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Change in physiological variables in the last 2 weeks of life: An observational study of hospitalized adults with heart failure.

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Abstract

Context: Recognition of dying is a difficult task in end-stage heart failure, yet it remains an important clinical skill in providing good palliative care to these patients.

Objectives: To use routinely collected data to explore evidence for physiological change in the final two weeks of life in end-stage heart failure.

Methods: This was a retrospective cohort study of routinely collected data from hospital in-patients dying as a result of heart failure during a 1-year period in a UK hospital. Data were analyzed using descriptive techniques and multilevel modelling.

Results: Results were obtained on 81 patients. Respiratory function (evidenced by falling oxygen saturation and rising respiratory rate) deteriorated by a clinically significant amount in the final two weeks of life ($p<0.001$). Renal function (evidenced by rising serum urea and creatinine) also demonstrated a clinically significant deterioration over the same time period ($p<0.001$ and $p=0.005$ respectively). Serum albumin fell over a period of months ($p<0.001$). Heart rate and blood pressure did not demonstrate clinically significant change over the same time period.

Conclusions: Deteriorating respiratory and renal function may indicate imminent dying in heart failure. A fall in serum albumin may signify poor prognosis over a timescale of weeks to months. Conversely, hemodynamic parameters may remain relatively stable in the final days of life, and should not be reassuring in end-stage heart failure patients.

Keywords.

Terminal care, heart failure, prognosis, clinical decisions

Introduction.

Management of heart failure has, for many years, focused on treatments and interventions designed to extend prognosis, limit disease progression and improve physical symptoms (1). Whilst these aims have dominated research and clinical practice, the progressive and ultimately life-threatening nature of the condition have created a remit for palliative care services to support heart failure patients (2); a recent US-based RCT demonstrated clear benefit from such involvement (3). As part of good palliative care, the accurate recognition of dying is an important clinical skill, allowing physicians to focus on symptom relief and minimizing unnecessary medical interventions(4).

Unfortunately, whilst recognition of dying is important to good care, the task remains challenging (5). The unpredictable trajectory of end-stage heart failure, typified by repeated acute hospital admissions on a background of inexorable deterioration, means that anticipating the final days of a patient's life is a complex task (6). Whilst various prognostic tools help to predict survival in heart failure populations at a longer time scale(7), existing models are much less suited to translating to the individual patient or to the timescale of days.

When developing tools to support prognostic decision-making, objectively measurable clinical parameters are valuable sources of information (8). There is evidence, however, that dynamic data, incorporating rate-of-change information, may provide further insight into end-of-life change in palliative conditions(9). By understanding those changes which occur in the final days to weeks of life, it may therefore be possible to improve recognition of dying in heart failure patients, both in supporting research into new predictive models and in clinical application at the patient level.

This study used routinely collected clinical data to explore evidence for objective physiological change in the final two weeks of life, with a view to improving the ability of clinical professionals to recognize dying. It is part of a larger mixed-methods study which includes similar data from cancer patients. Cancer data have been published elsewhere (10).

Method

This was a retrospective observational cohort study, using longitudinal modelling of routinely collected clinical data.

A review of prognostic literature identified a number of variables which were suitable for inclusion in the study, according to the following criteria: 1) Associated with poor survival in end-stage heart failure, 2) Routinely recorded in medical records, 3) Ability to exhibit change in the final two weeks of life, 4) Could be measured in advanced heart failure. The included variables are listed in table 1. Since this research was completed, the European Society of Cardiology have published updated information of prognostic factors in heart failure(2), consistent with those included in the study.

The study was conducted at a National Health Service (NHS) hospital in the UK with a specialist cardiology service. Cases were identified from computer coding records for

deaths between August 2009 and July 2010 inclusive. Adults (>18) in which the medical certificate of cause of death (MCCD) listed heart failure as a cause or contributing factor were included. Synonyms and abbreviations in common use in the UK were also included (cardiac failure, congestive cardiac failure, left/right ventricular failure, systolic/diastolic heart failure).

Cases were excluded for the following reasons: Where coroner's investigations or litigation were in place, as the notes would need to be rapidly accessible via medical records in such cases. Where deaths occurred in intensive care or high dependency settings, as this would introduce a subset of patients experiencing significantly different management approaches to the wider group. Where there were insufficient data in the notes to allow analysis (if, for example, time of death was not recorded).

Identified notes were screened by one researcher (PT) for evidence of clinical heart failure during the final admission, judged by medical case-notes and use of drugs to treat the condition. If no evidence was found for active heart failure in the final admission, the notes were to be excluded, although no cases were excluded on this basis alone.

Data were extracted from the medical records from the two weeks preceding death; extended to three months for hemoglobin and albumin levels. Data were anonymized at source and entered into a secure bespoke database according to study number. Variable values were recorded against time (for observations) or date (for blood tests).

Multilevel modelling was used to analyze the data. This is a longitudinal analysis technique suited to datasets where individual data sources contribute multiple data points. The technique involves performing a regression analysis on each "level" of data. In this study, the first level of data was the individual; an association between value and time prior to death was generated for each participant. The next level involved collating these individual sets to generate both an association between variable value and time prior to death, together with a measure of variation between individual trajectories. Analyses were performed in Stata Version 11.0(Statacorp) (11). The study size was determined by the duration of the study (one year).

The retrospective data collection technique meant that each participant contributed an unpredictable series of measures and there was scope for missing or censored data. Some would have had only a small number of results recorded before a clinical decision to discontinue recording was undertaken. Others would have contributed large and detailed data sets; this has the potential to introduce a degree of selection bias.

Whilst the use of multilevel modelling was intended as a strategy to attenuate the risk of selection bias, the presence and impact of potential bias was assessed by undertaking the analysis twice. In the first instance the complete dataset was used, including those participants with large amounts of missing or censored data. In the second, the analysis was restricted to those participants who had detailed data sets. Participant data was included in the restricted data set if values were recorded in the last day of life (or final week of life for hemoglobin and albumin), and at least 10 values were included.

Where both datasets ("full" and "restricted") could be generated, the analysis was performed on both. Any evidence of significant variation between the full and restricted datasets would be evidence of bias due to the selection method.

The study is reported according to the "Strengthening the Reporting of Observational Studies" (STROBE) guidelines(12).

Results

The coding search identified 151 potential records, of which 131 sets of notes were available. MCCD criteria were met in 99 cases. Of these cases, 18 were excluded (6 coroner's cases/litigation, 7 HDU/ICU, 7 insufficient data, some duplicated). This process resulted in 81 eligible records. Of these cases, 35 (43%) were male and 46 (57% were female). Number in each age range were: 61-70: 1; 71-80:16; 81-90: 51; 91-100: 13.

The number of data points collected for each variable, together with descriptive data, and the multilevel models are presented in table 1.

The results of the multilevel models are summarized in Table 2. These provide a description of the change in values of the parameters over time in the final two weeks of life. The intercept is the projected value at time zero (the time of death). This acts as an anchor point for the changing parameter and gives an indication of types of values seen. It is useful for understanding whether the results are clinically significant. The co-efficient demonstrates the rate of change over time prior to death. A variable decreasing as death approaches would therefore have a positive co-efficient.

Respiratory rate, serum urea, and serum creatinine show a statistically and clinically significant increase in the final two weeks of life. Oxygen saturation (as measured with an infra-red probe) demonstrates a statistically and clinically significant decrease in the final two weeks of life. Albumin also demonstrates a statistically and clinically significant decrease, measured over a timescale of three months.

Heart rate and serum sodium demonstrate a statistically significant increase, but their intercept values remain within the normal range and so clinical significance is limited. Blood pressure, serum potassium and hematological parameters demonstrate neither clinically or statistically significant change.

For parameters where sufficient data existed to provide a full and restricted data set, there was no evidence of significant difference between the two. Although this method does not provide a quantitative assessment of the risk of bias, it adds a degree of reassurance that the censored data has not had a major effect on the interpretation.

Discussion

These findings demonstrate that physiological change in the final two weeks of life in heart failure is characterised by progressive respiratory and renal dysfunction, but with comparatively stable haemodynamic parameters. These findings may be compared with the results of the earlier cancer study (10), which demonstrated similar respiratory dysfunction as death approached. Renal dysfunction was also noted in cancer, but the derangement in renal function was more pronounced in heart failure.

Falling albumin is also associated with approaching death, but these results were assessed over a longer time period. Cardiac cachexia, a cause of hypoalbuminaemia in this population, is well documented(13), but the degree and rate of decline of albumin level was less extreme than that seen in cancer.

Of particular interest, and potential for further study, is the relative normality of certain parameters, including heart rate, blood pressure and serum sodium/potassium. Given the extensive use of beta-blockers in this population (2), it may be expected that heart rate would not increase significantly above normal levels. The relative stability of blood pressure in end-stage heart failure is, however, counter-intuitive, given a progressive mechanical pump failure and hypotensive side-effects of commonly used drugs (Ace-inhibitors, Beta-blockers, diuretics) (2). The relative normality of serum sodium and potassium levels is similarly counter-intuitive. The aforementioned drugs, in combination with a context of renal dysfunction and the likely increased levels of endogenous natriuretic peptides (14), mean the relative normality of these parameters is unexpected. Furthermore, these observations are at odds with existing prognostic studies (2) which show these parameters have prognostic value at longer time scales.

This study, however, considers a much shorter time scale than existing prognostic research in heart failure, which may help explain this observation. Reverse epidemiology, a phenomenon which has been observed in heart failure (15), is one potential cause; this occurs where a known marker of poor prognosis is unexpectedly associated with better prognosis in certain subgroups, including when applied to different timescales. It is also possible that the final days of life in end-stage heart failure involve refractory responses to drugs, an observation which may be missed over the longer time-scales seen in prior prognostic studies.

Whilst anaemia of chronic disease is an observed phenomenon and predictor of poor prognosis in heart failure (16), and the study results show values at the lower end of the normal range, these findings do not support the presence of progressive anaemia as a predictor of poor prognosis at the short time-scales in this study. These findings do not preclude the potential for anaemia to have prognostic value over longer time scales.

Death from heart failure may therefore be understood as a multi-organ condition, with evidence of systemic cachectic effects over a longer time scale, and more rapid objective deterioration over the final days to weeks of life.

The observations highlighted warrant further study using prospective methods. In particular, we suggest that such studies collect sequential data where possible, that analysis techniques allow for strengths of association to be proposed, and that

additional clinical data on presenting symptoms, recognition of end-of-life and drug use be included.

Limitations

This is a study conducted in hospitalized patients outwith the HDU/ICU setting and, as a result, cannot necessarily be applied to other patient groups. Furthermore, the need to account for censored data highlights that there was variation in monitoring strategies within the patient group; this population included both those who were recognized as dying and those who were being actively treated, so cannot be applied uncritically to either population.

Legal stipulations on death certification in the UK do not permit the term "Heart Failure" alone as a primary cause of death, unless supported with a preceding qualifying condition. It is possible, therefore, that deaths in some cases with clinical heart failure were attributed to the primary cause and hence were not included in the sample.

The nature of this study method precluded the inclusion of a comparator group, and therefore no strength of association can be provided for the physiological changes observed here and the risk of death in a given time period. Instead these results are presented as the basis of future studies using prospective methodology, and for further understanding of the physiological changes in end-stage heart failure; findings from the related cancer study have been used for this purpose (17).

The proportion of deaths occurring due to heart failure by gender does not fully reflect the population burden of cardiovascular disease, in that women are over-represented (57%). However, statistics from the Office for National Statistics, which presents aggregated data on causes of death in the UK, highlights that heart failure as the cause of death is more common in women (18). Furthermore, whilst deaths from ischaemic heart disease are over-represented in men(18), other causes of heart failure are over-represented in women(19), with associated variation in mortality. This observation may therefore represent a genuine gender difference in recorded mortality rates from heart failure in hospital.

Conclusions

Respiratory and renal dysfunction are potentially useful markers for approaching death in heart failure, especially if measured values are abnormal and deteriorating. Falling albumin is consistent with poor prognosis over a longer time period. These findings are useful for understanding the biology of dying as a result of heart failure, for hypothesis generation, and for describing common change in the population of interest.

In terms of clinical application, the relative stability and/or normality of heart rate, blood pressure, sodium, potassium and haematological parameters in this data set indicate that a clinician should not necessarily be reassured if these values are stable in an otherwise deteriorating patient.

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In accordance with standard research processes at the time, the research was approved by the University Research Governance Committee, the local Research Ethics Committee and the hospital's Research and Development Department. Access to data was approved by the National Information Governance Board for Health and Social Care (NIGB).

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Table 1. Variables collected and descriptive statistics.

Variable	**Descriptive statistics**			
	Number of values (Patients)	Lower range	Median	Upper range
Heart rate (BPM)	2332 (79)	24	84	180
Systolic blood pressure (mmHg)	2433 (79)	44	118	237
Diastolic blood pressure (mmHg)	2433 (79)	16	63	141
Respiratory rate (breaths/min)	2299 (79)	6	20	47
Oxygen saturation (%)	2401(79)	60	95	100
White cells (x 10^9/L)	266 (79)	3	9.15	37.1
Lymphocytes (x 10^9/L)	264 (78)	0.16	0.8	3.85
Sodium (mmol/L)	326 (80)	119	137	157
Potassium (mmol/L)	311 (78)	1.9	4.4	7
Urea (mmol/L)	324 (79)	2.7	19.2	63
Creatinine (μmol/L)	325 (79)	19	172	901
Albumin (g/L)	767 (81)	15	30	43
Haemoglobin (g/L)	636 (81)	5.6	10.7	17.3

Table 2. Multilevel modelling. Co-efficients represent value change per hour for bedside variables, and change per day for blood results.

Variable	**Multilevel model**		
	Intercept (95% CI)	Co-efficient (95% CI)	Model p-value
Heart rate (BPM) Full data set	86.7 (83.2, 90.2)	-0.022 (-0.042, -0.001)	0.034
Heart rate (BPM) Restricted data set	87.7 (83.8, 91.6)	-0-026 (-0-050, -0-002)	0.036
Systolic blood pressure (mmHg) Full data set	119.5 (114.4, 124.6)	0.000 (-0.032, 0.032)	0.991
Systolic blood pressure (mmHg) Restricted data set	121.9 (116.2, 127.6)	-0-001 (-0-041, 0.040)	0.978
Diastolic blood pressure (mmHg) Full data set	64.4 (61.3, 67.5)	0.000 (-0.014, 0.014)	0.971
Diastolic blood pressure (mmHg) Restricted data set	66.1 (62.6, 69.7)	-0-004 (-0.020, 0.013)	0.672
Respiratory rate (breaths/min) Full data set	22.9 (21.8, 23.9)	-0.012 (-.0.18, -0.005)	<0.001
Respiratory rate (breaths/min) Restricted data set	23.3 ((22.1, 24.4)	-0.016 (-0-024, -0.009)	<0.001
Oxygen saturation (%) Full data set	93.0 (92.3, 93.7)	0.008 (0.004, 0.011)	<0.001
Oxygen saturation (%) Restricted data set	93.0 (92.2, 93.8)	0.007 (.004, 0.011)	<0.001
Albumin (g/L) Full data set	27.3 (26.20, 28.31)	0.082 (0.060, 0.105)	<0.001
Albumin (g/L) Restricted data set	25.6 (23.9, 27.3)	0.114 (0.074, 0.154)	<0.001
Haemoglobin (g/dL) Full data set	11.13 (10.69, 11.58)	0.003 (-0.004, 0.01)	0.425
Haemoglobin (g/dL) Restricted data set	10.32 (9.48, 11.17)	0.006 (-0.008, 0.020)	0.386
White cells (x 10^9/L) Full data set only	10.62 (9.54, 11.70)	-0.037 (-0.196, 0.121)	0.645
Lymphocytes (x 10^9/L) Full data set only	0.92 (0.79, 1.06)	0.005 (-0.010, 0.019)	0.502
Sodium (mmol/L) Full data set only	138.6 (137.0, 140.3)	-0.257 (-0.441, -0.072)	0.006
Potassium (mmol/L) Full data set only	4.5 (4.3, 4.7)	-0.014 (-0.036, 0.008)	0.205
Urea (mmol/L) Full data set only	22.5 (19.2, 25.8)	-0.562 (-0.871, -0.254)	<0.001
Creatinine (μmol/L) Full data set only	198.9 (171.1, 226.6)	-3.191 (-5.413, -0.970)	0.005