Profound Decrease of Liver Maximum Function Capacity Test of Isoflurane Sedated Patients: A Report of Three Cases

Elke Schwier (✉ elke.schwier@klinikum-herford.de)  
Ruhr University Bochum, Klinikum Herford  
https://orcid.org/0000-0002-9279-2986

Carmen Kirchner  
Ruhr University Bochum, Klinikum Herford

Claas Eickmeyer  
Ruhr University Bochum, Klinikum Herford

Günther Winde  
Ruhr University Bochum, Klinikum Herford

Dietrich Henzler  
Ruhr University Bochum, Klinikum Herford

Thomas Köhler  
Ruhr University Bochum, Klinikum Herford

Original Article

Keywords: LiMax, Isoflurane, AnaConDa, CYP1A2, case series

DOI: https://doi.org/10.21203/rs.3.rs-169402/v1

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Abstract

Background: Recently, inhaled sedation and liver function capacity measurement using $^{13}$C-methacetin breath test (LiMAx) have become an integral part of intensive care. The aim of this report is to present the results of LiMAx-testing during isoflurane sedation, which were unexpectedly low. The findings are discussed in view of the available literature.

Case presentation: We present a series of three patients in a university hospital surgical intensive care unit who had received inhaled isoflurane sedation by the Anaesthetic Conserving Device after trauma, sepsis or pulmonary hemorrhage. When isoflurane was administered, LiMAx values decreased profoundly (1 to 71 µg/kg/h), indicating significant liver damage. Before and after isoflurane administration, more plausible LiMAx values between 151 and 496 µg/kg/h were obtained, indicating only minor impairment of normal liver function. Neither the progression of the associated laboratory parameters (alanine aminotransferase, aspartate aminotransferase, international normalized ration, creatinine, bilirubin, lactate) nor the clinical condition (absence of ascites, hepatic coagulation disorders or icterus) were suggestive of temporary liver damage of this severity.

Conclusion: Measurement of enzymatic liver function capacity is practicable in intensive care patients and may help to determine liver function in different conditions. Unexpectedly low LiMAx values in isoflurane sedated patients may be caused by reduced cytochrome P450(CYP)1A2 enzyme activity due to a severe disease pattern, or by interaction of isoflurane with CYP1A2 or with the breath test itself. We propose that, until the breath test on enzymatic liver function has been validated in the critical care setting, LiMAx-test results should be interpreted with caution in patients sedated with isoflurane.

Background

Treatment of critically ill patients often requires mechanical ventilation accompanied by sedation. The most common first-line sedative drug is intravenous propofol [1]. Despite pharmacological advantages over other intravenous sedatives, propofol has substantial side effects. These are impairment of the cell function, overload with triglycerides and triggering or amplification of delirium. An increasingly used alternative to propofol is the inhalative sedation with isoflurane that is available for intensive care settings since the approval of the Anaesthetic Conserving Device (AnaConDa, 100ml, Sedana Medical, Sweden) in 2004. Due to its ease of use, safe application of volatile anesthetics and compatibility with all common types of intensive care respirators, the system has quickly found its way into many intensive care units [2]. We use isoflurane in cases of chronic obstructive pulmonary disease and pneumonia with recurrent bronchoobstruction, intracranial pathology, assuming an ICP measurement is established, or when the required sedation period exceeds the recommended limit of propofol application (seven days).

Intensive care patients are continuously monitored with regard to various organ systems and functional parameters. The development of acute liver failure (ALF) or acute-on-chronic liver failure (ACLF) is associated with increased mortality in sepsis [3]. In general, differentiated assessment of liver function is essential for early diagnosis and treatment. If treatment for ACLF is started during the therapeutic „golden window“ the chances for liver recovery are increased [4].

Only few parameters of liver function are available in septic patients, such as serum bilirubin concentration and INR [5]. The Model of end-stage liver disease (MELD) score [6] had been developed for non-ICU patients and is
unprecise for dialyzed patients. Other prognostic scoring systems such as the Chronic Liver Failure Consortium ACLF score (CLIF-C ACLFs), CLIF Consortium Acute Decompensation (CLIF-C ADs) score and the Child-Pugh score [7-9] assess among others the impairment of consciousness and are thus not suitable for sedated patients.

A prognostic test with higher sensitivity and specificity and a good correlation with Child-Pugh- and MELD-Score in non-sedated patients is the LiMAx-Test (Humedics GmbH, Berlin, Germany) [10, 11]. Measurements are independent of neurologic function, which allows application of the test in sedated patients in the intensive care setting. The LiMAx-test delivers a quantitative measurement of maximal liver function capacity within 60 min and has been evaluated in various clinical situations including mechanical ventilation [11, 12]. Briefly, the patient is injected 2 mg/kg body weight of $^{13}$C-methacetin intravenously, which is exclusively metabolized to paracetamol in subtherapeutic dose and $^{13}$CO$_2$ by the hepatic, microsomally localized, hemoprotein enzyme 1A2 (CYP1A2) from the cytochrome P450 group. $^{13}$CO$_2$ is a naturally occurring, stable non-radioactive carbon isotope. The exhaled amount of $^{13}$CO$_2$ is proportional to the total liver function capacity [13]. The measurement of $^{13}$CO$_2$ can also be performed via the expiration valve in ventilated patients. A value of 315 µg/kg/h or above is physiological [12, 14, 15]. Below this level, an impairment of liver function should be considered. Any value below 140 µg/kg/h strongly indicates significant hepatic injury [16] or an advanced liver-cirrhosis [17]. A value of less than 100 µg/kg/h in combination with respiratory dysfunction has been associated with increased mortality and may be of prognostic relevance with regard to patient survival [18]. A value of 29-98 µg/kg/h was observed for patients suffering from terminal liver cirrhosis [17].

We present a series of three patients from a university hospital surgical intensive care unit for whom extremely low LiMAx-test results were observed while receiving inhaled sedation with isoflurane, a finding that had not been reported before. The aim of our investigation was to discuss hypotheses helping to explain these data and a putative causal connection.

**Case Presentation**

Patient A: A 21-year-old, before healthy female patient suffered a severe polytrauma in a motorcycle accident with an injury severity score (ISS) of 75. The main injuries were severe craniocerebral trauma, severe blunt abdominal trauma with liver rupture and a decollement in the area of the left thigh extending to gluteal. Primary surgical treatment included laparotomy and liver suturing. On the first post-traumatic day LiMAx-value was 305 µg/kg/h, while static liver parameters were massively increased. Hemicraniectomy was performed due to rapidly increasing brain edema. Persistently high intracranial pressure (ICP) values prompted to change the sedation regimen to an inhalative concept with isoflurane under continuous ICP-control. While laboratory liver parameters quickly normalized, LiMAx-test results were 2 and 3 µg/kg/h after 25h and 123h. After the cessation of isoflurane, the LiMAx returned spontaneously to 180 µg/kg/h.

Patient B: A 65-year-old man who had undergone rectum resection for advanced rectal carcinoma developed anastomosis insucienctcy with abdominal sepsis. The antimicrobial chemotherapy included the liver-toxic antibiotic linezolid. LiMAx was used to monitor a possible deterioration of liver function at an early stage. The first test result was 151µg/kg/h. Since the respirator therapy had to be continued for longer than seven days, sedation was switched to isoflurane. In the further course of treatment LiMAx decreased to 2 and 10 µg/kg/h. After isoflurane was discontinued LiMAx increased to 254 µg/kg/h while transaminases also increased.
Patient C: A 49-year-old man had received thoracotomy for a suspicious pulmonary node. After an atypical resection of the right lower lobe he was transferred to the intensive care unit. In the course of the first postoperative day, an endobronchial hemorrhage occurred with acute deterioration of gas exchange. The bleeding from the middle lobe segment 4 was stopped by epinephrine instillation and tamponades in repeated bronchoscopies. A re-thoracotomy could be avoided. Due to recurrent bronchospastic episodes, isoflurane sedation was established early on. LiMAx-test was performed sequentially to assess liver function in perceived sepsis. After an initial reading of 376 µg/kg/h with propofol, LiMAx values of 33 and 77 µg/kg/h, respectively, were measured under isoflurane sedation. Clinical and laboratory assessment did not correlate with this decrease. After discontinuation of isoflurane LiMAx increased back up to 496 µg/kg/h, other parameters also indicated normal liver function.

The patient’s demographics and clinical data are listed in detail in Table 1 and Table 2, for LiMAx-tests results in correlation with standard liver parameter and isoflurane see Figure 1. The LiMAx-tests were performed according to the manufacturer's specifications (Humedics Inc. Berlin, Germany) and the clinical standard. To avoid a possible influence of the metabolism of the hydrophilic $^{13}$C-methacetin by the continuous renal replacement therapy (CRRT), the latter was paused directly before the start and during each measurement. CRRT was re-started immediately after the end of the measurement.

**Discussion And Conclusions**

Measurement of liver function capacity in patients at high risk for liver failure is a standard procedure in our institution as a diagnostic tool that can routinely be performed at the bedside when a compromise of liver function is suspected. Since LiMAx can be assessed independently from consciousness it may also be applied for sedated patients. In the three presented cases during isoflurane sedation the measured values were unexpectedly low in the range of 1 to 71 µg/kg/h (Figure 2). We consider several mechanisms for this observation: Interaction of isoflurane with the test procedure itself, interference of isoflurane with CYP1A2 or temporary decrease in liver enzyme activity without liver cell damage (“liver hibernation”).

None of the patients had a history of liver disease (e.g. alcoholic liver disease, hepatitis, non-alcoholic fatty liver or cirrhosis) that could have explained reduced liver enzyme activity. Under certain conditions (i.e. shock of different etiology) the liver enzyme activity may be temporarily reduced. The "standard liver parameters" are quantified from the blood and indicate liver damage, however without reflecting the CYP1A2 enzyme activity. Extremely low LiMAx values were measured in the three patients equally after the start of isoflurane that spontaneously returned to previous values after discontinuation of the inhaled sedative. Meanwhile, neither clinical nor laboratory findings suggested almost complete liver failure, which would be expected from such low LiMAx values [17].

To rule out toxic effects all administered drugs were scanned for a known interaction with CYP1A2 in the Flockhart Table [19] and for a high likelihood of hepatotoxicity in LiverTox [20]. With the exception of patient B, who received linezolid, none of the patients were treated with a listed drug during the relevant time (Figure 3). The hepatotoxic effect of the oxazolidinone antibiotic linezolid is well known. It is commonly associated with lactic acidosis and leads to an increase in transaminases. Lactic acidosis was not detected and an increase in transaminases was only observed at the time of the last LiMAx measurement, so that a serious impairment of liver function by linezolid at the time of CYP1A2 activity determination is not plausible. Therefore, true liver failure (pre-existing or toxic) as the cause for the significant decrease in LiMAx values seems quite unlikely.
The supply of $^{13}$C contained in food or infusions and oxygen have a major influence on the $^{13}$CO$_2$:$^{12}$CO$_2$ ratio measurement [21, 22]. Genetic polymorphisms of CYP1A2 and smoking are supposed only to have a slight influence on the test results [22]. During the investigated period, food, infusions and oxygen supply were almost unchanged suggesting no influence on test results.

The LiMAx instruction manual does not mention a possible influence of isoflurane on test results.

Only few studies have investigated a possible interaction of isotope measurement with isoflurane. After measurement of several pig breath samples that contained isoflurane the quality control drifted further and more quickly from its known value. The authors hypothesized that isoflurane was adsorbed by the gas chromatography column in isotope ratio mass spectrometry (IRMS) [23]. In contrast, LiMAx technology uses laser-based spectrometry and was validated in five patients with total intravenous anesthesia to avoid interference by volatile anesthetics [24]. Ensle et al [25] measured intestinal glucose absorption with a $^{13}$C glucose breathing test. Two isoflurane sedated patients were excluded from the analysis because of suspected isoflurane interaction with the $^{13}$C measured values, although no excluded values were reported. One could expect decreased LiMAx values if isoflurane prevents the $^{13}$C-methacetin pre-hepatic transport from the blood stream to the liver. This, however, is unlikely since lipophilic isoflurane accumulates in the fatty tissue while only low concentrations are available in the blood. We conclude that there is no evidence of a relevant interaction between methacetin or $^{13}$CO$_2$ and isoflurane.

Physiologically, isoflurane is almost inert in endogenous metabolism. It is oxidatively metabolized to a small extent (~ 0.2%) in the liver via CYP2E1 [19, 26] while an interaction of isoflurane and CYP1A2 activity has not yet been described [26, 27]. Even so, negative effects of isoflurane on the liver are well known. The liver damage is caused by trifluoroacetylation of liver proteins and a subsequent inflammatory reaction and rapid increase of transaminases termed hepatitis. This effect has been particularly well studied for halothane, but is also known for isoflurane [26]. If in fact isoflurane does compromise CYP1A2 activity genetic polymorphism could explain the differences in enzyme depression, which was less profound in patient C (-91%) as compared to the other patients (-98% and -99%, respectively) [28].

Finally, it remains unclear whether the apparent influence of isoflurane on the LiMAx test is substance-specific or whether other inhaled anesthetics cause similar effects.

To our knowledge, this is the first description of a profound decrease of LiMAx values during simultaneous isoflurane sedation, the reason for which remains unclear. Possible mechanisms are test-specific interactions, an isoflurane induced reduction in CYP1A2 activity or a temporary shut-down of enzymatic liver function without cell damage, suggesting a hibernating liver in the early phase of severe inflammatory disease. A more frequent measurement of Cyp1A2 activity would be desirable, to describe the development of enzyme activity more precisely. Due to the increasing use of both LiMAx and inhaled sedation in the ICU, we consider it important to further investigate this possible interaction in order to prevent erroneous measurements and possible wrong clinical decisions. We propose that, until the breath test on enzymatic liver function has been validated in the critical care setting, LiMAx-test results should be interpreted with caution in patients sedated with isoflurane.

List Of Abbreviations
AnaConDa: Aneasthetic Conserving Device; ACLF: Acute-on-chronic liver failure; ALF: Acute liver failure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body Mass Index; CLIF-C: Chronic Liver Failure Consortium; CLIF-C Ad: Chronic Liver Failure Consortium Acute Decompensation; CRRT: Continuous renal replacement therapy; CYP: Cytochrome P450; ICP: Intracranial pressure; INR: International normalized ratio; ISS: Injury Severity Score; LiMax: Liver maximum capacity; MELD: Model of end-stage liver disease

**Declarations**

**Postal address of all authors:** Klinikum Herford, Schwarzenmoorstr. 70, D-32049 Herford

**E-Mail Addresses:**

Elke.schwier@klinikum-herford.de,
Carmen.kirchner@klinikum-herford.de
Claas.eickmeyer@klinikum-herford.de
Guenther.winde@klinikum-herford.de
Dietrich.henzler@klinikum-herford.de
Thomas.koehler@klinikum-herford.de

**Corresponding author:** Thomas Köhler, MD

**Acknowledgment of grant support**

Not applicable

**Disclosure of financial arrangements**

There are no financial arrangements related to the report or assistance with manuscript preparation

The work originated from the Department of Anesthesiology, Surgical Intensive Care, Emergency and Pain Medicine, Ruhr University Bochum, Klinikum Herford, Herford, Germany

**Disclosure of conflict of interest**

The authors declare that they have no conflict of interest.
Ethics approval and consent to participate

The ethics committee of the medical faculty of the Ruhr University Bochum had approved the anonymous collection and publication of data.

Consent for publication

Patients or their representatives gave informal consent for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

ES performed literature research and wrote the manuscript.

CK analyzed and interpreted LiMAx data and reviewed the manuscript.

CE performed functional liver testing with LiMAx on intensive care unit, treated the patients, and reviewed the manuscript.

DH participated in analyzing and interpreting the data and revised the manuscript. GW helped to interpret the data and to review the manuscript.

TK treated the patients on intensive care unit and analyzed and interpreted data and was a major contributor in writing the manuscript.

All authors read and approved the final manuscript.

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Tables

Table 1

Patients’ demographics
|                         | Patient A | Patient B | Patient C |
|-------------------------|-----------|-----------|-----------|
| Gender                  | female    | male      | male      |
| Age (years)             | 22        | 65        | 48        |
| BMI                     | 21,7      | 30,9      | 29,8      |
| Major medical history   | polytrauma| rectum-cancer; post-operative complications | lung cancer, right upper lobe resection post-operation complications |
| History of liver disease| no        | no        | no        |
| CRRT treatment          | yes       | yes       | no        |
| Smoker                  | no        | no        | yes       |
| Reason for suspected liver damage | trauma | sepsis | sepsis |
| Source of a potential infection | pulmonary | abdominal | pulmonary |
| 28 day survival         | yes       | yes       | yes       |

BMI: Body Mass Index; CRRT: continuous renal replacement therapy;

**Table 2**

Patients laboratory parameters at the time of LiMAXx-testing
| Patient A | Patient B | Patient C |
|-----------|-----------|-----------|
| Time of LiMAx test in relation to start of isoflurane application [h] | -45 | 25 | 123 | 431 | -4 | 24 | 79 | 186 | -2 | 41 | 89 | 282 |
| LiMAx [µg/kg/h] | 305 | 3 | 1 | 180 | 151 | 2 | 10 | 254 | 372 | 33 | 71 | 496 |
| AST [U/L] (Ref. <35) | 1434 | 288 | 59 | 48 | nd | 34 | 63 | 1260 | 24 | 28 | 43 | 99 |
| ALT [U/L] (Ref. <35) | 968 | 209 | 19 | 36 | nd | 13 | 26 | 505 | 29 | 18 | 21 | 146 |
| Serum Albumin [g/L] (Ref. 35-52) | 23.5 | 15.5 | 21.5 | 18.9 | 20.8 | 20 | 24.2 | 16.4 | 32.6 | 31.3 | 30.7 | 32 |
| Serum Bilirubin [mg/dL] (Ref < 1.2) | 2.1 | 1.75 | 1.6 | 0.71 | 0.59 | 0.6 | 0.86 | 1.27 | 1.47 | 1.26 | 1.23 | 1.2 |
| Serum Sodium [mmol/L] | 139 | 138 | 141 | 144 | 135 | 137 | 140 | 136 | 141 | 148 | 145 | 138 |
| Lactate [mmol/L] | 2.33 | 3.29 | 1.62 | 1.01 | 4.02 | 3.43 | 1.1 | 4.5 | 0.8 | 1.32 | 0.68 | 0.43 |
| INR | 1.41 | 1.25 | 1.19 | 0.98 | 1.77 | 1.35 | 1.26 | 1.73 | 1.02 | 1.05 | 1.02 | 1.21 |
| GGT [U/L] (Ref. <40) | 31 | 69 | 36 | 76 | nd | 38 | 301 | 174 | 365 | 295 | 356 | 774 |
| Creatinine [mg/dL] (Ref. <0.95) | 2.06 | 2.33 | 1.87 | 3.12 | 1.18 | 0.81 | 0.91 | 1.24 | 0.85 | 0.84 | 0.83 | 0.74 |
| Platelet count [G//L] (Ref. 150-400) | 51 | 35 | 90 | 296 | 106 | 83 | 65 | 89 | 293 | 303 | 307 | 390 |
| MELD (pts) | 26 | 24 | 23 | 20 | 26 | 25 | 22 | 23 | 8 | 11 | 7 | 10 |
| Isoflurane dose [ml/h] | na | 4 | 5 | na | na | 6 | 3 | na | na | 10 | 10 | na |
| Isoflurane insp [%] | na | nd | 0.4 | na | na | 0.25 | 0.1 | na | na | 0.55 | 0.65 | na |
| Isoflurane et [%] | na | 0.4 | nd | na | na | 0.65 | 0.35 | na | na | 1.2 | 0.75 | na |
| Enteral feeding | yes | yes | yes | yes | no | yes | yes | yes | yes | yes | yes | yes |
| Norepinephrine [µg/kg/min] | 0.005 | 0.1 | 0.05 | 0 | 0.8 | 0.78 | 0.53 | 0.11 | 0 | 0.04 | 0.05 | 0 |
| FiO₂ | 0.25 | 0.35 | 0.35 | 0.3 | 0.7 | 0.8 | 0.65 | 0.45 | 0.5 | 0.5 | 0.5 | 0.45 |

LiMax: liver maximum capacity; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; PT: prothrombin time; INR: international normalized ratio; GGT: gamma glutamyltransferase; MELD: model for End-stage liver disease; insp: inspiratory; et: expiratory; na: not applicable; nd: no data. Laboratory parameter were taken for patient A: 18h, 20h, 51h, 22h, for patient B: 8h, 16h, 33h, 22h and for patient C: 15h, 44h, 20h, 42h after the corresponding LiMax-measurement. Isoflurane insp/et corresponds to the time of LiMax measurement. MELD Score was calculated according to http://www.klinikum.uni-muenchen.de/Lebercentrum/de/fuer_aerzte/meld_score_rechner/index.html.