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Systolic time intervals — Correction for heart rate

Systolische Zeitintervalle — Frequenzkorrekturmethoden

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With 6 figures and 2 tables

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Summary

Shortening or prolongation of the systolic time intervals (STI) are frequently used as non-invasive measure of drug influence upon the left ventricular function of the heart. STI, however, are shortened by increasing heart rate (HR) alone.

Because of the dependence on HR, STI may be changed though treatment did not influence the course of contraction.

In this study dependence of STI on HR and the corrections of STI for HR have been reevaluated. The analysis of data gained from 82 subjects under strictly standardized conditions has shown:

1. A linear relation between HR and STI cannot be confirmed. On the contrary it must be assumed that STI are dependent linearly on the R-R-interval (RRI).
2. On application of correction formulae deduced from other populations it is possible to arrive at results with a bias. That way, changes of HR may simulate or hide changes in the course of contraction.
3. In treatments that are effective on HR as well as inotropy, the inotropic action may be evaluated falsely by application of such a method.

As corrective methods not liable to such a bias, bivariate analyses, such as the analysis of covariance, are described, based on the relation between STI and RRI existing in the respective data.

For the evaluation of the mechanical heart function non-invasive methods gain increasing importance. Among these methods systolic time intervals (STI) as indicators of contractility are frequently used to analyze human pharmacology of cardioactive drugs (1, 2, 11, 12, 14).

Systolic time intervals (in detail: QS_2 = total electromechanical systole, PEP = pre-ejection period, and LVET = left ventricular ejection time) are recorded by simultaneous registration of ECG, phonocardiogram and carotid artery pulse. *Blumberger* (4, 5) has described this method about 35 years ago and has investigated the influence of various conditions and drugs on these parameters (5).

Among the factors influencing STI, heart rate (HR) is of major importance, and it is long known that STI are being shortened by increasing HR (4, 5, 21). HR is often altered directly by treatment and STI are being changed secondarily. In order to rule out the influence of HR, various correction formula were developed. Linear regressions between STI and HR according to *Weissler* have become most popular (31, 34).

In several papers (5, 9, 35) large sample investigations have been published. However, the shape of the respective scatter diagrams between HR and STI is non-linear. *Blumberger* (5) and *Willems* and *Kesteloot* (35) were the only ones to discuss this fact. *Willems* and *Kesteloot* (35) found a slightly higher correlation coefficient between the RR-interval (RRI) and LVET than between HR and LVET. But only for a population with ill patients they rejected the hypothesis of *Weissler*. For normal populations they come, nevertheless, to the conclusion, that a linear relation between HR and LVET can be accepted if the (related) correlation coefficients are tested.

May be that the comparison of related correlation coefficients is very popular, but it is surely not the best method to test for linearity.

Nevertheless, in the meantime many papers concerned with drug effects and STI have been published, applying the rate correction according to *Weissler* (1, 2, 3, 10, 11, 12, 14, 15, 22, 25, 29, 30, 32, 33).

Therefore the aims of this study are:

1. To perform a new analysis of the relation between STI and HR in a collective under strictly standardized conditions, and to compare the results with those of *Weissler*.
2. To adapt different biometric methods which are more adequate than those used so far. The adapted methods should allow a correction of STI for the influence of HR or rather the RRI.

Methods

Registrations

82 young, healthy, male, fasting (more than 10 h) students were the subjects of this study. Distribution of age, body weight, and height is shown in table 1. Investigations took place between 8.00 and 11.00 a.m. after a 30-minute resting period (head and upper part of the body tilted by 15 °) in a fully air-conditioned room (temperature 24 °C, relative humidity 60 %, constant artificial light).

Table 1. Distribution of age, body weight, and height in 82 subjects.

	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Age (years)	19	22	24	25	29
Weight (kg)	53	65	70	76	100
Height (cm)	167	176	180	183	196

The following parameters were registered simultaneously with a 3-channel-jet recorder (Cardirex 3 T, Siemens) at 100 mm/s:

Ecg (lead A according to *Nehb*),
Phonocardiogram in the 4th intercostal space left parasternal *(Nennfrequenz* according to *Maas* and *Weber* [20]: 140 Hz),
Puls of the right carotid artery with an *Infraton* puls receptor according to *Brecht* and *Boucke* (8). Figure 1 shows a representative registration.

For measurement of each variable ten consecutive heart actions were evaluated and their arithmetic mean utilized for the subsequent analysis.

From the ten heart cycles the following variables were measured estimating down to 0.1 mm (≙ 1 ms):

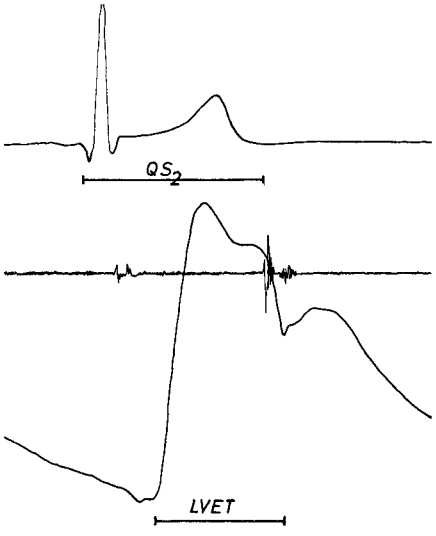


Fig. 1. Representative registration of electrocardiogram lead A *(Nehb)*, phonocardiogram, and carotid pulse.

RRI the RR-interval.
QS_2 from the beginning of the QRS-complex till the beginning of the high frequency portion of the aortic component of the second heart sound
LVET from the beginning of the steep rise till the incisura of the carotid pulse curve.
PEP as difference between QS_2 and LVET.
Heart rate was calculated by dividing 60 by the mean RRI.

Statistics

Because of the widespread use, for statistical analysis standard methods based on the assumption of linear models and the theory of normal distribution were used as far as possible. Necessary calculations were carried out as far as possible with standard programs, such as the SPSS and the SSP. For non parametric methods adequate computer programs have been developed using ISO-FORTRAN.

Calculations were done on the IBM/370–168 of the Heidelberg University computer center (Programs may be obtained from the first author. They are generally applicable as far as FORTRAN normcompilers are available).

The analysis of covariance is essentially a combination of analysis of variance and regression analysis. If we have to compare only two randomized treatment groups, the t-test being the square root of the analysis of variance-F-test in the two sample case, may be used.

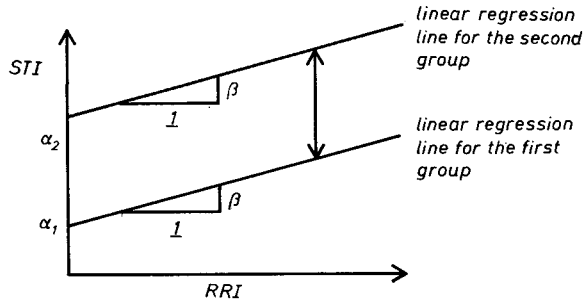
Thus, a combination of regression and t-test is described here as an analysis of covariance.

The statistical model is:

$y_{ij} = \alpha_i + \beta\, x_{ij} + e_{ij}$
$i = 1, 2$; i.e. the first and the second treatment group (sample)
$j = 1, 2, \ldots, n_i$; i.e. first to n-th subject within the i-th treatment group
y_{ij} : the observed STI
α_i : the expected value of STI after elimination of the influence of RRI, with other words: the "corrected STI"
β : regression coefficient, (slope) due to
x_{ij} : the RRI
e_{ij} : random error ($\sim N\,[O, \sigma^2]$)

We assume the x_{ij} to be measured with negligibly small error.

As a geometrical interpretation for the model of analysis of covariance we may use the following sketch:



The relation between RRI and STI of the two treatment groups is described by straight lines with slope β but different intercepts α_i. We are interested in the difference of the STI between the two lines. This is visualized by the arrow.

For practical purposes, first, the common regression coefficient b for both groups (samples) between RRI as independent variable and STI is calculated. b is the estimator for β. Then the t-test with the residuals is to be performed with only $n_1 + n_2 - 3$ degrees of freedom, because one degree of freedom is lost for the regression coefficient.

Using standard methods adapted to the special problem, calculation proceeds as follows:

Step 1

For both samples $i = 1$ resp. 2

SQ_{x_i} : the sums of squares for x_{ij}

$$SQ_{x_i} = \sum_{j=1}^{n_j} (x_{ij} - \bar{x}_i)^2 = \sum_{j=1}^{n_j} x^2_{ij} - \frac{1}{2} \left(\sum_{j=1}^{n_j} x_{ij}\right)^2$$

and

$SP_{x_i y_i}$: the sums of cross products for the corresponding x_{ij} and y_{ij}

$$SP_{x_i y_i} = \sum_{j=1}^{n_i} (x_{ij} - \bar{x}_i)\,(y_{ij} - y_i) = \sum_{j=1}^{n_i} x_{ij} y_{ij} - \frac{1}{n_i} \left(\sum_{j=1}^{n_i} x_{ij}\right) \left(\sum_{j=1}^{n_i} y_{ij}\right)$$

are calculated by using standard regression methods. After this calculation we obtain one SQ and one SP for each group.

Step 2

Then, the common empirical regression coefficient b, i.e. the slope of the regression lines is calculated:

$$b = \frac{SP_{x_1 y_1} + SP_{x_2 y_2}}{SQ_{x_1} + SQ_{x_2}}$$

The regression functions for the two different groups are:

$$\hat{y}_1 = (\bar{y}_1 - b\bar{x}_1) + bx$$
$$\hat{y}_2 = (\bar{y}_2 - b\bar{x}_2) + bx$$

Step 3

For any observed RRI the corresponding expected STI ($\hat{Y}_i$) is calculated using the regression line of the sample. Then, the difference between the observed and the calculated expected STI is formed (= △ STI).

These residuals (△ STI) are entered to the usual t-test for independent samples. In contrast to the usual t-test, however, we have only $n_1 + n_2 - 3$ degrees of freedom.

For presentation of results the following two ways seem to be adequate:

1. In a scatter diagram with single points the regression lines are plotted. The vertical distance between the two lines represents the difference between the two groups (compare to sketch page 88).
2. The STI are projected to the ordinate, which means to a hypothetical RRI with value zero. The corresponding formula is:

$$y_o = y_{ij} - bx_{ij} \qquad (STI_o = STI - b\ RRI).$$

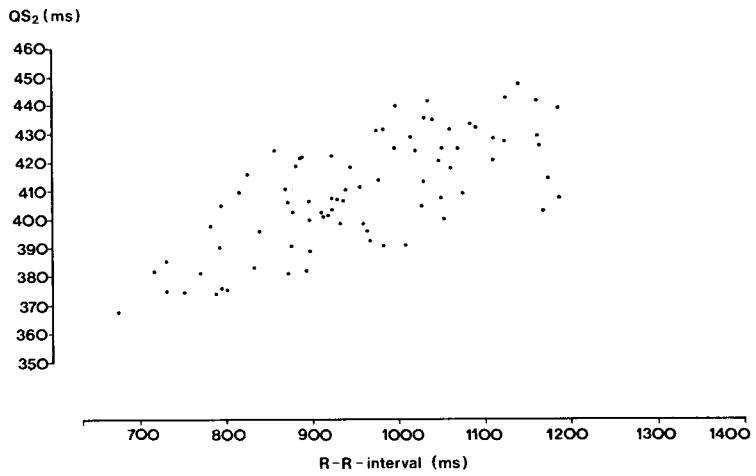


Fig. 2. Scatter diagram of total electromechanical systole (QS_2) versus R-R-interval.

Results of measurements

In figures 2 to 4 measured values of STI in dependence of RRI are shown in scatter diagrams. Between RRI and QS_2 resp. LVET obviously a higher degree of association exists than between RRI and PEP.

Biometric results, analysis and discussion

Linearity of interdependence between STI on the one hand and HR and RRI on the other hand has been tested by a method according to *Weber* and *Brott* (28). This method is based on the test for the square part of polynominal regression.

The results have shown that the hypothesis of linearity for the relation between HR and STI is rejected at the 5 % level of significance. For the relation between STI and RRI it can be maintained, though. As HR is proportional to the reciprocal value of RRI (HR = 60/RRI) the relation

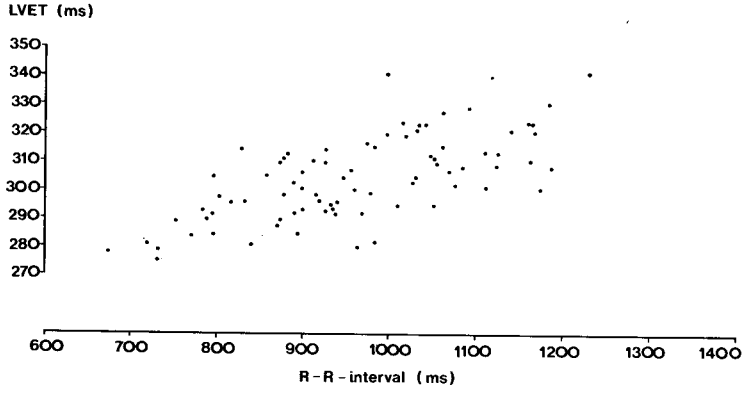


Fig. 3. Scatter diagram of left ventricular ejection time (LVET) versus R-R-interval.

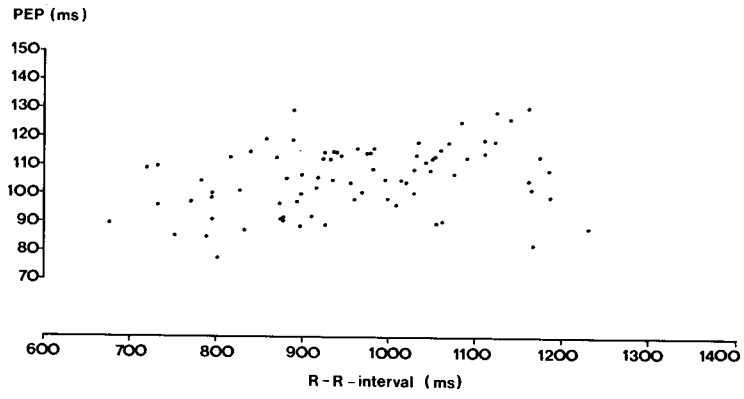


Fig. 4. Scatter diagram of preejection period (PEP) versus R-R-interval.

between HR and STI can only be described as a hyperbole. This is because linear relations of the form $y = ax$ become non linear if x is exchanged by $\frac{1}{x}$, and $y = \frac{a}{x}$ describes rectangular hyperboles.

Weber and *Brott*'s method is particularly suitable as it displays most accurately concave and convex alternatives. Comparisons of correlation coefficients obtained by application of different regression functions are inefficient and not a suitable test for linearity. This becomes obvious already in respect to the dependence obtained by common data in contrast to the independence required for comparison. Therefore other investigators (34, 35) were unable to reach a conclusion concerning the regression functions.

Correlations between STI and RRI are shown in table 2. It is remarkable that PEP, as a whole, is correlated with other variables on a lower scale than these variables among themselves.

Table 2. Correlation coefficients.

	QS_2	LVET	PEP
RRI	0.75	0.72	0.37
QS_2		0.81	0.66
LVET			0.11

Correlations between RRI and STI are somewhat lower than those mentioned by other authors (35), not because our deviations about the regression are larger, but because the dispersion of HR is reduced probably due to stricter standardization of test conditions. Thus in the *norm collective* of *Willems* and *Kesteloot* (35) the range of HR was between 40 and 120 beats/min. It is questionable whether such a wide range can still be called *normal*.

Comparison of Weissler's method with the here proposed correction method

The differences between the results of *Weissler* and results obtained by the new method may be thought to be small enough to be neglected. But the following three theoretical experiments are outlined and the newly proposed methods are delineated to demonstrate the shortcomings which may occur if the *Weissler* method is used:

1. Confrontation of two collectives different in HR only.
2. Influence of an exclusively rate-directed hypothetic therapy.
3. Influence of an exclusively contractility-directed hypothetic therapy.

Ad 1: Data of the 82 test subjects were arranged according to the RRI resulting in two approximately equally large groups, one above and one below the median. These two groups have to be considered similar in respect to their STI corrected for heart rate. But if the rate correction method according to *Weissler* is applied these two collectives differ sig-

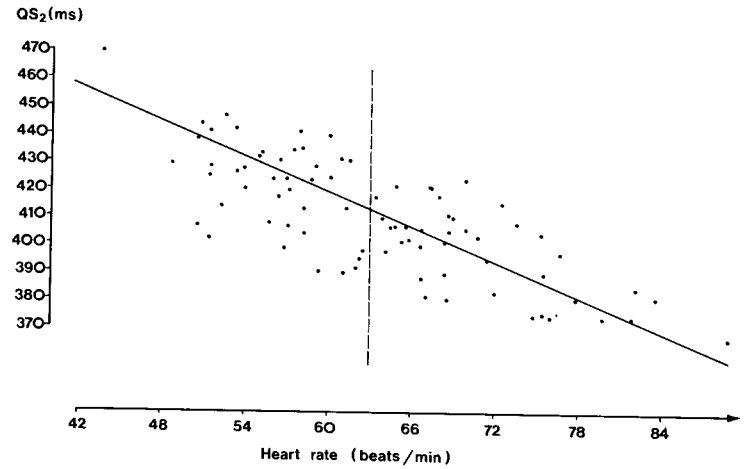


Fig. 5. Scatter diagram of QS_2 versus heart rate. The dashed line represents the median dichotomy of heart rates. The regression line according to *Weissler* (31, 34) is shown.

nificantly in respect to their *rate corrected* QS_2 ($t = 2.14$, $p < 0.05$). We arrive at a bias such that the group with the lower heart rate would be estimated to have a shorter duration of STI corrected for heart rate; a fact which may lead to the conclusion of a better contraction state of the latter group.

Figure 5 shows that dependence of QS_2 on HR existing in our collective is different from the regression line according to *Weissler*.

Ad 2: By randomization using random digits the whole sample is divided into two parts with 41 test persons each. Then the supposition was made that an exclusively rate-directed therapy was working on one of

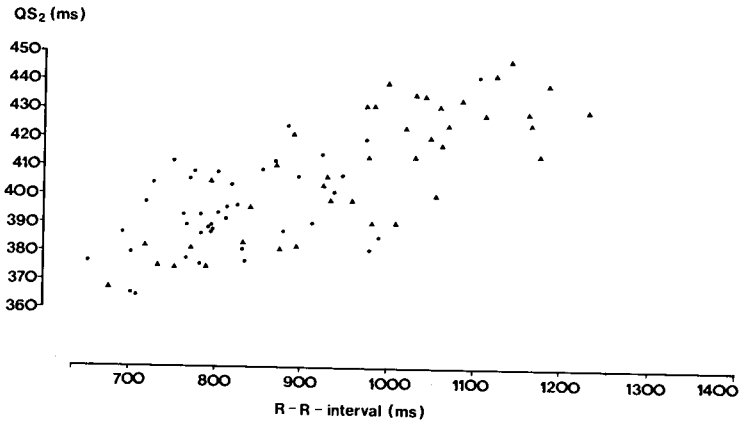


Fig. 6. Result of a hypothetical experiment with diminuation of heart rate for ten beats per minute. Triangles represent changed values.

the two collectives. This would mean a respective changing of QS_2 as well. This relation was computed according to that one present in the data between RRI and QS_2. The calculations were based on a rise of heart rate by 10 beats per minute.

The test-results thus obtained are depicted in figure 6. It was tested statistically whether a "change of contractility" had taken place. Once, a rate correction according to *Weissler* was performed. The result is a significant difference in the mean "*Weissler*-corrected" QS_2 between the two random samples ($t = 2.13$, $p < 0.05$). Such a difference should by no means arise, as a rate effect only was imitated. By applying an analysis of covariance no such differences can be demonstrated between the two collectives.

Another peculiarity arises, when the residuals are tested for normality after application of the two different correction methods. Application of the *Shapiro-Wilk*-test (24) yields the result that the hypothesis of normal distributions about regression can be maintained on the basis of a linear relation between RRI and STI. In the rate corrected results according to *Weissler* the hypothesis of normal distribution is rejected at the 5 % level of significance.

Ad 3: This test was performed like test 2, the only difference being that the rates were not changed, whereas QS_2 was changed for 5 ms in the direction of a prolongation. This corresponds to an effect exclusively directed on cardiac performance.

On application of analysis of covariance the expected significant difference ($t = 2.17$, $p < 0.05$) is found. On application of a rate correction according to *Weissler*, however, this difference is blurred by the correction method ($t = 1.98$, $p > 0.05$).

Discussion

The relation between RRI and STI used in this study was arrived at by an interindividual "epidemiologic" test. As in all such evaluation results a conclusion concerning the *causality* is not admissable (6, 17). In physiologic investigations, however, this connection has been established sufficiently (27).

If our method is used to evaluate data of therapeutic trials caution is recommended. Statistically speaking changes in the covariance matrix by treatment may be encountered under pathologic cardiac conditions, this means a possible change in the slope of the linear relationship between RRI and STI. Furthermore changes in the variance of RRI as well as in the variance about the regression between RRI and STI may occur. This is to be expected, as the basic pathologic derangements and their effects may influence STI (5, 32, 33). With an application of the method under conditions of human pharmacological experiments in normal individuals, however, slope and variance are unchanged (16).

Pathological conditions render methods mandatory that are robust towards deviations from the mathematical parametric model. Non parametric methods are especially adequate, and for this bivariate problem

with a monotone relation between STI and RRI the bivariate rankscore test according to *Puri* and *Sen* (23) is suitable. A respective computer-program was developed. Further experience will show whether differences in covariance matrices are eliminated by the sole application of rank-transformation. Otherwise methods as described by *Puri* and *Sen* (23, p. 398–399) have to be adopted.

Sometimes it is expedient for practical reasons – such as difficulty or danger in treatment – to devise unequal sample sizes; i.e. the control collective has to comprise more subjects than the treatment collective. Before starting the experiment, the statistical design of such a study has to be planned very carefully.

Conclusions

On the grounds of the dependence of STI on HR it appears necessary to eliminate the influence of HR. Otherwise biases may arise in the evaluation of treatments influencing HR as well as left ventricular function. We were able to demonstrate that methods performing such corrections by means of a regression between HR and STI gained only once in a (non-representative) collective may lead to new constant errors.

A solution to this problem is considered to be the application of analysis of covariance or bivariate analyses based on the correlation between RRI and STI to be determined anew for each of the respective experiments.

Zusammenfassung

Die systolischen Zeitintervalle (STI) werden häufig als noninvasive Maße für den Einfluß von Medikamenten auf die Funktion des linken Herzventrikels verwendet. STI werden jedoch auch bei isolierter Veränderung der Herzfrequenz beeinflußt.

Wegen der Abhängigkeit von der Herzfrequenz können die STI auch dann verändert werden, wenn die Behandlung den Kontraktionsverlauf nicht beeinflußt.

In der vorliegenden Arbeit wird die Abhängigkeit der STI von der Herzfrequenz und die Korrektur der STI für den Frequenzeinfluß überprüft. Die Analyse der Daten von 82 Versuchspersonen unter streng standardisierten Bedingungen zeigt:

1. Eine lineare Beziehung zwischen der Herzfrequenz und den STI läßt sich nicht bestätigen. Dagegen muß geschlossen werden, daß STI linear vom RR-Intervall abhängt.
2. Wenn Korrekturformeln angewendet werden, die von Daten herrühren, die an anderen als dem in der einzelnen Studie auftretenden Kollektiv gewonnen wurden, so ist es möglich, daß die Resultate verfälscht sind. Auf diese Weise können Veränderungen der Herzfrequenz Veränderungen im Kontraktionsverlauf vortäuschen oder verbergen.
3. Bei Behandlungen, deren Effekt sowohl auf die Herzfrequenz als auch auf die Inotropie gerichtet ist, kann die inotropische Wirkung bei Anwendung vorgegebener Korrekturformeln fehlerhaft eingeschätzt werden.

Als Korrekturmethoden, die solche Verfälschungen nicht hervorrufen, werden in dieser Arbeit bivariate Analysen wie die Kovarianzanalyse beschrieben. Diese Methoden stützen sich auf die Relation zwischen STI und RR-Intervall in den jeweiligen Daten.

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