Enhanced Analysis of Unipolar Intracardiac Impedance Measurements

M. FROMER, M. ARBANE, L. KAPPENBERGER
Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

P. ERNE
Department of Cardiology, Kantonsspital Luzern, Switzerland

A. DEL BUFALO
Department of Cardiology, Ospedale Civico, Lugano, Switzerland

Summary

One of the most promising signals for gaining cardiovascular control information is the unipolar intracardiac impedance. Long-term measurements and enhanced procedures of analysis of intracardiac impedance signals were performed. 8 patients (mean age 76 ± 8 years, 3 male, 5 female) received INOS² CLS dual-chamber pacemakers for various indications. Unipolar intracardiac impedance was measured after ventricular events. Measurement over 24 h was performed 7 weeks and 13 weeks after implantation. A comparison of the two follow-up sessions and the analysis of circadian changes was carried out. To distinguish autonomous activity between day- and nighttime different parameters were designed which compare mean curves with single impedance curves or with other mean curves. Data from different follow up procedures indicate the excellent long-term stability of unipolar intracardiac impedance signals. A number of parameters evaluated from those curves show different behavior during day and night, which could partially be caused by posture influences. A classification of different postural states, based on the analysis of peak-to-peak amplitudes of the impedance curves, is one of the possible practical applications resulting from this findings. Spectral analysis of variations of impedance curves yields additional information about physiologic and pathophysiologic mechanisms of the cardiovascular system. These results indicate a possibility of detecting sympatho-vagal dysbalance and, thus, extended automatic diagnostic options based on the analysis of intracardiac impedance.

Key Words

Intracardiac impedance, circadian variation, spectral analysis

Introduction

The detection and analysis of physiologic parameters that are closely correlated to cardiovascular control mechanisms is the prerequisite for realizing effective systems for diagnosis and therapy of cardiac dysfunction. The level of integration of the measured parameter into the natural control system plays a major role in the applicability and reliability of the signal toward obtaining diagnostic information and providing adequate therapy. One of the most promising signals for gaining cardiovascular control information are changes in the impedance which are caused by time-dependant properties of circulation [1-2]. In particular, the unipolar intracardiac impedance is the technical basis of the most effective pacing system for closed loop stimulation available for therapeutic use. In this system, impedance signals are analyzed with respect to myocardial contraction dynamics in order to enable physiologic and feedback-controlled rate-modulated pacing. In order to broaden the spectrum of knowledge and enlarge the field of application for the intracardiac impedance measurement, additional methods of analysis have to be taken into consideration. With the goal of improving diagnostic and therapeutic options and increasing the level of automaticity of cardiac implants, long-term measurements and enhanced procedures of analysis of intracardiac impedance signals were performed in the study presented here.

Methods

8 patients (mean age 76 ± 8 years, 3 male, 5 female) received INOS[2] CLS dual-chamber pacemakers for various indications. Unipolar intracardiac impedance was measured in a time-window starting 48 ms after ventricular events and was recorded by sampling 32 points at 128 Hz, thus reflecting the time course of contraction over 250 ms for each cycle. The pacemaker was programmed to DDD-mode at base-rates of 60 bpm or 70 bpm (mean 61.3 ± 3.5) in the patients participating in this investigation. Data was transferred to a Holter-monitoring device. Measurement over 24 h was performed 7 weeks and 13 weeks after implantation.

Night-detection was performed according to an algorithm described previously [3], which was in good agreement with the patient-logbook. Subsequently, a comparison of the two follow-up sessions and the analysis of circadian changes was carried out.

As a basis for the different procedures of analysis, mean impedance curves were generated. For each patient, three different mean curves were calculated for daytime, nighttime, and for the complete measurement time. For the analysis, only impedance curves generated by atrial and ventricular successive pacing were selected. For the analysis of N cycles ($j = 1, ..., N$) with 32 measurement points ($i = 1, ..., 32$) each, i. e. a set of impedance values

$$\{Z_{j,i}\} \quad , \quad i = 1, \ldots, 32 \quad , \quad j = 1, \ldots, N$$

the pointwise averaging is described by

$$\overline{Z}_i = \frac{1}{N}\sum_{j=1}^{N} Z_{j,i} \quad , \quad i = 1, \ldots, 32$$

and the mean curve results in the set

$$\{\overline{Z}_i\} \quad , \quad i = 1, \ldots, 32$$

To compare autonomous activity at day and nighttime that may be reflected in harmonic oscillations of the impedance signal at characteristic frequencies, different parameters were designed which compare mean curves with single impedance curves or with other mean curves. This included the calculation of the similarity of curves with a linear correlation coefficient r, the sum of differences between impedance curves D, and the absolute sum of differences $\hat{D}$, as described below. This methods of analysis were applied for the comparison of the mean values of different follow-up sessions, different patients, and day and night curves. Furthermore, single impedance curves were compared with mean values for each time, follow-up and patient. The similarity of a mean curve $\{\overline{Z}_i\}$ and a specific (single or mean) curve $\{\hat{Z}_i\}$ was characterized by the linear correlation coefficient

$$r = \frac{\sum_{i=1}^{32}\left(\overline{Z}_i - \overline{\overline{Z}}\right)\left(\hat{Z}_i - \overline{\hat{Z}}\right)}{\sqrt{\sum_{i=1}^{32}\left(\overline{Z}_i - \overline{\overline{Z}}\right)^2 \sum_{i=1}^{32}\left(\hat{Z}_i - \overline{\hat{Z}}\right)^2}},$$

where $\overline{\overline{Z}}$ denotes the mean value over an averaged curve and $\overline{\hat{Z}}$ the mean value over a specific curve.

Furthermore, the sum of differences of a specific curve $\{\hat{Z}_i\}$ with the average curve $\{\overline{Z}_i\}$

$$D = \sum_{i=1}^{32}\left(\overline{Z}_i - \hat{Z}_i\right)$$

and the absolute sum of differences

$$\hat{D} = \sum_{i=1}^{32}\left|\left(\overline{Z}_i - \hat{Z}_i\right)\right|$$

were also used to characterize the deviation of specific curves from mean curves.

Besides these parameters, the amplitudes of the mean curves at day and night-time were compared in order to detect circadian changes, namely to distinguish between day and nighttime. For a mean curve

$$\{\overline{Z}_i\} \quad , \quad i = 1, \ldots, 32$$

the amplitude A was defined as

$$A = \max\{\overline{Z}_i\}_{i=1,\ldots,32} - \min\{\overline{Z}_i\}_{i=1,\ldots,32}$$

Among the described parameters r, D, $\hat{D}$ and A, the sum of differences D was chosen for further calculations, as it provided the highest total power of harmonic oscillations. The values of D for subsequent single curves of a measurement represent a time series. A Fast Fourier Transformation (FFT) was performed to analyze the frequency distribution of this time series. To reveal quantitative information about possible circadian changes in autonomous activity, power in the low-frequency range of the spectrum ($\omega < 0.02$ beats/cycle, LF) and the high-frequency range (0.02 beats/cycle $< \omega < 0.5$ beats/cycle, HF) was integrated. The LF/HF-ratio of heart-rate variability is widely believed to be a measure of sympathovagal balance. From the resulting power spectra peak frequencies and LF/HF-ratio were determined. Differences between the peak frequency of oscillations at day and at nighttime were investigated, as were differences in LF/HF-ratio between the follow-ups at 7 weeks and at 13 weeks.

Results

Correlation coefficients

The linear correlation coefficient of the mean curve at 7 weeks compared to the mean curve at 13 weeks is a straightforward parameter to detect changes in morphology. The correlations were almost equal to $r = 1.0$ and in three patients slightly smaller than in the others (Figure 1). It is remarkable that the averaged curves are extremely stable in the long run, which needs not to be true for temporally localized slopes and single-curve morphology because averaging smoothes out beat-to-beat fluctuations. Nevertheless, aberrations from the global morphology in general seem to be statistically insignificant, although they might be dramatic in specific physiological states.

If the mean curves of different patients are compared, all cross-correlations are larger than $r = 0.92$ in the follow-up at 7 weeks; in the 13 weeks follow up correlation coefficients are decreasing down to $r = 0.64$. This indicates that morphologies which are more common at the first follow-up become less universal by the second follow-up, and thus are a result of a divergence of mean curve morphology between patients over time.

In the day-night correlation of mean curves most of the patients show a small decrease in correlation coefficient from 7 weeks to 13 weeks follow-up. Two patients show a distinct decrease in the day-night-correlation, which corresponds to the fact that the similarity of morphology to that of the other patients, is smaller in these patients (Figure 2).

After calculation of mean curves, the statistics for the extent to which single curves deviates from the average was investigated. The mean of the correlation-coefficient ranged from $r = 0.947$ to $r = 0.999$ in seven patients. One patient showed a mean correlation of $r = 0.510 \pm 0.697$ during daytime and of $r = 0.844 \pm 0.447$ during nighttime in the follow-up at 7 weeks. In the follow-up at 13 weeks, the patient fell within the limits set by the others. In the other patients, the rise or fall in the correlation coefficient between the two follow-up times was not statistically significant; this is also the case for the day- and night comparison, although

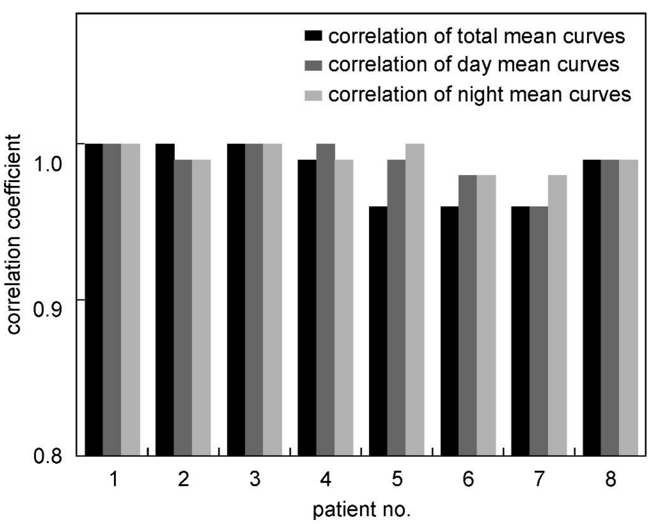

Figure 1. Correlation of mean curves at 7 weeks and at 13 weeks.

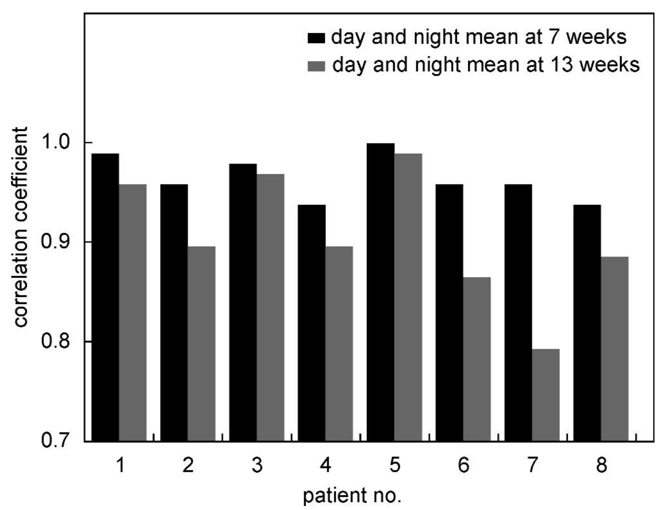

Figure 2. Correlation between day- and night-mean-curves.

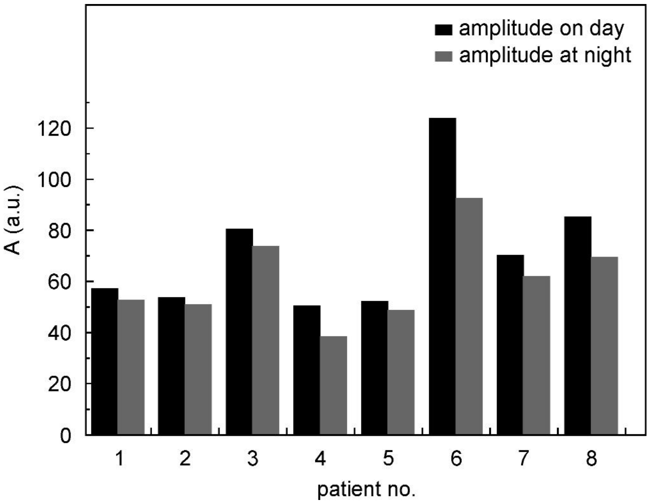

Figure 3. Amplitude A during the day and at night in the 13-week follow-up.

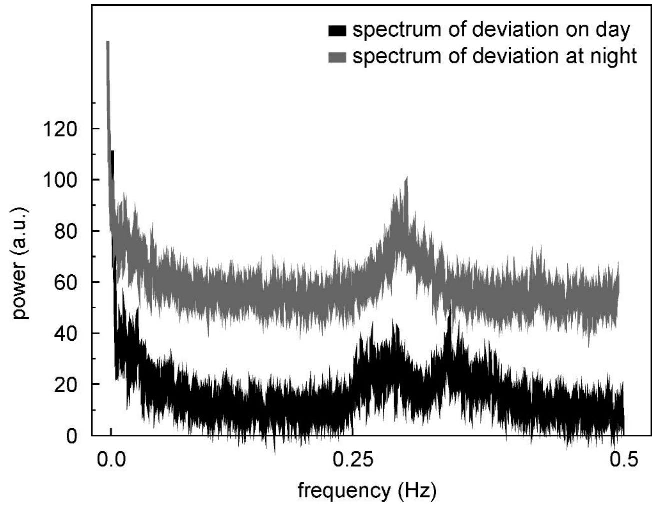

Figure 4. Example of changes in spectra between day and nighttime.

there was a slight tendency toward higher correlation coefficients at nighttime.

Amplitudes

Three months after implantation, the amplitudes *A* of day mean curves are clearly higher than those of night mean curves for all patients (Figure 3). There seems to be no general damping between the two follow-ups, as the average amplitude grows in a number of patients even after gain correction.

Sum of Differences and Sum of Absolute Differences

Calculation of the mean sum of differences *D* leads to values around zero, which makes value comparison difficult. Thus, even if there were differences between day and night, they would be not detectable using this parameter. Nevertheless, the standard deviation of *D* gives large values with significant differences between day and night. At both follow-ups, all but one patient had a lower standard-deviation of mean difference at night than at day. Daytime standard deviation is smaller than nighttime standard deviation for two of the patients, and it may be assumed that this parameter provides night-detection somewhat less accurately than other measures.

For almost all patients, the mean absolute difference $\hat{D}$ is larger during the day than at night in both follow-ups. Thus, the absolute difference in the time domain gives a possible measure for night detection, but based on the present data in this form it is not an improvement on previously-introduced measures for night detection.

Fast Fourier Transformation

In the patients who show harmonic oscillations, the mean peak frequency was determined manually. Double peaks were found in three patients. In all patients in which day/night comparison was possible, i.e. peaks for both day and nighttime were available, the frequency of the peak at nighttime is lower than at daytime (Figure 4). Frequencies range from 0.22 beats/cycle to 0.36 beats/cycle.

The time-resolved spectra were averaged for both day and nighttime. In general, the LF/HF-ratio is higher at day than at night (Figure 5). This is the case in 13 out of 16 measurements. There is no clear difference between the follow-ups at 7 weeks and 13 weeks. The paradoxical relation between the day and night LF/HF-ratio in one patient may indicate pathologic behavior, as the patient had many extrasystoles.

Discussion

The correlation coefficients close to 1 for data from different follow-up procedures indicate the excellent long-term stability of unipolar intracardiac impedance signals. Of course, long-term changes in the contractility due to progressive myocardial diseases might influence the impedance curves, but the results of the analysis performed indicate that the variations within the

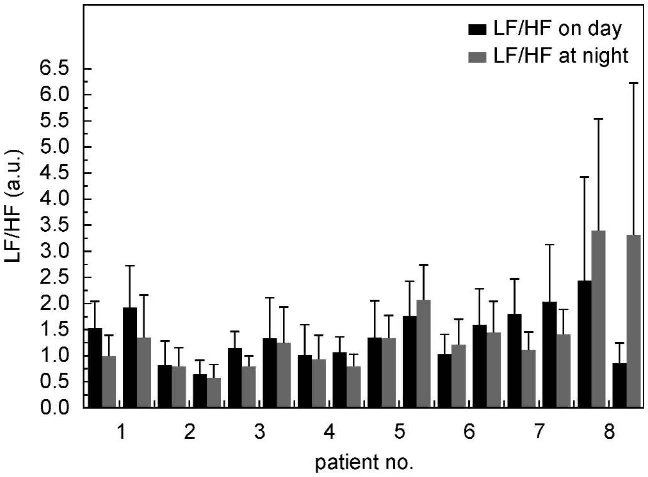

Figure 5. LF/HF-ratio in each patient at 7 weeks and 13 weeks.

investigated time interval are relatively small. However, a determination of the impact of dynamic diseases on the impedance morphology has to be investigated with the help of long-term measurements. The similarity of impedance signals from different patients is a quite unexpected result, as various factors were thought to significantly influence the shape of intracardiac impedance curves, including myocardial geometry and performance, electrode position and electrode-tissue interface properties. The finding of relatively close correlations between impedance curves of different patients may indicate a possibility of finding general design rules for morphologic analysis. The more pronounced differences of impedance curves between day and night could be caused by posture influences. Using this information to rate-modulate performance may lead to a further increase in specificity with respect to different reasons for changed myocardial movements. An even better classification of different postural states might be based on the analysis of peak-to-peak amplitudes of the impedance curves.

A spectral analysis of variations of impedance curves yields additional information about physiologic and pathophysiologic mechanisms of the cardiovascular system [4-5]. The higher values for LF/HF ratio in the power spectrum of mean absolute difference for the majority of the analyzed patients might be related to increased diurnal sympathetic drive [6]. This results indicate a possibility of detecting sympatho-vagal dysbalance and, thus, extended automatic diagnostic options based on the analysis of intracardiac impedance. Pathologic modifications of the myocardial wall or autonomic regulation might influence these results significantly, as the inverse behavior of LF/HF ratio in three patients indicates.

Conclusion

First of all, these investigations demonstrate the suitability and reliability of unipolar impedance measurements for a long-term stable monitoring of contraction dynamics. Statistical analysis of the mean absolute difference of impedance curves enables day-night, and possibly orthostasis detection. Spectral analysis seems to be a promising method for yielding additional physiologic information. Of course, due to the limited number of patients and the retrospective, empirical method of analysis, the data can only offer preliminary trends. Still, the results are very promising and further measurement and analysis should be performed in order to support the development of enhanced tools for optimal treatment of patients in the electrotherapy of the heart.

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