

Computerised ECG Repository in The Moli-Sani Project

L. Iacoviello*, A. Di Castelnuovo, L. Rago, M. Vaglio, F. Badilini, D. Assanelli, M. B. Donati, and G. de Gaetano.

Abstract — Computerized electrocardiogram (ECG) may be extremely useful to develop new tools for the definition of the risk and the prevention of cardiovascular disease. The Moli-sani project (<http://www.moli-sani.org>) is a population-based cohort study that recruited over 24,000 men and women, aged ≥ 35 year, from the general population. The aim was the evaluation of risk factors linked to chronic-degenerative disease with particular regard to cardiovascular disease and cancer and intermediate metabolic phenotypes such as hypertension, diabetes, dyslipidemia, obesity, and metabolic syndrome. Standard 12-lead resting ECG was performed by a Cardiette ar2100-view electrocardiograph and tracings stored in digital standard communication protocol format for subsequent analysis. The digital ECG database of the Moli-sani project is currently being used to assess the association between physiologic variables and pathophysiologic conditions and parameters derived from the ECG signal. This is a comprehensive review of the database and of the results until now obtained with its analysis.

I. INTRODUCTION

Resting electrocardiogram (ECG) carries important independent prognostic information for future cardiac events (1). However, the use of ECG in population-based studies may lead to enormous numbers of ECG to be interpreted. Computerized electrocardiogram (ECG) acquisition and interpretation may be extremely useful in handling analysis of data from large cohort studies and exploit research on the use of ECG data as prognostic markers for cardiovascular disease in normal and disease population (2).

The “Moli-sani” study (www.moli-sani.org) is a cohort study aiming at evaluating the risk factors linked to chronic-degenerative disease with particular regard to cardio- and cerebro-vascular disease and their intermediate phenotypes such as hypertension, diabetes, dyslipidemia, obesity and metabolic syndrome (3-5). Between March 2005 and April 2010, 24,325 people aged ≥ 35 years, living in the Molise region were randomly recruited.

II. THE MOLI-SANI COHORT RECRUITMENT.

The cohort of the Moli-sani Study was randomly recruited in the Molise region from city hall registries by a multistage sampling (3-5). First, townships were sampled in major areas by cluster sampling; then, within each township, participants aged 35 years or older were selected by simple random sampling. Recruitment was based on household to allow household and large pedigree construction for genetic

analysis. Exclusion criteria were pregnancy at the time of recruitment, disturbances in understanding or willingness, current poly-traumas or coma, or refusal to sign the informed consent. Thirty percent of subjects refused to participate; these were generally older and had a higher prevalence of CVD and cancer.

A follow-up based on linkage with hospital discharge records (SDO) and mortality regional registry was performed at December 2011 for a median of 4.2 years (maximum 6.5 years). Such a follow-up will be updated every 3 years (6). The Moli-sani study complies with the Declaration of Helsinki and was approved by the Catholic University ethics committee. All participants enrolled provided written informed consent.

Each subject was administered questionnaires on personal and medical history, food consumption quality of life (FS36) and psychometry. Glycaemia, cholesterol, HDL, LDL, C-reactive protein, D-Dimers and blood cell count were measured on fresh samples. Plasma serum, cellular pellet and urinary spots were stored in liquid nitrogen. Subjects were measured blood pressure, weight, height and waist and hip circumference and spirometry to evaluate pulmonary diffusion capacity, gas diffusion and pulmonary volumes.

III. ELECTROCARDIOGRAMS.

Electrocardiograms were performed by trained research personnel following standard procedures. To ensure standardization, periodic evaluation visits were made by an expert cardiologist. For quality control, ECGs performed by an individual operator were periodically replicated and evaluated. Standard 12-lead resting ECG was measured using a Cardiette ar2100-view electrocardiograph, a standard electrocardiographic acquisition unit which acquires synchronized 10-second, 12-lead ECG and can transmit the waveform data to a workstation in real time via a USB cable.

Digital ECGs, stored in standard communication protocol- ECG format (7) were subsequently processed by a commercial computerized system for the analysis of resting ECG (CalECG version 3.2.0, AMPS-LLC, New York, NY, USA) (8). CalECG has a built-in measuring algorithm for measuring/annotating ECGs; in addition, it embeds the “University of Glasgow” diagnostic algorithm (9). CalECG manages the link of all the patients' demographic data from the standard communication protocol-Cardiette data structure to the embedded Glasgow module.

IV. MAIN RESULTS

The digital ECG database of the Moli-Sani project is currently being used to assess the association between physiologic variables and patho-physiological conditions such as blood pressure, body mass index and metabolic syndrome and parameters derived from the ECG signal.

After exclusion of subjects with incomplete questionnaires and without ECG data, 24,090 subjects were

L.I., A.d.C., M.B.D., D.d.G. are with the Department of Epidemiology and Prevention. IRCCS Istituto Neurologico Mediterraneo, NEUROMED. Pozzilli., Italy (*corresponding author e-mail: licia.iacoviello@neuromed.it). L.R. is with Epicomed Research, S.r.l., Campobasso, Italy M.V. and F.B. are with AMPS LLC, New York, NY, USA D.A. is with Department of Sports-Internal Medicine, University of Brescia, Brescia, Italy

analyzed (10). The mean age of the population was 55±12 years in women and 56±12 years in men. Twenty six percent of the population currently smoked. The prevalence of obesity, hypertension, hypercholesterolemia, and diabetes was 30%, 29%, 8%. The metabolic syndrome was present in 27.5%. Electrocardiogram variable values were similar to those presented in an earlier report.18 Differences in numerical ECG values were observed between sexes and by age. Thirty nine % of ECG results in women and 42% in men were normal. Complete (right or left) bundle branch blocks were observed in 1.9% of women and in 5.0% of men. As expected, the prevalence of myocardial infarction was higher in men than in women. Abnormal T-wave axis deviation was found in 3% of both genders. Left ventricular hypertrophy defined by Cornell voltage-duration product and Sokolow-Lyon voltage criteria was found in 10 women and in 18 men.

Among ECG variables, T-wave axis deviation reflects abnormal ventricular repolarization which is associated with higher risk of arrhythmias and it is indicative of subclinical myocardial damage. T-wave axis deviation has been associated with increased risk of coronary heart disease (CHD) and total mortality, independently of other cardiovascular risk factors and particularly in the elderly population (11). We investigated the association between T-wave axis deviation, metabolic syndrome (MetS), its components and estimated risk of cardiovascular disease (CVD) at 10 years in the Moli-sani cohort population (12). T-wave axis was normal in 74.5% of men and 80.9% of women, borderline in 23.6% and 17.3% and abnormal in 1.9% and 1.8%. We found that T-wave axis deviation was strongly associated with components of the MetS, in particular high waist circumference and blood pressure and with an increased CVD risk at 10 years, particularly in men. ECG monitoring to identify T-wave axis deviation in obese, hypertensive or MetS subjects can be an early indicator of vascular disease and help in reducing cardiac events.

Moreover, we assessed the prevalence of ECG-Left Ventricular Hypertrophy (LVH), T wave axis (TA) abnormalities and their combination according to the presence or absence of diabetes and/or hypertension (13). Among subjects with ECG-LVH, prevalence of hypertension was 59.0% and 49.7%, respectively for men and women, whereas that of diabetes was 10.7% and 5.7%, respectively. In hypertensives, TA was normal in 72.3% of subjects, borderline in 24.8% and abnormal in 2.9%. In diabetics, TA was normal in 70.4% of subjects, borderline in 26.5% and abnormal in 3.1%. In both hypertensive and diabetic subjects, the prevalence of ECG-LVH, was significantly greater in subjects with borderline or abnormal TA. Hypertension was an independent predictor of abnormal TA (odd ratio: 1.38, P = .025), suggesting that that hypertension might play a relevant role in the pathogenesis of TA deviation.

Finally, we have observed that TA abnormalities are associated with elevated levels of C reactive protein, an inflammatory markers, prognostic markers for cardiovascular disease. Men with abnormal TA deviation had 32% higher

C-Reactive Protein level than men with normal TA deviation (p<0.0001, adjusted for age, smoke, social status, physical activity). Similarly women with TA abnormal T showed 25% higher C-Reactive Protein was found (adjusted p<0.0001).

V. CONCLUSION

This computerized ECG database on a comprehensive cohort from central Italy represents a unique opportunity to identify and assess prognostic factors associated with cardiovascular and metabolic diseases.

REFERENCES

- [1] E. A. Ashley, V. K. Raxwal, V. F. Froelicher, "The prevalence and prognostic significance of electrocardiographic abnormalities". *Curr., Probl., Cardiol.*, vol. 25, pp. 1-72, 2000.
- [2] R. Knutsen, S. F. Knutsen, J. D. Curb, D. M. Reed, J. A. Kautz, K. Yano, "The predictive value of resting electrocardiograms for 12-year incidence of coronary heart disease in the Honolulu Heart Program", *J. Clin. Epidemiol.*, vol. 41, pp. 293-302, 1988.
- [3] R. Di Giuseppe, A. Di Castelnuovo, C. Melegari, F. De Lucia, I. Santimone, A. Sciarretta, P. Barisciano, M. Persichillo, A. De Curtis, F. Zito, V. Krogh, M. B. Donati, G. de Gaetano, L. Iacoviello, "Moli-sani Project Investigators. Typical breakfast food consumption and risk factors for cardiovascular disease in a large sample of Italian adults", *Nutr. Metab. Cardiovasc. Dis.*, vol. 22, pp. 347-354, 2012.
- [4] I. Santimone, A. F. Di Castelnuovo, A. De Curtis A, M. Spinelli, D. Cugino, F. Gianfagna, F. Zito, M. B. Donati, C. Cerletti, G. de Gaetano, L. Iacoviello, "White blood cells count, sex and age are major determinants of platelet indices heterogeneity in an adult general population: results from the MOLISANI project", *Haematologica*, vol. 96, pp. 1180-1188, 2011.
- [5] A. Di Castelnuovo, S. Costanzo, M. Persichillo, M. Olivieri, A. de Curtis, F. Zito, M.B. Donati, G. de Gaetano, L. Iacoviello, "Distribution of short and lifetime risks for cardiovascular disease in Italians", *Eur. J. Prev. Cardiol.*, vol 19, pp. 723-730, 2012.
- [6] European standard (EN1064:2005), <http://www.openecg.net>.
- [7] F. Badilini, N. Sarapa, "Implications of methodological differences in digital electrocardiogram interval measurement", *J Electrocardiol.*, vol. 39, pp. 152-156, 2006.
- [8] P. W. Macfarlane, B. Devine, S. Latif, S. McLaughlin, D. B. Shoat, M. P. Watts, "Methodology of ECG interpretation in the Glasgow program", *Methods. Inf. Med.*, vol. 29, pp. 354-361, 1990.
- [9] A. Di Castelnuovo, A. de Curtis, S. Costanzo, M. Persichillo, M. Olivieri, F. Zito, M. B. Donati, G. de Gaetano, L. Iacoviello, "MOLI-SANI Project Investigators. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study", *Haematologica*, vol. 98, pp. 1476-80, 2013.
- [10] L. Iacoviello, L. Rago, S. Costanzo, A. Di Castelnuovo, F. Zito, D. Assanelli, F. Badilini, M. B. Donati, G. de Gaetano, "Moli-sani Project Investigators. The Moli-sani project: computerized ECG database in a population-based cohort study", *J. Electrocardiol.*, vol. 45, pp. 684-689, 2012.
- [11] J. A. Kors, M. C. de Bruyne, A. W. Hoes, G. van Herpen, A. Hofman, J. H. van Bommel, D. E. Grobbee, "T axis as an indicator of risk of cardiac events in elderly people", *Lancet*, vol. 352, pp. 352:601-605, 1998.
- [12] L. Rago, A. Di Castelnuovo, D. Assanelli, F. Badilini, M. Vaglio, F. Gianfagna, M. Salvetti, F. Zito, F. Alessandrini, M. B. Donati, G. de Gaetano, L. Iacoviello, "T-wave axis deviation, metabolic syndrome and estimated cardiovascular risk--in men and women of the MOLI-SANI study", *Atherosclerosis*, vol. 226, pp. 412-418, 2013.
- [13] D. Assanelli, A. Di Castelnuovo, L. Rago, F. Badilini, G. Vinetti, F. Gianfagna, M. Salvetti, F. Zito, M. B. Donati, G. de Gaetano, L. Iacoviello, "Moli-sani Project Investigators: T-wave axis deviation and left ventricular hypertrophy interaction in diabetes and hypertension", *J. Electrocardiol.*, vol. 46, pp. 487-491, 2013.