THE PREDICTION OF INDIVIDUAL SYSTOLIC TIME INTERVAL *v* HEART RATE REGRESSION EQUATIONS

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- 1 Twenty-eight sets of systolic time interval (STI) and heart rate (HR) data were available from studies in which small bolus doses of atropine had been given to alter heart rate.
- 2 Regression lines of the form

$$\begin{aligned}\text{LVET} &= A + B \cdot \text{HR} \\ \text{and } \text{QS}_2 &= C + D \cdot \text{HR}\end{aligned}$$

were calculated. There was no significant relationship between PEP and HR. The values of the parameters A–D were normally distributed.

- 3 The maximum likelihood function for each parameter was calculated using Bayes' theorem and Maximum Likelihood Estimation was used to obtain the most likely values of the parameters A–D for individual subjects.
- 4 The technique proved to be highly satisfactory and was subsequently validated with a further six sets of data.

Introduction

The measurement of systolic time intervals (STI) provides one of the most convenient noninvasive methods of assessing cardiac performance. This technique has been used to study established or potential cardiac abnormalities (Weissler & Schoenfeld, 1970; Lewis *et al.*, 1973; Kligfield, 1974; Waagstein, Hjalmarson & Wasir, 1974; Lewis, Milne & Goldberg, 1976; Sykes *et al.*, 1977) and to investigate the inotropic effect of both existing and new drugs (Das, Talmers & Weissler, 1977; Hinderling & Garrett, 1977). In many previous studies changes in STI (total electromechanical systole, QS_2 and left ventricular ejection time, LVET) occurring as a result of variations in heart rate (HR) have been accounted for by applying global regression equations (Weissler, Harris & Schoenfeld, 1968) and calculating the difference between the 'expected' and 'observed' STI values, namely

$$(\text{STI})_{\text{expected}} = P_1 + P_2 \cdot \text{HR} \quad (1)$$

so that $\Delta\text{STI} = (\text{STI})_{\text{measured}} - (\text{STI})_{\text{expected}}$

where P_1 and P_2 are the parameters of the STI *v* HR regression line. The order of magnitude of the LVET is

250–350 ms, and the QS_2 , 350–450 ms. The expected change in either of these measurements as a result of pharmacological activity is typically 10–20 ms, and this makes it essential that accurate heart rate corrections are made, especially since many cardio-active drugs themselves alter heart rate. Moreover, as the STI *v* HR regression relationship is likely to vary from individual to individual, small changes of the order of 10–20 ms may not be adequately characterised if the regression relationship is not defined on an individual basis. To achieve this, we initially modified a protocol which involved graded exercise on a bicycle ergometer (Van der Hoeven *et al.*, 1977) and used this to study several cardiac glycosides (Kelman *et al.*, 1980). While this protocol was satisfactory for healthy volunteers, its use in patients could not be contemplated and we have adopted the alternative approach of altering heart rate pharmacologically with small bolus doses of atropine (Burgess, Wadsworth & Warrington 1979; Holford *et al.*, 1980). In a group of normal volunteers this method was reproducible over a period of weeks, but there was a substantial degree of intersubject variability (Kelman, Sumner & Whiting, 1981). We now feel that even this type of protocol may not be appropriate for many patients and we believe that there would be some virtue in developing a method of predicting STI *v* HR regression relationships from

only minimal experimental data. This paper describes such a method and compares the results with those obtained by more traditional means.

Methods

Theory

The predictive technique is based on Bayes' theorem and Maximum Likelihood Estimation (Wonnacott & Wonnacott, 1970; Edwards, 1976; Sheiner *et al.*, 1979). The application of Bayes' theorem facilitates determination of the most likely values of an individual set of parameters when there is previous information about the distribution of the parameters in a population. This distribution is called the prior distribution. The probability with which the parameter values appropriate for an individual occur is derived from the prior distribution by weighting this to take account of any observations available. This leads to a revised, posterior, distribution which can be further modified when more data from an individual become available. The most likely parameter value is thus the one defining the peak (assumed to be singular) of the posterior distribution. If these distributions are assumed to be normal, then the variance of the posterior distribution will decrease as more data are added, i.e. there will be increasing confidence about the mean value.

Let a measure Y , be described by a function, g , in terms of k parameters, θ_i ($i = 1, k$) and an observation x of a measure X , so that the expected value of y , y_E is given by

$$y_E = g(x, \theta_1, \dots, \theta_k)$$

Thus, if a function can be found which expresses the statistical likelihood of a set of parameter values θ_i occurring, and also takes any observations into account, then the Maximum Likelihood Estimates (MLE) of the parameters, θ_i , are given by the set of values which maximise this function. The appropriate function is the posterior distribution arising from Bayesian methods, and is described mathematically by:

$$p(\theta|y) = \frac{p(\theta) \cdot p(y|\theta)}{p(y)} \quad (2)$$

where $p(\theta)$ is the joint probability density function for the set of parameters, θ_i , ($i = 1, k$) based only on information about the parameters, i.e. the prior distribution, $p(y|\theta)$ is the conditional probability density function for the observations y_j and the parameters θ_i , and $p(y)$ is the probability density function for the observations y_j . $p(\theta|y)$ is, then, the posterior distribution of the set of parameters θ_i , and

the MLE of the θ_i are the set of parameter values which maximise $p(\theta|y)$. $p(y)$ is independent of the θ_i and can be neglected in this process.

Some simplifying assumptions may be made, viz.

- (A) Each θ_i is normally distributed with mean $\bar{\theta}_i$ and variance σ_i^2
- (B) the θ_i are independent
- (C) each measurement y_j comes from a normal distribution with mean y_{Ej} (the expected value of y_j), and variance σ_y^2 .

The first assumption (A) leads to the probability density function for the i^{th} parameter, θ_i , being given by:

$$p(\theta_i) = \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{-\frac{(\theta_i - \bar{\theta}_i)^2}{2\sigma_i^2}}$$

Since the θ_i are assumed to be independent, (B), the prior distribution for the set of parameters, $p(\theta)$ is given by:

$$p(\theta) = \prod_{i=1}^k p(\theta_i) = k_1 \prod_{i=1}^k e^{-\frac{(\theta_i - \bar{\theta}_i)^2}{2\sigma_i^2}} \quad (3)$$

$$\text{where } k_1 = \prod_{i=1}^k \frac{1}{\sqrt{2\pi\sigma_i^2}}$$

Let there be n independent observations (x_j, y_j) ($j = 1, n$). The expected value of y_j , y_{Ej} , is given in terms of the dependent variable x_j and the parameters θ_i by the function, g :

$$y_{Ej} = g(x_j, \theta_1, \dots, \theta_k)$$

The conditional probability of y_j and the θ_i is then given by (C):

$$p(y_j|\theta) = \frac{1}{\sqrt{2\pi\sigma_y^2}} e^{-\frac{(y_j - y_{Ej})^2}{2\sigma_y^2}}$$

Since all of the observations are independent, the probability density function for all the observations can be expressed as:

$$p(y|\theta) = \prod_{j=1}^n p(y_j|\theta) = k_2 \prod_{j=1}^n e^{-\frac{(y_j - y_{Ej})^2}{2\sigma_y^2}} \quad (4)$$

$$\text{where } k_2 = \left(\frac{1}{\sqrt{2\pi\sigma_y^2}} \right)^n$$

Thus, omitting the constants k_1 and k_2 and also $p(y)$ which is independent of the θ_i , the posterior distribution ($p(\theta|y)$ in equation (2)) can be described by the Likelihood function L , where:

$$L = \prod_{i=1}^k e^{-\frac{(\theta_i - \bar{\theta}_i)^2}{2\sigma_i^2}} \prod_{j=1}^n e^{-\frac{(y_j - y_{Ej})^2}{2\sigma_y^2}} \quad (5)$$

The MLE of the θ_i are the set which maximises L. Equivalently, the negative of the log likelihood function, M, is defined by

$$M = -2 \ln(L) = \sum_i \frac{(\theta_i - \bar{\theta}_i)^2}{\sigma_i^2} + \sum_j \frac{(y_j - y_{Ej})^2}{\sigma_y^2} \quad (6)$$

and then the MLE of the θ_i are the set which minimise M. This form is more convenient computationally. Note that in the absence of any experimental observations, the MLE of the θ_i are merely the mean values of the parameters, $\bar{\theta}_i$, defined by the prior distribution, and that σ_i^2 represents the degree of variability in the population. Estimates for the population parameter values $\bar{\theta}_i$ and σ_i^2 must be obtained and this task can be accomplished by use of a recently developed computer programme, NONMEM (Beal & Sheiner, 1979). Based on a nonlinear mixed effects model, this programme simultaneously analyses data sets from many subjects in terms of a user specified function, and each model parameter, θ_i , is described in terms of a population mean value $\bar{\theta}_i$, and an additional term which reflects the characteristics of the individual, i.e. the value of the i^{th} parameter for the r^{th} subject, θ_{ir} , is given by:

$$\theta_{ir} = \bar{\theta}_i + \eta_{ir}$$

$\bar{\theta}_i$ is the population mean value for θ_i , and η_{ir} is the individual's deviation from $\bar{\theta}_i$. The η_{ir} are normally distributed with mean value zero, and variance $\sigma_{\eta_i}^2$. NONMEM provides estimates of the values of the $\bar{\theta}_i$ and σ_i^2 . σ_y^2 in equation (6) represents the variance in Y due to all forms of measurement error.

Data collection

There were 28 sets of STI/HR data available, all subjects being normal males between 25 and 35 years. Ten sets were obtained while screening volunteers to ensure good signal quality. The other 18 sets were obtained from six subjects who were studied three times each at weekly intervals. This formed part of an assessment of the reproducibility of regression equations obtained by giving repeated small bolus doses of atropine to alter heart rate pharmacologically (Kelman *et al.*, 1981). A further six sets of data were obtained using this protocol to validate the prediction technique described in this paper. The 28 data sets were considered to be independent for the present analysis.

The recording and data analytical techniques have been described previously (Kelman *et al.*, 1981). Standard statistical procedures were available on a

Table 1 The values of the parameters A-F and corresponding r values for the individual regression equations $LVET = A + B \cdot HR$, $QS_2 = C + D \cdot HR$ and $PEP = E + F \cdot HR$.

Subject	A	B	r	C	D	r	E	F	r	d.f.
1a	316.3	-0.68	-0.97	408.8	-0.68	-0.95	92.6	0.01	0.01	20
1b	321.1	-0.65	-0.93	424.0	-0.71	-0.82	102.9	-0.06	-0.16	20
1c	327.9	-0.82	-0.96	435.5	-0.79	-0.92	107.6	0.02	0.09	20
2a	374.3	-1.10	-0.92	288.2	-1.36	-0.92	113.3	-0.25	-0.46	20
2b	382.4	-1.12	-0.94	490.1	-1.44	-0.92	105.3	-0.27	-0.37	19
2c	373.0	-1.05	-0.91	487.9	-1.34	-0.90	114.9	-0.29	-0.48	20
3a	401.1	-1.27	-0.99	467.1	-1.15	-0.96	66.0	0.12	0.12	19
3b	428.0	-1.66	-0.99	469.8	-1.20	-0.99	41.8	0.46	0.84	19
3c	432.1	-1.78	-0.99	470.4	-1.13	-0.99	38.2	0.65	0.90	20
4a	394.2	-1.55	-0.99	488.6	-1.32	-0.98	94.4	0.23	0.65	20
4b	391.4	-1.37	-0.99	523.7	-1.48	-0.98	132.3	-0.11	-0.30	20
4c	391.2	-1.38	-0.99	511.3	-1.43	-0.97	120.2	-0.05	-0.14	20
5a	346.0	-0.83	-0.98	413.0	-0.73	-0.96	67.0	0.10	0.43	19
5b	351.3	-0.93	-0.99	436.1	-0.96	-0.91	84.9	-0.02	-0.06	17
5c	365.3	-1.04	-0.98	454.5	-0.97	-0.97	89.2	0.07	0.24	19
6a	389.8	-1.23	-0.99	463.0	-1.18	-0.99	73.1	0.06	0.28	20
6b	373.1	-1.08	-0.96	471.2	-1.12	-0.95	98.1	-0.04	-0.12	20
6c	380.9	-1.14	-0.98	469.0	-1.15	-0.99	88.0	-0.01	-0.04	19
7	388.0	-1.37	-0.98	480.4	-1.47	-0.92	92.5	-0.10	-0.15	17
8	418.8	-1.60	-0.99	453.7	-0.98	-0.89	34.9	0.62	0.74	22
9	384.1	-1.23	-0.99	511.8	-1.37	-0.99	127.7	-0.13	-0.56	22
10	372.7	-1.15	-0.89	450.0	-0.84	-0.88	77.4	0.31	0.67	23
11	370.0	-0.98	-0.98	477.6	-1.20	-0.99	107.6	-0.22	-0.63	21
12	374.3	-1.09	-0.99	469.1	-1.12	-0.95	94.9	-0.03	-0.08	22
13	359.4	-1.06	-0.99	430.7	-0.91	-0.97	71.3	0.15	0.51	22
14	347.2	-0.93	-0.95	440.0	-0.94	-0.97	92.8	0.00	-0.01	21
15	329.1	-0.76	-0.98	399.9	-0.49	-0.94	70.8	0.26	0.82	22
16	311.4	-0.59	-0.96	409.5	-0.67	-0.97	98.1	-0.07	-0.30	22

Varian V70 series digital computer, and the programme NONMEM was run on an ICL2976 computer (Glasgow University Computing Service).

Results

(a) Population parameter values

Regression analysis of STI/HR data was performed

on each of the 28 data sets to give values of the parameters A-F defined by:

$$\text{LVET} = A + B \cdot \text{HR}$$

$$\text{QS}_2 = C + D \cdot \text{HR}$$

$$\text{PEP} = E + F \cdot \text{HR}$$

where LVET = left ventricular ejection time,

QS₂ = time of total electromechanical systole

and PEP = pre-ejection period (= QS₂ - LVET.)

In every case there was a highly significant correlation

Figure 1 Relationship between A and B, where A and B are the parameters of the regression equation $\text{LVET} = A + B \cdot \text{HR}$. $\times$ is the point derived from the parameters of the global regression equation, $\text{LVET} = 413 - 1.7 \cdot \text{HR}$.

Figure 2 Relationship between C and D, where C and D are the parameters of the regression equation $\text{QS}_2 = C + D \cdot \text{HR}$. $\times$ is the point derived from the parameters of the global regression equation, $\text{QS}_2 = 546 - 2.1 \cdot \text{HR}$.

($P < 0.001$) between LVET and HR and QS_2 and HR, but no such consistent relationship existed between PEP and HR (Table 1). It was confirmed using both the χ^2 test and the Kolmogorov-Smirnov test that the parameters were Normally distributed, one of the essential conditions for NONMEM. However, the pairs of parameters A and B, C and D were not independent, but were linearly related, the mean regression equations being given by:

$$A = 254.3 - 104.2 B \quad (7)$$

$r = 0.97$, d.f. = 26, $P < 0.001$ (Figure 1), and

$$C = 333.3 - 118.2 D \quad (8)$$

$r = 0.95$, d.f. = 26, $P < 0.001$ (Figure 2).

(It should be noted that the points representing the commonly used regression equations $LVET = 413 - 1.7 HR$ and $QS_2 = 546 - 2.1 HR$ also lie close to the regression equations (7) and (8).)

All 28 data sets were analysed simultaneously using NONMEM to provide estimates of the population mean parameter values and their variances. The LVET and QS_2 models were parameterised only in terms of the slopes of the STI *v* HR regression equations (B and D) because of the relationships defined by equations (7) and (8). Thus for the i^{th} data point obtained from the r^{th} individual, the model equations are given by:

$$\begin{aligned} LVET_{ir} &= 254.3 - 104.2 (\bar{B} + \eta_{Br}) + (\bar{B} + \eta_{Br}) \cdot HR_{ir} + \varepsilon_{ir} \\ QS_{2ir} &= 333.3 - 118.2 (\bar{D} + \eta_{Dr}) + (\bar{D} + \eta_{Dr}) \cdot HR_{ir} + \varepsilon_{ir} \\ \text{and } PEP_{ir} &= (\bar{E} + \eta_{Er}) + (\bar{F} + \eta_{Fr}) \cdot HR_{ir} + \varepsilon_{ir} \end{aligned} \quad (9)$$

The η terms express the deviation of the parameter value from the corresponding population mean value for that individual, and the ε terms express all the error which is not accounted for by the η terms. The η are normally distributed with mean of zero. The values of $\bar{B}$, σ_B^2 , $\bar{D}$, σ_D^2 , $\bar{E}$, σ_E^2 , $\bar{F}$ and σ_F^2 are given in Table 2. The value of $\bar{F}$ (0.06) confirmed that using this type of protocol, there was no consistent regression relationship between PEP and HR, and no further analysis was carried out on the PEP data.

(b) Forecasting parameter values

Values of the parameters A, B, C and D were predicted when only minimal data were available. In the case of LVET, equation (6) reduces to:

$$M_1 = \frac{(A - \bar{A})^2}{\sigma_{EA}^2} + \frac{(B - \bar{B})^2}{\sigma_B^2} + \sum_j \frac{(LVET_j - LVET_{Ej})^2}{\sigma_{LVET}^2} \quad (10)$$

where the expected value of A, $\bar{A}$, replaces $\bar{A}$, and is given by equation (7) (i.e. θ_1 and θ_2 in equation (3) are

Table 2 The population mean values of the parameters B, D, E & F and also the population variances estimated by NONMEM.

Parameter	Population mean	s.d.	Population variance
B	-1.08	0.09	0.16
D	-1.15	0.12	0.15
E	87.30	— ^a	52.70
F	0.06	— ^a	0.04

^a standard deviation indeterminate

not independent). The value of the variance of A, σ_{EA}^2 , is the value σ_A^2 reduced by that part of the variance which is explained by the regression of A on B (Figure 3). σ_{EA} was calculated for B values ranging from -0.4 to -2.0 and remained almost constant, having the value $\sigma_{EA} = 10.0$ ms, thus giving a σ_{EA}^2 value of 100 ms². The expected value of $LVET_j$ is given by

$$LVET_{Ej} = A + B \cdot HR_j$$

where HR_j and $LVET_j$ are the measured values of heart rate and LVET. σ_{LVET}^2 is an estimate of the variance of the measurement of LVET due to all sources of experimental error. From preliminary studies and from knowledge of the resolution of the analysis system, σ_{LVET} was estimated to be of the order of 6 ms.

Similarly, for QS_2 equation (6) reduces to:

$$M_2 = \frac{(C - \bar{C})^2}{\sigma_{EC}^2} + \frac{(D - \bar{D})^2}{\sigma_D^2} + \sum_j \frac{(QS_{2j} - QS_{2Ej})^2}{\sigma_{QS_2}^2} \quad (11)$$

where C_E replaces $\bar{C}$ and is given by equation (8). The variances were estimated as $\sigma_{EC}^2 = 100$ ms², and $\sigma_{QS_2}^2 = 36$ ms², and the expected value of QS_{2j} is given by

$$QS_{2Ej} = C + D \cdot HR_j.$$

Thus by minimising the functions M_1 and M_2 in equations (10) and (11) it was possible to estimate the values of the parameters A, B, C and D. A programme was written to carry out this minimisation procedure on the Varian Computer (Appendix A). The final values of the parameters A and B are given in Table 3 where the subscripts 1, 5 and T refer to the parameter estimates obtained by using the first, the first five and all the data points in each set. Similar results were obtained for C and D. The subscript R refers to the parameter values obtained by linear regression using all the data points in each set. As expected, the values obtained using all the data points (e.g. A_T and A_R , etc.) showed very good agreement. This reflects the fact that the more data that are available, the less is the importance of the assumptions of the prior distribution in the minimisation of M, i.e., the relative magnitudes of the first two terms in equations (10) and (11) with respect to M_1 and M_2 decrease as n increases. Conversely, if there are only a few data points

Figure 3 Diagrammatic representation of the regression relationship between two parameters, e.g. A and B. σ_{EA}^2 is the value of σ_A^2 reduced by that part of the variance explained by the regression of A on B.

available, then the role of the prior distribution becomes relatively more important, and in the complete absence of data the best estimates of the parameter values are the population means. However, even using only the first data point (i.e. a resting, pre-dose value) there were highly significant correlations between the predicted parameter values and those obtained by linear regression of all data points (Figures 4 and 5) thus:

$$\begin{aligned} A_R &= 1.03 A_1 - 10.6, r = 0.96, \text{d.f.} = 16, P < 0.001 \\ B_R &= 1.06 B_1 - 0.09, r = 0.87, \text{d.f.} = 16, P < 0.001 \\ C_R &= 0.89 C_1 + 59.1, r = 0.97, \text{d.f.} = 16, P < 0.001 \\ \text{and } D_R &= 0.85 D_1 - 0.21, r = 0.91, \text{d.f.} = 16, P < 0.001 \end{aligned}$$

Figure 4 Relationship between parameter values predicted from one observation (A_1 or B_1) and values derived from regression of all available data (A_R or B_R). (●) represents the 18 data sets included in the population. (×) represents the six subjects not included in the population.

Table 3 Predicted values for parameters A and B using the first (A_1, B_1), the first five (A_5, B_5) and the total number of data points (A_T, B_T), and also the values of A and B obtained by linear regression of the total number of data points (A_R, B_R).

Subject	A_1	B_1	A_5	B_5	A_T	B_T	A_R	B_R
1a	313	-0.65	316	-0.68	314	-0.65	316.3	-0.68
1b	317	-0.67	332	-0.82	322	-0.66	321.1	-0.65
1c	336	-0.86	319	-0.69	329	-0.83	327.9	-0.82
2a	388	-1.29	383	-1.25	377	-1.15	374.3	-1.10
2b	392	-1.33	388	-1.31	380	-1.09	382.4	-1.12
2c	387	-1.28	383	-1.25	377	-1.12	373.0	-1.05
3a	405	-1.42	414	-1.51	403	-1.30	401.1	-1.27
3b	419	-1.53	422	-1.56	424	-1.61	428.0	-1.66
3c	418	-1.54	416	-1.52	430	-1.75	432.1	-1.78
4a	377	-1.19	381	-1.26	392	-1.51	394.2	-1.55
4b	388	-1.29	385	-1.25	391	-1.36	391.4	-1.37
4c	385	-1.27	387	-1.29	391	-1.38	391.2	-1.38
5a	350	-0.95	356	-1.01	344	-0.81	346.0	-0.83
5b	350	-0.95	354	-0.98	349	-0.91	351.3	-0.93
5c	363	-1.07	371	-1.14	365	-1.04	365.3	-1.04
6a	383	-1.24	396	-1.36	391	-1.25	389.8	-1.23
6b	379	-1.21	379	-1.18	374	-1.09	373.1	-1.08
6c	381	-1.23	391	-1.29	382	-1.15	380.9	-1.14

Figure 5 Relationship between parameter values predicted from one observation (C_I or D_I) and values derived from regression of all available data (C_R or D_R). (●) represents the 18 data sets included in the population. (×) represents the six subjects not included in the population.

Data from six other subjects who were studied with the same protocol were available and a single pre-dose reading from each was used to predict the values of the regression parameters. These are also shown in Figures 4 and 5 and tabulated in Table 4. Similarly, there was a fairly close agreement between the predicted and regression values. The expected values of LVET and QS_2 were calculated in the heart rate range of 40–70 beats/min on the basis of the regression lines and also those predicted from the single data point (Table 5). There was very good agreement between the

values obtained by both techniques, indicating that it was possible to predict prospectively the values of the regression parameters.

Discussion

Useful information about the inotropic effect of drugs can be gained from measurement of systolic time intervals. Considerable doubt, however, has been expressed about the methods used to correct STI for the variations in heart rate which often accompany drug induced inotropic effect. This has particular relevance when the effects of single doses are being studied in individual subjects. In this paper we present a method which allows the parameters of the LVET *v* heart rate and QS_2 *v* heart rate regression equations to be predicted for each individual when only resting values of heart rate, LVET and QS_2 are available. As the predictions agree well with parameter values obtained by increasing the heart rate pharmacologically with atropine, we feel confident that this kind of predictive approach could preclude other, more demanding protocols which would not be suitable for many patients.

The statistical technique is based on Bayes' theorem and the method of maximum likelihood, and is dependent on good estimates of population parameter values. In the present study, the population estimates were derived from 28 sets of data, 18 of which were obtained as repeated measures from six subjects although no allowance was made for replicates. The greater the number of data sets, the better will be the estimates of the population values, and the equations representing the relationship between the parameters, (7) and (8), will need slight adjustment as more data becomes available. However, even with these slight reservations about the size of the existing population sample, predictions made for six subjects whose data did not form part of the original population were very encouraging. Further study of the influence of population parameter values on the precision of predicted values is still required, and it remains to be determined whether the values obtained in this study from normal adult volunteers are equally applicable to patients.

Table 4 Predicted values for parameters A, B, C and D using the first data point (A_I , B_I , C_I , D_I) and also the values obtained by linear regression of the total number of data points (A_R , B_R , C_R , D_R).

Subject	A_I	B_I	A_R	B_R	C_I	D_I	C_R	D_R
TK	403	-1.43	394.2	-1.27	496	-1.36	492.2	-1.27
EM	375	-1.15	375.8	-1.20	470	-1.16	474.6	-1.26
RW	383	-1.25	407.2	-1.82	491	-1.33	500.5	-1.56
SM	371	-1.14	387.5	-1.45	505	-1.43	482.6	-1.11
MS	375	-1.17	375.5	-1.22	475	-1.19	459.9	-0.96
HD	382	-1.23	415.4	-1.73	488	-1.30	511.7	-1.67

Table 5 Expected values of LVET and QS₂ at different heart rates obtained using predicted (LVET₁, QS₂₁) and regression (LVET_R, QS_{2R}) parameter values.

Heart rate (beats/min)	40		50		60		70	
	LVET ₁	LVET _R	LVET ₁	LVET _R	LVET ₁	LVET _R	LVET ₁	LVET _R
Subject								
TK	346	343	332	331	317	318	303	305
EM	329	328	317	316	306	304	295	292
RW	333	334	321	316	308	298	296	280
SM	325	328	314	314	303	301	291	285
MS	328	327	317	315	305	303	293	291
HD	333	346	321	329	308	311	296	294

Heart rate (beats/min)	40		50		60		70	
	QS ₂₁	QS _{2R}	QS ₂₁	QS _{2R}	QS ₂₁	QS _{2R}	QS ₂₁	QS _{2R}
Subject								
TK	442	441	428	429	414	416	401	403
EM	424	425	412	412	400	399	389	387
RW	438	439	425	423	411	407	398	392
SM	448	439	434	428	419	416	405	405
MS	427	422	416	412	404	402	392	393
HD	436	445	423	429	410	412	397	395

Finally, it is possible that the parameters describing the relationship between A and B and also C and D in equations (7) and (8) should be modelled in a similar manner to the other model parameters, but the data in the present study did not allow this.

If small changes in inotropic activity are to be measured accurately, volunteer subjects or patients should be considered individually and careful corrections made for changes in systolic time intervals which result from fluctuations in heart rate. Without resorting to any kind of protocol—other than recording the heart rate and systolic time intervals at rest—individual correction factors can be obtained by applying the predictive techniques outlined in this paper. The prerequisite is a knowledge of the average values of the STI *v* HR regression parameters in the population of interest, but once these have been defined, a move from mean values to those appropriate to the individual should ensure a higher degree of confidence in the assessment of inotropic effect.

Appendix

Considering only the case of LVET, the log likelihood function M (equation (6)) reduces to equation (10) *viz.*

$$M_1 = \frac{(A - A_E)^2}{\sigma_{EA}^2} + \frac{(B - \bar{B})^2}{\sigma_B^2} + \sum \frac{(LVET_j - LVET_{Ej})^2}{\sigma_{LVET}^2}$$

The expected value for the parameter A, i.e. A_E, is dependent on B, thus

$$A_E = Q_1 + Q_2 \cdot B$$

and the variance for this parameter is therefore the reduced value σ_{EA}^2 .

The expected value for each LVET measurement is related to the corresponding HR by the equation

$$LVET_{Ej} = A + B \cdot HR_j$$

The problem thus simplifies to that of finding the values of the parameters A and B which minimise the function M₁. These can be obtained by solving simultaneously the two linear equations

$$\frac{\partial M_1}{\partial A} = 0$$

$$\text{and } \frac{\partial M_1}{\partial B} = 0.$$

$$\frac{\partial M_1}{\partial A} = 0 \text{ gives}$$

$$A \left(\frac{1}{\sigma_{EA}^2} + \frac{n}{\sigma_{LVET}^2} \right) - B \left(\frac{Q_2}{\sigma_{EA}^2} - \frac{\sum (HR_j)}{\sigma_{LVET}^2} \right) - \left(\frac{Q_1}{\sigma_{EA}^2} + \frac{\sum (LVET_j)}{\sigma_{LVET}^2} \right) = 0.$$

which can be written as

$$A \cdot k_1 - B \cdot k_2 - k_3 = 0 \quad (12)$$

where

$$k_1 = \frac{1}{\sigma_{EA}^2} + \frac{n}{\sigma_{LVET}^2}$$

$$k_2 = \frac{Q_2}{\sigma_{EA}^2} - \frac{\sum (HR_j)}{\sigma_{LVET}^2}$$

$$\text{and } k_3 = \frac{Q_1}{\sigma_{EA}^2} + \frac{\sum (LVET_j)}{\sigma_{LVET}^2}$$

$\frac{\partial M_1}{\partial B} = 0$ gives

$$A \left(-\frac{Q_2}{\sigma_{EA}^2} + \frac{\sum(HR_j)}{\sigma_{LVET}^2} \right) + B \left(\frac{1}{\sigma_B^2} + \frac{Q_2^2}{\sigma_{EA}^2} + \frac{\sum(HR_j)^2}{\sigma_{LVET}^2} \right) + \left(-\frac{\bar{B}}{\sigma_B^2} + \frac{Q_1 Q_2}{\sigma_{EA}^2} - \frac{\sum(HR_j \cdot LVET_j)}{\sigma_{LVET}^2} \right) = 0$$

which can be written as

$$A \cdot k_4 + B \cdot k_5 + k_6 = 0 \quad (13)$$

$$\text{where } k_4 = -\frac{Q_2}{\sigma_{EA}^2} + \frac{\sum(HR_j)}{\sigma_{LVET}^2} = -k_2$$

$$k_5 = \frac{1}{\sigma_B^2} + \frac{Q_2^2}{\sigma_{EA}^2} + \frac{\sum(HR_j)^2}{\sigma_{LVET}^2}$$

$$\text{and } k_6 = -\frac{\bar{B}}{\sigma_B^2} + \frac{Q_1 Q_2}{\sigma_{EA}^2} - \frac{\sum(HR_j \cdot LVET_j)}{\sigma_{LVET}^2}$$

Equations (12) and (13) are then solved for A and B to give

$$A = \left(\frac{k_3 k_5 - k_2 k_6}{k_1 k_5 + k_2 k_4} \right) \quad (14)$$

$$\text{and } B = -\left(\frac{k_1 k_6 + k_3 k_4}{k_1 k_5 + k_2 k_4} \right) \quad (15)$$

For QS_2 , HR data, the QS_2 values are substituted for LVET, and the optimal values of the parameters C and D obtained in a similar fashion.

Example

The first five date points measured for subject EM are given in Table 6.

Table 6 First five heart rate and LVET readings for subject EM.

Heart rate (beats/min)	LVET (ms)
55.1	312
55.5	312
49.0	318
51.1	318
49.1	318

If the population parameter values are taken as:

$$\bar{B} = -1.08, \quad \sigma_B^2 = 0.16.$$

with the expected value of A given by the relationship

$$A_E = 254.3 - 104.2 \cdot B$$

$$\text{i.e. } Q_1 = 254.3, \quad Q_2 = -104.2$$

and the reduced variance of A as $\sigma_{EA}^2 = 100 \text{ ms}^2$, the estimated variance in the LVET measurement given by

$$\sigma_{LVET}^2 = 36 \text{ ms}^2$$

then considering only the first data point, i.e.

$$HR = 55.1 \text{ bcats/min}, \quad LVET = 312 \text{ ms}$$

gives values for k_1 to k_6 of:

$$k_1 = 0.0378$$

$$k_2 = -2.574$$

$$k_3 = 11.210$$

$$k_4 = -k_2 = 2.574$$

$$k_5 = 199.37$$

$$\text{and } k_6 = -736.02.$$

Thus the estimated values for A and B (equations (14) and (15)) are:

$$A = 375.0, \quad B = -1.15.$$

Similarly if all five data points given in Table 6 are used, the values of k_1 to k_6 are

$$k_1 = 0.149$$

$$k_2 = -8.260$$

$$k_3 = 46.376$$

$$k_4 = -k_2 = 8.260$$

$$k_5 = 491.13$$

$$\text{and } k_6 = -2534.95$$

giving estimated values of A and B of

$$A = 375.2, \quad B = -1.15.$$

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