MYOCARDIAL ELECTRICAL IMPEDANCE SPECTROSCOPY IN TRANSPLANTED HUMAN HEART WITH AND WITHOUT GRAFT REJECTION

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Abstract: We measured the myocardial electrical impedance with a custom system using an intracavitary catheter to investigate whether cardiac rejection can be recognised in transplanted patients using the impedance spectrum. We measured 12 control patients without cardiac transplant and 8 transplanted patients undergoing routine right ventricular endomyocardial biopsy protocol. Impedance results for the transplanted group were compared with the level of graft rejection diagnosed using standard histological criteria. We made a total of 13 biopsies in the 8 transplanted patients. We measured the mean spectrum over time (magnitude and phase angle) and the modulation of the magnitude and the phase angle during the cardiac cycle. The transplanted heart has a low myocardial impedance and low phase angle compared to non-transplanted. Very moderate cardiac rejection (grade 1A) was detected in 6 biopsies and grade 3A in one biopsy. Biopsies 1A were associated with a higher impedance magnitude, measured in the atrium and ventricle, and lower phase angle at 300 kHz compared to negative biopsies.

Introduction

Cardiac rejection is an important cause of death after heart transplantation. Endomyocardial biopsy is the accepted routine test in these patients to uncover episodes of rejection while alternative less invasive diagnostic procedures are lacking.

It has been shown that catheter measurement of myocardial electrical impedance differentiates normal and ischemic tissue in experimental models [1][2]. Theoretically, inflammatory myocardial diseases such as myocarditis or cardiac graft rejection could be also recognized by local changes in tissue impedance. Up to now, the feasibility of electrical impedance to measure graft rejection has been studied in animals using an invasive method (4 needles probe). Preliminary studies in dogs with allograft transplant, monitored with an invasive permanent epicardial electrode, that measured myocardial electrical impedance, has shown very promising results [3][4].

The aim of this work is to investigate whether cardiac rejection can be recognised in transplanted patients by measuring the myocardial electrical impedance spectrum with an intracavitary catheter.

Materials and methods

A 4 mm tip standard ablation catheter (Blazer II, 7-Fr/4mm) with a thermistor at the tip was introduced through the femoral vein and was systematically placed to the superior and inferior vena cava (VC), right atrium and right ventricle.

Tissue temperature at the catheter tip and tissue impedance (magnitude (Z) and phase angle (ϕ) at 10, 30, 100 300 and 1000 kHz) were measured using a specifically designed amplifying system (Figure 1) [8]. The system uses a commercial impedance analyzer (HP4192A) and a custom isolated front end to ensure the electrical safety of the patient. A complete description of the system could be found in [5].

The system is capable of acquiring a maximum of 8 impedances (at a single frequency) per second with a resolution of 0.1 Ω and 0.1º. The impedance measurement system has a dynamic range from 10 Ω to 6.7 kΩ. The personal computer (laptop?) controls all the signal acquisition process and makes some calibrations using pre-acquired data. In the case of the impedance, the system transfer function is calibrated using a standard resistor and the acquired data is used to correct the gain and phase systematic errors of the system.

Electrical impedance was measured by injecting an alternating current between the distal electrode of a conventional ablation catheter and a skin electrode placed in the back. The impedance is measured between the tip of the catheter and the reference electrode using a three-electrode method, see Figure 2.

This method decreases the effect of the tip position in respect to the myocardial surface and its contact impedance [6]. The reference electrode on the skin is big enough to have a low impedance in comparison with the myocardial impedance. We used a patch for cardiac ablation. With this arrangement, the greatest current density is created on the internal myocardial wall, offering greater sensitivity in this area [7].

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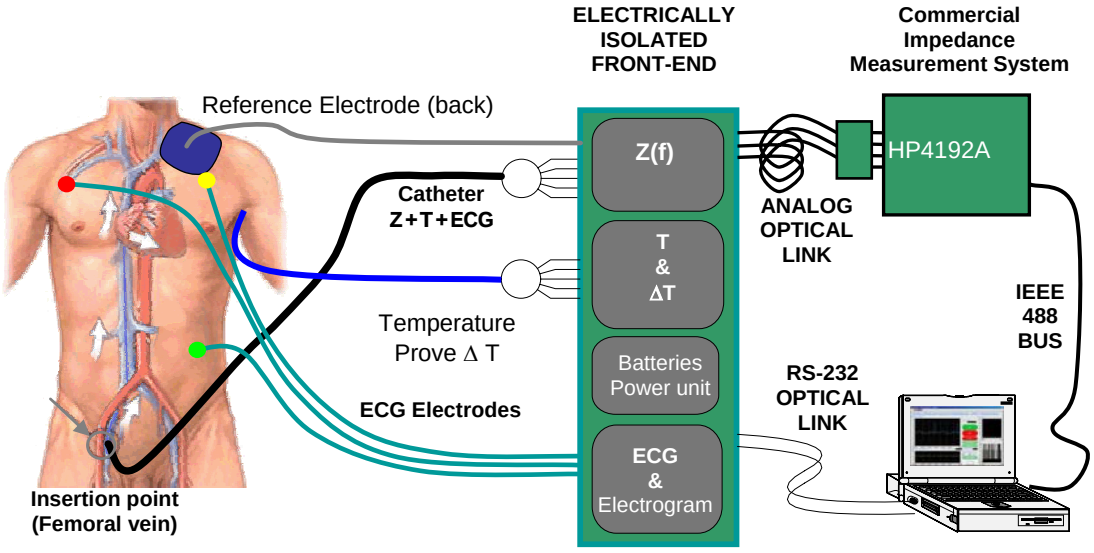

Figure 1: Measurement system. The following signals are measured: the impedance between the tip of the catheter and the reference electrode, the intracavitary temperature, the corporal temperature in the axilla region, the surface ECG and the endocardial electrogram.

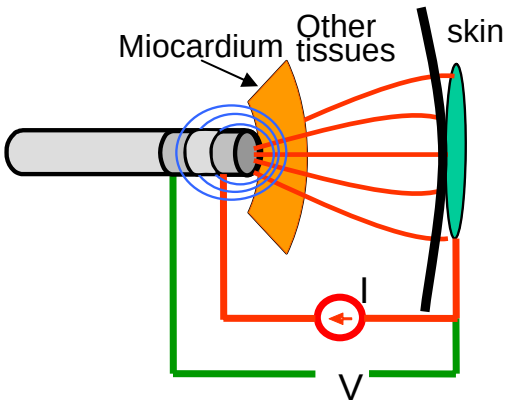

Figure 2: Three-electrode impedance measurement using an intracavitary catheter (current injection and voltage detection) and a reference skin electrode.

The surface ECG and the endocardial electrogram were acquired for synchronization purposes and also in the case of the endocardial signal to have a complementary method to radiography to evaluate the position of the catheter inside the heart chambers. We used the morphology of the signal and its amplitude to evaluate the position of the catheter tip inside the heart chambers, especially to know if the catheter tip is in contact or not with the epicardial wall.

Electrical impedance, ECG and temperature were measured in 12 control patients without structural heart disease undergoing electrophysiologic study and in 8 transplanted patients undergoing routine right ventricular endomyocardial biopsy protocol. Graft rejection was diagnosed by international histological criteria. Some patients were measured twice; in total we analysed 13 biopsies. Experiments conform to institutional guidelines and were approved by the ethical committee of the Hospital.

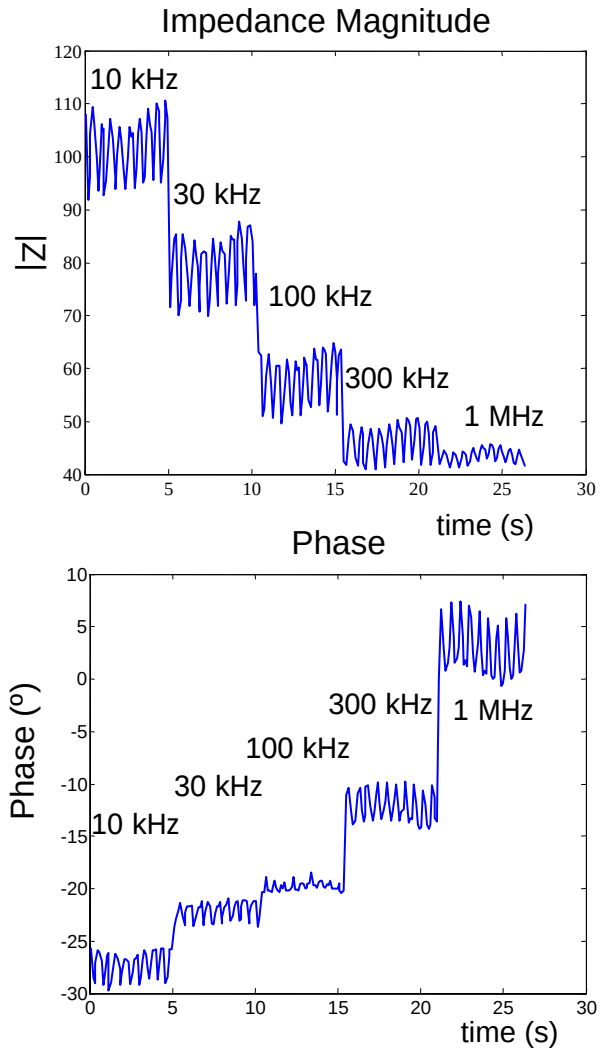

Figure 3: Raw impedance data measured with the catheter inside the heart using the three electrode method. It could be seen the modulation of the heart beat and the breathing.

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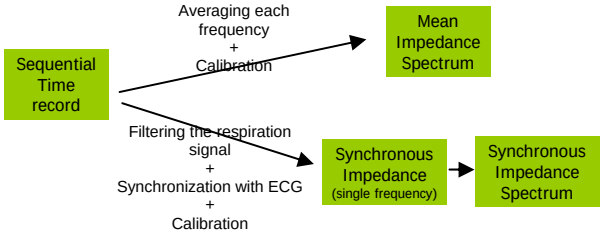

Figure 4: Signal processing to obtain the mean impedance spectrum and the impedance changes during the cardiac cycle.

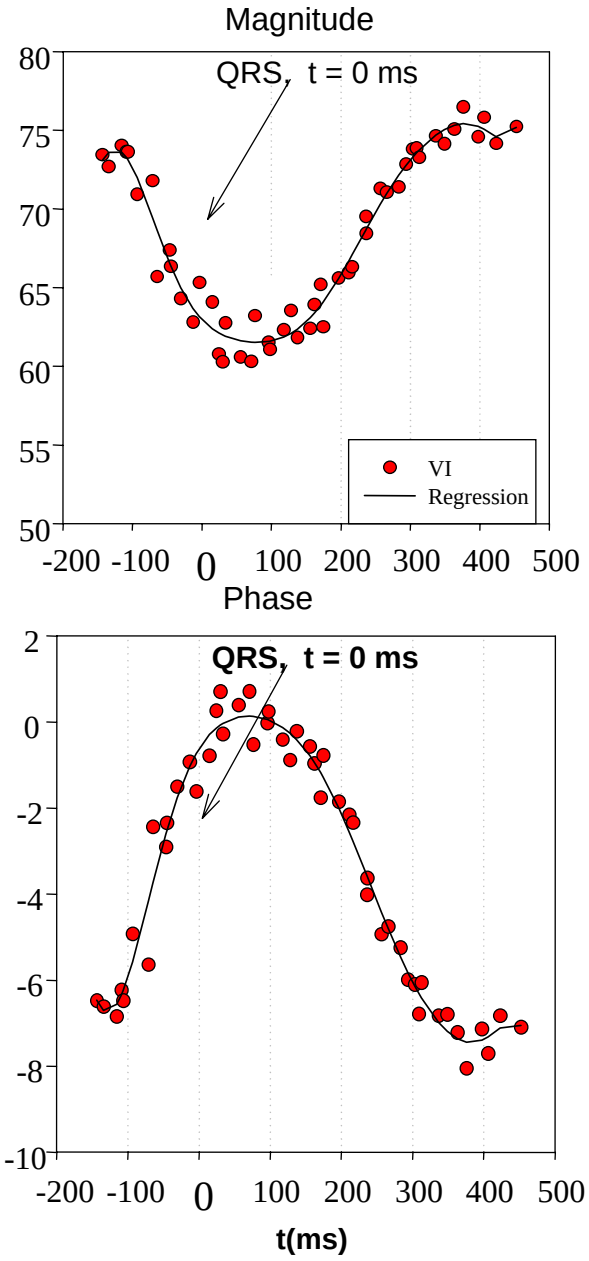

Figure 5: Impedance changes due to heart beating obtained with synchronous averaging of the impedance signal during different heart beats using the QRS complex on the ECG as time reference.

The impedance signal has changes (modulation) due to the heart beating and the breathing. Both modulations are due to changes in the geometry of the organs and whole thorax in the case of breathing. Also the changes of characteristic impedance of the organs could have some contribution to this modulation. To reduce the respiratory effect raw impedance data was high-pass filtered (corner frequency (-3dB): 0.4 Hz). After this filter we obtained the mean impedance spectrum averaging all the measured points at each frequency. For a further reduction of errors introduced by the impedance of the reference and the skin impedance, the phase spectrum was calibrated adjusting the phase angle at 30 kHz to zero. To obtain the changes of impedance inside a cardiac cycle we used the ECG to synchronize the impedance measurements in order to make a synchronous average that increases the resolution of the system in amplitude and time (figure 4 and figure 5).

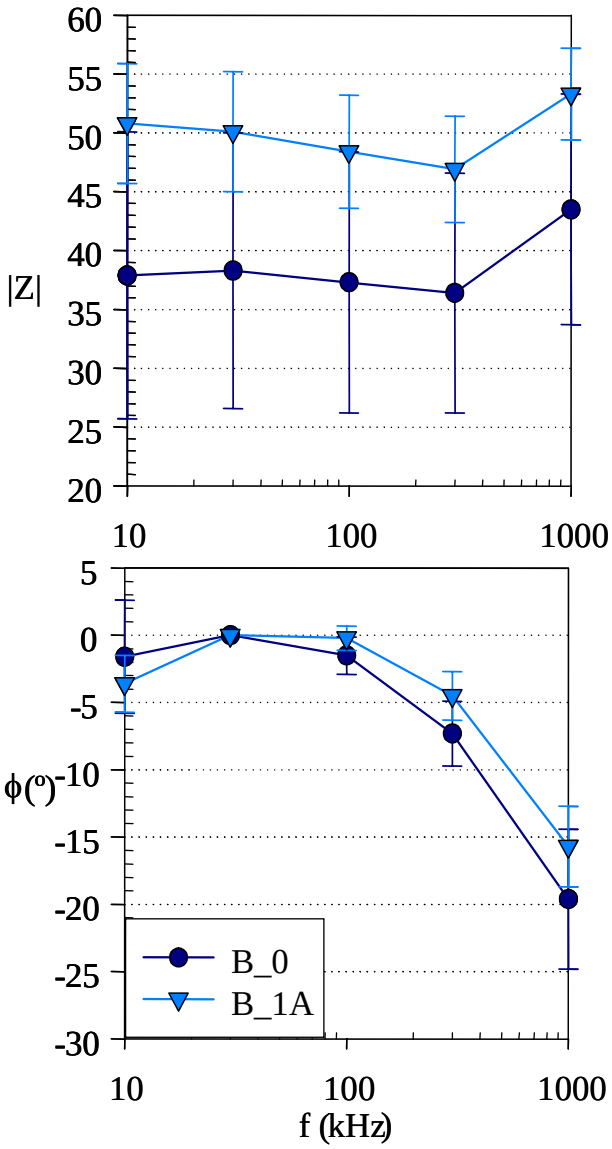

Figure 6: Impedance spectrum in the right atrium for groups with biopsy result 0 and 1A. Mean ± SD.

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Results

Right ventricular myocardial impedance was significantly lower in transplanted than in controls (magnitude at 10 kHz: 45.09 ± 8.2 Ohm vs. 55.02 ± 11.3 Ohm, p=0.004).

Myocardial impedance varied during the cardiac cycle and the modulation (expressed as the standard deviation of the mean value) was more marked in controls than in transplanted patients (magnitude at 300 kHz: 1.71 Ohm ± 1.06 Ohm vs. 0.83 Ohm ± 0.26 Ohm, p=0.004; phase angle at 300 kHz: 0.43º ± 0.11º vs. 0.23º ± 0.09º, p< 0.001).

Taking into account the histological results for the transplanted patients we created three groups: Group 0 (6 biopsies), Group 1A (6 biopsies) and Group 3A (1 biopsy). The biggest difference between groups 0 and 1A is at 10 kHz for the magnitude and at high frequencies (>300 kHz) for the phase angle. See Figure 6 for measurements in the atrium and figure 7 for the ventricle.

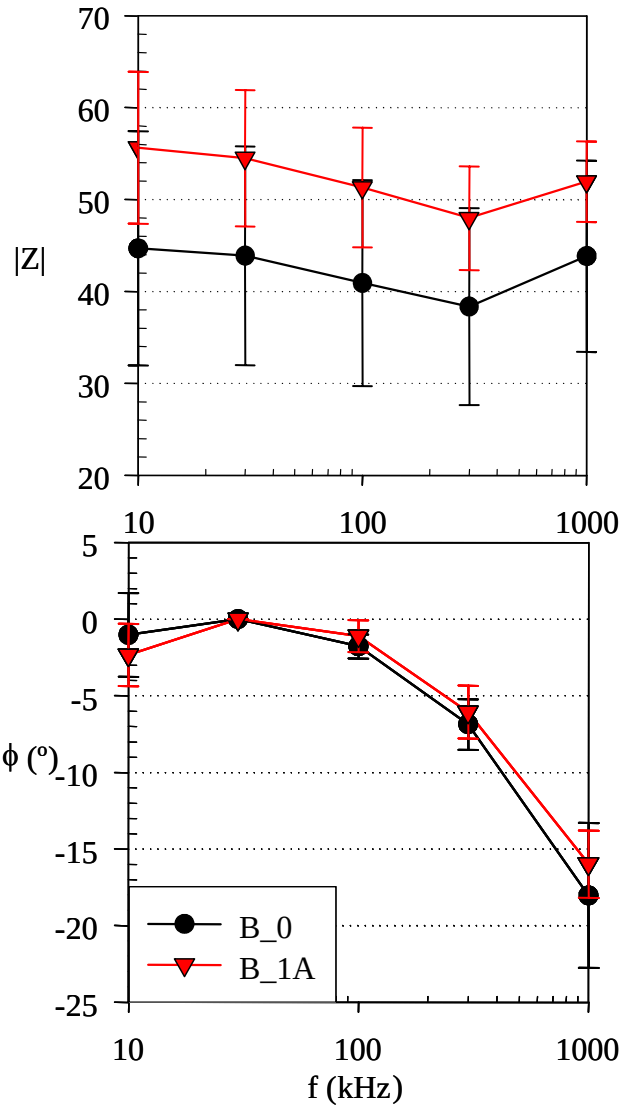

Figure 7: Impedance spectrum in the right ventricle for groups with biopsy result 0 and 1A. Mean ± SD.

We obtained the time evolution of impedance during the cardiac cycle but the intersubject variability was higher than the difference between the control group and the transplanted group.

Conclusions

Cardiac transplantation and moderate cardiac rejection causes a specific alteration of the myocardial impedance spectrum. A contact electrocatheter technique or an implanted device to measure impedance spectrum may have the potential to become a less invasive novel diagnostic tool for cardiac rejection.

Acknowledgments

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References

[1] M. WARREN, R. BRAGOS, O. CASAS, A. RODRÍGUEZ-Sinovas, J. Rosell, I. Anivarro, J. Cinca, "Percutaneous Electrocatheter Technique For On-Line Detection Of Healed Transmural Myocardial Infarction," PACE, vol. 23, pp. 1283-1287, 2000

[2] Y. SALAZAR, R. BRAGOS, O. CASAS, J. CINCA, and J. ROSELL "Transmural Versus Non-transmural In Situ Electrical Impedance Spectrum for Healthy, Ischemic, and Healed Myocardium," IEEE Trans. on Biomed. Engineering, vol. 51, no. 8, pp. 1421-1427, 2004

[3] R. PFITZMAN, J. MULLER, O. GRAUHAN, R. HETZER "Intramyocardial impedance measurements for dianosis of acute cardiac allograft rejection," Ann. Torca. Surg., vol. 70, pp. 527-532, 2000.

[4] R. GRAUHAN, J. MULLER, C. KNOSALLA, T. COHNERT, H. SINIAWSKI H. D. VOLK, E. FIETZE, W. KUPETZ, R. HETZER "Electric myocardial impedance registration in humoral rejection after heart transplantation," J. Heart Lung Transplant. , vol. 15, pp. 136-143, 1996.

[5] R. BRAGÓS, J. RAMOS, Y. SALAZAR, A. FONTOVA, M. FERNÁNDEZ, P. RIU, M. Á. GARCÍA GONZÁLEZ, A. BAYÉS-GENÍS, J. CINCA, J. ROSELL "Endocardial impedance spectroscopy system using a transcatheter method", Proc. XII-ICEBI, pp. 465-468, 2004

[6] Y. SALAZAR, J. CINCA and J. ROSELL-FERRER "Effect of electrode locations and respiration in the characterization of myocardial tissue using a transcatheter impedance method," Physiological Measurement, vol 25, no 5, pp. 315 – 323, 2004.

[7] Y. SALAZAR MUNOZ "Caracterización de tejidos cardíacos mediante métodos mínimamente invasivos y no invasivos basados en espectroscopia de impedancia eléctrica," PhD thesis, UPC, 2004.

[8] J RAMOS-CASTRO, R BRAGÓS-BARDIAL, M A GARSÍA-González, Y Salazar, A Fontova, A Bayés-Genís, J Cinca-Cuscullola and J Rosell-Ferrer."Multiparametric Measurement System for Detection of Cardiac Graft Rejection" Proc. 21th IEEE IMTC, pp. 1701-1705, 2004.

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