The Initial Systolic Time Interval in patients with spinal cord injury measured with impedance cardiography

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Abstract. The Initial Systolic Time Interval (ISTI), obtained from the electrocardiogram and impedance cardiogram, is considered to be a measure for the time delay between the electrical and mechanical activity of the heart. This time delay is influenced by the sympathetic nerve system. Therefore, an observational study was performed in a group of patients (SCI) with spinal cord injuries. The relationship between the ISTI and the total heart cycle (RR-interval) was established by varying the RR-interval using an exercise stimulus to increase the heart rate. The slope of this relationship was observed to be significantly higher in the SCI-group as compared with a control group, although there was no difference in ISTI in the range of common heart rates during the test between the groups. This slope and the ISTI was observed to be significantly different in an acute patient having a recent spinal cord injury at a high level. Because of the variety in injury levels and incompleteness of the injuries further, more specific research is necessary to draw decisive conclusions with respect to the contribution of autonomic nervous control on the ISTI in SCI, although the present observations are notable.

1. Introduction

When the electrical impedance of a human thorax is measured a variation synchronous with the heart activity can be observed. The time derivative of this variation is called the Impedance CardioGram (ICG). Numerous studies during the last decades have demonstrated that the origin of this ICG-signal is too complicated to interpret the amplitude of this signal simply as a measure of cardiac stroke volume \cite{1, 2, 3, 4}. However, Meijer \textit{et al} \cite{5} have suggested that an interesting aspect of the ICG can be found in the time relationships of this signal with the Electro CardioGram (ECG). Regardless of the multiple sources of the signal, the ICG reflects the mechanical aspects of cardiac activity, while the ECG reflects the electrical aspects. Therefore, by recording both signals simultaneously, the time difference between electrical and mechanical events in the cardiac cycle can be studied. This concept was implemented by defining the Initial Systolic Time Interval (ISTI) as the time difference between the R-point in the ECG and by the C-point in the ICG. ISTI can be studied in various physiological conditions and clinical circumstances and may be helpful to evaluate patho-physiological processes and rehabilitation processes. The use of ISTI for diagnostic purposes is attractive: both ECG and ICG
signals can be obtained fast and easily. The measurements are non-invasive, of low burden to patients and are not restricted to a clinical environment. The required technical equipment is relatively inexpensive, portable and easy to operate.

Up to date little is known about the behaviour of the ISTI in various patho-physiological and clinical circumstances. There is a need for observational research to reveal the behaviour of the ISTI under these circumstances. In theory the ISTI is influenced by at least three factors: the preload of the heart, afterload of the heart and autonomic nervous control. The influence of the preload on the ISTI was demonstrated in patients admitted to an intensive care unit after coronary artery bypass surgery [6]. The ISTI was measured before and after intravenous fluid administration. A significant relationship between the ISTI and the cardiac output was observed, reflecting the influence of preload on the ISTI. In another study [7] the influence of preload as well as sympathetic nerve activity on the ISTI was demonstrated during a breathing stimulus in a group of healthy subjects. The ISTI, and the related parameter PEP, has been reported to be controlled by the sympathetic nervous system [5,8]. These observations justify investigation of the possible use of the ISTI as a diagnostic measurement tool in rehabilitation medicine.

A spinal cord injury (SCI) leads to a partial or complete loss of function below the level of the injury. Depending on the level and (in)completeness of the lesion it leads to a wide range of different medical and health conditions including effects on cardiac function [9]. Factors such as inactivity of the ‘muscle pump’ in the legs, venous blood pooling in the legs can cause a reduced venous blood return to the heart resulting in a lower preload. Moreover, physical inactivity is often reported in the SCI population [10], which is a major risk factor for developing of cardiovascular diseases. Furthermore, in subjects with a lesion above level T4 problems with regulation of the heart rate and strength of contraction during exercise can occur, due to damaged sympathetic nerves [11]. Therefore, the aim of this study was to investigate whether the relationship between ISTI and RR-interval differed in subjects with a SCI compared with able bodied subjects.

2. Methods
2.1. ICG and ECG recordings
ICG recordings were made using the method described by Meijer et al. [5]. A typical example of a simultaneous recording of the ICG and ECG signal is shown in figure 1. The Initial Systolic Time Interval (ISTI) is the time interval between the R-peak in the ECG and C-wave in the ICG signal.

![Figure 1. Example of simultaneous registration of an ICG and an ECG](image)

| Table 1. Characteristics of the subjects |
|-----------------------------------------|
| SCI group (N=7) | controls (N=9) |
| age (years) | 46 ± 14 | 50 ± 11 |
| Male/Female | 2M/5F | 3M/6F |
| Height (cm) | 172 ± 7 | 170 ± 10 |
| Body mass (kg) | 73 ± 15 | 68 ± 11 |
| BMI (kg/m2) | 25 ± 5 | 24 ± 3 |
2.2. Subjects
Seven subjects with a motor incomplete SCI and nine age- and gender-matched able-bodied (controls) subjects participated in this study (table 1). The inclusion criteria for the SCI group were: paraplegia or tetraplegia as a result of a motor incomplete SCI (ASIA C, D) and a minimum age of 18 years. The time post-injury was at least a year (12 ± 11; 1-35 years). The level of the injury varied between the patients from L1-L2 to T1-C1. An eighth, acute patient (F, 33 years, 166 cm, 63 kg, lesion C5-T1, ASIA C) was tested for the first time 2.5 months and for the second time 7 months after injury, and is described separately. The exclusion criteria for both groups were: medical complications, such as unstable hypertension, uncontrolled cardiac dysrhythmia and other unstable cardiovascular problems, severe skeleton problems such as osteoarthritis or recent fractures of the lower limbs, severe cognitive and/or communicative disorders, other neurological and/or psychiatric disorders, or other problems which make it impossible to accomplish the tasks. The type and location of the spinal cord lesion was established by means of a clinical evaluation by a physician. After a detailed explanation of the purposes and the protocol of the experiment, all subjects signed an informed consent. The study was approved by the ethics committee of the VU University Medical Center Amsterdam and by the ethics committee of the Faculty of Human Movement Sciences of the VU University Amsterdam.

2.3. Procedure
The relationship between the ISTI and the RR-interval (RR) was established in each subject by varying the heart rate (HR). Each subject performed a discontinuous progressive graded exercise test on an Angio arm ergometer (Lode BV, Groningen, the Netherlands) to increase the HR. Before starting the exercise test resting values of ISTI and RR were measured during five minutes of rest in a sitting position. The exercise protocol consisted of minimal three blocks of three minutes arm pedalling with an individually adapted, increasing work load. One minute of rest after each block was included to facilitate the ICG and ECG measurements. During the first block of the exercise test, subjects started arm cranking at a low intensity (0 – 20 W) to get familiarized with the equipment. Subjects were instructed to exercise at a rate of 60 revolutions/min. Visual feedback about this cranking rate was provided. Subjects were verbally encouraged to exercise to exhaustion. The exercise test was ended when a subject was not able to continue due to exhaustion or when the subject indicated that he/she wanted to stop.

2.4. Analysis
Linear regression analysis was used to determine the relationship between ISTI and RR according to the following equation: ISTI = slope*RR + intercept.
To investigate differences in this relationship between both groups, the regression coefficient (slope) and the intercept were used as outcome variables. To evaluate differences in ISTI in the range of the operating heart rates during the test, the ISTI was calculated from the regression relationships for each subject at an RR of 500 ms and 700 ms: ISTI(500) and ISTI(700). Differences between groups were tested using an independent t test and eccentricity was tested using a z-test.

3. Results
3.1. Comparison of patient and control groups
All subjects showed a significant decrease in the ISTI with a decreasing RR as a consequence of the exercise stimulus (p < 0.005). The mean regression coefficient (slope) for the SCI group was significantly higher as compared with the mean for the control group (p < 0.005), while the intercept was significantly lower in the SCI group as compared with the control group (p < 0.025) (table 2 and figure 2). No differences were found in ISTI(500) and ISTI(700) (p > 0.05).
Table 2. Relationships between ISTI and RR-interval in the two groups and in the acute patient AP. Also the ISTI-values at RR-intervals of 500 and 700 ms are given.

|                      | SCI group (N=7) | controls (N=9) | AP first | AP second |
|----------------------|----------------|----------------|----------|-----------|
| slope (ms/ms)        | 0.11 ± 0.02    | 0.08 ± 0.01    | 0.29     | 0.26      |
| intercept (ms)       | 48 ± 22        | 73 ± 16        | -25      | -33       |
| ISTI(500) (ms)       | 104 ± 15       | 114 ± 15       | 119      | 96        |
| ISTI(700) (ms)       | 127 ± 13       | 130 ± 15       | 176      | 148       |

Figure 2. Mean relationship between ISTI and RR in the SCI group and in the control group.

3.2. Case report
A 33 years old acute patient having a high spinal cord injury at the level of C5-T1, ASIA C, was tested for the first time 2.5 months and for the second time 7 months after injury (see table 2). Both slope and intercept (see figure 3) of the relationship between ISTI and RR differed significantly from those in the SCI group as well the control group in the first and the second test (z-test, p < 0.005). ISTI(500) was not found to be significantly different on both occasions and compared with both groups (p > 0.05). The extrapolation to low heart rates: ISTI(700), was found to be significantly different at the first test compared with both groups (p < 0.005). At the second test, however, there was only a slight significance with the SCI-group (p < 0.05) but not with the control group (p > 0.05).

4. Discussion and conclusions
The present study is the first in which the relationship between the ISTI and RR-interval in patients with a spinal cord injury has been investigated. The results show that there is a significant difference in the slope of the relationship between ISTI and RR between subjects with a SCI compared with able-bodied persons, suggesting larger differences at higher heart rates. An acute patient showed a substantial difference with both groups, which was most prominent at lower heart rates. This difference in the acute phase indicate the presence of a process that develops in time. Also the development of ISTI at low heart rates during five months in this patient suggests a recovery process. The cause of the observed differences, however, may be multi-factorial. In people with spinal cord injury many control mechanisms are influenced by the lesion. An inactive lifestyle and cardiovascular adaptations can lead to a lower exercise performance [11]. Subjects with a SCI have an impaired muscle pump in the legs, which results in a lower preload to the heart. Differences in ISTI between high and low trained healthy subjects have been reported earlier [12]. In patients with a high lesion, cardiac control by the sympathetic nervous system can be impaired. The impairment depends on the
level and (in)completeness of the lesion. Claydon et al. [13] reported that blood pressure dysregulation after an arm exercise stimulus is common in subjects with a cervical lesion, but not in subjects with a thoracic SCI. The sympathetic fibers controlling the heart arise at the level from the first thoracic segment (T1) to the fourth thoracic segment (T4). In subjects with a lesion at or above T4 sympathetic pathways may be interrupted which can lead to cardiovascular impairments. With a complete lesion maximal heart rate is mostly limited to approximately 120 – 130 beats per minute. In the present study only three of the total of eight subjects had a lesion above T4. However, these subjects had an incomplete lesion. During the exercise test two of these patients had a peak heart rate of respectively 143 and 155, which indicates that the sympathetic control of the heart was not complete impaired. Another limitation of the present study is that the SCI group consisted of patients with incomplete lesions at various levels. Therefore, it is not possible to draw decisive conclusions with respect to the contribution of autonomic nervous control on the ISTI in SCI. More specific research is needed to investigate the determining factors in this group of patients.

Figure 3. Relationship between ISTI and RR in the acute patient and of the mean of the SCI group.

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