monitoring process is that the observer is aware of "the human factors error". The operating room, the recovery room and the Intensive Care Unit are cognitive complex environments where the number of pieces of information required by an operator to make a correct decision often ex-

ceed the five that can be held in conscious working memory simultaneously [16]. Triggering of critical incidents in these environments is dominated by human factors errors, defined as incorrect actions performed by the operators [16]. In anaesthesia the number of displays, alarms or waveforms on a top-of-the range monitor has increased from 4 in 1970 to 23 in 2000 [17]. All these features compete for attention along with clinical signs from the patient and thus are significant contributors to the overall cognitive load of the observer.

The reduction in human factors error incidence is known to be dependent on the design of the equipment [16]. Studies that have attempted to evaluate monitors are, however, often found to be inadequate. Four items are thought to be responsible: (1) rarely, there is a clear definition of the clinical issue that is studied which often results in a lack of specific measurable outcome, (2) the large number of patients necessary to detect clinically significant improvement in morbidity associated with rare critical incidents prevent the performance of randomised controlled trials, (3) the use of more frequently occurring intermediate outcomes, often have little direct relationship to true outcomes, and (4) finally, the lead-time provided by the introduced monitors may not necessarily result in an improved outcome as it may be insufficient to allow corrective behaviour, or as there may be no corrective behaviour be applicable [18]. The result is that there are only a few examples of systematic effectiveness measurement in literature [16]. A template to assess anaesthesia technology consists therefore, (1) basic science of the technology, (2) site and indications for use, (3) efficacy, and (4) effectiveness [18]. Better psychological understanding of the causes of human factors error must, furthermore, guide better human factors engineering [16]. So, patient monitor designers are thus obliged to make an important contribution to improve the safety of the monitored patient [16].

This thesis will present a lot of results based on monitoring processes. Therefore, the aspects that I mentioned above must be remembered when limitations of results are being considered.

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INTRODUCTION

CHAPTER 1

ASPECTS OF SIMULTANEOUS AORTOCAVAL OCCLUSION

Aspects of Aortic Cross-Clamping

Major elective surgery is known to contribute to intensive care occupancy, with a significant mortality rate [1, 2]. Routine preoperative optimisation of patients undergoing major elective surgery is found to give a significant and cost effective improvement in perioperative care [3]. Criteria that were used to select patients for routine preoperative optimisation for a large randomised controlled trial are shown at Table 1 [3]. When performing major surgery, the extent of necessary perioperative monitoring is usually dependent on the view of the anaesthetist, while the site of postoperative care is dependent on the anticipated development of complications and the availability of intensive care or high dependency beds [3].

Surgical view of single aortic cross clamping

Single aortic cross-clamping, thus considered to be a major surgical intervention, is most often performed for the treatment of abdominal or thoraco-abdominal aneurysm or of peripheral vascular disease that is complicated by ischaemia of the lower extremities, kidneys, or intestines [4]. Although endovascular stent-graft placement has been developed for the treatment of aortic aneurysm as a less invasive alternative to open surgery with a success rate of about 85%, unfortunately, most patients are no candidates because of insufficient normal proximal and distal aorta to engage the attachment systems [5-8]. Furthermore, beyond operative and postoperative complications like failure of the attachment system and persistent leaks with expansion of the aneurysm, renal dysfunction and intestinal infarction

Table 1: *Admission criteria for patients undergoing routine preoperative optimisation before major elective surgery, adapted from Wilson, et al. [3]*

Surgical admission criteria	**Medical criteria**
- Repair of aortic or common iliac aneurysm	- Ischaemic heart disease
- Planned resection of upper gastrointestinal malignancy	- Myocardial infarction in past 5 years
- Anterior resection	- Congestive cardiac failure
- Cystectomy	- Cerebrovascular disease
	- Hypertension
	- Peripheral vascular disease
	- Obstructive airway disease
	- Pulmonary embolus
	- Chronic renal insufficiency
	- Diabetes mellitus with end organ damage
	- Long term systemic steroid therapy

Table 2: *Risk factors for major vascular surgery*

Clinical assessment	**Laboratory investigations**	**Procedure related factors**
- Previous myocardial infarction	- Abnormal ECG	- Type of operation itself
- Angina pectoris	- Abnormal dipyridamole-thallium myocardial perfusion imaging	- Intraoperative hypotension or shock
- Silent myocardial ischaemia	- Radionuclide ejection fraction <0.35	- Intraoperative myocardial ischaemia
- Congestive heart failure	- Elevated serum creatinine	- Oliguric/anuric renal insufficiency
- Age > 70 years	- Abnormal dobutamine atropine stress echocardiography [9]	
- Significant aortic valvular stenosis		
- Cardiac arrhythmias		
- Renal insufficiency or failure		
- Pulmonary insufficiency		
- Diabetes mellitus		

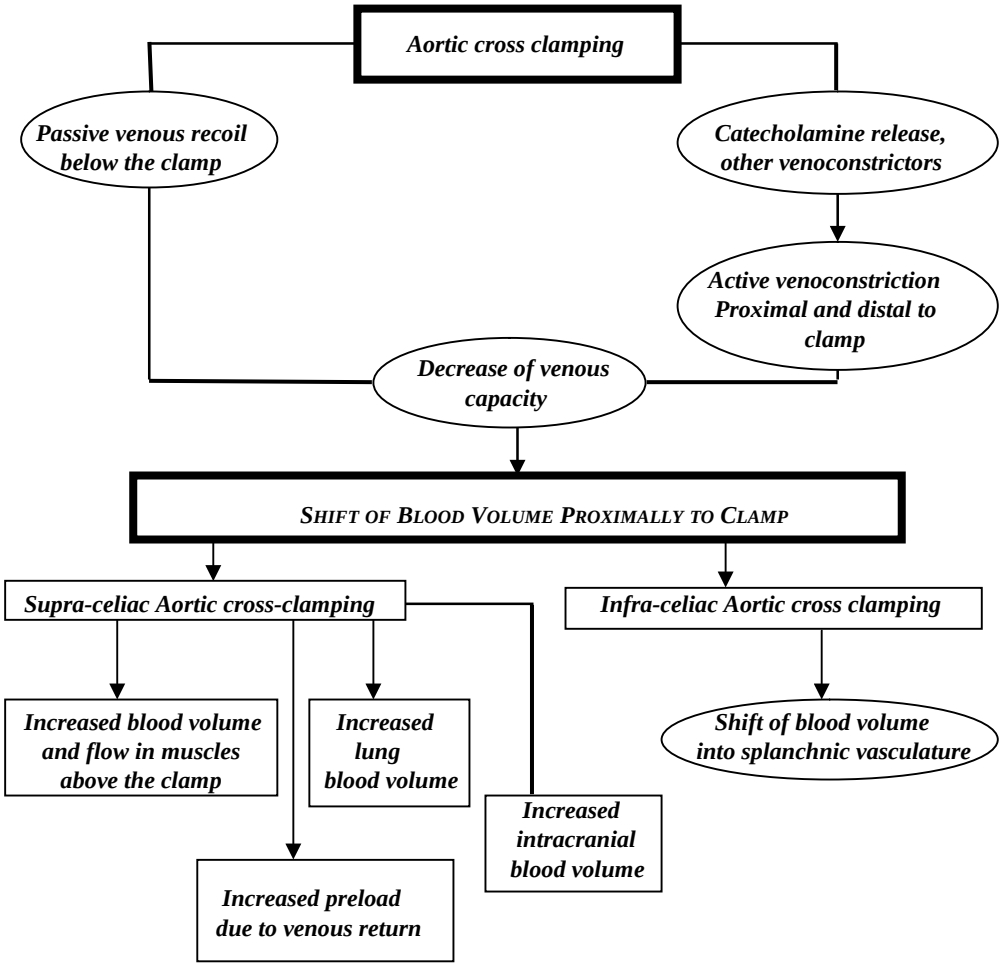
can be induced due to nephrotoxicicty of the contrast medium used for fluoroscopic monitoring and exclusion of inferior mesenteric and hypogastric arteries from the circulation by the graft, respectively [8]. Therefore, the open procedure remains very useful and most often performed. To evaluate the open surgical procedure for the Netherlands, a Dutch surgical retrospective single-centre study reported an analysis of 88 consecutive patients undergoing a thoraco-abdominal aortic aneurysm repair by single aortic cross clamping [10]. The authors described a hospital mortality rate of 11.4% for all patients, being 7% for elective cases [10]. The incidence of postoperative spinal cord injury was 13.8% and of postoperative renal failure requiring renal replacement therapy, 14.1% [10]. The surgeons concluded that thoraco-abdominal aortic aneurysm repair could thus be performed with an acceptable early mortality and with a significant improvement of the long-term survival compared with the natural course of the disease [11].

Anaesthetic considerations of aortic occlusion

In anaesthetic literature this high complication rate that is partly due to pathophysiological disturbances that occur due to cross-clamping and unclamping of the aorta is, however, thought to be discouraging [4]. To lower this complication rate, anaesthetists therefore usually starts immediately with the identification and if possible favourable modification of pre-existing conditions that are associated with an

adverse outcome (Table 2) [12]. Alas, there is no single peroperative anaesthetic management technique that is ideal for all patients undergoing abdominal aortic surgery [12]. Therefore, a variety of techniques have been tried, like neurolept-anaesthesia [13], opiod-oxygen anaesthesia [14-16], opiod-based anaesthesia

Figure 1: *Blood volume redistribution during aortic cross clamping, adapted from Gelman [4]*



supplemented with nitrous oxide and/or a volatile anaesthetic agent [16, 17], epidural anaesthesia alone [18, 19], and combinations of epidural and general anaesthesia [20-26]. Nevertheless, for any particular patient one anaesthetic technique may be more advantageous than another [12]. Therefore, the formulation of an appropriate anaesthetic plan requires expertise with a variety of these techniques [12]. Furthermore, to provide a basis for rational therapy, in order to decrease the complication rate and improve the outcome, a clear understanding of the pathophysiological derangements occurring during aortic cross clamping and unclamping is essential [4]. Clinical assessment of patients undergoing thoracic and supraceliac aortic cross clamping has, however, not uniformly confirmed the results of animal experiments [27]. A majority of clinical studies for instance, demonstrated a decreased cardiac output, whereas animal studies showed an increased blood flow through the proximal part of the body without a significant change in cardiac output during single cross-clamping of the thoracic aorta [28-33]. The main reasons for inconsistent and contradictory observations is thought to be the difference in degree of changes in pre-load, after-load, blood volume redistribution, coronary blood flow and myocardial contractility [4]. From these factors, the blood volume redistribution induced by the aortic cross clamping seems to play a key role (Fig. 1). Most therapeutic approaches that intend to decrease the harmful effect of aortic cross-clamping are therefore based on their possibility to influence this volume redistribution, e.g. normalisation of pre-load by using appropriate fluid load, use of vasodilators [4], or manipulation of the applied positive end-expiratory pressure (PEEP) level [34].

Another way to decrease the blood volume redistribution with its concomitant induction of arterial hypertension during performance of supra-celiac aortic cross-clamping is a blockade of the inferior vena cava flow above the level of the venae hepaticae as was successfully done in animals [32, 33, 35]. Results from studies performed in humans during simultaneous aortocaval occlusion are, however, conflicting. While Nishikimi and colleagues reported a successful attempt to control blood pressure by almost complete venous return occlusion by using two occlusion balloon catheters placed in the inferior and superior vena cava during transluminally placed endovascular grafts [36], Berkenstadt and colleagues have found similar cardiovascular effects during simultaneous aortocaval occlusion as are seen during single thoracic aorta cross-clamping when they performed abdominal isolation perfusion procedures in an attempt to treat abdominal malignancies [37].

Post-operative care after single-aortic cross clamping

Intensive Care Units (ICU's) are a place for monitoring and care of patients with potentially severe physiological instability requiring technical and/or artificial life support with recognition of the autonomy of the patient [38]. Guidelines for intensive care unit admission, discharge, and triage are recently re-established [38]. In general, ICU admission criteria should select patients who are likely to benefit from ICU care [39]. Specific criteria defining "substantial benefit" are, however, subject to interpretation [38]. Therefore, it is recommended that intensivists understand tools for assessing severity of illness and prognosis of critically ill patients [38]. It should be noted, however, that in general predictive instruments have only been applied to patients who have already been admitted to an ICU and have not been tested as *pre*-admission screening tools [38].

Usually, patients admitted for abdominal aortic surgery are "routinely" admitted to an ICU because of the expected high postoperative morbidity and mortality [40]. The influence on the incidence of postoperative complications in such patients when there is or is no daily support of an intensivist has been reported by Pronovost and colleagues (Table 3) [40]. They achieved a 3-fold reduction of in-hospital mortality in their patient groups by only introducing daily rounds by an ICU physician [40]. No randomised controlled trials that describe essentials for post-operative care and/or the level of necessary care that should be provided after performing single-aortic cross clamping in patients are, however, yet available. A search performed in December 2002 in the database of the National Library of Medicine[*], using the search terms: "PACU and aortic cross clamping", "ICU and aortic cross clamping", or "Care after aortic cross-clamping", revealed no hits addressing this subject. With the recent introduction of endovascular abdominal aortic aneurysm repair, a policy of selective utilisation of the ICU after elective infrarenal aortic aneurysm repair was also found to be safe, with a concomitant reduction of resource use and without a negative impact on the quality of care [41]. It may thus be expected that the criteria for admission of post-operative patients after abdominal aortic cross clamping at an ICU will be largely influenced by local policies that are specific for that particular unit. This situation is recommended in the Guidelines for ICU admission [38].

[*] *(http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=PubMed)*

Aspects of Isolation Perfusion

For most anti-neoplastic agents, first order dose-response curves are demonstrated [42]. Extensive side effects produced by the actions of chemotherapeutic drugs on non-neoplastic cells have resulted in efforts to develop procedures for targeting these drugs to tumour cells with the idea to maximise the exposure of tumour cells to the chemotherapeutic drugs while minimising the exposure to non-neoplastic cells. Therefore, encapsulation of drugs in liposome's, conjugation with monoclonal antibodies for targeting to tumour cell surface and regional infusions via intra-arterial channels or into the peritoneal cavity are tried [42]. The most effective targeting of the chemotherapeutic drugs, considering regional chemotherapy, is possible when complete vascular isolation of a region can be obtained, as is in isolated limb and isolated liver perfusion [43-48].

History of Isolation Perfusion

Vascular isolation followed by regional perfusion using an extra-corporeal perfusion circuit was for the first time applied by Creech and colleagues in the 1950s for patients with high-grade non-resectable extremity sarcoma or in-transit melanoma [49]. In the early 1960s additional experience with perfusion of limbs and liver were reported by a small number of centres [50-53]. Nowadays, isolation perfusion of limbs and liver are commonly performed procedures in regular cancer management [54]. Although, isolation perfusion has also been used for the treatment of other organs like lungs [55-57], kidney [58] and pancreas [59], only few data addressing the application of this perfusion technique to these organs are available [54].

Synergistic anti-tumour effects in treatment of pancreatic cancer

Several physical and biochemical methods are known to further improve the effectiveness of chemotherapeutic drugs. Isolated limb perfusion for instance, is more effective when hyperthermic conditions are applied [51, 52]. Oxygenated or just hypoxic conditions can also potentiate the anti-tumour effects of some chemotherapeutic drugs [60, 61]. Amongst these drugs is mitomycin C (MMC), an antibiotic isolated in 1958 from *Streptomyces caespitosus*, that is shown to have an up to 10-fold higher cytotoxic effect when hypoxic conditions are applied [60, 61]. MMC is generally accepted as one of the most effective chemotherapeutic drugs for the systemic treatment of pancreatic cancer [62].

Pancreatic cancers are highly aggressive and one of the dominant causes of cancer death. Aggressive tumours often have insufficient blood supply, partly because tumour cells grow faster than endothelial cells and partly because a new formed vascular supply is disorganized [63-65]. Despite poor blood supply, pancreatic cells survive and proliferate in severe hypoxia and nutrient deprivation. Oxygen sensing of cells may perhaps form an explanation for this phenomenon. Comparison of pancreatic cell lines with other cancer cell lines revealed that hypoxia-inducible factor 1α (HIF-1α) protein was constitutively expressed in 15 of 20 pancreatic cell lines but in none of other tested cell lines [66]. HIF-1α is a regulatory protein complex induced by hypoxia [67]. This protein complex influences multiple properties of vascular homeostasis during hypoxia through activation of multiple genes including (1) the erythropoietin gene, (2) the Vascular Endothelial

Table 3: *Risk of post-operative complications without daily rounds by an intensivist for patients after abdominal aortic surgery between 1994 and 1996, adapted from Pronovost, et al. [40].*

Complications	**Patients with complications %** (n = 2606)	**OR (95% CI) Without vs. With Daily Rounds of an Intensivist**
Medical Complications		
- Pulmonary insufficiency after procedure	11.8	1.9 (0.5 – 7.8)
- Cardiac complications after procedure	10.8	1.4 (0.7 – 2.4)
- Acute renal failure	4.7	2.2 (1.3 – 3.9)†
- Septicaemia	3.4	1.8 (1.2 – 2.6)†
- Acute myocardial infarction	2.6	1.4 (0.7 – 2.8)
- Cardiac arrest	1.2	2.9 (1.2 – 7.0)†
Surgical Complications		
- Surgical complications after the procedure	8.6	1.5 (0.8 – 2.0)
- Surgical E codes§	0.3	4.3 (0.9 – 20.0)
Interventions		
- Reintubation	14.1	2.0 (1.1 – 4.1)†
- Reoperation for bleeding	2.4	1.1 (0.5 – 2.6)
- Platelet transfusion	2.0	6.4 (3.2 – 12.4)†

OR = Odds Ratio; CI = Confidence Interval, † = Data are statistical significant $p<0.05$, ‡ = Defined as haemorrhage during a procedure. Accidental laceration during a procedure, or disruption of operation wound, § = Surgical E codes are used to identify environment events, circumstances, or conditions as the cause of injury

Growth Factor (VEGF) gene, influencing the angiogenesis and the revascularisation of ischaemic tissue, (3) genes for glycolytic enzymes and glucose transporters, thereby influencing the metabolic adjustment for energy generation in the hypoxic environment, and (4) genes for Haeme Oxygenase type I (HO-1) and inducible Nitric Oxide Synthetase (iNOS, type II NO synthase) [68]. Other transcription factors that regulate the cellular adaptation to oxygen deprivation are Early Growth Response-I (Egr-1) [69], that acts in the nucleus by binding to specific DNA sequences, resulting in the activation of multiple target genes, Activator Protein-I (AP-1) complex, Nuclear Factor kappa B (NF-κB) and Nuclear Factor Inter-Leukine-6 (NF-IL-6) [69]. The precise role of these factors for oxygen sensing of cells is currently under investigation [69].

The pancreatic cancer cells with constitutive expression of HIF-1α protein were found to be more resistant to apoptosis induced by hypoxia and glucose deprivation than those without constitutive expression of HIF-1α protein [66]. Other anaerobic metabolism-associated genes like *Glut-1*, an insulin independent facilitative glucose transporter, and *Aldolase A*, a glycolytic enzyme, were also more highly expressed in the cells with constitutive expression of HIF-1α protein than in cells without it [66]. These results suggest that constitutive expression of HIF-1α contributes to the survival and proliferation of pancreatic cells in hypoxia and glucose deprivation through the activation of anaerobic metabolism [66]. Under hypoxic conditions, anaerobic metabolism due to the constitutive expression of HIF-1α protein complex may thus prevent apoptosis of pancreatic cancer cells. Nevertheless, because of the very strong synergy with hypoxia, MMC for treatment of pancreatic cancer may perhaps still best be applied using regional hypoxic conditions.

Isolation Perfusion of the Abdomen

In 1993, an aortic stop flow infusion technique (ASI) to allow hypoxic abdominal perfusion (HAP) to treat bulky peritoneal carcinomatosis was described for the first time [70]. This technique used rigid double lumen balloon catheters introduced via the femoral artery and vein through a short cut down in the groin after which they were advanced to the level of the diaphragm [70]. In order to achieve isolation of the abdomen, two pneumatic cuffs were placed around both roots of the limbs. One year later this technique was simplified by using fine bore balloon occlusion catheters that could be inserted percutaneously instead of the open exposure of the femoral vessels [71]. This improvement was necessary, because 10 out of 149 patients had developed major vascular complications using the

open technique [72]. By using the simplified technique, only 1 patient in a series of 36 stop-flow infusion procedures needed formal repair of the femoral artery [72].

Distal oesophagus, disseminated gastric, gall bladder, pancreatic, colon and ovarian cancer, together with metastatic melanoma and sarcomas are thought to form indications for the application of this hypoxic abdominal perfusion technique [70-72].

Aspects of Oxygen Transport to the Abdomen

Normal oxygen transport

Normal blood flow, with its delivery of oxygen and other nutrients and removal of carbon dioxide and hydrogen ions, will be disturbed during the temporary vascular isolation that is necessary when isolation perfusion procedures of the abdomen or placement of endovascular grafts are performed. Oxygen transport to tissue and cells occurs usually in three major steps: (1) oxygen uptake in the lung, (2) oxygen transport in blood and (3) diffusion of oxygen from the capillaries, through the tissues and into the cell [73]. Normally, capillary perfusion and oxygen consumption are in balance and the oxygen supply to the cell is continuously auto-regulated to its needs [73, 74]. This local blood flow control can be divided into an *acute* control phase, control within seconds to minutes to provide a rapid means for maintaining appropriate perfusion, and into a *long term* control phase, control within days, weeks or even months [74]. Abdominal isolation perfusion procedures or placement of endovascular grafts with a vascular occlusion time of maximum 60 min [75], are thus likely to mainly interact with acute control mechanisms. Five main mechanisms are thought to obtain the auto-regulation: (1) redistribution of capillary perfusion by shunt regulation, (2) changes of perfusion pressure due to pre-capillary pressure changes, (3) changes in viscosity concomitant with changes in the oxygen transport capacity (red blood cells), (4) changes in oxygen extraction ratio and (5) changes of diffusion resistance in the tissues and across the cell membrane [73].

Measurement of oxygen consumption and delivery

Since Lavoisier at first measured oxygen consumption in whole animals in 1784, methodologies for this kind of monitoring have continued to improve in accuracy and become more users friendly [76]. Four main methods for the measurement of oxygen consumption are usually distinguished: (1) oxygen loss from (or replacement into) a closed breathing system, (2) subtraction of the expired from

the inspired volume of oxygen, (3) the ventilated hood and, (4) multiplication of cardiac output by arterial mixed-venous oxygen content difference [77].

Although volume loss from a closed breathing system (spirometer) is reported to be probably the simplest method of measuring oxygen consumption, the adaptation of the technique to conditions of artificial ventilation is, however, thought to be cumbersome [78]. At present the PhysioFlex® closed-circuit anaesthesia apparatus (Dräger, Zoetermeer, The Netherlands) is the only commercially available device that combines the possibility of artificial ventilation with this oxygen consumption measurement technique [79]. The device uses the alternative method, replacement of volume into a closed breathing system, by adding a known volume of oxygen into the closed-circuit in order to keep the volume of the circuit and it's oxygen concentration constant, a condition in which the oxygen volume inflow equals the oxygen consumption [79]. Although the experimentally and intraoperatively performed evaluation of the closed circuit of the PhysioFlex® revealed that closed-circuit anaesthesia can indeed be performed with it [80, 81], the measured oxygen consumption with the PhysioFlex® has till now, only been compared with calculated values valid for all homoiotherms based on equations that use bodyweight (for formula, see section "*Disturbance of oxygen transport to the abdomen*") [82].

For application of the subtraction technique (indirect calorimetry), it is important that the assumption of the patient being in equilibrium for nitrogen is fulfilled. The ratio between the concentration of nitrogen inspired and that being expired is known as the Haldane transformation factor. This transformation factor is used to calculate the inspired minute volume from the expired minute volume, the volume that is usually measured [77]. Using the indirect calorimetry measurement, the essential feature during artificial ventilation is the measurement of gas composition of inspired and expired gas by the same analysers under the same conditions of humidity, temperature and pressure, with a very high level of accuracy [77]. However, the potential for error is significantly increased when the inspired oxygen concentration is increased [83], when anaesthetic gases are used [84], or when ventilation has recently been reset [85].

In the approach of the ventilated hood, the subject's head is covered by a hood, through which a known flow rate of air is drawn, being sufficient to capture all the expired air [77]. Although the system is non-invasive and potentially accurate, it can only be used when the subject is breathing air [77].

In 1870, Adolf Fick defined the relationship between oxygen consumption, cardiac output and systemic arterial and mixed-venous oxygen contents [76]. This

relationship is now commonly known as the reversed Fick method. Although the technique is invasive, it is convenient in the intensive care situation where the necessary lines are usually in place [77]. The method is, however, known for its systematic error because it excludes the oxygen consumption of the lungs [76], and is also described to be less accurate because the physiologic measurements made are subject to larger measurement errors [86].

Oxygen delivery is only invasively determined being the product of cardiac output and arterial oxygen content [77]. It is important to remember that if the reversed Fick method is used for calculation of the oxygen consumption, mathematical coupling between these variables is introduced (by the use of cardiac output and arterial oxygen content) that may form a potential source of error when the critical oxygen delivery level is assessed [87].

Disturbance of oxygen transport to the abdomen

Whenever the availability of oxygen decreases, the blood flow to the tissues will increase [74]. Two basic theories addressing the regulation of organ perfusion during decreased oxygen availability are postulated [74]. The *vasodilator* theory assumes that vasodilation during hypoxia is achieved by increasing formation and release of special vasodilator substances, like e.g. adenosine. The *oxygen lack* theory states that vasodilation is the result of a decreased possibility to maintain normal vascular muscle contraction by the oxygen depletion itself. When the blood supply to the tissues is restored after some time, the blood flow through the tissues usually increases, which is called *reactive hyperaemia* [74]. The duration of this reactive hyperaemia phase is usually long enough to repay almost exactly the tissue oxygen deficit that has accrued during the period of occlusion. This mechanism emphasis the close connection between local blood flow regulation and oxygen delivery to the tissues.

In 1945, Brody introduced a formula, based on bodyweight and valid for all homoiotherms, in order to calculate the whole-body oxygen consumption. Within one year Kleiber simplified this formula for calculation at resting conditions [88, 89]. This latter formula is now known as the “Brody formula”, being:

$$Oxygen\ consumption\ (ml/min) = 10 \times \{bodyweight\ (kg)\}^{0.75}$$

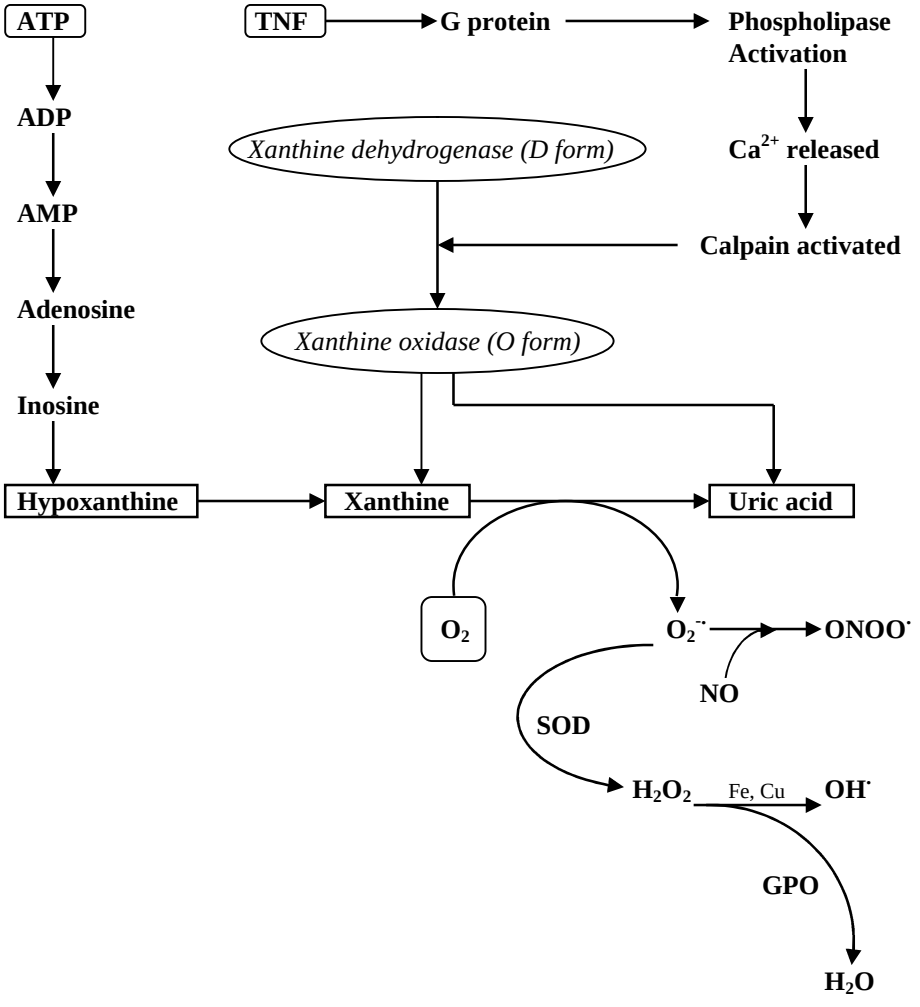
According to Low, during induction of anaesthesia, the oxygen consumption decreases by about 15-30% in comparison with the initial preoperative value [90]. This level was demonstrated to virtually correspond to the basal metabolic rate [91, 92]. Volatile anaesthetic agents are, however, not general metabolic depressants, but the decrease in whole-body oxygen consumption represents far more a summation of events in individual organs in which an anaesthetic induces changes in function which results in a changed metabolic requirement [93, 94]. During anaesthesia, the oxygen consumption may be influenced by a large number of different factors [95]. A decrease in body-temperature of e.g. 1 ºC induces a decrease in oxygen consumption of about 10% [95]. A recently published report described that different volatile anaesthetics not only differ in their effects between different individual organs, but also differ in the effects they have within an individual organ [96]. Isoflurane was in this report shown to better preserve the "reactive hyperaemia" after local ischaemia following completion of the bowel anastomosis during colorectal surgery than desflurane.

Under basal conditions the blood flow to the liver and kidneys take about 50% of the total body blood flow [74]. Because the whole skin and all skeletal muscles take about 21% of total body blood flow, isolation of the legs and the abdomen as done during simultaneous aortocaval occlusion necessary for isolation perfusion procedures of the abdomen, will thus interact with more than half of the total body blood flow. Although, the influence of the level at which single aortic cross-clamping is performed on the whole-body oxygen consumption is well known, nicely described by Viale and colleagues [97], showing that during infrarenal aortic cross-clamping the whole-body oxygen consumption decreased by 11%, while it decreased by 49% when supra-celiac clamping was performed, till now, no studies reveal the impact of simultaneous aortocaval occlusion on total body oxygen consumption.

Ischaemia-Reperfusion Injury of the Abdomen

Whenever the blood flow to a regional vascular bed is compromised, ischaemic disease will occur, which is responsible for a significant degree of morbidity and mortality [98]. Although restoration of blood flow to an ischaemic organ is essential to prevent irreversible cellular injury, reperfusion may augment tissue injury in excess of that produced by ischaemia alone [99]. Ischaemia-reperfusion may result not only in local but also in systemic inflammation and even, if severe enough,

Figure 2: *Cellular formation of Reactive Oxygen Species (ROS) during Ischaemia-Reperfusion Injury (IRI)*



The simultaneous conversion of xanthine dehydrogenase to its oxidase form and the breakdown of purine nucleotides (ATP etc.) to hypoxanthine create the ideal environment for the formation of the superoxide anion ($O_2^{-\bullet}$) when oxygen (O_2) is again available during reperfusion, which then proceeds to the formation of hydroxyl free radical ($OH^{\bullet}$) by the Fenton reaction. TNF = tumour necrosis factor, Ca^{2+} = calcium, NO = nitric oxide, $ONOO^{\bullet}$ = peroxynitrite, SOD = superoxide dismutase, H_2O_2 = hydrogen peroxide, Fe = ferrous ion, Cu = Copper ion, GPO = glutathion peroxidase, H_2O = water.

in systemic inflammatory response syndrome (SIRS) and/or multiple organ dysfunction syndrome (MODS) [99]. Ischaemia-reperfusion will thus extend beyond the ischaemic area at risk and includes injury of remote, non-ischaemic organs [99]. Ischaemia-reperfusion injury (IRI) is therefore of relevance when the blood supply to the gut is interrupted, as is in thoraco/abdominal aortic cross clamping [100].

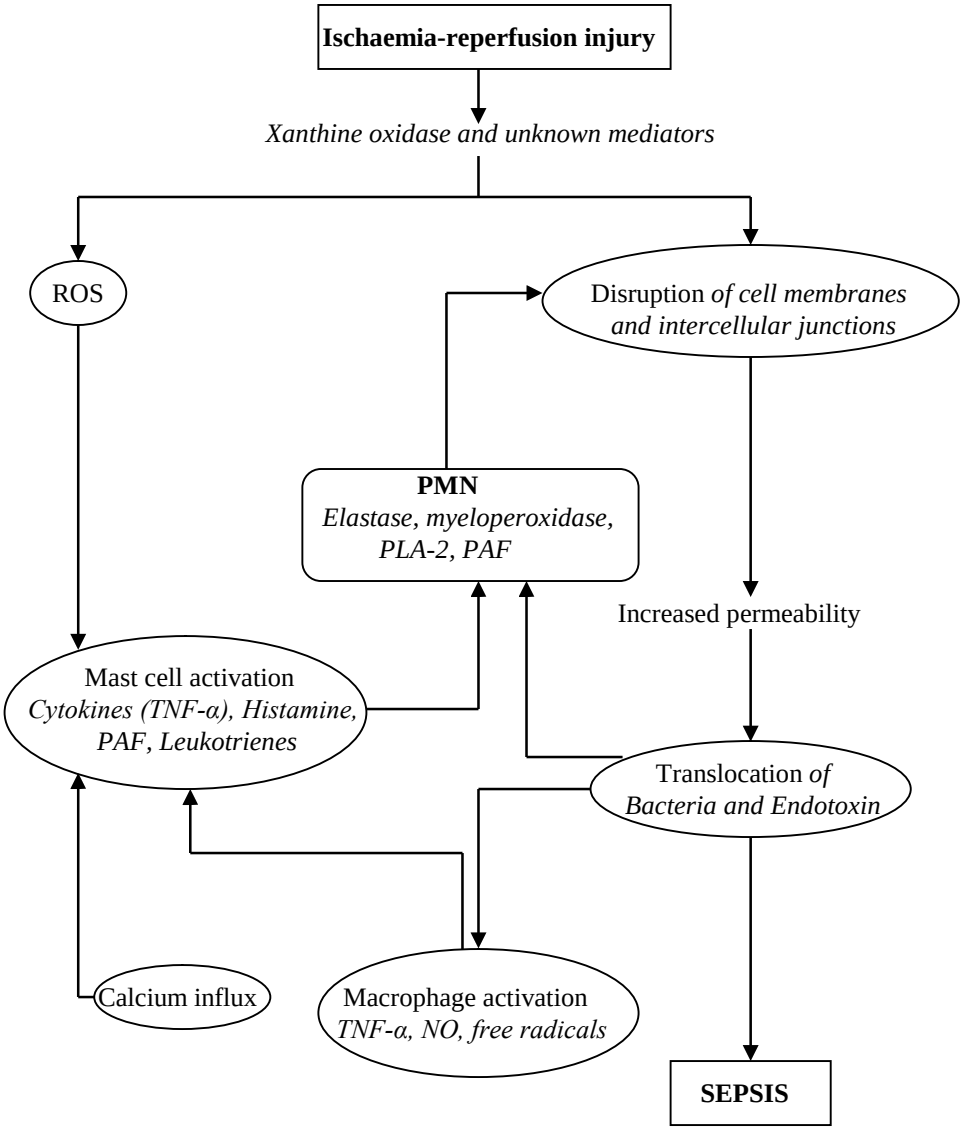
Prolonged ischaemia results in a variety of cellular metabolic and ultrastructural changes (Table 4) [99, 101]. The primary effects of IRI are mediated by reactive oxygen species (ROS) via the xanthine oxidase pathway (Fig. 2) [98-103]. Xanthine dehydrogenase is abundantly available in the intestinal mucosa where it has a physiological function in the purine-scavenging pathway. Within 60 min of the onset of ischaemia, xanthine dehydrogenase is converted to xanthine oxidase by a calcium-dependent proteolytic process (Fig. 2) [103]. The so formed ROS are potent oxidizing and reducing agents that can directly damage cellular membranes by lipid peroxidation [104], and induce indirect damage by secondary activation of polymorphonuclear neutrophils (Fig. 3) [100, 105]. Furthermore, ROS stimulate leukocyte activation and chemotaxis by activating plasma membrane phospholipase A_2 to form arachidonic acid, a precursor for eicosanoid synthesis (e.g. thromboxane A_2 and leukotriene B_4) and leukocyte adhesion molecule and cytokine gene expression via activation of transcription factors, e.g. NF-κB [104].

The recruitment of polymorphonuclear neutrophils (PMN) from the bloodstream is a multi-step process that involves an initial rolling of PMN on the endothelium, followed by adhesion and transmigration of the leukocyte [68, 99, 100, 106]. The initial "rolling" step is started by an ischaemia-reperfusion induced in-

Table 4: *Metabolic and ultra-structural changes associated with ischaemia*

- Changed membrane potential
- Changed ion distribution (sodium, potassium, calcium)
- Cellular swelling
- Disorganisation of cytoskeletal structures
- Formation of Reactive Oxygen Species (ROS)
- ATP loss
- Defective ATP re-synthesis
- Creatine phosphate loss
- Depletion of glutathion
- Cellular acidosis

Figure 3: *The role of polymorphonuclear neutrophils in IRI, adapted from Kong [100]*



ROS = reactive oxygen species, PMN = polymorphonuclear neutrophils, PLA-2 = Phospholipase A-2, PAF = platelet-activating-factor, TNF- α = Tumour necrosis factor alpha, NO = nitric oxide

crease in endothelial P-selectin expression that interacts with its leukocyte counter-receptor, P-selectine glycoprotein 1 (PGSL-1) [68, 99, 100, 106]. This is followed by an interaction of leukocyte β_2 integrins, CD11a/CD18 and CD11b/CD18, with endothelial intercellular adhesion molecule 1 (ICAM-1) resulting in firm leukocyte adherence and aggregation [68, 99, 100, 106]. Finally, transmigration of the leukocyte into the interstitial compartment is facilitated by platelet-endothelial cell adhesion molecule 1 (PECAM-1) within the endothelial cell junctions [68, 99, 100, 106]. When the activated leukocytes reach the extra-vascular compartment, they release ROS, proteases and elastases. The result is in creased micro-vascular permeability, oedema, thrombosis and finally cell death [107, 108].

Cell death during ischaemia or reperfusion can be due to a series of biochemical processes that are initiated by intrinsic signals sensed by a variety of intracellular proteins [98]. The mechanism by which a cell undergoes programmed cell death is called apoptosis [109]. The cellular apoptotic machinery is usually categorized into three groups: (1) pro-apoptotic proteins (e.g. bax and bid), (2) anti-apoptotic proteins (e.g. bcl-2 and bcl-xL) and (3) executors of the programmed cell death (caspases) [98]. The biochemistry of apoptosis has recently been reviewed and many of the key apoptotic proteins have now been identified [110]. Nevertheless, we still don't know the precise molecular action or activation of these proteins [110]. Recent work has, however, clearly demonstrated the existence of a direct link between the machinery of apoptosis and IRI [98]. The extent of IRI of the rat brain, was found to be reduced when selective caspase inhibitors where given intra-ventricularly [111]. A reduction in infarction size after administration of caspase inhibitors into rat hearts undergoing IRI has also been reported [112]. Furthermore, transgenic mouse models have provided evidence for the role of ROS in the promotion of apoptosis. The apoptotic activity was increased when glutathion peroxidase (GPO) was genetically disrupted in an isolated mouse heart model of IRI, while fewer apoptotic nuclei were found when the cells carried an extra copy of the GPO gene [113]. An extra superoxide dismutase (SOD) gene in transgenic mice also attenuated apoptosis compared to wild-type animals after pharmacological injury [114].

Modulating the expression of key molecular components of the cell death machinery is thought to be an attractive and obvious strategy for therapeutic intervention [115]. Three of the most advanced and promising opportunities are: (1) disruption of gene function with anti-sense oligo-nucleotides (Bcl-2 anti-sense showed anti-tumour responses [116, 117]), (2) recombinant biologicals (recombinant tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) (Apo-2L)

showed promising results in pre-clinical animal models involving anti-tumour therapy [118-120]), and (3) classical organic pharmaceuticals (caspases like e.g. interleukin-1-β-converting enzyme (ICE or caspase-1), a cysteine protease that is responsible for the maturation and concomitant activation of pro-inflammatory cytokines [121, 122], recently introduced for the treatment of rheumatoid arthritis) [115]. Furthermore, in different models of IRI, caspase inhibition showed remarkable efficacy [123-127], not only by decreased apoptosis, but also by improved survival, decreased infarct volumes and improved organ function [115]. A key consequence of gastrointestinal IRI is the breakdown of intestinal barrier function, which normally protects the body from the environment within the bowel lumen [99]. The increased permeability of the gut wall may be due to activation of inducible nitric oxide synthase (iNOS), produced by the enterocytes, that not only leads to mucosal hyper-

Table 5: *Therapeutic strategies to attenuate IRI, adapted from Collard & Gelman [99]*

- Graded reperfusion
- Ischaemic preconditioning
- Aspirin-Triggered Lipoxin (ATL) analogous
- Antioxidant therapy
    - *Superoxide dismutase (SOD)*
    - *N-AcetylCysteine (NAC)*
    - *Allopurinol*
    - *Iron chelators*
    - *Vitamin E*
    - *Catalase*
    - *Mannitol*
    - *Thiols*
- Calcium antagonists
- Angiotensine-Converting Enzyme (ACE) inhibitors
- Anti-Complement therapy
    - *Recombinant, humanized, single-chain Anti-C5 antibody (h5G1.1-scFv)*
    - *Soluble Complement Receptor-1 (sCR 1)*
- Leukocyte depletion / filtration
- Anti-Cytokine or Leukocyte Adhesion molecule (mAb)
- Anti-sense-Oligo-Deoxy-Nucleotides (ODNs) and Transcription Factor Decoys
- Endothelin receptor antagonists
- Platelet Activating Factor (PAF) antagonists
- Leukotriene-B4 (LTB4) antagonists

aemia, alterations in bowel motility, disruption of the actin cytoskeleton and inhibition of ATP, but also to the relaxation of cellular thight-junctions [128]. Furthermore, permeability of epithelial cells in the gut can be increased due to disruption of the cytoskeleton induced by excessive polymerisation of actin due to ROS formation [129]. Cytokines like interleukin-13 (IL-13), IL-4 and γ-interferon disrupt the tight junctions between adjacent enterocytes, thereby increasing paracellular permeability [130-132]. Thus, bacterial translocation from the gut will be the result [133-135], after which bacteria or endotoxins that reach the portal and systemic circulations will contribute to the development of MODS [100, 136]. Although many therapeutic strategies have successfully limited or prevented IRI in controlled experimental models (Table 5), only a few of these strategies are available for routine clinical practice [99]. Controlled graded reperfusion of the ischaemic area at risk is therefore at present still the cornerstone of clinical practice [99, 101].

A strategy that is available for routine clinical practice is the manipulation of tolerance for prolonged ischaemia of tissues by induction of adaptation of tissues for hypoxia, called ischaemic preconditioning. A protective effect in humans by using this manipulation technique was demonstrated not only for patients undergoing coronary artery bypass grafting but also for patients undergoing hepatic resection [137, 138]. Another strategy that is successfully used in humans is the use of antioxidant therapy. Significantly less severe organ failure, fewer days in the intensive care unit and lower serum phospholipase and PMN elastase concentrations are found in patients with haemorrhagic shock receiving a continuous infusion of superoxide dismutase (SOD) for 5 days [139]. Mannitol treatment prior to IRI has been found to afford some degree of protection in a variety of experimental models of acute renal failure [140, 141]. Mannitol is thought to protect against injury by reducing tubular obstruction, increasing renal blood flow via increased prostaglandin production, and acting as a free radical scavenger [142]. Although, mannitol has been shown to reverse oliguria in some patients if given early enough in the course of acute renal failure development, renal function may not improve [143-146]. Moreover, many antioxidant therapy studies have yielded equivocal outcomes regarding its efficacy in attenuating human IRI [147].

Anti-complement therapy may become useful for attenuating human myocardial IRI, as single-chain antibody specific for human C5 (h5G1.1-scFv) is demonstrated to significantly attenuate complement activation, leukocyte activation, myocardial injury, blood loss and cognitive dysfunction in patients undergoing coronary artery bypass grafting when cardiopulmonary bypass was used [148].

Another therapeutic strategy that limits leukocyte-mediated IRI is the inhibition of leukocyte adhesion molecule synthesis. Transcription factors like NF-κB are targets for in humans commonly used anti-inflammatory drugs like glucocortcoids, aspirin, salicylates, gold salts and D-penicillamine [108]. Reduction of bacterial translocation after intestinal IRI is another intervention that can be achieved by selective decontamination of the digestive tract using an appropriate antibiotic regimen [149, 150]. Finally, the use of Glucose-Insulin-Potassium (GIK) infusion to prevent reperfusion injury of the myocardium has recently been re-introduced [151, 152]. The infusion of glucose and insulin is thought to increase the glycolysis, thereby slowing the ATP depletion, which results in an improved energetic profile, after which a better systolic and diastolic function during IRI will remain [153].

Outline and Aim of this Thesis

In our hospital, the local medical ethical committee approved a regional hypoxic perfusion chemotherapy phase I-II trial for locally advanced pancreatic cancer. As pointed out above, a clear understanding of the pathophysiological mechanism involved in the simultaneous onset and removal of occlusion of the thoracic aorta and inferior vena cava necessary for this procedure, will be compulsory to promote rational and effective measures taken by the anaesthetist to prevent complications and to optimise the management for this patient group. So, the aim of this thesis is to find answers on the following questions:

1. Does additional vena cava inferior occlusion induce, or does it just prevent major cardiovascular effects during supra-celiac aortic occlusion in humans?
2. How reliable is the non-invasively intra-operatively measured oxygen consumption using a PhysioFlex® in comparison with values that are calculated using the reversed Fick method?
3. Does simultaneous aortocaval occlusion induce relevant effects on total-body oxygen up-take?
4. (a) Is a closed-circuit modification of the anaesthetic technique helpful for the optimisation of the anaesthetic management for the patients undergoing simultaneous aortocaval occlusion?
   (b) Does it make sense to apply xenon instead of isoflurane for this procedure?

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ORIGINAL STUDIES

CHAPTER 2

CARDIOVASCULAR EFFECTS OF SIMULTANEOUS AORTOCAVAL OCCLUSION

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Based on: Cardiovascular effects of simultaneous occlusion of the inferior vena cava and aorta in patients treated with hypoxic abdominal perfusion for chemotherapy.
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Summary

Background: Animal studies suggest less cardiovascular disturbance if the aorta and vena cava are occluded simultaneously. We set out to establish the effects of simultaneous clamping in humans, because oncologists suggested that perfusion for chemotherapy could be done under local anaesthesia without invasive haemodynamic monitoring.

Methods: We studied the cardiovascular effects of the onset and removal of simultaneous occlusion of the thoracic aorta and inferior vena cava, in 7 ASA II patients. Two stop-flow catheters positioned in the aorta and in the inferior cava were inflated, to allow hypoxic abdominal perfusion to treat pancreatic cancer. We measured arterial pressure, heart rate (HR), right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP) and cardiac output (CO), and calculated systemic vascular resistance index (SVRi), pulmonary vascular resistance index (PVRi), left ventricular stroke work index (LVSWi) and right ventricular stroke work index (RVSWi). Three patients were studied with trans-oesophageal echocardiography.

Results: Six patients needed intravenous nitroprusside during the occlusion because mean arterial pressure (MAP) increased to more than 20% of baseline (SVRi increased by 87%). One minute after occlusion release, all patients had a 50% decrease in MAP, and mPAP increased by 50%. The procedure had severe cardiovascular effects, shown by a 100% increase in cardiac index at occlusion release with increases in left and right ventricular stroke work indices of 75% and 147%. Left ventricular wall motion abnormalities were seen on trans-oesophageal echocardiography.

Conclusions: Serious haemodynamic changes occur during simultaneous occlusion of the thoracic aorta and inferior vena cava which may need invasive haemodynamic monitoring.

Background

Clamping the aorta has major cardiovascular effects [1]. In animal studies, clamping the inferior vena cava at the same time can prevent large haemodynamic changes [2, 3]. A single clinical report suggests that haemodynamic changes are not prevented by additional inferior vena cava occlusion [4].

A percutaneous aortic 'stop-flow' infusion technique has been used for regional cytotoxic therapy of the abdomen for a number of malignant conditions [5]. The method aims to reduce the systemic side-effects of the chemotherapeutic drugs, whilst simultaneously potentiating the cytotoxic action of the drugs by hypoxia [5-7]. In our hospital a phase I-II chemotherapy trial based on this hypoxic abdominal perfusion procedure (HAP) is taking place. The procedure achieves a greater dose and thus a greater local concentration of melphalan and mitomycin C with a 20-min isolation and perfusion of the abdomen.

The temporary vascular isolation of the abdominal cavity for this procedure is achieved with tourniquets placed around both upper thighs to exclude the lower limbs from the circulation, and by surgical insertion of stop-flow catheters, one into the aorta and a second into the inferior vena cava, to isolate the abdominal circulation.

We wished to measure the haemodynamic effects of this simultaneous clamping in humans, because oncologists suggested that the procedure could be done using local anaesthesia and without invasive haemodynamic monitoring.

Material and Methods

Seven consecutive patients, all ASA II, were enrolled in the HAP phase I-II trial for locally advanced pancreatic cancer after diagnostic work-up, written informed consent, and explanation of the anaesthetic procedure. The perfusion study, using melphalan and mitomycin C, was approved by the local medical ethical committee. We excluded patients with significant cardiovascular disease (NYHA class II, III or IV). Other patient characteristics are given in Table 1.

Anaesthetic Management

On the evening before the operation the patients were premedicated with lorazepam 1 mg orally. On the day of operation ranitidine 150 mg was added to their routine medication.

Table 1: *Characteristics of the patients (mean and range)*

Sex (F/M)	4/3
Age (years)	57 (49-65)
Weight (kg)	67 (54-97)
Height (m)	1.72 (1.62-1.90)
Body surface area (m^2)	1.78 (1.61-2.03)
Additional diagnoses	Non-insulin dependent diabetes mellitus (n=1) Insulin-dependent diabetes mellitus (n=1) Sick Sinus Syndrome with AAI pacemaker (n=1)

In the operating room, basic anaesthetic monitoring was started (HP M1166A OmniCare Anaesthesia Component Monitoring System Release F, Hewlett® Packard GmbH, Böblingen, Germany), followed by i.v. induction of anaesthesia with sufentanil 0.30 $\mu g.kg^{-1}$, thiopental 5 $mg.kg^{-1}$ and vecuronium 0.1 $mg.kg^{-1}$. After tracheal intubation, the lungs were ventilated with a closed-circuit anaesthetic machine (Physio BV. a Dräger company, Haarlem, The Netherlands), using IPPV with settings of FIO_2 0.35 (oxygen-air mixture), frequency 14 min^{-1}, tidal volume 8 $ml.kg^{-1}$, PEEP 5 cmH_2O, and I/E ratio 1:1.2. Respiratory frequency was adjusted to maintain $PaCO_2$ between 4.5 and 5 kPa. Anaesthesia was maintained with isoflurane 0.9% end tidal and sufentanil 0.20 $\mu g.kg^{-1}$ i.v. was given at the start of the surgical procedure. Fluid management was standardized for all patients. Ringer's lactate was given by i.v. infusion, 20 $ml.kg^{-1}$ in the first hour of the procedure to correct the pre-operative fluid intake restriction and venodilation caused by general anaesthesia, followed by 6 $ml.kg^{-1}$ hr^{-1} for the rest of the procedure. Fluid management was not adjusted for any change in cardiovascular measurements. Sodium nitroprusside (SNP) i.v. was given as necessary to control Mean Arterial Pressure (MAP) during the perfusion phase to within 20% of the preoperative value.

Additional monitoring was started. Blood pressure was measured using a radial artery cannula (Arrow radial artery catheterisation set 20 Ga; Arrow Deutschland GmbH, Erding, Germany). A pulmonary artery balloon flow catheter (Arrow Thermo-Pace® Hands off® Heparin-coated Thermodilution Catheter 7.5 Fr. 5 lumen 80 cm catheter length; Arrow Deutschland GmbH) was passed through an introducer sheath (Arrow Percutaneous sheath introducer set 8.5 Fr; Arrow Deutschland GmbH) placed in the right internal jugular vein. A cardiac output measurement system (Baxter CO-set® closed injectate delivery system; Baxter

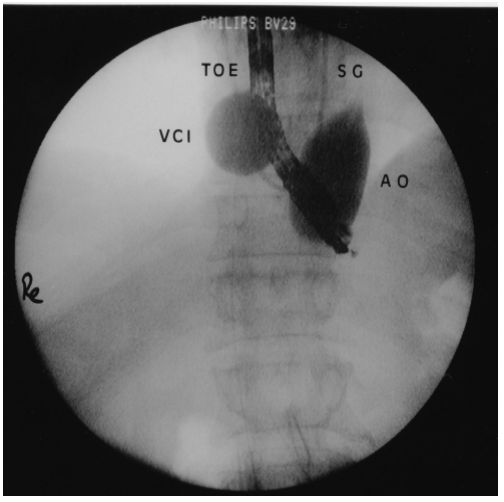


Figure 1: *Radiograph taken during HAP phase; AO = aortic catheter; VCI = inferior caval vein catheter; TOE = transoesophageal echo probe; SG = Swan-Ganz catheter (see text for details)*

Deutschland GmbH, Unterschleissheim, Germany) was connected to the Right Atrial Pressure (RAP) port of the thermodilution catheter. We used iced fluid. We studied three patients with per-operative trans-oesophageal echocardiography (TOE) (Sonotron Vingmed CFM 800; Vingmedsound Als, Horten, Norway) with a 5 MHz multi-plane trans-oesophageal echo (MPTE).

Surgical Procedure

Tourniquets were placed around the upper thighs to allow isolation of the legs from the circulation. Then a small incision in the right groin was made to insert two catheters (arterial stop-flow catheter F12-600 mm and venous stop-flow catheter F12-600 mm; PFM Produkte für die Medizin GmbH, Köln, Germany) into the femoral artery and vein. They were advanced to above the coeliac trunk in the aorta and the level of the diaphragm in the inferior vena cava, using radiological control (Fig. 1). Heparin 5000 IU was given i.v.

The abdomen was then isolated. First, the tourniquets on both upper thighs were inflated to a pressure of 350 mmHg. Then the balloon of the aortic catheter was inflated with a mixture of 25 ml NaCl 0.9% with contrast fluid and immediately afterwards the balloon of the caval catheter was also inflated. The maximum diameter of the balloons was 30 mm.

The cytotoxic drugs were perfused according to a set regimen using an extracorporeal circuit connected to both catheters (Hypoxic perfusion set; PFM Produkte für die Medizin GmbH, Köln, Germany), flow rate, 250 $ml.min^{-1}$. No oxygen

was added to this extra-corporeal circuit. The perfusion of the chemotherapy was maintained for 10 min, followed by a 10-min period without drugs. After a total of 20 min hypoxic abdominal perfusion, the circulation to the abdomen was restored by deflation of the balloon in the aorta, followed immediately by deflation of the inferior caval vein balloon. After a stabilization period of 10 min the tourniquets were released from the thighs.

Data Collection

ECG, MAP, Heart Rate (HR), RAP, mean Pulmonary Artery Pressure (mPAP), blood temperature (measured by the thermodilution catheter) and peripheral oxygen saturation (SpO_2) were measured continuously, and a record made of the values for each minute of the procedure.

Measurements were noted at previously defined times; these were 'Steady State' (SS), during stable anaesthesia before tourniquet inflation; 'Legs Separated' (LS), when the tourniquets around the thighs were inflated; early in the 'HAP phase' (HAPa), just after complete abdominal isolation; late in the 'HAP phase' (HAPb), within 5 min before removal of occlusion; 'Abdominal Recirculation' (AR), when only the balloons of the catheters were deflated; 'Complete Recirculation' (CR), the tourniquets were also deflated; and 'End Operation' (EO), just before reversal of anaesthesia was started. Cardiac output (CO) (measured in triplicate) and pulmonary artery wedge pressure (PAWP), measured just before CO, were measured at these times. If i.v. SNP was given during the perfusion phase, the infusion of SNP was turned off after determination of HAPb, but at least 4 min before abdominal reperfusion started. The time needed for the surgical preparation varied so that the time between SS and LS, was a mean 47 min (range 30-65 min); thereafter, a rigid time schedule was maintained starting with the separation of the legs. Thus, LS was defined as t=0 min; HAP, t=4 min; AR, t=24 min; CR, t=34 min; EO, t=54 min. Cardiac Index (CI), Stroke Index (SI), Systemic Vascular Resistance index (SVRi), Pulmonary Vascular Resistance index (PVRi), Left Ventricular Stroke Work index (LVSWi) and Right Ventricular Stroke Work index (RVSWi) were calculated with standard formulae. For each patient, these calculations were done using continuously measured variables that had been collected at the same time-points that CO was measured. Because CO and PAWP were measured ‘early in the HAP phase’ and not for instance always at ‘the third minute of the HAP-phase’, it was not possible to construct an exactly time related set of the values of these intermittently measured variables for the entire group. The function

of the left ventricle was monitored by TOE, with a trans-gastric short axis mid-papillary view, continually recorded on VHS videotape. Left Ventricle End Diastolic Area (LVEDA) and Left Ventricle End Systolic Area (LVESA) were traced by the contouring program of the TOE device. Fractional area change was calculated [(LVEDA-LVESA)/LVEDA x 100] and left ventricular wall motion was classified with a semi-quantitative scoring system [8]: a normally contracting wall segment is scored as 1, mild hypokinesis as 2, severe hypokinesis as 3, akinesis as 4, and dyskinesis as 5. The Left Ventricular Wall Motion Score index (LVWMSi) was calculated from the sum of all scores, divided by the number of segments observed.

Statistical Analysis

Results are expressed as mean and standard deviation (SD) unless otherwise indicated. Statistical analysis was with SPSS for Windows, version 10.0. Data were analysed with a Wilcoxon signed ranks test to compare the observed mean difference between a value of a defined time point with the value at SS as recommended by Myles and Gin [9]. A p-value <0.05 was considered significant.

Results

Figures 2 and 3 show the time course of changes in the continuously measured values MAP, HR, RAP, mPAP and temperature.

With simultaneous clamping, MAP quickly increased to greater than 120% of the preoperative value in six patients. To control MAP within 20% of this value, i.v. infusion of SNP was started. This infusion was continued until the end of the HAP phase to control MAP. Although the SNP infusion was stopped at least 4 min before balloon deflation, a 50% reduction in MAP occurred in all patients in the first minute after balloon deflation. One minute later, however, MAP recovered spontaneously (Fig. 2).

The pacemaker of the patient with the sick sinus syndrome was set at a fixed rate of 70 beats.min^{-1}. Except for HR, the haemodynamic changes in this patient were comparable with the changes measured in the other six patients. HR increased by 42% during the second part of the HAP phase (Fig. 2).

RAP changed little despite the other cardiovascular changes, except at the fourth and fifth minute after the abdominal clamping, when it increased by 15% (Fig. 3).

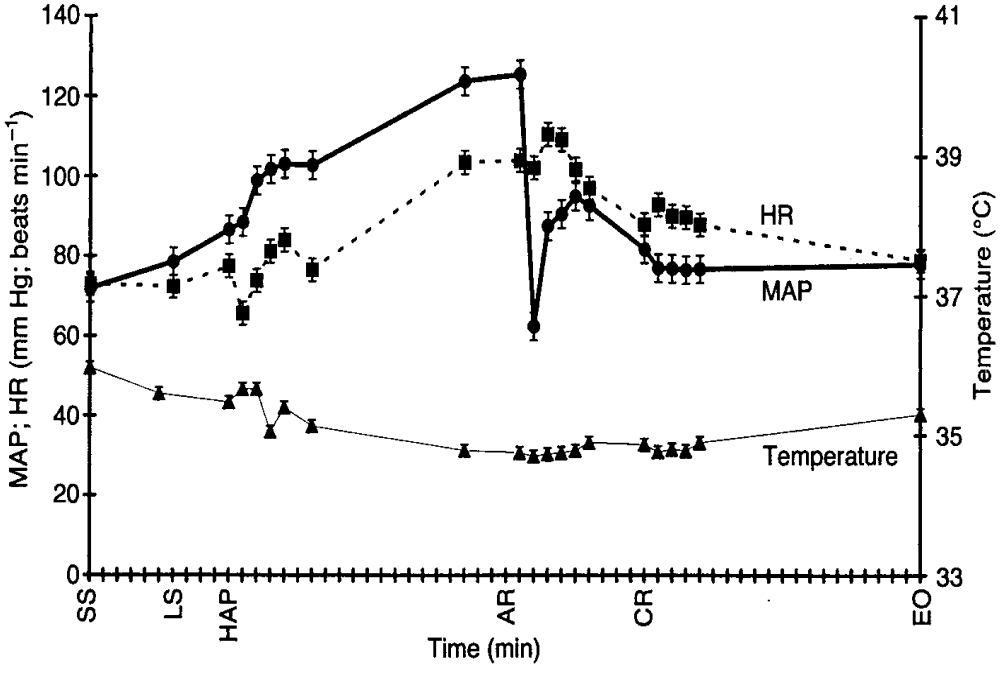
Three minutes after balloon deflation, all the patients developed pulmonary hypertension; mPAP increased by 50% (Fig. 3).

Table 2 shows the time course of changes in PAWP, CI, SI, SVRi, PVRi, LVSWi and RVSWi.

TOE was done in three patients. Because of recording problems in two procedures, we could only analyse and calculate the LVEDA, LVESA and FAC in detail in one patient. Global intra-operative analysis of changes in the left ventricular wall motion was possible in all three procedures and revealed the same trend in LVWMSi. Table 3 presents the time course of changes in LVEDA, LVESA and FAC in one patient and of the changes in LVWMSi in all three patients.

SVRi increased by 87% with simultaneous occlusion of the aorta and vena cava. At the end of the HAP phase, although SNP was given, a further increase by 98% was measured (Table 2, HAPb) and this immediately affected left ventricular

Figure 2: *HR, MAP and Temperature during the HAP procedure*

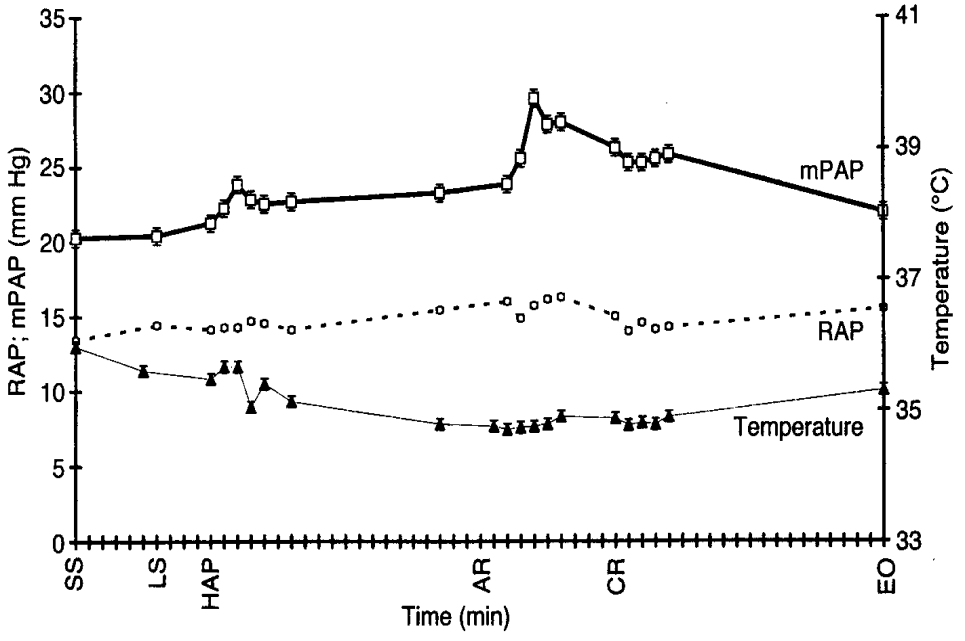


Each bar on the abscissa represents 1 min. Data are mean (SE).

filling. LVESA increased by 68% after 2 min, and LVEDA increased by 49% after 5 min (Table 3). PAWP increased by 73% at the end of the perfusion phase (Table 2, HAPb). Although the CI initially decreased in the patient who did not need an i.v. SNP infusion (by 50% at the start of the HAP phase) the overall CI of all the patients did not decrease significantly during the HAP phase (Table 2).

Immediately after opening both vessels, SVRi decreased by 35% compared with the baseline value, and by 67% compared with the value measured at the end of the HAP phase (Table 2; SS, HAPb, AR). Although left ventricular filling and left ventricular wall motion returned immediately to their steady state value in response to this decrease (Table 3), PAWP did not return to its baseline value until the end of the procedure (Table 2). CI increased by 100%, stroke index, and left and right ventricular stroke work indices also increased at this stage (Table 2). Simultaneously, pulmonary vascular resistance index decreased by 50%.

Figure 3: *RAP, mPAP and Temperature during the HAP procedure*



Each bar on the abscissa represents 1 min. Data are mean (SE).

Table 2: *Cardiovascular measurements during the procedure*

Parameter	**SS**	**LS**	**HAPa**	**HAPb**	**AR**	**CR**	**EO**
CI	2.7	2.4	2.3	2.5	5.5*	4.3*	2.9
($l.min^{-1}.m^{-2}$)	(0.9)	(0.6)	(1.1)	(0.5)	(2.2)	(1.4)	(0.7)
PAWP	11	14*	16	19*	18*	15*	14
(mmHg)	(3)	(4)	(7)	(5)	(8)	(6)	(3)
SI	40	34	31	28	57*	50*	38
($ml.m^{-2}$)	(21)	(6.7)	(13)	(11)	(22)	(18)	(6.4)
SVRi	1849	2244	3450*	3662*	1196*	1257*	1745
($dyne.s.cm^{-5}.m^2$)	(656)	(811)	(1152)	(959)	(384)	(414)	(675)
PVRi	279	230	256	200	148*	223*	222
($dyne.s.cm^{-5}\ m^2$)	(111)	(67.8)	(131)	(152)	(110)	(67.9)	(40.8)
LVSWi	32	30	38	39	56*	42*	34
($g.m.m^{-2}.beat^{-1}$)	(13)	(10)	(24)	(12)	(23)	(19)	(15)
RVSWi	3.8	2.9	4.2	3.1	9.1*	8.3*	3.6
($g.m.m^{-2}.beat^{-1}$)	(3.5)	(2.6)	(3.8)	(2.5)	(5.6)	(5.2)	(2.6)

*Values are mean (SD). * = P<0.05 compared with the value at Steady State (SS)*

Table 3: *TOE values measured during the procedure*

	SS	**LS**	**HAP 1**	**HAP 2**	**HAP 3**	**HAP 4**	**HAP 5**	**HAP I**	**HAP II**	**AR**	**CR**
Patient 1											
LVEDA (cm^2)	8.2	8.4	9.0	10.5	10.7	11.4	12.2		13.4	9.1	7.5
LVESA (cm^2)	3.7	4.6	4.8	6.2	6.1	6.7	7.0		8.1	3.6	3.7
FAC (%)	54	45	47	41	43	41	43		39	60	51
LVWMSi	1	1.9	1.6	1.3	1.8	1.8	1.8		1.5	1	1
Patient 2											
LVWMSi	1.1	1.6						1.8	1.4	1.1	1
Patient 3											
LVWMSi	1	1.4						2.5	2	1.1	1

HAPI = within 8 min after starting the Hypoxic Abdominal Perfusion phase; HAPII = within 8 min before the end of the Hypoxic Abdominal Perfusion phase;

Discussion

We found that additional occlusion of the vena cava had only a small stabilizing effect on haemodynamics when the thoracic aorta was occluded. Although RAP, mPAP, CI, SI, LVSWi and RVSWi were stable during simultaneous occlusion of the aorta and vena cava (HAP phase), large changes in important variables such as MAP, FAC and LVWMSi, followed by an increased PAWP, required infusion of SNP in six patients to control these changes. Although SNP infusion was stopped at least 4 min before abdominal reperfusion, opening of both vessels caused profound cardiovascular changes. MAP decreased by 50%, while CI increased by 100%, pulmonary hypertension developed, LVSWi increased by 75% and RVSWi increased by 147%.

Our data contrast with those of animal studies, which reported the additional vena cava inferior occlusion had a stabilizing effect [2, 3]. In mongrel dogs anaesthetized with sodium pentobarbital, systolic left ventricular pressure and superior caval vein flow did not change during simultaneous clamping; and left ventricular end diastolic volume decreased [2]. The decrease in stroke volume was assumed to be caused by reduced preload; no activation of the Frank-Starling mechanism was found [2]. Gelman and colleagues studied simultaneous clamping and declamping in pigs anaesthetized with sodium methohexital followed by enflurane [3]. Their report confirmed the data on clamping measured by Stokland and colleagues [2]; i.e. no significant change in MAP or superior caval vein flow, and reduced CO.

Our data confirm the results of the only published clinical report, which found haemodynamic changes similar to those described during thoracic aortic occlusion alone [4]. However, our methods were different. In the previous study, haemodynamic stability after inflation of the aortic balloon was sought by increasing isoflurane concentration, and by starting i.v. SNP, before the inferior caval vein balloon was inflated [4]. The authors speculated that the stepwise clamping, in which a few minutes elapsed between aortic balloon inflation and inferior caval vein balloon inflation, allows the typical, single thoracic aortic cross-clamping redistribution of blood volume, to occur [4]. In our study, less than 1 min elapsed between thoracic aorta and vena cava inferior occlusion. Nevertheless, we also observed changes comparable with those during single thoracic aortic cross-clamping. This is in contrast to the animal experiments, when occlusion of the cava during aortic cross-clamping resulted in the same flows and pressures whether the aorta and inferior caval vein were occluded simultaneously or at different time-points [2]. Nevertheless, the authors stated that end diastolic volume, superior vena cava flow

and systolic left ventricular pressure were very sensitive to changes in blood volume [2].

The effects of blood volume expansion on haemodynamic changes, studied by infusing blood in 50-ml volumes into the jugular vein during the simultaneous clamping, was found to depend very much on shunting between the upper and lower part of the body [2]. Anatomical shunts exist via the spinal arteries and veins and via azygos and hemi-azygos veins.

To explain the different results between animal and clinical studies, three differences in the conditions may be considered. First, anatomical and physiological differences between species must be taken into account. A second difference is the method of clamping. The clamps in the animal studies were 'extravascular', while both clinical studies used endovascular occlusion. Because MAP increased during the endovascular occlusion, the outside pressure put on the partly compliant balloons (which are only available with a maximum diameter of 30 mm), will be increased, which might have allowed leakage past these balloons during the HAP phase, and increased shunt between the upper and lower compartment. Extravascular cross-clamping with instruments will prevent leakage past the clamps. A third difference between the animal and the clinical studies is the use of atropine. Both animal studies used atropine in order to avoid reflex bradycardia before simultaneous clamping was started [2, 3], whereas the clinical studies did not [4]. Therapeutic doses of atropine can occasionally dilate cutaneous blood vessels, although the mechanism of this anomalous vascular response is unknown [10]. This dilation of cutaneous vessels could affect shunting.

Our data on occlusion release only partly confirm the results of the previously published clinical report [4]. We obtained more detailed data, than the study of Berkenstadt and colleagues, who presented values 1 min and 30 min after declamping [4]. We found significant changes in filling pressures. PAWP remained increased to the end of the procedure in all our patients (Table 2), whereas Berkenstadt and colleagues reported no significant changes in filling pressures during these phases [4]. Another difference was their use of ephedrine and phenylephrine to treat hypotension. We did not treat this response, although we found a significant decrease in MAP and increase in CI and HR [4].

Two patients in our study developed ventricular ectopic beats, PVC (premature ventricular complex) in bigeminy, after occlusion release. These changes in haemodynamic values and the observed arrhythmia are compatible with a post reperfusion syndrome (PRS). The existence of a PRS is known from studies de-

scribing liver transplantation [11, 12]. It is characterized by brady-arrhythmia, a decreased MAP, SVR and increased mPAP, PAWP and RAP. From studies on single aortic cross-clamping it is also assumed that splanchnic hypoperfusion releases myocardial-depressant factor(s) from the hypoxic tissues, causing myocardial dysfunction after declamping [1]. A rapid decrease in temperature may contribute to PRS [11, 12]. As a result of perfusion of the abdomen with fluid below room temperature, hypothermia develops during the HAP phase. There was, however, no immediate change in blood temperature in the AR phase or the CR phase (Fig. 2 and 3).

This less invasive perfusion procedure has been said to avoid significant pain or bleeding and be possible even in frail and debilitated patients [4, 5]. These studies reported cardiovascular changes, but neither mentioned changes in cardiac performance [4, 5]. We disagree that the procedure is trivial. Six patients in our study needed i.v. SNP to control cardiovascular changes. Cardiac wall motion abnormalities were observed in all the TOE monitored patients, probably as a result of myocardial ischaemia, and these abnormalities did not disappear until occlusion release. The increase in the left and right ventricular stroke work indices remained, accompanied by elevated PAWP. Carrying out perfusion under local anaesthesia, without invasive haemodynamic monitoring, in frail or debilitated patients, seems unwise because of the possible additional cardiac stress caused by awareness. The suggested stabilizing effect of additional vena cava occlusion was small. We therefore conclude that the large circulatory changes during simultaneous occlusion of the thoracic aorta and inferior cava make invasive haemodynamic monitoring necessary.

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CHAPTER 3

COMPARISON OF VO_2 MEASUREMENT TECHNIQUES DURING OLT

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Based on: Comparison of closed-circuit and Fick-derived oxygen consumption during anaesthesia for liver transplantation in patients.
Adv Exp Med Biol 2002; in press

Summary

Background: Orthothopic liver transplantation (OLT) in patients induces major cardiovascular effects. The VO_2 curves that are continuously shown by the PhysioFlex® quantitative closed system anaesthesia ventilator seem to follow the actual intra-operative cardiovascular responses due to surgical manipulation. We compared the PhysioFlex®-derived VO_2 measurements, VO_2(Flex), with the intermittently Fick-derived VO_2 calculations, VO_2(Pac) during OLT in patients.

Methods: Anaesthesia in 16 consecutive patients undergoing OLT consisted of sufentanil, midazolam and pancuronium. Measurements of cardiac output and immediate analysis of blood samples, necessary for calculation of VO_2(Pac), are done at six previously defined times that are equally divided over all stages of the procedure. VO_2(Pac) is then compared with the time corresponding VO_2(Flex).

Results: Mean VO_2(Pac): 167 ± 56 $ml.min^{-1}$ (range 79-416 $ml.min^{-1}$), mean VO_2(Flex): 219 ±52 $ml.min^{-1}$ (range 122-400 $ml.min^{-1}$). Linear regression analysis revealed: $VO_2(Pac) = 0.87\ VO_2(Flex) – 24$ ($ml.min^{-1}$); Spearman rank correlation: $r = 0.82$, $p<0.0001$ and analysis according to Bland-Altman: bias 52 $ml.min^{-1}$ and precision 33 $ml.min^{-1}$, no significant agreement between both measurement techniques; $r = 0.05$ ($p = 0.66$), difference between the 95% limits of agreement 134 $ml.min^{-1}$.

Conclusion: We conclude that although a significant correlation with a reasonable approximation of the expected linear regression curve is found, the level of agreement between VO_2(Pac) and VO_2(Flex) is poor making them clinically not interchangeable. In daily clinical practice the PhysioFlex® provides an immediate and accurate oxygen uptake value without the necessity of invasive monitoring.

Background

During liver transplantation in humans major cardiovascular effects are reported [1]. Changes in the VO_2 level during the intra-operative period of major surgery, e.g. liver reperfusion, are often not measured [2]. Before major elective surgery preoperative optimisation of oxygen delivery is recommended to improve outcome [3]. Since the 1980s, tissue oxygen debt, reflected by inadequate oxygen consumption (VO_2) in the intra-operative and immediate postoperative periods is considered a common determinant of multi-system organ failure and death [4]. The PhysioFlex® ventilator performs quantitative closed system anaesthesia; it shows continuously the intra-operative oxygen uptake [5]. These VO_2 curves seem to follow the actual intra-operative cardiovascular responses to surgical manipulation [6]. In this study we compared the continuous, PhysioFlex®-derived VO_2 measurements, VO_2(Flex), with the accepted method of intermittently Fick-derived VO_2 calculations by means of a pulmonary artery catheter, VO_2(Pac).

Patients and Methods

Sixteen consecutive patients, with liver failure, undergoing orthotopic liver transplantation (OLT), were included in the study. Patient characteristics are given in Table 1.

Anaesthesia consisted of sufentanil, midazolam and pancuronium. Ventilation is performed with a closed system anaesthesia machine (PhysioFlex®, Dräger, Best, The Netherlands), using FIO_2 0.40 (oxygen-air mixture), tidal volume 8 $ml.kg^{-1}$, PEEP 5 cm H_2O. The respiratory frequency is adjusted to achieve an end-expiratory CO_2 that corresponds to a $PaCO_2$ of 4.5-5.0 kPa. FIO_2 is maintained at a constant level during the entire procedure, to make continuous real-time VO_2 monitoring with the PhysioFlex® possible. A radial artery is cannulated and a pulmonary artery balloon flow catheter (Arrow Thermo-Pace® Hands off ® Heparin-coated Thermodilution Catheter 7.5 Fr. 5 lumen 80 cm length; Arrow Deutschland GmbH, Erding, Germany) is placed in the right internal jugular vein, to which a cardiac output (CO) measurement system (Baxter CO-set® closed injectate delivery system; Baxter Deutschland GmbH, Unterschleissheim, Germany) is connected. We used iced fluid. Just before CO is measured, blood samples are simultaneously drawn from the radial and pulmonary artery and immediately analysed for oxygen and acid-base parameters in an ABL 505 and an OSM 3 hemoxymeter (both Radiometer, Copenhagen, Denmark). Measurements of CO, measured in triplicate with an inter-measurement variance <10 %, with concomitant analysis of

the above-mentioned blood samples, necessary for calculation of VO_2(Pac), were done at six previously defined times; these were defined as “Pre-incision”, after stable anaesthesia was established, but before surgical incision was made; “Steady State”, during stable anaesthesia, before clamping of the inferior caval vein started; “Anhep”, within 10 min of the start of the an-hepatic phase; “Pre-declamp”, within 5 min before recirculation of the liver transplant will start; “Post-declamp”, about 15 min after recirculation of the transplanted liver started; “End operation”, after the surgical part of the procedure has finished.

Calculation of the Fick-derived oxygen consumption was done according to standard equations [7].

1. $VO_2(Pac)\ (ml.min^{-1}) = [CaO_2\ (ml.dl^{-1}) - C\bar{v}O_2\ (ml.dl^{-1})] \times CO\ (l.min^{-1}) \times 10$
2. $CaO_2\ (ml.dl^{-1}) = 1.31 \times Hb\ (g.dl^{-1}) \times SaO_2 + 0.0031 \times PaO_2\ (mmHg)$
3. $C\bar{v}O_2\ (ml.dl^{-1}) = 1.31 \times Hb\ (g.dl^{-1}) \times S\bar{v}O_2 + 0.0031 \times P\bar{v}O_2\ (mmHg)$

Continuous on-line monitoring of VO_2(Flex) was done using a PhysioFlex® quantitative closed system anaesthesia machine, which has a design analogous to a lung function spirometer with a computer performing the necessary calculations to carry out the minute-to-minute adjustments to ensure the preset parameters [5, 6, 8]. Oxygen is measured paramagnetically in the inspiratory part of the circuit. If the measured value is lower than the preset value, 5 ml oxygen volume boluses, calculated by the computer, are added into the system to reach and maintain the preset value. The system (patient plus PhysioFlex®) can be considered as a closed circuit when FIO_2 and expired minute volume are maintained; under these conditions the added oxygen volume equals the total body oxygen consumption [9]. No additional flushing of the closed-circuit was done. After the procedure data collection at one-minute based intervals from the PhysioFlex® was sent via the RS 232-C interface and converted by the PhysioFlexcom® program at a lap-top to an MS® Excel file.

Statistical Methods

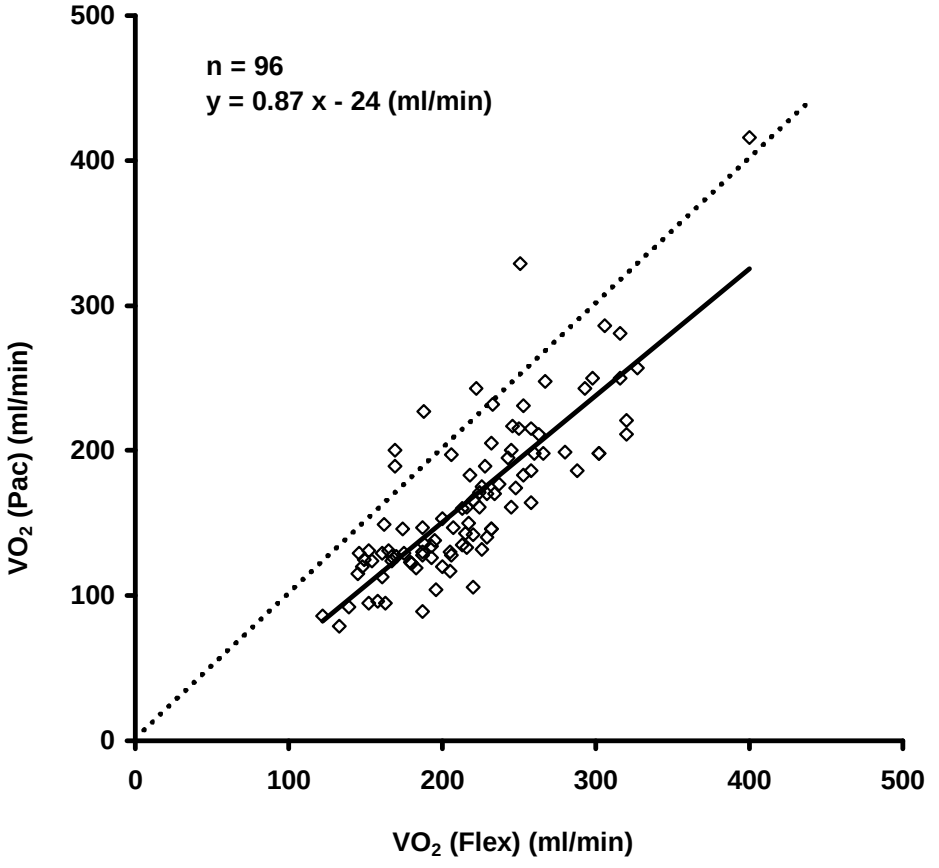
At the pre-defined times, VO_2(Pac) was compared with VO_2(Flex). The relation between the two sets of data was described using linear regression and correlation was tested with the Spearman rank correlation test. Correlation is the usual

Table 1. *Characteristics of the study patients (mean and range)*

Sex (F/M)	7/9
Age (years)	43 (17 – 60)
Body surface area (m^2)	1.68 (1.53 - 2.26)
Child-Pugh score	A: n = 2
	B: n = 5
	C: n = 9
Reasons for transplantation	- Post alcoholic cirrhosis: n = 4
	- Viral hepatitis: n = 4
	- Primary sclerosing cholangitis: n = 3
	- Primary biliary cirrhosis: n = 2
	- Wilson's disease: n = 1
	- Alagille's disease: n = 1
	- Progressive haemangioma: n = 1
Additional diagnosis	- Hypertension: n = 2
	- Protein C and S deficiency: n = 1
	- Sjögren's syndrome: n = 1
	- Rheumatoid arthritis: n = 1
	- Breast cancer T1N0, 9 years before transplant: n = 1
	- Diabetes Mellitus: n = 1
	- Pulmonary artery stenosis: n = 1
	- Hypothyroidism: n = 1

method for measuring the association between two numerical variables, whereas regression is used to describe its relationship [10-12]. Nevertheless it is better to use the Bland-Altman analysis, to describe the level of agreement between two measurement methods [12]. In this analysis the 'bias' is an estimate of how closely on average the two methods agree and the 'precision' indicates how well the methods agree for an individual [12]. By multiplying the precision with 1.96, we calculate the 'limits of agreement' which describes where 95% of the data lie [10-12]. The clinician must then decide, concerning the bias and these limits of agreement, if the two methods have a clinically useful agreement; decision about allowable error [12, 13]. We used the Bland-Altman method to analyse the level of agreement between the two VO_2 measurement techniques in order to evaluate their clinical inter-changeability. Statistical significance was considered to be at $p<0.05$.

Figure 1: *Relationship between Fick-derived oxygen consumption [VO_2(Pac)] and PhysioFlex®-derived oxygen consumption [VO_2(Flex)]*



Data are derived from 16 patients undergoing orthotopic liver transplantation, and are analysed using linear regression. The dashed line is the line of identity.

Results

The 6 defined measurement times in each patient revealed for 16 patients a total of 96 paired VO_2 values for analysis. This sample size can detect a difference of 25% between both VO_2 determinations with α=0.05 and β=0.10, assuming a standard deviation of 50. Mean VO_2 calculated using the reversed Fick method,

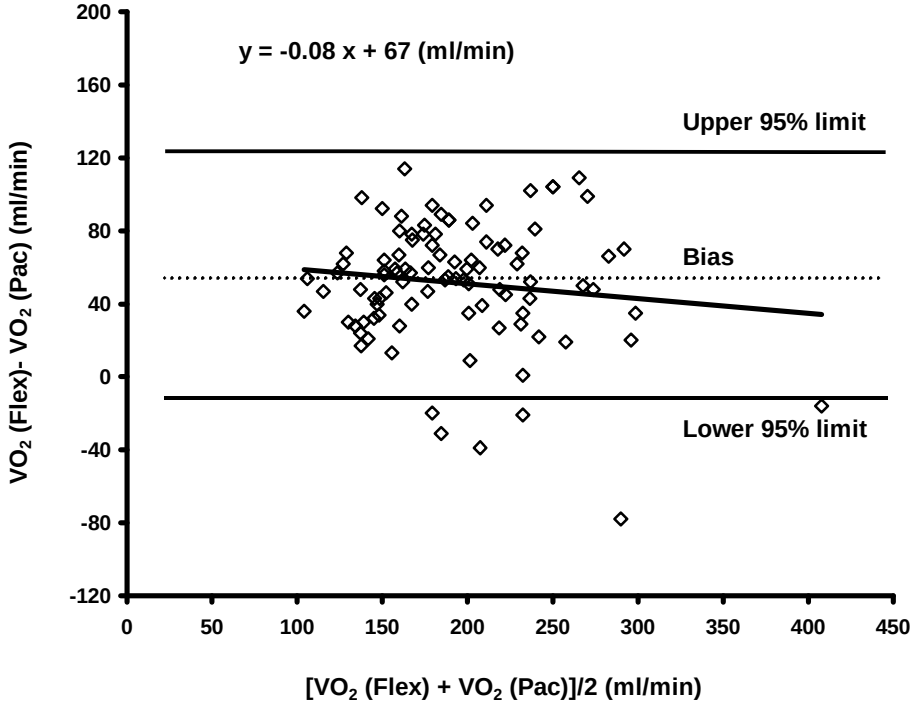
VO_2(Pac), was 167±56 ml.min^{-1}, range 79 to 416 ml.min^{-1}. Mean VO_2 measured with the PhysioFlex®, VO_2(Flex), was 219±52 ml.min^{-1}, range 122 to 400 ml.min^{-1}.

Figure 1 presents the linear regression analysis. [VO_2(Pac)=0.87.VO_2(Flex)–24 (ml.min^{-1})], 95% confidence interval (CI): 0.75<slope<1.0 and –53<y-intercept<4.8, standard deviation of residuals from line (Sy.x) = 32.75. If we force the linear regression line through x=0 and y=0, then [VO_2(Pac)=0.77.VO_2(Flex)], 95% CI: 0.74<slope<0.80, standard deviation of residuals from line (Sy.x)=33.05. The Spearman rank correlation was r=0.82 (p<0.0001; 95% CI: 0.74<r<0.88). Figure 2 presents the analysis according to Bland-Altman. The 96 paired VO_2 values were characterized by a bias of 52 ml.min^{-1} and precision of 33 ml.min^{-1}. Although the overall VO_2(Flex) was higher, the VO_2(Pac) of 6 measurement pairs (6.3%) was higher than VO_2(Flex). There was no significant agreement between both measurement techniques; r=0.05 (p=0.66; 95% CI: -0.16<r<0.25). Figure 3 presents the linear regression line between VO_2(Pac) and the difference between VO_2(Flex) and VO_2(Pac). The relationship was significant, r=-0.23 (p=0.03; 95% CI: -0.41<r<-0.02). Linear regression of VO_2(Flex) and the difference between VO_2(Flex) and VO_2(Pac) revealed: [y=0.13.x + 24 (ml.min^{-1})], slope not significant different from zero (p>0.05).

Discussion

This study describes the relation between calculated Fick-derived oxygen consumption, VO_2(Pac) and quantitative closed system (PhysioFlex®) measured oxygen consumption, VO_2(Flex), in patients undergoing orthotopic liver transplantation. We found that the VO_2(Flex) values were most often greater than the VO_2(Pac) values. These findings, a good correlation without agreement, confirm studies that have compared spirometric-derived VO_2 with Fick-derived VO_2 calculations, performed in ICU patients [14], and pigs [15]. In contrast to Stock and Ryan [15], Thrush calculated higher Fick-derived values than spirometrically measured values, in his pig model [14]; nevertheless, he also concluded that these two measurement methods are not interchangeable [16]. Amongst the methods for the measurement of VO_2, the simplest is reported to be observation of the loss of volume from a closed-circuit spirometer, with expired carbon dioxide being absorbed by soda lime [7]. The PhysioFlex® determines VO_2 by using electromagnetically measured oxygen inflow. The error of this oxygen inlet is reported

Figure 2: *Bland-Altman analysis comparing two oxygen consumption measurement techniques in 16 patients undergoing OLT*

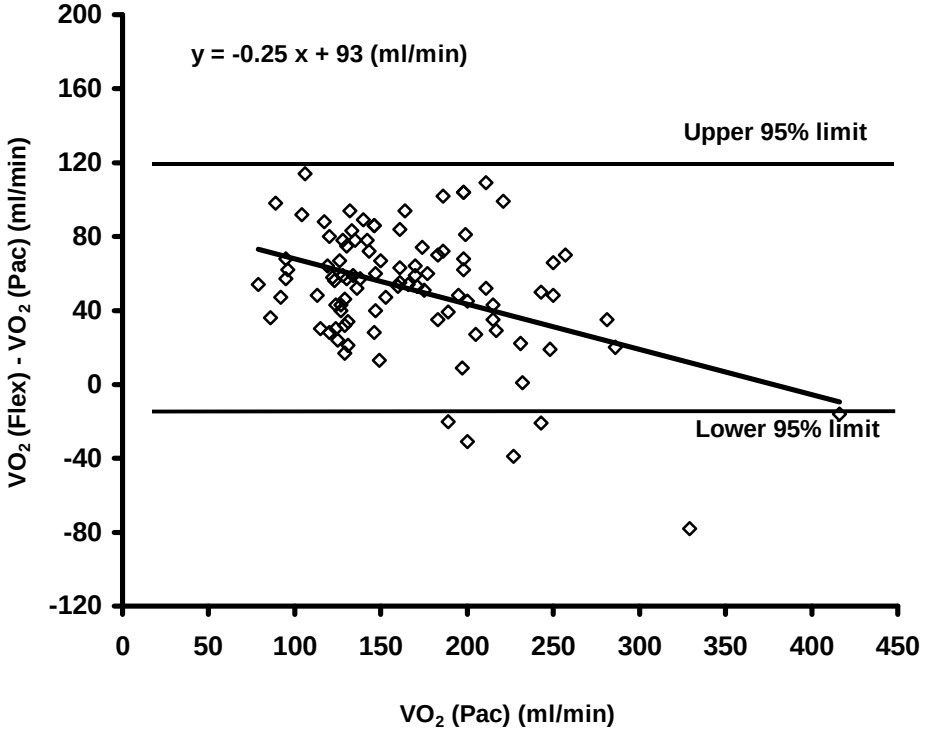


[VO_2(Flex)] = PhysioFlex®-derived oxygen consumption, [VO_2(Pac)] = Fick-derived oxygen consumption.

to be about 10% , whereas the error of the oxygen concentration analysis (done without reference gas, with a paramagnetic oxygen analyser) is reported to be about 1% [17].Measurement errors of the PhysioFlex® are thus at least 10%, if real closed conditions can be maintained. Mass spectrometric evaluation of the PhysioFlex® has shown that real closed-circuit conditions are indeed present [18, 19].

The reversed Fick method is convenient to use in the intensive care situation, where the necessary lines are commonly in place [7]. The method is described as

Figure 3: *Relationship between Fick-derived [VO_2(Pac)] oxygen consumption and the difference between closed-circuit [VO_2(Flex)] and Fick-derived oxygen consumption.*



technically simpler than the spirometer technique [14, 16], however, it has a greater variability than the spirometric method [14]. Our present study confirms the results of Smithies and colleagues [14]. The measurement of cardiac output (CO) by thermodilution is prone for many errors [20], which have their direct effect on the Fick-derived VO_2 calculations [Method section, Eq. (1)]. Another major problem with the reversed Fick method, especially in patients undergoing liver transplantation, is the poor accuracy in patients with a hyperdynamic circulatory pattern [21]. During such a circulatory pattern, the CO is large and, therefore, the arterial-venous oxygen content difference is reduced. Measurement errors of the arterial-

venous difference will then increase, 4% vs. 14%, with a concomitant increase of the error of the measured VO_2; 10% vs. 19% [21].

Comparison of spirometric or closed-circuit derived VO_2 with Fick-derived VO_2 introduces a systematic error, because blood samples drawn from peripheral and pulmonary arteries ignore the oxygen consumption of the lungs [7]. This systematic error is reported to have a mean of about 10% [7]. The expected relationship to be found by linear regression analysis is therefore at best $VO_2(Pac) = 0.9 \times VO_2(Flex)$. The linear regression lines that we found in our study, slope 0.87 or if forced through X = 0 and Y = 0, slope 0.77, seems therefore a reasonable approximation of this predicted equation, especially when we remember all the above mentioned error possibilities.

When we consider the normal VO_2 value for a 70-kg patient under general anaesthesia with a normal body temperature, being about 170 $ml.min^{-1}$ [8], the precision, inducing a difference between the 95% limits of agreement of 134 $ml.min^{-1}$, is, however, clinically unacceptable for us. Six measurement pairs (6.3%) are even outside the 95% limit of agreement. These pairs were not related to a specific part of the procedure, nor were they related to a specific patient. However, it is remarkable that in all these measurement pairs, $VO_2(Pac)$ was higher than $VO_2(Flex)$, while the $VO_2(Flex)$ was higher for the overall group. We have no explanation for this phenomenon.

The linear regression line in Fig. 2 shows a weak negative slope, which may suggest that the agreement between $VO_2(Pac)$ and $VO_2(Flex)$ becomes better when the level of the VO_2 increases [11]. This can be explained by the amplification of measurement errors when VO_2 values are low. Figure 3 shows a significant decline of impact on the difference between the VO_2 values, suggesting that measurement errors are more pronounced at lower VO_2 values. $VO_2(Flex)$, however, has almost no relationship with the difference between the VO_2 values, suggesting that measurement errors are more stable, whether the actual VO_2 is high or low.

We conclude that the level of agreement between $VO_2(Pac)$ and $VO_2(Flex)$ is poor, making them clinically not interchangeable, although a significant correlation was found, with a reasonable approximation ($y = 0.87 x – 24$) of the expected linear regression curve. In daily clinical practice the PhysioFlex® provides an immediate and accurate VO_2 value without the necessity for invasive monitoring.

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CHAPTER 4

COMPARISON OF VO_2 MEASUREMENT TECHNIQUES DURING HAP

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Based on: Comparison of closed circuit and Fick-derived oxygen consumption in patients undergoing simultaneous aortocaval occlusion.
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Summary

Agreement between continuously measured oxygen consumption during quantitative closed system anaesthesia and intermittently Fick-derived calculated oxygen consumption was assessed in 11 patients undergoing simultaneous occlusion of the aorta and inferior vena cava for hypoxic treatment of pancreatic cancer. All patients were mechanically ventilated using a quantitative closed system anaesthesia machine (PhysioFlex®) and had pulmonary and radial artery catheters inserted. During the varying haemodynamic conditions that accompany this procedure, 73 paired measurements were obtained. A significant correlation between Fick-derived and closed system derived oxygen consumption was found ($r=0.78$, $p=0.006$). Linear regression showed that Fick-derived measure = [(1.19 x closed system derived measure) – 72], with the overall closed-circuit derived values being higher. However, the level of agreement between the two techniques was poor. Bland-Altman analysis found that the bias was 36 $ml.min^{-1}$, precision 39 $ml.min^{-1}$, difference between 95% limits of agreement 153 $ml.min^{-1}$. Therefore we conclude that the two measurement techniques are not interchangeable in a clinical setting.

Background

Routine pre-operative optimisation of oxygen delivery to patients undergoing major elective surgery is now recommended [1]. Tissue oxygen debt, reflected by inadequate oxygen consumption (VO_2) in the intra-operative and immediate post-operative periods is thought to contribute to multi-system organ failure and death [2]. Nevertheless, changes in the VO_2 during the intra-operative period of major elective surgery are frequently not measured [3]. Intra-operative oxygen debt can be calculated from the difference between the measured and estimated VO_2, based on the pre-operative VO_2 corrected for the effects of anaesthesia and temperature [4]. With the development of the PhysioFlex® Rotterdam ventilator (PhysioFlex®, Dräger, Zoetermeer, The Netherlands) enabling quantitative closed system anaesthesia, intra-operative real-time curves of oxygen uptake became available [5]. These VO_2 curves appear to follow the intra-operative cardiovascular responses to surgical manipulation [6].

Significant cardiovascular effects are noted during simultaneous aortocaval occlusion [7, 8]. Simultaneous occlusion is necessary for hypoxic abdominal perfusion, a method used for regional cytotoxic therapy of the abdomen to treat pancreatic cancer [7-9]. In this study we compared continuous, PhysioFlex®-derived VO_2 measurements with intermittently Fick-derived VO_2 calculations from a pulmonary artery catheter.

Methods

Eleven consecutive patients, all classified as ASA physical status II, were enrolled after diagnostic work-up and written informed consent in the Hypoxic Abdominal Perfusion phase I-II trial for locally advanced pancreatic cancer [8]. This study was approved by the local medical ethics committee.

In the hypoxic abdominal perfusion procedure, temporary vascular isolation of the whole abdominal cavity is achieved by inflation of tourniquets placed around both upper thighs and by simultaneous inflation of two balloon catheters (arterial and venous stop-flow catheters, PFM Produkte für die Medizin GmbH, Köln, Germany), inserted in the right femoral artery and vein and advanced up to the level of the diaphragm [7-9]. Cytotoxic drugs are perfused according to a set regimen using an extra-corporeal circuit connected to both catheters (Hypoxic perfusion set; PFM Produkte für die Medizin). No oxygen is added to this extra-corporeal circuit. Hypoxic perfusion lasts 20 min, after which circulation is re-established.

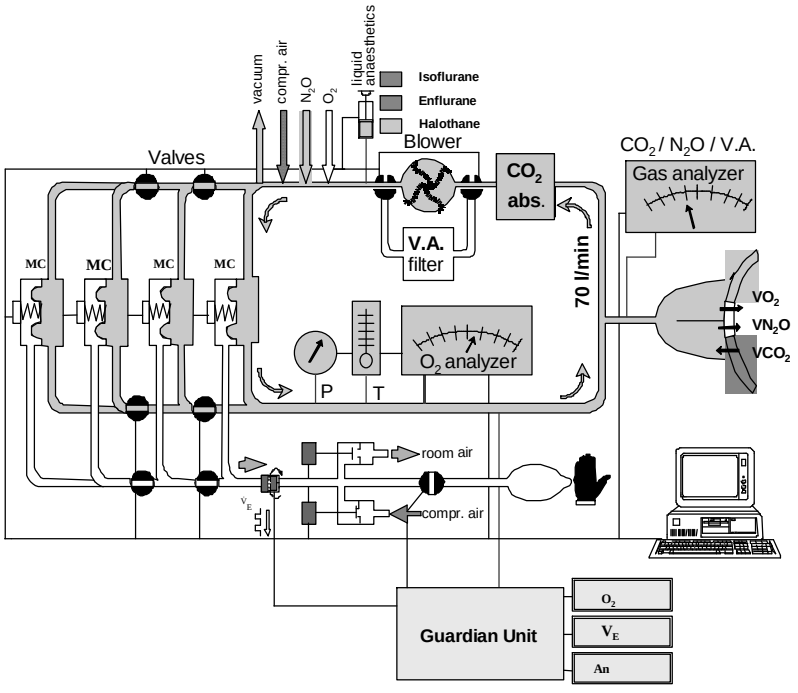
Table 1: *Characteristics of the study patients (mean and range)*

Sex; F/M	3/8
Age; years	60 (49-67)
Weight; kg	70 (54-97)
Height; m	1.74 (1.62-1.80)
Body surface area; m^2	1.82 (1.61-2.03)
Additional diagnoses; (n)	- Chronic Obstructive Pulmonary Disease (1) - Coronary artery disease (2) - Insulin-dependent diabetes mellitus (2) - Sick Sinus Syndrome with a pacemaker set in atrial pacing and sensing and inhibited (AAI) mode (1)

During anaesthesia, ventilation was provided by a PhysioFlex® closed system anaesthesia machine, using FIO_2 0.30, frequency 14 breath.min^{-1}, tidal volume 8 ml.kg^{-1}, positive end-expiratory pressure (PEEP) 5 cmH_2O, and inspiratory/expiratory ratio 1:1.2. Before induction, the PhysioFlex® set-up procedure, as detailed in the manual, was routinely performed in all patients [10]. This set-up procedure includes a leak test of the PhysioFlex® together with the breathing tubes and sample line. Gas leakage of <25 ml.min^{-1} at a test pressure of 10 cmH_2O was needed to make gas uptake measurements reliable [10]. To make continuous real-time VO_2 monitoring with the PhysioFlex® possible, the FIO_2 is held constant during the entire procedure. During the preparation phase of the groin, ventilation is adjusted to maintain $PaCO_2$ between 4.5 and 5 kPa and maintained within this range for the remainder of the procedure.

Anaesthesia was maintained using volatile anaesthetics, additional intravenous sufentanil (0.20 µg.kg^{-1}) given at the start of the surgical procedure and, if necessary, a neuromuscular blocking drug guided by a nerve stimulator (target train of four value was zero; TOF-guard; Biometer, Odense, Denmark). Ringer's lactate was given by infusion, 20 ml.kg^{-1} in the first hour of the procedure, followed by 6 ml.kg^{-1}.h^{-1} for the remainder of the procedure. Fluid management was not adjusted in response to cardiovascular measurements. A radial artery was cannulated and a pulmonary artery balloon flow catheter (Arrow Thermo-Pace® Hands off® Heparin-coated Thermodilution Catheter, Arrow Deutschland GmbH, Erding, Germany) inserted in the right internal jugular vein, to which a cardiac output measurement system (Baxter CO-set® closed injectate delivery system; Baxter Deutschland GmbH, Unterschleissheim, Germany) was connected. Just before cardiac output

Figure 1: *Schematic diagram of the closed-circuit anaesthesia machine (PhysioFlex®).*



Compr. Air = compressed air; V.A. filter = volatile anaesthetic filter (the charcoal adsorber); CO_2 abs. = carbon dioxide absorber; CO_2/ N_2O/V.A. gas analyser = an infrared spectrometer for analysis of carbon dioxide, nitrous oxide and volatile anaesthetics; MC = membrane chamber with moving membrane (necessary for regulation of artificial ventilation); VO_2 = oxygen uptake (ml.min^{-1}); VN_2O = nitrous oxide uptake (ml.min^{-1}); VCO_2 = expired carbon dioxide (ml.min^{-1}); P = pressure sensor; T = temperature sensor; O_2 analyser = paramagnetic oxygen analyser; O_2 = oxygen control in the oxygen control loop; V_E = expired minute ventilation (l.min^{-1}) in the volume control loop; An = volatile anaesthetic control (%) in the volatile anaesthetic control loop.

was measured, blood samples were simultaneously drawn from the radial and pulmonary artery and immediately analysed for oxygen and acid-base parameters in an ABL 505 and an OSM 3 haemoxymeter (Radiometer Copenhagen, Brønshøj, Denmark).

Cardiac output, measured in triplicate with an intermeasurement variance <10%, along with blood samples, necessary for calculation of Fick-derived VO_2, were performed at seven pre-defined times that were equally divided over the different stages of the procedure [8]. Fick-derived oxygen consumption was calculated according to standard equations [11].

(1) Fick-derived $VO_2(ml.min^{-1})=[CaO_2(ml.dl^{-1})-C\bar{v}O_2(ml.dl^{-1})] \times CO(l.min^{-1}) \times 10$

(2) $CaO_2(ml.dl^{-1})=1.31 \times Hb(g.dl^{-1}) \times SaO_2 + 0.023 \times PaO_2$ (kPa)

(3) $C\bar{v}O_2(ml.dl^{-1})=1.31 \times Hb(g.dl^{-1}) \times S\bar{v}O_2 + 0.023 \times P\bar{v}O_2$ (kPa)

Continuous on-line monitoring of VO_2 was performed using a PhysioFlex® quantitative closed system anaesthesia machine, which has a design analogous to a lung function spirometer with a computer performing the necessary calculations to carry out the minute-to-minute adjustments [5, 6, 12]. This closed system apparatus (Fig. 1) has a fan rotating the gases in one direction round the system at a flow rate of 70 $l.min^{-1}$. This high flow causes optimal gas mixing and immediate evaporation of computer-controlled injection of a volatile anaesthetic. Three gas management control loops operate feedback control system (an oxygen control loop which has the highest priority, a volatile anaesthetic control loop and a volume control loop).

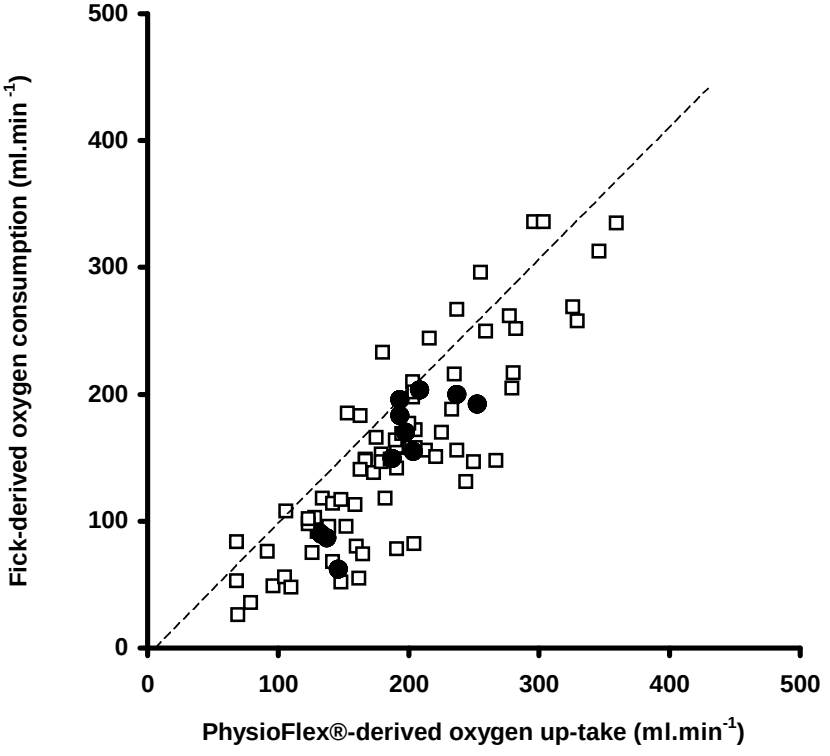
Oxygen is measured paramagnetically in the inspiratory part of the circuit. If the measured value is lower than the preset value, 5-ml oxygen boluses are added to the system to reach and maintain the preset FIO_2. If the FIO_2 and the expired volume are kept constant and the system leakage is very low, the system then functions as a closed-circuit system and the added oxygen volume equals the total body oxygen consumption of the patient [13].

The volatile anaesthetic control loop consists of an infrared spectrometer measuring the concentration of volatile anaesthetic and carbon dioxide sampling from the connection tube. A charcoal adsorber removes the volatile anaesthetic if the preset value is exceeded, and at the end of the procedure when wash-out of the volatile anaesthetic is needed. A soda-lime filled canister removes the carbon dioxide. The volume in the circle is regulated by addition of gas after each ventilation cycle, calculated by a computer using proportional integrating and differentiating algorithms. No additional flushing was used with the preset gas mixture during the measurement period. After the procedure data collection at 1-min intervals was sent from the PhysioFlex® via the RS 232C interface and converted by the PhysioFlexcom® program to a Micrsoft® EXCEL file.

Statistical Methods

At the predefined times, Fick-derived oxygen consumption was compared with the oxygen uptake measured with the PhysioFlex®. The relation between the two sets of data was described using linear regression and tested with the Spearman rank correlation test using the INSTAT 2.0 biostatistics package (GraphPad software, San Diego, USA). Bland-Altman analysis described the level of agreement between two measurement methods [14, 15]. In this analysis, the 'bias' is an

Figure 2: *Scatter diagram from 11 patients undergoing simultaneous aortocaval occlusion and occlusion release*



□ = *paired measurement (n = 73),* ● = *mean paired value (n = 11). The dashed line is the line of identity*

estimate of how closely on average the two methods agree and the 'precision' indicates how well the methods agree for an individual [14-16]. By multiplying the precision by 1.96, the 'limits of agreement' are calculated [14-16]. Special attention was given to the repeated measurements design of our study [14, 17-19]. Statistical significance was set at $p<0.05$.

Results

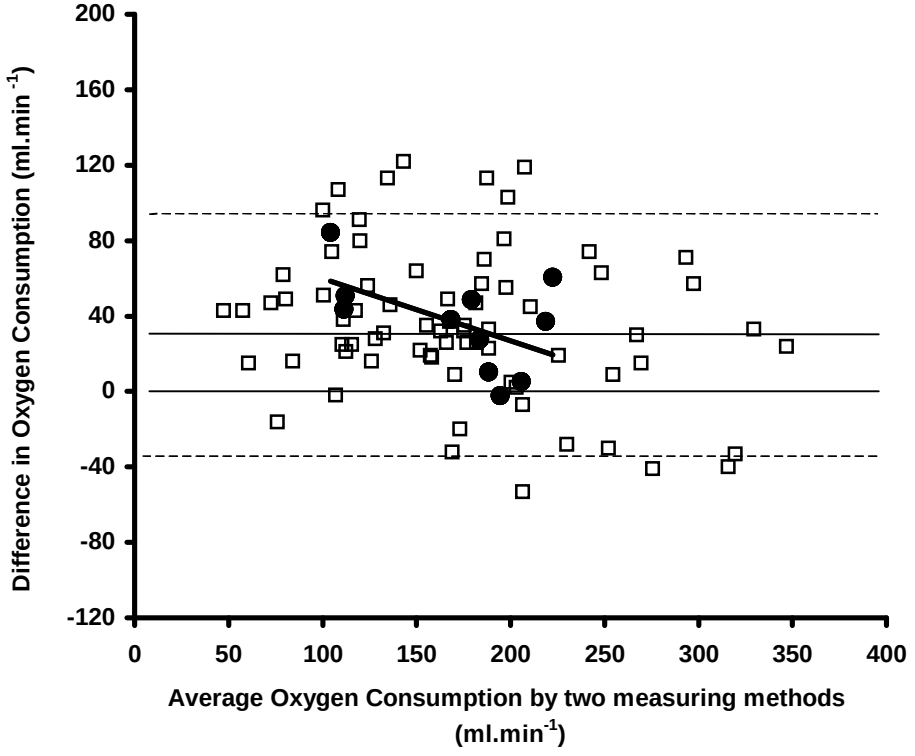
Patient characteristics are given in Table 1. In four patients, the data set at the time point 'late in the hypoxic abdominal perfusion phase' was incomplete and so a total of 73 paired VO_2 values (Fig. 2) are analysed. Mean (SD) VO_2 calculated using the reversed Fick method was 154 (76 [range 26 - 335]) $ml.min^{-1}$. Mean (SD) VO_2 measured using the PhysioFlex® was 190 (67 [range 68 - 359]) $ml.min^{-1}$. When data were corrected for body surface area (BSA), the data for Fick-derived VO_2 were, mean (SD) 83 (39 [range 16 - 189]) $ml.min^{-1}.m^{-2}$, and for VO_2 measured using the PhysioFlex®, mean (SD) 104 (35 [range 35 - 199]) $ml.min^{-1}.m^{-2}$.

Table 2: *Results of linear regression and Spearman rank correlation analysis*

Comparison of patient related mean values (n=11)	**Linear regression line**	**Spearman rank correlation (coefficient and p-value)**	**95% confidence intervals**
VO_2 pairs ($ml.min^{-1}$)	y = 1.19.x - 72	r = 0.78 p=0.006	Slope: 1.03 to 1.35 y-intercept: -103 to –41 r: 0.66 to 0.86
VO_2 pairs, line forced through origin ($ml.min^{-1}$)	y = 0.82.x		Slope: 0.79 to 0.86
VO_2I pairs ($ml.min^{-1}.m^{-2}$)	y = 1.20.x - 41	r = 0.73 p=0.01	Slope: 0.97 to 1.43 y-intercept: -65 to –17 r: 0.59 to 0.82
VO_2I pairs, line forced through origin ($ml.min^{-1}.m^{-2}$)	y = 0.81.x		Slope: 0.78 to 0.85

VO_2=oxygen consumption, VO_2I=oxygen consumption corrected for body surface area (m^2), y=Fick-derived oxygen consumption, x=PhysioFlex®-derived oxygen consumption.

Figure 3: *Bland-Altman analysis of the level of agreement between Fick-derived and PhysioFlex®-derived oxygen consumption*

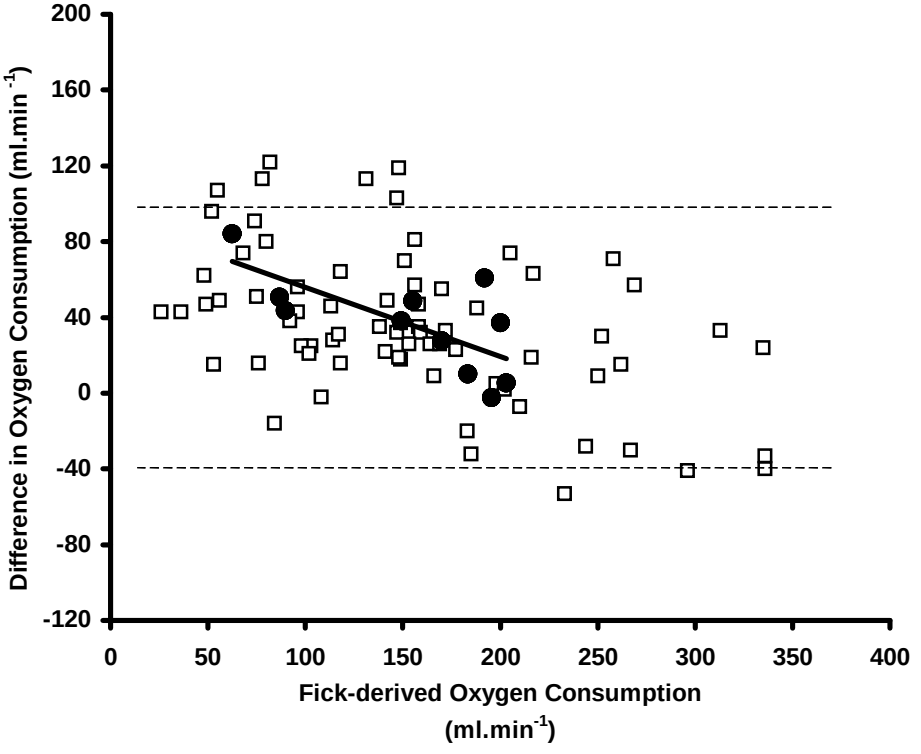


The 73 individual pairs (□) and the mean 11 pairs (●) for each patient are shown.. The linear regression line (y = -0.33.x + 93 [ml.min^{-1}]; based on 11 patients is in bold. Mean bias was36 ml.min^{-1}, indicated by the thin horizontal line. The dashed lines indicate upper and lower (95%) limits of agreement.

Table 2 presents the results of linear regression and Spearman rank correlation analysis based on the mean paired VO_2 values of 11 patients. Figure 3 shows the Bland-Altman plot. The 11 paired mean VO_2 values showed a bias of 36 ml.min^{-1} and precision of 39 ml.min^{-1}. Although the overall mean VO_2 measured with the PhysioFlex® was higher, in one paired measurement, the mean Fick-derived VO_2 was higher. The agreement between both techniques was not significant; r=-0.49 (95% CI: -0.65 to -0.28, p=0.16).

Figure 4 presents the linear regression line between mean Fick-derived VO_2 and the difference between mean VO_2 measured using the PhysioFlex® and the

Figure 4: *Relation between the Fick-derived oxygen consumption and the difference between the PhysioFlex® and the Fick-derived oxygen consumption*



The 73 individual pairs (□) and the mean 11 pairs (●) for each patient are shown. The linear regression line (y=-0.36.x + 92 [ml.min^{-1}]; based on 11 patients) is in bold. The dashed lines indicate upper and lower (95%) limits of agreement.

Fick-derived VO_2. A significant correlation between these variables was found; r=-0.71 (95% CI: -0.81 to -0.57, p=0.02). In contrast, no relationship was found between mean VO_2 measured with the PhysioFlex® and the difference between this mean value and the mean Fick-derived VO_2. Linear regression then revealed that [(Fick-derived VO_2)=-0.19.(PhysioFlex®-derived VO_2)+72] (ml.min^{-1}), Spearman rank correlation coefficient being r=-0.21 (95% CI: -0.43 to 0.03, p=0.57).

Discussion

This study describes the intra-operative relation between the calculated Fick-derived VO_2, and the quantitative closed system measured VO_2. Overall, the mean

PhysioFlex® VO_2 values were greater than the mean Fick-derived values. Agreement between these techniques reflected by the Bland-Altman analysis is poor. These findings confirm the results of an earlier study that compared spirometric derived VO_2 with Fick-derived VO_2 calculations, performed in critically ill patients [20].

Amongst the methods for the measurement of VO_2, the simplest is the loss of volume from a closed-circuit spirometer, with expired carbon dioxide being absorbed by soda lime [11]. An alternative is adding a known flow rate of oxygen to maintain the volume of the spirometer and keep its oxygen concentration constant [11]. Since 1989 our hospital has routinely used the PhysioFlex® closed-circuit anaesthesia machine which is safe and convenient and is the only commercially available device that makes quantitative closed-system anaesthesia possible in clinical practice [5, 12, 21].

Another way to monitor VO_2 is by the use of an indirect calorimeter [11]. This device is most often used at the bedside of critically ill patients in the intensive care unit, but it assumes that the patients are at steady state [11, 22, 23]. The use of a high FIO_2 and the presence of a anaesthetic gases are other reasons that make calorimetric measurements less reliable [11, 24, 25]. The reverse Fick method, a method using calculations for the VO_2 analysis, is convenient in intensive care where the necessary lines are usually in place [11]. However, the reverse Fick method has greater variability than spirometry [20]. Errors in the measurement of cardiac output by thermodilution have a direct effect on the Fick-derived VO_2 calculations (according to Eqn 1). Furthermore, because blood samples are drawn from peripheral and pulmonary arteries, the Fick-derived method systematically ignores the oxygen consumption of the lungs [11, 20, 22, 26-29]. This systematic error is reported to vary between 1% and 30%, with a mean value 10% [11, 22, 26, 29]. Another problem with the reversed Fick method is the poor accuracy in patients with a hyperdynamic circulatory pattern [28]. During such a circulatory pattern, the cardiac output is usually large and, therefore, the arterial-venous oxygen content difference reduced. It has been reported that measurement errors of this arterial-venous difference will significantly inflate the VO_2 measurement error [28].

We selected this group of patients undergoing a highly standardised procedure, because isolation of the lower part of the body induces serious variation in VO_2. This gave us the opportunity to evaluate the level of agreement at a large range of VO_2 levels in a clinical setting. The calculated total-body VO_2 is expected to be less than the measured VO_2 by the PhysioFlex®, by ≈10%, because the re-

verse Fick method ignores the VO_2 of the lungs. Thus, the expected relationship should be y=0.9.x; our results produced a slope=1.19 or if forced through the origin 0.82. This could be due to errors both in the PhysioFlex® and Fick calculation. The oxygen inlet error was reported as 10%, whereas the oxygen concentration analysis error was reported to be ≈1% [10]. Therefore, the overall error of the PhysioFlex® derived VO_2 measurements is likely to be at least 10% assuming truly closed conditions can be maintained. Mass spectrometric evaluation of the PhysioFlex® has shown that real closed-circuit conditions are in fact present [21, 30]. Considering all these sources of error, the bias of 19% of the mean Physio-Flex® derived VO_2, seems clinically acceptable. However, a normal VO_2 for a 70-kg patient under general anaesthesia with a body temperature of 37 °C, is about 170 $ml.min^{-1}$ [31]. The precision (difference between the 95% limits of agreement) was 153 $ml.min^{-1}$ which may be clinically unacceptable. Although none of the mean patient pairs and only three measurements are outside these 95% limits of agreement (Fig. 3) and were not related to any specific part of the procedure, this is considerable variability.

The linear regression line of the difference and the average (Fig. 3) showed a negative slope, which suggests that the agreement between Fick-derived VO_2 and VO_2 measured with the PhysioFlex® improved when the level of the VO_2 increased. When we plotted Fick-derived VO_2 against the difference in VO_2 (Fig. 4), the correlation (r=-0.71) was negative suggesting that the accuracy of calculated VO_2 improved as VO_2 increased. This could be explained by amplification of measurement errors when VO_2 values are low. Low VO_2 values are found during the simultaneous aortocaval occlusion, when small arterial-venous oxygen content differences are present. No relationship (p=0.57) was found between VO_2 measured with the PhysioFlex® and the difference, which suggests that the closed-circuit derived VO_2 measurements have the same accuracy independent of the VO_2 level.

We conclude that, although we found a very significant correlation (r=0.78) and an acceptable linear regression (y=0.82.x) between Fick-derived and Physio-Flex®-derived VO_2 measurements, the level of agreement between these techniques is poor. This means that they are not interchangeable. The error of the Physio-Flex®-derived VO_2 is independent of the actual VO_2 level and so monitoring of VO_2 during simultaneous aortocaval occlusion in patients can be better performed using the noninvasive VO_2 monitoring provided by the PhysioFlex®.

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CHAPTER 5

OXYGEN CONSUMPTION DURING SIMULTANEOUS AORTOCAVAL OCCLUSION

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Summary

Effects of simultaneous occlusion of the thoracic aorta and inferior vena cava on oxygen consumption (VO_2) have not yet been reported in humans. Ten patients, ASA 2, needed such simultaneous occlusion to allow hypoxic abdominal perfusion to treat pancreatic cancer. With the development of the PhysioFlex® anaesthesia machine for closed circuit anaesthesia, intra-operative real-time curves of VO_2 became available. Therefore, we were able to continuously measure VO_2, air consumption, FIO_2 and VE, and by placement of a pulmonary artery catheter, we could also intermittently calculate DO_2 during the several phases of the perfusion procedure. Immediately after simultaneous aortocaval occlusion started, VO_2 decreased by 35% (68 $ml.min^{-1}.m^{-2}$) and DO_2 then decreased below the critical value of 330 $ml.min^{-1}.m^{-2}$. At reperfusion, repayment of the oxygen debt was by a two-stage pattern: a fast repayment stage with an increase of about 65% was followed by a slow repayment stage of 14% increase (values compared to steady state). Oxygen consumption in women was found significantly lower than in men ($p<0.0001$) with significant variation between the sexes during different stages of the procedure. The oxygen debt was not completely repaid by the end of the procedure. We conclude that the found significant variation in oxygen consumption will have consequences performing low flow anaesthesia, that additional oxygen supply during the recovery period due to the initially incomplete repayment of oxygen debt may be useful and that studies on oxygen consumption must present gender specific data because of the found gender dependent variation in oxygen consumption.

Introduction

Due to clamping and subsequent declamping single aortic cross-clamping exerts major effects on both cardiovascular responses and on oxygen consumption [1-3]. The results from animal studies showing that additional clamping of the inferior vena cava can prevent severe haemodynamic effects [4, 5], could not be confirmed in clinical cardiovascular studies [6, 7]. At present, there are no reports that describe the effects on oxygen consumption (VO_2) during such simultaneous aortocaval occlusion in humans. In animals, only Gelman and colleagues compared the VO_2 changes induced by single aortic and simultaneous aortocaval cross-clamping [5]; however, they did not consider the effects on VO_2 due to declamping and they did not discuss their results.

The intra-operative effects on VO_2 are only occasionally measured during clamping procedures most likely because the measurement techniques generally used are either laborious, the spirometric method, or need invasive lines of monitoring, the reversed Fick method [8]. With the development of the PhysioFlex® anaesthesia machine in 1989 for closed-circuit anaesthesia, intra-operative real-time measurement curves of VO_2 became available [9, 10].

The aim of this study is to measure the effects of simultaneous aortocaval occlusion and subsequent occlusion release on VO_2 in patients undergoing hypoxic abdominal perfusion to treat pancreatic cancer to establish implications for perioperative management.

Methods

Ten consecutive patients (all ASA II) were enrolled in a hypoxic abdominal perfusion phase I-II trial for locally advanced pancreatic cancer after diagnostic work-up and written informed consent. This study was approved by the local medical ethical committee. Patients with significant cardiovascular disease (NYHA class II, III or IV) were excluded. Some patient characteristics are given in Table 1.

Temporary vascular isolation of the whole abdominal cavity, necessary to allow hypoxic abdominal perfusion to treat pancreatic cancer, is achieved by inflation of tourniquets , inflated to a pressure of 350 mmHg, placed around both upper thighs and by simultaneous inflation of two balloon catheters (arterial and venous stop-flow catheter, PFM Produkte für die Medizin GmbH, Köln, Germany), with a mixture of 25 ml NaCl 0.9% with contrast fluid, inserted in the right femoral artery

Table 1: *Characteristics of the patients (mean and range)*

Sex (F/M)	6/4
Age (years)	57 (48-65)
Weight (kg)	70 (45-100)
Height (m)	1.71(1.54-1.90)
Body surface area (m^2)	1.80 (1.40-2.18)
Additional diagnoses	- Non insulin dependent diabetes mellitus (n=1) - Insulin dependent diabetes mellitus (n=2) - Sick Sinus Syndrome with AAI pacemaker (n=1) - Pituitary insufficiency (n=1)

and vein and advanced to above the celiac trunc in the aorta and to the level of the diaphragm in the inferior vena cava, using radiological control [6, 7, 11]. The cytotoxic drugs are then perfused according to a set regimen using an extra-corporeal circuit connected to both catheters (Hypoxic perfusion set, PFM Produkte für die Medizin GmbH, Köln, Germany), flow rate 250 $ml.min^{-1}$. No oxygen is added to this extra-corporeal circuit. This hypoxic perfusion lasts 20 min, after which circulation of the abdomen is restored. After a stabilisation period of 10 min the tourniquets are released from the thighs.

Anaesthesia is induced with sufentanil 0.30 $\mu g.kg^{-1}$, thiopental 5 $mg.kg^{-1}$ and vecuronium 0.1 $mg.kg^{-1}$, all given intravenously. After tracheal intubation, ventilation is provided by a closed-circuit anaesthesia machine (PhysioFlex®, Dräger, Zoetermeer, The Netherlands), using IPPV with settings: frequency 14 min^{-1}, tidal volume 8 $ml.kg^{-1}$, PEEP 5 cm H_2O, and I/E ratio 1:1.2. During the preparation phase of the groin, ventilation is adjusted to maintain $PaCO_2$ between 4.5 and 5 kPa. Hereafter, the frequency remained unchanged for the remainder of the procedure. To make continuous real-time oxygen consumption monitoring with the PhysioFlex® possible, the FIO_2 is held constant at 0.35 (oxygen-air mixture) during the entire procedure. Anaesthesia is maintained with isoflurane, 0.9% end tidal, and sufentanil 0.20 $\mu g.kg^{-1}$ i.v. given at the start of the surgical procedure. Muscle relaxation is monitored continuously with a nerve stimulator (TOF-guard, Biometer, Odense, Denmark). Additional doses of i.v. vecuronium are given as needed to maintain a train-of-four value of zero. Fluid management is standardised for all patients. Ringer's lactate is given by i.v. infusion, 20 $ml.kg^{-1}$ in the first hour of the procedure, followed by 6 $ml.kg^{-1}.hr^{-1}$ for the remainder of the procedure. Sodium nitroprusside (SNP) i.v. is given as necessary to maintain mean arterial pressure during the perfusion phase to within 20% of the preoperative value. Arte-

rial pressure is measured via a radial artery cannula (Arrow radial artery catheterization set, Arrow Deutschland GmbH, Erding, Germany) and a pulmonary artery balloon flow catheter (Arrow Thermo-Pace® Hands off® Heparin-coated Thermodilution Catheter, Arrow Deutschland GmbH) is placed in the right internal jugular vein, to which a cardiac output measurement system (Baxter CO-set® closed injectate delivery system, Baxter Deutschland GmbH, Unterschleissheim, Germany) is connected. We used iced fluid. Blood samples, simultaneously drawn from the radial and pulmonary artery just before cardiac output is measured (measurement in triplicate with an intermeasurement variance <10%), are immediately analysed in an ABL 505 and an OSM 3 haemoxymeter (Radiometer Copenhagen, Brønshøj, Denmark).

The PhysioFlex® is at present the only commercially available quantitative closed system anaesthesia machine [9, 10, 12-14]. In brief, it is a closed-circuit ventilator-anaesthesia apparatus with a design analogous to a lung function spirometer with a computer performing the necessary calculations to carry out the minute-to-minute adjustments needed to ensure the preset parameters. After a procedure, a 1-min data collection from the PhysioFlex® can be sent via the RS 232C interface and converted by the PhysioFlexcom® program to a Microsoft® EXCEL file. During the current procedure, FIO_2, expired volume of ventilation per minute (VE), oxygen consumption (VO_2), and air consumption (VAIR), blood temperature and peripheral oxygen saturation (SpO_2) are measured continuously, and recorded at 1-min intervals. The oxygen delivery (DO_2) is calculated in seven patients according to a standard formula [8]. The necessary measurements for this calculation are recorded at predefined time points defined as: '*Steady State*' (SS), during stable anaesthesia before tourniquet inflation; '*Legs Separated*' (LS), the tourniquets around the thighs are inflated; '*Hypoxic Abdominal Perfusion*' (HAP), the abdominal circulation is isolated; '*Abdominal Recirculation*' (AR), only the balloons of the catheters are deflated; '*Complete Recirculation*' (CR), the tourniquets are also deflated; and '*End Operation*' (EO), just before reversal of anaesthesia will be started. During the abdominal perfusion phase, in two patients blood samples are also taken for analysis of oxygen and acid-base parameters from the abdominal circulation. For the purpose of our study, flushes of the closed-circuit system needed to avoid accumulation of foreign gases in the closed-circuit [13], are done before 'Steady State', or are postponed until 10 min after 'Complete Recirculation'. So, variation of VAIR is then only due to leakage or to changes in lung volume [15]. If i.v. SNP was necessary during the perfusion phase, the infusion was turned

off at least 4 min before abdominal reperfusion started. The time needed for the surgical preparation varied so that the time between SS and LS was (mean) 51 min (range 30–91 min); thereafter a rigid time schedule was maintained starting with the separation of the legs. Thus the periods can be defined as: LS t=0-3 min; HAP t=4-23 min; AR t=24-33 min; CR t=34-53 min; EO t=54 min.

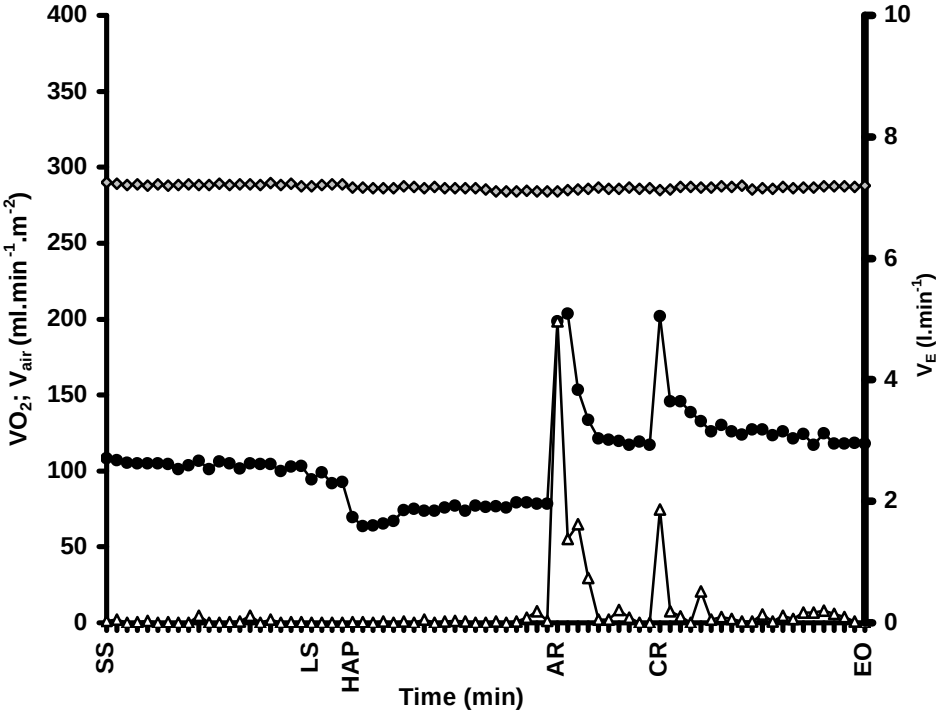
Statistical analysis

Results are expressed as mean and standard deviation (SD) unless otherwise indicated. Data were analysed using a repeated measures ANOVA to compare the mean difference between a value at a particular time point with the value at all the other time points. If $p<0.05$, a Tukey-Kramer Multiple Comparisons test was used for post-hoc analysis. A Welch test was used to compare the difference between the mean oxygen consumption level at a particular phase between men and women. A Kruskal-Wallis nonparametric ANOVA test, with Dunn's Multiple Comparisons Test for post-hoc analysis was used to compare the mean oxygen consumption differences between the sexes during the different stages of the procedure. A p-value <0.05 was considered significant.

Results

The time course of changes in the continuously measured values of VO_2, VE, and VAIR for the whole group are shown in Figure 1. At the beginning of the abdominal perfusion phase, HAP t=4-8 min, the oxygen consumption decreased by 35% (vs. SS: $p<0.001$). During the final stage of this phase, HAP t=20-23 min, this reduction was less, being 25% (vs. SS: $p<0.01$) (Fig. 1). Nine patients needed i.v. infusion of SNP during this perfusion phase in order to maintain their mean arterial pressure according to our protocol. During the first 4 min after simultaneous balloon deflation (AR t=24-27 min) an oxygen consumption peak was measured: 65% increase compared to SS ($p<0.05$). Hereafter, the oxygen consumption remained at a higher level: 15% increase compared to SS ($p<0.01$); or 50% increase compared to HAP t=23 min ($p<0.001$). After tourniquet deflation, at CR, there was another oxygen consumption peak which lasted 3 min (Fig. 1), after which the increased oxygen consumption that was already found during AR remained elevated until the end of the operation: 22% increase at EO compared to SS ($p<0.05$). As expected when using a volume controlled mode of ventilation, VE remained stable during the entire procedure (Fig. 1). Measuring air consumption (VAIR) revealed two significant peaks: one during the first minute of AR

Figure 1: Data on VO_2, VAIR, and VE during the abdominal perfusion procedure

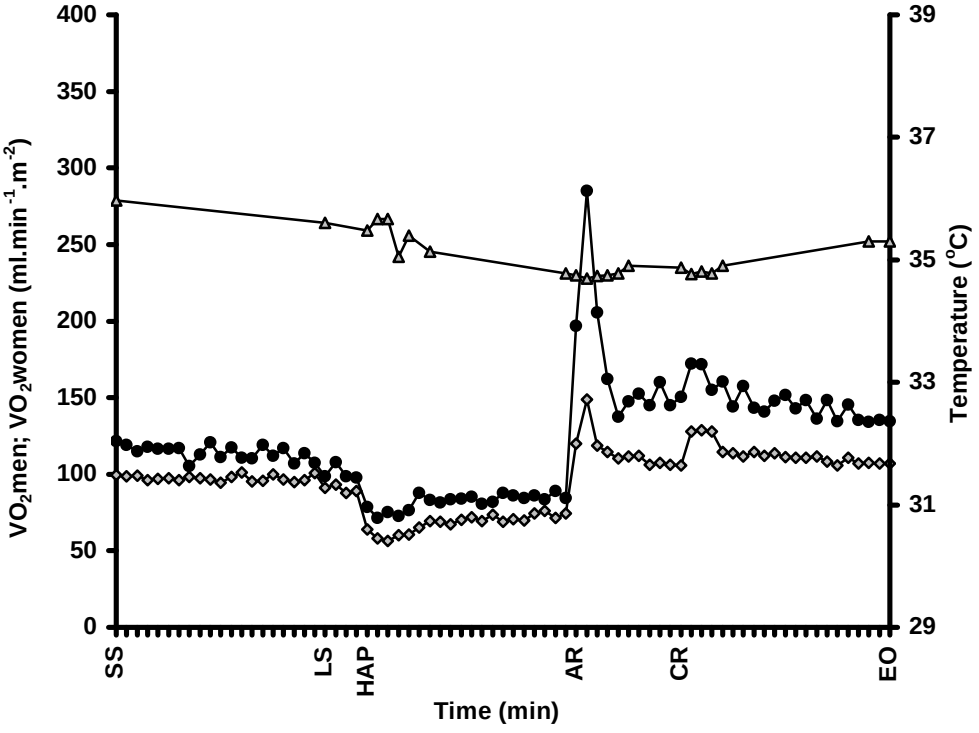


Oxygen consumption, ml.min^{-1}.m^{-2} (•), added amount of air, ml.min^{-1}.m^{-2} (Δ), and expired minute ventilation, l.min^{-1} (◊) during the procedure. SS = Steady State; LS = Legs Separated; HAP = Hypoxic Abdominal Perfusion; AR = Abdominal Reperfusion; CR = Complete Reperfusion; EO = End Operation (see text for details). Each bar on the abscissa represents one minute.

(vs. SS: $p<0.001$) and a second during the first minute of CR (vs. SS: $p<0.001$) (Fig. 1).

The difference in oxygen consumption between men and women together with the time course of changes in blood temperature is shown in Figure 2. The oxygen consumption was, with the exception of the LS phase (t=0-3 min), significantly lower by women than by men ($p<0.0001$). This difference in oxygen consumption between the sexes was significantly more pronounced during the two reperfusion phases than during the SS and HAP phases; at AR (t=28-33 min) the difference is 58 ml.min^{-1}.m^{-2}, and at CR (t=37-53 min) 35 ml.min^{-1}.m^{-2}, whereas at SS the dif-

Figure 2*: Difference in oxygen consumption between men and women, and temperature during the HAP procedure*



Oxygen consumption in men, ml.min^{-1}.m^{-2} (•), oxygen consumption in women, ml.min^{-1}.m^{-2} (◊) and blood temperature, °C (Δ) during the HAP procedure. SS = Steady State; LS = Legs Separated; HAP = Hypoxic Abdominal Perfusion; AR = Abdominal Reperfusion; CR = Complete Reperfusion; EO = End Operation (see text for details). Each bar on the abscissa represents one minute.

ference is 17 ml.min^{-1}.m^{-2}, and during the HAP phase (t=4-23 min) 14 ml.min^{-1}.m^{-2} ($p<0.001$) (Fig. 2).

Data on DO_2 calculations from seven patients, (3 men/4 women) are presented in Figure 3. Only during the HAP phase the oxygen delivery index decreased below the critical level of 330 ml.min^{-1}.m^{-2}. Table 2 gives data on blood gas analyses of the samples taken from the abdominal circulation during the HAP phase of two patients, showing the extreme hypoxia that develops in the abdominal compartment during the perfusion phase.

Table 2*: Results of analyses of blood drawn from the abdominal circulation during the HAP phase (n=2)*

Variable	**P (05 min)**	**P (10 min)**	**P (15 min)**	**P (20 min)**
Patient 1				
pH	ND	6.99	6.92	6.89
PCO_2 (kPa)	ND	10.6	11.1	12.5
PO_2 (kPa)	ND	2.6	2.6	1.4
HCO_3^- (mmol l^{-1})	ND	18.3	16.2	17.0
BE (mmol l^{-1})	ND	-13.5	-16.5	-16.8
SO_2 (%)	ND	13.1	11.6	4.6
Patient 2				
pH	7.24	7.25	7.22	7.06
PCO_2 (kPa)	8.0	7.4	7.6	10.7
PO_2 (kPa)	2.5	1.7	2.0	1.9
HCO_3^- (mmol l^{-1})	24.4	23.5	22.6	21.3
BE (mmol l^{-1})	-3.9	-3.2	-4.4	-9.2
SO_2 (%)	18.7	10.0	13.8	7.5

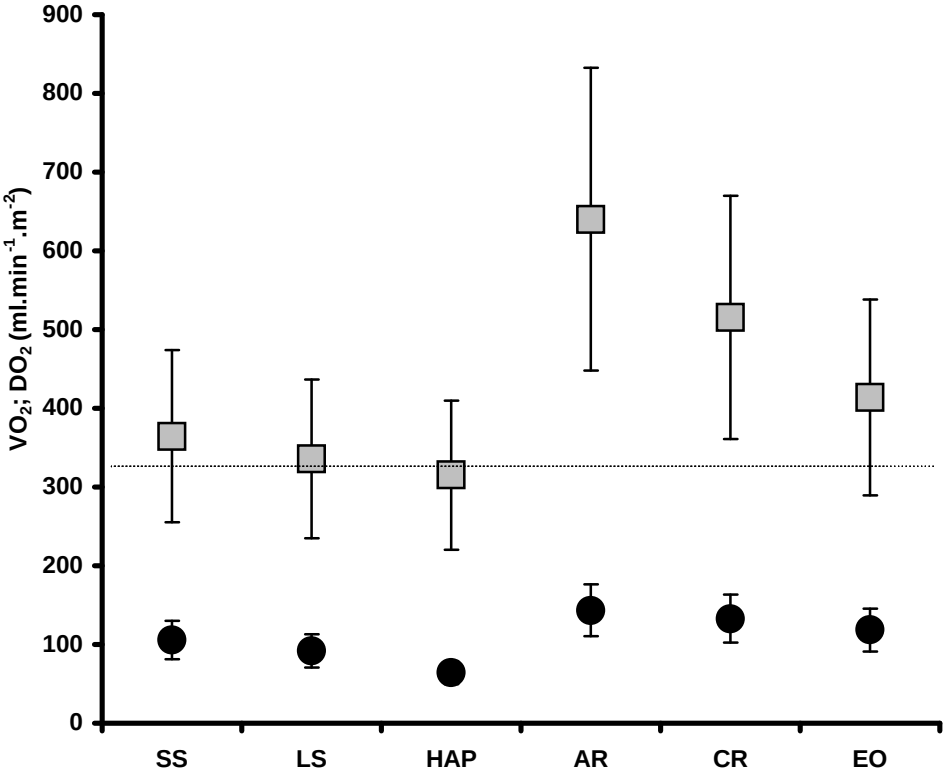
P (05 min) = blood sample drawn 5 min after perfusion started; P (10 min) = blood sample drawn 10 min after perfusion started; P (15 min) = blood sample drawn 15 min after perfusion started; P (20 min) = blood sample drawn 20 min after perfusion started; PCO_2 = partial pressure of carbon dioxide; PO_2 = partial pressure of oxygen; HCO_3^- = bicarbonate ion; BE = base excess; SO_2 = oxygen saturation. All blood samples were drawn from the perfusion catheter from the abdominal compartment. ND = No data available.

Discussion

To our knowledge, effects of simultaneous aortocaval occlusion and occlusion release on oxygen consumption have not yet been described in humans. We found that isolation of the abdomen induced a significant decrease in oxygen consumption that became less when the perfusion phase proceeded. After occlusion release and also after tourniquet deflation, we measured a biphasic repayment of the oxygen debt with the magnitude being gender related. At the end of the procedure the oxygen consumption in all patients was still increased.

Our data on occlusion partly confirm the result of a study in pigs, anaesthetised with sodium methohexital followed by enflurane, that reported that the oxygen consumption decreased by 25% during simultaneous aortocaval cross-clamping [5]. Usually, the capillary perfusion and the oxygen consumption are in balance with the oxygen supply to the cell continuously auto-regulated to its needs [16, 17].

Figure 3*: Data on oxygen consumption and delivery of 7 patients during the abdominal perfusion procedure*



Oxygen consumption, ml.min^{-1}.m^{-2} (•), and oxygen delivery, ml.min^{-1}.m^{-2} (□) during the procedure. SS = Steady State; LS = Legs Separated; HAP = Hypoxic Abdominal Perfusion; AR = Abdominal Reperfusion; CR = Complete Reperfusion; EO = End Operation (see text for details). Data are mean and SD.

Under basal conditions the blood flow to the liver and kidneys take about 50% of the total body blood flow [16], and so a reduction in oxygen consumption of at least 50%could be expected during total abdominal isolation. Actually, we found in our patients during abdominal isolation a reduction in oxygen consumption of only 35%. Known factors to influence the oxygen consumption are the level of the neuromuscular blockade, the body temperature and the infusion of SNP [8, 18]. In our patients, neuromuscular relaxation remained unchanged (with a target train-of-

four value kept at zero) and the blood temperature did not significantly change within 5 min of occlusion or occlusion release.

Although SNP infusion for mean arterial pressure control was necessary in nine of our patients, remarkably, the only patient not needing such SNP infusion had the same decrease in oxygen consumption as seen in the other 9 patients. Because we added no oxygen to the extra-corporeal abdominal perfusion circuit, which is illustrated by the induction of a deep hypoxia of the abdominal compartment during the perfusion phase (Table 2), an explanation for the less than expected reduction in oxygen consumption may thus be a disturbance of the auto-regulation during the abdominal perfusion phase. Two basic theories addressing the regulation of organ perfusion during decreased oxygen availability are postulated [16]. The *vasodilator theory* assumes that found vasodilation during hypoxia is achieved by increasing formation and release of special vasodilator substances, while the *oxygen lack theory* states that vasodilation is the result of a decreased possibility to maintain normal vascular muscle contraction by the oxygen depletion itself. During the abdominal perfusion phase, we found that the oxygen delivery (Fig. 3) decreased below the critical level for oxygen supply dependency during anaesthesia, 330 $ml.min^{-1}.m^{-2}$ [19]. It has been reported that if oxygen supply dependency is detected at the whole body level, then a significant fraction of body tissue must be dependent on oxygen supply [20]. Therefore, our findings might support the oxygen lack theory.

To our knowledge, there are no reports that describe the effects of release of simultaneous aortocaval occlusion on oxygen consumption. We found that such occlusion release induces a biphasic repayment of oxygen debt in our patients (Fig. 1). Such a biphasic repayment of oxygen is known to occur after the declamping of a single cross-clamped thoracic aorta [3, 21]. In the concept of oxygen debt, an early repayment phase in which the oxygen consumption is excessively elevated for only a few minutes in order to reconstitute the phosphagen system and the myoglobin stores, is followed by a second period (of about 1 hour) to repay the debt due to anaerobic glycolysis [22, 23]. Tourniquet deflation is also known to induce a biphasic oxygen repayment pattern [24]. Our study confirmed this finding (Fig. 1, CR). However, while the increase in oxygen consumption lasts only 10 min, irrespective of inflation time or temperature of the non-perfused extremity in the study of Takahashi and colleagues, in contrast, the oxygen consumption in our patients was still increased at the end of the procedure, 20 min after tourniquet deflation. A prolonged oxygen debt was found after abdominal aortic surgery and

thought to be related to hypothermia [22]. In our patients, the prolonged oxygen repayment time after tourniquet release might thus be due to the oxygen debt induced by the abdominal isolation, although a decreased blood temperature, which might prevent sufficient blood flow and oxygen redistribution to the peripheral tissues, was not found (Fig. 2). Other causes of elevated oxygen consumption like reversal of the neuromuscular relaxation near the end of the procedure, seems more obvious [8].

Although, gender and age are known to influence oxygen consumption [25], gender is usually not taken into account when oxygen consumption measurements during abdominal aortic cross-clamping are discussed, probably because this operation is performed more often in men than in women [3, 21, 22]. Data addressing the effects of tourniquet release on oxygen consumption do, however, confirm the existence of significant differences in oxygen consumption between the sexes [24]. Our study confirms this gender-related difference (Fig. 2). The lesser metabolic changes found in women, confirmed by our data (Fig. 2), are thought to depend on their smaller muscle mass, a known independent predictive value of peak oxygen consumption [24, 26]. Other mechanisms like differences in neuro-endocrine, metabolic and cardiovascular counter-regulatory responses to exercise, could also have induced this sexual dimorphism [27].

The PhysioFlex® facilitates quantitative closed system anaesthesia if FIO_2, and expired volume of ventilation per minute are kept constant, and if the system leakage is very low [9, 10, 12-14]. Our study protocol prescribed a fixed FIO_2 level and ventilation with a volume controlled mode maintained a constant expired minute volume (Fig. 1). As noted in the method section, variation of air consumption can be due to leakage or to changes in lung volume [15]. In our study, because air consumption was almost always zero, the system leakage must also have been almost always zero (Fig. 1). The two peaks of air consumption found during the first minutes of the abdominal and leg reperfusion (Fig. 1, AR and CR) can be explained by changes in lung volume. With occlusion release, blood will be transported from the thorax cavity to the abdominal cavity (at AR) and from the body to the legs (at CR) thereby changing the FRC [28]. This change in FRC will then be compensated by an influx of air into the closed system, thus inducing peak levels of air consumption [15].

Quantitative closed system anaesthesia can be achieved with the PhysioFlex®, while non- quantitative closed system anaesthesia can be performed in routine clinical practice with a variety of machines [10]. The oxygen flow into

the system is reduced during minimal flow and non-quantitative closed system anaesthesia, with total fresh gas flows of 400 $ml.min^{-1}$. The oxygen consumption is then usually calculated by applying Brody's formula; this oxygen consumption level is then assumed to remain stable during the entire procedure [29]. We conclude that there are dramatic changes in oxygen consumption during simultaneous aortocaval occlusion procedures. Moreover, occlusion release may also induce changes in lung volume. This may thus have consequences when low flow anaesthesia is performed. The fact that oxygen consumption is still increased at the end of the procedure may provide that additional oxygen supply is useful during the patients recovery phase. In the present study women had a less pronounced variation in oxygen consumption than men. Therefore, we recommend that future studies on oxygen consumption present gender-specific data.

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CHAPTER 6

XENON ANAESTHESIA FOR SIMULTANEOUS AORTOCAVAL OCCLUSION

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Summary

Xenon anaesthesia is safe and may be useful for cardiovascular stability. Serious cardiovascular effects occur during simultaneous aortocaval occlusion in humans. We assessed the haemodynamic effects of such occlusion in 6 male patients undergoing hypoxic treatment of pancreatic cancer during xenon anaesthesia. In all patients the heart rate decreased after xenon wash-in (28%, p=0.03). Two patients needed intravenous nitroprusside during the perfusion phase to keep mean arterial pressure within 20% of its preoperative value. The pulse pressure product (the product of arterial pressure and heart rate used as a clinical indicator for myocardial oxygen consumption) doubled during this phase (p=0.03). After occlusion release, cardiac index (65%), mean pulmonary artery pressure (60%), and left (36%) and right ventricular stroke work indices (67%) increased (all p=0.03), whereas mean arterial pressure decreased (25%, p=0.03). We conclude that the severe cardiovascular changes induced by simultaneous aortocaval occlusion remain present despite the use of xenon.

Background

According to the first randomised controlled multi-centre trial on the use of xenon as an inhalation anaesthetic, xenon is safe and effective with the advantage of a more rapid recovery compared with isoflurane-nitrous oxide for anaesthesia maintenance [1]. Although xenon use for anaesthesia is expensive, a medical advantage such as improved outcome in patients undergoing major surgery by providing more optimal haemodynamics, may justify extra costs [1, 2]. Studies in healthy patients and in cardiomyopathic dogs have demonstrated that xenon does not depress myocardial contractility [3, 4]. A study in pigs showed that xenon had no apparent effects on the systemic and pulmonary vascular resistance [5]. However, very little is known about the effects of xenon in the cardiovascular diseased human [6, 7]. No detrimental effects of xenon on haemodynamics were found in a patient with cardiac tamponade, and haemodynamic stability was maintained in patients undergoing coronary artery bypass grafting [7]. Xenon anaesthesia was also shown to be satisfactory for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome [8].

Clamping the aorta is known to induce major cardiovascular effects [9]. Although clamping the inferior vena cava at the same time could prevent large haemodynamic changes in animals, additional inferior vena cava occlusion in humans during isoflurane anaesthesia showed no significant prevention of these cardiovascular effects [10-13]. Simultaneous aortocaval occlusion is necessary for hypoxic abdominal perfusion, a technique used to treat cancer with regional cytotoxic therapy of the abdomen [13-16].

In this study, we assessed the cardiovascular effects induced by the onset and removal of simultaneous aortocaval occlusion during xenon use for anaesthesia maintenance in patients with pancreatic cancer undergoing a hypoxic abdominal perfusion procedure.

Methods

After diagnostic work-up, explanation of the anaesthetic procedure and written informed consent, six consecutive patients were enrolled in the Hypoxic Abdominal Perfusion phase I-II trial for locally advanced pancreatic cancer [13]. This study was approved by the local medical ethical committee; as was the use of xenon.

The temporary vascular isolation of the whole abdominal cavity in this hypoxic perfusion procedure was achieved by inflation of tourniquets placed around the upper thighs and by simultaneous inflation of two balloon catheters (arterial

and venous stop-flow catheters, PFM Produkte für die Medizin GmbH, Köln, Germany) inserted in the right femoral artery and vein and advanced up to the level of the diaphragm, using radiological control [12-14]. The cytotoxic drugs (melphalan and mitomycin C) were perfused according to a set regimen using an extra-corporeal circuit connected to both catheters (Hypoxic perfusion set; PFM Produkte für die Medizin GmbH) with a flow rate of 250 $ml.min^{-1}$. No oxygen was added to this extra-corporeal circuit. The hypoxic perfusion lasts 20 minutes, after which circulation to the abdomen was restored. Ten minutes thereafter, the tourniquets were also released from the thighs.

Patients were pre-medicated with lorazepam 1 mg orally (the evening before) and ranitidine 150 mg (on the day of the operation). Starting the procedure, basic anaesthetic monitoring (HP M 1166A OmniCare Anaesthesia Component Monitoring System Release F, Hewlett® Packard GmbH, Böblingen, Germany) together with bispectral index (BIS) monitoring (Aspect Medical Systems BIS™ monitor model A-2000™, Aspect® medical systems Inc, Natick, MA01760, USA) was initiated. After the patients had breathed 100% oxygen for 3 min (for nitrogen washout), intravenous induction of anaesthesia was with sufentanil 0.35 $\mu g.kg^{-1}$, propofol 2.0 $mg.kg^{-1}$ and *cis*-atracurium 0.17 $mg.kg^{-1}$. Then, the trachea was intubated after which the lungs were ventilated with a PhysioFlex® closed system anaesthesia machine (PhysioFlex®, Dräger, Zoetermeer, The Netherlands), using pressure-controlled ventilation (PCV) with settings of FIO_2 1.0, frequency 12 $breath.min^{-1}$, inspiratory pressure change 14 cmH_2O, positive end-expiratory pressure (PEEP) 5 cmH_2O, and inspiratory/expiratory ratio 1:1.2. A nasogastric tube was inserted and further nitrogen washout was continued for at least 5 min. If necessary, extra doses of propofol were given guided by the value displayed by the BIS monitoring system (target value <55). Anaesthesia was then maintained with xenon, washed in by using the 1-min flush of the PhysioFlex® to reach an inspiratory xenon concentration of at least 60%. Muscle relaxation was continuously monitored with a nerve stimulator (target train of four value was zero; TOF-Guard; Biometer, Odense, Denmark). At the start of the surgical procedure, additional sufentanil (0.17 $\mu g.kg^{-1}$) and if necessary, *cis*-atracurium (0.05 $mg.kg^{-1}$) were given intravenously. During the preparation phase of the groin, ventilation was adjusted to keep $PaCO_2$ between 4.5 and 5 kPa and maintained for the rest of the procedure. Ringer's lactate was given by infusion, 20 $ml.kg^{-1}$ in the first hour of the procedure, followed by 6 $ml.kg^{-1}.h^{-1}$ for the remainder of the procedure. Fluid management was not adjusted for any change in cardiovascular measurements. A radial artery was cannulated and a pulmonary artery balloon flow catheter (Arrow Thermo-

Pace®Hands off® Heparin-coated Thermodilution Catheter, Arrow Deutschland GmbH, Erding, Germany) was inserted the right internal jugular vein, to which a cardiac output measurement system (Baxter CO-set® closed injectate delivery system; Baxter Deutschland GmbH, Unterschleissheim, Germany) was connected. If necessary, sodium nitroprusside was given intravenously to control mean arterial pressure (mAP) during the abdominal perfusion phase to within 20% of the preoperative value. However, for practical reasons, after one-third of the perfusion phase had elapsed without the necessity for starting this drug, infusion of sodium nitroprusside was not longer started regardless of the mAP level. Transoesophageal echocardiography was not available. Twenty minutes before the end of the procedure, the patients were given intravenous ondansetron, 8 mg. At the end of the procedure, the neuromuscular block was antagonised as needed.

Data collection

Non-invasive derived blood pressure and heart rate (HR) were noted the day before the operation was scheduled. ECG, mAP, HR, right atrial pressure (RAP), mean Pulmonary Artery Pressure (mPAP), blood temperature (measured by the thermodilution catheter) and peripheral oxygen saturation (SpO_2) were continuously measured and a record was made of the values at each minute of the procedure. Because the PhysioFlex® Rotterdam ventilator facilitates quantitative closed system anaesthesia, we also were able to construct a 1-min record of the whole body oxygen consumption (VO_2) during the procedure [17]. Cardiac output (CO) measured in triplicate with an intermeasurement variance <10%, and pulmonary artery wedge pressure (PAWP), measured just before CO, were noted at previously defined times. These were *'Steady State'* ([SS], stable anaesthesia before tourniquet inflation), *'Legs Separated'* ([LS], only the tourniquets around the thighs were inflated), *'Hypoxic Abdominal Perfusion phase a'* ([HAPa], complete abdominal isolation had just been achieved by inflation of both balloon catheters), *'Hypoxic Abdominal Perfusion phase b'* ([HAPb], within 5 min before the deflation of the balloon catheters would start), *'Abdominal Recirculation'* ([AR], only the balloons of the perfusion catheters were deflated), *'Complete Recirculation'* ([CR], the tourniquets around the thighs were now deflated also), *'End Operation'* ([EO], just before reversal of anaesthesia would start), and *'Recovery'* ([REC], during the recovery from general anaesthesia, at the recovery room). The time needed for the surgical preparation of the groin varied.

Table 1: *Characteristics of the patients (mean and range)*

Sex; F/M	0/6
Age; years	63 (53 - 67)
Weight; kg	72 (54 - 85)
Height; m	1.77 (1.74 - 1.80)
Body surface area; m^2	1.88 (1.65 - 2.05)
ASA classification	I: n=1; II: n=5
Additional diagnoses	Chronic Obstructive Pulmonary Disease (n=1) Coronary artery disease (n=2) Insulin-dependent diabetes mellitus (n=1)

Thereafter, a rigid time schedule was maintained starting with the separation of the legs and lasting till the end of the operation. Therefore, we defined [LS] starting at t=0 min; [HAP] at t=4 min; [AR], at t=24 min; [CR] at t=34 min; and [EO] was at t=54 min. Cardiac index (CI), stroke index (SI), systemic vascular resistance index (SVRi), pulmonary vascular resistance index (PVRi), left ventricular stroke work index (LVSWi) and right ventricular stroke work index (RVSWi) were calculated using standard formulae. We also calculated the pulse pressure product (PPP), the product of AP and HR, that is used as a clinical indicator for myocardial oxygen consumption [18]. For each patient, these calculations were done using the continuously measured variables that were collected at the same time as CO had been measured. However, because CO and PAWP were measured "just after inflation of both balloon catheters" and not for instance always at "the third minute of the abdominal perfusion phase (t=6 min)", it was not possible to construct a precise time-related set of the values of these intermittently measured variables for the entire group. If sodium nitroprusside was given during the perfusion phase, the infusion of this drug was stopped after determination of [HAPb], but at least 4 min before abdominal reperfusion would be initiated.

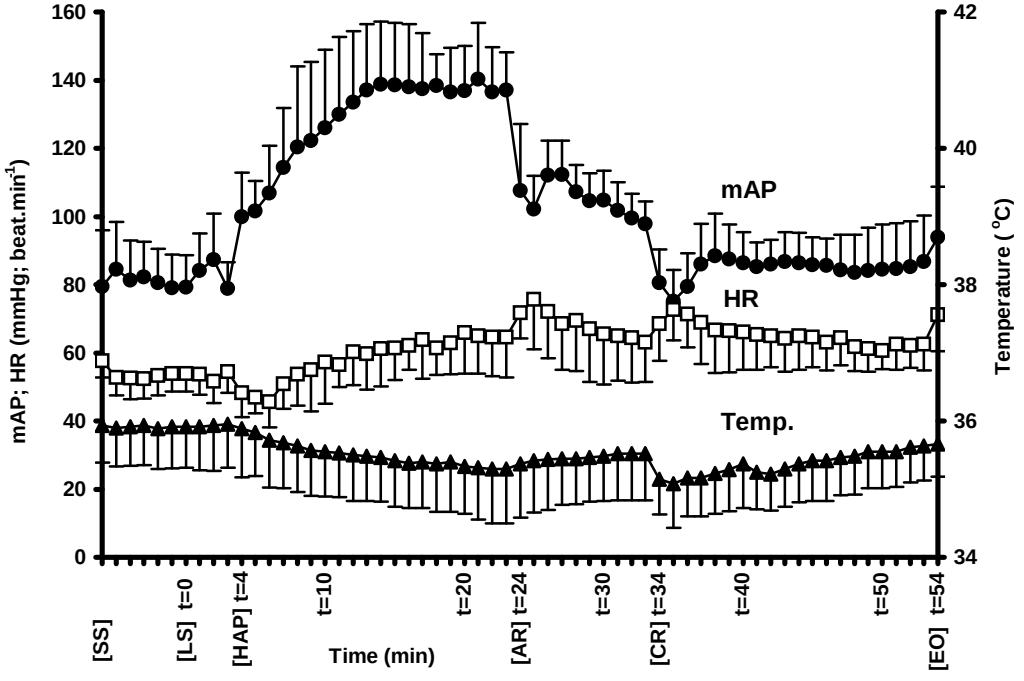
Statistical Methods

Results are expressed as mean and standard deviation (SD) unless otherwise indicated. Analysis were made with the Instat 2.0 biostatistics package (Graphpad software, San Diego, CA 92121, USA). Data were analysed with a Wilcoxon signed ranks test, as recommended by Miles and Gin, to compare the observed mean difference between a value of a defined time point with the value at steady state, or with the value of another relevant time point of the procedure [19]. A p-value <0.05 was considered significant.

Results

The patient characteristics are given in Table 1. Two patients had coronary artery disease: one patient underwent coronary artery bypass grafting (CABG) of the right coronary artery 14 years previously, and the other patient underwent percutaneous transluminal coronary angioplasty (PTCA) of the right coronary artery five years previously. Both were now classified as NYHA I.

Figure 1: *Data on mean arterial pressure, heart rate and blood temperature during the perfusion procedure*

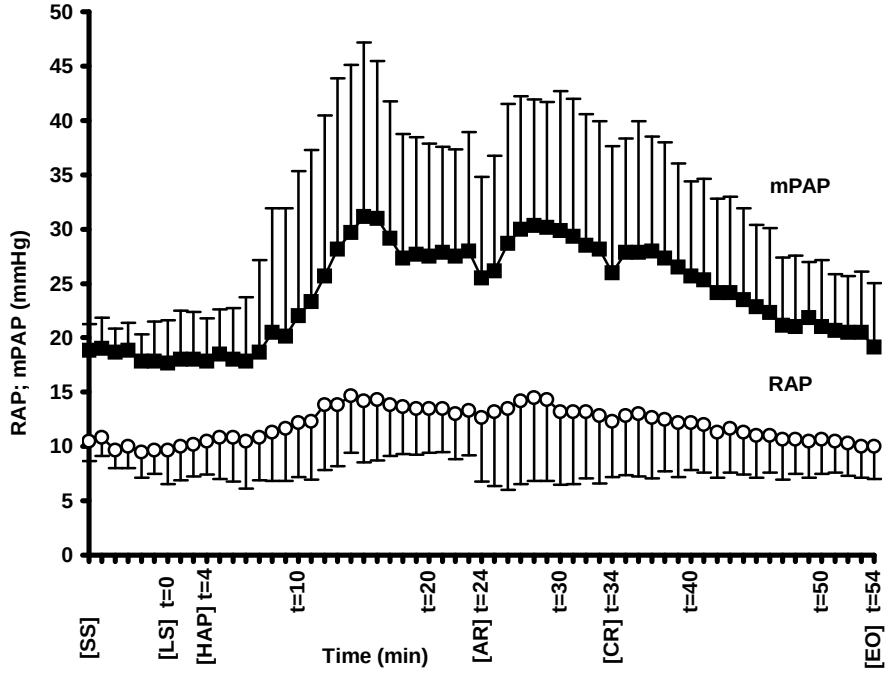


Mean arterial pressure, mmHg (•), heart rate, beats per min (?), and blood temperature, °C (?). [SS] = Steady State; [LS] = Legs Separated; [HAP] = Hypoxic Abdominal Perfusion; [AR] = Abdominal reperfusion; [CR] = Complete Reperfusion; [EO] = End Operation (see text for details). Each bar on the abscissa represents one minute. Data are mean (SD).

The time needed for the surgical preparation of the groin (time between 'steady state' and 'legs separated') was mean 72 min (range 20-115 min). The measurements performed during the recovery phase were at mean 77 min (range 52-96 min) after the time point 'end operation' (t=54 min).

Figures 1 and 2 show the time course of changes in the continuously measured variables mAP, HR, RAP, mPAP and blood temperature during the procedure. Table 2 gives data on these variables with xenon (at steady state) and without xenon (during the recovery phase), as well as data on preoperatively measured values of the non-invasively derived mean blood pressure and HR. The preoperatively measured value of the mean blood pressure was not significantly different from the

Figure 2: *Data on right atrial pressure and man pulmonary artery pressure during the perfusion procedure*



Right atrial pressure, mmHg (?), and mean pulmonary artery pressure, mmHg (¦). [SS] = Steady State; [LS] = Legs Separated; [HAP] = Hypoxic Abdominal Perfusion; [AR] = Abdominal reperfusion; [CR] = Complete Reperfusion; [EO] = End Operation (see text for details). Each bar on the abscissa represents one minute. Data are mean (SD).

Table 2: *Data derived before, during and after xenon use for anaesthesia for aortocaval occlusion*

Parameter	**mAP** (mmHg)	**HR** (beat.min^{-1})	**RAP** (mmHg)	**mPAP** (mmHg)	**Temp.** (ºC)
[Pre-op] (Air)	96.2* (9.0)	74.4* (6.0)	-	-	-
[SS] (Xenon-oxygen)	81.2 (10.9)	53.8 (5.1)	10 (1.9)	18 (3.0)	35.9 (0.6)
[REC] (Air)	88.8 (22.5)	76.7* (12.0)	5.3* (2.7)	16.8 (5.5)	36.5 (0.3)

*[Pre-op] = values derived the day before the operation was scheduled; [SS] = Steady State; [REC] = during recovery from anaesthesia at the recovery room; mAP = mean arterial pressure, RAP = right atrial pressure, mPAP = mean pulmonary artery pressure, Temp. = blood temperature. Values are mean and (standard deviation); * = p<0.05 compared with the value at steady state*

mAP value found during the recovery phase (Table 2, mAP: [Pre-op] vs. [REC], p=0.56). However, at steady state, mAP decreased by 16 % compared with the preoperative value, but it was not significantly different compared with the value during recovery (Table 2, mAP: [SS] vs. [Pre-op], p=0.03 and [SS] vs. REC, p=0.44). In two patients, the mAP increased during the first third of the perfusion phase to greater than 120% of the preoperative measured value. According to our protocol, infusion of sodium nitroprusside was started in these patients. After balloon deflation, a 20% reduction in the first min (t=24 min) and a 25% reduction in the second min (t=25 min) occurred in all patients (Fig. 1, mAP: [AR] (t=24 and t = 25 min) vs. [HAP] (t=23 min), p=0.03), although sodium nitroprusside infusion was stopped at least 4 min before deflation was initiated. This effect was also seen when the tourniquets were deflated (Fig. 1, mAP: [CR] (t=34 and t=35 min) vs. [AR] (t=33 min), p=0.03). The HR during steady state (with xenon use) decreased by 28% compared with preoperative and recovery values (no xenon use) (Table 2, HR: [pre-op] vs. [SS], and [SS] vs. [REC]; both p=0.03). When simultaneous occlusion started, the HR decreased further, maximum 16% at t=6 min (Fig.1, HR: [LS] (t=3 min) vs. [HAP] (t=4 to t=6 min, all p=0.04). The HR then slowly increased till the end of the perfusion phase (Fig. 1, HR: [HAP] (t=6 min) vs. [HAP] (t=23 min), increase 42%, p=0.04). After balloon ([AR]) and tourniquet ([CR]) deflation, the HR increased further for 3-min periods by about 11% (Fig. 1, HR: [AR] (t=26 min) vs. [HAP] (t=23 min), p=0.04 and [CR] (t=36 min) vs. [HAP] (t=23 min), p=0.03). The RAP remained unchanged during the procedure (Fig. 2, RAP). Patients developed pulmonary hypertension during the perfusion phase, which lasted after the tourniquets were released from the upper thighs (Fig. 2, mPAP: [HAP] (t=12 min) to [CR] (t=41 min), 0.03<p<0.05).

Table 3 gives data on CI, PAWP, SI, SVRi, PVRi, LVSWi, RVSWi, Pulse Pressure Product and VO_2 during different phases of the procedure. The VO_2 value that we have taken into account, was the value that we measured at the same time that CO was measured in a particular patient. During xenon use (at steady state) CI decreased, while SVRi and PVRi increased compared with values calculated when no xenon was applied (during recovery). At the start of the simultaneous

Table 3: *Results of cardiovascular and oxygen consumption measurements during the procedure*

Parameter	**[SS]**	**[LS]**	**[HAPa]**	**[HAPb]**	**[AR]**	**[CR]**	**[EO]**	**[REC]**
CI	1.8	1.6	1.1*	1.7	2.8*	2.8*	1.9	3.0*
($l.min^{-1}.m^{-2}$)	(0.6)	(0.5)	(0.2)	(0.9)	(1.4)	(1.0)	(0.6)	(0.6)
PAWP	10	10	12	22*	19	15	11	10
(mmHg)	(2)	(3)	(5)	(9)	(14)	(8)	(5)	(5)
SI	33	31	22*	25*	38	40	30	40
($ml.m^{-2}$)	(14)	(12)	(4.4)	(10)	(13)	(13)	(10)	(8.9)
SVRi	3575	3998*	8187*	7109*	3094	2070*	3413	2136
($dyne.s.cm^{-5}.m^2$)	(1286)	(1408)	(1770)	(3660)	(1328)	(1014)	(1561)	(310)
PVRi	451	410	412	488	300*	399	469	201*
($dyne.s.cm^{-5}.m^2$)	(186)	(189)	(27)	(220)	(227)	(106)	(169)	(60)
LVSWi	36	33	32	42*	57*	42	33	47
($g.m.m^{-2}.beat^{-1}$)	(15)	(13)	(7.5)	(14)	(22)	(15)	(13)	(16)
RVSWi	6.7	6.4	4.6	7.5	12.5*	13.2*	6.8	8.0
($g.m.m^{-2}.beat^{-1}$)	(2.0)	(2.4)	(2.7)	(2.9)	(5.7)	(5.8)	(2.6)	(2.3)
PPP	4287	4293	5092	8637*	7500*	5645	6732	6894
($mmHg.beat.min^{-1}$)	(787)	(823)	(960)	(1746)	(1961)	(854)	(1771)	(2184)
VO_2	188	159*	123*	149*	216	299*	215*	-
($ml.min^{-1}$)	(20)	(39)	(29)	(33)	(28)	(80)	(23)	

*[SS] = Steady State; [LS] = Legs Separated; [HAPa] = Hypoxic Abdominal Perfusion phase a; [HAPb] = Hypoxic Abdominal Perfusion phase b; [AR] = Abdominal Reperfusion; [CR] = Complete Reperfusion; [EO] = End Operation; [REC] = during recovery of anaesthesia in the recovery room (see text for details). CI = Cardiac index; PAWP = Pulmonary artery wedge pressure; SI = Stroke index; SVRi = Systemic vascular resistance index; PVRi = Pulmonary vascular resistance index; LVSWi = Left ventricular stroke work index; RVSWi = Right ventricular stroke work index; PPP = Pulse pressure product; VO_2 = Oxygen consumption; Values are mean (standard deviation); * = $p<0.05$ compared with the value at steady state.*

aortocaval occlusion, CI (39%) and VO_2 (35%) decreased, while SVRi (129%) increased (Table 3, CI, $VO_2$and SVRi: [SS] vs. [HAPa], all p=0.03). Although sodium nitroprusside was infused during the perfusion phase in 2 patients for mAP control, the SVRi increase (99% at [HAPb]) did not become significantly less elevated during this phase and the pulse pressure product then doubled (Table 3, SVRi: [HAPb] vs. [HAPa], p=0.31; PPP: [HAPb] vs. [SS], p=0.03). SVRi decreased (56%) when the balloons of the perfusion catheters were deflated, and decreased again (71%) when the tourniquets were released (Table 3, SVRi: [HAPb] vs. [AR], and [HAPb] vs. [CR], both p=0.03). At this stage, two patients developed ventricular ectopic beats, premature ventricular complex (PVC) in bigeminy. These patients were those that had received nitroprusside infusion during the perfusion phase, i.e. not the patients known to have coronary artery disease. After occlusion release, CI increased by 56% compared with steady state, and by 65% compared with the value found at the late abdominal perfusion phase (Table 3, CI: [SS] vs. [AR], and [HAPb] vs. [AR], both p=0.03). Then, SI (52%), LVSWi (36%) and RVSWi (67%) increased, while simultaneously PVRi decreased by 39% (Table 3, SI, LVSWi and RVSWi: [AR] vs. [HAPb], all p=0.03).

Discussion

Also with use of xenon for anaesthesia maintenance we found severe cardiovascular effects induced by the onset and removal of simultaneous aortocaval occlusion in our patients. At the onset of the perfusion phase, two patients needed intravenous nitroprusside to keep mAP within 20% of its preoperative value. Afterwards, although mAP had decreased by 25% (compared with the value at the end of the abdominal perfusion), left and right ventricular stroke work indices then significantly increased. However, during the perfusion phase the HR remained almost unchanged and the reduction in CI (39%), SI (33%) and VO_2 (35%) suggest that in the upper compartment of the body (thus, above the occlusion catheters) the CI also remained almost stable; these beneficial effects may be attributable to the use of xenon.

A review of the literature for effects on cardiovascular variables induced by the use of xenon in humans revealed that arterial pressure is better preserved [1, 3, 6-8, 20-22], HR has a tendency to decrease [1, 3, 6, 8, 20], RAP, PAWP, mPAP and SVRi increase [21], CI reduces [21], and LVSWi remains unchanged [21]. The fractional area change of the left ventricle is reported to be unchanged or to be less reduced [3, 7]. Most of these studies compared xenon with nitrous oxide [7, 20, 22], one study compared xenon with propofol [21], and Rossaint and col-

leagues compared it in the first randomised multi-centre trial with isoflurane-nitrous oxide anaesthesia [1].

Our data confirm most of these findings. The values of the cardiovascular variables that we found when the patients recovered (Table 3, [REC]) are very similar to the normal values reported in standard literature [23]. A comparison between the values at recovery (i.e. values that can be considered uninfluenced by the use of xenon) with the values measured during steady state (i.e. values during xenon use) is therefore meaningful. In our study patients the mAP was not significantly different between the steady state and the recovery phase (Table 2, mAP); however, mAP decreased by 16% when the value measured at steady state was compared with the pre-operative value. During xenon anaesthesia the HR of the patients decreased, compared with both the pre-operative values and values during recovery (Table 2, HR). A further comparison revealed that mPAP, PAWP, and left and right ventricular stroke work indices remained unchanged, while SVRi and PVRi increased (67% and 124%, respectively) during the use of xenon, with a concomitant decrease in CI by 40% (Tables 2 and 3).

Previous studies on simultaneous aortocaval occlusion using isoflurane anaesthesia for abdominal perfusion procedures in humans reported severe cardiovascular effects induced by the onset and removal of occlusion [12, 13]. In these latter studies, mAP increased during the perfusion phase by about 50%, which necessitates infusion of nitroprusside in combination with an increase in the given isoflurane concentration ([0.6 to 1.2]% to 2%) in all patients [12], or start of sodium nitroprusside infusion alone (isoflurane concentration maintained at 0.9% end tidal) in 86% of the patients [13]. After occlusion release SVRi decreased significantly in both studies (47% [12], and 87% [13]) and mAP was found to either immediately return to steady state [12], or to decrease below steady state by 13% [13]. The HR in these studies varied; increase during the perfusion phase 7% [12] and 42% [13], and increase after occlusion release 22% [12] and 40% [13]. The pulse pressure product at steady state was very similar in both studies (5293 [12], and 5249 $mmHg.beat.min^{-1}$ [13]). During the perfusion phase, this product increased (65% [12], and 144% [13]), and it remained increased compared with steady state after occlusion release (17% [12], and 29% [13]). The CI decreased during the perfusion phase by 29% [12] and 15% [13], and increased after balloon deflation had been performed by 82% [12], and 103% [13]. Only one of the studies presented data on left and right ventricular stroke work indices, increases after occlusion release being 75% and 139%, respectively [13].

Compared with the above studies [12, 13], the cardiovascular effects measured in the present study, using xenon for anaesthesia maintenance, are less severe. Two patients (33%) needed nitroprusside infusion for mAP control. After occlusion release, SVRi decreased by 13%, while mAP remained elevated (by about 20%) compared with steady state (Fig. 1, mAP; Table 3, SVRi). In our study, the absolute level of the pulse pressure product was lower than that was calculated from both isoflurane studies (Table 3, PPP). This may indicate that the myocardial oxygen consumption during xenon anaesthesia is less than during the use of isoflurane for maintenance. This finding is further supported by the increases of LVSWi (58%) and RVSWi (87%) found in our study (values that are less than during isoflurane use). Because the HR is a common determinant of all these variables, it is likely that the reduction of the HR induced by the use of xenon is the underlying mechanism for this beneficial cardiovascular effect.

Gelman and colleagues have suggested that the body surface area (BSA) necessary for calculation of the CI must be corrected during the aortic cross-clamping phase for the surface reduction that is due to the isolation of the lower part of the body [24]. They therefore calculated the reduced oxygen consumption in patients undergoing infra-renal single aortic cross-clamping, using the Fick equation [24]. Calculation of the reduced BSA was thereafter done by multiplying the initial calculated BSA with the ratio between the cross-clamped calculated oxygen consumption and the calculated oxygen consumption found before cross-clamping [24]. This is peculiar because there is a mathematical coupling due to the CO term that is used in the Fick equation. The corrected CI after cross-clamping the aorta then became dependent on the CI that was found before this cross-clamping started instead of the actual measured CO during the cross-clamping (see appendix for formulae). Because we measure VO_2 independently from CO by using the PhysioFlex® closed-system anaesthesia machine, this mathematical coupling is avoided. Correction of the BSA of the patients during the perfusion phase according to the formula suggested by Gelman and colleagues revealed for our study a corrected mean BSA of 1.23 m^2 (range 0.87-1.57 m^2), with a corrected mean CI of 1.7 (SD: 0.5) $l.min^{-1}.m^{-2}$. This corrected CI is not significantly different from the value we found during steady state (Table 3, CI at [SS] vs. corrected CI, p=0.84). This strongly suggests that the CI in the upper compartment of the body remained unchanged during the abdominal perfusion phase of the procedure. After balloon deflation, the CI increase (56%) is obviously less than the values reported in the human perfusion studies discussed above [12, 13]. An explanation for these less severe cardiovascular disturbances during subsequent occlusion and occlusion

release may be found in a better preservation of the vascular resistance and a reduction of the reperfusion-induced influence on myocardial performance when xenon is used [8, 25].

The ventricular ectopic beats that we observed after occlusion release, premature ventricular complex in bigeminy known to accompany a post reperfusion syndrome [13], were only seen in the two patients that needed nitroprusside infusion during the abdominal perfusion phase. Although this may be a coincidence, suspicion for future ischaemia-reperfusion studies using this combination of drugs seems warrantable.

We conclude that severe haemodynamic changes induced by the onset and removal of simultaneous aortocaval occlusion for hypoxic abdominal perfusion were still present during xenon anaesthesia. However, much lower values for HR, LVSWi, RVSWi and pulse pressure product were found than reported in earlier studies when isoflurane was used for anaesthesia maintenance. Moreover, there was a better preservation of the vascular resistance and a possible reduction of the reperfusion-induced influence on myocardial performance. These more optimal haemodynamics indicate that xenon is beneficial for anaesthesia maintenance in patients undergoing these perfusion procedures.

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Appendix:

(1) $$CI_{(preclamp)} = \frac{CO_{(preclamp)}}{BSA_{(preclamp)}}$$

(2) $$CI_{(corrected)} = \frac{CO_{(clamp)}}{BSA_{(corrected)}}$$

(3) $$BSA_{(corrected)} = BSA_{(preclamp)} \times \frac{\dot{V}O_{2(clamp)}}{\dot{V}O_{2(preclamp)}}$$

(4) $$\dot{V}O_{2(preclamp)} = (a - \bar{v})\dot{D}O_{2(preclamp)} \times CO_{(preclamp)} \times 10$$

(5) $$\dot{V}O_{2(clamp)} = (a - \bar{v})\dot{D}O_{2(clamp)} \times CO_{(clamp)} \times 10$$

Substitution of equations (1), (4) and (5) in equation (3) reveals:

$$BSA_{(corrected)} = \frac{CO_{(preclamp)} \times (a-\bar{v})\dot{D}O_{2(clamp)} \times CO_{(clamp)}}{CI_{(preclamp)} \times (a-\bar{v})\dot{D}O_{2(preclamp)} \times CO_{(preclamp)}} =$$

(6)

$$\frac{CO_{(clamp)} \times (a-\bar{v})\dot{D}O_{2(clamp)}}{CI_{(preclamp)} \times (a-\bar{v})\dot{D}O_{2(preclamp)}}$$

Substitution of equation (6) in equation (2) reveals:

(7) $$CI_{(corrected)} = \frac{CO_{(clamp)} \times CI_{(preclamp)} \times (a-\bar{v})\dot{D}O_{2(preclamp)}}{CO_{(clamp)} \times (a-\bar{v})\dot{D}O_{2(clamp)}}$$ or

(8) $$CI_{(corrected)} = CI_{(preclamp)} \times \Delta(a-\bar{v})\dot{D}O_{2(preclamp-clamp)}$$

CI = Cardiac index; CO = Cardiac output; BSA = Body surface area; $\dot{V}O_2$ *= Oxygen consumption;* $(a-\bar{v})\dot{D}O_2$ *= arterial-mixed venous oxygen content difference; preclamp = before aorta cross-clamping; clamp = during aorta cross-clamping.*

CHAPTER 7

INTRAPULMONARY SHUNT: XENON VS. ISOFLURANE ANAESTHESIA

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Based on: Comparison of the influence of Xenon vs. Isoflurane on ventilation-perfusion relationships in patients undergoing simultaneous aortocaval occlusion.
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Summary

Background: While in vitro, isoflurane is known to inhibit hypoxic pulmonary vasoconstriction (HPV) with a concomitant increase of intrapulmonary shunt (IPS) and subsequent impairment of PaO_2, data from in vivo studies are conflicting. To our knowledge, there are no reports that describe the effects of xenon on ventilation-perfusion relationships. We hypothesized that because of the suggested minimal cardiovascular effects of xenon, a lesser influence on IPS during anaesthesia would occur.

Methods: Thirteen consecutive patients needed general anaesthesia for simultaneous aortocaval occlusion to allow hypoxic abdominal perfusion (HAP) to treat pancreatic cancer. For anaesthesia maintenance, 7 patients received isoflurane, ISO group, whereas 6 patients had xenon, Xenon group. At seven predefined times, equally divided over all stages of the procedure, we calculated [$(A\text{-}a)DO_2$], [DO_2I], [VO_2I], [$(a\text{-}v)DO_2$], [PaO_2/FIO_2], [O_2ER] and [Qs/Qt].

Results: To control mean arterial pressure, 6 patients of the ISO group vs. 1 patient of the Xenon group needed nitroprusside infusion during the HAP-phase. IPS in the Xenon group decreased by 50% during most parts of the procedure, while the patients in the ISO-group remained a more or less unchanged IPS level. No concomitant influence on PaO_2 was found using xenon, while PaO_2 increased by 3.8 kPa during the HAP-phase when isoflurane was used. During the perfusion and reperfusion stages of the procedure, [$(a\text{-}v)DO_2$] and [O_2ER] differed significantly between the groups; both variables were reduced by 18-46% and 30-40% respectively, in the ISO group, while they were stable during xenon anaesthesia.

Conclusion: We conclude that xenon anaesthesia does not impair [$(a\text{-}v)DO_2$] and [O_2ER], and it reduce IPS significantly without having an effect on PaO_2. The preservation of HPV during xenon anaesthesia in humans seems thus very likely. Xenon anaesthesia may therefore be more suitable for anaesthesia maintenance during procedures in which ischaemic-reperfusion is known to appear.

Background

In vitro, isoflurane is known to inhibit hypoxic pulmonary vasoconstriction (HPV) with a concomitant increase of intrapulmonary shunt (IPS) and subsequent impairment of PaO_2 [1-3]. Data from in vivo studies are conflicting. IPS fractions are found to be unchanged [4], decreased [5], non-significant small increased [6], and significant threefold increased [7]. None of these studies reported impairment of PaO_2. Changes in cardiac output (CO) can be the reason for these conflicting results [8]. Solares and colleagues found a direct relationship between IPS and CO during balanced anaesthesia with isoflurane [9].

To our knowledge, there are no reports that describe the effects of xenon on ventilation-perfusion relationships. Clinical data suggest that the effects of xenon on the cardiovascular system are minimal [10, 11].

In our hospital, a phase I-II chemotherapy trial with melphalan and mitomycin C to treat pancreatic cancer based on hypoxic abdominal perfusion (HAP) is taking place [12]. This highly standardised surgical procedure gave us the opportunity to compare the influence of xenon vs. isoflurane on ventilation-perfusion relationships during different levels of CO. We hypothesized that because of the suggested minimal cardiovascular effects of xenon, a lesser influence on IPS during anaesthesia would occur.

Material and Methods

Thirteen consecutive patients, ASA I or II, were enrolled in the HAP phase I-II trial for locally advanced pancreatic cancer after diagnostic work-up, obtained written informed consent and explanation of the anaesthetic procedure. The local medical ethical committee approved the perfusion study and the use of xenon. The first 7 patients received isoflurane for anaesthesia maintenance (ISO group); in the next 6 patients anaesthesia was maintained with xenon (Xenon group). We excluded patients with significant cardiovascular disease (NYHA class II, III or IV). Patient characteristics are given in Table 1.

Anaesthetic Management

After starting basic anaesthetic monitoring (HP M1166A OmniCare Anaesthesia Component Monitoring System Release F, Hewlett® Packard GmbH, Böblingen, Germany) in all patients, bispectral index (BIS) monitoring (Aspect medical systems BIS™ monitor model A-2000™, Aspect® medical systems Inc,

Table 1: *Characteristics of the patient groups (mean and range)*

	ISO group (n=7)	**Xenon group (n=6)**
Sex (F/M)	4/3	0/6
Age (years)	57 (49 - 65)	63 (53 - 67)
Weight (kg)	67 (54 - 97)	72 (54 - 85)
Height (m)	1.72 (1.62 - 1.90)	1.77 (1.74 - 1.80)
Body surface area (m^2)	1.78 (1.61 - 2.03)	1.88 (1.65 - 2.05)
ASA classification	I: n = 0 II: n = 7	I: n = 1 II: n = 5
Additional diagnosis	-Diabetes Mellitus (n = 2) -Sick sinus syndrome with AAI pacemaker (n = 1)	-Diabetes Mellitus (n = 1) -Coronary heart disease (n = 2) -Chronic obstructive pulmonary disease (n = 1)

Natick, USA) was added for the Xenon group. Induction of anaesthesia was with thiopental 5 $mg.kg^{-1}$ and vecuronium 0.1 $mg.kg^{-1}$ for the ISO group and with propofol 2.0 $mg.kg^{-1}$ and *cis*-atracurium 0.17 $mg.kg^{-1}$, all i.v. given after nitrogen washout with 100% oxygen for 3 min. All patients received i.v. sufentanil 0.30 $\mu g.kg^{-1}$. After tracheal intubation, the lungs were ventilated by using 8 $ml.kg^{-1}$ tidal volume at a respiratory rate of 12 $breath.min^{-1}$, PEEP 5 cm H_2O, with a PhysioFlex® closed-circuit anaesthesia machine (Dräger, Zotermeer, The Netherlands). In the Xenon group, further nitrogen washout was now continued for at least 5 min. If necessary, additional doses propofol 0.42 $mg.kg^{-1}$ were i.v. given to keep the BIS value below 50. Anaesthesia was then maintained with isoflurane 0.9% end tidal in the ISO group or with xenon, washed in using the 1-min flush of the PhysioFlex®, reaching an inspiratory concentration of at least 60%. At the start of the surgical procedure, additional i.v. sufentanil was given, for both groups 0.20 $\mu g.kg^{-1}$. Muscle relaxation was continuously monitored with a nerve stimulator. During the procedure, the TOF value was kept zero by using additional doses muscle relaxant as necessary. Fluid management was standardized for all patients. Ringer's lactate was given by i.v. infusion, 20 $ml.kg^{-1}$ in the first hour of the procedure, followed by 6 $ml.kg^{-1}.h^{-1}$ for the rest of the procedure. Sodium nitroprusside (SNP) i.v. was given as necessary to control mean arterial pressure (MAP) during the perfusion phase to within 20% of the preoperative value. Arterial blood pressure was measured via a radial artery cannula, a pulmonary artery balloon flow catheter was placed in the right internal jugular vein. A CO measurement system was connected to the right atrial pressure port of this Swan-Ganz catheter. We used

iced fluid. Blood samples, simultaneously drawn from radial and pulmonary artery were immediately analysed in an ABL 505 (Radiometer, Copenhagen, Denmark) and an OSM 3 hemoxymeter (Radiometer, Denmark).

Surgical Procedure

Tourniquets were placed around the upper thighs to allow isolation of the legs from the circulation. Then a small incision in the right groin was made to insert two catheters (arterial and venous stop-flow catheters F12-600 mm, PFM Produkte für die Medizin GmbH, Köln, Germany) into the femoral artery and vein. They were advanced to above the celiac trunk in the aorta and the level of the diaphragm in the inferior vena cava, using radiological control. After 5000 IU of heparin, i.v. given, the abdomen was isolated, starting with inflation of the tourniquets on both upper thighs, followed by inflation of the balloon of the aortic catheter with a mixture of 25 ml NaCl 0.9% with contrast fluid and immediately afterwards inflation of the balloon of the caval catheter. The cytotoxic drugs were perfused according to a set regimen using an extra-corporeal circuit connected to both catheters (Hypoxic perfusion set, PFM Produkte für die Medizin GmbH, Köln, Germany), flow rate 250 $ml.min^{-1}$. No oxygen was added to this extra-corporeal circuit. The perfusion of the chemotherapy was maintained for 10 min, followed by a 10-min period without drugs. After a total of 20 min hypoxic abdominal perfusion, the circulation to the abdomen was restored by deflation of the balloon in the aorta, followed immediately by deflation of the inferior caval vein balloon. After a stabilization period of 10 min the tourniquets were released from the thighs.

Data Collection

During the procedure, VO_2 is continuously measured by the PhysioFlex®. After the procedure, a 1-min-interval based record is made by using the PhysioFlexcom® program and sent to a MS® EXCEL file at a lap-top. Measurements are noted at previous defined times. These are “Steady State” (SS), during stable anaesthesia before tourniquet inflation; “Legs Separated” (LS), when the tourniquets around the thighs are inflated; “Hypoxic Abdominal Perfusion” (HAP), when the abdominal circulation is isolated; “Abdominal Recirculation” (AR), when only the balloons of the catheters are deflated; “Complete Recirculation” (CR), the tourniquets are also deflated; “End Operation” (EO), just before reversal of anaesthesia is started and “Recovery” (RECOV), at the recovery room, during the recovery from

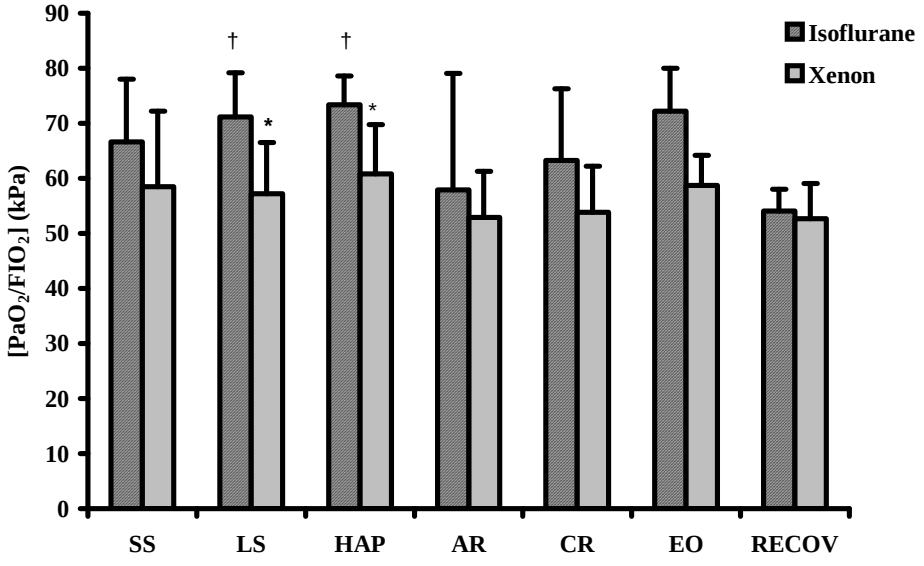
general anaesthesia. The simultaneously drawn blood samples are taken at these time points, just before CO, measured in triplicate with an inter-measurement variance <10%, is determined. If i.v. SNP is given during the perfusion phase, the infusion is turned off at least 4 min before abdominal reperfusion starts. The ratio between arterial oxygen tension and inspired oxygen fraction [PaO_2/FIO_2], the body surface indexed oxygen delivery [DO_2I], the alveolar-arterial oxygen content difference [$(A\text{-}a)DO_2$], the arterial-mixed-venous oxygen content difference [$(a\text{-}v)DO_2$], the oxygen extraction ratio [O_2ER] and the intrapulmonary shunt [Qs/Qt] are calculated according to standard formulae, using 1.31 ml O_2 as combining factor for haemoglobin [13].

Table 2: *Oxygen transport measurements during the procedure using xenon (n=6) or isoflurane (n=7)*

Variable	**SS**	**LS**	**HAP**	**AR**	**CR**	**EO**	**RECOV**
[$(A\text{-}a)DO_2$] (kPa)							
Xenon	4.3±3.5	5.1±2.6	4.7±2.4	5.4±2.3	4.8±2.0	4.3±0.6	4.5±4.3
Isoflurane	5.3±3.8	3.8±2.7	3.4±2.0	10.8±14	7.2±7.3	4.1±3.3	2.2±1.5
[DO_2I] ($ml.min^{-1}.m^{-2}$)							
Xenon	274±90†	222±77†	154±38†*	406±209	410±154	441±103	ND
Isoflurane	365±101	336±140	315±193*	640±202	515±117	414±121	ND
[VO_2I] ($ml.min^{-1}.m^{-2}$)							
Xenon	100±4.9†	83±16†	65±11†	117±10	150±23†	114±6.8	ND
Isoflurane	102±16	90±21†	66±13†	158±79	130±25	124±26	ND
[$(a\text{-}v)DO_2$] ($ml.dl^{-1}$)							
Xenon	4.7±0.6*	4.4±0.6*	4.1±1.0*	3.7±0.6*	5.0±1.1*	4.4±0.3	4.1±0.6
Isoflurane	3.2±1.0*	3.1±1.1*	2.2±0.7*†	2.1±0.7*†	2.4±0.7*†	3.5±0.3	3.9±0.4

** p<0.05 between xenon and isoflurane for a specific variable at a specific time point. † p<0.05 within a group, between a specific phase and RECOV [$(A\text{-}a)DO_2$], [$(a\text{-}v)DO_2$] and EO [DO_2I], [VO_2I]. ND = not done; values are mean ± SD.*

Figure 1: *Differences between "Xenon" (n=6) and "Isoflurane" (n=7) groups for the ratio between PaO_2 and FIO_2 during different stages of the procedure.*



** = p<0.05 between xenon and isoflurane at a particular time point of the procedure, † = p<0.05 within groups between a particular phase and RECOV. Data are mean (SD).*

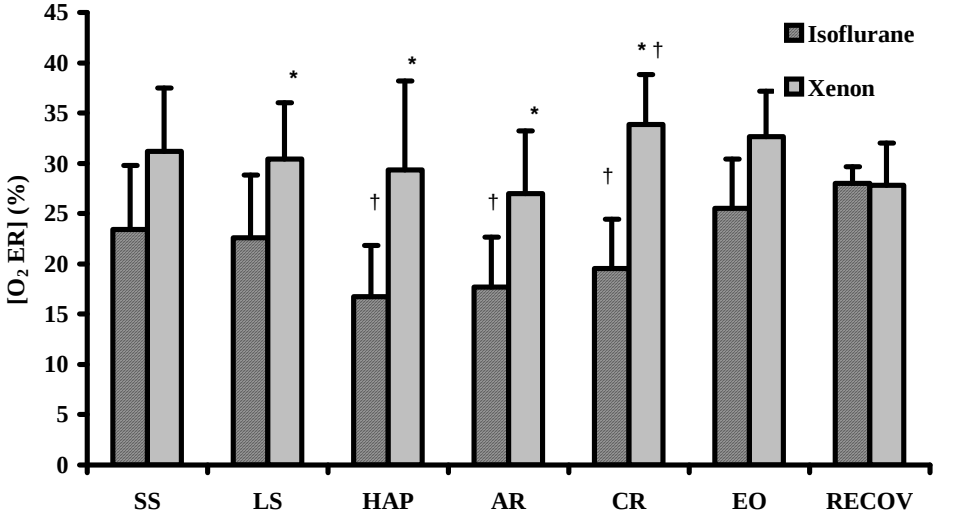
Statistical Analysis

Results are expressed as mean ± standard deviation (SD) unless otherwise indicated. Data were analysed using a Mann-Whitney U-test to compare the observed mean difference between the groups at a particular phase and to compare the observed mean difference within a group between a particular phase with RECOV or, if not available, EO. A p-value <0.05 was considered significant.

Results

Table 2 presents the time course of changes of [(A-a)DO_2], [DO_2I], [VO_2I] and [(a-v)DO_2]. [(A-a)DO_2] was not significantly different between the groups, nor within the groups when compared to RECOV. [DO_2I] was only significantly different between the groups during the HAP phase, xenon being decreased. It must be noticed that only one patient of the Xenon group needed SNP infusion in order to control MAP, while such an infusion was necessary for six patients of the

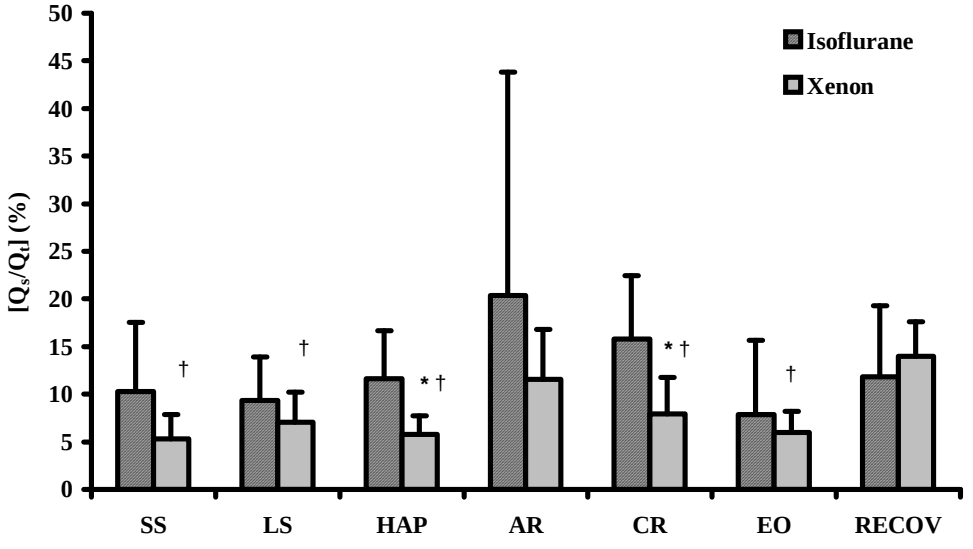
Figure 2: *Difference between "Xenon" (n=6) and "Isoflurane" (n=7) groups for oxygen extraction during different stages of the procedure.*



** = p<0.05 between xenon and isoflurane at a particular time point of the procedure, † = p<0.05 within groups between a particular phase and RECOV. Data are mean (SD).*

ISO group. [VO_2I] was equal in both groups, being significantly decreased during LS and HAP stage. In contrast, [(a-v)DO_2] was different between the groups during almost the entire procedure. Figures 1, 2 and 3 presents the time course of changes of [PaO_2/FIO_2], [O_2ER] and [Qs/Qt], respectively. Normal arterial oxygen tension has a progressive decrease with age [14]. This means that normal PaO_2 for the ISO group is 11.1 kPa, whereas for the xenon group this value is 10.8 kPa. Normal [PaO_2/FIO_2] levels will thus be 52.8 and 51.6 kPa for the ISO and Xenon group, respectively. [PaO_2/FiO_2] values for both groups were, during the entire procedure, always above these levels. [PaO_2/FIO_2] in the Xenon group is very stable during the different stages of the procedure, in the ISO group, it increases in LS and HAP compared to RECOV (Fig. 1). The oxygen extraction ratio is significantly different between the groups during almost the entire procedure, isoflurane is lower than xenon, during major part of the procedure (Fig. 2). Intrapulmonary shunting decreased significantly during xenon anaesthesia, except for the AR stage (Fig. 3, xenon). Significant shunt differences between the groups were found at the HAP and CR stage (Fig. 3, HAP, CR).

Figure 3: *Difference between "Xenon" (n=6) and "Isoflurane" (n=7) groups for intrapulmonary shunt during different stages of the procedure.*



** = p<0.05 between xenon and isoflurane at a particular time point of the procedure, † = p<0.05 within groups between a particular phase and RECOV. Data are mean (SD).*

Discussion

We present the first clinical study that describes the influence of xenon on ventilation-perfusion relationships during xenon anaesthesia in humans. Intrapulmonary shunting was significantly reduced during xenon anaesthesia compared to RECOV, while the patients in the ISO-group remained a more or less unchanged IPS level. No concomitant influence on PaO_2 was found using xenon, while PaO_2 increased during the perfusion phase when isoflurane was used. During perfusion and reperfusion stages of the procedure (HAP, AR and CR), [(a-v)DO_2] and [O_2ER] show a significant difference between the ISO and Xenon groups; both variables are stable during xenon anaesthesia, while they are reduced in the ISO group.

Some considerations must be made before our data can be analysed. First, it is not a randomised study design; halfway the study we switched to xenon for its presumed haemodynamic stability. So we used different drugs for induction of anaesthesia in the two patient groups. In the Xenon group we chose propofol because repeated doses had to be given during the wash in phase [10, 11]. In the ISO

group, the single-shot dose thiopental was unlikely to have considerable effects on measured variables during the procedure because the time needed for surgical preparation varied so that the time between SS and LS was a mean 47 min (range 30-65 min), whereas SS was usually obtained 30 min after i.v. induction of anaesthesia started. A second consideration is the necessity of equal lung ventilation between different patients and patient groups in order to allow a proper comparison between the different ventilation-perfusion relationships. We therefore calculated the [PaO_2/FIO_2] ratio during the different stages of the procedure for both patient groups. As shown in Fig. 1, this ratio was only significantly different between the study groups during the isolation stages (Fig. 1, LS and HAP). A third consideration is the difference of i.v. SNP use for MAP control between the groups, one vs. six patients in Xenon and ISO group respectively. SNP influences HPV in dogs [15], and reduces VO_2 during aortic cross-clamping below the clamping level, with a concomitant increase of oxygen content and saturation below this level [16]. This may be due to increased arterial-venous shunting in tissues below the clamp [16]. Finally, at AR and CR, CO in the ISO group is about two times higher than during the other stages of the procedure [12]. This is important, because IPS is found to be directly related to CO in the presence of isoflurane [9].

Our data from the ISO group during simultaneous aortocaval occlusion are comparable with that found during single aortic cross-clamping in patients anaesthetized with nitrous oxide/isoflurane concerning the decrease of [$(a\text{-}v)DO_2$] and [O_2ER] [17]. In contrast, during xenon anaesthesia, the [$(a\text{-}v)DO_2$] level and the [O_2ER] (except the CR stage) remained unchanged during the procedure. Because no significant differences were found in VO_2I levels between the groups, these found [$(a\text{-}v)DO_2$] and [O_2ER] differences cannot be explained by differences in oxygen demand by the tissues. An explanation may be found by assuming that there is a hyperdynamic circulatory pattern in the upper part of the body during isoflurane anaesthesia, while a normal circulatory pattern exists during xenon anaesthesia. The adventitious necessity of i.v. SNP infusion and the increased CO during reperfusion, are phenomena that makes the existence of a hyperdynamic circulatory pattern during isoflurane anaesthesia even more likely [12, 16].

In our study, the intrapulmonary shunt remained more or less unchanged in the ISO group. The non-siginificantly increase at AR and CR when isoflurane was used (see Fig. 3) may be related to the CO increase [9]. The decreased IPS that we found in our Xenon group confirms the data from a recently published abstract that reported the effects of 70% xenon anaesthesia on pulmonary artery pressure in pigs [18]. Schmidt and colleagues found that HPV is preserved during xenon anaesthe-

sia, while being abolished using 1 MAC halothane [18]. The found unchanged levels of [(a-v)DO_2], [O_2ER], decreased IPS, without any effect on [PaO_2/FIO_2] in our study, makes the preservation of HPV during xenon anaesthesia in humans very likely. This seems clinically relevant to us, because some patients in the ISO group show an increased IPS, thereby presuming ventilatory problems when the abdominal reperfusion stage started (Fig. 3). It is known that myocardial depressant factors, endotoxins, cytokines and other mediators may be released after reperfusion of the intestine [19]. The influences of these substances on HPV and IPS are, however, not well known.

We conclude that the influence of isoflurane on ventilation-perfusion relationships in patients is unclear. We found significant decreases of [(a-v)DO_2], [O_2ER], without impairment of PaO_2 in our ISO group. However, it cannot be excluded that some of these changes are significantly influenced by changes in CO and the adventitious necessity for i.v. SNP infusion for MAP control. Xenon anaesthesia does not impair [(a-v)DO_2], or [O_2ER] and it reduces intrapulmonary shunting significantly without effects on PaO_2. The preservation of HPV during xenon anaesthesia in humans seems very likely, which makes it probably more suitable for procedures in which ischaemic-reperfusion is known to appear.

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SUMMARY AND CONCLUSIONS

Summary and Conclusions

In the **Preface** of this thesis, some aspects are described that are important for the monitoring process of patients, in particular for the critically ill patients, that play a major role on the background of this thesis. Described are (1) data reduction induced by the way of measuring itself, also known by physicists as "*The wave function collapse theor*y" described by Heisenberg, (2) the necessity to synchronise the time-unit of different monitors in order to enable comparisons of different measurements that are derived by using different monitors, (3) the necessity to understand the variation of the physiological variable that is measured/monitored in order to enable the understanding of what really happened with the patho-physiological system; especially was described the way research is developing today, answering the question "How do anaesthetics work?", and (4) the role that "human factors error" play during patient monitoring in a cognitive complex environment, together with the manufacturers obligation to make an important contribution to improve the safety of the monitored patient by doing better humans factor engineering.

In **Chapter 1**, the introduction, aspects that are expected to be involved in simultaneous occlusion of the aorta and the inferior vena cava are described.

At first, the necessity for routine preoperative optimisation of patients undergoing major elective surgery, found to give a significant and cost effective improvement in perioperative care, is described. For the Netherlands, single aortic cross clamping, considered being a major surgical intervention, was evaluated by a Dutch surgical retrospective single-centre study. This study also illustrated that surgeons and anaesthetists interpret the results of such intervention in a different way. While surgeons conclude that thoraco-abdominal aneurysm repair can be performed with an acceptable early mortality and with a significant improvement of the long-term survival compared with the natural course of the disease, anaesthetists feel that the high complication rate that is partly due to patho-physiological disturbances induced by the sequence of clamping and unclamping of the aorta is discouraging. This dissatisfaction induced research, in order to find the best anaesthetic technique for any individual patient in order to optimise the outcome. Because there is no single peroperative anaesthetic management technique ideal for all patients undergoing abdominal aortic surgery, the anaesthetist must formulate an appropriate anaesthetic plan, which require expertise with a variety of these techniques. Furthermore, to provide a basis for rational therapy for reduction of the complication rate and for improvement of the outcome, a

clear understanding of the patho-physiological derangements that may occur during these procedures is essential. The question whether additional inferior vena cava occlusion can stabilise or even prohibit cardiovascular changes induced by aortic occlusion can thus be raised. Because literature is not consistent on this point, further research seems necessary. Also very little is known about the best way of treating these patients in the postoperative phase. Although patients are usually admitted to an ICU after abdominal aortic surgery has been performed, criteria for admission to an ICU will be largely influenced by local policies that are specific for that particular unit. Although this situation is recommended in the Guidelines for ICU admission that are formulated by the ACCCM and SCCM, criteria to decide whether a patient must be admitted to a general ward, a high-care unit or an intensive care unit are lacking.

Secondly, aspects of *"Isolation-Perfusion"*, a technique used for targeting chemotherapeutic drugs by performing regional chemotherapy, are described. After a review of the history of "Isolation-Perfusion", synergistic anti-tumour effects that are common in the treatment for pancreatic cancer are discussed. In particular the reason for applying hypoxic treatment is highlighted. Then, aspects of *"Isolation-Perfusion of the abdomen"* are described. Because *"Ischaemic Reperfusion Injury"* can be expected when the "Isolation-Perfusion" technique is applied, the normal oxygen transport to the abdomen is described, with special attention given to available measurement techniques of oxygen consumption and delivery. The disturbance of the oxygen transport to the abdomen is reviewed, and the two existing basic theories addressing the regulation of organ perfusion during decreased oxygen availability, *"The vasodilator theory"* and *"The oxygen lack theory"* are described. This illustrates the existing close connection between the local blood flow regulation and the oxygen delivery to the tissues. Because anaesthesia *per se* and the level of aortic cross-clamping are known for their influence on total body oxygen consumption, these items are discussed also. Finally, different aspects of *"Ischaemic Reperfusion Injury (IRI)"* are highlighted. (1) The cellular formation of *"Reactive Oxygen Species"*, via (2) the *"Xanthine Oxidase Pathway"*, (3) the role of the *"Polymorphonuclear neutrophils (PMN's)"* inducing systemic inflammatory response syndrome (SIRS), sepsis and multi-organ dysfunction syndrome (MODS), ending in (4) programmed cell death (*apoptosis*), together with possible therapeutic strategies to attenuate IRI are described. The chapter ends with the outline and aim of this thesis.

Chapter 2, the first chapter of the original studies section, deals with the cardiovascular effects induced by simultaneous aortocaval occlusion, necessary to allow hypoxic abdominal perfusion (using melphalan and mitomycin C) to treat pancreatic cancer in seven consecutive patients. These patients were anaesthetised by using a routine balanced anaesthesia technique. The intravenous induction was with thiopental, vecuronium and sufentanil; maintenance was with isoflurane added to an oxygen-air mixture. Data were collected at predefined times that were equally divided over the different stages of the procedure. In contrast to animal studies that had reported that cardiovascular disturbances induced by aortic cross clamping is prohibited by additional clamping of the inferior vena cava, we found in our patients no such effects. The major disturbance of the cardiovascular variables illustrated that isolation perfusion procedures of the abdomen in humans must be considered as major surgery, with a frequent necessity for infusion of vasodilators to regulate the arterial pressure. During reperfusion, phenomena were observed that indicate that *"Ischaemic Reperfusion Injury"* is indeed present during these procedures. Furthermore, significant leakage along the perfusion catheters and/or increased blood flow via existing anatomical shunt lines, like spinal arteries and veins and venae azygos and hemi-azygos that induce for instance increases of arterial and pulmonary artery pressures was observed. Although this less invasive perfusion procedure had been said to avoid significant pain or bleeding and be possible even in frail and debilitated patients, we conclude that the large circulatory changes during simultaneous aortocaval occlusion indicates that this procedure must not be performed under local anaesthesia alone because of the possible induction of additional cardiac stress caused by awareness, but must be done applying general anaesthesia, for this makes the necessary invasive haemodynamic monitoring better possible.

In order to enable comparison of intra-operatively measured oxygen consumption, derived by using "closed-circuit anaesthesia", with oxygen consumption measurements that were previously reported but were derived by using other measurement techniques, we studied the relation between PhysioFlex®-derived oxygen consumption measurements with Fick derived oxygen consumption calculations in two independent patient groups. The results of these studies are described in **Chapter 3**, for 16 consecutive patients undergoing orthotopic liver transplantation and in **Chapter 4**, for 11 patients undergoing a hypoxic abdominal perfusion procedure. Both studies showed that the measurement errors of the PhysioFlex® derived oxygen consumption are independent of the level of the

actually measured oxygen consumption, while in contrast, the error of the Fick derived calculated oxygen consumption is dependent on the actually calculated value; this latter error being increased when the oxygen consumption level decreased. Both studies revealed a significant correlation and a reasonable approximation of the expected relation, under consideration of the methodological differences that exists between the two different measurement techniques; by using Spearman rank correlation and linear regression for statistical analysis. However, both measurement techniques were clinically not interchangeable, because the level of agreement between the two techniques was poor when we used the Bland-Altman method for data analysis. We concluded that in daily clinical practice the PhysioFlex® can provide an immediate and accurate oxygen uptake value without the necessity of invasive monitoring.

In **Chapter 5**, the effects of simultaneous aortocaval occlusion on oxygen consumption derived by the PhysioFlex® in ten patients undergoing a hypoxic abdominal perfusion procedure necessary to allow chemotherapeutic drugs to treat their pancreatic cancer during routinely performed general anaesthesia, induced with thiopental, vecuronium and sufentanil, and maintained with isoflurane added to an oxygen-air mixture are described. Also, the oxygen delivery of the patients during the several phases of the procedure is calculated. The found variation in oxygen consumption and delivery in this study could be attributed to a disturbed auto-regulation of the abdominal organs during hypoxic abdominal perfusion. This is probably induced by the oxygen depletion itself. Furthermore, the results showed that an oxygen dept remained long after occlusion release, because this oxygen dept was found still being present at the end of the procedure. Besides, the level of the oxygen dept was found to be significantly gender-dependant. Immediately after occlusion release, we measured changes in the oxygen and air-uptake of the patients that could only be explained by a changed FRC. This FRC variation must have been induced by the blood shift that was induced by the occlusion release, and has been described in the literature before. The found variation in gas uptake makes clear that the basic conditions on which “low-flow anaesthesia” is stated are not fulfilled during this procedure. Therefore, we concluded that a “low-flow anaesthetic technique” for patients undergoing this procedure could not be implemented without further notice of the phase of the procedure.

In an attempt to make hypoxic abdominal perfusion procedures with chemotherapeutic drugs suitable for patients with concomitant cardiovascular disease,

we studied the effects on the cardiovascular variables during xenon anaesthesia for maintenance in six consecutive male patients undergoing such isolation perfusion procedure. The results of this study are described in **Chapter 6**. At first, because xenon anaesthesia is a novel anaesthetic technique being still in development, we compared the induced variation of cardiovascular variables by xenon itself, with the literature. The results of our study supported the findings on xenon anaesthesia that were previously reported. Although xenon anaesthesia is thought to induce cardiovascular stable anaesthesia maintenance, our study showed that serious variation of cardiovascular variables induced by the simultaneous aorto-caval occlusion or subsequent occlusion release applying xenon anaesthesia is still present. However, comparison of our results with earlier reported studies performed in humans when hypoxic abdominal perfusion procedures were with isoflurane for anaesthesia maintenance revealed that the necessity for infusion of vasodilators to regulate the arterial pressure was decreased, as was the workload for the left and right myocardial ventricles. Also, the absolute level of the "pulse pressure product", a variable used to estimate the myocardial oxygen consumption clinically, was less during xenon anaesthesia than during the balanced anaesthesia technique with isoflurane. Therefore, we concluded that xenon anaesthesia could be recommended for anaesthesia maintenance in patients undergoing hypoxic abdominal perfusion procedures, in particular when they suffer from ischaemic cardiovascular disease also.

Chapter 7 reports the results of the last presented study of the original studies section. Described are the results of a comparison between the induced changes on the intrapulmonary shunt that were found when xenon or isoflurane anaesthesia was applied to a group of 13 patients undergoing simultaneous aorto-caval occlusion. The intrapulmonary shunt was found being reduced when xenon anaesthesia was applied, while being increased (in particular after occlusion release had been performed) in patients anaesthetised with isoflurane. However, it could not be excluded that (in part) the effects on intrapulmonary shunting found during isoflurane anaesthesia were induced by the higher necessity of sodium nitroprusside infusion, necessary to control the arterial pressure during the perfusion phase of the procedure, instead of the use of isoflurane itself. We conclude (1) that xenon anaesthesia decreased intrapulmonary shunting with a concomitant preservation of the hypoxic pulmonary vasoconstriction, and (2) that xenon anaesthesia is more suitable for anaesthesia maintenance in procedures in which ischaemic reperfusion is known to occur, than is isoflurane.

The results of the studies that are described in this thesis illustrate that additional occlusion of the inferior vena cava during occlusion of the aorta does not reduce cardiovascular instability when a routinely used conventional anaesthesia technique is applied. A significant leakage along the perfusion catheters, and/or the shunting of blood via anatomical shunt lines is found to play a major role in the induction of cardiovascular instability during hypoxic abdominal perfusion procedures. However, it cannot be excluded that surgically performed simultaneous external cross clamping of the aorta and the inferior vena cava can prohibit the above-mentioned cardiovascular instability. Furthermore, it becomes clear that the use of fully closed circuit anaesthesia, as provided by the PhysioFlex® closed-circuit anaesthesia machine, enables accurate intra-operative oxygen consumption measurements. The PhysioFlex® derived oxygen consumption measurements revealed that the auto-regulation of the abdominal organs is disturbed during the hypoxic abdominal perfusion phase of the abdominal isolation perfusion procedure, probably induced by the hypoxia itself. We found a significant gender difference in the way the oxygen dept was being repaid after occlusion release. Future studies, that want to describe the effects of a specific provocation on the human metabolism, must therefore take gender difference into account. Finally, we elucidated that modification of the anaesthetic technique by introducing closed-system anaesthesia is useful for the optimisation of the anaesthetic management of patients undergoing major surgery. The metabolic changes that are induced by the surgical intervention can then be monitored, and xenon anaesthesia can be applied, which may allow patients suffering from significant cardiovascular disease to undergo major surgery; in particular when induction of "Ischaemic Reperfusion Injury" is expected. In future research the performance of simultaneous surgical external vascular cross clamping of the aorta and the inferior vena cava must elucidate whether severe variation in cardiovascular variables is prohibited in humans or not. Furthermore, research on other anaesthetic techniques, e.g. a combination of epidural anaesthesia with xenon for anaesthesia maintenance, must clarify whether further optimisation of the anaesthetic management of patients undergoing simultaneous aortocaval occlusion is possible. It also is necessary that criteria be formulated that enable the decision making about the best place for admittance (a general ward, a high-care unit or an intensive-care unit) of a patient after the performance of major surgery on rational grounds. Finally, technical improvement of the abdominal isolation is necessary before future studies on hypoxic abdominal isolation perfusion are going to be performed be-

cause severe leakage now prohibit a further dose increase of the chemotherapeutic drugs, or a change to other, more aggressive cytotoxic drugs. Also more research is necessary to improve the sensitivity of the pancreas carcinomas for hypoxia, e.g. by manipulating the HIF-1α protein.

Samenvatting en Conclusies

In het **voorwoord** van dit proefschrift worden enkele aspecten beschreven die een belangrijke rol spelen bij het proces van meten en bewaken van patiënten, in het bijzonder die van vitaal bedreigde patiënten. Het zijn aspecten die op de achtergrond van dit proefschrift een rol van betekenis spelen. Het betreft (1) de data reductie die samenhangt met, en veroorzaakt wordt door, de manier waarop wordt gemeten; dit fenomeen staat in de fysica bekend als de "*wave function collapse theory*" van Heisenberg, (2) de noodzaak tot exacte afstemming van de tijd van de verschillende monitoren indien men de resultaten van metingen, verkregen met die verschillende monitoren met elkaar wil vergelijken, (3) de noodzaak tot het begrijpen van de (patho-) fysiologische werking van het te meten/monitoren systeem teneinde de resultaten van de gemeten variabelen op hun juiste waarde te kunnen schatten; hierbij is extra aandacht besteed aan de richting waarin het onderzoek naar het werkingsmechanisme van anesthetica zich heden ten dage lijkt te ontwikkelen, en (4) de rol die de "menselijke fout" speelt in het proces van patiënten observatie, en hoe deze mogelijk kan worden verbeterd door aanpassing van de monitor "lay-out".

Hoofdstuk 1, de inleiding, geeft een overzicht van aspecten die een rol kunnen spelen bij de gelijktijdige afsluiting van de aorta en de vena cava inferior.

Allereerst is beschreven dat het optimaliseren van de conditie van de patiënt in de preoperatieve fase voor een grote chirurgische ingreep van nut is. Een onderzoek dat werd verricht bij een Nederlandse groep patiënten die een operatieve ingreep moesten ondergaan waarbij de aorta gedurende enige tijd werd afgeklemd maakte duidelijk dat er verschil van inzicht bestaat tussen de chirurg en de anesthesioloog over het bereikte resultaat van deze ingreep. De chirurg kijkt met name naar de verkregen uitkomst ten opzichte van het natuurlijke beloop van de ziekte en is dus tevreden met het uiteindelijke resultaat van de verrichtte ingreep. De anesthesioloog kijkt echter met name naar de door het afklemmen van de aorta veroorzaakte verstoring van het patho-fysiologisch systeem met de daarbij behorende inductie van complicaties en is daar niet tevreden over. Deze ontevredenheid vormt de aanleiding tot onderzoek ter beantwoording van de vraag hoe de toegepaste anesthesie techniek het beste kan worden geoptimaliseerd voor een willekeurige individuele patiënt. Er blijken vele anesthesie technieken voor deze ingreep te bestaan waaruit gekozen kan worden en de anesthesioloog heeft derhalve de taak dit spectrum te overzien en te komen tot een specifieke keuze voor een specifieke patiënt. Duidelijk is dat hiervoor een groot inzicht nodig is in het

fysiologisch systeem van de mens. Alleen zo kunnen de door de ingreep geïnduceerde verstoringen van het fysiologisch systeem worden opgevangen. De vraag rijst of een gelijktijdig afklemmen van de vena cava inferior, bij een procedure waarbij de aorta wordt afgeklemd zinvol kan zijn, voor een beter behoud van de homeostase. Ter beantwoording van deze vraag blijkt nader onderzoek nodig te zijn. Hoewel intensive care opname van een patiënt in de postoperatieve fase na afklemmen van de aorta mogelijk van nut is, blijkt er een hiaat in kennis te bestaan omtrent het te volgen postoperatieve beleid en speelt de 'couleur locale' een grote rol. Gerelateerd aan intensive care maatstaven moet dit ook zo zijn, maar een nadere formulering van criteria waarop de beslissing tot opname op een gewone afdeling, een high care afdeling, dan wel een intensive care afdeling kan worden gebaseerd, is gewenst.

Vervolgens is ingegaan op aspecten van "*Isolatie-Perfusie*", een techniek die een rol speelt in het doelgericht toedienen van cytostatica voor regionale chemotherapie bij kanker. Na een historisch overzicht, werden behandelingsaspecten beschreven die gericht zijn op het verkrijging van een synergistische werking binnen de toegepaste therapeutische strategie. Hierbij is met name de reden voor het aanleggen van hypoxie bij de behandeling van het pancreas carcinoom belicht. Daarna is ingegaan op de *"Isolatie-Perfusie van het abdomen"*. Aangezien bij toepassing van deze techniek *"Ischemisch reperfusie letsel"* verwacht kan worden, is allereerst het fysiologische zuurstof transport naar het abdomen beschreven met de mogelijkheden die er bestaan tot het meten en monitoren van dit transport. Er zijn hierna twee theorieën beschreven, de *"Vasodilator theory"* en de *"Oxygen lack theory"*, die de regulatie van orgaan perfusie tijdens hypoxische omstandigheden postuleren. Het is dan duidelijk dat er een nauwe relatie bestaat tussen de regulatie van de lokale bloedstroom en het zuurstof aanbod aan de weefsels. De verstoring van het zuurstoftransport naar het abdomen in relatie tot de gegeven anesthesie, alsmede in relatie tot het niveau waarop de aorta wordt afgeklemd, is vervolgens beschreven. Tenslotte is uitvoerig ingegaan op verschillende aspecten van het "*Ischemisch reperfusie letsel*". (1) De vorming van *"Reactive oxygen species"* op cellulair niveau via de (2) *"Xanthine oxidase pathway"*, (3) de rol die de neutrofiele granulocyten (PMN) in dit proces spelen, uitmondend in een systemische ontstekingsreactie (SIRS), sepsis en meervoudig orgaan falen (MODS), uiteindelijk leidend tot (4) geprogrammeerde celdood (*"apoptosis"*), alsmede (5) de vele mogelijke therapeutische interventie strategieën die bij de behandeling, of wel voorkoming van dit letsel een rol zouden kunnen spelen

kwamen aan bod. Het hoofdstuk eindigt met de beschrijving van de doelstellingen en de daarbij behorende vraagstellingen van dit proefschrift.

In **Hoofdstuk 2**, het eerste hoofdstuk van het deel met de oorspronkelijk verrichte studies, zijn de effecten op variabelen van hart en bloedsomloop veroorzaakt door het gelijktijdig afklemmen van de thoracale aorta en de vena cava inferior bij zeven patiënten die voor de behandeling van pancreaskop carcinoom met behulp van regionale chemotherapie, een geïsoleerde hypoxische abdominale perfusie met melphalan en mitomycine C ondergingen, beschreven. Deze patiënten zijn onder algehele anesthesie gebracht met een routinematig in gebruik zijnde, gebalanceerde anesthesie techniek, bestaande uit een intraveneuze inductie met thiopental, vecuronium en sufentanil, gevolgd door isoflurane toegevoegd aan een zuurstof/lucht mengsel. Data zijn verzameld op vooraf vastgestelde tijdstippen die gelijkelijk verdeeld waren over de verschillende fases die bij zo een hypoxische abdominale perfusie procedure voorkomen. Enerzijds blijkt dat er bij de mens geen belangrijk stabiliserend effect geïnduceerd wordt op variabelen van hart en bloedsomloop door aanvullende afsluiting van de vena cava inferior tijdens afsluiting van de aorta, in tegenstelling tot gerapporteerde resultaten van uit in het verleden onderzochte diermodellen, anderzijds wordt duidelijk dat er bij deze abdominale perfusie ingreep inderdaad sprake is van een grote ingreep, gezien de majeure effecten die de gelijktijdige vaatafsluiting op hart en bloedsomloop variabelen heeft. Hierbij is het frequent nodig tot agressieve bloeddruk regulatie met behulp van snelwerkende vaatverwijdende medicamenten over te gaan en treden er reperfusie fenomenen op als uiting van *"Ischemisch reperfusie letsel"*. Tevens blijkt er zich tijdens de abdominale perfusie fase ofwel een belangrijk lekkage langs de perfusie katheters, ofwel een belangrijke bloedstroom via de in het lichaam reeds bestaande shuntlijnen, te weten de spinaal arteriën en venen en de azygos en hemi-azygos venen, voor te doen. Een lekkage en/of shunting die zich o.a. uit tijdens de perfusie fase in het oplopen van de systemische en de pulmonale bloeddrukken. We trekken de conclusie dat er voor een optimale uitvoering van deze procedure, hoewel in de literatuur gesuggereerd wordt dat deze minder invasieve techniek door voorkoming van pijn en bloeding geschikt zou zijn voor gecompromitteerde patiënten, volgens oncologen eventueel zelfs onder lokaal anesthesie uit te voeren, algehele anesthesie gewenst is, zodat gemakkelijker gebruik kan worden gemaakt van invasieve technieken voor de bewaking van variabelen van hart en bloedsomloop.

Teneinde de waarde van de resultaten van intra-operatieve zuurstof consumptie metingen verricht met gebruikmaking van *"Closed-circuit anaesthesia"* te kunnen relateren aan literatuur betreffende zuurstof consumptie metingen verricht met behulp van andere meettechnieken, hebben we in twee onafhankelijk patiënten groepen, tijdens algehele anesthesie voor een grote chirurgische ingreep, gekeken naar de relatie tussen de met de PhysioFlex® gemeten zuurstof consumptie en de met de Fick methode berekende waarde. De resultaten van deze vergelijkingen zijn beschreven in **Hoofdstuk 3**, voor wat betreft 16 achtereenvolgende patiënten die een orthotope levertransplantatie hebben ondergaan, en in **Hoofdstuk 4**, voor wat betreft 11 patiënten die een hypoxische abdominale perfusie procedure hebben ondergaan. Beide studies laten zien, dat de fout grootte in zuurstof consumptie metingen verricht met behulp van de PhysioFlex®, onafhankelijk is van de actueel gemeten zuurstof consumptie, terwijl de fout grootte in zuurstof consumptie berekeningen met de omgekeerde Fick methode sterk afhankelijk is van de actueel gemeten zuurstof consumptie; bij lagere zuurstof consumptie waardes nam de fout grootte sterk toe. We vonden in beide patiënten groepen een significante correlatie en een redelijke benadering van de te verwachten relatie tussen beide bepalingsmethoden, rekening houdend met het methodologische verschil tussen de methoden bij gebruikmaking van lineaire regressie methodiek. De twee bepalingsmethodes bleken echter klinisch niet uitwisselbaar te zijn, gezien de slechte mate van overeenkomst bij gebruikmaking van de Bland-Altman methodiek. We concludeerden dat de PhysioFlex® voor de dagelijkse praktijk een accurate, onmiddellijk beschikbare zuurstof consumptie waarde weer kan geven, zonder noodzaak tot het toepassen van invasieve meettechnieken.

In **Hoofdstuk 5** is het effect beschreven van gelijktijdige afsluiting van de aorta en de vena cava inferior op de zuurstof consumptie van 10 patiënten tijdens een hypoxische abdominale perfusie procedure voor chemotherapeutische behandeling van pancreaskop carcinoom gemeten met behulp van de PhysioFlex® tijdens algehele anesthesie, welke werd geïnduceerd met thiopental, vecuronium en sufentanil en werd voortgezet met isoflurane toegevoegd aan een zuurstof luchtmengsel. Tevens werd de variatie in zuurstof aanbod tijdens de diverse fases van de abdominale perfusie procedure berekend. Hierbij bleek dat de gevonden variatie in zuurstof consumptie en zuurstof aanbod tijdens de abdominale perfusie fase kon passen bij een verstoorde autoregulatie van de verschillende buikorganen, waarschijnlijk geïnitieerd door het zuurstof gebrek zelf. Voorts bleef er na het

opheffen van de abdominale isolatie een langdurige zuurstofschuld bestaan, waarbij het niveau van de zuurstofschuld sterk geslachtsbepaald was. Direct na het opheffen van de abdominale isolatie, werd er tevens een door de op dat moment optredende bloedshift geïnduceerde verandering in FRC gemeten, met de daarbij behorende toename van de gasstroom naar de longen van de patiënten, die tezamen met de variatie in zuurstof consumptie zo groot was, dat aan de basisvoorwaarden voor het toepassen van "low-flow anaesthesia" niet meer voldaan was. Dit betekent dat dit soort procedures niet zonder meer met behulp van een dergelijke "low-flow" anesthesie techniek kunnen worden uitgevoerd.

In **Hoofdstuk 6** is beschreven of een variatie in anesthesie techniek, door xenon anesthesie toe te passen, zinvol is voor het verkrijgen van meer stabiliteit in hart en bloedsomloop variabelen tijdens gelijktijdige afsluiting van de aorta en de vena cava inferior nodig voor uitvoering van hypoxische abdominale perfusie procedures, zodat in de toekomst met name ook meer cardiovasculair bedreigde patiënten voor deze procedures in aanmerking zouden kunnen komen. Zes opeenvolgende mannelijke patiënten werden bestudeerd. Omdat xenon anesthesie nog een anesthesie techniek in ontwikkeling is werd eerst een algemene vergelijking gemaakt met variabelen van hart en bloedsomloop die tijdens xenon anesthesie in andere humane studies zijn gevonden en toegeschreven kunnen worden aan het gebruik van xenon zelf. Hierbij bleek dat onze meetresultaten de resultaten van eerder gepubliceerde xenon anesthesie studies ondersteunen. Uit onze studie bleek echter duidelijk dat er nog steeds een behoorlijke variatie in hart en bloedsomloop variabelen werd geïnduceerd door het gelijktijdig afklemmen van de aorta en de vena cava inferior. Niettemin was er minder noodzaak tot toediening van vaatverwijdende medicamenten tijdens xenon anesthesie en lag de mechanische belasting voor zowel de rechter als de linker hartshelft veel lager dan tijdens eerdere studies verricht met isoflurane voor het onderhouden van de anesthesie was gevonden. Ook bleek tijdens xenon anesthesie de absolute waarde van het "pulse pressure product", een klinische maat voor het zuurstof verbruik van het hart, lager te liggen, dan tijdens toepassing van een gebalanceerde anesthesie techniek met gebruikmaking van isoflurane. We trokken de conclusie dat xenon anesthesie kan worden aanbevolen voor hypoxische abdominale perfusie procedures, met name als er cardiovasculair bedreigde patiënten moeten worden behandeld.

Om meer duidelijkheid te krijgen in de oorzaken die ten grondslag kunnen liggen aan het verschil in beïnvloeding van de homeostase van de mens door xenon dan wel isoflurane, is in **Hoofdstuk 7**, als afsluiting van het deel dat de ver-

richtte originele studies beschrijft, een vergelijking getrokken tussen de mate van beïnvloeding van de intra-pulmonale shunt door deze middelen in een groep van 13 patiënten. De resultaten van de studie lieten zien dat tijdens xenon anesthesie de intra-pulmonale shunt grootte afnam, terwijl in de groep patiënten waarbij de isoflurane techniek werd toegepast, met name in de abdominale reperfusie fase, de shuntgrootte toenam. Doordat in de isoflurane groep veel vaker toediening van intraveneus nitroprusside voor bloeddruk regulatie nodig was dan in de xenon groep, bleef er echter onzekerheid bestaan omtrent de oorzaak van dit fenomeen. Wel kon worden geconcludeerd dat xenon anesthesie de intra-pulmonale shunt doet dalen, waarbij de hypoxische pulmonale vasoconstrictie goed gehandhaafd blijft. Dit maakt xenon daarom goed bruikbaar voor onderhoud van de anesthesie voor ingrepen waarvan bekend is dat zich "ischemische reperfusie" kan gaan voordoen.

De resultaten van de studies die beschreven zijn in dit proefschrift, laten zien dat additionele afsluiting van de vena cava inferior tijdens afsluiting van de aorta, niet leidt tot een belangrijke reductie in cardiovasculaire instabiliteit indien gebruik gemaakt wordt van een conventionele anesthesie techniek. Lekkage langs de occlusie katheters, dan wel shunting van bloed via bestaande shuntkanalen speelt bij de inductie van deze instabiliteit een belangrijke rol. Het kan echter niet worden uitgesloten dat gelijktijdig *chirurgisch uitwendig* afklemmen van de thoracale aorta en de vena cava inferior, dus bijvoorbeeld met behulp van klemmen, wel zou kunnen leiden tot beperking van genoemde cardiovasculaire instabiliteit. Verder is duidelijk geworden dat het gebruik van een volledig gesloten beademingscircuit, zoals toegepast in de "PhysioFlex® closed-circuit anaesthesia machine", betrouwbare niet invasieve *intra*-operatieve zuurstof consumptie metingen mogelijk maakt. Met behulp van de, via deze PhysioFlex®, verkregen zuurstof consumptie metingen werd het duidelijk dat de autoregulatie van organen in het hypoxische gebied verstoord raakt tijdens de hypoxische abdominale perfusie fase van de abdominale isolatie-perfusie procedures, waarschijnlijk door het gebrek aan beschikbaarheid van zuurstof zelf. Tevens is duidelijk geworden dat er een belangrijk verschil in wijze van zuurstof schuld aflossing bestaat tussen mannen en vrouwen. Dit heeft consequenties voor toekomstige studies die de reactie van het menselijk metabolisme op een bepaalde uitlokkende factor willen bestuderen. Tot slot is duidelijk geworden dat modificatie van de toegepaste anesthesie techniek door gebruik te gaan maken van een volledig gesloten beademingssysteem van nut kan zijn voor de optimalisatie van de anesthesie voor de patiënt die een

grote chirurgische ingreep moet ondergaan. Enerzijds kan door goed gebruik te maken van deze modificatie, de verandering in metabolisme tijdens een chirurgische ingreep beter worden bestudeerd, anderzijds kan met behulp van dit systeem bijvoorbeeld xenon anesthesie worden toegepast, een techniek die het beter mogelijk maakt cardiovasculair bedreigde patiënten in aanmerking te laten komen voor grote chirurgische interventies met name als daarbij ischemisch reperfusie letsel is te verwachten. Toekomstige studies zullen niet alleen duidelijk moeten maken of gelijktijdig *chirurgische uitwendig* afklemmen van de aorta en de vena cava inferior belangrijke veranderingen in hart en bloedsomloop variabelen kan doen voorkomen, maar ook of gebruik van andere anesthesie technieken, zoals bijvoorbeeld een combinatie van epidurale anesthesie met xenon anesthesie een verdere optimalisatie kan bewerkstelligen. Voorts dient te worden uitgezocht welke inclusiecriteria moeten worden gehanteerd om te kunnen beslissen of een patiënt in de postoperatieve fase opgenomen moet worden op een gewone afdeling, een High-Care afdeling, of een IC afdeling ter verkrijging van een optimaal resultaat. Verder lijkt het nodig dat de abdominale perfusie techniek wordt verbeterd voor wat betreft de mate van isolatie. Belangrijke lekkage vormt nu een beletsel voor een verdere dosisverhoging of verandering van toe te dienen chemotherapeutica. Ook moet worden onderzocht of pancreastumoren zodanig kunnen worden gemanipuleerd (bijvoorbeeld door manipulatie van het HIF-1α eiwit) dat behandeling met hypoxie beter zal kunnen aanslaan.

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THE AUTHOR

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Full papers:

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 11 mei 1965 te Bloemendaal. Na de lagere school ging hij naar het Christelijk College “Marnix van St. Aldegonde” te Haarlem, alwaar hij in 1982 het HAVO diploma en in 1984 het Atheneum-B diploma behaalde. Aansluitend begon hij met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam. Deze studie werd in 1991 afgesloten met het behalen van het arts examen. Na de militaire dienstplicht, welke hoofdzakelijk werd doorgebracht op de afdeling Inwendige Geneeskunde van het Westeinde Ziekenhuis te Den Haag, ging hij in 1992 werken als AGNIO op de afdelingen inwendige geneeskunde en cardiologie van het Spaarneziekenhuis te Heemstede (opleiders Dr. K. Bakker, internist en Dr. H. H. Kruyswijk, cardioloog). De belangstelling voor de cardiaal bedreigde patiënt werd hier flink aangewakkerd en de auteur ging vervolgens dan ook werken als AGNIO cardiologie in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider Dr. R. M. Schuilenburg). In 1995 kwam hij echter tot de conclusie dat met name de Intensive Care behoeftige patienten zijn belangstelling trokken en hij begon met zijn specialisatie tot anesthesioloog. In eerste aanleg was hij werkzaam als AGNIO anesthesiologie in het Academisch Ziekenhuis Rotterdam; vanaf 1997 kon hij zijn officiële opleiding beginnen (opleiders Prof. Dr. W. Erdmann, later Prof. Dr. J. Klein). Ten tijde van deze opleiding werd een aanvang gemaakt met het in dit proefschrift weergegeven onderzoek. De opleiding tot anesthesioloog werd in 2002 afgerond, waarna in het Onze Lieve Vrouwe Gasthuis te Amsterdam gestart werd met de vervolgopleiding voor het aandachtsgebied ‘Intensive Care Geneeskunde’ (opleider Dr. D. F. Zandstra, anesthesioloog-intensivist). Naast alle verplichte opleidingsmomenten, volgde de auteur cursussen voor de opvang van verschillende soorten trauma slachtoffers: “Advanced Trauma Life Support (ATLS)” en “Emergency Management for Severe Burns (EMSB)”, bekwaamde hij zich in het verrichten van transoesophageale echo-cardiografie (“Basic” en “Advanced training in Transoesophageal Echocardiography”, onder auspiciën van de Belgische en Nederlandse Vereniging voor Anesthesiologie), werd hij reanimatie-instructeur voor het Oranje Kruis en de Nederlandse Hartstichting en “colonne arts” bij het Rode Kruis, afdeling Velsen. Vanaf april 2003 is hij als staflid werkzaam op de afdeling anesthesiologie van het Academisch Medisch Centrum te Amsterdam.