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Cardiovascular Response to Hyperoxemia, Hemodilution and Burns

A clinical and experimental study

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ABSTRACT

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During the last decades less invasive monitoring and analytical tools have been developed for the evaluation of myocardial mechanics in clinical practice. In critical care, these are complements to pulmonary artery catheter monitoring, additionally offering previously inaccessible information. This work is aimed, during fluid-replacement and oxygen treatment, to find out the physiological interface of ventricular and vascular mechanical properties that result in the transfer of blood from the heart to appropriate circulatory beds. We investigated in prospective clinical studies previously cardiovascular healthy adults during hyperoxemia and patients with severe burns during fluid resuscitation, and before spine surgery during preoperative acute normovolemic hemodilution. Echocardiography was used in all studies, transthoracic for healthy volunteers and transesophageal for patients. For vascular variables, and for control purposes, pulmonary artery Swan-Ganz catheter, calibrated external pulse recordings, whole body impedance cardiography, and transpulmonary thermodilution method were used.

We detected no significant change in blood pressure or heart rate, the two most often used variables for monitoring patients. During *preoperative acute normovolemic hemodilution* a reduction in hemoglobin to 80 g/l did not compromise systolic or diastolic myocardial function. Cardiac volumes and flow increased with a coexisting fall in systemic vascular resistance while oxygen delivery seemed maintained. *Supplemental oxygen treatment* resulted in a linear dose-response between arterial oxygen and cardiovascular variables, suggesting a direct vascular effect. Cardiac flow decreased and vascular resistance increased from hyperoxemia, and a reduction in venous return implied extracardial blood-pooling. *Severe burns* result in hypovolemic shock if not properly treated. The commonly used Parkland fluid replacement strategy, with urinary output and mean arterial pressure as endpoints, has recently been questioned. Applying this strategy, only transient early central hypovolemia was recorded, while dimensional preload, global left ventricular systolic function, and oxygen delivery or consumption, remained within normal ranges during the first 36 hours after the accident. Signs of restrictive left ventricular diastolic function were detected in all patients and regional unstable systolic dysfunction was recognized in every other patient, and was consistent with leakage of myocardial markers. Severe burns cause myocardial stiffness and systolic regional dysfunction, which may not be prevented by central normovolemia and adequate oxygenation alone.

Key words: global and regional systolic left ventricular function, diastolic function, hemodilution, fluid-replacement, hyperoxemia, normocapnia, non-invasive hemodynamic monitoring, stroke volume, arterial compliance, end-diastolic area, Windkessel model, echocardiography, fractional area change, global end-diastolic volume, impedance-cardiography, burns, troponin.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following four articles, which will be referred to by their Roman numerals:

- I.** Bak Z, Abildgård, L, Lisander B, Janerot-Sjöberg B. Transesophageal echocardiographic hemodynamic monitoring during preoperative acute normovolemic hemodilution. *Anesthesiology* 2000, 92,1250-1256.
- II.** Bak Z, Sjöberg F, Rousseau A, Steinvall I, Janerot-Sjöberg B. Human cardiovascular dose-response to supplemental oxygen. In Press *Acta Phys.*
- III.** Bak Z, Sjöberg F, Eriksson O, Steinvall I, Janerot-Sjöberg B. Hemodynamic changes during resuscitation after burns using the Parkland formula. Accepted *J of Trauma*.
- IV.** Bak Z, Sjöberg F, Eriksson O, Steinvall I, Janerot-Sjöberg B. Cardiac dysfunction after burns. Submitted.

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ABBREVIATIONS

AC	Arterial compliance (mL mmHg ⁻¹)
ANH	Acute normovolemic hemodilution
AR _{dur}	Maximal duration of atrial pulmonary flow reversal (ms)
ARV _{max}	Maximal velocity of atrial pulmonary flow reversal (m/s)
CO	Cardiac output (L/min)
CVP	Central venous pressure (mmHg)
DO ₂	Oxygen delivery (mL min ⁻¹)
DT	Mitral inflow deceleration time (ms)
EDP	End diastolic pressure
EDV	End diastolic volume (ml)
EF	Ejection fraction
EVF	Erythrocyte volume fraction (%)
EVLW	Extra vascular lung water
FAC	Fractional left ventricular area change ([LVEDA-LVESA]/LVEDA)
FiO ₂	Inspired O ₂ air fraction
GEDV	Global end-diastolic volume
icg	Obtained by whole-body impedance cardiography
ITBV	Intrathoracic blood volume
IVRT	Isovolumic relaxation time (ms)
LMAM	Lateral mitral annular motion (mm)
LTAM	Lateral tricuspid annular motion (mm)
LV	Left ventricular
LVEDA	End-diastolic cross-sectional area of the left ventricular cavity (cm ²)
LVESA	End-systolic cross-sectional area of the left ventricular cavity (cm ²)
LVS _W	Left ventricular stroke work (g/m)
L _V WMA	Left ventricle regional wall motion analysis/abnormality
L _V WMSI	Left ventricular regional wall motion score index
MA _{dur}	Mitral atrial filling flow duration (ms)
MAP	Mean systemic arterial pressure (mmHg)
MAV _{max}	Mitral atrial filling maximal flow velocity (m/s)
MEV _{max}	Mitral early filling maximal flow velocity (m/s)
MI	Myocardial infarction
MPAP	Mean pulmonary artery pressure (mmHg)
PAWP	Pulmonary artery wedge pressure (mmHg)
pCO ₂	Arterial carbon dioxide partial pressure (kPa)
pO ₂	Arterial oxygen partial pressure (kPa)
PtcCO ₂	Transcutaneously measured partial CO ₂ pressure
PtcO ₂	Transcutaneously measured partial O ₂ pressure
PTT	Pulse transmission time (ms)
PVD	Maximal diastolic forward pulmonary venous flow velocity (m/s)

PVR	Pulmonary vascular resistance (dyne s cm^{-5})
PVS	Maximal systolic forward pulmonary venous flow velocity (m/s)
PWV	Pulse wave velocity (m/s)
RMD	Reversible myocardial dysfunction
RV	Right ventricular
RVSW	Right ventricular stroke work (g/m)
SV	Stroke volume (mL)
SvO ₂	Mixed venous oxygen saturation (%)
SVR	Calculated systemic vascular resistance (dyne s cm^{-5})
TBSA	Total burned body surface area (%)
TD	Thermodilution
TDI	Tissue Doppler imaging
TEE	Transesophageal echocardiography
trT	Troponin T ($\mu\text{kat/L}$)
TTE	Transthoracic echocardiography
VO ₂	Oxygen consumption (mL min^{-1})
VTI	Doppler velocity-time integral of the aortic flow (cm)
Z	Characteristic impedance (dyne s cm^{-5})
σ	Systolic wall stress
HR	Heart rate (beat min^{-1})

INTRODUCTION

Since the 1990s, besides pulmonary artery catheterisation, the combination of echocardiographic imaging, quantitative Doppler measurements, calibrated external pulse recordings, and whole body impedance cardiography together with newer indicator dilution methods has provided a new set of less invasive tools in the monitoring and analytical assessment of myocardial mechanics when clinically appropriate. The present work emerged from the desire to assess the mechanistic coupling within the cardiovascular system during critical care related hemodynamic changes and apply the extended use of these less invasive methods.

Intensive care aims to optimise oxygen delivery (DO_2) to the tissues. The assessment of ventricular performance, function, and the properties of the vascular system is important to avoid insufficient oxygen supply or disproportionately high oxygen demand and consumption (VO_2), which could induce organ and heart failure [1].

Fluid replacement causing hemodilution, and the use of supplemental oxygen to maintain a partial oxygen pressure (PaO_2) sufficient to obtain arterial hemoglobin saturation at least 85%, are two of the most often used measures used to deal with critically ill patients, who need intensive care for different reasons. Both fluid replacement and hyperoxemia influence central hemodynamic variables and cardiovascular coupling. The latter refers to the physiological interface of ventricular and vascular mechanical properties that results in the transfer of blood from the heart to appropriate circulatory beds [2].

VENTRICULAR PERFORMANCE

Ventricular performance is related to the simple pumping function of either the left (LV) or right (RV) ventricle of the heart, and may be expressed as cardiac work, or as volume output; per stroke as stroke volume (SV), or per minute as cardiac output (CO). *Ventricular function* relates these variables of ventricular performance to some measure of preload, such as end-diastolic volume (EDV), dimension, pressure, or wall stress.

SV is proportional to the *ejection fraction* (EF) of the ventricle and to the ventricle's EDV ($EF = SV / EDV$). EF is also dependent on ventricular *wall motion*, which is governed by adequate tissue perfusion and oxygenation. EF as the overall systolic performance indicator can be estimated clinically through echocardiographic ventricular area estimations as percentage left ventricular fractional area change (FAC%) [3,4], which is equal to the change in two-dimensional LV area from diastole to systole in relation to the end-diastolic area ($FAC = EDA - ESA / EDA$), and reflects the net effects of afterload, preload, heart rate (HR), and contractility.

Preload is the load imposed on resting muscle that stretches the muscle to a new length. It is clinically often estimated as end diastolic pressure (EDP),

pulmonary artery wedge pressure (PAWP), or end diastolic volume (EDV) [5,6].

Contractility is the velocity of muscle contraction when the muscle load is fixed. Clinically used estimates of contractility often falsely presuppose constant preload and afterload as when measuring SV or the fast time-derivative of LV pressure change (dP/dt) [6,7].

Afterload is the total load that must be moved by the cardiac muscle when it contracts, and is clinically often estimated as calculated pulmonary or systemic vascular resistance (PVR, SVR), or systolic wall stress (σ) [8].

PRELOAD

In the normal heart, diastolic volume is the principal force that governs the strength of ventricular contraction. This is the Frank-Starling relationship of the heart [9]. In clinical practice this relationship has been visualized with ventricular function curves using flow-pressure diagrams of the left ventricle, where flow i.e. SV or CO compares with belonging end-diastolic pressures. Nevertheless the volume of blood in the ventricle not only governs the stretch imposed on cardiac muscle, but also the tendency of the ventricular wall to distend in response to the filling. This is the *compliance of the ventricle* that can be described as $\Delta\text{EDV}/\Delta\text{EDP}$, and deteriorated by ischemic heart disease, hypertrophic cardiomyopathies, diabetes [5]. Diminished ventricular compliance may lead to a deterioration of *left ventricle diastolic function*, decreased EDV and CO and a resulting restrictive *diastolic heart failure*. Diastolic relaxation rate is known to be early affected by e.g. ischemic heart disease but when EDP increases symptoms are already developed [10]. Abnormalities of *LV diastolic function* play a major part in producing the clinical signs and symptoms of heart failure. Previous studies have shown that transmitral flow, and pulmonary venous flow velocity patterns assessed by Doppler echocardiography are useful variables for evaluating left atrial and LV diastolic events [11]. However, loading conditions, particularly preload, influences these variables, and it has recently become increasingly clear that abnormalities of LV diastolic function, such as relaxation and filling, can be assessed using color Doppler M-mode echocardiography and pulsed *tissue Doppler imaging* (TDI) less influenced by preload [12,13]. Transmitral valve flow and TDI of the mitral annulus had the highest recording success rate and lowest inter-reader variability in assessing LV diastolic function [14].

AFTERLOAD

Afterload is the load imposed on the ventricle after the onset of muscle contraction, and unlike the preload force, opposes muscle contraction. This afterload force in the normal heart is equivalent to the peak tension developed across the wall of the ventricles during systole and can be identified using the Laplace relationship [5,9,15] (Figure 1). During ventricular systole, the LV cavity and the systemic arterial system are in continuity. Flow

and pressure are the physiological mediators that connect the heart and the systemic circulation. LV systolic load is a function of both internal cardiac properties and external vascular factors described below.

Impedance is a hydraulic force that is a principal determinant of afterload. This force opposes phasic changes in pressure and flow. The impedance is most prominent in the large arteries, where it opposes the pulsating output of the ventricles. *Aortic impedance* is the major afterload force of the left ventricle. Impedance is influenced by a force that opposes the rate of change in flow, known as *compliance*, and a force that opposes steady flow called *resistance*. The resistance to ejection by the aortic valve and the proximal aorta are summerized in *Characteristic Impedance (Z)*.

Peripheral arterial resistance may play a less important part in impedance to ventricular emptying, but influences pressure and flow events in the large proximal arteries because it acts as downstream resistance for the main arteries [16,17]. Peripheral arterial resistance, arterial compliance (AC), and Z can be estimated from the simultaneous estimates of aortic root pressure and flow by use of a three element windkessel model [18]. *Systemic mean blood pressure* depends on CO and SVR and the transmission of pressure and flow waves (with different velocities) through the circulatory system following the ejection of SV. When vascular impedance is reduced, pressure can be diminished while flow is increased and vice versa. This explains why arterial pressure is not a reliable index of blood flow when vascular impedance is abnormal [19].

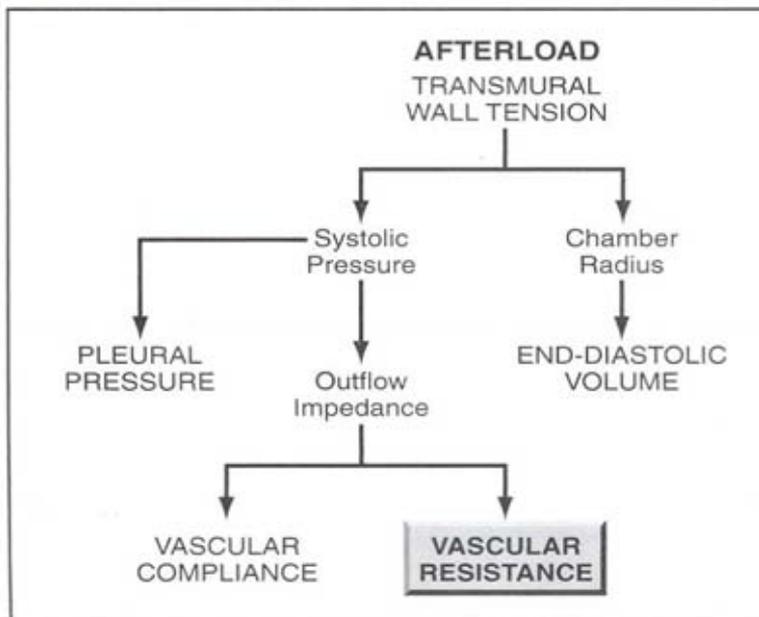


Figure 1. The forces that contribute to ventricular afterload.

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The resistance to flow (Q) in small rigid tubes was described by Hagen and Poiseuille: $Q = \Delta P \times (\pi r^4 / 8\mu L)$ where r is the inner radius of the tube, L is the length of the tube and μ is the *viscosity* of the fluid. Flow through compressible tubes like blood vessels, are influenced by the external pressures surrounding the tubes. When a tube is compressed by external pressure, the driving force for flow is independent of the pressure gradient along the tube [20]. The principal determinant of the whole body viscosity is the concentration of circulating erythrocytes, the *hematocrit* (EVF). Fluid replacement for any reason lowers the value of hematocrit and causes *hemodilution*. In the human body pressure, viscosity and flow changes influence each other, and the increased flow can further entail flow-increase [21]. A two-fold increase in the radius of the tube (a vessel) will result in a sixteen-fold increase in flow [19,22].

This dissertation, using the hemodynamic concepts shortly summarized above, is about those basic cardiovascular relations, applied in two efforts used in practically all critical care: fluid resuscitation and oxygen treatment. In previously cardiovascular healthy adults we examined these relations a) during acute normovolemic hemodilution before operations for scoliosis, b) severe burns during fluid resuscitation and c) healthy volunteers during hyperoxemia. As well as echocardiography (in patient studies), for complementary vascular variables and for control purposes pulmonary artery Swan-Ganz catheter (Paper I and III), calibrated external pulse recordings (Paper II), whole body impedance cardiography (in Paper II), and transpulmonary thermodilution (PiCCO) (Paper III) were also used.

ACUTE PREOPERATIVE NORMOVOLEMIC HEMODILUTION

Preoperative acute normovolemic hemodilution (ANH) is used to reduce the loss of blood cells during intraoperative bleeding and to avoid or reduce the need for homologous blood transfusion. The efficacy of hemodilution is somewhat controversial [23,24]. The hemodynamic effects of ANH using non-oxygen-carrying exchange solutions have been studied mainly in animal experiments [25,26] and have been shown to cause a reduction in blood viscosity, decreased systemic vascular resistance, and increased venous return [27,28]. These changes result in increased SV and CO [29]. There are few central hemodynamic data available in humans [30-36] and even such an essential, previously generally accepted compensatory mechanism, as increased CO has been contradicted [37].

HYPEROXEMIA

Oxygen supplementation is a first line treatment for critically ill patients, irrespective of cardiovascular, pulmonary, traumatic, infective or other causes. Apart from the lung [38] and persistent ductus arteriosus [39], however, the blood vessels react to hyperoxia by arterial vasoconstriction [40-46]. This is true also for the coronary circulation where a

normally functioning endothelium effectively regulates the arterial resistance and thereby the flow, in order to maintain adequate myocardial oxygenation irrespective of activity [47-49]. Although hyperoxia is universally used for support in critically ill patients and has therefore been investigated in numerous studies, the combined dose-response effects on central and peripheral circulatory variables and their coupling have not to our knowledge been evaluated in a controlled way.

BURN INJURIES

The main immediate hemodynamic consequences of severe burns involving more than 20% total burned body surface area (TBSA%) are wellknown and lead above all to hypovolemic shock if not treated properly. There are multiple pathophysiological effects that cause this life-threatening condition.

First, a strong negative interstitial fluid pressure develops almost immediately after the injury and is responsible for the main acute fluid shift into the thermally injured skin. This occurs within 1- 2 hours [50]. Later, mainly during the first 8 to12 hours increased vascular permeability is seen as a consequence of mediator release [51-57]. In parallel, decreased cardiac contractility, slowed isovolemic relaxation, and decreased diastolic compliance as seen in isolated hearts after thermal trauma or as recorded in human studies further explains the reduced CO seen after burns [58-60].

Since the 1960s Dr. Baxter's Parkland formula has become one of the most used and most dissected fluid replacement strategies because of its simple and objective criteria for resuscitation of the thermally injured [61-66]. Recently, however, this strategy has been questioned and larger fluid volumes than those originally described by the Baxter formula have been suggested [67,68]. Several studies concluded that the use of traditional variables (urine output and mean arterial pressure), as end points might lead to inadequate fluid resuscitation of burns [69-71] and that the resuscitation should rely on central circulatory measurements such as CVP, PAWP, and CO. Furthermore, and possibly as a result of the arguments presented above, there has been a general tendency to increase the fluid provided for burn resuscitation, particularly when central circulatory endpoints have been used rather than urine output and mean systemic arterial pressure (fluid creep) [72,73]. Despite this, there are few central hemodynamic data available in the clinical setting during the early part of the fluid resuscitation when properly using this formula (2-4ml/kg/TBSA%) in conjunction with the endpoints already described.

Cardiac dysfunction early after burn based on myocyte damage, during fluid resuscitation has special importance [57-60,74-77]. As pathogenesis has both the destruction of myocytes due to inflammatory mediators [78-81] and myocardial ischemia on the basis of hypovolemia been suggested [80]. The evidence of reversible myocardial dysfunction (RMD) [82], or the diagnosis of myocardial infarction (MI), based on the joint definition of the European Society of Cardiology (ESC)/American College of Cardiology (ACC) [83], is important, and influences further treatment, and outcome [84-86]. This definition of MI is: a typical rise or fall of an increased troponin measurement in addition to ischemic symptoms; ischemic ECG changes; coronary artery intervention; or a new

cardiac wall motion abnormality. Though there are several diagnostic difficulties. Correct ECG recordings are often difficult in a bandaged burn patient. Narcotics and sedatives, unconsciousness, thoracic and other wounds, and mechanical ventilation make it impossible both for the patient to communicate chest pain, and for the physician to differentiate the diagnosis of possible coexisting myocardial damage.

The current troponin threshold is defined for non-critically ill populations. It is not known whether this threshold differs in intensive care units (ICU) [84]. Even if an increased troponin concentration indicates myocardial injury, this alone has shown to be not an independent predictor of ICU or hospital mortality, and cannot establish the diagnosis of MI alone [84]. Diastolic functional disturbance in connection with thermal injury in an animal study has been described by [58], but there are few human studies in burned patients.

AIMS

Generally: to investigate and assess the cardiovascular coupling, the LV global, and regional systolic and overall diastolic function and loading conditions, and to find contributing mechanisms behind variations in cardiac performance. All were obtained by using a combination of invasive monitoring complemented by repeatable, less invasive techniques, particularly echocardiography.

Specifically:

1. To evaluate a) whether flow and hemodynamic measurements with transoesophageal echocardiography (TEE) are possible with a reproducibility similar to that reported with transthoracic echocardiography (TTE) studies, b) whether a normovolemic hemodilution to 80 g/l compromises the left ventricular systolic or diastolic functions, c) to evaluate the mechanism behind increased CO during ANH before scoliosis surgery (Paper I).
2. To evaluate the short time effects of increasing degrees of hyperoxemia in healthy volunteers, a) on central and peripheral circulatory variables, b) to find out whether the possible effects are dose-related, and c) to find out whether two non-invasive methods, used simultaneously in a blinded hyperoxemic protocol give similar results and are applicable (Paper II).
3. To assess whether the fluid resuscitation according to the Parkland formula results in adequate cardiac filling, function, and DO_2 in patients with severe burn injuries needing mechanical ventilation (Paper III).
4. To examine the occurrence, timing, and incidence of the left ventricular regional wall motion abnormalities (LVWMA), the signs of diastolic dysfunction as evaluated by TEE, and their association with increased troponin concentrations in patients with major burns during the resuscitation period, using the Parkland formula (Paper IV).

METHODS

All healthy volunteers, patients or their relatives were informed and gave consent to participate in the studies, which all were approved by The Ethics Committee of Linköping University Hospital. The healthy subjects in the study on hyperoxemia (Paper II) were volunteers, recruited from medical students and co-workers, and patients were consecutively studied during their clinically indicated hospital stay. The patients and volunteers are further described in the results, and for the protocols see respective papers. None had evidence of hypertension [mean (SD)] (Study I: systolic blood pressure (SBP) 101 (13) mmHg, diastolic blood pressure (DBP) 82 (12) mmHg. Study II: SBP 126 (18), DBP 64 (10) mmHg. Study III & IV SBP 97 (18), DBP 67 (13) mmHg) or heart disease in their history (all studies), on physical examination, electrocardiography, or transthoracic echocardiography (study I-II). The patients in whom TEE were performed (studies I, III, IV) had no history of problems with swallowing or hemostasis and no esophageal disease. In study III and IV with patients over 20 TBSA% we also excluded patients known to have lung disease.

PULMONARY ARTERY SWAN-GANZ CATHETER

Although recent advances in catheter technology have produced devices that require only central venous catheterization combined with arterial catheterization (PiCCO), and also echocardiographic techniques such that one can estimate mean pulmonary artery pressure and LV preload and function at the bedside, the pulmonary artery catheter has some unique features. These are continuous monitoring of: a) LV filling pressures; b) pulmonary arterial pressures, and c) mixed venous oxygen saturation (SvO₂) [7,87-89]. The pulmonary artery catheter as the clinical golden standard, with an experience of almost 40 years, has also been used to show the ability of other techniques to measure similar variables.

Brief method description of the technique (Paper I, III)

A 7.5 F pulmonary artery catheter (Swan-Ganz flow-directed, thermodilution (TD) fiberoptic pulmonary artery catheter; Model P7110 Abbot Laboratories North Chicago, IL, USA) was introduced into the right internal jugular or subclavian vein and attached to the monitor system (Hewlet Packard M1092; Palo Alto, CA, USA), for measurement of CO_{TD}, SV_{TD}, PAWP and mean pulmonary artery pressure (MPAP). SVR and PVR were calculated (Paper I, III). For CO measurements three injections of 10 ml ice-cold normal saline were used. Transpulmonary thermodilution CO, and Doppler recording of aortic systolic time-velocity curves (VTI) were made simultaneously with CO_{TD} in paper III.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

The advent of two-dimensional TEE has created a non-invasive means of evaluating cardiac anatomy, performance, and cardiovascular volume status, which is becoming recognised increasingly as a valuable adjunct to critical care [90]. Besides the fact of our inability to explore the thorax in many critically ill patients because of postoperative chest incisions and dressings, TTE has major disadvantages, because it may not adequately depict cardiac structures in patients with obesity, emphysema, and prosthetic valves or when the lung is inflated from respiratory care. In addition, certain regions, such as the left atrial appendage, are commonly inaccessible to TTE even in normal patients [91,92]. The reproducibility of the location of the probe for comparisons is also higher with TEE. Among others Clements et al. evaluated the relationship between TEE LV short-axis image measurements and “gold standard” first-pass radionuclide angiograms LV end-diastolic volume (EDV) estimates. The correlation between 2D-echo LV end-diastolic planed area and radionuclide angiograms EDV was close ($r = 0.85$) and even better at end-systole ($r = 0.94$). They also illustrated the accuracy of echocardiographic estimation of overall LV contractility. LV ejection fraction (LVEF), as estimated by LV short-axis-planimetered FAC%, can represent LVEF accurately, as measured by radionuclide angiograms and scintigraphy [3,90]. LVWMA as indicators of ischemia assessed by two-dimensional echo have an early association with coronary flow deprivation. Electrocardiographic (ECG) changes follow after a variable latency period. TEE LVWMA has also been shown to have superior sensitivity when it was compared with Holter monitoring [93-95]. In the present work (Paper I, II and IV) the left ventricle (LV) was conventionally divided into 16 segments off-line for LVWMA and scored as the sum of segment scores over the number of segments assessed (left ventricle wall motion score index, LVWMSI) according to the recommendation of The American Society of Echocardiography [94] (Figure 2a – 2b). CO measurements using TEE Doppler recordings correlate well with thermodilution techniques showing reproducibility similar to that reported with TTE studies [4,96].

Brief method description of the technique (Paper I, III, IV)

We used a transesophageal, phased arrays multiplane ultrasound probe (5MHz imaging, 2,5 MHz spectral Doppler, Vivide Five, GE Vingmed Ultrasound, Horten, Norway) for TEE in the study of burns (Paper III and IV), and another type of multiplane ultrasound probe (3.5 MHz imaging, 2.5 MHz spectral Doppler, CFM800, Vingmed Sound, Horten, Norway) for monitoring and data acquisition at ANH (Paper I). An ultrasound scanner (CFM 750, Vingmed Sound, Horten, Norway) was used for transthoracic parasternal and apical echocardiographic imaging (frequency 3.25 MHz) and Doppler velocity recording (frequency 2.5 MHz) for the healthy volunteers in hyperoxemia (Paper II). Transgastric, midpapillary short-axis views of the LV, and transgastric long-axis two-dimensional views of the LV and the LV outflow tract were obtained. We recorded flow velocities from the LV outflow tract by continuous-wave spectral Doppler [56]. Two-dimensional and Doppler images were analysed off-line either from videotapes (Paper I) or digitally sorted cine-loops (Paper II-IV) stored in the EchoPac system (GE Medical, Vingmed Ultrasound Horten, Norway). Left ventricular end-diastolic (LVEDA) and end-systolic

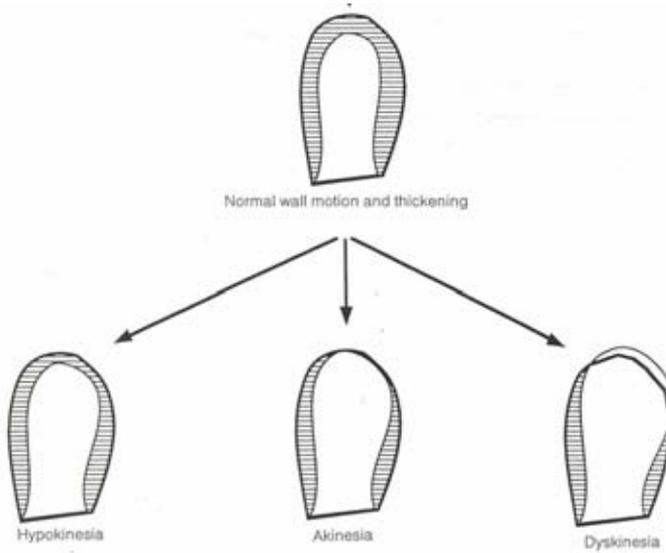


Figure 2a. Echocardiographic signs of abnormal wall motion. *Modified, from Eugenio Picano, Stress Echocardiography, Springer Verlag, Second edition 1994*

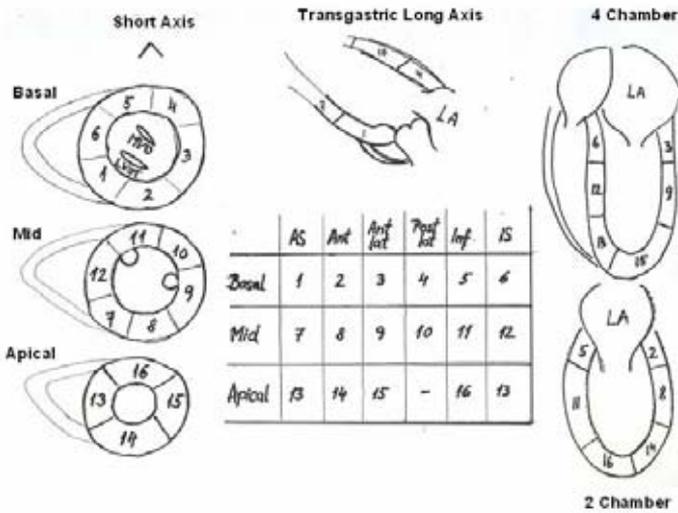


Figure 2b. Sixteen-segment model for regional wall motion analysis proposed by The American Society of Echocardiography. Modified to optimise visualization of the LV outflow tract and aortic valve. AS=anteroseptal, IS=inferoseptal

(LVESA) areas were defined as the largest and smallest area of the transgastric short-axis LV cavity at the level of the papillary muscles, after the electrocardiographic T-wave, and after the R-wave, respectively. These areas were measured by manual planimetry of the area circumscribed by the leading edge of the endocardial border in this position, omitting the papillary muscles. High quality images from three cardiac cycles were averaged. FAC; were calculated in percentages. To calculate $CO_{Doppler}$ and $SV_{Doppler}$ the VTI was multiplied by heart rate (HR) and flow area, respectively. Flow area was assumed circular and constant, and was calculated from the systolic inner-to-inner diameter of the aortic annulus [56]. All TEE measurements were made, recorded and calculated by experienced observers, blinded to the results of the hemodynamic measurements.

DOPPLER ECHOCARDIOGRAPHY AND PULSE TRACING

Doppler echocardiography together with non-invasive estimates of aortic root pressures by external subclavian arterial pulse tracing (Paper II). Pressure and flow recorded in the root of the aorta can be used to calculate the values of the compartments of the three-element windkessel model (Figure 3).

Peripheral resistance, AC and Z can be estimated. In this, non-invasive model calculated peripheral resistance is assumed constant, flow out of the systemic arteries is proportional to the pressure drop, venous pressure is negligible, the pressure is equal in the entire systemic tree, and AC is assumed constant during the cardiac cycle. Despite these assumptions this model has proved useful in many different clinical studies [16,97,98], and has been further developed and evaluated against invasive pressure measurements by Aakhus et al. [18,99]. Aortic Z ($Z_{Doppler}$; proximal arterial (i.e. Aortic) resistance to LV ejection of blood), the total volume compliance of the arterial tree expressed as $SV/$ pulse pressure ($AC_{Doppler}$), peripheral arteriolar resistance ($PR_{Doppler}$), and total peripheral resistance ($TPR_{Doppler}$) were calculated. The sum of $PR_{Doppler}$ and $Z_{Doppler}$ is the $TPR_{Doppler}$.

WHOLE BODY IMPEDANCE CARDIOGRAPHY

Whole body impedance cardiography (Paper II) is a non-invasive operator-independent CO measurement technique that was developed by Tischenko in the 1970s, and revised, introduced, and validated by Kööbi et al in the 1990s [100,101]. We used the method for control measurements, and for complementary cardiac and vascular parameters i.e. SV_{icg} , CO_{icg} , SVR_{icg} , pulse transmission time (PTT_{icg}), and pulse wave velocity (PWV_{icg}). SV was calculated by the equation in Figure 4. Commercially available whole-body impedance cardiography equipment (CircMon™ B202, JR Medical Ltd, Tallinn, Estonia) was used. Data were collected and analyzed in a computer with the CircMon® software from the same company (Paper II).

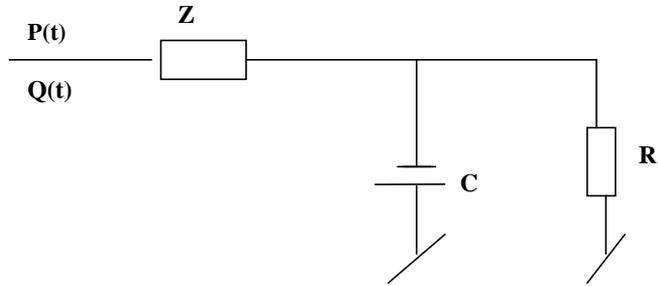
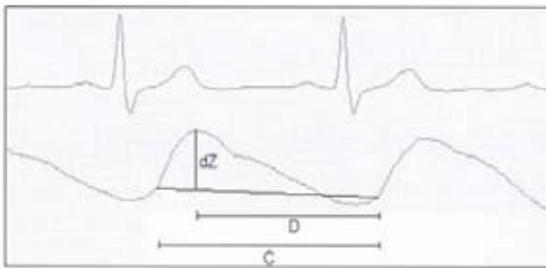


Figure 3. The electric equivalent of the 3-element Windkessel model of the systemic arterial tree. Aortic rote pressure (P) and aortic flow (Q) as functions of time (t) are input variables. Characteristic impedance (Z), total arterial compliance (AC, corresponding to C in the electrical model), and peripheral resistance (PR, corresponding to R in the electrical model) are estimated variables. *Modified from Aakhus et al. [18].*



$$SV = k \times H^2 \times \frac{dZ / Z_c}{Z_0} \times \frac{C}{D}$$

Figure 4. Whole body impedance cardiography. Measuring points and time intervals used for estimation of SV. H is height (cm), delta Z the amplitude of heart synchronous impedance variation (Ω), Z_c is the calibration factor (0.1Ω), and Z_0 is the baseline impedance of the body (Ω). C is the duration of the cardiac cycle, and D the duration between peak heart synchronous impedance variation and the onset of the next cycle. The coefficient k ($\Omega \cdot \text{cm}$) is derived from the resistivity of the blood, the relation between the distance of the voltage electrodes and body height, and includes a correction for measured body mass index and a default hematocrit of 0.45. *Modified from the Operator`s Manual CircMonTM Model B202 JR Medical Ltd Tallinn Estonia.*

TRANSPULMONARY THERMODILUTION WITH PULSE CONTOUR ANALYSIS

Adequate cardiac preload without fluid overloading is important to obtain and assure in critically ill patients. Cardiac filling pressures (central venous pressure CVP, PAWP) are known to have their obvious limitations. EDA measurements by TEE has been proposed as gold standard for preload estimation, but because of possible complications of keeping the probe in position for a longer period and because an experienced examiner is usually not routinely available, TEE as every day monitoring device is still limited.

Transpulmonary thermodilution technique (PiCCO system) by measuring the mean transit time and exponential decay time of thermodilution curve detected in the abdominal aorta makes it possible to calculate preload variables. The method that is less invasive than the pulmonary artery catheter (only central venous catheter and artery catheter are necessary) also contains a system for measuring continuous SV that is based on a computerised pulse contour analysis [102].

Brief method description of the technique (Paper III)

CO_{PiCCO}, SV_{PiCCO} and global end-diastolic volume (GEDV_{PiCCO}) were measured using three injections of 20 ml ice-cold normal saline through an additional 8.5 F central venous catheter introduced in the right jugular or subclavian vein. GEDV_{PiCCO} is calculated from the difference of mean indicator transit time and exponential indicator down-slope time and from the CO obtained from transpulmonary thermodilution. The basis of this method has been described in detail previously [102]. The PiCCO system also displays intrathoracic blood volume (ITBV) as an additional volume preload variable, and extra vascular lung water (EVLW). These variables are calculated from GEDV_{PiCCO} based on a fixed algorithm, established from data obtained from earlier double-indicator transpulmonary thermodilution. The bolus thermodilution measurements were made by the same observer to avoid interobserver variation.

STATISTICS

Data are presented as mean (SD). Probabilities of less than 0.05 were considered significant. Commercially available computer software was used for statistical analysis (Statview®, Abacus Concepts/Microsoft, USA (Paper I) and Minitab, release 13, State College, PA, USA (Paper II-IV)).

We used analysis of variance (ANOVA) repeated measures (Paper I-III) with Tukey simultaneous posthoc tests to find out if flow and echocardiographic Doppler variables changed among the different occasions of measurements during hemodilution and in hyperoxemia (Paper II-III).

The effects of oxygen dose-response on variables reflecting central and peripheral hemodynamics were analysed using linear regression and analysis of covariance where the dose was used as a covariant and each subject was a factor. The linear regression lines, standard error (SE), and coefficient of determination for the different variables were calculated. $Y = m + k \cdot X$, Y was the hemodynamic variable, m the intercept of the line when X=0, k the slope, and X the transcutaneously measured oxygen level in kPa. The F-

test was added to see whether a third degree polynoma described the dose-response significantly better than a straight line ($F>3.40$) (Paper II).

The comparison between two “non-gold standard” measurements of cardiac and vascular variables, was accomplished as described by Bland & Altman [103] and with regression analysis (Paper I-II).

For echocardiographic reproducibility inter-individual coefficients of variation of repeated measurements were calculated by dividing the SD of the differences by the mean value of the samples (Paper I).

The correlation between biomarkers of myocardial injury and LVWMA measurements expressed as the wall motion score index (derived by dividing the sum of wall motion scores by the number of segments seen LVWMSI) was accomplished by a linear-by-linear association test after both were graded as normal, moderate (II), or pronouncedly (III) increased values. LVWMSI indicates the extent of regional wall motion abnormalities, in which higher scores indicate more severe abnormalities (1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis, and 5 = aneurysmal) (Paper IV).

The correlation coefficient was calculated for comparison of preload equivalent variables measured by two different methods (Paper I and III).

SUMMARY OF SUBJECTS AND RESULTS

PAPER I

In this study, we investigated eight patients (seven women, mean age 28 years (range 13 – 61), mean weight 55 kg (range 44-71) who had ANH before operation for scoliosis. Measurements were made during a stabilisation period 15, 30, and 45 (n = 6) minutes after induction of anesthesia, and during two stages of ANH (n = 8) when hemoglobin from a baseline of 122.1 (7.9) was decreased to 98.0 (3.2) and to 79.7 (4.9). There were no hemodynamic changes 15, 30 and 45 min after induction of anesthesia. **Invasive measurements:** During ANH HR, mean radial systemic arterial pressure (MAP), and MPAP remained constant. No ECG changes were recorded. CO increased in steps from 16% to 26% and the change in CO correlated with the change in hemoglobin concentration ($r=0.85$). HR remained constant and the increase in CO was a result of an increased SV. SVR (= (MAP-CVP) / CO) fell accordingly, but CVP remained at the same level. A slight increase in PAWP was seen by the end of ANH. **Echocardiographic measurements:** No LVWMA were observed. VTI did increase at both stages (16% and 27% respectively), reflecting the increase in SV or CO as HR remained constant. A 20% decrease in LVESA and an 11% increase in LVEDA resulted in an increase in FAC from 44% to 60%. Lateral mitral annular motion (LMAM) increased by 38%, mostly at the final stage of the ANH and correlated with the changes in FAC ($r=0.78$). Of the diastolic variables only mitral early filling maximal flow velocity (MEV_{max}) and maximal systolic forward pulmonary venous flow velocity (PVS) changed significantly compared with baseline values, but the

trend for mitral atrial filling maximal flow velocity (MAV_{max}) and maximal diastolic forward pulmonary venous flow velocity (PVD) was also upward in all patients during ANH. DT and isovolumic relaxation time (IVRT) did not change significantly and the ratio between duration of atrial-related mitral and pulmonary venous flow remained around 2 throughout the study. **Comparative studies:** $CO_{Doppler}$ measurements correlated with CO_{TD} ($n=36$, $r=0.78$, $SEE=1.1$) and the line ($y=0.71x + 1.1$) did not differ significantly from the line of identity. The change in MEV_{max} correlated poorly with the change in CO ($r=0.42$) but the degree of hemodilution correlated well with the change in CO ($r=0.85$), the change in FAC ($r=-0.81$), and the percentage change in SVR ($r=0.80$). There was no correlation between LVEDA and PAWP ($r=0.07$) despite of the fact that both increased slightly but significantly during hemodilution. **Reproducibility:** The inter-individual coefficients of variation for measurements of aortic annulus diameter, VTI, and LV-areas were small ($<4\%$). For diastolic Doppler measurements the reproducibility was less, particularly for pulmonary venous flow variables and IVRT.

PAPER II

In this study we investigated nine healthy volunteers, 7 men, aged 23-48 years [mean (SD) 31 (8)], height 179 (9) cm, weight 76 (15) kg, and body surface area 1.9 (0.2) m². They were divided into two groups to blind the investigators and participants to the time when increasing oxygen-delivery was started by a third party. This blinding was maintained throughout the study until all the results were available. Transcutaneously measured partial O₂ pressure ($P_{tc}O_2$) matched the aimed values well, from a baseline value of 10.4 (1.2) to 18.0 (2.4), to 36.3 (5.5) and to 57.2 (11.4) kPa. CO decreased as a result of decreasing SV and VTI, without diminishing HR. Behind this we noted a decreasing LVEDA, while LVESA and FAC% did not change. Associated with hyperoxemia we recorded an increase in SVR or TPR, Z, and PR, while MAP, AC, PTT and PWV remained unchanged. **Dose-response studies:** All variables that changed significantly from hyperoxemia showed a dose-response relation to increasing oxygen-pressures as analyzed by linear multiple regression. For example, the calculated regression equation predicts a mean loss of 4 ml in $SV_{Doppler}$ for every 20kPa-increase in $P_{tc}O_2$ when increased above normal. In all variables a straight-line model described the relation better than a third degree polynomial. Similar results were obtained if $P_{tc}O_2$ were grouped either in categories or continuous values. Using inspired air O₂ fraction (FiO_2) instead in the analysis did not change the results. **Comparative studies:** There were no significant differences between the data generated by the Doppler echocardiography and those obtained by the whole body impedance method, and correlation coefficients for the regression lines were 0.64 for SV, 0.59 for TPR/SVR, 0.54 for AC and 0.95 for $MAP_{Oscillometric} / MAP_{Subclavian}$; regression lines did not differ significantly from lines of identity. With Altman and Bland analysis there was no bias: Mean SV_{icg} was 8 ml higher than $SV_{Doppler}$ (SD_{diff} 12.6), and mean $TPR_{Doppler}$ was 220 $dyne*s*cm^{-5}$ higher than SVR_{icg} (SD_{diff} 203).

PAPER III

In this study we assessed the systemic cardiovascular response of burns during fluid resuscitation using the Parkland formula. Ten consecutive patients, two women, with more than 20 TBSA%, needing mechanical ventilation, and arriving at the burn unit within 12 hours were investigated 12, 24, and 36 hours after injury. Baux-index was 92 (15.7), TBSA% 35 (15.1), Age 57 (14.7) years, weight 80 (11.7) kg, fluid replacement during first 24 hours 4 (1.2) ml kg⁻¹ TBSA%⁻¹, urinary output 0.77(0.39) ml kg⁻¹ h⁻¹. Fluid replacement induced significant hemodilution. There were tendencies to a rising DO₂ and decreasing oxygen consumption, but these changes together with a slight increase in SvO₂ did not reach significance. **Invasive Measurements:** HR, MAP, and MPAP remained constant during the fluid resuscitation. CVP, PAWP with SV_{TD} and CO_{TD} increased at every time interval of measurements during fluid resuscitation, but CVP increased only after 36 hours. Calculated SVR and PVR, the values of the PiCCO measurements of GEDV_{PiCCO} and ITBV_{PiCCO} increased significantly by the end of the 36th hour of fluid resuscitation after the burn. **Echocardiographic measurements:** VTI increased both after 12 and 24 hours of fluid resuscitation, reflecting the increase in SV and CO. A pronounced increase in LVEDA and increased LVESA did not lead to an additional rise in FAC. Both end diastolic, and end systolic area measurements showed values below normal [94,104-106] at 12 hours after injury. **Comparative studies:** The degree of hemodilution, CO and SV measurements with three different methods showed a good correlation with each other, as the degree of hemodilution, with CO. LVEDA measurements with TEE correlated with transpulmonary GEDV_{PiCCO}, and both methods showed preload equivalent values below their normal levels [107-109] at the 12 hours measurement series.

PAPER IV

In this study, performed simultaneously and on the same patients as in paper III, using TEE we compared the association of LVWMA, and diastolic Doppler flow variables with raised plasma troponin T (tr T) concentrations in severe burns during the resuscitation period. Half the patients had unstable LVWMA, and all of these had simultaneous leakage of the myocardial biomarker. There was a significant categorical correlation between these two variables of myocardial damage at both 12 and 36 hours after the burn (p = 0.01, and 0.02, respectively). All patients with LVWMA had a decreasing LVWMSI at 36 hours, even the patient who died of an MI 3 days later. There was a tendency for the LVWMA to peak earlier than the trT leakage. Two of the patients with LVWMA needed temporary inotropic/vasoactive support because of low MAP. In two patients, trT measurements were missing. Both had varying LVWMA and increased plasma asparaginic acid concentrations not seen in patients without LVWMA and who had no signs of hepatic insufficiency (Table 1). None of the patients had LVWMA with normal concentrations of trT, or vice versa. SV increased significantly in all patients during fluid resuscitation, even in patients who developed LVWMA. Variables of Doppler flow chosen to evaluate diastolic function showed a tendency towards a disturbed pattern of relaxations with low MEV_{max} : MAV_{max}

that did not change during the study even though MEV_{max} increased significantly as did SV, and there was a tendency towards decreased HR. Mitral flow deceleration time (DT) was pathologically low on admission and remained so during the study, even if there was an increase after 24 hours. The other diastolic variables and indices were stable within reference ranges.

Table 1. Association of LVWMSI (echocardiography) with leakage of troponin

Case No	Age (years)	TBSA (%)	LVWMSI			trT (n=8)			A	Bilirubine
			Time (hours)							
			12	24	36	12	24	36		
1	47	25	1.05 ^{II}	1.05 ^{II}	1.11 ^{II}			A1.0 ^{II}	1.0	11
2	48	32	1.09 ^{II}	1.62 ^{III}	1.43 ^{III}		A1.1 ^{II}	A3.0	1.1, 3.1	17
3 ^c	70	20	2.04 ^{III}	1.33 ^{III}	1.3 ^{III}	1.1 ^{III}	2.8 ^{III}	2.1 ^{III}	1.4, 1.1	30
4	53	51	1	1	1	0	0	0	0.69	9
5 ^c	89	27	1.16 ^{II}	1.16 ^{II}	1	0.1 ^{III}	0.4 ^{III}	0.3 ^{III}	0.59	12
6	36	48	1.11 ^{II}	1	1	0.07 ^{II}	0.58 ^{III}	0.09 ^{II}	5.5	86
7	58	46	1	1	1	0	0	0	1.2	101
8 ^d	65	21	1	1	1	0	0	0	0.39	26
9 ^d	53	60	1	1	1	0	0	0	0.8	24
10 ^d	52	25	1	1	1	0	0	0	0.8	12

LVWMSI=left ventricle regional wall motion score index = sum of wall motion scores: number of segments visualised; TBSA=total burned body surface area (%); ^{II}moderate, ^{III}pronounced deviation from normal values.A=asparaginic acid aminotransferase (μ kat/l, reference < 0.8); trT=troponinT (μ g/l, normal value < 0.01); plasma bilirubine concentration (reference <25 μ mol/l) ^c=died after the study period; ^d=inhalation injury.

DISCUSSION

HEMODILUTION (I,III)

We investigated two different types of hemodilution: one that is deliberately conceived to reduce the loss of blood cells during intraoperative bleeding (ANH), and the other that is a result of fluid replacement, in our case in severe burn injuries.

Hemodilution reduces the viscosity of the blood and causes dilatation in some vascular beds, which then changes the pressure profile in the series-coupled vascular components and causes alterations in capillary pressures and hence changes in net filtration. The sympathetic and myogenic tone of the vessels may also change [21]. Indeed, at constant intravascular fluid volume the cardiac filling pressure increases. The fall in SVR and increase in CO have been attributed to reduced blood viscosity [27,28] and increased venous return. In our study, as in earlier human studies of ANH [32], HR, MAP, and MPAP remained constant.

Anesthesia itself affects the cardiovascular response to hemodilution. Volatile anesthetics including isoflurane, have negative inotropic effects, reduce CO, prolong isovolemic relaxation, reduce coronary flow (because coronary flow is highest during this phase of diastole), and reduce indices of early LV filling. They probably do not affect the elastic properties of the LV myocardium itself [110,111]. Even if the effect of anesthesia was not evaluated in this study, during the prolonged anesthesia, hemodynamic variables were stable before ANH.

Animal studies have shown that normal coronary arteries respond to acute anemia by substantial dilatation before DO_2 is affected [112]. This is in agreement with our study when hemoglobin was reduced to less than 80 g/l and neither global systolic function of the LV nor CO deteriorated. Catoire et al. 1992 even showed improved hemodynamic tolerance to aortic clamping by a similar degree of hemodilution in patients with coronary artery disease [113].

As far as regional LV wall motion were concerned, the answer to hemodilution was different after burn injury, where 50% of the patients reacted with regional dysfunction and biomarker leakage, whereas patients during ANH showed no regional wall motion abnormalities. As the pathogenesis of myocardial damage during burns includes both the destruction of myocytes by inflammatory mediators [77,80,81] and myocardial ischemia on the basis of early hypovolemia [71,80], this could also be the reason why FAC did not increase in burned patients but did during ANH despite hemodilution and the simultaneous increase in venous return in both studies.

The importance of diastolic function to overall LV performance is well established. Most often, abnormalities of systolic and diastolic function coexist and act together to contribute to heart failure [114,115]. Assessment of transmitral filling patterns is typically combined with analysis of pulmonary venous blood flow velocity waveforms obtained with Doppler echocardiography to provide a comprehensive analysis of diastolic

function. The deterioration of diastolic function is one of the earliest signs of acute myocardial ischemia [116]. Unlike regional deterioration of systolic function, there is no mechanism during advanced hemodilution to compensate for regional diastolic dysfunction in territories where the coronary flow is compromised [117]. Measurement of diastolic function both during hemodilution and during resuscitation of severe burns may therefore help to reveal early disturbances and avoid inadequate DO_2 and uptake. Both transmitral and pulmonary venous flow are influenced by the early transmitral pressure gradient and left atrial properties. As pathological filling profiles abnormal relaxation, restrictive physiology and so called pseudonormalisation can be differentiated. The prolongation of LV relaxation results in a lower peak gradient between the left atrium and ventricle, a lower transmitral E-wave flow velocity, an increased DT of the flow early in diastole and an increased A:E ratio. Decreased LV compliance together with increased preload may normalize the mitral flow pattern, and is called “pseudonormal mitral flow”[11].

During acute normovolemic hemodilution increased end-diastolic areas of the LV were seen in all but one patient and PAWP also increased slightly. In single patients, however, PAWP was not predictable from LVEDA-increase or from the diastolic echocardiographic measurements of mitral inflow and pulmonary venous flow. At low normal filling pressures the changes in pressures are small and normal variations in compliance possibly play an important part [118] and may contribute to the inter-individual discordance between volume and pressure. A lower reproducibility of diastolic Doppler measurements and a limited number of patients may, however, all contribute to these results.

Our findings, however, suggest that, in physiologically normal people, the increase in preload during ANH is an effect of increased venous return and is not the result of decreased LV diastolic function. The finding of short early mitral flow DT during rapid fluid replacement using the Parkland formula, however, supports impaired LV distensibility after burns.

HYPEROXIA (II)

The changes in systemic resistance and CO in this study are of the magnitude usually seen when healthy volunteers are exposed to increased arterial oxygen tensions – that is, roughly a 10% effect at the highest oxygen tension [119]. We examined the effect of oxygen after early acute adaptation, and searched the changes elicited by oxygen in the minute-hour time perspective, usually used in acute intensive care.

There was a linear dose-response relationship between arterial oxygen and cardiovascular variables when the systemic oxygen tension increased above normal. It has been suggested that the oxygen-related effects are mediated either by primary cardiovascular effects or secondary by changes in the hemoglobin. The latter is not supported by the findings in this study, where the linear dose relation found at supranormal arterial oxygen values – where the oxygen saturation of the hemoglobin may further be assumed to be almost constant and close to 100% – was inversely related to the arterial partial pressure of oxygen without sigmoid shape. A direct effect of supplemental oxygen

on the vessels, also suggested by others [120,121] may therefore be considered. The vasculature in skeletal muscle, where the vascular bed is most important for the regulation of systemic vascular resistance, has shown a similar relation to the partial pressure of oxygen in arterial blood [122] and a decrease in sympathetic outflow to vessels of skeletal muscle resistance during hyperoxia is described [123]. It has also been shown that supplementary oxygen/hyperoxemia increases both the cardiac parasympathetic activity and the arterial-cardiac baroreflex function in a dose-dependent manner secondary to the increased blood pressure [124]. This suggests that the vasoconstriction of peripheral arteries is a local primary event preceding these secondary neural consequences.

A recurring phenomenon in hyperoxia models in our study too is the finding of a large interindividual variability in the oxygen response and adaptation. This applies to the magnitude as well as to the time factor. A possible explanation could be that different subjects may differ in their genetic predisposition to produce superoxide dismutase [125], which belongs to an endogenous protection system against free oxygen radicals.

Early studies of hyperoxemia claimed that the primary effect of oxygen was to stimulate the parasympathetic nervous system leading to a decrease in HR and in CO, which in turn lead to a secondary increase in SVR. Given the order of development known today, and supported by the fact that we were unable to detect any change in HR, this line of reasoning is less likely. Instead, the results of the present study support previous assumptions that the primary, physiological effect of hyperoxemia is the increase in vascular resistance to which the central circulation slowly adapts. This adaptation is made after a transient increase in blood pressure and a decrease in HR as shown previously, but not recorded later during oxygen treatment as in our study. The early changes in the vasculature are modified by local and systemic adaptation (for example, autoregulation of local flow and systemic baroreceptor function), normally within 10-15 minutes [46]. It is therefore important to stress that the effects measured in this study were obtained after 15 minutes steady state, when increased SVR, decreased SV and LVEDV persisted. The assumption that the peripheral vascular effect is the initiating event is strengthened by the fact that we were unable to record any direct effects on the heart, as for example, a change in FAC and that the vascular changes could be elicited in a “heart free” preparation, such as in patients on a heart-lung machine [121].

A significant confounding factor that must be considered in all experimental settings where oxygen tension is modified is a change in arterial carbon dioxide partial pressure (pCO₂). Theoretically the decrease in pCO₂ that is seen during hyperoxia elicits vasoconstriction. Contrary to several previous publications, we were unable to record any effect of hyperoxia on the pCO₂, which reduces the likelihood of us eliciting a secondary CO₂ effect on the vasculature. Possibly, the lack of effects of pCO₂ in this study may depend on the longer time periods studied after the first exposure to oxygen. Hyperoxia studies are less confounded by strong compensatory mechanisms, than hypoxia studies such as increase in sympathetic tone and breathing stimulus.

Another important finding is the reduction in LVEDV, which may explain the decrease in CO. There are several tentative explanations for this. The observed rapid decreases in LVEDV and SV without a change in HR indicate a decreased venous return

and reduced central blood volume. Sympathetic receptor stimulation may decrease venous return but the results are conflicting [126]. Our results, however, indicate pooling of arterial or venous blood, which normally occurs in the capacitance vessels or in the larger veins [22], but for example the splanchnic vasculature may also be involved [127]. In the lung, hypoxic constriction is described [38], but not the contrary. A secondary sympathicolysis of the capacitance vessels and larger veins caused by increased parasympathetic activity and arterial-cardiac baroreflex function [124], and decreased sympathetic outflow to skeletal muscle resistance vessels [123], may contribute here. The location of blood pooling is, however, not indicated by this study, and to our knowledge there have been no studies on hyperoxemic volume effects on veins or pulmonary circulation.

BURN INJURIES (III, IV)

This study has shown that the Parkland resuscitation strategy maintains central circulatory measures within the normal ranges at the end of the first 24 hours, as assessed by three standard methods of central circulatory surveillance including echocardiography (the gold standard) [3,90]. The lack of base deficit, which indicates acidosis, and preserved oxygen delivery and consumption, further supports the hypothesis that the circulatory support obtained by using the Parkland protocol is adequate. Our results show that this outcome could be obtained by the simultaneous use of the two standard endpoints: urine output and mean arterial pressure, as suggested in the original description of the Parkland formula. Central circulatory data were recorded, but not used as endpoints in this study.

The new finding of this study, as was also hypothesised, is that there seems to be a minor and transient tendency towards central circulatory hypovolemia during the early part of resuscitation (the first 12 hours after the burn). The origin of this is difficult to establish from our data. It may be that the fluid provided was not delivered as rapidly as the fluid was lost into the tissues, or that the start of fluid resuscitation was delayed because of transport or other reasons. Small LV cavity size with hypercontractile walls is the typical sign of hypovolemia measured by echocardiography, which is claimed to be the most valuable diagnostic tool at the bedside to evaluate hypotension or shock syndromes [90,104]. Hypovolemia was recorded at this time by both transesophageal echocardiography and transpulmonary thermodilution, and the two independent investigators were unaware.

Both the end-diastolic and end-systolic areas and the global end-diastolic volume of the heart were below their normal values [94,104-106] 12 hours after the injury, which may be one reason why other investigators have infused larger fluid volumes when resuscitating their patients [67,68,71]. A possible prehospital delay, or giving fluid too slowly at this stage, is less likely as a strict protocol was used during the trial.

Even when oxygen delivery or consumption was assessed, there was no indication that more fluid was required. Despite the fact that urine output and MAP were endpoints, there were no signs of late hypovolemia, but instead optimised central circulation by 24 hours after the burn. This finding contradicts what others have seen when

using central circulatory endpoints for fluid resuscitation [67,71]. In our unit several studies have been conducted using the Parkland formula [128-131], but this rarely forced us to infuse larger volumes of fluid than recommended in the original protocol.

Even though LVEDA measurements by TEE have been proposed as the gold standard for estimation of preload, transpulmonary thermodilution, together with pulse contour analysis (PiCCO-system), offer further hemodynamic information. GEDV correlated well with measurements of the preload indicator area by echocardiography, but the use of these variables in individual patients needs further evaluation [102].

EVLW is an important variable that shows extravasation of fluid from the pulmonary circulation. We found that there is a tendency towards early increased permeability that normalises within 36 hours of injury. This tendency contradicts the findings presented previously [67,132], but is supported by another study by our group in which we found a significant correlation between the EVLW:ITBV ratio and creatinine-adjusted microalbuminuria soon after the burn [52,133]. Because there is normally a positive correlation between increasing filling of the heart as assessed by the ITBV and extra vascular lung water, the use of EVLW value alone without adjusting for the corresponding ITBV may be misleading.[109] The recorded EVLW:ITBV quotient was increased 12 hours after the burn, suggesting a minor increase in lung water on this occasion.

The strength of the present investigation was that three methods were used simultaneously to assess the central circulation. Others have used these methods separately in studies in which central circulatory endpoints have been evaluated for the fluid support of patients with burns. This study may therefore contribute to a better understanding of the coupling between traditional (urinary output and MAP) and central circulatory end points. It should also be emphasised that irrespective of the central circulation monitoring technique chosen, all outcome measures were similar and no method suggested that more fluid should have been provided 24 hours after the burn.

Limitations of the study: This study was based on a selected group of patients: burns of more than TBSA 20% with a parallel need for mechanical ventilation. Patients with this size of burn are usually resuscitated with intravenous fluid support [134]. This was the case in the present study as well. Our selection of patients was ethical, as both pulmonary artery catheterisation with Swan-Ganz catheters and repeated transesophageal echocardiography are invasive or semi-invasive, and are not suitable for awake patients who are not intubated. The amount of fluid provided for this selected group should at least theoretically be larger than for an unselected population. Our group may be assumed to contain more inhalation injuries, larger burns, and had the circulatory effects of mechanical ventilation and sedation. These circumstances together would increase the fluid volume needed to optimize preload. Despite this consideration the fluid volume provided in the study was within the range of the Parkland formula. Another consideration was that a restricted number of patients were examined and there were no long term outcome measures, such as organ failure scores [135]. The low level of dispersion of central hemodynamic data, however, improves the credibility of the results.

Though the finding of our study does not support the hypothesis that oxygen transport is affected at the global level, and there were no signs of impairment of global systolic function of the left ventricle, the oxygen supply locally might have been compromised. Hemodilution caused by the large amount of crystalloids results in diminished overall arterial oxygen content. This together with possible toxic, inflammatory, and stress reactions caused by the burn itself implies further risk for possible reversible or irreversible myocyte damage in these patients. Homologous blood transfusion provided to the burned patient has, however, unfortunately been shown to increase mortality in itself [70].

Regional cardiac dysfunction, however, as assessed both by echocardiography (LVWMSI) and leakage of biomarker, are common (50 %); they appear early, and seem to be closely correlated; they are relatively mild, and of short duration. Although SV increases during fluid resuscitation, the mitral flow Doppler pattern suggests a restrictive filling of the LV in all patients with major burns. The finding that all patients with leakage of the cardiac biomarker also had a raised LVWMSI, and vice versa, contradict most previous studies in which patients in bigger, mixed general ICUs had raised troponin concentrations with no other signs (ECG, chest pain, or echocardiography) of ischemic changes. We have found no study restricted to major burns in adults. In the studies of Lim et al. [84] 47% of critically ill patients had raised troponin concentrations but only 26% of these met the criteria for myocardial infarction [82]. In our group one patient died from cardiac arrest after the burn; otherwise we had no clinical or historical signs of cardiac disease during their continued stay in hospital. However, the TEE were not repeated, and transthoracic echocardiography was not possible in most of the patients before discharge [136]. Cardiac changes induced by the burn may differ from those caused by critical illnesses from other causes. There have been many reports in sepsis and septic shock [137,138] that showed correlations between increased troponin concentrations and LV dysfunction recorded by echocardiography, a lower survival rate, higher APACHE II scores, and greater need for inotropic drugs. The conclusion of these studies was that troponin indicates irreversible myocardial damage.

In contrast, there have been studies that have shown release of troponin in reversible ischemia [139,140]. Ellrodt et al. found normalization of LV function using radionuclide techniques in patients who survived septic shock [141].

Burn-induced myocardial damage may be thought of as a toxic or inflammatory consequence of the burn itself, as a result of hypoxia, ischemia because of insufficient fluid resuscitation, or traumatic stress after the burn, or underlying cardiovascular disease [79,80]. Thermal injury also initiates metabolic alterations, which may contribute to subsequent myocardial dysfunction and to diastolic restrictiveness. Alteration in calcium homeostasis has been proposed as a mechanism [142,143]. In these aspects both reversible and irreversible myocardial damage has been described. It may also be considered as a direct consequence of the burn-induced changes in the myocardium, or it may result from myocardial dysfunction for other reasons, such as secondary complications of the burn, including pulmonary edema, myocarditis, intoxication, sepsis, pulmonary embolism,

surgical intervention, heart trauma, uremia, and renal insufficiency, which could also explain a restrictive dysfunction.

We found early changes, suggesting a primary effect of the burn itself. Cardiac dysfunction in burns appears within the first 24 hours after the burn [78], and as in our study, affects both ventricles [60] as well as diastolic function [58]. The reduction in diastolic compliance found by Adams et al. [58] in guinea pigs supports our findings that the short DT might indicate a restrictive filling caused by the burn itself as it also was seen in patients who not had signs of LVWMA and systolic dysfunction. Diastolic changes also seem to develop early after the burn, and to vary less than the systolic changes during the first days of resuscitation.

Both echocardiography which illustrates disturbances of global or segmental LV function and cardiac troponin, a regulatory protein of the thin filament (actin) of cardiac muscles as a biomarker, are accepted tools for the diagnosis and differentiation of possible reversibility of myocardial damage [83].

Two mechanisms of the leakage of the biomarker have been described. One is increased permeability of the myocyte to macromolecules, which may be caused by the release of inflammatory substances such as tissue necrosis factor (TNF) [79,80] and other inflammatory products that are released after a burn [80], or the presence of hypoxia caused by hypovolemia or pre-existing ischemic heart disease, or both. The latter has no support from our results. The other mechanism of leakage is ischemic degradation of native troponin into smaller fragments within the myocyte which, when released from the myocardium, is recognised by some commercial assays of troponin [85].

CONCLUSIONS

CO measurements using transgastric Doppler from the LV outflow tract are possible with availability, reproducibility, and accuracy similar to those reported with transthoracic echocardiographic studies.

A degree of hemodilution to 80g/l does not normally compromise systolic or diastolic myocardial function.

ANH causes a decrease in vascular resistance and an increase in CO. This increase in CO is proportional to the degree of hemodilution and is generated by an increased ejection fraction and increased preload.

Hyperoxia causes systemic vasoconstriction and reduces CO by reducing preload and venous return.

At hyperoxemia there is a positive linear dose-response between arterial oxygen and SVR, an inverse linear dose-response between arterial oxygen and SV and a direct effect on the vessels is plausible.

The Parkland formula for fluid resuscitation of severe burn injuries does not compromise LVEF DO_2 , or uptake or base deficit when only urinary output and mean arterial pressure are used as end points. Low cardiac filling during the first 12 hours after injury suggests a more rapid initial giving but no increase in total fluid volume during the first 36 hours.

This may be one factor of importance in the development of acute ischemic myocardial damage, with wall motion abnormalities and troponin leakage. Acute myocardial damage recorded by both echocardiography and leakage of the marker was common, and there was a close correlation between them.

The mitral flow Doppler pattern suggests restrictive filling of the LV in all patients with major burns.

Myocardial stiffness and systolic regional dysfunction caused by severe burns may not be prevented only by central normovolemia and adequate oxygenation.

Even if conventional endpoints such as MAP, urine output, HR, PAWP, and CO are well-founded, echocardiography gives additional information about hemodynamic mechanisms and myocardial damage in ANH, hyperoxemia, and major burns.

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