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Dynamic determination of functional liver capacity with the LiMAx test in post-cardiac arrest patients undergoing targeted temperature management—A prospective trial

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Background: Transiently increased transaminases is a common finding after cardiac arrest but little is known about the functional liver capacity (LiMAx) during the post-cardiac arrest syndrome and treatment in the intensive care unit (ICU). The aim of this trial was to evaluate liver function capacity in post-cardiac arrest survivors undergoing targeted temperature management (TTM) in ICU.

Methods: Thirty-two post-cardiac arrest survivors were prospectively included with all patients undergoing TTM at 33°C for 24 hours. Blood samples were collected, and LiMAx testing was performed at days 1, 2, 5, and 10 post-cardiac arrest. LiMAx is a non-invasive, in vivo, dynamic breath test determining cytochrome P450 1A2 (CYP1A2) capacity using intravenous (IV) ^{13}C-methacetin, thus reflecting maximum liver function capacity. Static liver parameters were determined and compared to LiMAx values.

Results: A typical pattern of transiently, mildly increased transaminases was demonstrated without fulfilling the criteria for hypoxic hepatitis (HH). CYP1A2 activity was reduced with slow normalization over 10 days (lowest median 48 hours after cardiac arrest: 228.5 (25-75 percentile 105.2-301.7 µg/kg/h, $P < .05$). Parameters reflecting the liver synthetic function were not impaired, as assessed by, in standard laboratory testing.

Conclusion: Liver functional capacity is impaired in patients after cardiac arrest undergoing TTM at 33°C. More data are needed to determine if liver functional capacity may add relevant information, especially in the context of pharmacotherapy, to individualize post-cardiac arrest care.

1 | INTRODUCTION

Elevated liver transaminases are frequently observed in survivors of cardiac arrest. This increase can range from mild to severe in the initial phase; typically, the increase in aspartate aminotransferase (ASAT) is most marked, with a peak in the first 2 days followed by a normalization within 5-7 days.[1] The clinical practice guidelines by the European Association for the Study of the Liver (EASL) define the elevation of ASAT, often >10 000 U/L, as hypoxic hepatitis (HH).[2] HH as a secondary form of acute liver failure (ALF) often presents in the clinical setting as a rapid, 20-fold increase above the upper reference range limit of ASAT (>1000 U/l), together with shock or hypoxemia. These findings lead to a diagnosis of HH following exclusion of other potential causes.[3] Little is known regarding the characteristics of HH in post-cardiac arrest patients, but the current literature places the incidence of HH in this patient group between 11.4% and 13.5%.[4 5] Furthermore, for comatose survivors after cardiac arrest, guidelines recommend post-cardiac arrest targeted temperature management

(TTM).[6] TTM ameliorates the severity of the post-cardiac arrest syndrome.[7] However, influencing the body temperature has an impact on pharmacokinetics and pharmacodynamics, which results in elevated drug concentrations or reduced drug effects during TTM.[8-11]

The cytochrome P450 (CYP450) liver enzyme system plays a central role in hepatic drug metabolism, and with the introduction of the dynamic LiMAx test, CYP450 1A2 (CYP1A2) activity can be directly measured.

The aim of this prospective pilot trial was to determine the functional liver capacity using the LiMAx test in relationship to the severity of occurring HH evaluated by standard liver function parameters in post-cardiac arrest patients undergoing TTM.

Editorial Comment

How the liver fares for survivors of cardiac arrest was explored in a cohort who were treated post-arrest/resuscitation for a day with controlled hypothermia to 33 degrees C. Some transaminase release was observed, though for most not extreme. Metabolic function as indicated by activity level of one cytochrome showed reduced levels over the early post-arrest days, then recovery over many days. These findings give reason to have concern about the quality of liver function in the early post-arrest period.

2 | METHODS

This prospective clinical trial was approved by the local ethics committee of the Charité-Universitätsmedizin Berlin (EA1/002/13). Written informed consent was provided by a legal representative. All patients received TTM according to our local standard protocol in line with current guidelines. TTM was initiated after admission, with a targeted temperature of 33°C attained for 24 hours and subsequent rewarming to 37°C at a rate of 0.25°C per hour up to 37°C.

Inclusion criteria were adult age (≥18 years) and cardiac arrest. Exclusion criteria were any known prior liver disease (alcohol abuse, tumor, hepatitis, prior liver surgery, liver transplantation, and autoimmune diseases) or known allergy to paracetamol or methacetin. Patients prospectively independent of initial rhythm (shockable or non-shockable) or location (out-of-hospital or in-hospital) of cardiac arrest were included. Blood samples were taken at days 1, 2, 5, and 10 with extended laboratory parameters: total bilirubin, triglycerides, cholesterol, high-density lipoprotein- (HDL-) cholesterol, low-density lipoprotein- (LDL-) cholesterol, protein, albumin, C-reactive protein (CRP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (AP), gamma-glutamyltransferase (GGT), pseudocholinesterase (CHE), ammonium, glutamate dehydrogenase (GLDH), prothrombin time, aPTT, factor II (prothrombin), factor VII (proconvertin), and lactate. Standard laboratory results are given using the Système international d'unités (SI units). HH was determined as a rapid, early 20-fold increase above the upper limit of ASAT within the clinical setting of shock or hypoxemia and following exclusion of other potential causes.

LiMAx (maximum liver function capacity) testing was performed at day 1 (33°C), day 2 (end of TTM), day 5, and day 10 post-cardiopulmonary resuscitation (CPR). LiMAx is a non-invasive, in vivo, dynamic breath test determining CYP1A2 capacity using intravenous (IV) ^{13}C-methacetin adjusted to body weight. It is utilized at specialized centers to assess functional liver capacity prior to hepatectomy. The method has been introduced and characterized elsewhere in detail.[12] Briefly, the test is based on the hepatocyte-specific metabolism of the ^{13}C-labeled substrate (^{13}C-methacetin; Humedics GmbH, Berlin, Germany) by the cytochrome CYP1A2 enzyme, which is ubiquitously active in the liver. After IV injection, the ^{13}C-methacetin is instantly metabolized into acetaminophen and the demethylated ^{13}C-group is converted into $^{13}CO_2$, which is exhaled and measured by the analyzer device (FLIP™ Analyzer, Humedics GmbH, Berlin, Germany).[12,13] Hence, the administration of ^{13}C-methacetin leads to a significant alteration of the normal $^{13}CO_2$:$^{12}CO_2$ ratio (Pee Dee Belemnite standard 1.1237%) in the expired breath. This alteration is determined by a suitable device that is directly connected to the patient. Breath analysis is performed automatically over time. Before injection of the ^{13}C-methacetin, the individual baseline of $^{13}CO_2$ and $^{12}CO_2$ has to be recorded and compared to measurements after injection of ^{13}C-methacetin to yield the delta over baseline (DOB). Liver function capacity is calculated from the kinetic analysis of the $^{13}CO_2$:$^{12}CO_2$ ratio over a period of up to 60 min. In healthy volunteers, the normal range of LiMAx was found to be 425 ± 67 µg/kg/h (mean ± SD; range, 311-575 µg/kg/h) with a maximum $^{13}CO_2$ excretion 10 ± 6 minutes after methacetin injection.[12,14] The LiMAx test has been approved in the European Union but not yet in the United States.

The Flockhart Table™ (https://drug-interactions.medicine.iu.edu/Main-Table.aspx) was used to determine the potential inhibitors and inducers of the CYP1A2 system given to the patient prior to admission or during ICU care (Table S1). A strong inhibitor is defined as the one that causes a >5-fold increase in the plasma area under the concentration-time curve (AUC) value or more than 80% decrease in clearance, a moderate inhibitor is one that causes a two- to fivefold increase in the plasma AUC values or 50%-80% decrease in clearance, and a weak inhibitor is one that causes a >1.25- 2-fold increase in the plasma AUC values or 20%-50% decrease in clearance.

Neurological outcome was determined at discharge from ICU (similar to discharge from hospital in all patients) using the Pittsburgh Cerebral Performance Category (CPC) scale; CPC 1-2 was defined as good and 3-5 as poor outcome according to our local standard, in agreement with national and international guidelines.

2.1 | Statistical analysis

Each dependent variable is reported as a proportion (%), median with interquartile range (IQR), or arithmetic mean with 95% confidence interval (95% CI). For comparison of dependent variables, a paired

t-test was used. Multiple linear regression analysis was performed with independent variables of time to return of spontaneous circulation (tROSC), gender, and shockable rhythm, and dependent variables of ASAT and LiMAx course. A Pearson correlation was used to analyze the relationship between duration of resuscitation (tROSC) and measured LiMAx levels.

A *P*-value of less than .05 was considered statistically significant. Figures were prepared with GraphPad Prism® (Version 7). SPSS® (version 22) was used for statistical analysis. The sample size calculation was based on the primary endpoint defined by the mean change of LiMAx values between day 1 and day 2. The difference in means between days was expected to be at least 100 points with a standard deviation of 190. A total number of 31 patients was required to detect the difference with a paired t-test at a significance level of 5% (two-tailed) with a power of 80%. The power calculation was performed using G*Power 3.1.9.3. [15]

3 | RESULTS

3.1 | Baseline characteristics

Between January 2014 and January 2015, a total of 38 patients were prospectively enrolled in the study; 32 patients were included in final analysis (Figure 1). Reasons for exclusion from analysis were diagnosis of hepatocellular carcinoma (1), technical reasons (1), withdrawal of written consent (1), hemodynamic instability and interruption of measurement (1), diagnosis of cirrhosis (1), and death after first measurement (1). The LiMAx setup at the bedside is shown in Figure 2. Baseline characteristics and outcome of all included patients are given in Table 1. Median age of patients was 65 (53-74) years, 69% were male (22/32), and most had an initially shockable rhythm (21/32; 66%). Etiology of arrest was a cardiac cause in 21/32 (66%) of patients. Prior to admission to the ICU, five patients received amiodarone, which is known to be a weak CYP1A2 inhibitor; four patients received amiodarone after admission to ICU (Table S1). One patient received ciprofloxacin, a strong CYP1A2 inhibitor, after admission to ICU. Insulin, a CYP1A2 inducer, was given to 18 patients during the first day in the ICU. In addition, three patients were active smokers prior to hospital admission, and tobacco is known to be a potential inducer of CYP1A2. All administered drugs for sedation and analgesia, such as propofol, isoflurane, opiates, or benzodiazepines, are not known to interfere with the CYP1A2 but with other CYP450 enzymes and were given within a recommended dosing.

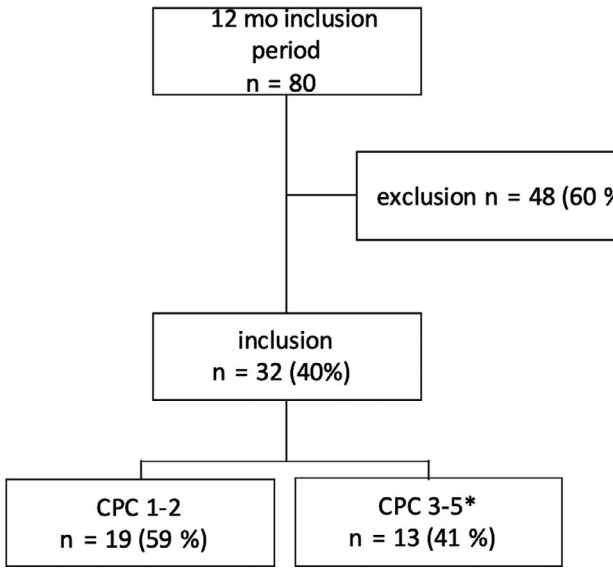

FIGURE 1 Study flowchart of all post-cardiac arrest patients within inclusion time between January 2014 and January 2015, exclusion criteria were any known prior liver disease (alcohol abuse, tumor, hepatitis, prior liver surgery, liver transplantation, and autoimmune diseases), CPC, Cerebral Performance Category; * in three patients, withdrawal of ICU treatment was performed due to poor prognosis

3.2 | Static liver parameters

Laboratory results of extended liver parameters are given in Table 2. Mean ASAT and ALAT were initially elevated (ASAT median 2734 (1320-3992) nkat/l, ALAT median 2175 (1270-3712) nkat/l) with slow normalization over 10 days. In addition, GLDH was elevated (600 (208-1699) nkat/l) following the same pattern

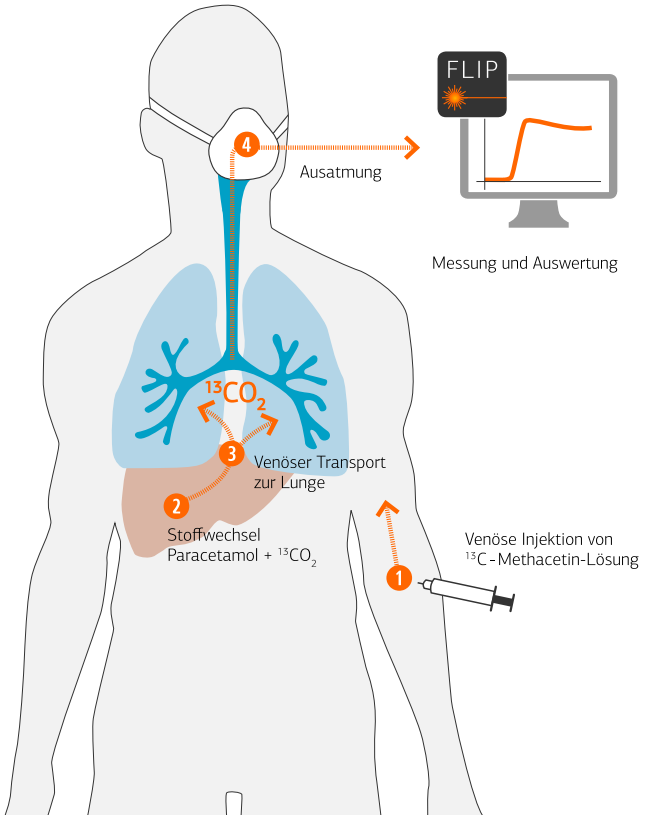

FIGURE 2 Setup of LiMAx breath test; individual liver function can be assessed by continuous measurement of $^{13}CO_2/^{12}CO_2$ ratio after injection and metabolism of ^{13}C-methacetin *(reproduced with permission of Humedics GmbH, Berlin, Germany)* [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline parameters of study population

Baseline parameters	
Variable	**n = 32**
Age (years)	65 (53-74)
Gender (male)	22 (69)
tROSC (min)	13 (8-24)
Shockable rhythm	21 (66)
Epinephrine (mg)	2.0 (1.2-5.0)
Cardiac cause of arrest	21 (66)
AMI	14/21
Primary arrhythmia	7/21
Non-cardiac cause of arrest	11 (34)
Respiratory	9/11
Other	2/11
Ventilator time (hours)	184 (121-290)
LOS (days)	12 (7-17)
APACHE	24 (18-34)
Outcome	
CPC 1-2	19 (59)
CPC 3-5	13 (41)
CPC 5	7 (22)

Note: Baseline characteristics of study cohort; numbers are given as median and interquartile range or absolute numbers and percent; * data about epinephrine given during resuscitation were only available in 21/32 patients. Time to return of spontaneous circulation tROSC, length of ICU stay LOS, Acute Physiology and Chronic Health Evaluation Score APACHE-score, Cerebral Performance Category CPC, acute myocardial infarction AMI.

of normalization. Bilirubin, coagulation parameters (aPTT), factors II and VII, and lactate were within the reference ranges at all time points. Albumin levels were slightly lower than the normal range at all time points.

3.3 | Dynamic liver function by LiMAx

Median LiMAx values at day 1 (during TTM at 33°C) and day 2 (after rewarming), and 5 days after ROSC were below the normal range of 425 ± 67 μg/kg/h. The minimum of LiMAx was at day 2 (median 228.5 (25-75 percentile 105.2-301.7 μg/kg/h)) and a recovery was seen at measurement 4 after 10 days (Figure 3). The change in LiMAx between the measurements were statistically significant (all $P < .05$; Figure 3).

3.4 | Multiple regression

Multiple regression (independent variables: tROSC, gender, shockable rhythm) revealed a significant influence of tROSC ($P = .02$) on ASAT at day 1 (highest ASAT level), whereas no significance was found for tROSC, gender, or initial shockable rhythm with LiMAx values on day 2 (lowest median LiMAx levels; Table S2).

3.5 | Pearson Correlation

There was no significant correlation between tROSC and the delta of LiMAx between days 1-2 and days 2-5.

4 | DISCUSSION

This study evaluated dynamic functional liver capacity by determining the CYP1A2 enzyme activity in post-cardiac arrest survivors undergoing TTM (33°C for 24 hours). Our main findings were as follows: (1) CYP1A2 activity was significantly decreased on day 2 after cardiac arrest in patients undergoing TTM, followed by a slow recovery over 10 days; (2) post-cardiac arrest patients showed a typical blood chemistry pattern with a transient mild increase in ASAT and ALAT without reaching the criteria for HH; (3) tROSC was significantly associated with the change of static liver parameters but not with functional liver parameters.

4.1 | Static liver parameters

A transient elevation of transaminases is more frequent in post-cardiac arrest patients than in the general cohort of critical care patients.[4,5,16] One mechanism for this transaminase elevation is absent or decreased blood flow during arrest and CPR. Another mechanism is disturbed microcirculation during reperfusion syndrome after ROSC.[3,17] Our results are in line with previously published data concerning ASAT and ALAT patterns after cardiac arrest, although in our cohort no patient met the criteria for diagnosis of HH (ie, at least 20-fold elevation of ASAT above the upper limit of the reference range). Therefore, in multivariate testing, an ASAT elevation of 10-fold above the upper limit was used and was significantly associated with time of ROSC without fulfilling the diagnostic laboratory criteria for HH. However, the resolution pattern was typical for a transient, mild ischemic liver injury.

4.2 | Dynamic liver parameters

Activity of CYP1A2, as measured by LiMAx, was reduced with a slow normalization over 10 days. LiMAx has been developed and mainly studied in patients undergoing liver transplantation or surgery, such as partial hepatectomy, but has not previously been used to characterize CYP1A2 activity in post-cardiac arrest patients. Current guidelines recommend TTM in a wide temperature range of 32-36°C in nearly all comatose survivors after cardiac arrest. Little is known regarding the influence of TTM on pharmacokinetics and -dynamics. In general, enzymes have a pH and temperature optimum

TABLE 2 Laboratory results of study population

Laboratory results						
Variables	**SI unit**	**Normal range**	**Day 1**	**Day 2**	**Day 5**	**Day 10**
Creatinine	µmol/l	45-103.43	88.4 (70.7-97.2)	79.6 (61.9-114.9)	70.7 (61.9-114.9)	79.6 (53.0-106.1)
Urea	µmol/l	2.8*10^3-7.9x10*3	6.4*10^3 (5.1-9.4 *10^3)	6.4*10^3 (3.9-10*10^3)	6.9*10^3 (5.1-14.4*10^3)	7.4*10^3 (5.3-16.3*10^3)
Ammonium	µmol/l	21-71	24.4 (18.6-33.4)	22.8 (18.0-30.9)	29.4 (23.0-42.4)	36.8 (26.7-42.5)
Bilirubin serum	µmol/l	0-20.52	8.6 (6.8-17.1)	6.8 (3.4-10.3)	6.8 (5.1-8.6)	8.6 (5.1-12.0)
Bilirubin direct	µmol/l	0-5.13	5.1 (3.4-10.3)	3.4 (1.7-6.8)	3.4 (3.4-5.1)	5.1 (3.4-6.8)
Albumin	g/l	35-52	33.2 (30.0-37.7)	29.5 (26.3-31.4)	28.5 (26.5-30.6)	31.4 (26.4-33.5)
Protein	g/l	64-83	56.5 (52.0-63.5)	53.0 (49.7-56.0)	54.0 (51.0-58.0)	61.0 (56.0-66.0)
Cholesterol	mmol/l	0-5.17	3.6 (2.8-5.0)	2.9 (2.5-3.5)	2.9 (2.5-3.7)	3.6 (2.7-4.7)
HDL-Cholesterol	mmol/l	>1.16	1.1 (0.9-1.5)	0.8 (0.6-1.2)	0.7 (0.6-1.0)	0.6 (0.2-0.9)
LDL-Cholesterol	mmol/l	0-3.36	2.0 (1.3-2.9)	1.2 (0.9-1.9)	1.4 (1.1-1.9)	2.0 (1.4-3.1)
AST	nkat/l	0-833.5	2.7*10^3 (1.3-3.9*10^3)	1.3*10^3 (783-2.6*10^3)	1.3*10^3 (733.5-2.3*10^3)	917 (60-1.5*10^3)
ALT	nkat/l	0-683.47	2.2*10^3 (1.3-3.7*10^3)	1.4*10^3 (828-1.9*10^3)	883.5 (533.4-1.2*10^3)	900 (733-1.7*10^3)
AP	nkat/l	666.8-2.1x10*3	1.0*10^3 (908-1.3*10^3)	1*10^3 (783-1.2*10^3)	1.3*10^3 (1-1.8 *10^3)	1.7*10^3 (1.5-2.6*10^3)
CHE	nkat/l	88.3*10^3-216.7*10^3	115*10^3 (90-126*10^3)	86*10^3 (68.1-101.6 *10^3)	73.3*10^3 (56.6-90*10^3)	88.3*10^3 (58.3-106.6*10^3)
GLDH	nkat/l	0-106.69	600.1 (208.4-1.6*10^3)	195.0 (85.0-395.1)	123.4 (71.7-276.7)	228.4 (103.4-381.7)
GGT	nkat/l	133.36-1*10^3	1.3*10^3 (869-2.8*10^3)	1.1*10^3 (525.1-2.0*10^3)	1.4*10^3 (1-4.2*10^3)	3.4*10^3 (2-7.2*10^3)
CRP	g/l	0-0.01	0.0 (0.0-0.1)	0.2 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.0-0.1)
PT	%	70-130	72.5 (59.7-82.7)	66.0 (59.0-76.0)	79.0 (70.5-83.0)	79.0 (66.0-85.0)
aPTT	sec	26-40	43.2 (36.7-55.7)	43.1 (38.8-48.2)	41.6 (34.1-47.9)	36.3 (33.5-43.9)
F II	%	70-120	78.0 (67.0-92.0)	76.0 (68.5-85.5)	95.0 (82.0-101.0)	90.0 (76.0-101.2)
F VII	%	60-170	85.0 (69.7-108.7)	66.0 (52.0-85.5)	100.0 (90.0-124.0)	93.5 (70.2-125.5)
Lactate	mmol/l	0.5-2.2	1.8 (1.3-3.5)	1.2 (1.0-2.0)	0.9 (0.7-1.3)	0.8 (0.7-1.1)

Note: Detailed results of standard laboratory parameter, numbers presented in median and 25-75 percentiles, number of patients at time point d1 n = 32, d2 n = 30, d5 n = 29, d10 n = 15, high-density lipoprotein- (HDL-) cholesterol, low-density-lipoprotein- (LDL-) cholesterol, C-reactive protein CRP, Aspartate Aminotransferase ASAT, Alanine Aminotransferase ALT, alkaline phosphatase AP, gamma-glutamyltransferase GGT, pseudocholinesterase PCHE, glutamate dehydrogenase GLDH, partial prothrombin time aPTT, prothrombin time PT, factor II (prothrombin), factor VII (proconvertin).

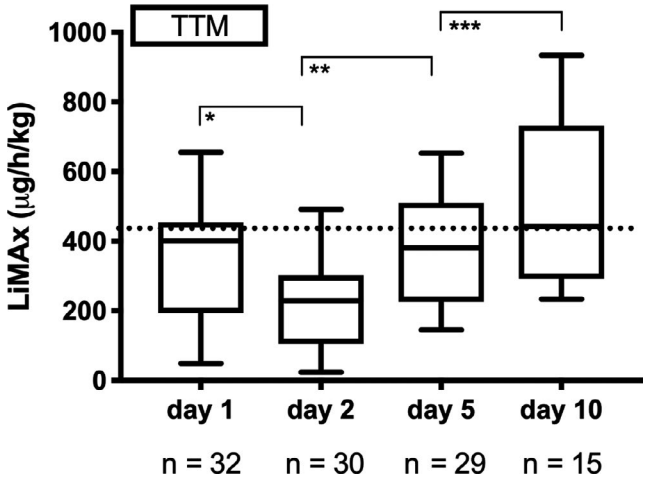

FIGURE 3 LiMAx course; dotted line represents mean normal range of liver function capacity, results are given as median and 25/75 percentiles. *P = .00, **P = .00, ***P = .01

(normothermia), so TTM can disturb this balanced system. In a review by Tortorici et al, it was hypothesized that drug concentrations are influenced by TTM via the alteration of CYP450 activity.[9] However, the duration and severity of those effects are unknown. In some cohorts, basal enzyme activity was persistently low even after rewarming.[18,19] Animal and clinical data suggest combined effects of HH and TTM in inducing alteration of CYP450 activity.[11] In a review by Crombez et al, reduced cardiac output associated with TTM was suggested as a reason for reduced liver blood flow resulting in suppression of CYP450 function.[20] However, the long duration of the effect and slow normalization in our cohort point toward a combination of several factors. In our cohort, the liver functional capacity was mildly impaired, suggesting potentially a greater impact of TTM itself on suppressing CYP1A2 activity. Furthermore, lowest LiMAx levels at day 2 were not significantly associated with tROSC and there was no significant correlation between tROSC and the change of LiMAx between all four measurements, indicating that duration of liver hypoxia was not the main factor for reduced liver function. In a rat model, Zhou et al reported that TTM-mediated changes were CYP450 isoform specific, which preclude the generalization of our results to all CYP450 enzymes.[21]

The reduced liver function capacity measured by LiMAx most likely reflects a combination of elevated systemic inflammation during reperfusion syndrome, the severity of the hypoxic liver injury, and TTM effects. These findings may be relevant as metabolism of sedative and other drugs seems altered by these effects during initial ICU treatment, including TTM.[22,23] We found reduced liver function capacity to be prolonged up to 10 days, overlapping with the window widely used for prognostication. Prognostication was, however, not included in this study. It seems prudent to consider impaired liver functional capacity in the clinical decision-making for administering prodrugs, such as platelet inhibitors, that require activation by liver enzymes. Current data suggest an insufficient reduced platelet activity when clopidogrel was used during TTM.[8,10] Indeed, recent published data show a correlation of linezolid plasma levels with the maximum liver function capacity measured by LiMAx, as linezolid is metabolized mainly by the liver.[24] However, LiMAx has been used to test only CYP1A2 and the described effects cannot be translated to other CYP450 enzyme systems directly; that being said, an influence of the different isoforms seems possible. Several patients received drugs known to be CYP1A2 inhibitors or inducers prior to admission or during ICU treatment. However, as the LiMAx test involves bolus injection of the dose in 20-30 seconds, competitive inhibitors play a minor role as long as they are not given exactly at the same time, which was not the case in this cohort. At the moment, no good clinical data exist regarding the influence of CYP1A2 inducers on results of the LiMAx tests, so a possible interaction cannot be fully ruled out. The effect of tobacco, a known potential inducer of CYP1A2, seemed limited in this study and was negligible after 1-3 days.[25] Future clinical trials should further evaluate these effects and focus on adjustment of drug dosage according to liver function capacity. As current international guidelines for TTM in post-cardiac arrest care recommend a targeted temperature between 32° and 36°C, LiMAx testing should also be performed at different targeted temperature levels in future trials.

4.3 | Limitations

Several limitations need to be addressed. First, LiMAx testing was started after 33°C was reached, and therefore, no baseline measurements were available. However, the test has previously been evaluated in healthy volunteers for definition of normal values. Second, the number of patients in this pilot trial was small and not all measurements could be performed in all patients. Third, a control group without TTM treatment after cardiac arrest was not included for comparison, preventing quantification of the TTM effect on the CYP1A2 system. Fourth, the clinical value of our results is reduced as data regarding drug concentration or metabolic alterations associated with decreased functional liver capacity is lacking.

5 | CONCLUSION

A reduction of liver functional capacity in patients after cardiac arrest undergoing TTM at 33°C was demonstrated. More data are needed to determine if liver functional capacity may add relevant information, especially in the context of pharmacotherapy, to individualize post-cardiac arrest care.

CONFLICT OF INTEREST

C. Storm has received remuneration for presentations, travel costs, and partial technical or material support from Philips, BD BARD, and Zoll. C. Leithner has received remuneration for presentations and travel costs from BD BARD. M. Stockmann is the inventor of the LiMAx test and has capital interest in Humedics, the company marketing the LiMAx test. J. Nee received honorarium and travel costs for presentations from BD BARD and Xenios AG.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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