Short- and Long-term Outcomes of Heatstroke Following the 2003 Heat Wave in Lyon, France

Laurent Argaud, MD, PhD; Tristan Ferry, MD; Quoc-Hung Le, MD; Aurélia Marfisi, MD; Diana Ciorba, MD; Pierre Achache, MD; Roland Ducluzeau, MD; Dominique Robert, MD

Background: During August 2003, Europe sustained a severe heat wave that resulted in 14 800 heat-related deaths in France. Most of these excess deaths occurred in urban areas, where maximal temperatures broke all records. Heatstroke is the most severe form of heat-related illness. The clinical course of heatstroke in urban areas of temperate countries is poorly documented.

Methods: During the French heat wave (August 1-20, 2003), we conducted a prospective study in a university hospital located in Lyon, one of the largest metropolitan areas in France. We evaluated survival and functional outcome for 2 years and looked for factors influencing the prognosis.

Results: A total of 83 patients presented with heatstroke. The 28-day and 2-year mortality rates were 58% and 71%, respectively. Mortality was influenced as early as admission by the level of fever and the number of organ dysfunctions. Multivariate analysis revealed an independent contribution to mortality if patients came from an institution (hazard ratio [HR], 1.98; 95% confidence interval [CI], 1.05-3.71), used long-term antihypertensive medication (HR, 2.17; 95% CI, 1.17-4.05), or presented at admission with anuria (HR, 5.24; 95% CI, 2.29-12.03), coma (HR, 2.95; 95% CI, 1.26-6.91), or cardiovascular failure (HR, 2.43; 95% CI, 1.14-5.17). Most surviving patients exhibited a dramatic alteration of their functional status at 1 and 2 years.

Conclusions: Heatstroke is associated with poor outcomes in temperate urban areas. This could be explained at least in part by our lack of experience. Western temperate countries need to be more prepared for future heat waves.

Arch Intern Med. 2007;167(20):2177-2183

Author Affiliations: Pôle d'activité d'Urgence et Réanimation Médicales, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, and Lyon-Nord Medical School, University Claude Bernard Lyon I, Lyon, France (Drs Argaud, Ferry, Marfisi, Ciorba, Achache, Ducluzeau, and Robert); and Département de Biostatistiques, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France (Dr Le).

EUROPE SUSTAINED AN EXCEPTIONAL heat wave during the summer of 2003.[1,2] This heat wave began in early August, and extreme temperatures not observed in France since 1873 were recorded.[1] Lyon is a large city, located in the center of eastern France in an industrialized region, with 1 200 000 inhabitants in the metropolitan area. Temperatures were markedly higher than normal in Lyon during the national alert, which was provided by the Ministry of Health from August 1 until August 20.[3] French national reports revealed an excess mortality of 14 800 individuals during this period.[3]

See also page 2170

Heatstroke is the most severe heat-related illness and is defined by an elevated core body temperature above 40°C, associated with central nervous system abnormalities.[4] In contrast to exertional heatstroke related to strenuous exercise, classic heatstroke results only from exposure to a high environmental temperature and is very uncommon in Europe.[4,5] Much relevant clinical experience comes from tropical areas such as Saudi Arabia and from the United States during heat waves.[6-11] Associated epidemiological risk factors such as age, low socioeconomic conditions, chronic diseases, and drugs that impair thermoregulatory function have been described.[4,5,12-14] Previous clinical descriptions of heatstroke have revealed that the occurrence of multiorgan dysfunction leads to death and that sequelae among survivors are common.[11-15] Until 2003, the clinical course of heatstroke was unknown in Europe.

We hypothesized that initial features of heatstroke influence the prognosis, including long-term outcome. Thus, during the 2003 French heat wave, we initiated a prospective observational study in an urban population with a 2-year follow-up to identify factors associated with death.

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013

METHODS

The study was performed according to the Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996) and according to the European Guidelines of Good Clinical Practice (version 11, July 1990) and French laws.

PATIENTS

During the national alert (August 1-20, 2003), we enrolled all patients diagnosed as having heatstroke at admission to the emergency department of Edouard Herriot Hospital, a 1100-bed, inner-city university hospital in Lyon, France. This is the main hospital of this regional capital, which received 62% of the adult medical emergencies of the metropolitan area during the study period. As previously described, heatstroke was defined by a core temperature higher than 40°C, associated with central nervous system abnormalities such as delirium, convulsions, alteration of consciousness, or possible coma in the absence of any other evident cause for the fever or central nervous system dysfunction.[4] Recent history of exercise was ruled out.

STUDY DESIGN

During the study period, the daily number of medical emergency admissions was recorded. For all patients with heatstroke, demographic characteristics, living situation (at home or in an institution for the elderly such as a long-stay ward or retirement home), functional status (adapted from the Knaus et al classification[16]), medical history (cardiovascular, neurological, psychiatric, respiratory, and neoplastic), severity of the underlying illness (McCabe and Jackson scale[17]), and long-term use of medications (such as antihypertensive and psychotropic agents) were recorded at admission. Standard clinical features were registered, and biological data were assessed at admission. Organ dysfunctions (respiratory, cardiovascular, renal, neurological, hepatic, or hematological) were assessed in accordance with the Fagon et al classification.[18] Coma was defined as a Glasgow coma score of 8 or lower. Disseminated intravascular coagulation was defined as described elsewhere.[19] According to our clinical practices, classic intensive care unit (ICU) admission criteria (ie, invasive mechanical ventilation or ≥2 organ dysfunctions) were used. To cope with this medical crisis, dying patients and those with another rapidly fatal disease were not admitted to the ICU. Within the first 24 hours after admission, the Simplified Acute Physiology Score II[20] and therapy were recorded. External cooling was defined as the application of cold packs of ice and/or cold water to the skin. Meteorological data were provided by Météo France (Centre Départemental du Rhône, Bron, France).

In-hospital, day 28, and 2-year outcomes were assessed. In addition, the functional status and living situation of survivors were evaluated at 1 and 2 years. For hospital survivors, patients or their family were contacted and interviewed by telephone. If contact could not be made, tracking was attempted through health care providers or acquaintances identified in the medical record.

STATISTICAL ANALYSIS

Baseline characteristics of the study patients were reported in number and percentage or mean±SD, as appropriate. Comparisons of both characteristics at admission and therapeutic medications according to the day-28 outcomes of patients were performed using the unpaired *t* test for continuous variables and a 2-sided χ^2 test or Fisher exact test for categorical variables, as appropriate. Long-term health evaluations of surviving patients between preadmission and both 1- and 2-year outcomes were compared by means of a paired 2-sided χ^2 test for the living situation and a linear mixed model for functional limitation status.

Survival curves were generated by means of Kaplan-Meier estimates, and differences were compared by use of the log-rank test. Continuous variables, such as temperature, were transformed into dichotomous variables for log-rank tests.

The independent contribution to mortality by parameters possibly influencing the 2-year outcome was tested by a multivariate Cox proportional hazard model, using time to death as the dependent variable. Independent variables were selected for their statistical significance on univariate analysis. Moreover, we chose only pertinent clinical variables that were easy for the physician to identify on admission. Thus, 6 independent variables of interest were retained: origin of admission, long-term use of antihypertensive medication, body temperature, cardiovascular failure, anuria, and coma. In addition, we introduced age and sex in the model to avoid retaining confounding factors related to these 2 major demographic covariates.

Statistical calculations were performed using MedCalc software version 7.4.3.0 (Medcalc, Mariakerke, Belgium) and S-Plus version 6.0 (Insightful Software, Seattle, Washington). $P<.05$ was considered statistically significant.

For sodium, potassium, and bicarbonate, the conversion from milliequivalents per liter to millimoles per liter is a 1-to-1 conversion. To convert creatinine and urea nitrogen to millimoles per liter, multiply by 88.4 and 0.357, respectively. To convert arterial oxygen pressure to kilopascals, multiply by 0.133. To convert alanine aminotransferase to microkatals per liter, multiply by 0.0167. For thrombocytes, the conversion from 10^3/μL to 10^9/L is a 1-to-1 conversion. To convert fibrinogen to micromoles per liter, multiply by 0.0294. To convert C-reactive protein to nanomoles per liter, multiply by 9.524.

RESULTS

DEMOGRAPHIC AND EPIDEMIOLOGIC FINDINGS

During the study period, 83 patients presented with heatstroke among the 1827 emergency admissions (5%). Most of the admissions (73 patients [88%]) occurred from August 3 to August 13, 2003,when the maximum daytime and minimum nighttime temperatures were above 35°C and 20°C, respectively (**Figure 1**). The maximal incidence of heatstroke (14 of 87 medical emergency admissions [16%]) occurred on August 13, the hottest day in Lyon. Days later, 8 patients were admitted while only the nighttime minimum temperature remained elevated. Demographic characteristics of patients with heatstroke are summarized in **Table 1**. Seventy patients (84%) were elderly (age >70 years), 29 (41%) lived in institutions, and 48 (69%) had strong to severe functional limitation according to the Knaus et al classification. Twenty-seven patients (33%) were 85 years old or older. Among all patients, 80 (96%) had at least 1 coexisting medical condition, and 63 (76%) were being treated with an antihypertensive drug (mainly diuretics) and/or a neurotropic medication (mainly tranquilizers).

CLINICAL AND BIOLOGICAL FEATURES OF HEATSTROKE

Clinical findings are presented in **Table 2**. Thirty-nine patients (47%) had a temperature of 41°C or higher, 47 (57%)

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013

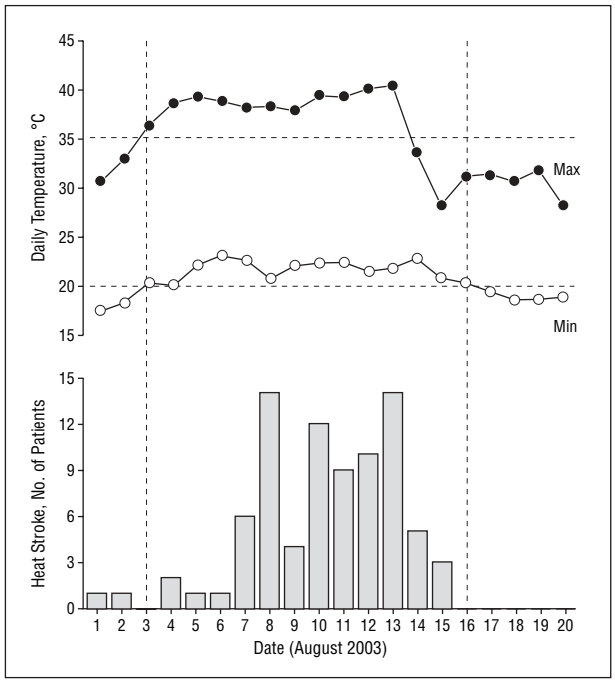

Figure 1. Relation between admissions for heatstroke and daily temperature. Admissions for heatstroke at the emergency department (bar graph) increased dramatically 24 hours after the heat wave, worsening on August 3, 2003, with maximal (Max) and minimal (Min) daily temperatures greater than 35°C and 20°C, respectively (line chart). The incidence of heatstroke decreased immediately when Max daily temperatures returned to more normal values, from August 14, 2003.

Table 1. Characteristics of the 83 Patients With Heatstroke[a]

Characteristic	All Patients (n = 83)
Age, mean ± SD (range), y	79.6 ± 9.9 (50-99)
Sex	
Male	35 (42.2)
Female	48 (57.8)
Origin of admission	
Home	52 (62.7)
Institution for the elderly	31 (37.3)
Functional status (Knaus et al classification[16])	
No limitation	2 (2.4)
Moderate limitation	31 (37.3)
Strong limitation	35 (42.2)
Severe limitation	15 (18.1)
Life expectancy (McCabe and Jackson scale[17])	
None or nonfatal underlying disease	60 (72.3)
Ultimately fatal disease (death ≤5 y)	20 (24.1)
Rapidly fatal disease (death ≤1 y)	3 (3.6)
Coexisting medical conditions	
Cardiovascular disease	59 (71.1)
Neurological disease	40 (48.2)
Psychiatric disease	39 (47.0)
Respiratory disease	14 (16.9)
Neoplasm	11 (13.3)
Long-term medications	
Antihypertensive agents	46 (55.4)
Diuretics	25 (30.1)
ACE inhibitors and AR blockers	19 (22.9)
Other	25 (30.1)
Psychotropic agents	44 (53.0)
Phenothiazines	14 (16.9)
Benzodiazepines	29 (34.9)
Antidepressant drugs	26 (31.3)

Abbreviations: ACE, angiotensin-converting enzyme; AR, angiotensin II receptor.

[a] Data are given as number (percentage) of patients unless otherwise specified.

presented with coma, 36 (43%) were in shock, and 19 (23%) had anuria. Associated with the constant neurological dysfunction, 53 patients (66%) had at least 1 additional organ failure. Even if standard biological data assessed at admission averaged normal values, many patients had ionic disorders. Hyponatremia (sodium level, 126±6 mEq/L) was detected in 40 patients (48%); hypernatremia (sodium level, 152±5 mEq/L) in 21 (25%); hypokalemia (potassium level, 3.0±0.3 mEq/L) in 14 (17%); and hyperkalemia (potassium level, 6.2±1.6 mEq/L) in 28 (34%). The mean values of both creatinine and urea nitrogen were slightly elevated: 1.76±0.93 mg/dL and 39.50±23.53 mg/dL, respectively. When blood gases and pH were tested (45 patients), a respiratory alkalosis was found in 23 patients (51%) and a metabolic acidosis in 12 patients (27%). The mean ±SD arterial oxygen pressure was 75±39 mm Hg. The level of creatinine kinase was elevated over twice the normal limit in 45 patients (54%). Electrocardiography revealed ischemic abnormalities in 30 patients (36%); these were confirmed by an enhanced troponin I level in 20 patients (29%). Twenty-five patients (40%) displayed hepatic cytolysis (alanine aminotransferase enzyme level, 268±528 U/L) without cholestasis. Thrombopenia (thrombocyte level, 95±37 $\times 10^3/\mu L$) and low prothrombin index (53%±16%) were detected in 23 (28%) and 30 patients (36%), respectively. No patient had hypofibrinogenemia (fibrinogen level, 460 ± 150 mg/dL). C-reactive protein level was slightly elevated (30±58 mg/L) in the total population.

Of the 83 patients, 36 (43%) presented with indications for ICU admission. Sixteen patients (19%) received critical care in the emergency department but developed rapid unfavorable outcome before their ICU admission. Only 1 patient could not be admitted to the ICU owing to lack of beds. The 19 remaining patients (23%) were admitted to the ICU.

The mean hospital stay was 24±39 days (median, 3 days; range, 1-199 days). Fifty-five patients (65%) died in the hospital; only 35 patients (42%) were alive at day 28. Demographic characteristics (ie, age and sex) were not significantly different between survivors and nonsurvivors at day 28 (Table 2). However, nonsurviving patients more often came from an institution for the elderly (24 of 48 nonsurvivors vs 7 of 35 survivors; $P=.005$) and had more long-term use of antihypertensive (33 of 48 nonsurvivors vs 13 of 35 survivors; $P=.004$) or phenothiazine medications (12 of 48 nonsurvivors vs 2 of 35 survivors; $P=.02$). As described in Table 2, initial clinical features such as temperature or hemodynamics were more altered in the nonsurvivor group. In this group, patients exhibited more respiratory, cardiovascular, and/or renal dysfunctions associated with neurological disorders. Moreover, 39 nonsurviving patients (81%) presented with coma vs only 8 (23%) among the survivors ($P<.001$). The 19 patients with anuria (23%) were also in the nonsurvivor group ($P<.001$ vs survivors). Mean

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013

Table 2. Clinical Severity of Patient Illness at Admission (Day 0) for All Patients and According to Day 28 Outcome[a]

Variable	All Patients (n = 83)	Survivors (n = 35)	Nonsurvivors (n = 48)	*P* Value, Survivors vs Nonsurvivors
Clinical features				
Age, y	79.6 ± 9.9 (50-99)	78.9 ± 9.4 (50-95)	80.1 ± 10.3 (53-99)	.57
Sex, male	35 (42.2)	14 (40.0)	21 (43.8)	.73
Body temperature, °C	41.1 ± 1.3 (40.0-43.3)	40.7 ± 1.1 (40.0-43.3)	41.3 ± 1.3 (40.0-43.3)	.02
Heart rate, beats/min	89 ± 49 (0-200)	100 ± 23 (60-150)	80 ± 60 (0-200)	.06
Systolic blood pressure, mm Hg	94 ± 61 (0-200)	128 ± 36 (50-189)	69 ± 64 (0-200)	<.001
Respiratory rate, breaths/min	26 ± 10 (12-49)	22 ± 7 (12-40)	29 ± 10 (12-49)	<.001
Daily diuresis, mL	837 ± 661 (0-2000)	1357 ± 392 (600-2000)	364 ± 473 (0-1500)	<.001
Glasgow Coma Score	8.2 ± 4.4 (3-14)	11.3 ± 3.5 (3-14)	5.9 ± 3.5 (3-14)	<.001
Convulsions	3 (3.6)	0	3 (6.3)	.13
Rhabdomyolysis	29 (34.9)	16 (45.7)	13 (27.1)	.10
Myocardial cytolysis	20 (24.1)	6 (17.1)	14 (29.2)	.16
Disseminated intravascular coagulation	7 (8.4)	1 (2.9)	6 (12.5)	.29
SAPS II	61.2 ± 24.7 (21-108)	43.1 ± 16.2 (21-88)	74.5 ± 21.1 (31-108)	<.001
Organ dysfunctions				
Type				
Respiratory	39 (47.0)	11 (31.4)	28 (58.3)	.01
Cardiovascular	36 (43.4)	4 (11.4)	32 (66.7)	<.001
Renal	29 (34.9)	2 (5.7)	27 (56.3)	<.001
Neurological	83 (100)	35 (100)	48 (100)	NA
Hepatic	2 (2.4)	1 (2.9)	1 (2.1)	>.99
Hematological	3 (3.6)	0	3 (6.3)	.36
Number				
1	30 (36.1)	23 (65.7)	7 (14.6)	
2	18 (21.7)	8 (22.8)	10 (20.8)	
3	17 (20.5)	3 (8.6)	14 (29.2)	<.001
4	16 (19.3)	1 (2.9)	15 (31.2)	
5	2 (2.4)	0	2 (4.2)	
Mean ± SD	2.3 ± 1.2	1.5 ± 0.8	2.9 ± 1.1	<.001

Abbreviations: NA, not applicable; SAPS II, Simplified Acute Physiology Score II.
[a]Data are given as number (percentage) of patients or mean ± SD (range) value, unless otherwise specified.

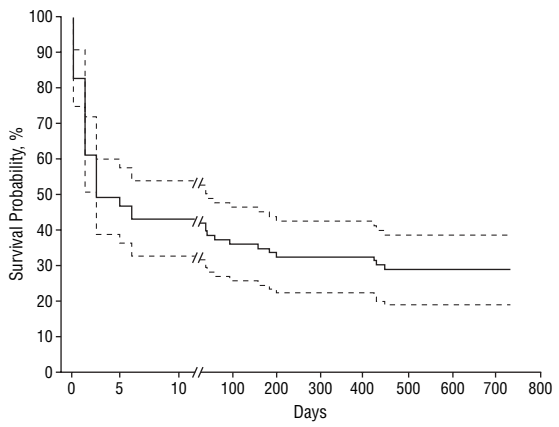

Figure 2. Two-year survival curve of the 83 patients with heatstroke. The dashed lines indicate 95% confidence intervals.

bicarbonate value was significantly lower in nonsurvivors: 18.4±4.3 mEq/L vs 21.4±3.3 mEq/L (*P*=.001).

In addition to the symptomatic care related to their organ dysfunctions (including, as required, mechanical ventilation, vasoactive and/or inotropic agents, and volume expansion), all patients received liquid infusion (2.5±1.0 L during the 24 first hours), and 79 (95%) received antipyretic agents (acetaminophen). External cooling was performed on only 41 patients (49%). No differences in heatstroke-related therapy, such as cooling, antipyretic agents, or liquid infusion were observed between survivors and nonsurvivors.

LONG-TERM OUTCOME

The global survival curve is shown in **Figure 2**. Twenty-seven patients (33%) were alive at 1 year and 24 (29%) at 2 years, with none lost to follow-up. Kaplan-Meier curves comparing survival with interesting factors influencing outcome are presented in **Figure 3**. The multivariate Cox proportional hazard model revealed an independent contribution to mortality if patients came from an institution, had long-term use of antihypertensive medication, or presented at admission with cardiovascular failure, anuria, or coma (**Table 3**).

Functional outcome at 1-year revealed that 6 patients (22%), who lived at home before the heat wave, required care in institutions for elderly patients because of severe functional limitations. Similarly, a dramatic alteration in functional status was recorded in most surviving patients (**Table 4**). At 2 years, similar alteration of the functional outcome according to the Knaus et al classification was observed in surviving patients (*P*=.002 vs baseline).

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013

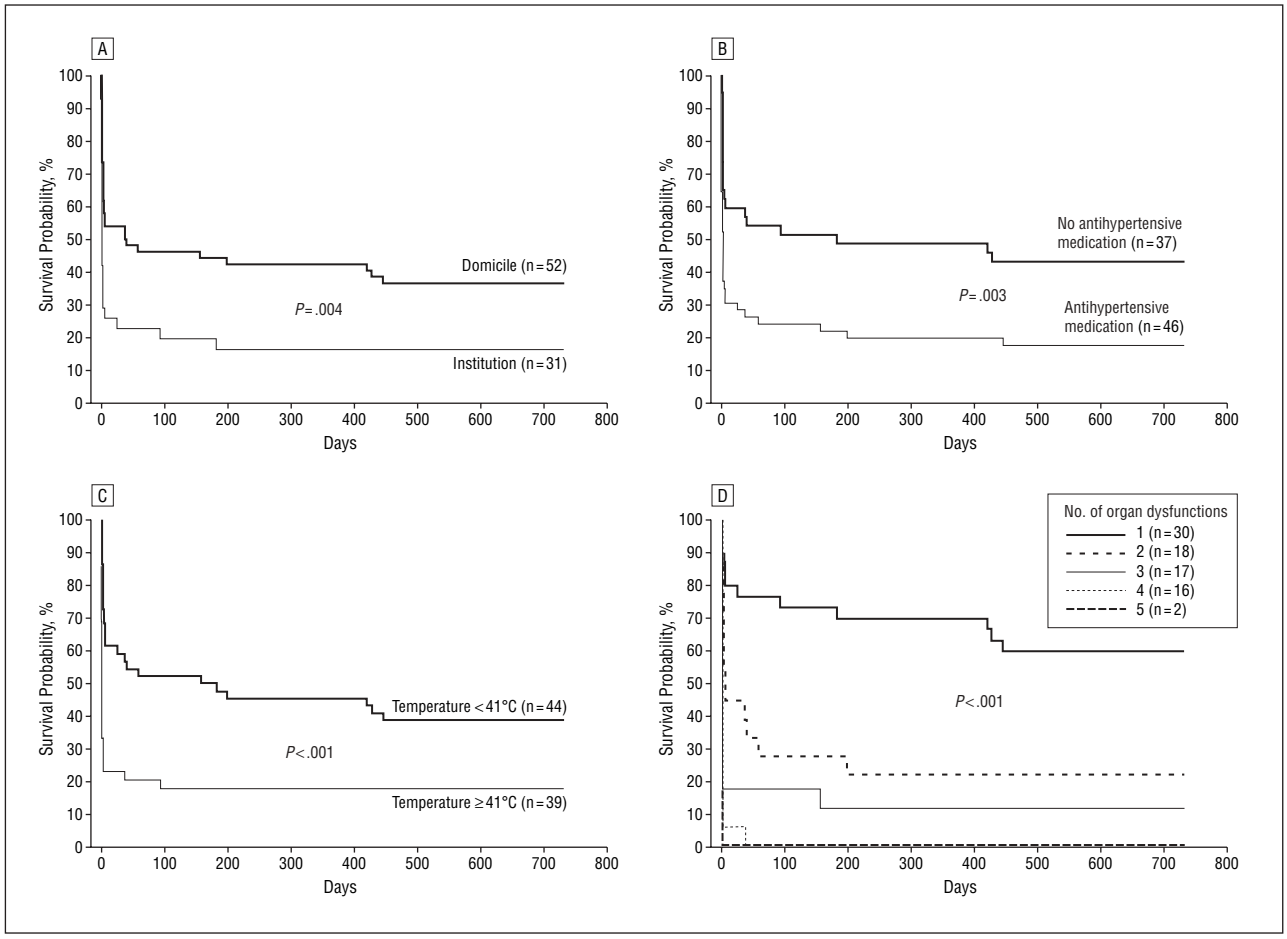

Figure 3. Kaplan-Meier plots showing representative factors influencing probability of survival. A, Origin of admission. Living in an institution before admission for heatstroke was associated with a significantly higher rate of mortality ($P<.004$ by the log-rank test). B, Long-term use of antihypertensive medication. The absence of an antihypertensive agent was associated with a significantly higher rate of survival ($P=.003$ by the log-rank test). C, Temperature. Patients with severe hyperthermia (≥41°C) had significantly decreased survival ($P<.001$ by the log-rank test). D, Number of organ dysfunctions. The greater the number of organ dysfunctions at the onset of heatstroke, the more survival decreased ($P<.001$ by the log-rank test).

COMMENT

This long-term follow-up study conducted during the exceptional 2003 French heat wave describes singular clinical characteristics of heatstroke in urban temperate areas, including initial factors associated with death.

The 2003 French heat wave broke all records during 9 consecutive days, exceeding the maximal temperatures observed in previous heat waves during the 20th century.[1-3] This heat wave was associated with an exceptionally increased mortality in the whole of France, and especially in 7 metropolitan cities, including Lyon.[3,21] Indeed, a well-known climatic effect called an urban heat island, which exposes inhabitants to extreme temperature at night, is thought to be at least partly responsible for this excess mortality.[22,23] This phenomenon is characterized by the modification of meteorological parameters induced by anthropogenic heat production and limited airflow.[22]

Sustained heat waves are known to be responsible for life-threatening illness, including heatstroke.[4,6,13,14,24] Some patients are particularly vulnerable to heat. In our study, the mean age of approximately 80 years was older than in previous reports, and most of our patients had a cardiovascular, neurological, or psychiatric disease associated with long-term use of antihypertensive or neurotropic agents. The risk for heat-related illness among elderly people, persons with chronic illness, and those with long-term use of these medications has been described.[4,12-14,22]

The clinical course of heatstroke in urban areas of temperate countries is poorly documented. Previously, only

Table 3. Hazard Ratio of Death According to the Multivariate Cox Proportional Hazard Model

Factor	Hazard Ratio (95% Confidence Interval)	*P* Value
Age	1.02 (0.99-1.06)	.19
Sex	1.31 (0.74-2.34)	.36
Origin of admission	1.98 (1.05-3.71)	.03
Long-term use of antihypertensive medication	2.17 (1.17-4.05)	.01
Body temperature	0.97 (0.76-1.26)	.84
Cardiovascular failure	2.43 (1.14-5.17)	.02
Anuria	5.24 (2.29-12.03)	<.001
Coma	2.95 (1.26-6.91)	.01

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013

Table 4. Functional Outcome in the 27 Patients Alive at 1 Year[a]

Variable	Before Admission	At 1 Year	*P* Value
Living situation			
Home	22 (81.5)	16 (59.3)	.01
Institution for the elderly	5 (18.5)	11 (40.7)	
Functional status (Knaus et al classification[16])[b]			
A, No limitation	1 (3.7)	0	<.001
B, Moderate limitation	10 (37.0)	6 (22.2)	
C, Strong limitation	15 (55.6)	10 (37.0)	
D, Severe limitation	1 (3.7)	11 (40.7)	

[a] Data are given as number (percentage) of patients unless otherwise specified.

[b] A, "No limitation" indicates no daily activity limitation; the patient was in good health. B, "Moderate limitation" indicates mild to moderate limitation of activity because of a chronic medical problem; the patient saw a physician monthly and had long-term use of medication; or the patient was mildly limited in his or her activity level because of illness. C, "Strong limitation" indicates chronic disease causing serious but not incapacitating restriction of activity; the patient's usual daily activity was limited; or symptoms occurred with mild exertion. D, "Severe limitation" indicates severe restriction of activity due to disease; the patient was bedridden or institutionalized owing to illness; or the patient was unable to work because of illness.

the 1995 Chicago, Illinois, heat wave study reported 58 suspected patients with near-fatal heatstroke admitted to the ICU, with a 21% in-hospital mortality.[11] In that survey, the diagnosis of heatstroke was supported even though most of the patients (57%) had evidence of infection on admission. We report herein, at the same latitude and in a similar urban area, the largest study yet of pure classic heatstroke to our knowledge (omitting cases with infection-related fever or strenuous exercise), with a high in-hospital mortality rate of 65%. The severity of this heat-related illness was in agreement with the death toll observed in France during the 2003 heat wave, which represents more than 20 times the excess deaths reported during the 1995 Chicago heat wave.[1,3,11]

The present study reveals that clinical features at admission influence the prognosis of heatstroke. First, in agreement with previous reports, our results indicate that the level of fever (when ≥41°C at admission) may influence the severity of the disease.[4,24] However, the main insight provided by this survey is to identify initial organ dysfunction as a factor influencing the outcome. It has been known for decades that organ impairment (ie, dysfunction or failure) can affect the length of ICU stay and the morbidity and mortality of critically ill patients.[25] Previous reports described coma and shock as the most frequent organ dysfunction in severe heatstroke.[5,11,15] Nevertheless, the literature lacks information regarding which organ dysfunction occurred at the onset of heatstroke and what the effects of various organ dysfunctions are on the outcome. A state of coma at admission, observed in our study in 57% of cases, was independently associated with a high risk of death. The central nervous system, which is particularly vulnerable to direct thermal effects, could also be injured by disruption of the blood-brain barrier and brain edema.[26,27] Hemodynamic failure was equally observed in approximately half of our patients, with an independent contribution to outcome. The pathophysiologic mechanisms of this organ dysfunction is complex and mainly related to an inability to increase cardiac output in a context of heat-related dehydration and vasoplegia enhanced by a proinflammatory response.[4,5] This cardiovascular dysfunction could be exacerbated in patients with preexisting treated cardiovascular disease.[4] Indeed, in our study, long-term use of antihypertensive medication was also an independent factor associated with death. In the same way, the occurrence of renal dysfunction was higher in nonsurvivors, with anuria being the main independent factor influencing the prognosis. The occurrence of both hematological failure and disseminated intravascular coagulation was rare in our study. However, activation of the coagulation cascade associated with vascular endothelial activation may be an important pathologic mechanism in heatstroke.[4,9] Nevertheless, it appears that these mechanisms, including disseminated intravascular coagulation and hemorrhagic complications, tend to be more frequent in exertional than in classic heatstroke.[9,27] Respiratory dysfunction in our patients was frequent. It was mainly characterized by hypoxia and ineffective respiratory compensation of metabolic acidosis. However, in approximately half of the cases, it was also explained by mechanical ventilation required for coma. Whatever the nature of the organ impairments may be, their number directly influences the outcome. Our study demonstrates that the occurrence of at least 1 organ failure associated with neurological dysfunction induced by heatstroke was associated with a significantly lower probability of survival.

In addition to being responsible for high early mortality, heatstroke was also associated with a dramatic alteration in the functional status of survivors. Most of our patients exhibited significantly decreased function that restricted discharge to home. More than one-third of survivors became bedridden and required referral to a long-stay ward or retirement home. Previously, only the 1995 Chicago heat wave study, which is often cited for comparison, has spotlighted functional impairment at discharge persisting at 1 year.[11]

Early recognition and prompt treatment are recommended to reduce the high mortality of classic heatstroke.[4,5] Along with support of organ system function, aggressive cooling, whatever the method used, is one of the main therapeutic objectives during heatstroke.[4,5] A recent report suggested that air conditioning can also improve the outcome by accelerating the transfer of heat from the skin to the environment without compromising the flow of blood to the skin.[24] In our hospital, which lacks air conditioning, only roughly half of the patients received cooling therapy. Furthermore, during the 2003 heat wave in France, as in other temperate countries, physicians lacked experience with these specific treatments. For this reason, we did not assess whether the method of cooling was sufficiently rapid and aggressive. Taken together, this could explain, at least in part, the high initial mortality we observed.[28]

Preventive measures are the cornerstone of the treatment of heatstroke.[4,5] This point is crucial because climate models suggest that both the frequency and inten-

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013

sity of heat waves are almost certain to increase in temperate areas.[2] As a consequence, the incidence of heatstroke and heat-related deaths will increase in European countries, especially in urban areas where the urban heat island effect enhances thermal stress.[2,22,28,29] Many risk factors for heat-related illness have already been described.[4,12-14] Our study identified 2 factors that independently contribute to mortality in patients with heatstroke: coming from an institution for elderly patients and long-term use of antihypertensive medication. In this population, it appears essential to prevent heat stress during heat waves by optimizing, as much as possible, the use of antihypertensive medication and by facilitating heat acclimatization, ideally provided by air conditioning. Drinking additional water, reducing the level of physical activity during warmer times of the day, and increasing the amount of time spent in air-conditioned environments are also recommended.[4,5]

In conclusion, this study illustrates the clinical details of classic heatstroke in temperate countries and identifies early factors influencing short- and long-term prognosis. Our findings emphasizes the necessity for future improvements in outcome by means of enhancing prehospital prevention and providing rapid and aggressive therapy to patients at high risk of death at admission.

Accepted for Publication: June 13, 2007.
Published Online: August 13, 2007 (doi:10.1001/archinte.167.20.ioi70147).
Correspondence: Laurent Argaud, MD, PhD, Service de Réanimation Médicale, Groupement Hospitalier Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon CEDEX 03, France (laurent.argaud@chu-lyon.fr).
Author Contributions: Drs Argaud and Ferry had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data synthesis. *Study concept and design*: Argaud, Robert, and Ducluzeau. *Acquisition of data*: Argaud, Marfisi, Ciorba, and Achache. *Analysis and interpretation of data*: Argaud, Ferry, and Le. *Drafting of the manuscript*: Argaud, Ferry, and Robert. *Critical revision of the manuscript for important intellectual content*: Argaud, Ferry, Le, Marfisi, Ciorba, Achache, Ducluzeau, and Robert. *Statistical analysis*: Argaud and Le. *Administrative, technical, and material support*: Argaud. *Study supervision*: Argaud and Robert.
Financial Disclosure: None reported.
Funding/Support: All authors are supported by the Hospices Civils de Lyon. No specific funding was received for this study. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Additional Contributions: Jerome Etienne, MD, PhD, provided helpful comments regarding the manuscript.

REFERENCES

1. Bouchama A. The 2003 European heat wave. *Intensive Care Med.* 2004;30(1):1-3.
2. Meehl GA, Tebaldi C. More intense, more frequent, and longer lasting heat waves in the 21st century. *Science.* 2004;305(5686):994-997.
3. Hemon D, Jougla E. Surmortalité liée à la canicule d'août 2003: rapport d'étape: estimation de la surmortalité et principales caractéristiques épidémiologiques. September 25, 2003. Paris, France: Institut national de la santé et de la recherche médicale (INSERM). http://www.sante.gouv.fr/htm/actu/surmort_canicule/rapport_complet.pdf. Accessed January 2, 2007.
4. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med.* 2002;346(25):1978-1988.
5. Grogan H, Hopkins PM. Heat stroke: implications for critical care and anaesthesia. *Br J Anaesth.* 2002;88(5):700-707.
6. Khogali M, Weiner JS. Heat stroke: report on 18 cases. *Lancet.* 1980;2(8189):276-278.
7. Khogali M. Epidemiology of heat illnesses during the Makkah Pilgrimages in Saudi Arabia. *Int J Epidemiol.* 1983;12(3):267-273.
8. Bouchama A. Heatstroke: a new look at an ancient disease. *Intensive Care Med.* 1995;21(8):623-625.
9. Bouchama A, Hammami MM, Haq A, Jackson J, Al-Sedairy S. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med.* 1996;24(7):1173-1178.
10. Bouchama A, De Vol EB. Acid-base alterations in heatstroke. *Intensive Care Med.* 2001;27(4):680-685.
11. Dematte JE, O'Mara K, Buescher J, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med.* 1998;129(3):173-181.
12. Kilbourne EM, Choi K, Jones TS, Thacker SB. Risk factors for heatstroke: a case-control study. *JAMA.* 1982;247(24):3332-3336.
13. Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med.* 1996;335(2):84-90.
14. Centers for Disease Control and Prevention. Heat-related illnesses and deaths—United States, 1994-1995. *MMWR Morb Mortal Wkly Rep.* 1995;44(25):465-468.
15. Varghese GM, John G, Thomas K, Abraham OC, Mathai D. Predictors of multi-organ dysfunction in heatstroke. *Emerg Med J.* 2005;22(3):185-187.
16. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med.* 1981;9(8):591-597.
17. McCabe WR, Jackson GG. Gram-negative bacteremia: etiology and ecology. *Arch Intern Med.* 1962;110(6):847-855.
18. Fagon JY, Chastre J, Novara A, Medioni P, Gibert C. Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. *Intensive Care Med.* 1993;19(3):137-144.
19. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost.* 2001;86(5):1327-1330.
20. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;270(24):2957-2963.
21. Vandentorren S, Suzan F, Medina S, et al. Mortality in 13 French cities during the August 2003 heat wave. *Am J Public Health.* 2004;94(9):1518-1520.
22. Koppe C, Kovats S, Jendritzky G, et al. Heat waves: risks and responses. Copenhagen, Denmark: World Health Organization; 2004. Health and Global Environmental Change, Series No. 2. http://www.euro.who.int/document/e82629.pdf. Accessed January 2, 2007.
23. Haines A, Kovats RS, Campbell-Lendrum D, Corvalan C. Climate change and human health: impacts, vulnerability, and mitigation. *Lancet.* 2006;367(9528):2101-2109.
24. Misset B, De Jonghe B, Bastuji-Garin S, et al. Mortality of patients with heatstroke admitted to intensive care units during the 2003 heat wave in France: a national multiple-center risk-factor study. *Crit Care Med.* 2006;34(4):1087-1092.
25. Vincent JL, de Mendonca A, Cantraine F, et al; Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med.* 1998;26(11):1793-1800.
26. Sharma HS, Hoopes PJ. Hyperthermia induced pathophysiology of the central nervous system. *Int J Hyperthermia.* 2003;19(3):325-354.
27. Yaqub B, Al Deeb S. Heat strokes: aetiopathogenesis, neurological characteristics, treatment and outcome. *J Neurol Sci.* 1998;156(2):144-151.
28. Bouchama A. Heatstroke: facing the threat. *Crit Care Med.* 2006;34(4):1272-1273.
29. Dessai S. Heat stress and mortality in Lisbon, part II: an assessment of the potential impacts of climate change. *Int J Biometeorol.* 2003;48(1):37-44.

©2007 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/20/2013