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Is there an association between body temperature and serum lactate levels in hip fracture patients?

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ABSTRACT

INTRODUCTION Hyperlactataemia is associated with adverse outcomes in trauma cases. It is thought to be the result of anaerobic respiration during hypoperfusion. This produces much less energy than complete aerobic glycolysis. Low body temperature in the injured patient carries an equally poor prognosis. Significant amounts of energy are expended in maintaining euthermia. Consequently, there may be a link between lactate levels and dysthermia. Hyperlactataemia may be indicative of inefficient energy production and therefore insufficient energy to maintain euthermia. Alternatively, significant amounts of available oxygen may be sequestered in thermoregulation, resulting in anaerobic respiration and lactate production.

Our study investigated whether there is an association between lactate levels and admission body temperature in hip fracture patients. Furthermore, it looked at whether there is a difference in the mean lactate levels between hip fracture patients with low (<36.5°C), normal (36.5–37.5°C) and high (>37.5°C) body temperature on admission, and for patients who have low body temperature, whether there is a progressive rise in serum lactate levels as body temperature falls.

METHODS The admission temperature and serum lactate of 1,162 patients presenting with hip fracture were recorded. Patients were divided into the euthermic (body temperature 36.5–37.5°C), the pyrexial (>37.5°C) and those with low body temperature (<36.5°C). Admission lactate and body temperature were compared.

RESULTS There was a significant difference in age between the three body temperature groups (p=0.007). The pyrexial cohort was younger than the low body temperature group (mean: 78 vs 82 years). Those with low body temperature had a higher mean lactate level than the euthermic (2.2mmol/l vs 2.0mmol/l, p=0.03). However, there was no progressive rise in serum lactate level as admission temperature fell.

CONCLUSIONS The findings suggest that in hip fracture patients, the body attempts initially to maintain euthermia, incurring an oxygen debt. This would explain the difference in lactate level between the low body temperature and euthermic cohorts. The fact that there is no correlation with the degree of temperature depression and lactate levels indicates that the body does not fuel thermohomeostasis indefinitely with oxygen. Instead, in part, it abandons thermoregulatory mechanisms. Consequently, in this population, active rewarming may be indicated rather than depending on patients' own thermogenic ability.

KEYWORDS
Hip fracture – Body temperature – Lactate – Mortality

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Hypothermia and hyperlactataemia form two-thirds of the deadly triad.[1] This reflects the fact that both are associated with a very high mortality in the context of trauma cases. With regard to lactate, Odom *et al* reported admission lactate to be a potent predictor of mortality, independently of a host of confounders.[2] A lactate level of >4mmol/l increased the odds of death by a factor of 3.8, compared with those with a lactate level of <2.5mol/l. This was in spite of adjustment for age, injury severity score (ISS), Glasgow coma scale (GCS) score, heart rate and blood pressure.

Maintaining core temperature is equally critical for survival. In 1987 Jurkovich *et al* observed a 100% mortality rate for major trauma patients with a body temperature of <32°C, irrespective of shock, fluid resuscitation or ISS.[3] A retrospective analysis of 1.1 million patients in the American National Trauma Data Bank found a 60% mortality rate for those with an admission temperature of <32°C and a 25% mortality rate for those under 35°C.[4] This was in stark contrast to a mortality rate of only 3% for those whose body temperature was greater than 35°C. The same

research group found that adjusting for confounders, hypothermia was an independent predictor of mortality (odds ratio: 1.5, 95% confidence interval: 1.4–1.7).

Up to 53% of total energy expenditure is sequestered in homeothermy.[5] In postoperative patients, reductions in core temperature of 0.3°C and 1.2°C have been found to result in 7% and 92% increases in oxygen consumption respectively.[6] This betrays the critical importance and metabolic expense involved in maintaining body temperature in the recognised euthermic band of 36.5–37.5°C.[7] This temperature optimises enzymatic and biomolecular functions. Low body temperature thus impacts adversely on every cellular process. This explains the high mortality engendered by this condition, in conjunction with the trauma.[8]

The mechanisms by which hyperlactataemia is associated with high mortality are less clear. There may be a relationship between lactate level and low body temperature. Elevated serum lactate results from anaerobic respiration, when oxygen demand outstrips supply. In these conditions, the glucose molecule undergoes incomplete metabolism. The glycolytic pathway is truncated at the level of pyruvate. This is then converted to lactate.

The process is inefficient and generates much less energy than complete aerobic respiration. Thirty molecules of adenosine triphosphate (ATP) are generated by complete aerobic catabolism of glucose. Only two molecules result in anaerobic respiration, truncated at the level of pyruvate.[9] This energy deficit may render it impossible to maintain euthermia. Low body temperature may therefore reflect thermoregulatory failure due to insufficient energy secondary to a lack of oxygen or metabolite. Seekamp *et al* observed ATP depletion in trauma patients with hypothermia and concluded that low body temperature in the injured patient is a result of 'insufficient heat production due to utilization of ATP under anaerobic metabolic conditions'.[10]

Low body temperature also shifts the oxygen dissociation curve to the left and restricts the liberation of oxygen.[8] Shivering increases oxygen requirement by 400%.[6] This further promotes tissue hypoxia, inefficient anaerobic respiration and lactate production.

Maintaining pyrexia is metabolically expensive. It places a high oxygen demand on the body. Kirita *et al* reported a 15% increase in energy requirements for every Celsius degree rise.[11] If one assumes that the post-traumatic state is analogous to the postoperative state, the effects would be even more dramatic. In patients who had undergone cardiac surgery, Akasu reported a 28% increase in energy requirements for every degree rise in body temperature.[12] This suggests that even more energy is required to maintain pyrexia following injury than in the atraumatic state.

It is becoming increasingly apparent that a hip fracture in an elderly patient, with limited physiological and metabolic reserve, is equivalent physiologically to major trauma in a young patient. Greenspan *et al* observed that 50% of patients over the age of 65 with an ISS of >20 did not survive.[13] This was effectively half the ISS that resulted in 50% mortality in the young (aged 24–44 years).[14] Major trauma is defined as an ISS of >15.[15] Using the same crude extrapolation, this corresponds to a score of >8 for those over 65 years. Interestingly, an isolated hip fracture equates to an ISS of 9.

Salottolo *et al* found that serum lactate was a superior predictor of mortality compared with traditional vital signs in a cohort of elderly patients (>65 years), even when correcting for injury severity, age and GCS.[16] We have previously reported an adjusted twofold increase in the odds of 30-day mortality for hip fracture patients with an admission venous lactate of ≥3mmol/l, compared with those whose lactate was lower.[17] We have also shown that low body temperature (<36.5°C) is very common in hip fracture patients and associated with high mortality.[18]

Parameters that were traditionally thought to be only of relevance in polytrauma patients appear equally significant in hip fracture patients. No previous studies have evaluated whether there is an association between body temperature and lactate level. This is important in elucidating some of the pathogenic mechanisms of hypothermia and determining the most effective means of treatment. This study therefore sought to determine whether there was an association and/or correlation between lactate level and admission temperature in patients presenting with a hip fracture.

Methods

Institutions in England, Wales and Northern Ireland are required to collate data prospectively on all patients presenting with hip fractures in the National Hip Fracture Database. This is a necessary requirement if they are to receive full remuneration for treatment of this group of patients.

The National Hip Fracture Database was interrogated to evaluate patients presenting to our institution with hip fractures between June 2011 and February 2013. Patient age and sex are also recorded in the database. All patients presenting to our unit have tympanic temperature recorded at initial presentation in triage. A single model of infrared aural thermometer is used at our institution. All hip fracture patients also undergo phlebotomy for near patient testing. This records the admission venous lactate. This work involved our original hip fracture patient cohort in whom we had evaluated the effect of admission serum lactate and survivorship.[17] This was also the same cohort in whom we had demonstrated a high prevalence of low body temperature, and an association between this and low survivorship in hip fracture patients.[18]

Statistical analysis

The patients were divided into three cohorts according to admission temperatures. The euthermic cohort had a temperature of 36.5–37.5°C, those with low body temperature presented with a temperature of <36.5°C and the pyrexial cohort with a temperature of >37.5°C. Continuous variables, relating to these groups, were compared using analysis of variance with Tukey's post-hoc test. Categorical parameters were assessed with chi-squared analysis. For each of the three temperature cohorts separately, multiple linear regression analysis was performed comparing admission

temperature with admission lactate, adjusting for age and sex. The purpose was to determine whether there was any continuous relationship between the extent of low or high body temperature and lactate level.

It was not possible to perform single linear regression analysis for the entire dataset because we sought to determine whether body temperatures that were increasingly above or below euthermia resulted in elevated lactate. A single regression model would not be able to demonstrate this as this would not constitute a linear relationship between the entirety of the temperature range and serum lactate levels.

Results

A total of 1,482 hip fracture patients presented to our institution in the relevant timeframe. Of these, 158 were referred from within the hospital. In the ward setting, they did not undergo near patient testing and so had no lactate measurements available. Of the remaining 1,324 patients, 1,162 had retrievable admission temperature readings and admission venous lactate levels. Of those patients whose lactate values were missing, this was mostly because of maintenance of the blood analyser.

The mean age was 81 years (range: 21–105 years). On admission, 38% of patients had low body temperature (<36.5°C), 58% were euthermic (36.5–37.5°C) and 4% were pyrexial (>38.5°C) (Table 1). There was no difference in sex distribution between the three temperature groups but they did differ with regard to age (p=0.007). On Tukey's post-hoc analysis, those with low body temperature were significantly older than the pyrexial cohort (mean: 82 vs 78, p=0.03). Tukey's post-hoc assessment also showed that those with low body temperature had a significantly higher mean lactate than the euthermic patients (2.2mmol/l vs 2.0mmol/l, p=0.03).

Low body temperature patients

This group consisted of 440 patients. On multiple linear regression, there was no progressive increase in lactate as the admission temperature decreased (Table 2). However, increasing age was associated with decreasing lactate level. This trend was only observed in this cohort. On average, every year increase resulted in a mean decrease in lactate level of 0.1mmol/l.

Table 1 Comparison of different admission temperature hip fracture groups

	Low body temperature	Euthermia	Pyrexia	*p*-value
n	440 (38%)	670 (58%)	52 (4%)	
Mean age in years (range)	82 (21–105)	80 (21–101)	78 (36–96)	**0.007**
Female	331 (71%)	504 (75%)	39 (75%)	0.92
Mean lactate in mmol/l (range)	2.2 (0.5–10.1)	2.0 (0.4–11.7)	2.2 (0.9–6.1)	**0.024**

Pyrexial patients

There were 52 patients in this cohort. On multiple linear regression, there was no progressive increase in lactate with increasing temperature, age or sex for these patients (Table 3).

Euthermic patients

There were 670 patients in this group. On multiple linear regression, there was no relationship between temperature and admission lactate, age or sex for these patients (Table 4).

Discussion

Low body temperature and lactate

In our study, there was an association with low body temperature and admission serum lactate levels in hip fracture

Table 2 Multiple linear regression for hip fracture patients with low tympanic temperature (<36.5°C), correlating serum lactate with admission temperature, age and sex

	Regression value	95% confidence interval	*p*-value
Temperature	-0.138	-0.345–0.069	0.191
Sex	0.127	-0.101–0.356	0.274
Age	-0.011	-0.020–-0.003	0.009

Table 3 Multiple linear regression for hip fracture patients with fever (>37.5°C) on presentation, correlating serum lactate with admission temperature, age and sex

	Regression value	95% confidence interval	*p*-value
Temperature	0.211	-0.982–1.403	0.724
Sex	-0.072	-0.910–0.766	0.863
Age	0.009	-0.016–0.035	0.464

Table 4 Multiple linear regression for hip fracture patients with normal tympanic temperature (36.5–37.5°C), correlating serum lactate with admission temperature, age and sex

	Regression value	95% confidence interval	*p*-value
Temperature	0.111	-0.149–0.372	0.401
Sex	0.082	-0.088–0.251	0.345
Age	-0.004	-0.011–0.002	0.224

patients. Those with an admission temperature of <36.5°C had a higher mean serum lactate than euthermic hip fracture patients (2.2mmol/l vs 2.0mmol/l). However, this is a dichotomous phenomenon. There was no continuous correlation between the temperature and lactate levels. Consequently, progressive decreases in admission body temperatures were not linked to progressive increases in serum lactate level.

This is significant and may aid in the understanding of the physiological response to hypothermia. It suggests that in hip fracture patients with low body temperature, the body aborts or attenuates attempts at homeothermy and may preferentially redirect resources to the injury. If the body persisted, unwaveringly, in attempts at maintaining euthermia, one would expect to observe a progressive rise in lactate with progressive declines in body temperature. The difference in the mean lactate levels between the euthermic and low body temperature patients possibly represents the body's initial attempts at homeothermy in the low body temperature cohort. This incurs an oxygen debt and energy deficit, which manifests as increased lactate.

Low body temperature may be primary or secondary. The primary form occurs when thermogenesis is unimpaired but when the environment is excessively hostile for maintaining euthermia. The secondary manifestation results from ineffectual homeothermy even in an environment in which it is easy to maintain euthermia. The fact that lactate does not increase with declining body temperature points to the fact that low body temperature, in this context, appears to be (in some part) secondary. The body abandons or at least curtails energetically expensive homeothermic measures.

This has implications for treatment. In the event of low body temperature, rewarming may be achieved passively or actively. The former involves measures to prevent further heat loss and requires patients' endogenic thermogenesis to effect rewarming. This presupposes thermogenic competence and requires additional oxygen demand. Typically, this involves the use of additional blankets. Active rewarming involves the use of exogenic heating devices such as warm saline and forced-air warming devices.[6] Our findings would suggest that it may not be sufficient to perform passive rewarming measures for hip fracture patients with low body temperature. In such circumstances, active rewarming may well be preferable. This is because homeothermy may have been suspended but also because of the additional calorific/oxygen burden involved in passive rewarming.

Acceleration of metabolic activity is germane to the process of thermogenesis. Only 40% of energy generated by glycolysis is captured in ATP. The remainder is liberated as thermal energy.[8] However, this acceleration requires considerable increases in oxygen and metabolite consumption, which may already be restricted in the context of trauma.

This is particularly important for hip fracture patients. The National Institute for Health and Care Excellence guidance recommends that hip fracture patients undergo surgery on the day of admission or the following day.[19] The Department of Health best practice tariff requires surgery to be performed within 36 hours.[20] Both demands mean that hip fracture patients are fasted routinely at presentation to hospital. Half of calorific consumption is used in maintaining body temperature. Fasting may therefore exacerbate low body temperature.[5] Interestingly, Mizobe *et al* reported that infusion of fructose for fasting preoperative surgical patients led to an increase in core temperature compared with those receiving normal saline infusion.[21] This was achieved by increasing oxygen consumption and metabolic rate. The authors postulated that fructose provided metabolic substrate for thermogenesis.

Our observations are consistent with clinical findings that show that the initial response to low body temperature is an increase metabolic rate and shivering as the body attempts to maintain euthermia.[6] As the core temperature drops, the body adopts a more permissive attitude to hypothermia with the cessation of shivering and diminution in the basal metabolic rate. The mean age of our cohort was 80 years. The elderly may tend to abort homeothermic mechanisms prematurely simply because they lack the necessary thermogenic repertoire. Reduction in lean body mass, dietary inadequacy and attenuated shivering response to cold are features of senescence that also impair thermoregulation.[22]

The mean admission lactate levels for the low body temperature and euthermic cohorts were 2.2mol/l and 2.0mmol/l respectively. This is less than the standard normal value for serum lactate of 2.5mmol/l. The difference between the two cohorts may be clinically significant, however. Lactate levels that fall within the normal range do not necessary imply physiological normality in the elderly. Callaway *et al* reported that increasing lactate levels were associated with increasing mortality in normotensive elderly patients.[23] The mortality rates were 15%, even in those whose lactate fell within the normal physiological range.

In our study, increasing age was associated with a decline in the serum lactate levels for hip fracture patients. Nevertheless, this was only observed in those with low body temperature on admission. This is consistent with findings of other studies, which consistently show an age related decline in peak lactate levels following a physiological challenge.[24,25] The greater the challenge, the more demonstrable this effect becomes. In our study, only the combined physiological stresses of a low body temperature and a hip fracture were sufficient to show this trend.

The effect is thought to be due to a reduction in metabolically active body mass, especially a reduction in muscle mass associated with age.[25] However, it has also been found that increasing age is associated with a decline in the anaerobic metabolic apparatus and a reduction in the lactate generator, lactate dehydrogenase, in particular.[26] A less pronounced rise of lactate in response to a physiological stress may therefore be the norm for the elderly. Elevated levels, even those that fall within the normal physiological range, are thus associated with physiological extremes, as reported by Uzoigwe *et al* and Callaway *et al*.[16,23]

Pyrexia and lactate

There was no statistically significant difference in the mean lactate levels of the pyrexial and euthermic hip fracture cohorts. Furthermore, there was no relationship

between the degree of pyrexia and lactate levels. As maintaining pyrexia remains expensive in calorific terms, this suggests that it appears to be a response reserved for the metabolically replete. Those with sufficient cellular oxygenation and thermogenic substrate tend to mount this response as there appears no associated hyperlactataemia. It is noteworthy that those with pyrexia tended to be younger than those with low body temperature (mean: 78 vs 82 years).

In trauma cases, elevated temperature may occur secondary to infection or as a response to the injury. Mizushima *et al* found that trauma patients who displayed a pyrexial reaction (temperature >37.5°C) to injury enjoyed improved survivorship compared with those who failed to develop a fever.[27] It was suggested that this facilitated cellular responses necessary for healing. Increasing temperature acts to shift the oxygen–haemoglobin dissociation curve to the right. This improves oxygen liberation to the tissues. In the case of infection, a fever is thought to improve immunocyte function while shifting the body temperature from that optimal for bacterial and viral activity.[28] Indeed, hypothermia is a pathological response in infection associated with adverse outcomes.[29,30]

Study limitations

There is variability in body temperature dependent on the site of measurement and the time of day. At our institution, all recorded temperatures were tympanic and measured with the same model of infrared thermometer. This would minimise the effect of differing temperature resulting from different body sites. Tympanic temperature has been found to correlate well with core temperature.[31] Euthermia was defined as encompassing the physiological band of temperatures from 36.5°C to 37.5°C rather than a single temperature of 37°C. This approach was adopted to cater for the possibility of diurnal variation in body temperature. The retrospective nature of the study meant that not every episode was captured. We believe, however, that the sample size of over 1,100 makes the study a valid endeavour.

No previous studies have explored the relationship between serum lactate and body temperature. Martin *et al* found decreasing core temperature was associated with a progressive decline in base deficit.[4] Nevertheless, base deficit and lactate are distinct parameters. The former is a composite index of the factors that tend to promote acidosis.[32] It also incorporates metabolic ability to correct an acid load, and hence (to some extent) reflects renal and hepatic function.[22] The function of both organs is affected adversely by a decline in body temperature. Base deficit is used as surrogate marker for lactate but this is misleading.[33] Serum lactate has been found to be an independent predictor of mortality in a number of contexts whereas the prognostic ability of base deficit is dependent on lactate level. Lactate is regarded as the superior indicator of metabolic derangement.[34,35]

Conclusions

This is the first study demonstrating that low body temperature is associated with an increased mean lactate level in hip fracture patients. However, there is no progressive increase in admission lactate in hip fracture patients with decreasing temperature. This may have ramifications for understanding the pathogenesis of hypothermia, the physiological response and considering optimum therapeutic strategies.

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