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Impact of body temperature on in-hospital and long-term mortality in patients with acute heart failure

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Abstract

Objectives: Body temperature (BT) was shown to have impact on outcome in several medical conditions. This study investigated the prognostic impact of BT in patients with acute heart failure (HF).

Design and patients: The B-type natriuretic peptide for Acute Shortness of breath EvaLuation (BASEL) study prospectively enrolled 452 consecutive patients presenting with acute dyspnoea to the emergency department. Among these, 170 patients had a final discharge diagnosis of acute HF and a documented BT on presentation. The primary endpoint was cardiovascular mortality during long-term follow-up. Morbidity was documented as secondary endpoint.

Results: BT on presentation was 37.2 ºC (SD 0.9) and ranged from 34.8–40.4 °C. Patients were divided into quartiles of BT. Initial morbidity as reflected by intensive care unit admission rate was significantly higher among patients in the highest quartile (38% versus 13% in the first quartile, p <0.05). Length of stay in hospital was significantly increased by 2.7 days per one degree rise in BT. A total of 64 cardiovascular deaths occurred (38%). Kaplan-Meier analysis showed no apparent difference in long-term cardiovascular mortality among quartiles of BT. Cardiovascular mortality rate was 47% in the first (<36.6 ºC), 26% in the second (36.7–37.2 ºC), 44% in the third (37.3–37.8 ºC) and 35% in the fourth quartile (37.9 ºC; P = 0.31) at 720 days. In addition, Cox regression analysis adjusted for age and sex showed no association between BT and either in-hospital (HR 0.59, 95% CI 0.26–1.35; P = 0.21) or long-term cardiovascular mortality (HR 0.91, 95% CI 0.67–1.24; P = 0.55).

Conclusion: In patients with acute HF, BT on presentation is not associated with in-hospital or long-term cardiovascular mortality, but is associated with short-term morbidity. However, it is important to stress that our findings relate to central BT and do not negate the undisputed value of assessing peripheral BT, which reflects peripheral hypoperfusion.

Key words: body temperature; heart failure; prognosis

Introduction

Body temperature (BT) is an important vital sign. It must be maintained within a certain range to support the chemical and metabolic functions sustaining life. Thermal dysregulation can affect several organ systems including cardiovascular, respiratory, neurological, renal, musculoskeletal, haematological and gastrointestinal [1]. The prognostic impact of BT has been investigated in several medical conditions [2–8]. While spontaneous hypo- or hyperthermia seem to have detrimental effects on the state of health [2–4], there might be a benefit of therapeutically-induced hypothermia in patients with cardiac arrest or stroke [9, 10].

In acutely ill patients, BT as a vital sign needs to be determined immediately during the initial assessment. Hypothermia and hyperthermia are one of four factors that define the systemic inflammatory response syndrome (SIRS) and sepsis [11]. Thus, BT is a useful marker to identify potential life-threatening clinical situations that require rapid intervention.

Heart failure (HF) is a major public health concern and associated with considerable morbidity and mortality. Community-based surveys show that 30–40% of patients die within a year of diagnosis and 60–70% die within five years, most

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from worsening heart failure or suddenly [12]. In contrast to chronic HF, risk-stratification and initial management is poorly validated in patients presenting with acute HF. Hence, current ACC/AHA and ESC initiatives call for more research targeting acute HF [13, 14]. It is unknown as to whether BT has an impact on outcome in patients with acute HF. Therefore, the aim of our study was to analyze the prognostic significance of BT on presentation to the emergency department in consecutive patients with acute HF.

Methods

Subjects

This study examined the prognostic impact of BT in 170 patients with acute HF enrolled in the B-type natriuretic peptide for Acute Shortness of breath EvaLuation (BASEL) study [15]. The BASEL study was a prospective, randomized, controlled study conducted in the emergency department of the University Hospital of Basel, Switzerland. A total of 452 patients with acute shortness of breath were enrolled consecutively from May 2001 to April 2002. Acute HF was judged to be the final diagnosis in 217 patients by applying the current guidelines for the diagnosis of HF [13, 14]. The final discharge diagnosis of acute HF was based on clinical presentation and the investigations carried out upon admission to hospital. It was determined by an internal medicine specialist not involved in the emergency department care. The diagnosis was finalised on the basis of all available medical records pertaining to the individual patients. These included response to therapy and autopsy data of those patients dying in hospital. Of these, BT was documented on admission to hospital in 170 patients (78%). The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

Measurement of BT

Patients underwent an initial clinical assessment that included clinical history, physical examination, electrocardiography, pulse oximetry, blood tests and chest radiography.

BT was obtained by infrared tympanic measurement without need for direct contact with the tympanic membrane (FirstTemp Genius, Sherwood Medical Company, UK). It is a method for the determination of central BT and is standard practice in most institutions [16]. Furthermore, it is a simple, rapid, and convenient method of BT measurement and has a high acceptability to patients.

Endpoints

The primary endpoint of this analysis was cardiovascular mortality. Cardiovascular death was defined as any death for which there was no clearly documented non-cardiac cause [17]. Patients were contacted at specified intervals by telephone interview performed by a single trained researcher. Referring physicians were contacted in case of uncertainties regarding health status. The administrative databases of the respective hometowns were assessed to ascertain the vital status of those patients who could not be contacted by telephone. Secondary endpoints were length of stay in hospital and admission to the intensive care unit.

Statistical analysis

We examined the association between BT on presentation to the emergency department and cardiovascular mortality. The statistical analyses were performed with the use of the SPSS/PC software package (version 15.0, SPSS). Results were expressed as number, frequency and point estimate (95% confidence intervals) and mean with standard deviation or median (interquartile range, IQR) as indicated. Cox proportional hazard models were used to evaluate the association of BT with in-hospital and long-term cardiovascular mortality. Analyses were adjusted for age and sex. Since low values of body temperature might also be predictive of adverse health outcomes we considered two additional models for the influence of body temperature, i.e. one with the absolute difference of BT from the reference value of 37 °C [18] as predictor variable and the other with body temperature divided into the four quartile categories. For the analysis of length of hospital stay, values from patients who died whilst still in the hospital were excluded. The influence of age on outcome measures was controlled using a linear spline with knots placed at the quartiles of age. The statistical significance of factors involving more than two levels was assessed using likelihood ratio tests.

Survival probabilities were estimated with the Kaplan-Meier method. A P value of less than 0.05 was considered to indicate statistical significance. A sensitivity analysis was also done using all cause instead of cardiovascular mortality.

Results

The analysis comprised 170 patients with acute HF on presentation to the emergency department. Clinical and demographic characteristics of patients in which BT was obtained and those patients excluded due to missing BT are displayed in table 1. With the exception of a higher ICU admission rate in patients in whom BT was not available, patients with and without BT available were comparable. The mean age of the included patients was 76 years (SD 11), and 42% of patients were female. The vast majority (87%) of patients were in NYHA class III and IV, left ventricular ejection fraction was 43% (SD 16%). Among those patients with acute HF, six patients (3.5%) were diagnosed with concomitant lower respiratory tract infection and three patients

Table 1

Variable	BT available (n = 170)	BT not available (n = 47)
Baseline characteristics		
Age, years	76 (SD 11)	71 (SD 12)
Male, %	58	55
Dyspnoea		
NYHA I, %	1	0
NYHA II, %	12	11
NYHA III, %	55	60
NYHA IV, %	31	30
Heart rate, bpm	96 (SD 25)	103 (SD 33)
Systolic BP, mm Hg	146 (SD 30)	148 (SD 38)
Diastolic BP, mm Hg	88 (SD 19)	87 (SD 26)
Respiratory rate, pm	22 [18–30]	20 [15–32]
Oxygen saturation, %	95 [89–98]	92 [84–98]
Medical history		
Coronary artery disease, %	69	77
Hypertension, %	63	66
COLD, %	25	21
Diabetes mellitus, %	34	21
Renal insufficiency, %	39	38
Medication on presentation		
Diuretics, %	65	53
Betablockers, %	31	43
ACE-inhibitors/ARB, %	51	38
Nitrates, %	21	19
Inhalative betamimetics, %	11	9
Inhalative corticosteroids, %	7	6
Systemic corticosteroids	9	4
Physical examination		
Rales, %	58	68
Wheezing, %	14	13
Oedema, %	50	34
Elevated JVP, %	22	23
Hepato-jugular reflux, %	17	13
Laboratory parameters		
BNP, pg/ml	813 [370–1300]	855 [535–1300]
Creatinine, µmol/L	130 (SD 50)	142 (SD 110)
Creatinine clearance *, ml/min/1.73 m^2	47 [37–61]	51 [35–68]
C-reactive protein, mg/L	14 [5–39]	10 [3–38]
Leucocytes, 10^9/L	9.80 [7.18–13.04]	10.58 [8.02–15.22]
Neutrophils, %	76 (SD 11)	74 (SD 14)
Echocardiography		
LVEDD, mm	53 (SD 9)	55 (SD 10)
LVEF, %	43 (SD 16)	34 (SD 16)
Endpoints		
Cardiovascular mortality		
In-hospital, %	5	13
Long term, %	38	45
Admission to ICU, %	22	43
Length of stay, days	11 [6–18]	10 [3–25]

* calculated by the abbreviated MDRD formula [27]

(1.8%) had concomitant exacerbation of COPD or asthma. The mean BT was 37.2 ºC (SD 0.9) and ranged from 34.8–40.4 ºC. Patients were stratified into quartiles of BT: 1) <36.6, 2) 36.7–37.2, 3) 37.3–37.8 and 4) 37.9 ºC. Baseline characteristics including vital status, symptoms, clinical signs and medication were comparable among groups. However, as expected, patients in the highest BT quartile had more extensive systemic inflammation. This was shown by higher values for respiratory rate, C-reactive protein levels and the percentage of neutrophils. Initial morbidity as reflected by the necessity for admission to the intensive care unit (ICU) was significantly higher among patients in the highest quartile of BT. Initial morbidity as reflected by intensive care unit admission rate was significantly higher among patients in the highest quartile (38% versus 13% in the first quartile, p <0.05). The reason for increased ICU admission rate in febrile acute heart failure patients was organ dysfunction. 62% of patients in the highest quartile of BT admitted to the ICU had hypoxic respiratory failure and 69% met the SIRS criteria. Severity of heart failure as quantified by the BNP level was comparable in all quartiles. Length of stay in hospital was significantly increased by 2.7 days per one degree rise in BT (0.7–4.7, P = 0.01). Figure 2 shows the association between length of stay and BT for patients who died in hospital of cardiovascular causes and patients surviving hospital stay. In-hospital cardiovascular mortality was comparable among groups.

Median time to last patient contact or patient death was 679 days. A total of 64 patients died of cardiovascular causes (38%), 12 patients died of other causes. Kaplan-Meier analysis showed no apparent difference in long-term cardiovascular mortality among quartiles (figure 1). Cardiovascular mortality rate was 47% in the first (<36.6 ºC), 26% in the second (36.7–37.2 ºC), 44% in the third (37.3–37.8 ºC) and 35% in the fourth quartile (>37.9 ºC; P = 0.31) at 720 days.

In addition, in multivariate model adjusted for age and sex, BT as continuous variable, quartiles of BT and absolute difference from normal BT had no significant impact on in-hospital and long-term cardiovascular mortality (table 2). The impact of BT on all-cause in-hospital (HR 0.74, 95% CI 0.40–1.36; P = 0.33)or long-term mortality (HR 1.02, 95% CI 0.78–1.34; P = 0.86) was also not significant.

Discussion

This study evaluated the prognostic impact of BT in patients with acute HF on presentation to the emergency department. We report three major findings. Firstly patients with higher BT had more extensive systemic inflammation as, for example, shown by higher values for C-reactive protein and percent of neutrophils. Secondly acute HF patients with higher BT had increased morbidity as reflected by a higher need for intensive care and increase in length of stay in hospital. However, severity of heart failure as quantified by the BNP level was comparable in all quartiles, suggesting that concomitant disorder or merely the additional oxygen consumption in febrile patients were the underlying causes for increased ICU admission rate. Thirdly in this cohort of unselected consecutive patients with acute HF, BT did not predict short-term or long-term cardiovascular mortality. This important finding is consistent irrespective of whether BT was investigated as a categorical (quartiles), a continuous variable or as the absolute difference of normal body temperature.

Our results complement and extend the findings of some earlier pilot studies on this topic. Casscells et al. suggested that hypothermia, defined as BT 35.3 °C, is a bedside predictor of imminent death in HF patients [19]. In-hospital mortality was 40% in patients with BT 35.3 °C as compared to 14% in patients with BT <35.3 °C. In agreement with this observation, lower BT was reported to predict worse outcome during the first year after initial hospitalization in HF patients [20]. Mortality was 45.3% in patients with BT <36 °C compared to 35.7% in patients with BT 36 °C. Unfortunately, these studies had several limitations which at least in part may explain the different results to our study. First of all BT was not collected using uniform methods, whereas infrared tympanic measurement was used uniformly in all patients investigated in our study. This is of great importance, because temperature varies with different methods of measurement. Tympanic measurement has high correlation with pulmonary artery temperature. In contrast, oral and axillary measurement results in lower values with deviation up to –0.7 °C from core temperature [21]. Furthermore infrared tympanic measurement shows the lowest variability between patients, whereas oral and axillary measurement are highly variable (SD 0.6 °C) [21]. This may explain the distinctly lower values of mean BT of these studies compared to our and other study populations of HF patients [22, 23]. In addition, a further important explanation for the differences in distribution of BT might be the inclusion of highly selected patients in prior studies: Casscells et al. have excluded patients with comorbidities potentially confounding BT, including sepsis, acute stroke, thyroid disease, hepatic failure, ethanol intoxication and environmental factors [19]. Nallamothu et al. included only patients with an age of greater than 65 years. It is known that persons of older age are at higher risk for hypothermia [20]. Their cohorts are therefore only partly representative of real life HF patients presenting to the emergency department. Thus conclusions drawn from these populations concerning the prognostic impact of BT do not seem to apply to unselected consecutive patients. A second limitation of prior studies is the retrospective analysis of charts whereas we analyzed prospectively enrolled patients. There was a trend towards a lower mortality in euthermic patients in our study (P = 0.13), when considering the second quartile of body temperature as euthermic (36.7–37.2 °C). Additional studies will have to confirm or rebut whether acute heart failure patients with normal body temperature have a favourable outcome.

BT obtained from infrared tympanic measurement, as demonstrated in our study, seems not to predict outcome in HF patients. Ear-based temperature approximately reflects the central BT. Our data should in no way question the

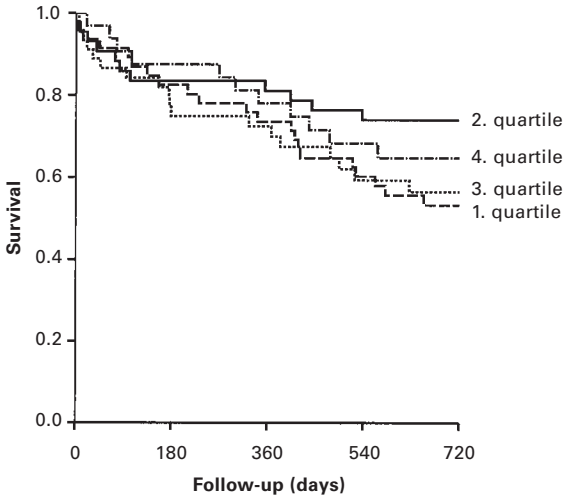

Figure 1
Survival analysis of 170 patients with acute heart failure stratified by quartiles of body temperature (1. quartile 36.6 °C, 2. quartile 36.7–37.2 °C, 3. quartile 37.3–37.8 °C and 4. quartile >37.9 °C).

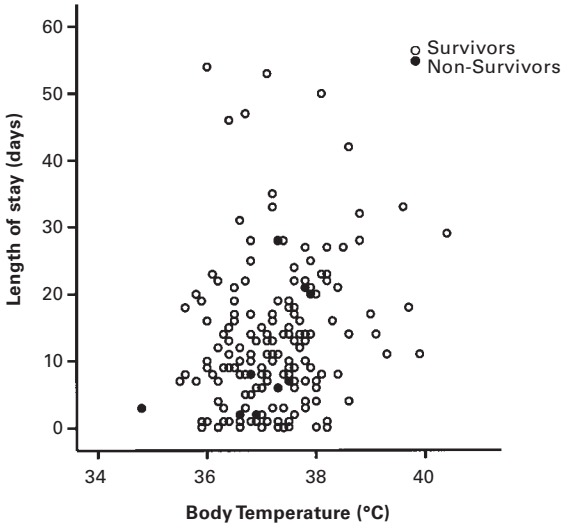

Figure 2
Scatterplot of length of stay against BT, black points indicating patients who died in hospital of cardiovascular causes and white points indicating patients surviving hospital stay.

Table 2

Multivariate cox regression analysis for in-hospital and long-term cardiovascular mortality with BT entered as a continuous variable (BTc), quartiles of BT (BTq1–4; 1.quartile 36.6 °C, 2. quartile 36.7–37.2 °C, 3. quartile 37.3–37.8 °C and 4.quartile 37.9 °C) and absolute difference from normal BT (BT-n) entered into the model, each variable adjusted for age and sex.

Variable	Hazard ratio (confidence interval) in-hospital	p value	Hazard ratio (confidence interval) long-term	p value
BTc	0.59 (0.26–1.35)	0.21	0.91 (0.67–1.24)	0.55
BTq1	1		1	
BTq2	0.97 (0.13–7.2)		0.53 (0.26–1.10)	
BTq3	2.3 (0.38–14.5)	0.51	0.83 (0.43–1.61)	0.33
BTq4	0.43 (0.04–5.1)		0.68 (0.33–1.39)	
BT-n	0.61 (0.17–2.2)	0.46	1.32 (0.86–2.0)	0.20

Demography and clinical characteristics of 170 patients with acute heart failure
BP, blood pressure; COLD, chronic obstructive lung disease; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; JVP, jugular venous pressure; BNP, B-type natriuretic peptide; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction). Results are given as %, mean (SD, standard deviation), or median [interquartile range]

undisputable relevance of peripheral temperature assessment for patient management. "Cold extremities", reflecting forward failure with peripheral hypoperfusion, are associated with increased mortality [24]. Patients with the combination of cold extremities and signs of congestion have a significantly worse outcome as compared to patients with warm extremities without signs of congestion ($p < 0.001$). They had a 2.48 fold higher risk for mortality or urgent heart transplantation ($p = 0.003$) during the first year. On this background it is questionable whether a central measure of BT, as utilized in our and previous studies, is the correct method to assess the risk profile in HF patients. Maybe a quantitative estimation of peripheral temperature, reflecting the degree of perfusion and vascular resistance, would be more meaningful. Further studies are needed to compare the effect of different sites of temperature measurement in relation to prognosis.

A central measurement of BT, for example by infrared tympanic determination, is especially sensitive for detecting high temperature [25]. However, high BT did not predict outcome in our analysis. For the prediction of outcome in HF, other quantitative markers of inflammation, such as C-reactive protein, seem to be preferable [26].

This study has four strengths. First of all we analyzed unselected consecutive patients presenting with acute HF. Therefore our study population reflects real life HF patients. Secondly, we documented morbidity as well as cardiovascular mortality. Thirdly, our study included long-term follow-up. Fourthly, we uniformly used infrared ear thermometry for BT measurement, whereas previous studies included a mixture of methods. Since BT strongly varies with different methods, it is of great importance to select only one method for the prediction of outcome. Several limitations should be kept in mind. Firstly, BT was not available in 47 patients. This might have introduced some selection bias. However, as shown in table 1, patients with and without BT measurement were comparable in nearly all baseline variables. Secondly, the power of our study is limited and cannot rule out a weak association between body temperature and mortality.

In conclusion, although patients with acute HF and BT in the highest quartile display higher morbidity as compared to the other BT quartiles, central BT measured on presentation does not predict long-term cardiovascular mortality. Studies with focus on the quantification of peripheral hypoperfusion by measuring skin temperature of extremities might reveal more useful information.

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