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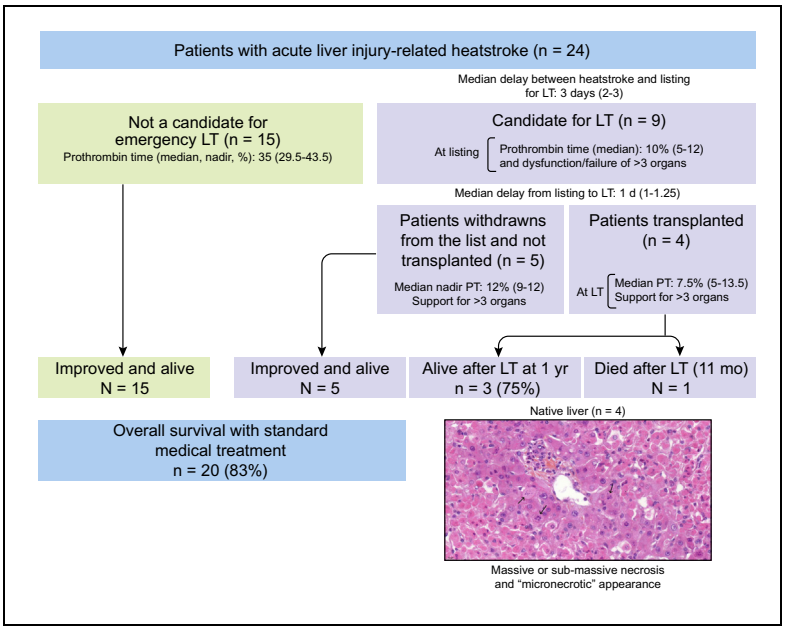
Liver transplantation in patients with liver failure related to exertional heatstroke

Graphical abstract



Highlights

- The first-line treatment for heatstroke that causes severe liver injury is medical.
- Liver transplantation (LT) is a rare alternative that achieves good survival rates.
- The decision to transplant must consider the kinetics of PT and patients' clinical status.
- All explanted livers were characterised by a "mitonecrotic appearance on histology.

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Lay summary

Acute liver injury due to heatstroke can progress to acute liver failure with organ dysfunction despite medical treatment; in such situations, liver transplantation (LT) may offer a therapeutic option. The classic criteria for LT appear to be poorly adapted to heatstroke-related acute liver failure. We confirmed that medication is the first-line therapy acute liver injury caused by heatstroke, with LT only rarely necessary. A decision to perform LT should not be made hastily. Fluctuations in prothrombin time and the patient's clinical status should be considered even in the event of severe liver failure.

http://dx.doi.org/10.1016/j.jhep.2018.11.024

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Liver transplantation in patients with liver failure related to exertional heatstroke

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Background & Aims: Severe acute liver injury is a grave complication of exertional heatstroke. Liver transplantation (LT) may be a therapeutic option, but the criteria for LT and the optimal timing of LT have not been clearly established. The aim of this study was to define the profile of patients who require transplantation in this context.

Methods: This was a multicentre, retrospective study of patients admitted with a diagnosis of exertional heatstroke-related severe acute liver injury with a prothrombin time (PT) of less than 50%. A total of 24 male patients were studied.

Results: Fifteen of the 24 patients (median nadir PT: 35% [29.5–40.5]) improved under medical therapy alone and survived. Nine of the 24 were listed for emergency LT. At the time of registration, the median PT was 10% (5–12) and all had numerous dysfunctional organs. Five patients (nadir PT: 12% [9–12]) were withdrawn from the list because of an elevation of PT values that mainly occurred between day 2 and day 3. Ultimately, 4 patients underwent transplantation as their PT persisted at <10%, 3 days (2.75–3.25) after the onset of exertional heatstroke, and they had more than 3 organ dysfunctions. Of these 4 patients, 3 were still alive 1 year later. Histological analysis of the 4 explanted livers demonstrated massive or submassive necrosis, and little potential for effective mitoses, characterised by a "mitonecrotic" appearance.

Conclusion: The first-line treatment for exertional heatstroke-related severe acute liver injury is medical therapy. LT is only a rare alternative and such a decision should not be taken too hastily. A persistence of PT <10%, without any signs of elevation after a median period of 3 days following the onset of heatstroke, was the trigger that prompted LT, was the trigger adopted in order to decide upon LT.

Lay summary: Acute liver injury due to heatstroke can progress to acute liver failure with organ dysfunction despite medical treatment; in such situations, liver transplantation (LT) may offer a therapeutic option. The classic criteria for LT appear to be poorly adapted to heatstroke-related acute liver failure. We confirmed that medication is the first-line therapy acute liver injury caused by heatstroke, with LT only rarely necessary. A decision to perform LT should not be made hastily. Fluctuations in prothrombin time and the patient's clinical status should be considered even in the event of severe liver failure.

Introduction

Exertional heatstroke is a rare but serious complication that can occur during intense and prolonged physical exercise in a hot and humid climate. It is mainly characterised by hyperthermia higher than 40 °C associated with central neurological disorders. It occurs in individuals who were previously in good health.[1]

Liver injury is common in the context of exertional heatstroke. It is usually moderate and characterised by elevated aminotransferase levels. This injury is generally reversible and asymptomatic, although more rarely it may be accompanied by severe liver injury (sALI) or acute liver failure (ALF), both of which have a poor prognosis. This liver injury is clearly due to multiple factors: lesions induced by hyperthermia, hypoxia, endotoxemia, blood coagulation disorders or sepsis. It is often one symptom of severe multiple organ dysfunction or multiple organ failure. The control of body temperature by cooling as soon as the patient is taken in charge is essential and will influence the severity of organ injury.

Keywords: Heatstroke; Acute liver injury; Acute liver failure; Liver transplantation; Survival with and without liver transplantation; Histological feature.
Received 16 May 2018; received in revised form 7 November 2018; accepted 19 November 2018; available online 4 December 2018
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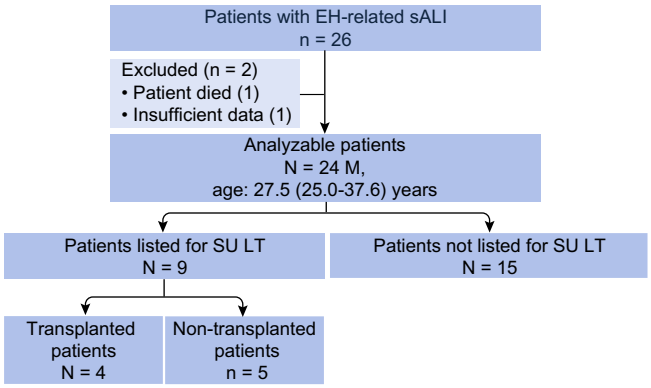

Fig. 1. Study flow diagram. EH, exertional heatstroke; LT, liver transplantation; sALI, severe acute liver injury; SU, super-urgent.

The indication for liver transplantation (LT) is not clearly established, for 3 main reasons. Firstly, the criteria for LT may be interfered with by the existence of a coagulation disorder (disseminated intravascular coagulation [DIC]), which combined with the hepatic lesions may lead to overestimation of the severity of liver failure.[2] Secondly, liver failure may be reversed at the same time as the failure of other organs, using resuscitation techniques. And thirdly, only a few cases of LT have been reported, so it is not possible to clarify its indication in this context.

The aim of this study was therefore to define a clinical, biological, static and dynamic profile of patients in whom LT should be considered.

Patients and methods

Between 1995 and 2016, we identified 26 patients who were admitted to 7 tertiary centres with a diagnosis of exertional heatstroke associated with sALI defined by a prothrombin time (PT) <50% (at admission or during hospitalisation) or ALF defined by PT <50% and hepatic encephalopathy.[3] The criteria for a diagnosis of exertional heatstroke and thus inclusion in our study were a core body temperature higher than 105°F (40 °C) and evidence of central nervous system dysfunction (seizures or altered senses such as disorientation, delirium or coma). Out of the 26 patients initially included, 2 were excluded from the analysis because no data or insufficient data were available (1 of these 2 patients died within 2 h of suffering from heatstroke, with multiple organ failure including lactic acidosis, a state of shock refractory to noradrenaline, coma with a Glasgow score of 3 and respiratory distress), so that 24 patients were finally studied (see Fig. 1). All had previously been in good health. All clinical, biological and histological data (when available) were collected from the onset of heatstroke, daily during hospitalisation in the ICU, and at the time of LT or death. The most severe biological values, per 24 h period, were considered when several values were available during that period.

The indication for LT in patients with ALF was determined in accordance with the Clichy-Villejuif criteria[4] and/or King's College Hospital criteria.[5]

All patients were managed at the site of their heatstroke by a mobile medical team. Patients with a Glasgow score <7 were intubated and placed under mechanical ventilation. Their mean arterial pressure was maintained above 70–75 mmHg. In patients with systemic hemodynamic instability who did not respond to volume expansion, the adjunctive use of noradrenaline was considered. Continuous venovenous haemofiltration was used for renal replacement therapy. The external temperature of patients was lowered by cooling them or medication (paracetamol). All these measures were pursued following their admission to the ICU. Patients under mechanical ventilation were sedated, and all patients received an N-acetyl cysteine regimen.[6]

Multiple organ dysfunction or failure was defined using clinical, biological, electrical and ultrasound criteria.[7,8]

Pathology

The native livers of all 4 transplanted patients and liver biopsies from 3 patients who were not listed for LT were collected 2.6 days (range, 1.7–4) and 5 days (range, 2–5) after exertional heatstroke, respectively, and were available for histological analysis. All 7 cases were reviewed by 2 pathologists (ALB, CG) using a semi-quantitative assessment method as described in the supplementary information.

Statistical analysis

Continuous variables were reported as medians and 25th to 75th percentiles (Q1-Q3). Patients listed for emergency LT (super-urgent, SU) were compared with those not listed. Because the patient sample was small, the 2 groups were compared using non-parametric Wilcoxon or Kruskal-Wallis tests. Categorical variables were reported as percentages and compared using the χ^2 or Fisher's exact tests. A value of p <0.05 was considered significant.

Statistical analyses were performed using R Statistical Software version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria, 2015).

Results

Characteristics of the 24 patients with heatstroke

All 24 patients were male, with a median age of 27.5 years (25.0–37.6). All had previously been in good health and were athletes. Ten were career military personnel and 4 were completing their military service. Heatstroke occurred in all patients between April and October in very hot conditions following vigorous exercise (jogging, marathon, half-marathon, "iron man" race, training run or commando march), all those in races reached the finish line. The median distance travelled before the onset of heatstroke was 10 km (8–15).

The clinical and biological characteristics of the patients are provided (Table 1). Their median body temperature was 40.7 °C (40.0–41.4). All patients presented with incipient neurological signs: 6 with convulsive seizures then coma (25%); 14 (58%) with initial coma and 4 with confusion (17%). The median Glasgow score at the arrival of the mobile medical team was 7 (3–10). Twelve patients (50.0%) were placed under mechanical ventilation because of consciousness disorders. Nine patients (37.5%) presented with signs of mesenteric dysfunction that manifested itself in the form of diarrhoea. All patients received large quantities of intravenous fluids (glucose, physiological saline and/or Ringer's lactate solution). Six patients (25.0%) presented initially with collapse that was reversible after vascular filling with macromolecules (n = 2) and the administration of noradrenaline (n = 4).

Immediately after the heatstroke, the body temperature was lowered by external cooling using ice packs placed on

Table 1. Clinical and biological characteristics of patients immediately after the onset of heatstroke and following admission to the intensive care unit.

	Total (n = 24)	Patients listed for SU LT (n = 9)	Patients not listed for SU LT (n = 15)	*p* value
Age (years)	27.5 (25.0–37.6)	28.2 (26.2–37.3)	26.3 (24.9–37.0)	n.s.
Initial body temperature	40.7 (40.0–41.4)	41.0 (40.0–42.0)	40.0 (40.0–41.0)	n.s.
Glasgow score in the field	7 (3.00–10.25)	6 (3.00–7.00)	7 (4.00–12.50)	0.19
Heart rate in the field	150 (130.0–160.0)	155 (141.0–66.2)	140 (130.0–160.0)	n.s.
Systolic blood pressure (mmHg)	100.5 (80.0–121.2)	84.0 (75.0–120.0)	106.0 (90.0–117.5)	n.s.
Diastolic blood pressure (mmHg)	50 (40.00–64.25)	45 (40.00–60.00)	50 (44.50–64.50)	n.s.
Collapse (Yes)	25.0 (6)	44.4 (4)	13.3 (2)	0.15
Initial test (H0)				
PT (%)	70 (55.75–82.00)	69 (55.00–82.00)	71 (57.00–78.50)	n.s.
Total bilirubin (μmol/L)	14.0 (10.00–20.75)	12.5 (11.25–16.75)	16.5 (7.00–22.25)	n.s.
AST (IU/L)	57.4 (32.5–119.5)	65.0 (38.5–267.5)	51.0 (31.0–80.0)	n.s.
ALT (IU/L)	37.5 (23.75–74.50)	39.0 (34.00–78.00)	29.0 (23.00–52.00)	n.s.
Creatinine (μmol/L)	173.5 (157.2–181.8)	173.0 (156.2–193.2)	173.5 (158.2–180.8)	n.s.
Urea	7.3 (6.46–9.76)	7.6 (6.58–8.85)	7.3 (6.14–10.10)	n.s.
CPK (μmol/L)	526 (271–1,870)	476 (255.5–1,197)	526 (284–1,870)	n.s.
Troponin (IU/L)	0.81 (0.19–1.52)	2.40 (1.54–4.30)	0.35 (0.16–1.04)	0.055
Lipase (IU/L)	55 (31.50–75.25)	73 (51.50–131.50)	41 (31.00–72.50)	n.s.
Platelets (10^3/mm^3)	178.0 (126.5–211.5)	132.0 (112.0–178.5)	189.5 (143.2–216.5)	0.17
pH	7.32 (7.29–7.36)	7.29 (7.29–7.38)	7.32 (7.29–7.35)	n.s.
HCO_3^-	20.00 (18.10–21.75)	19.00 (17.25–21.50)	20.25 (18.85–21.25)	n.s.
Lactate (IU/L)	2.70 (2.30–4.10)	2.70 (2.23–3.08)	2.70 (2.55–4.80)	n.s.
SAPS II	29.0 (17.0–48.5)	60.0 (36.0–71.0)	23.5 (15.0–28.5)	0.008
Extrahepatic involvement after HE, % yes (n)*				
Cardiac involvement	41.7 (10)	55.6 (5)	33.3 (5)	n.s.
Pancreatic involvement	29.2 (7)	55.6 (5)	13.3 (2)	0.061
Muscle involvement	79.2 (19)	66.7 (6)	86.7 (13)	n.s.
Renal involvement	91.7 (22)	88.9 (8)	93.3 (14)	n.s.
Mesenteric injury	37.5 (9)	66.7 (6)	20.0 (3)	0.036
Neurological involvement	54.5 (12)	88.9 (8)	30.8 (4)	0.011
Organ support, % yes (n)*				
Renal dialysis	20.8 (5)	55.6 (5)	0 (0)	0.003
MARS	20.8 (5)	55.6 (5)	0 (0)	0.003
Haemodynamic support	20.8(5)	44.4 (4)	6.7 (1)	0.047
Mechanical ventilation	50.0 (12)	88.9 (8)	26.7 (4)	0.009

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphokinase; LT, liver transplantation; MARS, molecular adsorbent recirculating system; n.s., not significant; PT, prothrombin time; SAPS 2, Simplified Acute physiology Score 2; SU, super-urgent.
Comparisons of clinical and biological values on the day of heatstroke following admission for emergency care (Wilcoxon non-parametric test).
* The most severe value during the 24 h period

the vascular axes and by the intravenous infusion of refrigerated fluids. Five patients received paracetamol (between 1 g and 2 g in total). The median delay between the onset of heatstroke and transfer to a tertiary centre was 0 day (0–1).

After admission to the ICU unit, cooling was pursued and supplemented with a fan and a hypothermic blanket. The median body temperature measured at admission to the ICU had fallen to 38.7 °C (38.4–39.1). A brain scan was performed in 14 patients (58.5%) and the findings were normal. When performed, an analysis of the cerebrospinal fluid was normal (n = 7). Twenty-two patients (92%) presented with renal damage, 19 (79%) with rhabdomyolysis, 7 (29%) with biological pancreatitis, 10 (42%) with myocardial injury, 5 (21%) with haemodynamic instability, and 4 (17%) with acute respiratory distress syndrome. All developed sALI/ALF after their admission to hospital. The median SAPS 2 (Simplified Acute Physiology) score at admission to the ICU was 29 (17.0–48.5).

The median values at ICU admission with respect to PT, Factor V, international normalized ratio and total bilirubin were 70.5% (55.25–82.75), 75% (52.0–84.5), 1.2 (1.1–1.6) and 14 μmol/l (10.00–20.75), respectively.

Clinical outcomes

Candidates for LT

Nine (37.5%) of the 24 patients with heatstroke were listed for LT on a super-urgent basis. The demographic, clinical and biological characteristics of these patients at and after admission and listed or not for SU LT are shown in Table 1. At the time of heatstroke, the 2 groups of patients (listed or not for SU LT) were similar in terms of their demographic characteristics, Glasgow score, blood pressure, collapse and heart rate (Table 1). The median nadir PT value in the 15 non-listed patients was 35% (29.5–43.5). The median period elapsing between heatstroke and registration on the waiting list was 3 days (2–3). At the time of listing, 6 patients were placed on mechanical ventilation and sedated, 5 required haemodynamic support, 5 with renal failure received renal replacement therapy (continuous venovenous haemofiltration) and 5 were treated with albumin dialysis (GAMBRO®, Lund, Sweden). All 9 patients presented with signs of DIC (Table 2). Five of the 9 listed patients received fresh frozen plasma. The median values at the time of listing for SU LT with respect to PT, Factor V, bilirubin, alanine aminotransferase and creatinine were 9% (5–13), 12% (4–14), 90 μmol/l (65–119), 6,500 IU/L (5,200–10,000) and 155 μmol/L (104.8–321.8), respectively.

Table 2. Principal clinical and biological characteristics of patients registered for SU LT, whether they were transplanted or not.

	At the time of SU registration			At the time of LT (n = 4)
	All patients (n = 9)	Non–transplanted patients (n = 5)	Transplanted patients (n = 4)	
HE (yes)	9	5	4	4
MV	6	3 (60%)	3 (75%)	3 (75%)
Sedation	6	3 (60%)	3 (75%)	3 (75%)
Inotrope+	5 (55%)	3 (60%)	2 (50%)	1 (25%)
RRT	5 (55%)	4 (80%)	1 (25%)	–
MARS + RRT	5 (55 %)	3 (60%)	2 (50%)	2 (50%)
PT (%)	10 (5–12)	12 (12–13)*	6.5 (4–9.25)	7.5 (5–13.5)
TB (μmol/L)	97 (84–111)	102 (90–112)	81 (59.75–100.5)	95 (82.5–107.5)
AST (IU/L)	5,361 (4,494–10,077)	5,361 (4,540–5,986)	7,286 (4,368–12,596)	7,852 (5,718–15,353)
ALT (IU/L)	7,854 (6,394–10,969)	8,070 (6,394–10,969)	7,196 (5,880–9,476)	7,594.5 (5,512–12,460)
Creatinine (μmol/L)	168 (147–323)	168 (101–281)	238.5 (149.2–406.8)	178 (106–401)
CPK (μmol/L)	10,639 (4,116–65,318)	10,639 (4,658–51,551)	19,450 (4,116–106,683)	19,311 (4,470–17,7835)
Platelets (10^3/mm^3)	36 (33–47)	47 (39–51)	33 (30.75–34.5)	29.5 (26.5–42.5)
Fibrinogen (g/L)	0.79 (0.59–0.86)	0.84 (0.78–0.90)	0.65 (0.53–0.72)	0.55 (0.33–0.77)
Soluble complexes+,$	4	1	3	3
Delay between SU and EH (d)	3 (2–3)	3 (3–3)**	1.5 (1–2.25)	–
Delay between EH and LT (d)	–	–	–	3 (2.75–3.25)
Delay between SU and LT (d)	–	–	–	1 (1–1.25)
KCH criteria	8/9	4/5	4/4	4/4
Clichy–Villejuif criteria	6/9	3/5	3/4	3/4
Duration of stay in the ICU	17.3 (10.0–26.0)	10.0 (6.0–16.0)	33.6 (25.3–53.1)	–

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HE, hepatic encephalopathy; KCH criteria, King's College Hospital criteria; LT, liver transplantation; MARS, Molecular adsorbent recirculating system; MV, mechanical ventilation; PT, prothrombin time; RTT, renal replacement therapy; SU, super-urgent; TB, total bilirubin.
+presence of soluble complexes. $available in 4 patients. *p <0.07, (p value comparison using the Wilcoxon test between SU LT and SU non-LT patients). **p <0.40.

Between H0-24 (D1) and H96-120 (D5), PT levels were significantly lower among listed patients, while bilirubin was significantly higher after D2 (Fig. 2A, B). In the same patients after H0-24, the platelet counts were significantly lower, while aspartate and alanine aminotransferase values were significantly higher after H24-48 (data not shown).

Between H0-24 (D1) and H48-72 (D3), PT levels fell more (>70%) in listed patients than in those not listed; in the latter, the reduction was not only less marked, but a rise was seen between D2 and D3 (from −51% to + 73%) (data not shown).

Patients who were transplanted

Four of the 9 listed patients (44.5%) underwent LT, their principal clinical and biological characteristics are provided (Table 2). The median periods elapsing between the onset of heatstroke and registration for SU LT among transplanted and non-transplanted patients were 1.5 days (1.00–2.25) and 3 days (3–3), respectively (p = 0.040). At the time of SU registration, the median PT and platelet values were lower than those seen in non-transplanted patients (p <0.07, Wilcoxon non-parametric test) (Table 2). The median serum ammonia level at admission was 70 μmol/l (62–233) (normal <45). The median period elapsing between heatstroke and LT was 3 days (2.75–3.25). At the time of transplant surgery, 3 of the 4 patients were ventilated, 1 required haemodynamic support (noradrenaline), and 2 were under continuous veno-venous haemofiltration and receiving liver support (MARS®). Three of the 4 patients were administered fresh frozen plasma prior to transplantation. The median PT values at H24-36, H36-48 and H48-60 in transplanted patients (9%; 5% and 5%, respectively) were lower than those of SU-registered patients who were not transplanted (18%, 13% and 11%, respectively) (p <0.2) (Table S2 and Fig. 3A). At the time of LT, median total bilirubin, PT, Factor V, alanine aminotransferase and creatinine values were 84.5 μmol/L (range 66–118), 7.5% (range 5–17), 10% (range 1–15), 6,970 IU/L (range 5,003–15,752) and 401 μmol/L (range 178–457), respectively. The nadir PT value in non-transplanted patients was 11% (9–12) and rose from H60-72 in 2 patients, from H72-84 in 2 patients and from H84-96 in 1 patient. Transplanted patients presented with low bilirubin values (lower than 20 μmol/l) at admission, and then a marked elevation was seen at D3 (rising by more than 200%) (Fig. 3B).

Survival

The overall survival rate among patients presenting with heatstroke-related ALI/ALF was 96%. Survival rates without transplantation and after transplantation were 100% and 75%, respectively. One of the transplanted patients died at 11 months, 2 months after re-transplantation for chronic rejection. All patients not listed for SU LT recovered their normal liver function and were discharged from hospital, and none of them presented with any after-effects. The median ICU and hospital length of stay of patients not listed and listed for SU LT were 3.0 days (2.0–6.7) and 10.0 days (5.0–12.8), and 17.3 days (10.0–26.0) and 34.3 days (26.0–62.0), respectively.

Histological findings

A summary of the histopathological findings in explanted livers is provided (Table 3 and Fig. 4). The livers of the transplanted patients were not atrophic. The cut surface, when depicted, was generally yellowish and soft, suggesting steatosis. All native livers displayed a normal architecture without any portal fibrosis. The portal tracts contained a mild inflammatory infiltrate without significant periportal activity. The bile ducts were present, occasionally with non-destructive lymphocytic or neutrophilic cholangitis. There was a constant intraportal cholangiolar reaction with frequent acute neutrophilic cholangiolitis. Massive coagulation lobular necrosis was always observed in the centrilobular and mediolobular areas (zones 3 and 2), sparing only a few hepatocellular plates around the por-

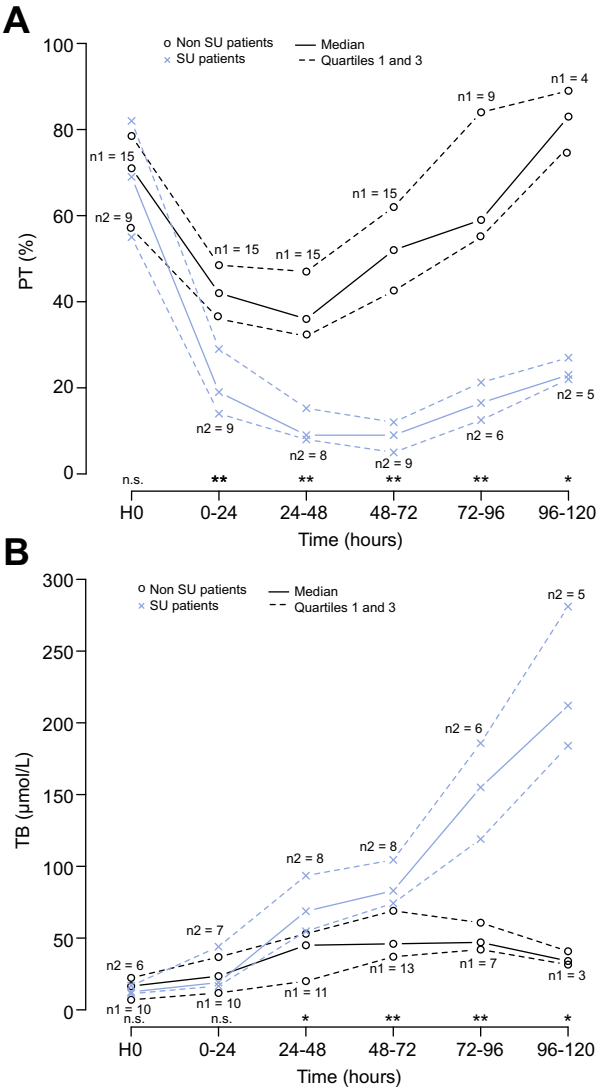

Fig. 2. Prothrombin time and total bilirubin as a function of patient status. (A) PT and (B) TB from day 1 to day 5 as a function of patient status (SU patients and non-SU patients). n1, number of non-SU patients; n2, number of SU patients. $^{*}p$ <0.05; $^{**}p$ <0.01 (p value of daily comparisons using the Wilcoxon test between SU and non-SU patients); n.s., not significant. PT, prothrombin time; SU, super-urgent, TB, total bilirubin.

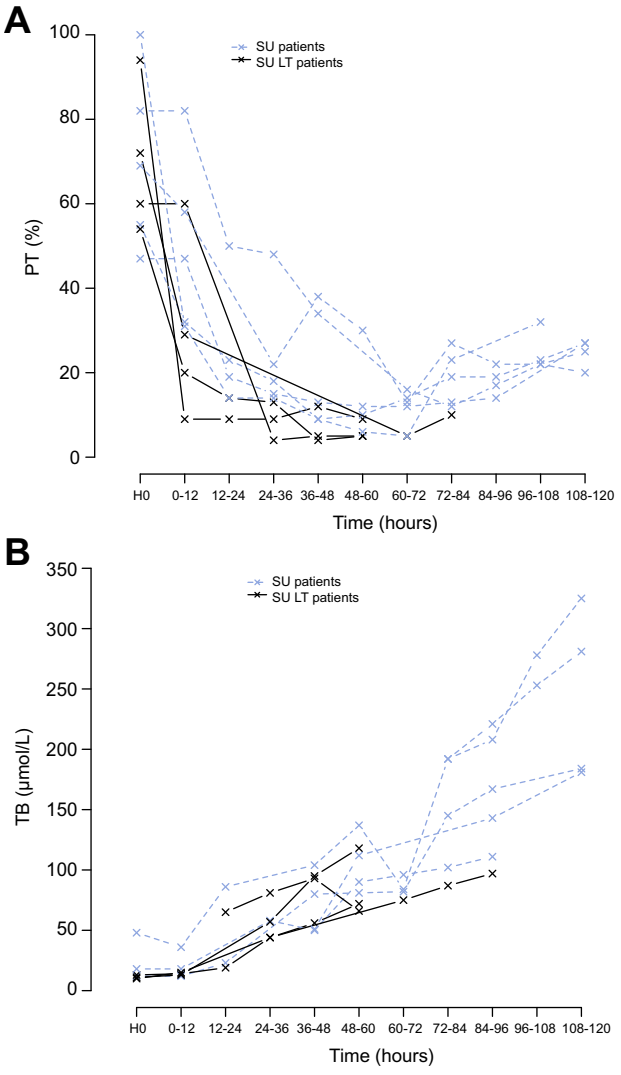

Fig. 3. Prothrombin time and total bilirubin in patients listed for LT as a function of patient status. (A) PT and (B) TB from day 1 to day 5 in patients listed for LT and as a function of patient status (transplanted and non-transplanted patients). PT, prothrombin time; SU, super-urgent, TB, total bilirubin; LT, liver transplantation.

tal tracts. Lobular necrosis affected 60% to 90% of the hepatic parenchymal surface. This hypoxic necrosis was accompanied by a moderate macrophage cleansing reaction. The remaining hepatocytes were frequently clarified and swollen. In 1 patient (n°4), a periportal ductular reaction was observed at the interface with the damaged hepatic parenchyma. Steatosis was present and involved 5% to 90% of hepatocytes, sometimes visible within the necrotic area. Steatosis was both macro- and microvacuolar. Mild lobular inflammation was seen in 3 of the 4 native livers (lymphocytes, sometimes with neutrophils). The mitotic count within the remaining hepatocytes was high (17 to 82 mitoses for 10 HPF) and these mitoses were highlighted by Ki-67 immunostaining. However, these mitotic figures always displayed a very peculiar aspect of chromosomal material dispersion giving them a mitonecrotic appearance.

The lesions observed in the 3 liver biopsies from non-transplanted patients (n = 3), were by contrast less severe. The portal tracts contained a mild inflammatory and cholangiolar reaction in only 1 case. The same patient displayed centrilobular coagulation necrosis affecting 15% of the hepatic parenchymal surface. Only sparse necrotic hepatocytes were visible in the 2 other cases. Hepatocytes were frequently clarified and swollen (in 25% to 80% of cases). Steatosis was present and involved 5% to 15% of hepatocytes. The mitotic count was less remarkable (1 to 11 mitoses for 10 HPF) but the mitotic figures had the same mitonecrotic appearance.

Discussion

One of the serious complications of heatstroke is the onset of multiple organ dysfunction or failure, which notably includes ALI or ALF. The spontaneous prognosis of exertional heatstroke-related ALF may be poor. If there is no improvement in liver function, LT may offer a therapeutic option. The KCH (non-paracetamol) and Clichy-Villejuif criteria appear to be poorly adapted to HE-related ALF.[4,5] One of the principal prog-

Table 3. Summary of pathological findings.

Patients	LT	Delay HE–Biopsy	Portal fibrosis	Portal inflammation	Cholangitis	Cholangiolar reaction	Steatosis Type	Steatosis %	Lobular necrosis topography	Lobular necrosis %	Hepatocellular clarification and swelling %	Lobular inflammation	Mitotic count (/10 HPF)	Cholestasis
N°1	Yes	1.7	0	Mild: Ly, N	+	+	MaV and MiV	10 (within necrosis)	Confluent, zones 2 and 3	85	5	Mild: Ly, N	19	0
N°2	Yes	2.3	0	Mild: Ly, N	+	+	MaV and MiV	5 (within & outside necrosis)	Confluent, zones 2 and 3	80	5	0	82	0
N°3	Yes	3	0	Mild: Ly, N	+	+	MaV and MiV	80 (within necrosis)	Confluent, zones 2 and 3	90	5	Mild: Ly	37	0
N°4	Yes	4	0	Mild: Ly, N	+	+	MaV and MiV	90 (within & outside necrosis)	Confluent, zones 2 and 3	60	20	Mild: Ly, N	17	+
N°5	No	5	0	0	0	0	MaV and MiV	15	Sparse	1%	30	Mild: Ly	1	0
N°6	No	5	0	Mild: Ly, N	0	+	MiV	5 (within & outside necrosis)	Confluent Zone 3 + sparse	15%	25	Moderate: Ly, N	4	0
N°7	No	2	0	0	0	0	MaV and MiV	5	Sparse	1%	80	Mild: Ly, N	11	+

HPF, high-power fields; Ly, lymphocytes; MaV, macrovesicular; MiV, microvesicular; N, neutrophils; n.a., not available.

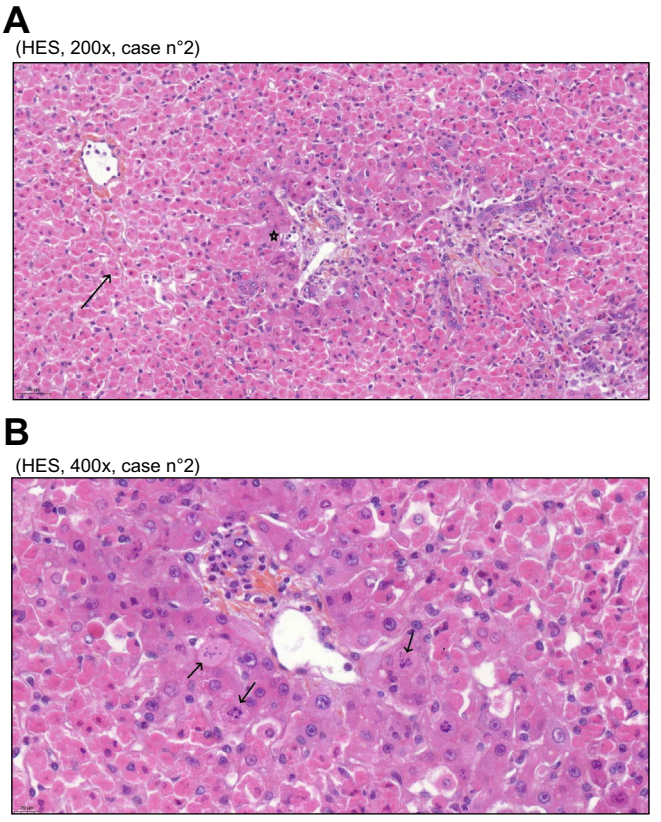

Fig. 4. Histological images of explanted liver. (A) (HES, 200×, patient n°2): massive coagulation lobular necrosis (zones 2 and 3, arrow), note the thin rim of hepatocytes around the portal tract (star), the absence of inflammatory cells within the necrosis and the cholangiolar portal reaction. (B) (HES, 400×, patient n°2): abortive mitoses around a portal tract (arrows). HES, haematoxylin eosin saffron. (This figure appears in colour on the web.)

nostic factors included in these criteria is hepatic encephalopathy, which together with initial and constant neurological dysfunction in the context of heatstroke may become superimposed and make it difficult to distinguish one from the other. The determination of arterial ammonia levels, and the monitoring of electrical activity by an electroencephalogram, may help to make a distinction between these 2 mechanisms.[9,10]. Furthermore, many of these patients require mechanical ventilation and sedation, which adds a further element of confusion. The distinction between ALI and ALF is therefore very unclear and the severity of liver failure may be overestimated. In our series, 12 patients were ventilated and sedated at admission, 6 at the time of registration on the transplant list and 3 at the time of LT. Thus, removal from the waiting list of 3 of the 6 listed patients coincided with their extubation.

A second element that may distort a decision concerning LT is the onset of DIC and/or fibrinolysis. These coagulation abnormalities develop as from the onset of heatstroke.[11] A normalisation of body temperature can inhibit fibrinolysis. However, DIC persists and may exacerbate the drop in prothrombin activity, which could lead to an emergency listing that is too early and incorrect.[12–14] This was probably the case in some of our patients who were listed for SU LT but not transplanted. Thus, above all, it is the evolving dynamics of the patient that will enable clinicians to make a decision about the appropriateness of LT.

This series of 24 patients with exertional heatstroke-related sALI/ALF highlighted several points. Firstly, 20/24 (83%) patients

presented with a severe form of liver injury, associated or not with the dysfunction of one or more other organs, which improved under medical therapy alone. Five of them, initially listed for LT, were subsequently removed from the list because of an improvement in their liver function. The median nadir PT of these patients was 12% (9–12). Survival without transplantation reached 100% and they all recovered normal liver function. Secondly, 4/24 (16.5%) patients were transplanted as an emergency. Their median PT value at the time of transplantation was <10%, 2 to 4 days after suffering from heatstroke, and at least 4 of their organs were dysfunctional. Their survival a year after LT reached 75%. Finally, the histological analysis of all native livers from transplanted patients revealed massive or sub-massive hepatocyte necrosis and inefficient mitoses.

Three evolving profiles could be seen among our patients who presented with severe liver injury related to heatstroke.

The first corresponded to patients with moderate liver injury who started to improve from D2; in most cases, no other organs were affected by the heatstroke. The liver function of these patients improved rapidly without transplantation being envisaged or discussed. This profile does not generally pose any decision-making problems.

The second profile corresponded to patients with liver injury that was more severe, persisted or continued to worsen significantly after D2 (PT <20%). Most of them were suffering from other organ dysfunctions and usually required organ support (haemodynamic, replacement renal therapy, mechanical ventilation). However, only 4 of them were transplanted. The other 5 improved under medical treatment. Analysis of the kinetics of prothrombin levels identified minimal but unquestionable differences between these 2 groups of patients, such as a persistence of PT <10% in the patients scheduled for transplantation until the surgical procedure, without any initiation of elevation, and the start of an elevation of prothrombin levels in patients who survived without transplantation, mainly between H60 and H72. So there was a possible chance of recovery without transplantation, even in the case of major hepatic failure, thus clearly underlining the need for any decision on transplantation to be considered carefully. Inversely, the lack of even a minimal improvement required the indication of LT in these patients, who also presented with the dysfunction or failure of other organs. In the literature, most patients presenting with exertional heatstroke-related ALF died; either they were not transplanted, or they were transplanted too late, after D4-D6.[15–21] Thus, the probability of an improvement without LT seems to diminish after that period and any decision regarding liver transplantation must be envisaged before that time point.

A third profile can be seen from the literature. These are patients who present with heatstroke involving the very rapid installation of non-reversible multiple organ failure that causes the patient's death within a very short time after its onset (within 48 h).[22] This was the case in 1 of the 2 patients excluded from our study, who died within 2 h of heatstroke from multiple organ failure.

Heatstroke-related histological lesions affecting the liver (swelling, clarification, vacuolization, steatosis and massive centrilobular necrosis) are probably the consequence of 2 separate mechanisms:[13,21,23–27] the direct effects of heat and hepatic hypoxia (hepatic hypoperfusion, cardiac failure). This liver damage, which in some cases may be extremely severe, gives rise to hepatocyte regeneration and cholangiolar reaction. Massive coagulation necrosis confirmed the severity of liver injury in our 4 transplanted patients and added a further retrospective argument in favour of transplanting these patients. Mitoses were numerous in all native livers and less frequent in the liver biopsies obtained from 3 other patients. They had an abortive appearance that has not been described until now in the relevant literature. The positivity of these figures for Ki-67 led us to think that they were mitoses rather than karyorrhexic nuclei. However, their appearance suggested that they would be inefficient in terms of hepatocellular regeneration. This impression was reinforced by the fact that the condition of none of the 4 transplanted patients improved spontaneously before surgery. These abortive mitoses, to our knowledge rarely observed in other types of hepatitis (infectious, autoimmune, toxic), might have been another adverse effect of heatstroke. A liver biopsy in patients with sALI and sALF caused by exertional heatstroke can provide interesting and reliable information on the extent of liver necrosis and the number of hepatocellular mitoses. However, only 3 patients were biopsied during our study, at a different time in the course of their disease, and none of these 3 patients ultimately required a LT. Moreover, none of the 4 patients transplanted during this study underwent a liver biopsy prior to liver surgery. We cannot therefore deduce from this study alone a histological threshold regarding the extent of necrosis or number of mitoses that might help to predict the outcomes of such patients. Therefore, we cannot yet recommend the systematic use of liver biopsies in patients with sALI and sALF as a helpful tool to select patients who are in need of LT.

Auxiliary LT may constitute an alternative to a conventional, whole liver transplant. If the native liver can subsequently regenerate, this has the advantage of enabling the withdrawal of immunosuppressive medications. However, the procedure is lengthier and the graft is smaller, which means that this technique should be reserved for carefully selected patients.[28–30] One of our transplanted patients appeared to be in a less serious state (not ventilated, no haemodynamic failure and low-grade hepatic encephalopathy); this option was discussed but not retained for logistical reasons. Subsequent histological findings on the native liver revealed the appearance of abortive mitoses (mitonecrotic aspect) which could have compromised regeneration of the native liver in the event of auxiliary LT.

The role of liver support in patients with severe hepatic dysfunction or ALF has not yet been clearly established. Several non-controlled studies have suggested the value of MARS in patients presenting with ALF.[31] However, the FULMAR controlled, randomised study comparing standard treatment *vs.* standard treatment plus MARS in patients with ALF awaiting LT was not able to confirm the usefulness of MARS in terms of survival at 6 months. The principal explanation was the short period elapsing between randomisation and the proposal of a compatible graft (16.2 h), which prevented evaluation of this system.[32] Despite the fact that this system has not proved its impact on survival, it nevertheless forms part of our therapeutic strategy when managing these patients. Thus, in our series, 5 of the 9 patients listed for SU transplantation received support of the MARS® type. Three of them improved and 2 underwent transplantation.

Although the present study was able to better comprehend patients with exertional heatstroke requiring LT (or potentially qualifying for transplantation in the future), it did have certain objective limitations.

The first and principal limitation of this study was that it was not possible to affirm that the transplanted patients might not

have improved without this surgery. The persistence of a median PT <10% a median of 3 days after heatstroke led us to opt for transplantation. However, this value cannot be retained as the only criterion for LT, particularly since 2 of the 5 patients listed but not transplanted had PT values below the 10% threshold before they started to rise and normalise. Thus, an improvement in liver function is possible, and a decision on LT must not be taken hastily. The severity of clinical status, marked by the presence of several organs affected by heatstroke and requiring different types of support, and the absence of any improvement in PT values were also key elements in the decision for LT. The massive hepatocyte necrosis observed retrospectively during histological studies of the native livers reinforced the approach adopted with respect to transplantation. However, further studies are necessary to validate these results.

The second limitation of this study mainly concerned the selection of patients. This was a retrospective, non-consecutive and probably non-exhaustive study where the impact of liver failure on prognosis could have been biased. To be as exhaustive as possible, all patients presenting with heatstroke-related sALI/ALF and listed for LT during the study period were screened via the Agence de la BioMedecine, and the principal tertiary centres dealing with this type of pathology were contacted.

The final limitation concerned the administration of fresh frozen plasma in 3 of the 4 patients listed for SU LT and subsequently transplanted, which overestimated their PT values. The routine use of fresh frozen plasma should be limited to specific situations, such as invasive procedure or active bleeding.[33,34]

However, at the time of SU registration, and despite this transfusion, the patients listed for transplant presented with more severe liver failure than those who were not transplanted, with a statistical tendency towards significance. This therefore reinforced our findings.

Conclusion

Heatstroke involving severe liver injury, associated or not with the dysfunction of other organs, improves in more than 80% of cases with medical therapy alone. An improvement in liver function is possible, even with low prothrombin values. LT only represents a rare alternative and achieves good survival rates after surgery. However, the decision to transplant should not be taken hastily and must take account of the kinetics of PT and of the patient's clinical status. The peculiar histological features observed on all explanted livers and the aspect of abortive mitoses in hepatocytes could be attributed to the effects of heatstroke and help explain the severity of transplanted patients. However, given that only a few patients were biopsied, we cannot yet recommend liver biopsy to help select the patients who would require LT.

Financial support

This study did not receive any external financial support.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

PI conceived and wrote the first draft of the paper. CG and ALB performed histological reviews of all the native livers. ALB wrote the section on histology. DM provided support with biostatistics. All authors reviewed and approved the final version, and made the decision to submit the manuscript for publication.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.11.024.

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