APPENDIX 2

Telemonitoring in patients with chronic pulmonary and cardiac illnesses can significantly decrease hospital admissions, emergency department visits, and hospital length of stay [1-6] Many commercial products with different characteristics have been devised and utilized for different purposes up to now [7-10]. Two recent exhaustive reviews on the development and characteristics of wearable and unobtrusive monitoring devices have been published [11,12], but this topic will be exhaustively treated in the next paragraphs.

Wearable devices with high accuracy and usability for many clinical measures in chronic patients offer application prospects in many fields, like the measure of environmental parameters as ozone concentration, temperature and relative humidity, other than individual measures like heart rate, electrocardiography, body position, oxygen saturation, expiratory airflow and others [13]. The use of wearable sensors to get precious information of these signals is a particularly attractive (and likely cost-effective) system for monitoring the health status in chronic diseases [14]. Monitoring of cardiovascular functions has recorded a rapid evolution in last years by means of electrodes safely and tolerably inserted in chest bands or vests [15-17] or wrist worn electrocardiogram monitor [18-20], and a machine learning system has been proposed to empower an ear-lobe sensor monitor blood pressure and heart rate [21].

A systematic review of 11 studies on heart failure revealed that all trials found cost reductions with telemonitoring, ranging between 1.6% and 68.3% , compared with usual care. Cost savings were mainly attributed to reduced hospitalization expenditures [22].

In a recent study [23] on 326 patients decreased hospital utilization rate and average cost per hospitalization were confirmed in the remote monitoring group of patients with heart failure after discharging.

A problem that recently has been emphasized is the need for a prompt detection of cardio-respiratory instability, that is abnormalities of heart rate, blood pressure, respiratory rate and oxygen peripheral saturation (SpO_2), because this can lead to adverse events like in-hospital cardiac arrest, whose outcome is generally very poor [24]. In this context telemedicine may be of help because it allows continuous monitoring and rapid consultation of expert physicians when patient's conditions deteriorate, yet this practice does not have a large hospital diffusion for various reasons, not least the cost [25]. Its utility might be even greater in cardiac patients out of hospital, whose continuous monitoring would be essential to prevent acute worsening.

A conspicuous amount of clinical experiences are continuously published about the positive effects of home-based cardiac tele-rehabilitation, especially when wrist monitors are employed, so that patients can avoid the traditional center-based cardiac rehabilitation and the barriers that non rarely are related to it [26,27].

An integrated tele-rehabilitation home-based program in old patients affected with concomitant chronic obstructive pulmonary disease and heart failure has been conducted and it proved effective in terms of exercise tolerance, length of time to hospitalization/death, and value of Medical Research Council (MRC) dyspnea scale in comparison to matched patients treated with a conventional program [28]. A randomized clinical trial demonstrated that home monitoring as add-on to an integrated care model in patients with advanced chronic heart/lung diseases is cost-effective because can decrease mortality, emergency visits, and hospital admissions, and improve the health status of patients and their health-related quality of life (HRQoL) [29].

In another study on the feasibility of wearable healthcare monitoring in the elderly, a significant positive association was found between the use of wearable devices and technology efficacy, health conditions and gender as well as race, education and annual income; patients who got used to report via web to their doctors and those who online looked for health information were more likely to use wearable systems [30]. Thus, the level of patients' understanding of health information need to be absolutely checked when deciding to structure online health information for older patients [31,32].

Many studies concerned with the use of telemonitoring in COPD have been published, but telemonitoring interventions and cost-effectiveness yielded conflicting results [33].

To determine if self-monitoring via home-based telehealth equipment could reduce the incidence of hospitalizations and emergency department (ED) presentations for people with COPD, another investigation was carried on [34]. A randomized controlled trial was used to compare the outcomes for participants receiving the telehealth equipment and monitoring with those for participants in an information-only control group, over a period of 6 months. The telehealth group had fewer presentations to emergency department and admissions, and a reduced length of hospital stay in comparison with the control group, even if these results were not statistically significant. However, telehealth monitoring of patient vital signs reduced health service utilization for individuals with COPD and resulted in significant cost savings.

A systematic review and meta-analysis [33] performed in COPD patients according to the severity of the disease showed that telemonitoring reduced the emergency room visits and hospitalizations (risk ratio 0.88). The subgroup analysis of patient severity showed that telemonitoring more effectively reduced emergency room visits and hospitalizations in patients with severe vs. moderate disease. Thus, such application of integrated telemonitoring (the delivery of education, exercise, etc. in addition to telemonitoring) seems more useful for patients with severe COPD.

A recent study (34) evaluated the effect of a program of *Remote Patient Monitoring* (RPM) lasting at least one year in 126 patients with COPD through a comparison between the study year with RPM and the previous year in terms of non scheduled hospital admissions for all causes (primary objective) , admissions for cardiorespiratory problems , length of hospital stay , number of emergency visits , number of visits for respiratory problems , adherence to the monitoring program and others (secondary objectives).The number of admissions for all causes during the RPM period decreased (-65%; from 137 to 48) compared to previous year.Similarly, admissions for cardiorespiratory problems decreases (- 63%; from 88 to 32). Analogamente I ricoveri per problemi cardiorespiratori diminuivano del 63% (da 88 a 32), so as the emergency visits (-44%; from 20 to 36). The whole adherence percentage to RPM program resulted 88,6% .

Another interesting metanalisis founf that hoaspital re-admissions and unscheduled visits to emergency department after a recent hospital admission for COPD exacerbation decreased by telemonitoring patients at home , while their health related quality of life increased (35).

Rehabilitation is a fundamental component of COPD patients treatment , but its use is not so extended as it would deserve in association to pharmacologic therapy. In last years are increasing the studies of telerehabilitation (36) that demonstrate that this procedure is able to reduce the admissions to emergency and to hospital with improvement of patients health status.

There are, however, opposite experiences in patients with severe COPD, as defined on respiratory function parameters, after one year of observation, in terms of emergency visits or hospital admission even though the hospital stay tended to be shorter in patients telemonitored [37]. Similar results were

obtained in a randomized clinical trial, even if in a further analysis telemedicine was associated with fewer repeat hospitalizations [38].

Negative results in terms of HRQoLre were obtained in a wide Danish study comparing telehealth care and usual practice [39]. The same trial has been evaluated in terms of cost-effectiveness always with negative results [40]. Instead, the HRQoLre improved after 6 months in patients given telemonitoring as an add-on to usual care [41].

The effects of telemonitoring interventions (TI) for COPD on mortality, quality of life, exercise capacity, and exacerbation-related resulted poor in an overview of systematic reviews, but authors recommend caution in the interpretation of the results because most of the considered studies had low methodological quality and probably the role of TI in COPD needs further investigation [42].

A systematic literature review on these topics demonstrated that the favorable effects of telemonitoring consisted in reduced need for visits, improved disease management and patient-provider relationships, while a possible low quality of data, increased work for health providers and, above all, relevance of costs were spotted as barriers to telemonitoring [43].

Most studies are in progress to investigate the ability of a telemonitoring-based algorithm to reduce exacerbations occurrence in COPD [44] but previous reviews of published studies have suggested that the use of telemonitoring as add-on to usual care can reduce unnecessary emergency visits but not hospitalizations due to COPD exacerbation [45].

More promising are the results of a Spanish real world clinical study investigating the utility of telemonitoring after discharge of patients admitted to hospital for severe COPD exacerbation: telemonitoring was associated with less mortality and readmission rates in 12 months [46]. Positive results of a telemonitoring follow-up (TF) after discharge were obtained also in another study from Spain, where the number of visits was reduced with TF in spite of the same exacerbation rate [47]. Even more interesting results emerged from a recent Chinese review and metanalysis whose conclusions were that telemonitoring of patients with history of previous exacerbations of COPD can reduce emergency room visits, hospital readmissions due to exacerbations, length of hospital stay, mortality, and improved HRQoL as measured with the St. George's Respiratory Questionnaire (SGRQ) [48].

As already emphasized, these conflicting results concerning telemonitoring of COPD patients probably depend on the type and structure of telemonitoring used. Also the different number of subjects enrolled in each study, the various grade of severity of patients studied, and the length of the monitoring can have a weight. The discrepancies between results of different studies are well examined in another comprehensive review of the literature where the authors highlight the characteristics that should be observed in studies comparing the effects of telemonitoring in COPD patients: adequate length of the study and number of participants, procedures non exacting and invasive for patients, investigation of exacerbations through parameters able to reveal them, and healthcare utilization, subgroup analysis to discern the most appropriate subjects for telemonitoring [49]. In this respect, a recent European Respiratory Society (ERS) statement has pointed out the need for a better homogenization of the outcome parameters aimed at evaluating the management of acute exacerbations of COPD in clinical trials [50]. Among others, survival, breathlessness, quality of life, activities of daily living, arterial blood gases, disease progression, future exacerbations and hospital admissions were included in the outcome set.

Moreover, a critical point to be taken into account is the acceptance of telehealth interventions by the patients. In fact, a systematic review [51] has investigated the role that clinical setting,

sociodemographic factors, and intervention factors might have on the acceptance and completion of telehealth interventions. The results of this review revealed that acceptance and dropout rates may be influenced by factor related to the type of intervention and to sociodemographic status. Technical difficulties and complexities of the protocol were the main reasons for patients' withdrawal, while time constraints, and reduced interest in continuing were minor causes.

Finally, the above mentioned findings emphasize the importance that in the development and implementation of telehealth programs the health knowledge and the feelings and needs of (aged) people, as mainly are patients affected with COPD, be taken into account together with an efficacious support by health care providers in order to obtain the best results (52).

Summarizing, in chronic respiratory and cardiac diseases, there are needs both for early diagnosis and for monitoring of established diagnosis which only can be fulfilled by devices able to record vital parameters during normal activities. Both in patients' hands as well as in remote telemonitoring. The problem is that neither of the two options is easy to carry out, since the current available devices to measure main vital parameters only partially meet these needs. Clearly, there is a (urgent) need for new devices, able to record vital parameters continuously in real life, at least for 24 hours, so that a reliable picture of the patient's conditions can be composed during his/her normal activities.

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