Cardiovascular findings in Echocardiography in a post Covid-19 mild infection population in Argentina

Short Title: Echocardiography in mild Covid-19 infection

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Abstract

Objectives: The aim of this study was to assess differences in echocardiographic findings between a normal adult and a post Covid-19 population.

Background: Coronavirus disease (Covid-19) is known to produce a systemic inflammatory syndrome, with pulmonary and cardiac involvement. However, the cardiovascular impact in patients with mild clinical forms of the disease is uncertain. There is small evidence supporting the finding of global ventricular longitudinal strain (GLS) alterations in these patients.

Methods: One hundred and five consecutive patients admitted to an ambulatory care center, underwent a conventional transthoracic echocardiographic (TTE) study with acquisition of GLS. Patients were included if they underwent a positive diagnostic reverse transcriptase polymerase chain reaction (PCR) test, having no relevant preexisting conditions, with exception of obesity. Demographic and clinical data were prospectively obtained. For this purpose, we considered a normal cut off point of -17,09%, based on previous studies. Echocardiographic findings were compared with those of 67 healthy individuals.

Results: Out of 172 patients, 105 correspond to Covid-19 group, and 67 to healthy individuals. There were no significant differences in GLS regarding age, left ventricular mass index (LVMI) and E/e' ratio. The multivariate analysis showed that the percentage of patients with pathological GLS values was significantly higher within the Covid-19 and male groups (OR 6.02 IC 1.88-22.57; p 0.004 and OR 3.17 IC 1.03-10.50; p 0.05, respectively).

Conclusion: These data support that Covid-19 infection could affect ventricular GLS and encourage the use of conventional TTE with GLS measurements in patients with non-significant forms of the disease.

Key words: Covid-19, Echocardiography findings, Myocardial Strain.

INTRODUCTION

It has been reported that between 20-30% of hospitalized patients for Covid-19 infection show some evidence of myocardial involvement [1-6]. The incidence of cardiac disease caused by Covid-19 is yet uncertain in non-hospitalized patients. Viral acute myocardial injury (including myocarditis, acute plaque rupture, secondary ischemia, direct viral injury) is related with higher morbidity and mortality, and worse clinical outcome, among these patients. Convalescent phase post Covid-19 infection could eventually represent a group in risk of developing myocardiopathy, ventricular arrhythmia and atrial fibrillation, and sudden cardiac death[7,8]. There are still few data regarding long term cardiovascular sequelae, although recent small publications show basal longitudinal strain alterations among diverse clinical forms of the disease, with no or non-significant alterations of other echocardiographic parameters [9,10]. Searching for residual myocardial damage in convalescence phase in this group seems mandatory in order to understand, and eventually give specific therapeutic options, to diminish long term cardiovascular complications of a "post Covid-19 cardiac syndrome", looking forward to improving morbimortality.

Methods:

STUDY POPULATION. This study was performed in an ambulatory diagnostic center in Buenos Aires, Argentina. We included a total of 105 consecutive patients in Covid-19 convalescent phase (after clinical recovery), all of them diagnosed with a positive PCR test, according to recommendations of the World Health Organization, from June 1st, 2020 to January 30th, 2021. Adults >18 years, men, and women, who had a positive PCR test in the clinical context of asymptomatic or mild/moderate forms of the disease were prospectively identified and included in an electronic database. Exclusion criteria included a) any previous relevant medical condition that may alter echocardiographic parameters, with exception of obesity, and b) left ventricular ejection fraction (LVEF) <50%. Obesity was defined as a body mass index equal to or higher than 30 [11]. The control group consisted of 67 healthy adults, on the basis of medical history, physical examination, and echocardiographic measurements.

The study complied with the edicts of the 1975 Declaration of Helsinki and was approved by the institutional ethics board.

TRANSTHORACIC ECHOCARDIOGRAPHY. TTE examinations were performed in all patients using commercially available ultrasound systems (GE Systems). Two-dimensional, Doppler echocardiography and GLS measurements were performed on the basis of the guidelines of the American Society of Echocardiography.

ECHOCARDIOGRAPHIC ANALYSIS. Left ventricular (LV) end-systolic and end-diastolic diameters and volumes, and LVEF were measured using biplane Simpson's method [9]. LVMI was calculated from the parasternal view based on Devereux´s formula[12]. LV diastolic function was estimated using the ratio of early transmitral flow velocity (E) to late transmitral flow velocity (A), and the ratio of transmitral E to the averaged early diastolic septal and lateral tissue velocity (E/e´). GLS was conducted according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [10] (Fig.1). Every image was analyzed using a 2D Autostrain software (GE systems) in the apical 3, 4 and 2-chamber views, at a frame rate of 50-70 frames/s.

STATISTICAL ANALYSIS. Descriptive statistics are only reported for demographics findings. For echocardiographic measurements, continuous numeric variables are expressed as mean SD or median (interquartile range) and were compared using a 2-sample Student's t-test and 1-way analysis of variance (for normally distributed data) or the Mann-Whitney U test and Kruskal-Wallis test (for non-normally distributed data). Categorical variables are expressed as frequency (percentage) and were compared using the chi-square test or the Fisher exact test. Estimations of the predictors of pathological GLS were performed using univariate and multivariate logistic regression models. A $p < 0.005$ value was considered statistically significant.

Statistical analyses were performed using EpiInfo version 7.2.3.1 (Centers for Disease Control and Prevention) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results:

CLINICAL CHARACTERISTICS. During the study period, 105 patients with diagnosis of asymptomatic or mild/moderate Covid-19 were admitted to our center, and underwent a conventional TTE study. The median time from diagnosis of the disease to the completion of the study was 32 days (IQR 11-46), without significant differences between genders (male 31 days IQR 11-48; female 34 days IQR 15-46; p = ns). We compared findings with a control group of 67 healthy patients.

Eighty-four patients were male (48,84%) and 88 females (51,16%). The median age was 43 years old (IQR 35-50); 148 patients (86%) were younger than 55. There were 82 patients with a body mass index above 30. There was a lower percentage of males in patients with Covid-19, without significant differences between groups regarding age and obesity

ECHOCARDIOGRAPHIC CHARACTERISTICS. Though without clinical relevance, in univariate analysis, we observed that LV diastolic diameter and left atrial volume index were smaller, and LVMI and E/e' ratio were lower in patients with Covid-19. GLS was significantly lower in patients with Covid-19 compared with controls (Table 1).

For the purpose of this study, we considered a normal GLS cut off point of -17.09%, based on previous studies in a similar population (normal value 21.01±1.96)[13]. Grounded on these data, we divided the patients into 2 groups with normal or abnormal GLS. For the multivariate analysis, we considered variables with significant differences in the univariate analysis that could affect the GLS from a rational point of view, such as the history of Covid-19, gender and obesity (Table 2). As E/e' ratio could have an influence in the results, it was also included, despite the absence of significant statistical differences in the univariate analysis.

The multivariate analysis showed that the percentage of patients with pathological GLS was significantly lower in Covid-19 group (OR 6.02, CI 95% 1.88-22.57; p<0.01) and male gender (OR 3.17, CI 95% 1.03-10.50; p=0.05) (Fig. 2). The Hosmer-Lemeshow test showed the goodness of fit test (p=0.34).

Notably, when we analyzed each gender separately, we found no significant differences in GLS in women, as found in men (OR 5.00, 95% CI 1.40-20.98; p=0.02) (Fig. 3).

Discussion:

The Covid-19 pandemic caused by severe acute respiratory syndrome coronavirus has demonstrated a broad spectrum of presentations, ranging from asymptomatic disease to severe respiratory failure, myocardial injury, and death. Up to 20%–30% of patients hospitalized with Covid-19 have evidence of myocardial involvement [1-6].

Because most patients recover from the illness, anticipating cardiovascular complications seems very important. Available and easy to perform TTE measurements could recognize subtle cardiac damage, providing adequate monitoring of adverse outcomes during follow-up. GLS provides additive value over other echocardiographic parameters, being easily obtained during conventional TTE performance. Compared with LVEF, GLS has the advantage of being less influenced by loading conditions, myocardial compliance, and afterload, as it measures myocardial deformation directly [14-16]. In follow-up, these results may identify patients at higher risk for poor outcomes who might benefit from close monitoring and diverse therapeutic strategies.

Our colleagues are constantly publishing articles related to the importance and value of TTE in the setting of critically ill Covid-19 patients. In a case-control study including 214 hospitalized Covid-19 patients, Højbjerg Lassen et al found that reduced LVEF and GLS were all significantly associated with a higher risk of total deaths, and Covid-19 related mortality [17]. Croft et al showed lower values of mean GLS in a hospitalized Covid-19 cohort, despite preserved LVEF, suggesting the presence of myocardial injury [18]. Although more severe GLS reduction showed only a trend towards predicting hospital death or need for mechanical ventilation, they found non-significant differences in deaths among these patients.

To our knowledge, there is still little echocardiographic evidence of myocardial damage in non-hospitalized patients, with mild or even asymptomatic forms of Covid-19 disease, in the convalescent phase. Our data demonstrated that Covid-19 was a powerful and independent negative predictor of GLS in this group as well.

Furthermore, although prevalence of infection with Covid-19 seems to be quite similar between sexes, we found higher number of patients with pathological GLS values, almost exclusively in male population, as recently suggested by other publications. These results could open debate for some possible gender-related differences, which could account, at least partially, for the worse prognosis and higher mortality rates described in other publications of Covid-19 in this group [19]. Male hospitalization rates were higher than female ones, in all countries which reported them, ranging from 55 % to 62 % [20-24]. The proportion of male admissions to the intensive care units was even higher, ranging from 65 % to 74 %. Some authors suggested that the reduced susceptibility of women to viral infections could be attributed to the protection from the X chromosome as well as from sex hormones, which play an essential role in innate and adaptive immunity [25]. Women seem to have a more robust immune system [26]. It has been reported that women have stronger immune responses to infections and vaccinations than men. This is, among other factors, due to the documented effects of estrogens, progestogens, and androgens. Also, sex differences in the expression of ACE genes have been reported [27,28].

CLINICAL IMPLICATIONS. Our data demonstrated that Covid-19 was a powerful independent negative predictor of GLS in previously healthy patients, providing additive value over other echocardiographic parameters, being easily obtained during conventional TTE performance. In follow-up, these results may identify patients at higher risk for poor outcomes who might benefit from close monitoring and diverse therapeutic strategies.

STUDY LIMITATIONS. Although our findings in GLS are most probably the consequence of viral aggression (given the cohorts' characteristics), there are no previous TTE to ensure these changes might not have been present *before* Covid-19 infection. Furthermore, there is still little evidence to conclude that certain pathological TTE parameters are, or not, exclusive of Covid-19 myocardial damage, and no other common viral agents with myocardial tropism.

As regards the differences found in gender, it is not clear whether this is due to biological differences between men and women, differences in behavioral habits, or differences in the rates of comorbidities. Countries and studies should report their data by age, gender, and comorbidities. This may have implications in terms of vaccination strategies, the choice of treatments and future consequences for long-term health issues concerning gender equality.

Therefore, further multicenter analyses are needed to determine the exact effects of Covid-19 and adverse outcomes in all clinical subgroups.

CONCLUSIONS. Our study showed that Covid-19 infection resulted the only independent negative predictor of pathological GLS, even in mild forms of the disease and subtle cardiac damage, showing some possible gender-related differences. In this matter, GLS may in the future have an additional predictive value over other echocardiographic parameters in terms of prognosis. Therefore, evaluation of GLS should be included in all patients, despite of the severity of the disease, to assess risk stratification and future treatments strategies. Further multicenter analysis, including differences in age, sex, and comorbidities for individualized risk assessment and management strategies are crucial.

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Abbreviations: coronavirus disease (Covid-19); transthoracic echocardiogram (TTE); global longitudinal strain (GLS); left ventricular (LV); left ventricular ejection fraction (LVEF); reverse transcriptase polymerase chain reaction (PCR).

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Figure 1. Left Ventricular GLS in a normal patient.

Figure 2. Multivariate analysis. Covid-19 and male gender were the only independent predictors of pathological GLS.

Figure 3. Multivariate analysis, male population. Covid-19 was the only independent predictor of pathological GLS.