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Cardiovascular Monitoring and Substitution of the Blood Volume During Liver Transplantation

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1. Introduction

Orthotopic liver transplantation (OLT) became a treatment modality in Denver (Starzl *et al.*, 1963) and Cambridge, England in 1968 (Calne, 2008) although exposing critically ill patients to extensive surgery was a challenge and in the 1970s, the one year survival rate remained in the vicinity of only 25% (Starzl *et al.*, 1981). One problem was to manage the often impressive blood loss and rapid infusion devices were developed to provide large amounts of blood products at body temperature (Stammers *et al.*, 2005). During OLT the blood loss has, fortunately, declined and in the 1980s, the average number of blood units administered was reduced to 20 and in some centres, ~ 80% of patients are now without a need for administration of blood (Massicotte *et al.*, 2004). Yet, there remains differences among centres and for a number of patients, OLT is associated with a significant blood loss (Massicotte *et al.*, 2004). Furthermore, haemodynamic challenges are inevitable during the operation. Corresponding to the metabolic activity of the liver, the hepatectomy is likely to reduce cardiac output (CO) and in cases for which caval and portal clamping are used, blood accumulates in the splanchnic region and in the lower part of the body which together leads to a decline in CO by 40%-50% (Ozier & Klinck, 2008). Conversely, CO often doubles during reperfusion of the grafted liver as peripheral vasodilatation is provoked by the release of blood from the splanchnic region mixed with the chilled outflow from the liver, potentially with a high potassium concentration (Ozier & Klinck, 2008). Also it may be that the heart is unable to respond with an adequate increase in CO to reperfusion of the grafted liver, or that there is a reduction in CO despite an, apparently, adequate central blood volume (CBV), accepting that reperfusion of the liver and re-establishing splanchnic blood flow may release some cardio-inhibiting factor (Jordan *et al.*, 1999). Given redistribution of the blood volume during OLT, monitoring of the circulation is, ideally, directed to secure CBV rather than the total blood volume.

As for other types of surgery, there is no universally accepted strategy for haemodynamic monitoring during OLT, save a mandatory arterial line and recording of heart rate (HR) by ECG (Ozier & Klinck, 2008). Yet, mean arterial pressure (MAP) and HR are inadequate for monitoring CBV (Bundgaard-Nielsen *et al.*, 2007a). For example, there may be no significant deviations in these variables until a hypovolaemic shock is provoked (Murrell *et al.*, 2009).

Furthermore during surgery, HR and especially MAP are affected by the anaesthetic agents and by the surgical stress (Ejlersen *et al.*, 1995a). Despite these limitations in the use of HR and MAP to detect deviations in CBV, the capability to balance CBV is of importance for tissue perfusion and oxygenation and notably for oxygenation of the brain (S_cO_2) (Nissen *et al.*, 2009a), indicating that advanced cardiovascular monitoring is required to secure the well-being of the patient (Yao *et al.*, 2004;Bundgaard-Nielsen *et al.*, 2007a;Murkin *et al.*, 2007)

In order to maintain CBV during surgery, it is important that normovolaemia is defined. For supine humans the heart operates on the upper flat part of the Frank-Starling curve (Harms *et al.*, 2003) and to establish and to maintain a maximal resting stroke volume for the heart (or CO) secures that the patient remains normovolaemic during the operation and that fluid administration strategy reduces postoperative complications to an extent that affects the hospital stay (Bundgaard-Nielsen *et al.*, 2007a). Such goal directed fluid therapy was introduced by Shoemaker et al. (Shoemaker, 1972;Shoemaker *et al.*, 1988) in regard to CO but without taking the individual and partly genetically determined differences in CO (Snyder *et al.*, 2006) into account. Accordingly, this chapter focuses on how normovolaemia can be established and maintained during OLT despite the difficulties confronting the definition of normovolaemia by the spontaneous changes in stroke volume, CO and (mixed) venous oxygen saturation (S_vO_2) during the different phases of the operation. A second goal of this chapter is to introduce devices that can be applied for intraoperative monitoring of CBV and S_cO_2. Focus is on the importance of maintaining a normal CBV to secure cerebral blood flow (CBF) and S_cO_2 since these variables are taken to express the integrity of the cardiovascular system and their defence, at least potentially, prevents postoperative complications and cognitive dysfunction (Murkin *et al.*, 2007). In addition, the volume administration strategy applied during the operation is addressed.

2. Normovolaemia

By definition it seems difficult to defend that any patient should be provided with a fluid overload or be maintained hypovolaemic and yet, even hypovolaemic shock is sometimes treated with sympatomimetic drugs (De Backer D. *et al.*, 2010). For balancing volume administration it is of interest that normovolaemia can not only be defined but also defended during surgery. For healthy supine humans stroke volume, CO, and S_vO_2 do not respond to expansion of CBV and, therefore for supine humans, a volume administration strategy that secures that the heart operates on the upper ceiling of the Frank-Starling curve maintains the patient normovolaemic (Harms *et al.*, 2003;Jans *et al.*, 2008;Bundgaard-Nielsen *et al.*, 2009c) (Fig. 1).

For individualized goal-directed fluid therapy, volume is administered until a flow related parameter such as stroke volume, CO or S_vO_2, reaches a maximal value (Jenstrup *et al.*, 1995), i.e. volume is administrated until cardiac function does not depend on preload to the heart. This volume administration strategy is of interest not only because it remains elusive what volume rate a fixed volume administration strategy should aim at (Bundgaard-Nielsen *et al.*, 2009b), but also because an individualized fluid administration strategy, in contrast to a fixed volume strategy, consistently improves outcome for surgical patients (Bundgaard-Nielsen *et al.*, 2007a; Lopes *et al.*, 2007; Donati *et al.*, 2007; Abbas & Hill, 2008; Mayer *et al.*, 2010).
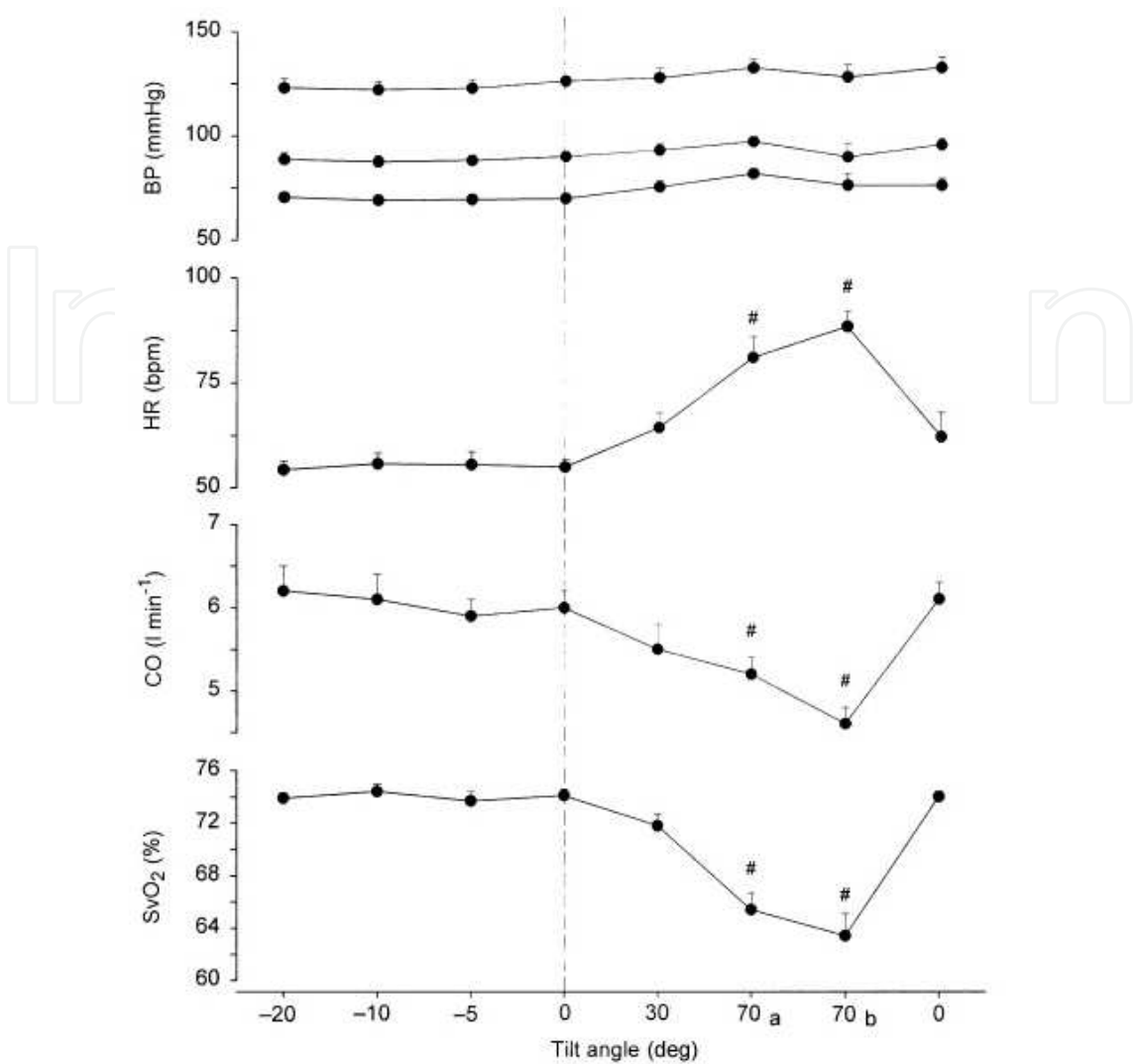
Fig. 1. Relationship between systemic haemodynamic variables, mixed venous oxygen saturation and tilt angle. BP, systolic, mean and diastolic blood pressure; HR, heart rate; CO, cardiac output; S_vO_2 mixed venous oxygen saturation. Variables are mean ± S.E.M. # P < 0.05 vs. 0 deg. Dashed line represents the supine position; 70 a, 70 deg head-up tilt for 10 min; 70 b, last minute of 70 deg head-up tilt for nine subjects (From Harms et al., 2003 with permission)

Based on administration of a crystalloid or a colloid, an inherent difficulty for individualized goal directed fluid therapy is, however, that a reduction in haematocrit is associated with an increase in CO, i.e. normovolaemic haemodilution increases CO (Krantz et al., 2005). In other words, it is not CO but S_vO_2 that is the regulated variable since the red cells create their own flow regulation through the release of ATP and NO when oxygen is released from oxyhaemoglobin (Gonzalez-Alonso et al., 2006). To direct fluid administration on the basis of establishing maximal values for stroke volume or CO requires that there is added a rule to limit the fluid administered. A common algorithm implies that a 10%, or larger increase in stroke volume justifies further administration of 200–250 ml of colloid, thereby minimizing the risk of creating a fluid overload (Bundgaard-Nielsen et al., 2007a). In contrast, during isovolaemic haemodilution, S_vO_2 remains stable until the haemoglobin level

is reduced by approximately 50% (Krantz *et al.*, 2005) and volume administration based on the recording of S_cO_2 is therefore widely independent of the type of fluid used.

When CBV is normalized by fluid to establish a maximal S_vO_2, the administration of 100 ml fluid results a ~1% increase in S_vO_2 for the adult patient (~ 70 kg) (Ejlersen *et al.*, 1995a) and that relationship applies also to children when the volume is adjusted according to body weight. For supine humans, S_vO_2 is on an average 75% (Harms *et al.*, 2003) but for patients undergoing OLT, S_vO_2 is typically ~ 85% (Ejlersen *et al.*, 1995b) reflecting that for these patients CO is larger (7-9.5 l/min) (Table 1) than for a reference population (6.5 l/min).

	Dissection phase	Anhepatic phase	Reperfusion	End of operation
HR (bpm)	95	90	87	97
CI (l m^{-1} min^{-1})	4.4	3.3	5.0	4.5
S_vO_2 (%)	85	81	86	82
TA (Ohm)	29	28	29	26
MAP (mmHg)	88	89	85	87
CVP (mmHg)	10	10	14	11
PAMP (mmHg)	18	17	26	21
SVRI (mmHg m^2 min l^{-1})	142	195	105	120
PVRI (mmHg m^2 min l^{-1})	11	14	9	12
Temperature	36	35	35	35

HR, hear rate; CI, cardiac index; S_vO_2, mixed venous saturation; TA, thoracic electric admittance; MAP, mean arterial blood pressure; CVP, central venous pressure; PAMP, pulmonal arterial mean pressure; SVRI, systemic vascular resistance index; PVRI, pulmonal vascular resistance index (Modified from Skak et al., 1997).

Table 1. Cardiovacular variables during OLT

Reperfusion of the grafted liver is associated with peripheral vasodilatation and although CO is likely to increase (Table 1), situations associated with peripheral vasodilatation, as during heating (Wilson *et al.*, 2009), are likely to reduce CBV. The importance of establishing normovolaemia from the induction of anaesthesia is illustrated by an increase in S_cO_2 as determined by near infrared spectroscopy (NIRS) and similarly determined muscle oxygenation (S_mO_2) since both these indices of tissue oxygenation increase in parallel with CO as the heart becomes filled with blood and decrease with the filling of the heart during a bleeding episode (Fig. 2).

Conversely, to maintain the commonly accepted 70% value for S_vO_2 (Rivers, 2006) is likely to represent a 1.5 l volume deficit for the patient undergoing OLT, considering the 1% reduction in S_vO_2 to 100 ml blood volume relationship during hypovolaemia (Ejlersen *et al.*, 1995a). A 1.5 l volume deficit is so large that it compromises MAP and S_cO_2 (Secher *et al.*, 1992) since a ~30 % reduction of the blood volume and, hence CBV elicits a Bezold-Jarisch-like reflex including a critical reduction in CBF (van Lieshout *et al.*, 2003;Secher & van
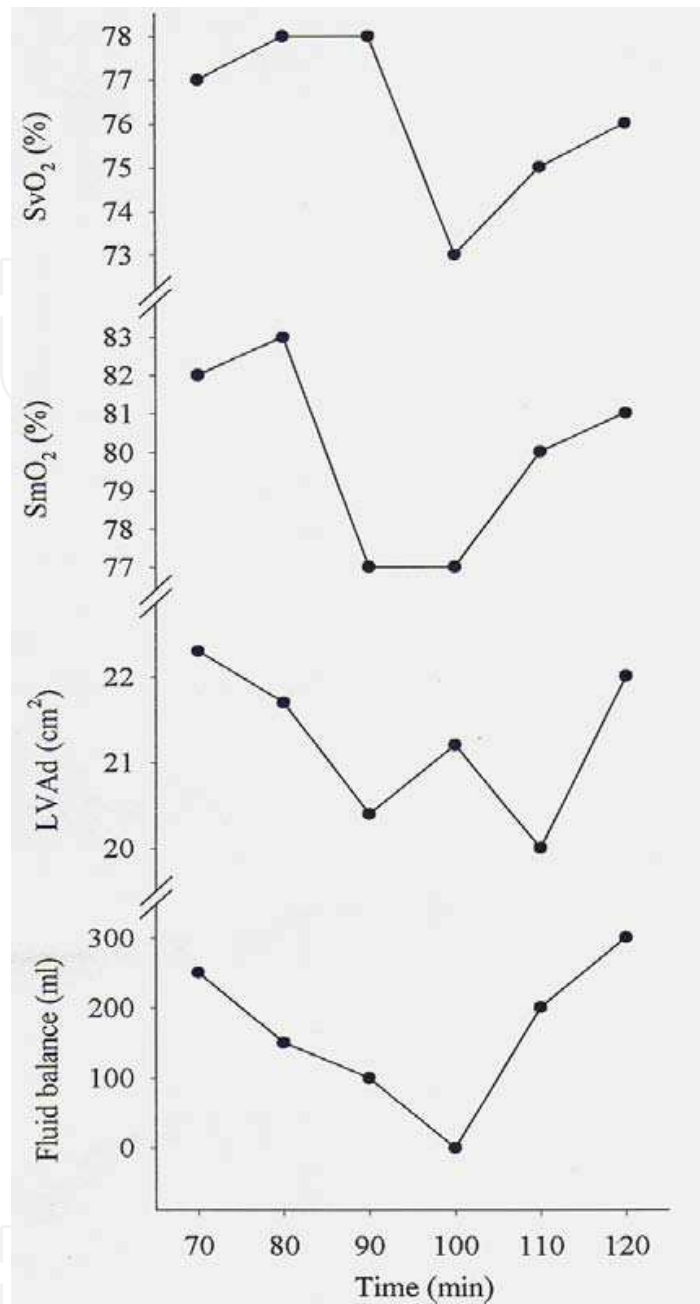
Fig. 2. Venous (S_vO_2) and muscle oxygen saturation (S_mO_2) plotted together with filling of the left ventricle (LVA_d), and volume balance in a patient exposed to an episode of intraoperative bleeding and following volume expansion (C. Tollund unpublished)

Lieshout, 2009;Madsen & Secher, 1999). The Bezold-Jarisch-like reflex also provokes a marked (30-fold) increase in plasma vasopressin (Sander-Jensen *et al.*, 1986) with long-lasting effect on urine production and could explain a potential difficulty in maintaining a reasonable urine production after surgery. Typically, the patients are in need of 0.5 l of volume before OLT (Ejlersen *et al.*, 1995b), a value that corresponds to that found also for other groups of patients before surgery (Jenstrup *et al.*, 1995;Bundgaard-Nielsen *et al.*, 2007b;Bundgaard-Nielsen *et al.*, 2009a). If it is felt desirable to maintain urine production, it is important that such an initial volume deficit is corrected and, eventually, a larger

fluid load may be required than that which establishes that the patient has been provided with a normal blood volume. For additional volume threatment of patients, the administration of lactated Ringer solution is preferable to the administration of saline (Waters et al., 2001).

3. Cardiac output

With a definition of normovolaemia based on the ability of the heart to establish an adequate flow, CO is of interest. As mentioned, patients undergoing OLT present a large CO while MAP may be low (el-Masry et al., 2009; Ejlersen et al., 1997). Yet MAP often normalises when the blood volume, and hence CBV, is expanded to an extent that it does not limit CO, i.e. the patients are provided with the CBV that healthy subjects are provided with when supine (Harms et al., 2003). However, significant ascites may affect venous return to the heart by pressure on the inferior caval vein that can be relieved by tilting the patient to the left - as known from women before birth - but that pressure is eliminated as the abdominal cavity is opened at start of surgery. As indicated, however, OLT is associated with significant changes in the cardiovascular system from the dissection phase to the anhepatic phase and following reperfusion of the donor liver and CO normalises only slowly by the end of the operation (Table 1).

To attenuate a reduction in venous return to the heart from the clamped inferior caval vein during the hepatectomy and insertion of the donated liver and thereby stabilize CO, an extra-corporeal veno-venous bypass shunt (VVBP) can secure portal and femoral venous drainage to one or two veins on the arm or to a central venous access (Ozier & Klinck, 2008). Veins on the arm are preferred to central veins to avoid that blood accumulates in the mediastinum in the case the catheter(s) has perforated the vein(s). Before a central vein receives blood from the shunt, it needs to be secured that blood can be aspirated from the catheter. The VVBP has a flow of 1.5-3 l/min, but for children and patients with a portal hypertension, venous return to the heart may be maintained by spinal and abdominal veins and veins along the oesophagus and there may, accordingly, be no need for a VVBP in these patients accepting substantial accumulation of blood in the splanchnic region. Yet surgical bleeding may be reduced if blood does not accumulate in distended abdominal veins.

At any rate, blood accumulates in the splanchnic region while the portal vein is clamped for establishing the VVBP and when it is seponated the accumulated amount of blood helps to fill the donor liver. Alternatively, the "piggyback" technique for which the inferior caval vein is side-clamped can reduce the restrain on venous return to the heart during the hepatectomy and surgery on the vessels to the donor liver. Notably, stability of the circulation is secured if reperfusion of the liver is graded by declamping the caval vein above the liver followed by declamping the vein below the liver and thereafter establishing its arterial flow.

3.1 Monitoring of cardiac output

For monitoring of CO several methods are applicable and not all will be addressed here. Ideally the chosen method should be reliable, continuous, and easy to set-up and to use and

at the same time possess the capability for a fast response time. Of these priorities, the accuracy of the absolute value is of least relevance due to the marked inter-individual variations in CO among the patients, e.g. 2.5 to 17 l min^{-1} (Nissen *et al.*, 2009b) and the often 2-fold change in CO during the operation, but the method should be able, at all times, to report the changes in CO faithfully and most importantly so during reperfusion of the grafted liver.

A pulmonary artery catheter (PAC) determines CO by thermodilution based on the Henriques-Stewart-Hamilton equation (Pinsky, 2007) and is for clinical use regarded as the golden standard, but it then requires an average of three or probably four determinations (Nilsson et al., 2004) based on bolus injection of (10 ml) cooled saline. Furthermore, it remains a problem that the baseline temperature is often too unstable to make a thermodilution determination of CO possible within the first minutes after reperfusion of the grafted liver. That problem is exaggerated with the version of PAC that uses heating filaments for "continuous" CO determination because the appreciated change in temperature is small and it may take 15 –20 min, or more, after reperfusion of the grafted liver before such a CO can be determined (De Wolf, 2006; Bao & Wu, 2008).

The advantage of transoesophageal echocardiography (TEE) is that it provides a real-time image of the heart and thereby on-line information not only about filling of the heart but also about the structure and contractility of the myocardium (Della *et al.*, 2009) of relevance especially during reperfusion of the grafted liver in case CO does not increase. Thus, TEE allows for distinction between a need for administration of volume versus sympatomimetic drugs. Unfortunately, however, mainly cardiac anaesthesiologists are familiar with the use of TEE and it remains a concern that TEE requires high costs and a need for training (Della *et al.*, 2009). It should also be mentioned that although individualized goal directed fluid administration aims at filling the heart with blood (Figs. 1 and 2), a detailed TEE evaluation of whether that is the case requires off-line evaluation.

Studies comparing CO determined by transoesophageal echo-Doppler (TED) against PAC show conflicting results (Shimamoto et al., 1992; Boucaud et al., 2008; Laupland & Bands, 2002; Colbert et al., 1998) although there seems to be agreement to that changes in CO are reflected by TED. A disadvantage with TED is, however, frequent dislocation of the ultrasound probe (Lefrant et al., 1998) of relevance for the in general long-lasting OLT and TED is counter-indicated in patients with oesophageal disorders of relevance for many of the OLT patients and once a Doppler probe is in place it hinders TEE (de Waal *et al.*, 2009).

For continuous recording of CO, several methods appreciate the arterial waveform. The PiCCO and LiDCO generate a continuous CO by analysis of the arterial pulse pressure (PP). For both methods, an independent technique is used to calibrate the continuous CO analysis since the arterial pulse-pressure analysis does not account for variables such as changing compliance of the vascular bed. Recalibration of CO is recommended after changes in patient position, therapy, or condition (de Waal *et al.*, 2009) of relevance for OLT encompassing marked changes in the vasculature through the different phases of the operation.

In the case of PiCCO, transpulmonary thermodilution is used for calibration. As with the PAC, PiCCO appreciates transpulmonary thermodilution according to the Henriques-Stewart-Hamilton principle but considers that a determination of a change in temperature from a central venous line to an arterial line (e.g. femoral or axillary) is less invasive than a determination based on a PAC catheter. The CO derived from this cold-saline

thermodilution is used to calibrate the arterial pulse-pressure contour that then provides the continuous CO. The PiCCO algorithm appreciates the blood pressure waveform morphology (i.e. mathematical analysis of the pulse-pressure waveform) and calculates a continuous CO as described by Wesseling et al (Wesseling *et al.*, 1993). Transpulmonary thermodilution includes both the right and left side of the heart as well as the pulmonary circulation and that allows for further analysis of the thermodilution curve with measures of the cardiac filling volume, the intrathoracic blood volume, and the extravascular lung water, the latter addressing wheather pulmonary oedema is developed (Oren-Grinberg, 2010; Costa *et al.*, 2007). Accepting that transpulmonary thermodilution may be a less invasive procedure for determination of CO than one based on PAC, it is also less accurate and still requires central venous and arterial lines.

In the case of LiDCO, the independent calibration technique is lithium dilution, again according to the Henriques-Stewart-Hamilton principle. LiDCO uses lithium dilution from a peripheral vein to an arterial line and, thereby, does not express information on cardiac filling volumes or the extravascular lung water. It is also a concern that calibration cannot be performed frequently and calibration may be unreliable in patients with grave hyponatreamia (Morgan et al., 2008) that may manifest in some OLT patients. The PulseCO algorithm used by LiDCO is based on pulse power derivation rather than on waveform morphology.

Continuous tracking of changes in stroke volume by arterial pulse wave analysis in Modelflow provides flow from pressure and has the potential to appreciate the importance of systemic blood flow (Wesseling *et al.*, 1993;Harms *et al.*, 1999). With Modelflow®, beat-to-beat CO is estimated from the arterial pressure wave (Wesseling *et al.*, 1993). Pressure from an arterial line is, after calibrating and zeroing to the mid-axillary level used as input to the model to calculate CO. The method uses a non-linear three-element model of the aortic input impedance and simulates the aortic flow waveform from the pressure signal. Two of the three model elements (aortic characteristic impedance and arterial compliance) depend on the elastic properties of the aorta and are computed using a built-in database of arctangent aortic pressure-area relationships given age and gender of the patient. Integrating the aortic flow waveform per beat provides left ventricular stroke volume and CO is the product of stroke volume and HR while the third model element, peripheral vascular resistance is calculated for each heartbeat as the quotient of arterial pressure to CO (Fig. 3A). The software used is an online real-time version of Beatscope® (FMS, Amsterdam, The Netherlands).

The Modelflow method is fully automatic, self-recording, has a fast response time, a high precision, and has been successfully validated against a thermodilution estimate of CO during cardiac surgery (Jansen *et al.*, 2001), intensive care medicine (Jansen *et al.*, 2001;Jellema *et al.*, 1999), and notably during OLT (Nissen *et al.*, 2009b) and, surprisingly, without a need for taking potential differences in vascular tone during the operation into account (Fig. 3 B). That is the case although Modelflow appears to underestimate deviations in CO during manipulation of body temperature with a significant increase in vascular conductance during heating (Shibasaki *et al.*, 2011).

4. Thoracic electric admittance

With the large spontaneous changes in CO during OLT, it may be an advantage to monitor CBV separately and, as indicated, evaluate the pulmonary water content. According to
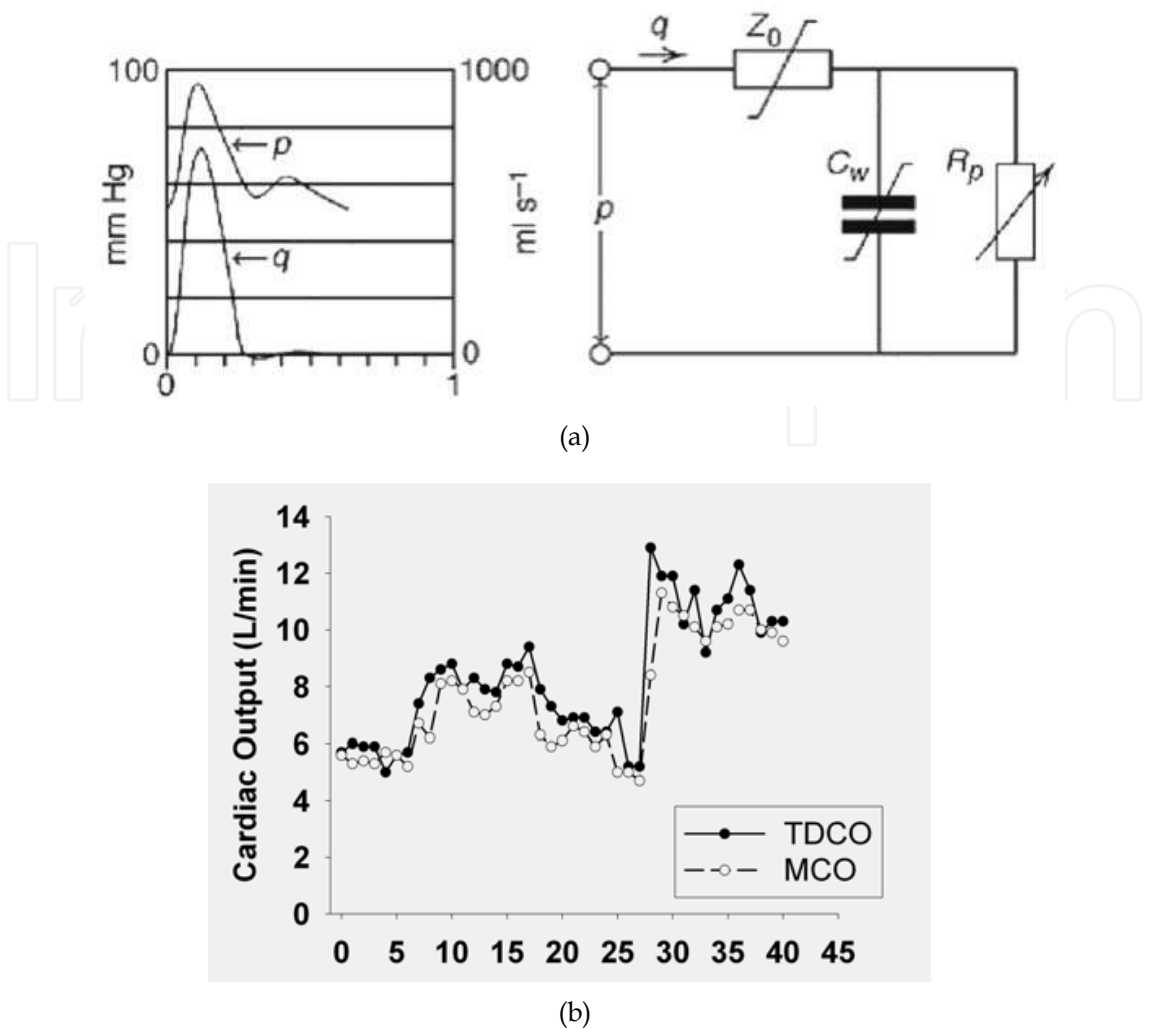
(a)

(b)

Fig. 3. a) Diagram of the three-element non-linear, self-adapting model (right) and input pressure and simulated flow pulse (left) used for Modelflow. Arterial pressure p is applied to the model input. Z_o, characteristic impedance of the proximal aorta; C_w, arterial Windkessel compliance; R_p total systemic peripheral resistance. The non-linear properties of Z_0 and C_w are indicated by a stylised "S" symbol. R_p has an arrow indicating that it adapts to changes in systemic resistance. The result of the model simulation is a flow curve q. Integrated per beat (area under the curve) yields stroke volume. (From Wesselring et al. 1993 with permission). b) Cardiac output followed by Modelflow (MCO) and thermodilution (TDCO) during liver transplantation surgery. (From Nissen et al., 2009 b with permission)

Ohm's law changes in CBV can be assessed by thoracic electrical admittance (TA) and the obtained value is expressed in milli-Siemens (mS). Using a low (e.g. 1.5 kHz) and a high frequency current (e.g. 100 kHz), TA distinguishes between the extracellular ($TA_{1.5}$) and total water (TA_{100}) content. Accordingly, changes in the difference between the high and the low frequency current reflects those in the intracellular water content (TA_{ICW}) (Cai *et al.*, 2000), i.e. red cell volume within the thoracic region (Fig. 4) and TA_{ICW} can, thereby, indicate a need for transfusion of blood while $TA_{1.5}$ monitors the (pulmonary) water content.

With the use of goal-directed approach to the administration of fluid and blood information about CBV becomes important in the anhepatic phase of OLT when approximately one third

of the circulation is eliminated causing a similar decrease in CO (Table 1), not necessarily due to hypovolaemia. Similarly when the donor liver is reperfused, an increase in CO requires that CBV is maintained despite the blood needed to fill the liver, while care is directed also to avoid distension of the liver by administrating a too large volume load.

With TA, evaluation of CBV is continuous with the use of, e.g. two ECG electrodes on the right side of the neck and two other electrodes placed high in the midaxillay line on the left side of the thorax (Ejlersen *et al.*, 1997;Matzen *et al.*, 1991) in order to include the heart and central vessels in the evaluation and at the same time exclude the abdominal fluid content. With a four electrode arrangement, skin resistance is eliminated from the evaluation making changes in TA an almost perfect report of those in the thoracic fluid / blood volume (Krantz *et al.*, 2000). Similarly, it is possible to monitor accumulation of blood in the legs during cross-clamping of inferior caval vein by changes in TA over one leg or the glutal region (Ejlersen *et al.*, 1997).
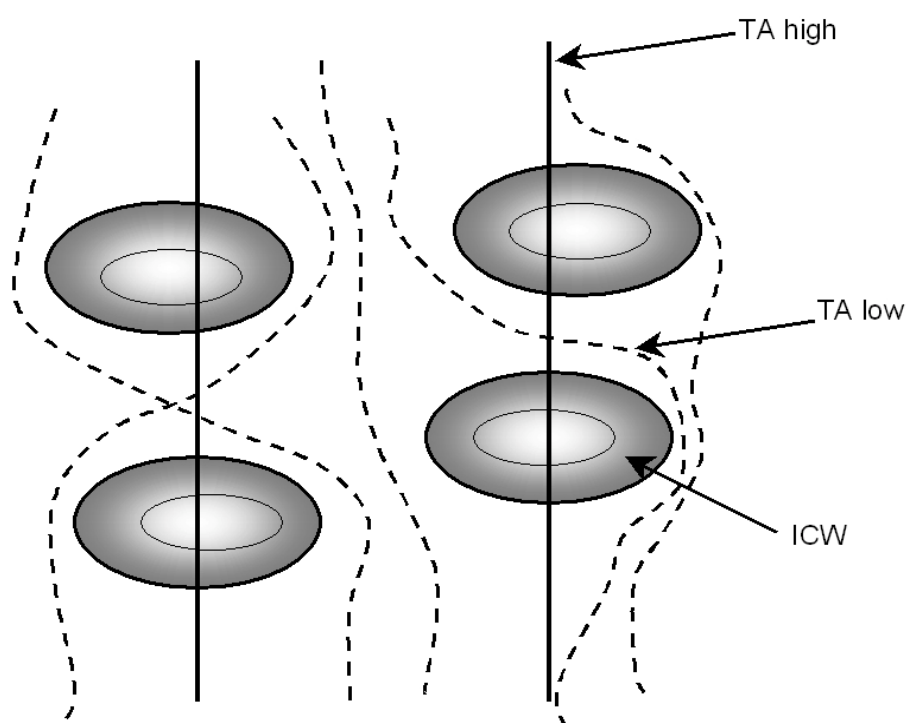

Fig. 4. At low and high frequencies, thoracic electric admittance (TA) distinguishes between the extracellular (ECW) and total body water (TBW). The difference reflects the intracellular water content (ICW) and changes respond to haemorrhage versus administration of blood

When volume is administered according to individualised goal directed fluid therapy, an increase in TA reflects that CBV is increased, as does pulmonary artery mean and wedge pressures and that is the case although there may be no changes in HR, central venous pressure (CVP), or MAP as CO increases during OLT (Ejlersen *et al.*, 1995b).

5. Venous saturation

For continuous reading of S_vO_2, a PAC catheter is ideal but a central S_vO_2 may be similarly obtained from a central venous line using a catheter with the same type of fiberoptic

oxymeter. Central S_vO_2 values are about 5% larger than those obtained from the PAC catheter (Krantz *et al.*, 2005; Rivers, 2006) but with parallel changes in response to deviations in blood volume (el-Masry *et al.*, 2009; Krantz *et al.*, 2005). Alternatively, S_vO_2 may be obtained by blood sampling during the different phases of the operation or, eventually, at times when there is a need to check volume administration during a major blood loss.

Thus, in order to evaluate whether a hypotensive incident is due to a reduced CO or to a reduced afterload, monitoring of S_vO_2 is well suited (Fig. 2). Considering that the patient's (basal) metabolic rate (Vo_2) does not change during the operation (despite the hepatectomy), there is a direct relationship between S_vO_2 and CO as described by Fick's equation: ($Vo_2 =$ ($C_a – C_v$) Q), where C_a and C_v represent the arterial and venous oxygen content. Therefore, a continuous recording of S_vO_2 may be applied in situations where devices for continuous recording of stroke volume or CO are not available of relevance, as mentioned, especially for the first minutes after reperfusion of the donor liver. Typically, a low arterial pressure reflects a blood loss in the dissection phase of the operation, while reperfusion of the liver is likely to be associated with a low blood pressure due to loss of peripheral resistance as detected by an increase in muscle blood flow as recorded easily by an increase in muscle oxygenation (S_mO_2). Surprisingly, also CBF increases during reperfusion of the grafted liver despite MAP may decrease to a level that is lower than normally considered to represent the lower level of cerebral autoregulation (60 mmHg) and an increase in the arterial carbon dioxide tension (P_aCO_2) seems only partly to explain an elevated CBF during reperfusion of the liver (Pott *et al.*, 1995; Larsen *et al.*, 1999). However, during reperfusion of the liver, function of the heart may be affected by a lowering of HR in response to an abrupt increase in plasma potassium as detected by blood sampling or indicated by the ECG and before the liver is reperfused, a small dose of adrenaline (4-6 µg kg^{-1} h^{-1}) prevents this slowing of the heart since adrenaline promotes clearance of potassium from the circulation (Struthers et al., 1983) besides its chronotropic effect.

Generally, a reduction in S_vO_2 should be considered as an indication for a low CO due to hypovolaemia and treated accordingly by applying the principles of individualised goal directed fluid therapy. That is the case although with the often marked increase in CO during early reperfusion of the grafted liver, S_vO_2 may reach extreme values (>95%) and, as mentioned, TA can indicate whether CBV is maintained or whether further volume treatment would be likely to increase CO even more and thereby stabilize MAP. Thus S_vO_2 values derived from either a PAC or a central venous catheter have potential as variables for goal directed fluid therapy (Fig. 2) although outcome and comparative studies are available only in regard to monitoring stroke volume or CO (Bundgaard-Nielsen *et al.*, 2007a).

6. Vascular pressures

Monitoring arterial pressure is often by way of a catheter in the radial artery, but in case of central hypovolaemia, the radial artery constricts to dilate again as the hypovolaemic shock develops (Iversen et al., 1995) making the pressure in the radial artery a potential underestimate of the systemic pressure (De Wolf, 2006; Krenn & De Wolf, 2008). In contrast, the use of a femoral artery catheter is reliable for recording of MAP (Arnal et al., 2005) but never the less, a radial artery catheter can be used for blood sampling and as back-up for the determination of MAP. For example in case the hepatic artery needs to be grafted to the

aorta, partial or complete clamping of the abdominal aorta may eliminate pressure recording in the femoral artery.

The CVP is often taken to express filling of the right ventricle but CVP is not well correlated with preload to the heart as expressed by its diastolic filling (De Wolf, 2006). A correlation between CO and CVP is established during acute changes in the CBV as induced by head-up-tilt (Ogoh *et al.*, 2003) or lower body negative pressure (Murray *et al.*, 1999), while for most patients CO is not related to CVP although there is a relation between CO and diastolic filling of the heart as indicated by echocardiography (Thys et al., 1987).

In order to limit the blood loss during surgery, a strategy of keeping CVP low has been suggested and studies on liver resection patients show a reduction in the blood loss, in morbidity, as in the hospital stay when the intraoperative CVP is kept < 5 mmHg (Jones et al., 1998;Chen et al., 2000). Implementing the same strategy to OLT, one study found that a low CVP increased morbidity as expressed as postoperative renal failure and mortality (Schroeder et al., 2004), while an other study came to the opposite conclusion (Massicotte et al., 2006). We hold it that volume therapy during OLT is better detected by flow related parameters than by vascular pressure(s) (Bundgaard-Nielsen *et al.*, 2007a;Jenstrup *et al.*, 1995;Ejlersen *et al.*, 1995b).

A PAC allows for monitoring pulmonary artery (mean) pressure (PAMP) as well as wedge pressure (PAWP). These values are relevant to patients undergoing OLT since some patients develop both portal and pulmonary hypertension (Krenn & De Wolf, 2008). It remains, however, elusive whether monitoring of PAWP provides advantages over the continuous recording of PAMP. At least it should be considered that a determination of PAWP carries the risk of rupturing a branch of the pulmonal artery and that is likely to be fatal.
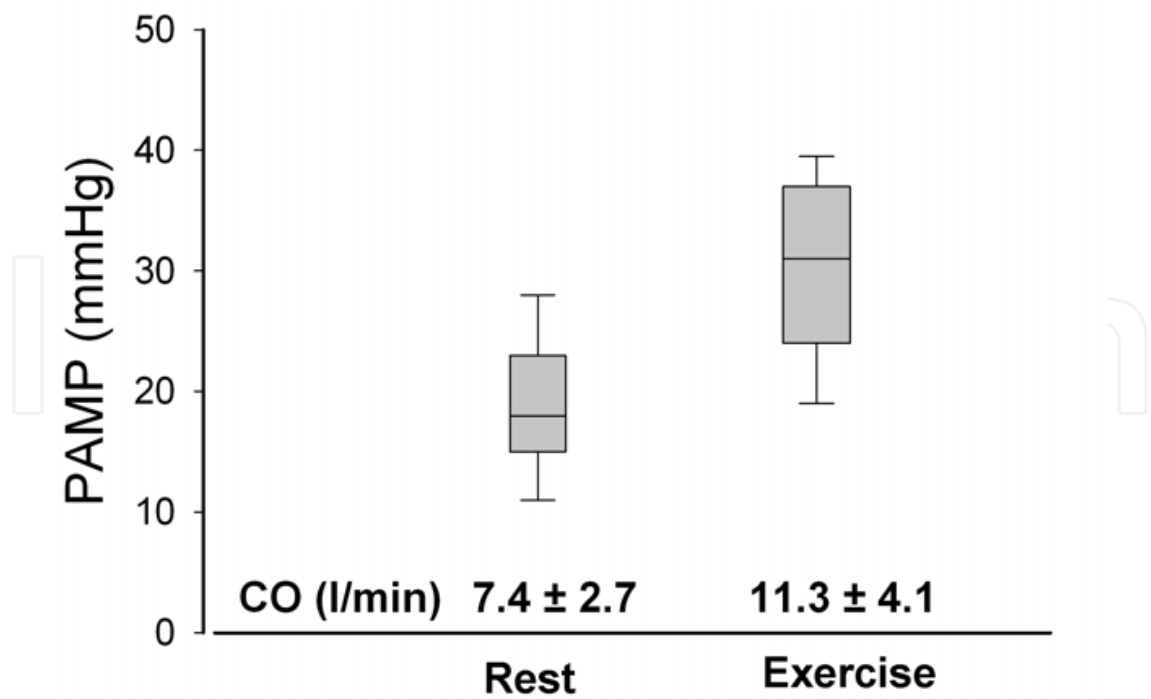

Fig. 5. Pulmonary artery mean pressure (PAMP) (±SD and 5th and 95th percentile) and cardiac output (CO) (±SD) for 33 candidates for OLT at rest and during exercise (P. Nissen, unpublished)

A PAMP limit of 30 mmHg may be considered to indicate pulmonary hypertension, but it should be taken into account that there is a direct relationship between PAMP and CO as illustrated during physical exercise (Tolle *et al.*, 2008) and that is also the case for patients under evaluation for OLT (Fig. 5).

If a candidate OLT patient presents a high PAMP, it should accordingly be considered whether the high pulmonary pressure is because of a large CO and thereby unrelated to pulmonary disease. As for other patient categories, it seems more important that the heart is able to generate a reasonable CO than at what pressures it operates. For example, a successful OLT is reported for a patient with a PAMP of 44 mmHg and a CO of 5.7 l/min and with an ability to increase CO to 10 l/min (at a PAMP of 51 mmHg during reperfusion of the liver) (Liu *et al.*, 1996). Similarly, there is even for patients without pulmonary hypertension an often impressive increase in PAMP concomitant with the increase in CO during reperfusion of the grafted liver (Table 1). Furthermore hypoxia leads to pulmonary hypertension of relevance for OLT patients with associated significant pulmonary shunt and at least in case of hypoxia, pulmonary hypertension seems to be related to the patient's iron status (Smith *et al.*, 2008). Accordingly, the iron status of the OLT candidate with pulmonary hypertension and hypoxia should be checked.

7. Heart rate

It is probably without exception that HR is monitored during OLT and deviations in HR in response to variation in CBV are therefore of interest. In textbook descriptions of hypovolaemic shock it is stated often that tachycardia is the arterial baroreceptor response to a low blood pressure (Secher & Bie, 1985). Yet the common, both experimental and clinical finding is that the HR response to central hypovolaemia encompasses three stages (Secher *et al.*, 1992) (Fig. 6).

With a small reduction in CBV, there is a moderate increase in HR, most often to less than 100 bpm and as indicated, the increase in HR may be so small that it does not become statistically significant (Murrell *et al.*, 2009). However, with a 30% reduction of CBV, both HR and MAP decrease as known from a vasovagal syncope and cerebral perfusion and oxygenation become affected (Madsen & Secher, 1999;van Lieshout *et al.*, 2003). Such an incident is fatal if CBV is not restored immediately (Madsen *et al.*, 1998), but with partial restoration of CBV, intense sympathetic activation in response to (central) hypovolaemia elicits a marked increase in HR (>120 bpm) may be in response to cerebral hypoperfusion. Thus, adequate restoration of CBV in stage II of shock secures the well-being of the patient, while manifest tachycardia (stage III) appears to indicate a transition to an irreversible stage of shock since the patient then is likely to need eventually prolonged intensive care and is then exposed to the associated grave prognosis (De Backer D. *et al.*, 2010). It should also be noted that the administration of atropine to treat bradycardia during haemorrhage is likely to enhance the haemorrhage and, thereby, could be fatal (Bertolini, 1995). At any rate, the administration of atropine hinders the use of HR to monitor an eventual volume deficit. In case of a low HR, volume should be administrated with an expected moderate increase in HR before the "resting" HR is established (Fig. 6). Conversely, it should be checked whether any increase in HR is due to an otherwise undetected (small) volume deficit by supplementing (100-200 ml) of volume and thereby keep HR low and the volume administration can then stop when HR does not decrease further.
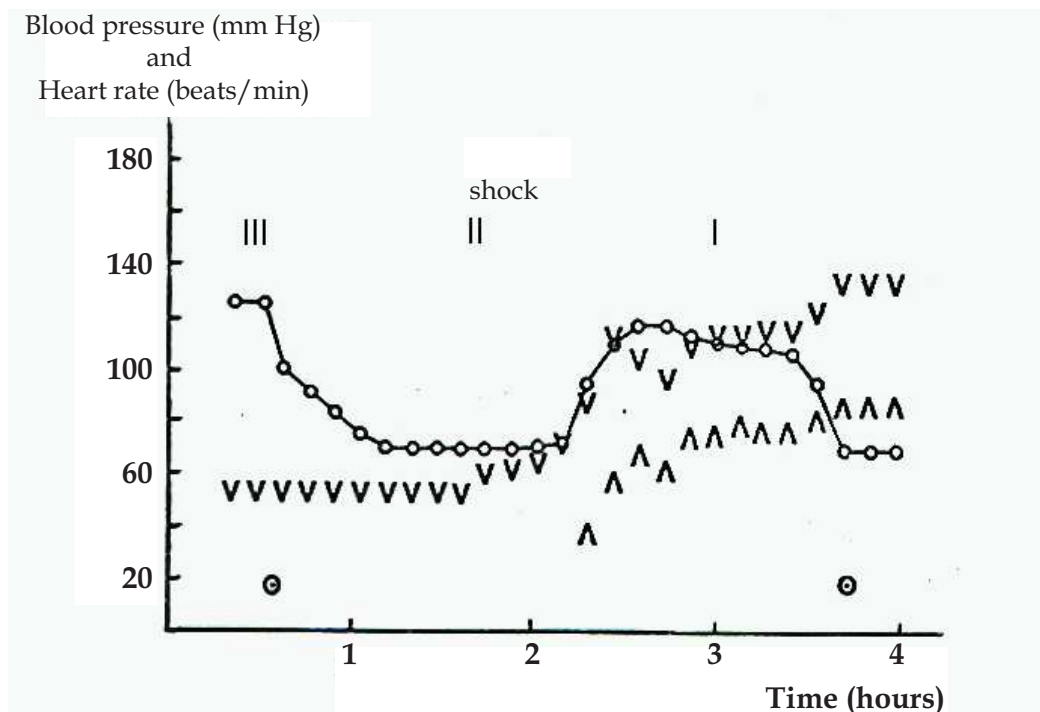
Fig. 6. Heart rate (HR) and blood pressure (systolic **v** and diastolic **^**) responses of a patient treated for a ruptured abdominal aneurism. At admission the patient had thacycardia and low blood pressure (stage III of hypovolaemic shock). During volume loading a decrease in HR (stage II) is seen followed by an increase (stage I, preshock) as blood pressure began to increase before stable values were reached; beginning and end of the operation indicated by circles. (From Jacobsen & Secher, 1992 with permission)

8. Cerebral autoregulation

Central to this chapter is the ability to secure CBF and S_cO_2 during the OLT and thereby, presumably, maintain the patient's well being after the operation (Murkin *et al.*, 2007).

Interest in recording CBF or S_cO_2 for the OLT patient is relevant not only because these variables may be affected by hypotensive events during the operation in case a low blood pressure reflects a reduced CO, but also because some acute liver disease patients demonstrate impaired cerebral autoregulation (Larsen *et al.*, 1999; Nissen P. *et al.*, 2009; Ejlersen *et al.*, 1994) (Fig. 7).

Cerebral perfusion may be followed by transcranial Doppler (TCD) derived middle cerebral artery mean blood velocity (MCA V_{mean}) (Pott *et al.*, 1995) and evaluation of cerebral tissue flow by clearance of ^{133}Xe has been carried out during OLT(Larsen *et al.*, 1999). However, it remains that NIRS is, by far the most feasible method for routine monitoring of cerebral perfusion during surgery (Nissen *et al.*, 2009a;Steiner *et al.*, 2009). NIRS reflects changes in brain capillary saturation and mitochondrial oxygen tension in response to manipulation of the inspired oxygen and CO_2 tensions (Rasmussen *et al.*, 2007) although a potential influence of skin blood flow needs to be considered (Sato et al., 2011).

While a determination of CBF requires extensive apparatus and calculations, the recording of S_cO_2 is as readily available as the recording of arterial oxygen saturation by pulsoximetry
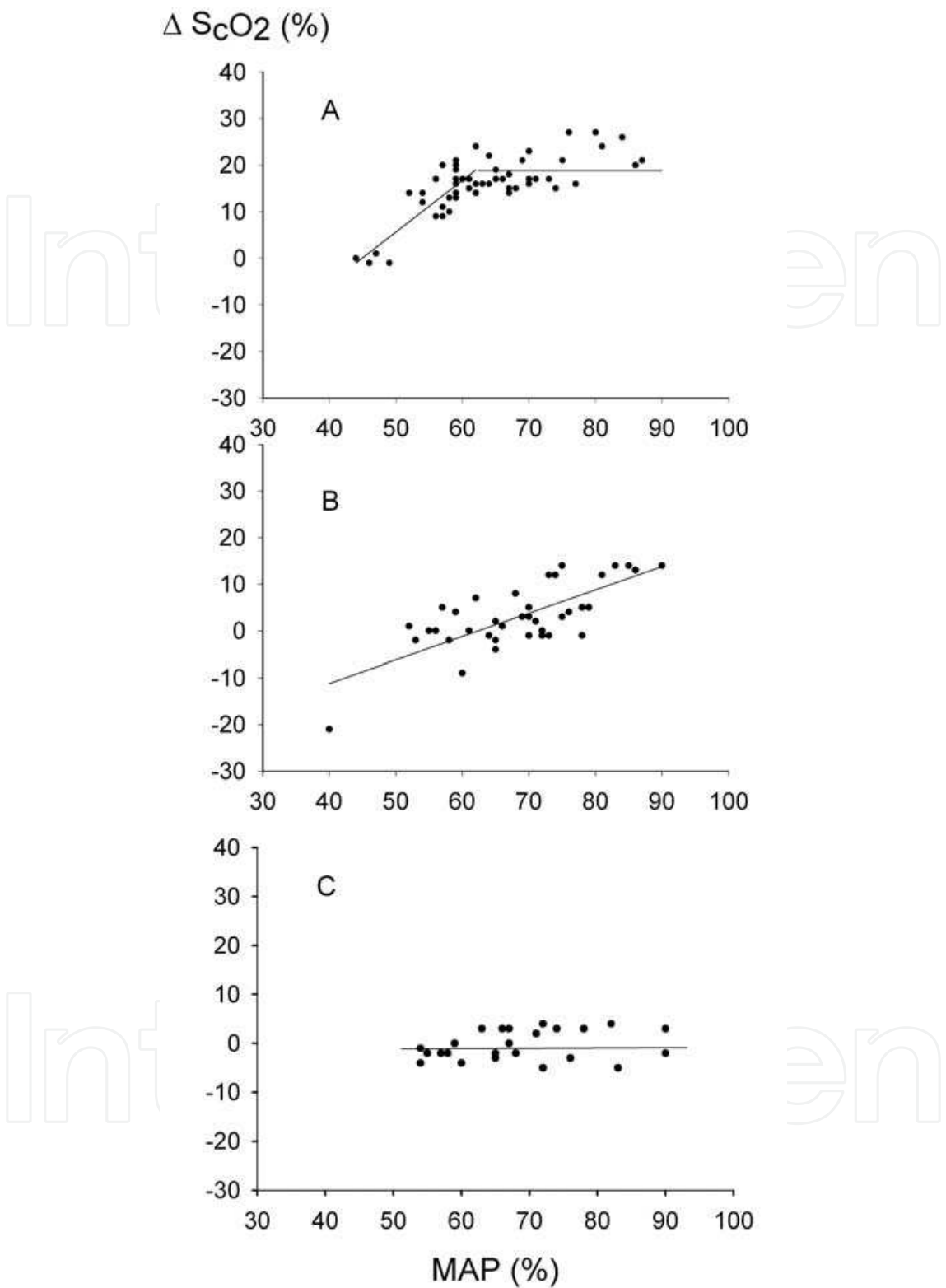
Fig. 7. Changes in frontal lobe cerebral oxygen saturation (ΔS_cO_2) related to mean arterial pressure (MAP) for three patients undergoing liver transplantation (A) A patient for whom a lower limit of cerebral autoregulation can be defined. (B) A patient who demonstrates no cerebral autoregulation. (C) A patient for whom no lower limit of cerebral autoregulation was detected (From Nissen et al., 2009 with permission)

and builds on the same technology of protons absorbance in the near infrared spectrum (NIRS) (Madsen & Secher, 1999). However in contrast to pulsoximetry, S_cO_2 is not coupled to the recording of pulse and, thereby, expresses an average rather than a maximal oxygen concentration of the tissue, i.e. of the brain or skeletal muscles. With spatial resolution NIRS, light is sampled at two distances from the emitter to prioritise absorption of light in the deep tissue, for the head assumed to represent the cerebral cortex (S_cO_2) and over a muscle (S_mO_2) oxygen saturation of haemoglobin and myoglobin. Yet, a sustained subcutaneous fat deposit may hinder detection of S_mO_2 and the thenar muscle is ideal for monitoring S_mO_2 since there is no subcutaneous fat over that muscle group (Thomson et al., 2009).

Thus frontal lobe oxygenation by NIRS is a non-invasive recording of changes in CBF (Madsen & Secher, 1999) with a correlation between S_cO_2 and MCA V_{mean} (Steiner et al., 2009). Also changes in S_cO_2 parallel those in internal jugular venous O_2 saturation (Pott et al., 1995;Skak et al., 1997) and NIRS is able to detect cerebral hypoperfusion (Plachky et al., 2004). The NIRS determined S_cO_2 is based on the absorption of light in the spectra for oxygenated and deoxygenated haemoglobin and reports tissue oxygenation as a percentage of light absorption by oxygenated to total haemoglobin. An emitter generates light at, e.g. 733 and 808 nm and the reflection is registered by two or more optodes placed at a distance of, e.g. 3 and 4 cm from the emitter to allow for the subtraction of reflections derived from superficial tissues of the scalp and the skull for detection of S_cO_2 (Grubhofer et al., 1997) (Fig. 8). Thus with increasing distance between the emitter and the optodes, light penetrates deeper into the tissues and with evaluation of absorption at two distances (spatial resolution), absorption in deep tissue, i.e. brain, is appreciated.
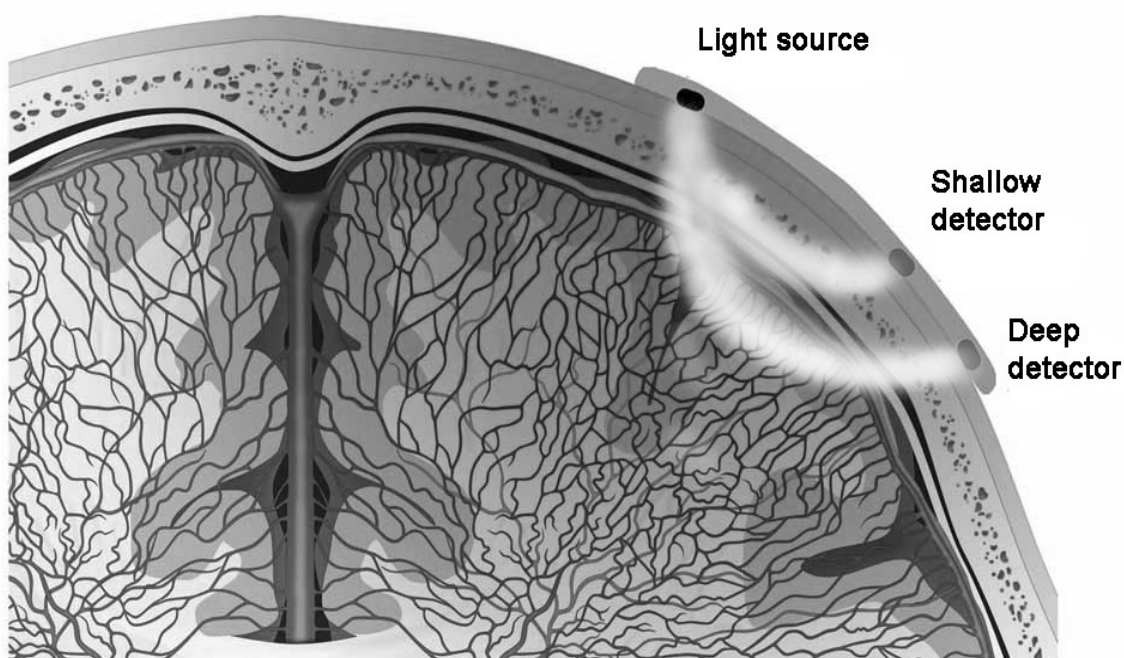

Fig. 8. Near infrared spectroscopy applied to the brain. Distance between the light emitter and the optodes 3 and 4 cm. By subtracting the superficial from the deeper reflections, oxygenation of brain cortex is appreciated (from Covidien, Denmark with permission)

Of relevance for the recording of S_cO_2 during OLT, bilirubin absorbs light in the same wavelength as haemoglobin and depending of the wavelength used to derive S_cO_2, there

may be a negative influence of plasma bilirubin of the detected S_cO_2 (Madsen *et al.*, 2000). However, even when plasma bilirubin is elevated and the reported S_cO_2 is low, the derived value reacts on changes imposed by bleeding and changes in P_aCO_2.

The significant haemodynamic changes associated with OLT may lead to neurological complications and increased mortality in reflection of reduced cerebral vascular resistance in the first hour after reperfusion of the liver exposing the brain to hyperperfusion (Ardizzone et al., 2006). Thus in case of lacking cerebral autoregulation, CFB is affected both by a low and a high blood pressure and during OLT, blood pressure is likely to increase markedly when surgery leads to manipulation of the adrenal gland with, presumably, release of adrenaline into the circulation. Normally CBF is considered to be maintained within a MAP range from approximately 60-150 mmHg (Paulson et al., 1990). However, cerebral perfusion decreases already at a MAP of 80 mmHg when the decrease in blood pressure is caused by a low CBV and thereby a lowered CO (Madsen *et al.*, 1995). On the other hand, cerebral perfusion and S_cO_2 may be preserved even at a MAP below 40 mmHg if CBV is not affected (Nissen P. *et al.*, 2009) (Fig. 9).

A given MAP therefore does not guarantee that cerebral perfusion is secured leading to the conclusion that CBF or, more likely, S_cO_2 should be monitored during the operation (Nissen *et al.*, 2009a).
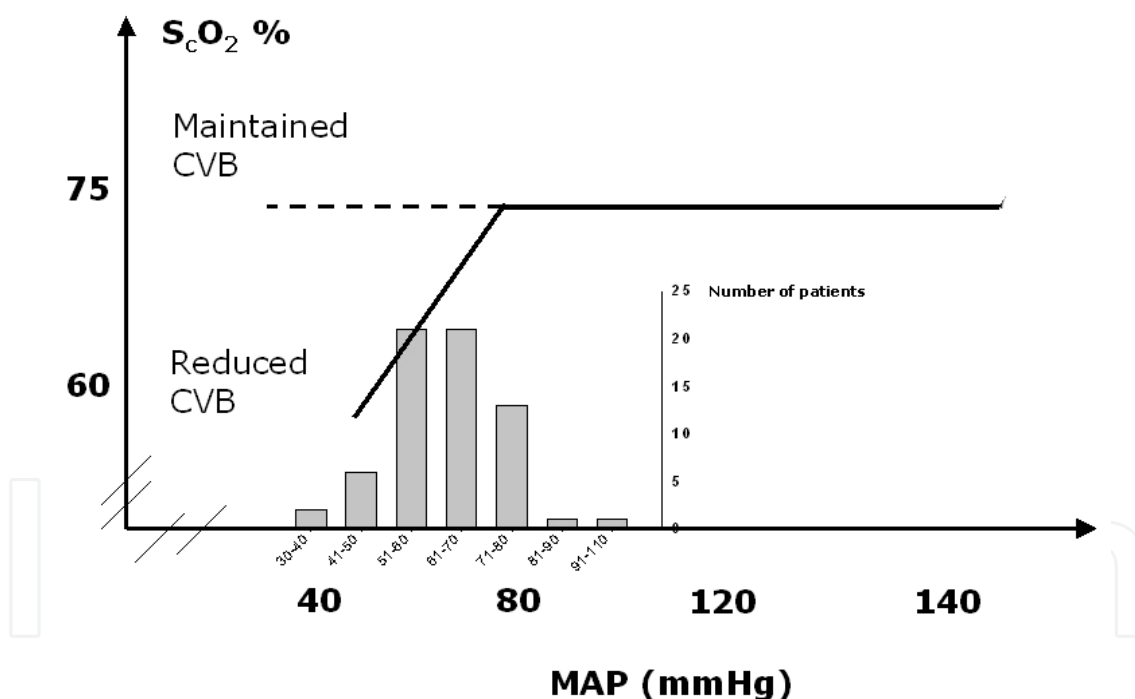

Fig. 9. Cerebral oxygen saturation (S_cO_2) related to mean arterial pressure (MAP) including data obtained with a maintained central blood volume (CBV) during anaesthesia (broken line) and from subjects for whom the central blood volume was reduced deliberately during head-up tilt (full line). Normogram illustrates distribution of the lowest MAP in the anaesthetized patients (Modified from Nissen et al., 2009 with permission)

Also it is to be considered that administration of phenylephrine in case of a low blood pressure, in an attempt to increase blood pressure to above what is might present the lower limit of cerebral autoregulation, is associated with a decrease rather than with the probably

intended increase in S_cO_2 (Nissen et al., 2010). Alternatively, hypotension should be considered in relation to a decrease in plasma calcium in response to administration of blood products and calcium should be supplemented to restore the physiological level (1.2 mM). However, the use of phenylephrine may be indicated during reperfusion of the donor liver to reduce peripheral vasodilatation and thereby to centralise of blood accumulated in the splanchnic region. Alternatively, the administration of phenylephrine to increase the blood pressure may be replaced by the use of ephedrine that does not demonstrate the same negative influence on S_cO_2 (Nissen *et al.*, 2010; Meng *et al.*, 2011).

P_aCO_2 has a significant influence on CBF and P_aCO_2 is regularly monitored by a continuous recording of the end-tidal CO2 tension to maintain a value of, e.g. 4,5 kPa. In that regard OLT is no exception, but with the reduction of the metabolic rate during the anhepatic phase of the OLT, a given setting of ventilation may lower P_aCO_2 and ventilation then needs to be reduced in order to maintain CBF and S_cO_2 (Madsen & Secher, 1999). Conversely, with reperfusion of the donor liver, P_aCO_2 increases again and often to values that exceed the level established in the dissection phase of the operation. Accordingly, ventilation should be increased at, or likely before reperfusion of the liver in order to prevent cerebral hyperperfusion and ventilation is thereafter gradually reduced towards the end of the operation guided by S_cO_2 as the CO_2 load is eliminated by the exhaled air.

With optodes placed over a muscle NIRS monitors muscle oxygen saturation (S_mO_2) and decreases before central hypovolaemia affects blood pressure. However, haemorrhagic hypotension is likely to be caused by a Bezold-Jarisch-like reflex including loss of sympathetic activity and, therefore, an increase in muscle blood flow and in turn S_mO_2 (Madsen *et al.*, 1995). S_mO_2 effectively detects central hypovolaemia (Soller *et al.*, 2008) (Fig. 2) and supplements, or may be used as an alternative non-invasive monitoring modality to S_vO_2 for detection of a blood loss. Ideally S_mO_2 provides for an early warning of ongoing haemorrhage and allows for direction of fluid administration before the blood loss affects CBF and in turn S_cO_2.

9. Support to the central blood volume

An OLT may be associated with a severe blood loss in about 20% of the patients (Massicotte *et al.*, 2004). Bleeding during OLT is most common during the dissection phase for the cirrhotic liver associated with distended abdominal veins. Accordingly, rapid infusion systems have been developed which that can deliver 1.5 l of heated fluid per minute through 7 F venous catheter is recommended for infusion of fluids and blood products. The rapid infusion machine reports the accumulated amount of fluid (blood) administered and is also suited for infusion of small volumes to children as the fluid can be administrated with an accuracy of millilitres. To adults it is common to administer bolus infusions of 100 ml (occasionally 500 ml) over 1 min since, as mentioned, a lowering of S_vO_2 by 1 % corresponds typically to a volume deficit of ~100 ml (Ejlersen et al., 1995a). Furthermore, one or two i.v. lines can be placed for supplementary administration of fluid and medication.

Since patients with end-stage liver decease present with serious haemostatic defects, management of coagulation during OLT is a challenge. Coagulopathy can be aggravated by hypothermia and acidemia, associated with increased risk of uncontrolled bleeding and mortality (Lier et al., 2008). Accordingly fluid, including blood products, is preheated and the patients are provided with a warm airflow blanket (e.g. "Bair Hugger") covering the

upper part of thorax, the neck, and arms and that arrangement is usually able to maintain the patient's temperature above 36°. Furthermore, frequent adjustment of CBV according to the individualized goal directed fluid administration strategy prevents marked changes in pH and arterial lactate and frequent monitoring of the plasma calcium level, with appropriate substitutions, supports coagulation competence.

Yet, in order to preserve coagulation competence, there remains some disagreement. While one review finds that correction of coagulation defects with fresh frozen plasma (FFP) and platelets does not reduce the blood loss and has a negative influence on outcome (Dalmau et al., 2009), the local experience is that timely administration of FFP and platelets improves outcome (Johansson *et al.*, 2010), a strategy supported by other studies demonstrating a decrease in blood loss and improvement in 24 hour and 30-day survival following early use of plasma and platelets (Holcomb, 2010; Holcomb et al., 2008). Discrepancy between views likely relate to which patients are addressed with the need for FFP and platelets indicated only for patients presenting with a deficit in consequence of their liver disease or provoked by major haemorrhage.

It is important to monitor the OLT patient's coagulation competence and in that regard a determination of the protrombin time (PT) and activated partial protrombin time (APPT) seems inadequate since these variables do not correlate well with clinically coagulopathy or bleeding condition (Murray *et al.*, 1999; Segal & Dzik, 2005). For on-line evaluation of haemostasis, thrombelastographhy (TEG) is used as pioneered during OLT by Kang et al (Kang *et al.*, 1985). TEG records the viscoelastic changes during coagulation by analysing whole blood placed in a rotating cup (Fig. 10) while a pin suspended in the blood from a torsion wire records the resistance to motion.
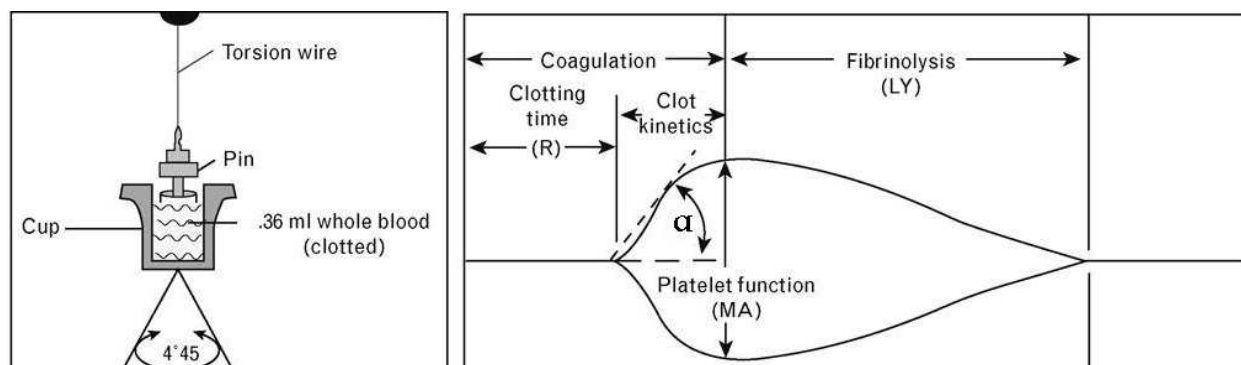

Fig. 10. Thrombelastograph technology and measured variables: The clotting time (R), the angle (α) representing the progressive increase in clot strength, the maximal clot strength (MA) and the fibrinolysis (LY) (From Johannson et al,. 2010 with permission)

Four TEG parameters are regularly reported: the clotting time (R), the angle (α) representing the progressive increase in clot strength, the maximal clot strength (MA), and fibrinolysis (LY) (Fig. 10) (Johansson, 2009). The TEG reported values correlate well with the clinical bleeding conditions and are recommended to direct blood product treatment together with a platelet count and check of the haemoglobin concentration (Plotkin et al., 2008). The TEG analysis can be performed in the laboratory and is locally displayed in real-time in the operating theatre to enable for early intervention, e.g. by administration of platelets and plasma in case of significantly attenuated coagulation competence. In this endeavour, it is considered that transfusion of platelets to 100×10^9 L^{-1} (rather than to the commonly used

guideline of 50 X 10^9 L^{-1}) secures coagulation competence and additional administration of platelets is routinely performed before the reperfusion of the donor liver associated with significant use of platelets (Johansson *et al.*, 2010). Thus, the coagulation competence of the patient's blood is accentuated by the administration of FFP and saline-adenine-glucose-mannitol (SAGM) erythrocyte suspension to a haemoglobin concentration of 6 mM (haematocrit 30%), making sure that plasma calcium does not decrease and calcuimcloride is administered frequently to maintain a reference value of 1.2 mM.

Yet it has to be accepted that some patients have intraoperative increased consumption of fibrinogen and if a diffuse bleeding in combination with a reduced α and MA manifest, we suggest monitoring functional fibrinogen to decide whether the reduction in MA relates to platelet or to fibrinogen function. Attention has also been directed to the endothelial barrier function in response to haemorrhagic shock and the role of glycocalyx appears important to endothelial permeability, intracellular dysfunction, and oedema (Holcomb, 2011).

Until recently, infusion of aprotinin was an option for OLT and aprotinin reduces haemorrhage by hindering fibrinolyses and thereby stabilizes the formed blood clots. Aprotinin has, however, been withdrawn from the marked (Dietrich, 2009) and tranexamic acid is the (cheaper) alternative to be administrated before surgery and again before reperfusion of the donor liver (Takagi et al., 2009).

Further refinement of treatment includes control of plasma concentration of magnesium (Skak et al., 1996) and corrected if low (reference value 0.8 mM) and maintenance of the blood glucose or, conversely, administration of insulin in case the blood glucose level increases beyond 10 mM. Surprisingly, the blood glucose level does not decrease during the anhepatic phase of OLT, presumably because the kidneys supplement glucose production (Lauritsen *et al.*, 2002). Also it should be considered that during massive administration of blood products, HR might be affected by the potassium concentration of Sag-M blood of approximately 50 mM. It is advised that massive administration of blood is paralleled by infusion of adrenaline (4-6 mg kg^{-1} min^{-1}) to eliminate potassium from blood.

10. Conclusion

During OLT it is possible to maintain coagulation competence by timely administration of fresh frozen plasma and platelets together with SAGM-blood while body temperature and plasma pH and calcium are controlled. Notably platelets are supplemented to a reference value of 100 X 10^9 L^{-1} rather than 50 X 10^9 L^{-1} seems to increase survival. Even massive bleeding can be coped with if CBV and thereby S_cO_2, at all times is kept within narrow limits. To maintain a stable central blood volume requires that treatment of patients with liver disease is focused on eventually high maximal values for CO and S_vO_2.

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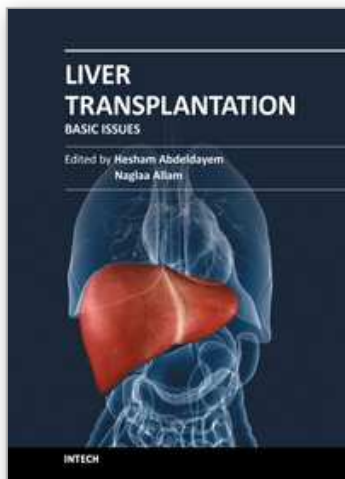
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Edited by Prof. Hesham Abdeldayem

This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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