# Telemonitoring Protocol for Prevention and Comorbidity Screening, in Paediatric Patients with Cystic Fibrosis and/or Diabetes, by HVR index

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*Abstract* - **This pilot project is one of the first applications of Telemedicine solution (Telemonitoring) for comorbidity and translational study. A total of 20 patients with Diabetes and/or Cystic Fibrosis were enrolled to a telemedical intervention and assigned to different Groups. The patients, who enrolled voluntarily, were as follows: 5 with consecutive Type1 Diabetes Mellitus and assigned to Group 1; 5 with Cystic Fibrosis already under Telemonitorig protocol and assigned to Group 2; 5 with consecutive Type 1 Diabetes Mellitus and Cystic Fibrosis already followed at Bambino Gesù Children's Hospital, Unit of Endocrinology and Diabetes and by Telemedicine group of Cystic Fibrosis Unit and assigned to Group 3; and 5 voluntary without disease assigned to Group 4 (Control group). The Aim of this study was to analyze possible variation of Heart Rate Variability, depending on the glycaemia value or Forced Expiratory Volume in 1 second in adolescent and adult patients with diabetes and/or Cystic Fibrosis by telemedicine protocol and analyze the correlation between compliance and patients technology background. In the first four months of Telemonitoring, we received 855 glycaemia transmissions and 378 spirometry test transmissions. We show a good compliance trend, especially in the patients with technology background. For the patients or patient family members without technology background, we offered telephonic assistance to verify the home procedures, and to store and download the data. Preliminary analysis of data showed no overall significant differences in Heart Rate Variability parameters among the three groups. More months of observation are needed to show possible correlation between Forced Expiratory Volume in 1 second, glycaemia value and Health Rate Variability. Various Telemonitorig solutions could be important tools for new international comorbidity research, but an easy methodology to share the data from Home to Hospital has to be taken into consideration when planning a Telemedicine protocol assistance.**

***Keywords- Heart rate variability; Diabetes; Cystic Fibrosis; eHealth; Telemonitoring; Prevention; Equipment.***

## I. INTRODUCTION

Heart Rate (HR) can appear static and regular at rest, during exercise or recovery after exercise. However, HR is constantly adjusted due to factors such as breathing, blood pressure control, thermoregulation and the renin-angiotensin system, leading to a more dynamic response that can be quantified using Heart Rate Variability (HRV).

HRV is defined as the deviation in time between successive normal heart beats and the total HR variation in a certain interval can be measured by non-invasive methods [2].

HRV can serve as measure of autonomic activity of sino-atrial node [1]. The clinical relevance of heart rate variability was first appreciated in 1965 when Hon and Lee [3] noted that fetal distress was preceded by alterations in interbeat intervals before any appreciable change occurred in the heart rate itself [4].

The clinical importance of HRV became apparent in the late 1980s when it was confirmed that HRV was a strong and independent predictor of mortality following an acute myocardial infarction [4].

A high degree of HRV is found in compensated hearts with good function, whereas HR variability can be decreased with severe coronary artery disease, congestive heart failure, aging and diabetic neuropathy [5].

Diabetes is a hormonal disorder that affects around three hundred million people worldwide [6]. Several therapies have been proposed and a good compliance to treatment offers patients a good quality of life. Diabetes is a disease characterized by a group of metabolic disorders caused by defects of insulin's secretion and / or activity.

The first condition is represented by a pancreas inability to produce insulin and the latter is characterized by incorrect use of normal secreted insulin (insulin resistance). Literature data concerning bronchial

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reactivity in diabetic patients is controversial [7]. Changes in the respiratory system are little known, tardive complications of diabetes. The mechanisms which lead to dysfunctions of the respiratory system in patients with diabetes might be: microangiopathy of pulmonary vessels, changes of alveoli's structure, vegetative neuropathy of the respiratory system, changes of bronchi's reactivity and dysfunctions of the mobility of the thorax [8].

The prevalence of complications such as micro and macro angiopathy involving heart, kidney, eyes, Central Nervous System (CNS) are also increasing, causing severe economic and social burden [9].

Uz-Zaman, Salim et al. [9] show significant changes of Forced Expiratory Volume in 1 second (FEV1), and related pulmonary function indicators, in Type-2 diabetes patients and it has been correlated with poor glycemic control. The above pattern of changes are possibly due to hyperglycemia induced non enzymatic glycosylation of tissue proteins and chronic diabetic microangiopathy causing basement membrane thickening (capillaries and endothelium) leading to reduction in strength and elasticity of connective tissues and reduced pulmonary blood volume.

Another chronic disease with impact on pulmonary function is Cystic Fibrosis (CF). CF is characterized by progressive lung destruction, caused by obstruction of the airways due to dehydrated thickened secretions, which results in endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airways disease [10].

In these patients, spirometry shows a reduction in Forced Expiratory Volume in the first second (FEV1), and in Current Volume (FVC), (around 2 % of the expected yearly value) [11]. In previous study [12], we have shown how the Telemedicine can improve the management of CF disease and prevent complications.

In the Pediatric Hospital Bambino Gesu', Telemedicine is also offered in the follow up of diabetes patients as additional service. In previous trial research [13][14], we have also shown the impact of long-term use of eHealth systems in adolescents with Type 1 diabetes. We demonstrated a favorable impact of monthly tele-assistance (as phone call) on treatment compliance.

We have shown how patients receiving frequent feedback provided by the medical/multidisciplinary team, on telemonitoring procedure, were more compliant in self-management of diabetes. In particular, Telemonitorig protocol can help the medical team to promptly give feedback on behavioral errors, and insulin therapy adjustments. The aim of this study was to find the correlation between HVR and FEV1 and glycemia variations of patients with diabetes and/or CF and control group in a pilot study of 4 months.

The main aim of this research was to understand if HRV could be a cardiovascular prevention indicator also in patients with diabetes and/or CF followed with additional Telemonitoring assistance. The rest of this paper is organized as follows. Section II describes our methods, including the enrolling criteria. In Section III, we present our results. Section IV presents our conclusions and ideas for future works.

## II. METHODS

We have performed an observational study with 20 volunteer patients already followed at Bambino Gesù Children's Hospital. The patients enrolled had different diseases: Diabetes and/or CF. They were assigned to a telemedical intervention and divided in 3 Groups, plus one Control group with volunteers, without disease. The voluntary patients enrolled were as follows: 5 with consecutive T1DM (SAP-treated) and assigned to Group 1; 5 with CF already under Telemonitorig protocol and assigned to Group 2; 5 with consecutive T1DM and CF already followed at Bambino Gesù Children's Hospital, Unit of Endocrinology and Diabetes and by Telemedicine group of Cystic Fibrosis Unit and assigned to Group 3; and 5 assigned to Group 4 (Control group).

The Telemonitorig intervention guaranteed tele-assistance and tele-interaction between the medical team, engineers and the patients/families.

All the enrolled patients were monitored and followed for a study-period. Patients with a Tanner Stage <IV (pre-pubertal) were excluded from this study. The Tanner System describes the sequence of changes in secondary sexual characteristics and is the staging system utilized most frequently in children and adolescents.

Moreover, in order to exclude a potential effect of duration of disease on diabetes compliance and management capacities, patients with diabetes duration <1 year were excluded from the randomization. Furthermore, the mean HbA1c level in the year before randomization was evaluated for each study group.

### *A. Standard protocol*

During the whole study, all patients had a regular standardized protocol training of education about correct diabetes and CF control provided by a multidisciplinary team (diabetologist, specialized doctor, nurse, dietician, and psychologist). All the patients and their families were given instruction in carbohydrate counting, spirometry and RR test (RR interval variations present during resting conditions represent beat-by-beat variations in cardiac autonomic inputs ) procedures and were recommended to follow a balanced nutritional program with a calorie intake regularly distributed between carbohydrate (55%), protein (15%) and lipids (30%).

Moreover, all of the enrolled subjects followed a similar and regular aerobic physical activity program for a total commitment of three hours per week with or without oxygen, depending on the clinical conditions. All patients were equipped with a Glycaemia kit consisting of an Android Tablet [Noesis- Infosolution Spa].

In addition, all patients were equipped with a watch Polar V800 and heart rate sensor able to record RR value for the HRV analysis, for one week a month for 4

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months.

Patients in the telemedicine group and control group were asked to do a glycaemia control 5 times/day and an RR measure for 5 minutes/day for one week a month for 4 months and spirometry.

The Telemonitorig window period for this pilot study was fixed for only four months because of the median stability of HVR of each patient, in the short period.

Also, patients with CF were asked to perform a spirometry test every day, as usual, using the CF Telemonoring protocol. All the other enrolled patients not having CF were asked to perform a spirometry test during a hospital visit with Spirobank-MIR, during the equipment meeting, and not less than once per month. All spirometer tests were analysed with WinSpiroPro Software (MIR developer).

A personal online website profile on Polar, Noesis.Infosolution and dedicated internal Network EAD1 (Food Diabetes Education), was edited in order to receive regular feedback provided by the medical team during the virtual sessions at one-month intervals, by the engineer with one week intervals to have information about the quality of the transmissions or about equipment information. They were also educated and periodically (at 4 week intervals) retrained to use App updates.

*B. Data Analysis*

All data received by mobile devices was stored on the Noesis web server and exported from the local server.

The spirometry file could be exported directly on .xls, otherwise the data related on fitness activity could be exported on .csv and it was converted into .xls format afterwards. The same was done for the first App release and so for glycaemia data.

*C. Data Transfer*

The patients were able to share the data in different ways, depending on the device. RR value was stored by USB connection on the PolarFlor software on each patient profile.

The data transfer, from spirometry to hospital, was done by an integrated SIM for internet connection.

The glycaemia values were transferred by USB connection from glucometer to Android tablet and shared onto the Noesis server thanks to SIM for Internet connection. The RR value was acquired by Polar V800, downloaded by Polarflow software, exported in .csv file and analysed with HRV-Kubioshrv Software.

*D. Data Storage*

All patients accepted the analysis of the data in line with the international guideline for the privacy of the data.

The data was stored on Polar web-site (PolarFlow); for the spirometry data was stored on MIR server and at Bambino Gesù Children's Hospital. The glycaemia data was stored on Noesis server and shared with the hospital as .csv file.

## III. RESULT

Patients with Diabetes and/or CF were enrolled, assigned to a telemedical intervention and divided into 4 groups.

In the first two months of Telemonitoring, we received 322 transmissions. We recived a total of 855 glycaemia transmissions in the last month of Telemonitoring.

In the first two months of monitoring, the most compliant with the protocol were 2 patients with only diabetes and 3 patients with diabetes and CF. The glycemia transmissions from most complaint patients are shown in Figure 1 and Figure 2.

For the spirometry test, we received data from CF patients only by Spirotel II-MIR. During the 1th period of trail, 3 CF patients were hospitalized, so they did not send the data and 1 patient asked to be enrolled in a different time period. Nevertheless, we received 378 transmissions with spirometry test.

-All RR data, downloaded on PolarFlow (Figure 4), was analysed with HRVkubioshrv Software and exported as .pdf file, as shown in Figure 3. All values were acquired with Polar V800 (Figure 5).

For this project we chose an observational window of 4 months because 3/4 weeks of HRV screening was valued enough for this kind of patients, to show some cardiac dysfunction or index of cardiovascular risk associated on glycaemia value.

Preliminary analysis of data showed no overall significant differences in HRV parameters among the three groups. In detail, no overall significant reduction in HRV parameters could be observed in DM1 and CF patients as compared to normal subjects, suggesting the lack of significant abnormalities in our selected group of patients. It is important to highlight that a significant reduction in (Root Mean Square of Successive Differences) RMSSD was found in CF patients when reduction in FEV1 was reported, often preceding acute respiratory complications. This finding is in accordance to the notion that acute increase in the patient inflammatory status reduces HR variability, through a mean increase in heart rate. Nonetheless, in our study population, this finding might be of interest as it shows that acute reduction in HRV in these high-risk patients might represent, similarly to what is already known for acute reduction in FEV1, a preclinical sign of incoming complications, thus suggesting more aggressive monitoring and need for prompt clinical evaluation.

We did not observe any learning difference depending on the age of the patients, but we showed some learning difficulty, depending of the technology background.

## IV. CONCLUSIONS AND FUTURE WORK

This pilot project is one of the first applications of Telemedicine solution (Telemonitoring) for comorbidity and translational study.

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In our study, we started a new Telemedicine protocol for cardiologic prevention screening in-patient with CF and or Diabetes to show the possible correlation between FEV1, glycaemia value and HRV index.

We show a good compliance rate, especially for patients with technology background. For the patients or patients family members without technology background, we offered telephonic assistance to verify the home procedures, and to store and download the data.

A long period of time of several months of Telemonitoring is needed to find more co-morbidity correlation between decrease in FEV1 and RMSSD.

After 4 months of Telemonitoring, it was possible to detect some important reduction of RMSSD in association with FEV1 reduction, before unpredictable hospitalisation.

More months of observation are needed to show possible correlation between FEV1, glycaemia value and HRV.

The pilot study will be extended for patients with CF and diabetes, so with higher risk of cardiovascular complications.

More pilot studies are needed using the Telemonitoring program for comorbidity analysis. Care must be taken when purchasing devices in order to choose the most accurate, intuitive and with an accepted communication protocol.

## V REFERENCES.


[1] GRAD C. “Heart rate variability and heart rate recovery as prognostic factors”. Clujul Medical. 2015;88(3):304-309. doi:10.15386/cjmed-498.

[2] American Society of Pacing and Electrophysiology. “Heart rate variability. Standards of measurement, physiological interpretation, and clinical use”. Task Force of the European Society of Cardiology and the North Eur Heart J. 1996 Mar; 17(3):354-81.

[3] Hon EH, Lee ST. “Electronic evaluations of the fetal heart rate patterns preceding fetal death, further observations”. Am J Obstet Gynec 1965; 87: 814–26.

[4] Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology . “European Society of Cardiology. Guidelines. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use.” European Heart Journal (1996) 17, 354–381

[5] Kleiger R.E., Miller J.P.,. Bigger Jr. J.T, Moss A.J. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. The American Journal of Cardiology, Volume 59, Issue 4, 1 February 1987, Pages 256-262

[6] Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ et al. “National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants”. Lancet, 2011, 378(9785):31–40.

[7] Pieron. M., Scheen A. J., Corhay J.L., Radermecker M.F.,Lefebyre P.J. “Bronchial reactivity in diabetic patients”. Revue des Maladies Respiratoires, (1997). 14, 379–385.

[8] Pieniawska A., Horodnicka-Józwa A., Petriczko E., Walczak M. “Evaluation of respiratory function tests in children and adolescents with Type 1 diabetes”. Pediatric Endocrinology, Diabetes, and Metabolism, (2012). 18, 15–20.

[9] Uz-Zaman, Salim et al. “Assessment of Lung Function by Spirometry and Diffusion Study and Effect of Glycemic Control on Pulmonary Function in Type 2 Diabetes Mellitus Patients of the Eastern India.” Journal of Clinical and Diagnostic Research : JCDR 8.11 (2014): BC01–BC04. PMC. Web. 3 Dec. 2015.

[10] Mogayzel P.J Jr., Naureckas E.T.,. Robinson K.A, Mueller G., Hadjiliadis D., et al. "Cystic Fibrosis Pulmonary Guidelines", American Journal of Respiratory and Critical Care Medicine, Vol. 187, No. 7 (2013), pp. 680-689.doi: 10.1164/rccm.201207-1160OE

[11] Meystre S. “The current state of telemonitoring: a comment on the literature”. Telemed J E Health 2005;11:63-9

[12] Murgia F., Corona B., Bianciardi F., Romano P., Tagliente I., Bella S. “The application of telemedicine in the follow-up of lung transplantation in a patient with cystic fibrosis”. Clin Ter. 2014;165(5):e382-3. doi: 10.7417/T.2014.1769.

[13] Tarvainen MP1, Niskanen JP, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV--heart rate variability analysis software. Comput Methods Programs Biomed. 2014;113(1):210-20. doi: 10.1016/j.cmpb.2013.07.024. Epub 2013 Aug 6.

[14] Tagliente I, Ullmann N, Ritrovato M, Trujillo F.J.L and Riccardo Schiaffini, "Benefit of Telemedicine for patients with diabetes mellitus" The Seventh International Conference on eHealth, Telemedicine, and Social Medicine, eTELEMED 2015. IARIA, 2015. ISBN: 978-1-61208-384-1.

[15] Schiaffini R, Tagliente I, Carducci C, Ullmann N, Ciampalini P, Lorubbio A, Cappa M. “Impact of long-term use of eHealth systems in adolescents with Type 1 diabetes treated with sensor-augmented pump therapy”. J Telemed Telecare. 2015 Aug 18. pii: 1357633X15598425. [Epub ahead of print]

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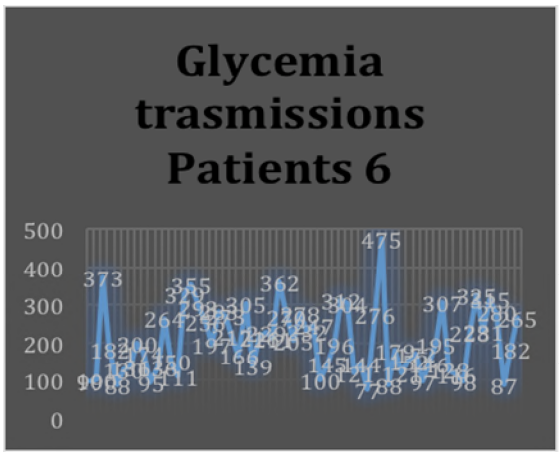


Figure 1.Glycemia’s transmissions from most compliant patients.

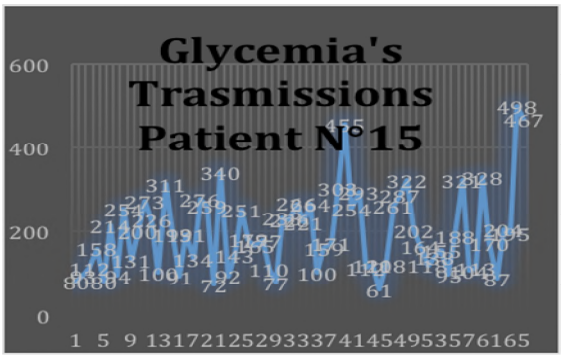


Figure 2. Glycemia's transmissions from compliant patients

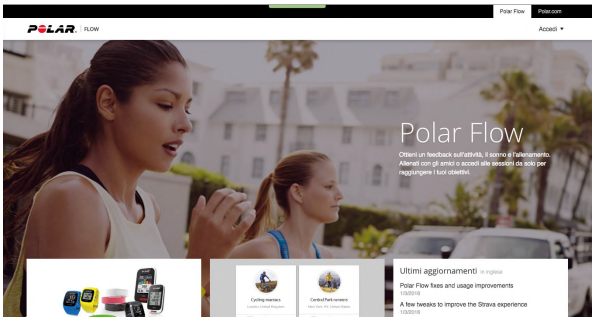


Figure 4. PolarFlow Web-site

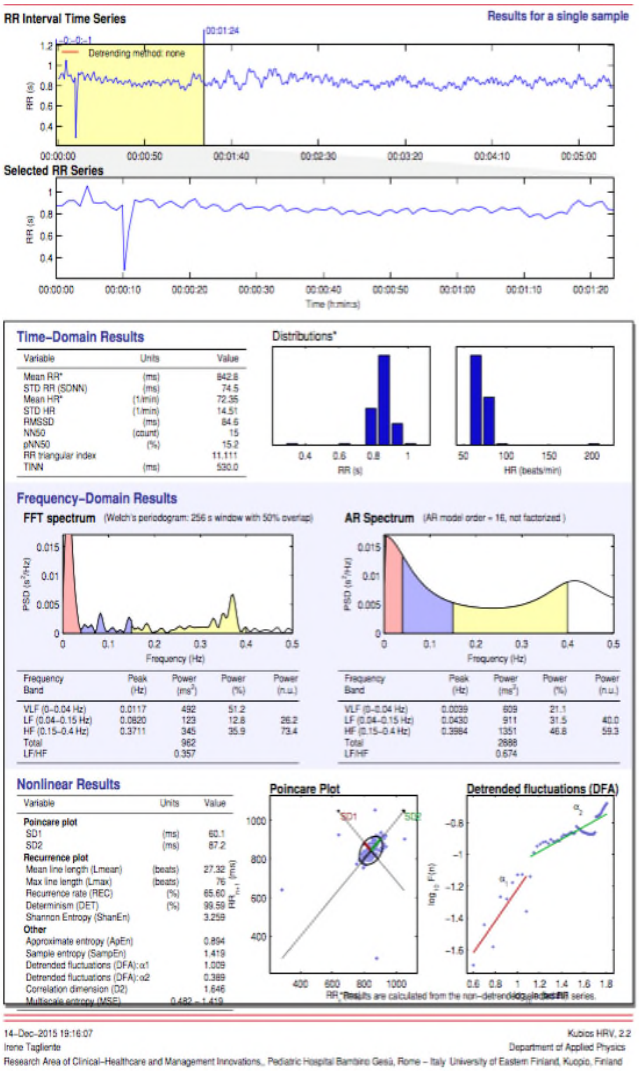


Figure 3. RR Analysis


Figure 5. PolarV800