Modulation of Cardiac Injury by ACE inhibitor/ARB in Patients with Severe COVID-19

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Abstract

Introduction: Cardiac injury occurs in 7-22% of patient hospitalized with COVID-19 and an elevation in troponin is associated with a 4.2-fold increase in the risk of mortality. Preliminary data showed ACEi/ARB usage might not increase mortaily in COVID-19 patients. However, it is unknown if cardiac injury in patients with severe COVID-19 can be modulated by ACEi/ARB usage during evolution of the cardiac injury.

Methods: In 154 COVID-19 patients with cardiac injury, the effect of ACEi/ARB treatment (17 patients) was compared with 137 patients without ACEi/ARB treatment. Cardiac injury was indicated by cTnI level.

Results: In ACEi/ARB treatment group and no ACEi/ARB treatment group, peak cTnI level did not show significant difference (150.5 pg/ml [31.75-1179], vs 207 pg/ml [54.65-989.4], respectively, P = 0.21). Evolution of Cardiac injury (temporal change of cTnI at day 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33) showed no statistical difference. Mortality (ACEi/ARB group vs no ACEi/ARB group; 52.9% vs 69.9%, P = 0.17), atrial arrhythmias (11.7% vs 24.4%, P = 0.36), requirement for invasive ventilatory support (29.4% vs 48.2%, P = 0.14) also showed no significant difference in two groups.

Conclusions: ACEi/ARB usage during the COVID-19 was not associated with exacerbation of cardiac injury. These data should be interpreted as essentially hypothesis-generating due to small sample size.

Clinical Trial Registration: This retrospective study was registered in Chinese clinical trial registry (ChiCTR 2000031301).

Introduction

There have been conflicting views on the subject whether to continue ACE inhibitor (ACEi) and ARBs in COVID-19 patients. Several recent studies have reported the effect of ACEi/ARB use in COVID-19[1–3]. These studies of ACEi/ARB, studied their effect on mortality in COVID-19 patients with hypertension. ACEi/ARB treatment was not associated with a higher mortality[1] or associated with a reduced all cause mortality (HR 0.30, 95% CI, 0.12–0.70) [2]. Others have suggested that ACEi and ARBs may actually help diminish the deleterious effects of COVID-19 in infected patients by up-regulating ACE2 receptors, and could even be used as therapeutics in some patients[4]. ACE2 metabolizes angiotensin I to angiotensin-(1–9), and angiotensin II to angiotensin-(1–7), thus converting vasoconstrictor, pro-inflammatory peptides to vasodilatory, anti-inflammatory peptides. Upregulation of ACE2 receptors may be particularly important in patients with COVID-19, as the virus enters the host cell, it takes the ACE2 receptor with it, creating a relative lack of ACE2 receptors and thereby enhancing the deleterious effects of the disease. However, the upregulation of ACE2 with ACEi/ARB treatment is controversial, and is only seen mainly in cardiac injury[5]. Thus, this issue of cardio-protection in COVID-19 is particularly pertinent as in COVID-19, where cardiac injury appears to be common and associated with worse outcome.

Cardiac injury occurs in 7–22% of patient hospitalized with COVID-19 and an elevation in cardiac troponin I (cTnI) is associated with a 4.2-fold increase in the risk of mortality[6, 7]. Although ACEi/ARB effect on mortality in COVID-19 patients with hypertension have been reported, the effect of ACEi/ARB on evolution of cardiac injury in COVID-19 patients who present with cardiac injury at admission has not been studied. We evaluated this specific question in this retrospective analysis by assessing the effect of ACEi/ARBs treatment on peak cTnI level and temporal change of cTnI levels, in severe COVID-19 patients with documented cardiac injury at admission.

Methods

This retrospective study (Chinese clinical trial registry, ChiCTR2000031301) was approved by the research ethics board of the Third Hospital of Jilin University (approval number 2020032619), Tongji Hospital, Huazhong University of Science and Technology (approval number TJ-IRB20200345) separately.

A total of 1,284 patients with CT-proven COVID-19-associated pneumonia were admitted, directly to the Tongji Hospital (Zhongfaxincheng District) or transferred there from several delegated COVID-19 care centers from January 29 to March 8, 2020. All patients were diagnosed according to WHO interim guidelines, including typical symptoms, clear contact history, and positive SARS-CoV-2 nucleotide PCR. If the patients also presented with typical pulmonary infiltrations on CT scan, they were defined as CT-proven COVID-19 patients. Data corresponding to 170 patients who exhibited cardiac injury (i.e., positive cTnI levels above the 99th percentile of the upper reference limit [> 26.2 pg/mL]) upon admission were extracted and analyzed. The number of patients with clear and documented histories of treatment with ACE inhibitors, ARBs, or neither totaled 154 (17 patients with history of ACEi/ARBs treatment, and 137 patients with no history of ACEi/ARBs treatment). The other 16 patients died before therapy on ACEi/ARB could be determined (Figure 1). The history of ACEi/ARBs treatment was confirmed by past medical information provided by the patient or family and transferred hospital/clinic medical records. All 17 patients undergoing ACEi/ARBs treatment in our cohort continued ACEi/ARB after admission.

The primary outcome was cardiac injury which was assessed as peak cTnI level during the admission. Admission cTnI level was defined as the first cTnI test (all within 72 hours of admission). cTnI was measured depending on the physicians' decision. Peak cTnI was the highest cTnI concentration measured during hospitalization. ΔcTnI was defined as peak cTnI minus admission cTnI. The evolution of cardiac injury was assessed with mean cTnI level every 3 days (day 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33). We compared several factors including cardiac injury (cTnI level), in-hospital outcome (discharge/death), requirement for ventilation, and atrial arrhythmias. The classification of arrhythmias was based on arrhythmia monitors or 12-lead ECGs diagnosed by the cardiologist in each COVID-19 medical care team. Atrial arrhythmias were defined as frequent premature atrial complex (fPAC), atrial tachycardia /atrial fibrillation. fPAC was defined as ≥ 3PAC for every 10 beats as observed on monitor screen or on an ECG.

Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]). The Mann-Whitney test was used to compare the between-group differences. Categorical variables are expressed as counts and percentages. The Fisher's exact test was used to compare the differences (including in-hospital death, ventilation, and atrial arrhythmias). Multivariate linear regression analysis was performed to assess the effect of ACEi/ARB on peak cTnI levels, adjusted for age, sex and hypertension. Statistical significance was defined as $P \leq 0.05$. Data analysis was performed with GraphPad Prism 7.00 (San Diego, CA, USA) and R version 3.6.3 software (University of Auckland, Oakland, New Zealand).

Results

Patient group demographic information

The two patient groups were similar in age and sex, and most had no known pre-existing CVD, suggesting that most patients were undergoing ACEi/ARBs treatment for hypertension (Figure 1). All patients with a history of ACEi/ARBs treatment were hypertensive, compared to 38.7% patients with no ACEi/ARBs treatment. The number of diabetic patients in the ACEi/ARBs-treatment group was higher than that in the no ACEi/ARBs-treatment group (41.2% vs 19.0%, P = 0.06) (Table 1).

Effect on cardiac injury

There were no significant differences in admission cTnI levels between the two groups (median [IQR], ACEi/ARBs group, 33pg/ml [19.3-157.7], vs no ACEi/ARBs group, 52.6 pg/ml [21.63-211.8], P = 0.56). ACEi/ARBs treatment did not result in increased cardiac injury compared to no ACEi/ARBs treatment, as determined by peak cTnI, (150.5 pg/ml [31.75-1179], vs 207 pg/ml [54.65-989.4], respectively, P = 0.21). In addition, the ΔcTnI was not significantly different between the two groups (ACEi/ARBs treatment, 0 pg/ml [0-292.3] [12/17 patients with ΔcTnI = 0], vs no ACEi/ARBs treatment, 20 pg/ml [0-305.9], P=0.13) (Table 1). Moreover, evolution of cardiac injury was compared with temporal changes in cTnI, no statistically significant difference was found between any two points in the daily measurements including day 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33 (Figure 2). After adjustment with age, sex and a diagnosis of hypertension, multivariate regression analysis revealed that ACEi/ARBs treatment was not associated with the peak cTnI level (P = 0.65) (Table 1).

Effect on in-hospital death, ventilatory support, and atrial arrhythmias

The mortality rate in the ACEi/ARBs treatment group was 52.9% compared to a rate of 69.9% in the no ACEi/ARBs treatment group (P = 0.17). Also, the ratio of ventilated patients was lower in the ACEi/ARBs treatment group than that in the no ACEi/ARBs treatment group (29.4% vs 48.2%, respectively, P = 0.14). Atrial arrhythmias were documented in 11.7% of the ACEi/ARBs treatment group, vs 24.4% in the no ACEi/ARBs treatment group (P = 0.36) (Table 1).

Table 1. ACEi/ARB Treatment and In-hospital Outcomes of COVID-19 Patients

	ACEi/ARB (n=17)	No ACEi/ARB (n=137)	P value
Age, yrs	**71** (63.5, 77)	**69 (62, 77)**	ns
Male (%)	**7** (41.2%)	**72 (52.6%)**	ns
Hypertension (%)	**17** (100%)	**53** (38.7%)	0.0001
Diabetes (%)	**7** (41.2%)	**26** (19.0%)	ns
Pre-existing CVD (%)	**5** (29.4%)	**25** (18.3%)	ns
Admission cTnI (pg/ml)	**33** (19.3, 157.7)	**52.6** (21.63, 211.8)	ns
Ventilated patients (%)	**5** (29.4%)	**66** (48.2%)	ns
Peak Creatinine (umol/L)	**81** (67.5, 124.5)	**99.6** (74.25, 198)	ns
Peak cTnI (pg/ml)	**150.5** (31.75, 1179)	**207** (54.65, 989.4)	ns
ΔcTnI (pg/ml)	**0** (0, 292.3)	**20** (0, 305.9)	ns
In-hospital death (%)	**9** (52.9%)	**95** (69.3%)	ns
Atrial arrythmias (%)	**2** (11.8%)	**33** (24.1%)	ns
Multivariate Adjusted prediction of ACEi/ARB treatment for cTnI level			
	**β Coefficient* **	**95%CI***	**P value**
ACEi/ARB treatment	-0.095	(-0.51, 0.33)	ns

CVD: cardiovascular disease; cTnI: cardiac troponin I; CI: confidence intervals.

*Adjusted by age, sex, and a diagnosis of hypertension.

Discussion

In this cohort study of cardiac injury, in severe COVID-19, ACEi/ARBs treatment upon admission was not associated with increased risk of cardiac injury. Our findings are especially interesting because, despite a worse CV risk profile, ACEi/ARBs usage was not associated with increased peak cTnI, atrial arrhythmias, intubation or mortality.

The basis for the elevated cTnI likely represents type 2 myocardial injury in this setting from a combination of systemic and myocardial inflammation and microvascular dysfunction. In post-mortem autopsy heart tissues from 20 SARS-CoV patients, 7 heart samples had detectable viral SARS-CoV genome, which was characterized by increased myocardial fibrosis, inflammation and reduced myocardial ACE2 expression, providing evidence that myocardial injury from SARS-CoV is mediated through interactions with the myocardial ACE2 pathway[8].

The COVID-19 pandemic is driven by the unique ability of SARS-CoV-2 to bind tightly to its receptor, ACE2, which is widely expressed in the lungs and cardiovascular system. Notably, SARS-CoV-2 binding to ACE2 results in a marked downregulation of the receptor. This is due to a combination of receptor-mediated endocytosis and activation of ADAM metallopeptidase 17, which leads to proteolytic cleavage, and subsequent loss of ACE2. This cascade likely results in marked activation of systemic and tissue RAS genes in patients with COVID-19-associated pneumonia[4]. Pharmacological RAS blockade agents are effective in suppressing both systemic and tissue RAS, while simultaneously increasing ACE2 expression and activity. Consequently, our data could be interpreted as hypothesis generating, and in support of randomized studies testing the theory that blocking Ang II signaling with ACEi/ARBs might be an effective therapeutic option for COVID-19 patients.

Limitations

Our data were generated from a small patient cohort with possible selection and inherent immortal time bias. The study also does not address whether ACEi/ARBs treatment increases susceptibility to infection by SARS-CoV-2, the effect on individuals without cardiac injury, and the differential effect of ACEi compared to ARBs, due to the small number of patients. We urge readers to consider these data as hypothesis-generating, and confirmation of our theory will require randomized data on prospective ACE2 modulation and COVID-19.

Conclusions

Our results, of patients with COVID-19-associated cardiac injury, treatment with ACEi/ARBs was not associated with exacerbation of cardiac injury, atrial arrhythmias, or mortality. The data must be cautiously interpreted due to the limitations we have detailed. These important findings require validation. The active modulation of ACE2 in patients after admission is being tested in randomized controlled trials currently in progress (ClinicalTrial.gov number NCT04312009, NCT04311177, and NCT04318418). Our data supports the American Heart Association (AHA) recommendations to maintain ACEi/ARB usage even after cardiac injury during COVID-19 pneumonia, blood pressure permitting.

Declarations

Ethics approval and consent to participate: Written informed consents were waived during this pandemic, verbal consents from all the patients were obtained for the publication of this study and any accompanying images. This was approved by the research ethics board of the Third Hospital of Jilin University (approval number 2020032619), Tongji Hospital, Huazhong University of Science and Technology (approval number TJ-IRB20200345) separately, and strictly conformed to the ethical guidelines of the Helsinki Declaration. Also, this study was registried in Chinese clinical trial registry (ChiCTR2000031301).

Consent to publish: I have obtained consent to publish from the participants.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: Dr. K. N. is consultant for Servier, Biosense Webster, Abbott and Blue Rock. Dr JR is a consultant for AstraZeneca and Novartis and Dr. GO has received grant support from Sanofi-Genzyme and Takeda. The remaining authors have nothing to disclose.

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Authors' Contributions: BD, BY and DS were the patient’s physicians. BD, GL and DS applied for the IRB approval, and registered the retrospective study, QZ, YY, LJ and BY extracted the data. QZ, YY, LJ, and SM analyzed the data and prepared the figures, BD, PY and KN reviewed the literature and contributed to manuscript drafting, GO, and JR reviewed and edited the manuscript, BD, SD, PY and KN were responsible for the revision of the manuscript for important intellectual content. All authors issued final approval for the version to be submitted.

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Figures

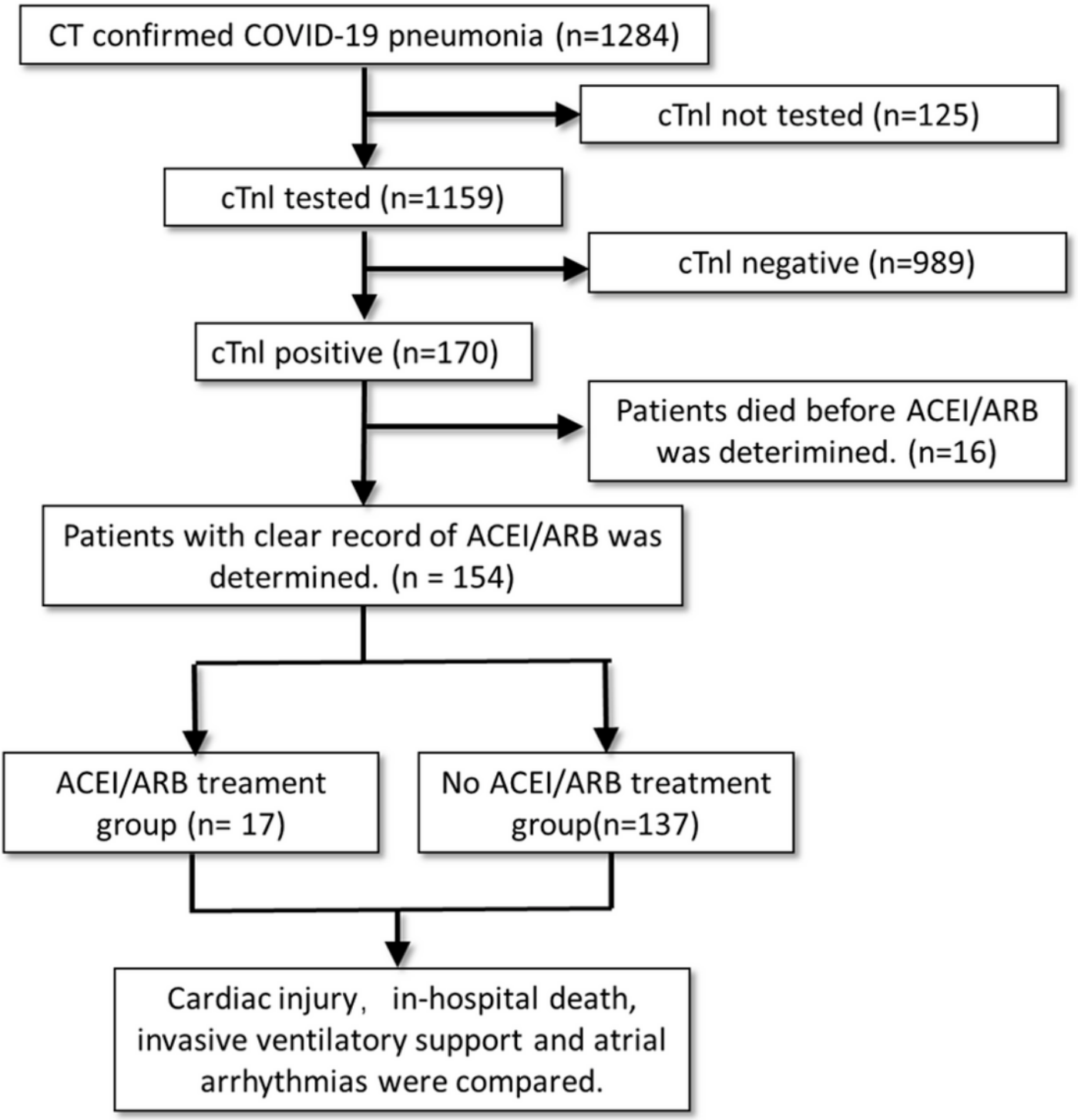

Figure 1

The flow chart of the study. Among the 1284 COVID-19 pneumonia patients transferred to Tongji Hospital, 1159 patients were tested for cTnI concentration. In the 170 patients with elevated cTnI level, 16 died before ACEi/ARB was determined. 17 patients with ACEi/ARB treatment and 137 patients without history of ACEi/ARB usage were studied. cTnI: Cardiac troponin I.

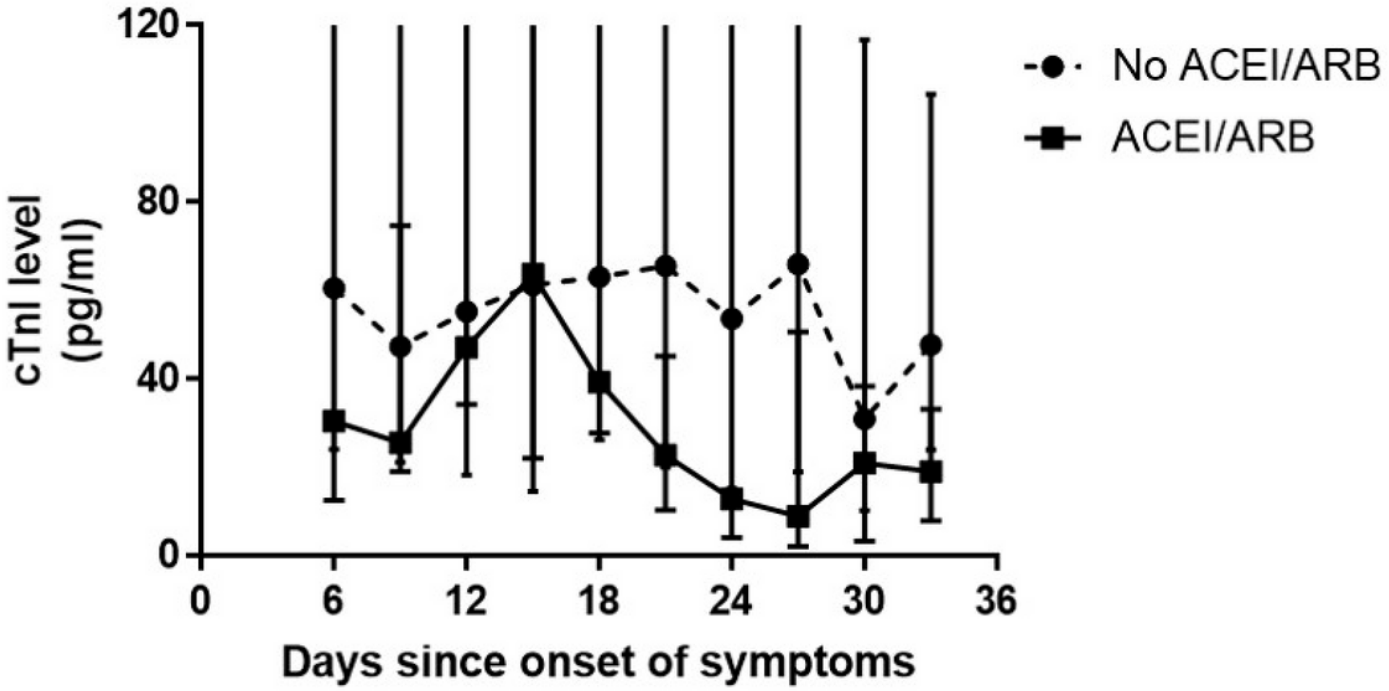

Figure 2

Temporal change of cTnI level in ACEi/ARB group and no ACEi/ARB group cTnI levels in two groups were compared at each time point (day 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33), no statistical differences were found.