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Telehealth: A winning weapon to face the COVID-19 outbreak for patients with pulmonary arterial hypertension

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ABSTRACT

Background: COVID-19 pandemic severely affected national health systems, altering the modality and the type of care of patients with acute and chronic diseases. To minimize the risk of exposure to SARS-CoV2 for patients and health professionals, face-to-face visits were cancelled or postponed and the use of telemedicine was strongly encouraged. This reorganization involved especially patients with rare diseases needing periodic comprehensive assessment, such as pulmonary arterial hypertension (PAH).

Main body: The paper reports a proposal of strategy adopted for patients followed at our PAH center in Rome, where patients management was diversified based on clinical risk according to the European Society of Cardiology/European Respiratory Society PH guidelines-derived score and the REVEAL 2.0 score. A close monitoring and support of these patients were made possible by policy changes reducing barriers to telehealth access and promoting the use of telemedicine. Synchronous/asynchronous modalities and remote monitoring were used to collect and transfer medical data in order to guide physicians in therapeutic-decision making. Conversely, the use of implantable monitors providing hemodynamic information and echocardiography-mobile devices wirelessly connecting was limited by the poor experience existing in this setting. Large surveys and clinical trials are welcome to test the potential benefit of the optimal balance between traditional PAH management and telemedicine opportunities.

Conclusion: Italy was found unprepared to manage the dramatic effects caused by COVID-19 on healthcare systems. In this emergency situation telemedicine represented a promising tool especially in rare diseases as PAH, but was limited by its scattered availability and legal and ethical issues. Cohesive partnership of health care providers with regional public health officials is needed to prioritize PAH patients for telemedicine by dedicated tools.

Abbreviations: 6MWD, Six-min walk distance; AI, Artificial Intelligence; COVID-19, Coronavirus disease-2019; CPET, Cardiopulmonary exercise test; HF, Heart failure; HIPAA, Health Insurance Portability and Accountability Act; IHM, Implantable hemodynamic monitors; ML, Machine learning; NYHA, New York Heart Association; PAH, Pulmonary arterial hypertension; RHC, Right heart catheterization; RV, Right ventricular; SARS-CoV2, Severe acute respiratory syndrome-coronavirus-2.

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1. Introduction

During coronavirus disease-2019 (COVID-19) pandemic, telemedicine represented a cornerstone in the management and treatment of chronic diseases, allowing patients to be visited at home in complete safety [1]. Indeed, to avoid access to the hospitals and minimize the risk of exposure to SARS-CoV2 for patients and health professionals, face-to-face visits were abolished or postponed and the use of telemedicine was strongly encouraged. However, not all countries were ready to virtually manage patients using telehealth modalities. Every effort was made to overcome the barriers which had previously limited the widespread adoption and the success of telemedicine: legal and ethical issues, reimbursement regulations, low adherence and confidence of patients to telecardiology, lack of well-structured organizations and the need of a properly trained team. In this emergency situation, the international societies provided guidance documents to help physicians on how to prioritize access to care for individual patients [2–4]. However, the few data available on the impact of COVID-19 pandemic on rare diseases limited the reports of evidence-based recommendations in this population.

The Authors aim to point out the potential role of telecardiology in the management of PAH patients during the pandemic, and report the strategy adopted in Rome to manage PAH patients followed at our center. Future investigations are needed to test its efficacy and impact on patients' prognosis.

2. Guidelines-directed medical management in pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare, progressive and chronic disease characterized by an upregulation of neurohormonal systems, ultimately leading to right ventricular (RV) dysfunction and heart failure [5–7]. Despite the substantial progress made over the past two decades [8–11], PAH prognosis is still poor and mortality is unacceptably high (median survival of 7 years) [12].

As well as for other severe chronic heart and lung diseases, periodic comprehensive assessment is essential to monitor disease progression, evaluate treatment response and the achievement of treatment goals [13–15].

Regular follow-up of PAH patients includes the evaluation of NYHA/WHO functional class, exercise capacity through the six-min walk distance (6MWD) and cardiopulmonary exercise test (CPET), RV function by imaging modalities, biomarkers and invasive hemodynamics [16]. Multidimensional assessment of all these parameters contribute to risk stratification of PAH patients, ending in a low-, intermediate- or high-risk status according to the expected 1-year mortality.

Various equations and scores have been derived and validated to predict PAH outcome but the European Society of Cardiology/European Respiratory Society PH guidelines-derived score [13] and the REVEAL 2.0 score [17,18] are the most used tools in clinical practice, allowing a more effective decision-making process for patients management.

As suggested by the 6th World Symposium on Pulmonary Hypertension recommendations, PAH medical treatment should be initiated based on risk stratification and escalated during follow-up when necessary, in order to achieve a low-risk status [19].

Given the large amount of PAH patients (around 70%) considered at intermediate risk according to the current scores, research has been focusing on how to improve the risk stratification of this heterogeneous group [20–24]. Studies conducted in recent years in this field have increased considerably the awareness of the importance of the RV as the major determinant of functional state and prognosis in PAH [25], showing that complete evaluation of RV function and adaptation to the increased afterload through echocardiography and CPET could improve risk assessment in this setting [26–28].

3. Telecardiology modalities and clinical applications

The aging of the population with the consequent increase in the prevalence of chronic diseases and in health-related costs have led to promote telemedicine as a promising approach to provide a high level of care to patients [29]. Indeed, providing outpatient support programs, telemedicine combines the needs of patients and physicians, allowing continuing monitoring and care and reducing incidence of all-cause hospitalizations.

In the field of cardiology, one of the leading medical specialties embracing telemedicine, telehealth modalities reduced mortality due to acute myocardial infarction, helped clinicians in heart rhythm disorders diagnosis and reduced rate of hospitalizations and early clinical decompensations of patients with chronic heart failure (HF) [30]. As reported in the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, non-invasive home telemonitoring may be considered (class IIbB) for HF patients to reduce the risk of recurrent cardiovascular and HF hospitalization and of cardiovascular death [31].

Telehealth modalities include [32]:

1. **Synchronous modality** referring to a real-time telephone or live audio-video interaction between the patient and the health care provider located at a distant site;
2. **Asynchronous modality** referring to the “store-and-forward” technique. Medical data collected by the patient or care giver are transmitted and later reviewed by the specialist physician;
3. **Remote monitoring** including the continuous evaluation of the patient's clinical status by reviewing data and images collected remotely (e.g. remote monitoring in the management of patients with cardiac implantable electronic devices to avoid frequent and potentially time-consuming follow-up visits) [33].

Advances in technology expanded the possibilities for home-based care, leading to the approval of a huge variety of telemonitoring devices [34], including non-invasive and implantable/invasive solutions.

Smartphones and tablets are playing an increasingly important role in telemedicine, in prevention, screening and diagnosis of cardiac diseases [35]. In contrast to early mobile phones mainly used for voice communications, the newest generation of smartphone allows to a) perform video callings, b) measure remotely blood pressure, weight and oxygen saturation, c) estimate the heart rate and classify through photo-plethysmography rhythm as regular or irregular, detecting atrial fibrillation episodes [36], d) quantify patients' physical activities through inbuilt sensors smartphones (such as *Global Positioning System sensors*), offering a solution for outpatient cardiac monitoring and rehabilitation programs.

Moreover, smartphones and tablets enable remote assessment of echocardiographic images, turning into handheld ultrasounds simply by plugging in a transducer or connecting wirelessly. The recorded images are then uploaded and reviewed by physicians through web-based platforms. Despite the limited-spectrum functionality, handheld devices help physicians in clinical-decision making providing a focused cardiac examination at the point of care [37].

Easy to use, low costs and the absence of safety concerns are the major advantages of these mobile devices. Conversely, invasive telemonitoring devices are more sophisticated but more sensitive, allowing registration of intrathoracic impedance, arrhythmias, pulmonary and left atrial pressure and the evaluation of ventricular filling pressures. For instance, implantable hemodynamic monitors (IHM) measure and store hemodynamic information that can be reviewed remotely by clinicians. Given the well-established relationship between elevated pulmonary artery pressure and risk of HF hospitalization [38], the use of wireless hemodynamic monitoring system may be considered in symptomatic patients with heart failure with reduced ejection fraction (HFrEF) for the monitoring of

pulmonary artery pressure in order to improve clinical outcomes (class IIb, Level of recommendation B). [31].

4. Telemedicine in PAH: current available tools and future challenges

As for other chronic cardiovascular diseases, telemedicine could represent a winning weapon also in the setting of PAH, as recently shown in the review by Gonzalez-Garcia M.C. et al. combining the results of 18 studies (6 peer-reviewed journal papers and 12 conference papers). To date, the evidence supporting the use of the electronic health (eHealth) in the management of PAH patients is still limited to few studies of small sample-size but further imminent investigations, encouraged by the current pandemic, could contribute to spread telemedicine in this field [39].

PAH patients require a regular and comprehensive assessment in expert PH centers to evaluate a) the presence of clinical deterioration, caused by progression of PH or by concomitant diseases; b) the basic laboratory workup (including BNP/NT-proBNP values); c) exercise capacity, determined by 6MWD and/or CPET, d) RV function by echocardiography, e) invasive hemodynamic assessment when necessary, and e) the patient's risk for clinical worsening or death.

Thanks to advances in technologies, much of this information that previously required in office visits, could be obtained remotely.

How to monitor functional capacity outside of the clinical setting?

We report below the main remote strategies that clinicians could adopt with this goal [40]:

- **Questionnaires** investigating patients level of activity, such as the Duke activity Status Index (DASI), a self-assessment tool including 12 questions, validated in patients with HF and chronic obstructive pulmonary diseases but not yet in PAH patients [41,42].

In the setting of PAH, Highland K.B. and colleagues have recently developed the Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR). It's a patients-completed assessment of function class for PAH patients adapted from the WHO-FC, derived from two round of semi-structured interviews conducted in 14 PAH patients. Further studies are needed to support its use in clinical practice and to explore its correlation with the clinicians assessed WHO-FC [43];

- **The incremental shuttle walk test (ISWT)**, requiring to patients to walk around a 10 m course in time to an external audible signal. The test consists of 12 levels, for a total distance of 1020 m. Patients continue walking until they can no longer keep pace with the speed indicated by recorded beeps. Being a maximal test and do not suffering from the "ceiling effect", the ISWT allows better assessment in patients with less severe symptomatic disease who have high baseline walk distance, as younger patients [44]. Recent finding demonstrated that in PAH the ISWT distance correlates with hemodynamic parameters, predicts survival [45] and stratifies mortality risk at baseline and follow-up [46];
- **The smartphone-based self-administered 6MWT (SA-6MWTapp)**, simple and easy to use. An instructional video describes the proper conduct of the test. At the end, the patient checks its pulse, completes the Borg dyspnea scale and reports symptoms limiting his exercise. All recorded data, including step counts, heart rate and the estimated distance travel, are finally transmitted wirelessly to a central database [44]. The evaluation of the utility of Mobile Apps testing functional capacity for evaluation of clinical response to therapies in PAH is the aim of an interventional study involving about 80 PAH participants [47]. The trial wants to determine accuracy and reproducibility of data collected via the participant-operated Walk.Talk.Track (WTT) app combined with Apple Watch and to prospectively monitor changes in 6MWTs recorded with this app after the start of therapy in a treatment naïve cohort of PAH patients. The results of this study, whose estimated completion date

is December 31, 2021, could represent a further step forward in the remote management of PAH patients;

- **Activity monitors using accelerometers.** These tools enable an automatic, continuous and long-term activity measurement of patients in a free-living environment and allow the detection of sedentary time (minutes or proportion of daily awake time spent at <1.5 METs), which is closely associated with cardiovascular outcomes and reduced quality of life [48]. Using accelerometers for 7 consecutive days, Pugh M.E. and colleagues observed that sedentary time was significantly higher in PAH patients than in control subjects (mean, 92.1% of the awake time vs 79.9% daily activity, respectively) [49].

Which is the best device to determine activity level in PAH is not yet known. To address this question, Lachant D. et al. compared total physical activity time measurements and total daily steps between a chest/leg based accelerometer and a wrist-based device in 22 PAH patients [50]. The study showed significant differences among data measured with the two activity trackers: the chest-based device was less influenced by sedentary arm movements but the wrist tool's metrics of daily activity time correlated strongly with REVEAL 2.0 score and functional class. Thus, further studies are needed to determine the best device for PAH patients' monitoring of physical activity.

Telemedical visits allow patients' clinical assessment but don't provide information neither on RV structure, function and remodeling nor on hemodynamic.

The echocardiographic evaluation of the RV is essential in the management of PAH patients, helping clinicians with the difficult task of predicting morbidity and mortality in clinical practice [51,52]. Thus, a tele-echocardiography program with the use of handheld ultrasounds could represent an important breakthrough in the management of PAH patients limiting the number of in clinic echocardiograms at accredited PH centers. Indeed, imaging exams could be performed by specialized sonographers at patients home and then securely transferred through a web-based system to PAH cardiologists.

The other issue of telemedicine in PAH concerns the periodical right heart catheterization (RHC), which is required to assess the severity of hemodynamic impairment and gauge the treatment effect of specific drugs [53]. Its invasive nature precludes its regular use in clinical practice. Newer technologies could overcome this limitation providing periodical measurement of pulmonary arterial systolic, diastolic and mean pressures and of cardiac output assessed through a validated algorithm [54]. In this regard, Benza et al. recently evaluated the feasibility and early safety of monitoring PAH patients using an IHM implanted in a distal branch of the pulmonary artery, previously tested in patients with heart failure [55]. Enrolling 27 PAH patients with NYHA class III or IV right-sided heart failure, the authors showed that this device could provide a close home monitoring of hemodynamic parameters with logistical advantages over the current risk assessments which require face-to-face clinic visits. Nevertheless, the experience of IHM in the management of PAH patients is still limited and randomized trials are needed before they can be used routinely in clinical practice.

In spite of the great potential of telemedicine in bridging the gap between patients, physicians and health systems, some barriers still limit the spread of this new modality of care. The emergency caused by COVID-19 pandemic could give the opportunity to solve these challenges.

- **Lack of patients' acceptance:** given the rise in chronic diseases, the target population is usually represented by older patients with less understanding of the new healthcare solutions and less confidence in the innovative technologies. The presence of a family member or a formal caregiver assisting elderly patients could contribute to overcome this drawback. Moreover, many patients fear losing the existing relationship with their health care provider and are worried

about receiving a poorer level of care due to the impersonal nature of telehealth services. Patient education and reassurance programs are pivotal to address this barrier.

- **Regional differences in Internet connectivity:** broadband, referring to technologies providing a high-speed connection to the internet, has become a social determinant of health given the disparities in its access among different areas. Indeed, a high percent of rural residents, who could benefit telemedicine approach, lacks broadband services. Financial supports are needed for the broadband infrastructure development in order to remove the “digital barrier” and allow greater provision of telehealth in rural or underserved areas [56].
- **Patient Privacy and security:** to ensure privacy, security and protection for health information remotely collected, clinicians have to use platforms encrypted and in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Indeed, the HIPAA Privacy Rule establishes national standards to protect patients’ medical records and reduce healthcare fraud and gives patients rights over their protected health data, as the right to obtain a copy of their health records [57];
- **Fragmented legal frameworks, including the lack of reimbursement for e-health services:** in most European countries, lack of reimbursement has hampered the widespread of telemedicine. COVID-19 pandemic has encouraged more states to enact telehealth reimbursement laws. In Italy, the new national guidelines provided by the Ministry of Health now apply the same remuneration system for virtual and in-person modalities of healthcare delivery [58].
- **Licensing:** physicians should be licensed in the state where the patient is located; the licensure process is long and in some states physicians have to pay annual license renewal fees. The pandemic allowed to remove many licensure-related hurdles.

5. An ambitious project: treating the patient, not the disease

Smartphones, electronic patient health record systems and sensing devices, wearable and implantable, provide all a huge amount of data that could quickly analyzed and combined through artificial intelligence (AI), with the aim to realize the ambitious project of precision medicine. Indeed, using the advances in technologies and panomics, precision medicine wants to overcome the current limitations of reductionism and treat the patient, not the disease.

Machine learning (ML), a subset of AI, could play a pivotal role having the ability to learn from data and make predictions without priori explicit programming. In this way, cardiologist’s workflow, from diagnosis to therapy, could be greatly enhanced [59].

In the setting of PAH, investigations on AI are still limited.

Kwon J. et al. recently developed and validated a deep learning based AI algorithm for early detection of PH using a 12-lead electrocardiography (ECG) and a single-lead ECG. Although the several limitations of this study and the current limited investigations in this field, the future looks bright for the diffusion of AI and ML in the management of PAH patients [60].

Finally, computational simulators reproducing PAH patients’ hemodynamic conditions and simulating the effect of different therapeutic interventions in real time might contribute to realize the precision medicine project. However, to date only few systems include hemodynamic and ventilatory variables coupling the cardiovascular and respiratory system. A strict cooperation between model developers and PAH specialists is therefore required for the optimization and the widespread diffusion of computational PAH simulators in daily clinical practice [61].

6. COVID-19 impact on patients management in PAH

COVID-19 pandemic severely affected national health systems, altering the modality and the type of care, especially for patients with

rare diseases: the survey carried out between 18 April and 11 May 2020 by the European organization for Rare Diseases (EURORDIS) showed that 84% of European rare diseases patients experienced a disruption of their care due to the COVID-19 outbreak [62].

In the setting of PAH the virus hampered the possibility to access usual systematic activities, such as WHO functional class evaluation, six-min walk, cardiopulmonary exercise and echocardiographic tests, limiting the multiparametric patient’s periodic risk assessment [63–65]. Moreover, the SARS-CoV2 caused a deferral of RHC, frequently postponed to a safer date, delaying PAH new diagnoses and the initiation of specific therapies. As reported in a multi-centre study performed in Germany investigating the impact of SARS-COV2 on PH patients, during the study period (from 1 March 2020 to 30 April 2020) the number of admissions and therapy initiations decreased by almost 50% compared to corresponding time periods in previous years [66].

In this emergency situation, many PAH centers adopted telehealth to virtually manage PAH patients not needing urgent hospitalization neither immediate clinical assessment, in order to avoid a negative impact on patients’ prognosis. Telemedical tools were adopted to provide close monitoring and serial evaluation of PAH patients: phone-based interactions, video visits and emails were used to close monitor patients’ parameters (blood pressure, heart rate, oxygen saturation and cardiac rhythm tracings) and to evaluate the need of hospital admissions.

Such close management and support were made possible by policy changes that reduced barriers to telehealth access and promoted the use of telemedicine during the COVID-19 outbreak as a way to deliver primary and specialty care for acute and chronic diseases. Indeed, the use of smartphones, emailing and/or webcam-enabled computers as an alternative mode for patient communication and medical data collection and transfer has finally been authorized by the HIPAA [67]. This quick and easy way of communication gave patients a high-level medical support, while limiting travel and exposure to SARS-CoV2 [68].

7. An Italian proposal of PAH patients management

In Italy such virtual management was hampered by the limited availability and diffusion of telemedical tools and the poor widespread of telemedicine among PAH centers, which therefore had to categorize and reprioritize PAH patients.

Below we report a proposed strategy coming from a recent patient-level survey by the IPHNET during the first COVID-19 outbreak, when face-to-face visits were established according to a phone-call basis and risk assessment (Fig. 1).

In patients known to be at low-risk and found in stable clinical condition on a phone call-basis, a conservative approach was adopted postponing the in-person visit to a safer date.

Conversely, in high risk patients the scheduled in-person visit was maintained and weekly or biweekly check-in calls were performed to monitor clinical conditions. Patients with worsening symptoms and/or congestive heart failure were hospitalized, using safe-controlled procedures when possible or through the Emergency Department.

Finally, for patients at intermediate risk an individualized approach was undertaken, balancing the risk for COVID-19 exposure versus delay in disease progression recognition and treatment up-titration. In this subgroup, check-in calls were performed every 1 to 3 months.

The periodical recommended basic laboratory workup, including brain natriuretic peptides [6], was checked in all patients using the email service.

The health care impact of this strategy was reported in a multicenter nationwide survey, including 1922 PAH patients managed in 25 centers participating to the Italian Pulmonary Hypertension Network (IPHNET) between 1st March and 1st May 2020. Number of in-person visits, 6MWTs, echocardiographic tests, BNP/NT-proBNP tests, WHO class assessment, the presence of elective hospitalization for RHC, non-elective hospitalization, need for treatment escalation/initiation and

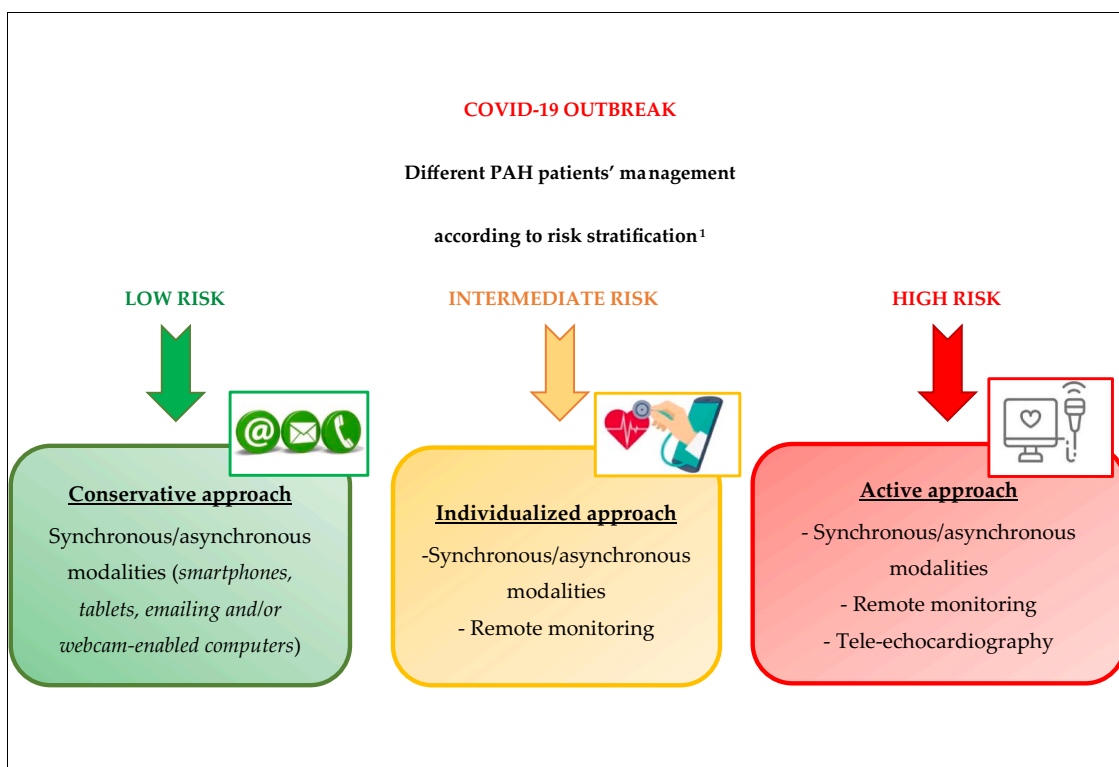


Fig. 1. Proposal for PAH patients' management during the COVID-19 pandemic. ¹ Risk stratification according to the European Society of Cardiology/European Respiratory Society PH guidelines-derived score and the REVEAL 2.0 score.

mortality rate of these 1922 PAH patients were compared with the data from patients managed in the same period of the previous year. As reported by Badagliacca et al., COVID-19 outbreak was associated with a down-sizing of systematic activities in PAH, with a dramatic reduction of in-person visit, elective hospitalization and RHC. Of course, PAH patients were less likely to receive elective sequential add-on therapy. Nevertheless, the reduction in therapy optimization did not result associated with increased mortality during short-term follow-up [69]. Networking among clinicians and sharing experiences between high- and low-volume centers, reprioritizing of PAH patients and their self-isolation during the pandemic have all contributed to this paradoxical finding.

Further surveys are welcome to improve the management of PAH patients in the COVID-19 era and to promote telemedicine as a novel method of providing medical care in the PAH setting. Indeed, in contrast to heart failure [70], to date studies reporting the success of telehealth services in this setting are still poor: no clinical trials showed that telecardiology is associated with lower mortality and hospitalization compared with usual care in PAH patients.

8. Conclusion

COVID-19 has posed unique challenges to health care delivery, especially for patients affected by rare disease, who experienced a dramatic disruption of their medical support during the pandemic. In this context, telehealth represented an ideal solution to continue providing a high level of care to patients, allowing virtual interactions with clinicians. However, important changes are needed for telemedicine to become the standard of care. Health authorities are working to implement and improve telemedicine program establishing a real trained team and providing clear guidelines, to overcome the scattered distribution and heterogeneity of available tools and to solve the ethical and legal challenges and the heavy privacy regulations. Telecardiology has shown great promise to support PAH patients care especially during

COVID-19 pandemic and could become part of normal practice in the near future.

Authors contributions

Conceptualization: G.M., R.B., R.M., C.D.L. and C.D.V.; methodology: G.M., R.B., S.P., and G.S.; resources: B.D.L., C.M., F.I.A., D.F. and N.C.; writing—original draft : G.M., R.B., S.P., G.S. and A.C.; writing—review and editing: G.M., G.S., T.R. and M.V.M.; supervision: R.B., R.M., and C.D.V.; visualization: G.M. and C.D.V.; project administration: R.B. All authors contributed to the work. All authors have read and agreed to the published version of the manuscript.

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R. Badagliacca received fees for participating in advisory boards and received benefits (travel and accommodation for scientific meetings) from Actelion, Bayer, Dompè, Ferrer, GSK, MSD. C.D. Vizza received fees for serving as a speaker, consultant and an advisory board member, from the following Companies: Actelion, Dompè, GSK, Italfarmaco, Lilly, Pfizer, United Therapeutics. The other authors reported no conflicts of interest.

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