

The Effect of Angiotensin II Infusion on Markers of Organ Function in Invasively Ventilated COVID-19 Patients

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Research

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Abstract

Background: The use of angiotensin II (ANGII) in invasively ventilated COVID-19 patients is controversial. Its effect on markers of organ function is unknown.

Methods: We used ANGII either as rescue vasopressor agent or as low dose vasopressor support. Patients treated before ANGII availability or in an adjacent COVID-19 ICU served as controls. For data analysis, we applied Bayesian modelling as appropriate. We assessed the effects of ANG on markers of organ function.

Results: We compared 46 ANGII patients with 53 controls. Compared with controls, ANGII increased MAP (median difference, 9.05 mmHg [95% confidence interval, 1.87 to 16.22]; $p = 0.013$) and $\text{PaO}_2/\text{FiO}_2$ ratio (median difference, 23.17 [95% confidence interval, 3.46 to 42.88]; $p = 0.021$). ANGII had no effect on lactate, urinary output, serum creatinine, C-Reactive protein, platelet count, or thromboembolic complications. However, it significantly decreased the odd ratio of liver dysfunction (odds ratio: 0.32; 0.09 to 0.94) and, on Bayesian modelling, in patients with abnormal baseline serum creatinine, ANGII carried a 95.7% probability of decreasing renal replacement therapy use.

Conclusions: In ventilated COVID-19 patients, ANGII therapy was associated with increased blood pressure and $\text{PaO}_2/\text{FiO}_2$ ratios, decreased odds ratio of liver dysfunction, and a high probability of decreasing renal replacement therapy use in patients with abnormal baseline serum creatinine.

Background

Coronavirus infectious disease 2019 (COVID-19) can cause severe acute respiratory syndrome [1]. Once ventilated, the majority of such patients develop vasodilatory shock [2]. The renin-angiotensin-aldosterone system (RAAS) may play an important role in these patients because angiotensin converting enzyme (ACE) type 2 is the viral receptor [3,4] with the spike protein on the viral surface of SARS-CoV-2 binding ACE2 with high affinity [3,4]. Moreover, ACE2 expression may be affected by the use of drugs that inhibit the RAAS [1,5].

Angiotensin II (ANGII) is an FDA and EMA approved vasopressor for the treatment of catecholamine resistant vasodilatory shock [6] and a substrate for ACE2. In a phase III double blind randomized trial, ANG II as rescue vasopressor improved blood pressure in such vasodilatory shock [6], increased survival in patients with a high angiotensin I/II ratio [7] and in those with a high renin level [8]. Moreover, in patients receiving renal replacement therapy (RRT) at randomization, ANG II increased the likelihood of recovery to RRT independence [9]. Its physiological effect on oxygenation in patients with COVID-19 was recently assessed in an uncontrolled case series [10] which reported an improvement of $\text{PaO}_2/\text{FiO}_2$ ratio with ANGII. In contrast, more recently, in an even smaller case series, investigators from Germany reported that ANGII was associated with poor outcomes in COVID 19 patients [11]. However, this observational assessment also lacked controls.

Given the above findings, we conducted a controlled assessment of the impact of ANGII infusion in patients with COVID-19 receiving invasive mechanical ventilation in a referral center in Milan, Italy [12]. After comparison with controls and adjustment for key baseline risk factor imbalances, we aimed to explore whether ANGII would affect markers of organ function.

Methods

Study design

The COVID-BioB study is an investigation performed at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute, a 1,350-bed university hospital in Milan, Italy. The study was approved by the Hospital Ethics Committee (protocol no. 34/int/2020), was registered on ClinicalTrials.gov (NCT04318366). Full description of patient management and clinical protocols at San Raffaele were previously published [9,10].

Enrolment criteria

After ANGII was obtained from the manufacturer for compassionate use, all patients aged ≥ 18 admitted to an intensive care unit (ICU) with confirmed SARS-CoV-2 infection were consecutively enrolled. Confirmed infection was defined as positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with signs, symptoms, and radiological findings suggestive of COVID-19 pneumonia. Only patients completing their 28-day follow-up were included.

Study intervention and control group

Following delivery of the drug to our ICU, a group of consecutive patients received ANGII (Giapreza[®], La Jolla, San Diego, CA, USA) infusion under compassionate use. The drug is approved by both the European Medicines Association and by the US FDA. All patients received ANGII at ICU admission, as vasopressor dose when needing vasopressor therapy or at low dose prophylaxis if vasopressor therapy was not needed. When used as a vasopressor, ANGII was used in addition to norepinephrine, and when used at low dose, there was the possibility to increase the dose if shock developed. All patients received venous thromboembolic events prophylaxis. Patients in the control groups never received ANGII and always received venous thromboembolic events prophylaxis.

The control group was made up of consecutive invasively ventilated patients treated before its introduction in one of several COVID-19 ICUs and consecutive invasively ventilated patients admitted to an adjacent COVID-19 ICU where ANG II was not made available. In both ICUs, patients were under the care of the same team of doctors and nurses who rotated across the various COVID ICUs during the pandemic.

Data collection

Medical records were used for data collection. We obtained data on contact exposure, onset of symptoms and presenting symptoms, medical history and ongoing medications at time of symptoms onset, daily clinical and laboratory data, treatment data, and outcome data. All data were collected by trained investigators independent from the clinical teams. Before analysis, an extensive round of data cleaning was performed by a dedicated data manager, together with clinicians, to check for data accuracy.

Outcomes

All outcomes reported in this study are exploratory in nature and related to the following markers of organ system function:

1. Mean arterial pressure and norepinephrine dose for the cardiovascular system
2. PaO₂/FiO₂ ratio for the respiratory system
3. Urinary output, serum creatinine, and use of renal replacement therapy for the renal system
4. C-Reactive protein level for the inflammatory arm of the immune system
5. Lactate for the metabolic system
6. Elevated liver enzymes for the hepatic system
7. Platelets for the coagulation and bone marrow system
8. Clinical thromboembolic complications for the coagulation system

Additional exploratory analyses included the following clinical outcomes:

1. The composite of failure to be discharged alive from the ICU at day 28 or death.
2. Hospital mortality at day 28
3. Duration of mechanical ventilation at day 28
4. Hospital length of stay at day 28.

Safety was evaluated by assessment of development of complications until the completion of follow-up (complete definitions of the complications in **Online Supplement**).

Statistical analysis

A convenience sample was considered for this analysis, with consecutively patients included until the 28 days of follow-up. No missing data for any of the outcomes are present in the dataset, thus, all analyses were complete case analyses without imputation. Continuous variables are presented as medians (quartile 25% - quartile 75%) and categorical variables as number and percentages. Baseline and clinical characteristics of the patients were compared among the groups using Fisher exact tests and Wilcoxon rank-sum tests. Development of complications are presented as unadjusted odds ratios from generalized linear models considering Binomial distribution. Daily data are compared using mixed-effect quantile models accounting for repeated measures, with day as a continuous variable and with day and group (and an interaction among them) as fixed effect. Quantile models considered $\alpha = 0.50$ and an asymmetric

Laplace distribution. P values were extracted after 1,000 bootstrap samplings. Overall p values from this analysis represent the overall difference among groups over time and p values from interaction represent a statistical assessment of whether the trend over time differed among the groups.

Primary and key secondary outcomes were explored and assessed using a Bayesian perspective. The analysis of key outcomes was done using a Bayesian model considering a Bernoulli distribution or using a Bayesian Cox proportional hazard model as appropriate. All models were developed using a Markov Chain Monte Carlo simulation with four chains, and considered a burn-in of 1,000 iterations, with sampling from a further 10,000 iterations for each chain. To monitor convergence, trace plots, and the Gelman-Rubin convergence diagnostic (Rhat) were used for all parameters. As is conventional for such analyses, results are presented as hazard ratio (HR) or odds ratio (OR) with 95% credible intervals (CrI) and as the probability of minimum clinical benefit. All models were adjusted by key prognostic variables at baseline (age, presence of diabetes and SpO₂).

Hospital length of stay, and duration of ventilation were assessed under the frequentist approach using sub-distribution HR derived from a Fine-Gray competing risk model with death before the event treated as competing risk and presented in cumulative incidence plots.

It was expected that the effect of ANGII would be influenced by the presence of renal dysfunction. Thus, in the present study we assessed the different effect of the drug in the subgroup of patients with abnormal serum creatinine at admission (defined as creatinine > 1.10 mg/dL in females and > 1.20 mg/dL in males). To explore the potential heterogeneity of treatment effect among these subgroups, a Bayesian binomial model was applied and the posterior distribution was sampled using Markov Chain Monte Carlo simulations. Results are displayed through the probability distribution of HR or OR for the subgroups, and as the probability of a higher benefit in a specific subgroup. Since no previous information about the impact of ANGII in COVID-19 is available, all analyses used non-informative flat priors, to have the posteriors completely dominated by the likelihood (reflecting the data).

Due to the nature of the study, and since the sample size was small and the number of events was low, all analyses should be considered exploratory and hypothesis generating only. All analyses were conducted in R v.3.6.3 (R Foundation) [13].

Results

Population

From February 25th, 2020 to May 07th, 2020, 99 patients with COVID-19 received mechanical ventilation with complete 28-day follow-up and were included in the study. Of these, 46 received ANGII and 53 did not (controls). Patient characteristics were balanced at baseline. Most patients were male, median age was 62 years and >35% were obese (**Table 1**). The most frequent co-morbidities were hypertension and diabetes. ACEIs or ARBS use was common. The majority of those treated with ANGII received it as rescue vasopressor. Overall, on day one, the maximum ANGII dose used was 5.0 (5.0 - 20.0) ng/kg/min, but it

was higher in patients receiving it as vasopressor (20.0 [5.0 - 20] vs. 5.0 [5.0 - 5.0] ng/kg/min; median difference, 11.34 [95% CI, 3.56 to 19.13]; $p = 0.004$).

Time from symptoms to hospital admission and ICU admission was 7.0 (4.0 - 10.0) days and 10.0 (7.0 - 14.0) days, respectively (**Table S1** in **Online Supplement**). At hospital admission, fever was present in 56.4% of patients, median SpO₂ was 92 (84 - 96) %, and median respiratory rate was 30 (25 - 36) breaths per minute. All characteristics were similar among the groups (**Table 1** and **Table S1** in **Online Supplement**).

Exploratory physiological outcomes

Over the first three days, compared with controls, mean arterial pressure was significantly higher in ANGII patients (median difference, 9.05 [95% confidence interval, 1.87 to 16.22]; $p = 0.013$ for group comparison over time), but norepinephrine dose was similar (**Figure S1** and **Table S2** in **Online Supplement**).

The PaO₂/FiO₂ ratio was also significantly higher during the first seven days in patients receiving ANGII (median difference, 23.17 [95% confidence interval, 3.46 to 42.88]; $p = 0.021$ for group comparison over time) (**Figure 1** and **Table S2** in **Online Supplement**). After adjustment for potential confounding effect of different levels of PEEP and use of prone positioning among the groups, the use of ANG II was still associated with a higher PaO₂/FiO₂ ratio (median difference, 19.76 [95% confidence interval, -0.13 to 39.65]; $p = 0.051$ for group comparison over time).

Daily laboratory data are shown in **Table S3** in **Online Supplement**. There were no differences between ANG II patients and controls for lactate, urinary output, serum creatinine, and C-reactive protein levels (**Figure 2**). There was, however, a decreased incidence of liver dysfunction in ANGII patients (**Table S4** in **Online Supplement**).

Moreover, in the ANGII therapy group, there was no difference in platelet count (**Table S3** in **Online Supplement**) and there were 2 (4.3%) episodes of clinically relevant pulmonary embolism compared with 4 (7.5%) in the control group. There was one episode of clinically relevant limb ischemia in the ANGII group vs. three such episodes in the control group.

Overall, 7 ANGII patients and 10 non-ANGII patients received RRT with an adjusted OR of 0.87 (95% CrI, 0.25-2.97) and a probability of benefit in terms of avoiding renal of replacement therapy with ANGII of 58.9%. However, such probability was higher (95.7%) in patients with abnormal renal function at baseline with an adjusted OR of 0.23 (0.04 to 1.23). (**Figure 3**).

Exploratory clinical outcomes

Younger age and higher baseline SpO₂ values were present in patients who were discharged alive at day 28 and diabetes was twice as common among patients who failed to be discharged alive from ICU (**Table S5** in the **Online Supplement**).

Results for exploratory clinical outcomes are presented in **Table 2** and **Figure S2** in **Online Supplement**. After accounting for confounders and considering all patients together, compared to patients not receiving ANGII, the probability of ANG II patients showing a reduced risk of developing the composite primary outcome of failure to be discharged or death at day 28 was 58.1% with a Bayesian adjusted effect estimate odds ratio of 0.91 (95% Credible interval: 0.38 to 2.18). For all patients, similar overall results were seen for hospital mortality, overall need for RRT, duration of mechanical ventilation or hospital length stay (**Table 2**).

Discussion

Key findings

In a cohort of almost one hundred consecutive invasively ventilated patients with COVID-19, we conducted an exploratory study of the effects of introducing ANGII therapy or markers of organ function. We found that ANGII therapy was associated with increased mean arterial pressure levels and PaO₂/FiO₂ ratios, decreased risk of liver dysfunction, no effect on urinary output, creatinine, lactate, platelet count, thromboembolic complications, and C-reactive protein levels and limited overall effects on renal replacement therapy use. However, ANG II therapy was associated with a high -probability of decreased use of renal of replacement therapy among patients with elevated serum creatinine at admission. Finally, ANGII was not associated with harm in relation to mortality, length of mechanical ventilation, thromboembolic events, and length of stay in hospital.

Relationship with previous studies

This is the first controlled evaluation of ANGII as adjunctive treatment in ventilated patients with COVID-19 pneumonia. However, a recent case series had shown evidence of increased PaO₂/FiO₂ over time [9]. Our findings confirm this effect on oxygenation. ANGII has been previously shown to increase blood pressure in catecholamine refractory vasodilatory shock in a randomized placebo-controlled trial [6,7]. Our findings confirm this effect on blood pressure.

ANGII has been previously reported as beneficial in patients with markedly abnormal renal function at randomization [9]. Our findings of a >95% probability of decreasing renal of replacement therapy use in COVID-19 patients with abnormal renal function at admission support such previous findings.

Our findings of a possible protective liver function effect are novel and require confirmation in future studies. Our findings of no effect on platelet count or thromboembolic complications are reassuring given previous theoretical concerns [14,15]. The lack of adverse effects on lactate, C-reactive protein levels are novel and also reassuring.

In a recent research letter [11], concern was raised that ANG II may contribute to mortality. However, this report only involved 6 patients and did not have any controls. Our findings which did not show an adverse

effect on mortality, time on mechanical ventilation, or duration of hospital stay compared with controls, provide a degree of reassurance.

Implications of study findings

Our findings imply that ANGII is an effective vasopressor agent in patients with COVID-19 pneumonia. They also imply that it is associated with greater improvements in PaO₂/FiO₂ ratio in such patients and possibly decreased liver enzyme release. In addition, they imply no adverse effects on lactate, platelets, or thromboembolic complications, mortality, or duration of mechanical ventilation and hospital stay. Finally, our findings imply that ANG II may decrease the risk of renal replacement therapy in COVID-19 patients with abnormal kidney function at ICU admission.

Strengths and Limitations

The strengths of our study relate to the presence of a control population, and the availability of a detailed dataset of physiological and clinical observations. In addition, this is the first controlled study of any vasopressor in patients with COVID-19. The comparative safety and efficacy of other vasopressors (norepinephrine, epinephrine or vasopressin) remains untested. Moreover, our findings have implications in relation to the use of ANGII in patients with abnormal creatinine at baseline.

We acknowledge several limitations to our study. It is single center. It is limited in size, not randomized, and open-label in design. Such characteristics open its findings to concerns about external validity, limited statistical power, and potential performance and selection bias. The lack of differences in urinary output and serum creatinine may appear contradictory given a possible effect on renal replacement therapy use. However, RRT was started early and would have markedly affected serum creatinine measurements, thus making their interpretation problematic. In addition, urinary output was easily modified by the use of diuretics, which have been used widely in COVID-19 patients as a lung protective strategy and for which we do not have data. A randomized trial would have been desirable. However, in the setting of the dramatic COVID-19 wave in Italy, the conduct of a double-blind randomized trial was logistically impossible. Moreover, we had detailed information on both patients and controls and similarities were strong and baseline imbalances negligible. In addition, we applied appropriate statistical analyses and took major confounding factors and baseline imbalances into account in the adjusted analyses. Finally, we did not demonstrate a survival advantage. However, this study was markedly underpowered to detect such an effect.

Conclusion

In a controlled exploratory assessment on markers of organ function during ANGII therapy in invasively ventilated patients with COVID-19 pneumonia, we found that ANGII increased blood pressure and PaO₂/FiO₂ ratio, and carried a >95% estimated probability of decreasing renal replacement therapy use in patients with abnormal baseline serum creatinine at admission. Moreover, it carried no signal of other

organ function or clinical harm. These findings imply the need to continue investigations of this agent to a larger population and a multicenter setting.

Declarations

Ethics approval and consent to participate

Ethical Committee approved the compassionate use of the study drug for this study (which is approved by European Medical Association [EMA], but not yet commercialized).

Consent for publication

Not applicable.

Availability of data and materials

Full de-identified dataset and codes of the analyses are available upon request to the corresponding authors.

Competing risk

The authors declare that they have no competing interest.

Funding

None.

Authors contributions

Concept: AZ, GL and RB

Data collection: All authors.

Data cleaning and statistical analysis: GL and ASN

Manuscript preparation: AZ, GL, ASN and RB

Review of the manuscript: All authors

Administrative support: AZ, GL and RB

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Tables

Table 1 - Baseline Characteristics of the Patients According to the Use of Angiotensin II			
	Angiotensin II (n = 46)	No Angiotensin II (n = 53)	p value
Age, years	62 (54 – 69)	62 (53 – 68)	0.653
Male gender – no. (%)	41 (89.1)	42 (79.2)	0.274
Body mass index, kg/m ^{2,a}	27.7 (25.9 – 30.5)	27.7 (24.8 – 32.3)	0.910
Normal – no. (%)	4 / 28 (14.3)	7 / 34 (20.6)	0.427
Overweight – no. (%)	16 / 28 (57.1)	13 / 34 (38.2)	
Obesity class 1 – no. (%)	5 / 28 (17.9)	9 / 34 (26.5)	
Obesity class 2 – no. (%)	2 / 28 (7.1)	5 / 34 (14.7)	
Obesity class 3 – no. (%)	1 / 28 (3.6)	0 / 34 (0.0)	
Coexisting disorder – no. (%)			
Hypertension	19 / 41 (46.3)	23 / 46 (50.0)	0.682
Diabetes	11 / 41 (26.8)	5 / 43 (11.6)	0.100
Coronary artery disease	4 / 41 (9.8)	2 / 45 (4.4)	0.418
Cardiac arrhythmias	3 / 41 (7.3)	4 / 45 (8.9)	0.999
Cerebrovascular disease	1 / 41 (2.4)	1 / 44 (2.3)	0.999
Chronic respiratory disease*	1 / 41 (2.4)	0 / 44 (0.0)	0.482
Asthma	1 / 41 (2.4)	3 / 44 (6.8)	0.617
Chronic obstructive pulmonary disease	1 / 41 (2.4)	1 / 44 (2.3)	0.999
Chronic neurological disease**	2 / 40 (5.0)	0 / 44 (0.0)	0.224
Moderate/severe chronic kidney disease ^b	3 / 40 (7.5)	3 / 43 (7.0)	0.999
Solid tumor	2 / 39 (5.1)	1 / 42 (2.4)	0.606
Tobacco smoker			0.999
Current	1 / 34 (2.9)	1 / 32 (3.1)	
Former	2 / 34 (5.9)	1 / 32 (3.1)	
Medications on chronic use – no. (%)			
Angiotensin converting enzyme inhibitors	6 / 43 (14.0)	6 / 42 (14.3)	0.999
Angiotensin 2 receptor blockers	6 / 43 (14.0)	6 / 42 (14.3)	0.999

Table 1 - Baseline Characteristics of the Patients According to the Use of Angiotensin II			
	Angiotensin II (n = 46)	No Angiotensin II (n = 53)	p value
Calcium channel blockers	6 / 43 (14.0)	2 / 42 (4.8)	0.265
Beta-blockers	8 / 43 (18.6)	6 / 42 (14.3)	0.771
Vitamin-K antagonists	0 / 43 (0.0)	1 / 43 (2.3)	0.999
Novel oral anticoagulants	1 / 43 (2.3)	0 / 43 (0.0)	0.999
Anti-arrhythmic	2 / 43 (4.7)	3 / 43 (7.0)	0.999
Aspirin	10 / 44 (22.7)	5 / 44 (11.4)	0.256
Other antiplatelets	2 / 43 (4.7)	1 / 43 (2.3)	0.999
Statins	7 / 43 (16.3)	3 / 44 (6.8)	0.196
Corticosteroids	0 / 43 (0.0)	3 / 44 (6.8)	0.241
Use of angiotensin II			
Vasopressor	26 (56.5)	—	—
Low dose	20 (43.5)	—	—
Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding			
* excluding asthma and chronic obstructive pulmonary disease			
** excluding dementia and cerebrovascular disease			
^a body mass index is the in kilograms divided by the square of the height in meters			
^b on dialysis, post kidney transplant, uremia or creatinine > 3 mg/dL			

Table 2 - Primary, Key Secondary Outcomes and Secondary Outcomes According to the Use of Angiotensin II

	Angiotensin II (<i>n</i> = 46)	No Angiotensin II (<i>n</i> = 53)	Effect Estimate (95% CrI or CI)	Probability of Benefit*	Absolute Difference (95% CrI)**
Clinical outcomes					
Failure to be discharged or death at day 28	28 (60.9)	31 (58.5)	0.91 (0.38 to 2.18) ^a	58.1%	2.35% (-16.69% to 21.08%)
Hospital mortality at day 28	15 (32.6)	14 (26.4)	0.99 (0.61 to 1.60) ^b	51.4%	5.98% (-11.57% to 23.54%)
Need for renal replacement therapy at day 28	7 (15.2)	10 (18.9)	0.87 (0.25 to 2.97) ^a	58.9%	-3.55% (-17.71% to 11.05%)
Duration of mechanical ventilation at day 28, days	13.1 (9.3 – 24.5)	16.1 (9.1 – 28.0)	1.07 (0.56 to 2.07) ^c	0.830***	-2.76 (-8.89 to 3.35)
In survivors	16.0 (10.6 – 28.0)	18.6 (9.9 – 28.0)			
Hospital length of stay at day 28, days	28.0 (16.2 – 28.0)	28.0 (20.0 – 28.0)	0.82 (0.23 to 2.93) ^c	0.760***	0.92 (-2.13 to 3.97)
In survivors	28.0 (28.0 – 28.0)	28.0 (28.0 – 28.0)			

Table 2 - Primary, Key Secondary Outcomes and Secondary Outcomes According to the Use of Angiotensin II

	Angiotensin II (<i>n</i> = 46)	No Angiotensin II (<i>n</i> = 53)	Effect Estimate (95% CrI or CI)	Probability of Benefit*	Absolute Difference (95% CrI)**
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Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding

ICU: intensive care mortality; CrI: credible interval; CI: confidence interval

* defined as HR or OR < 1.00

** unadjusted

*** *p* value

^a effect estimate is an odds ratio and its 95% credible interval from a Bayesian model with a Bernoulli distribution adjusted by age, diabetes and SpO₂ at admission

^b effect estimate is a hazard ratio and its 95% credible interval from a Bayesian Cox proportional hazard model adjusted by age, diabetes and SpO₂ at admission

^c effect estimate is subdistribution hazard ratio from an unadjusted Fine-Gray competing risk model with death before the event as competing risk adjusted by age, diabetes and SpO₂ at admission

Figures

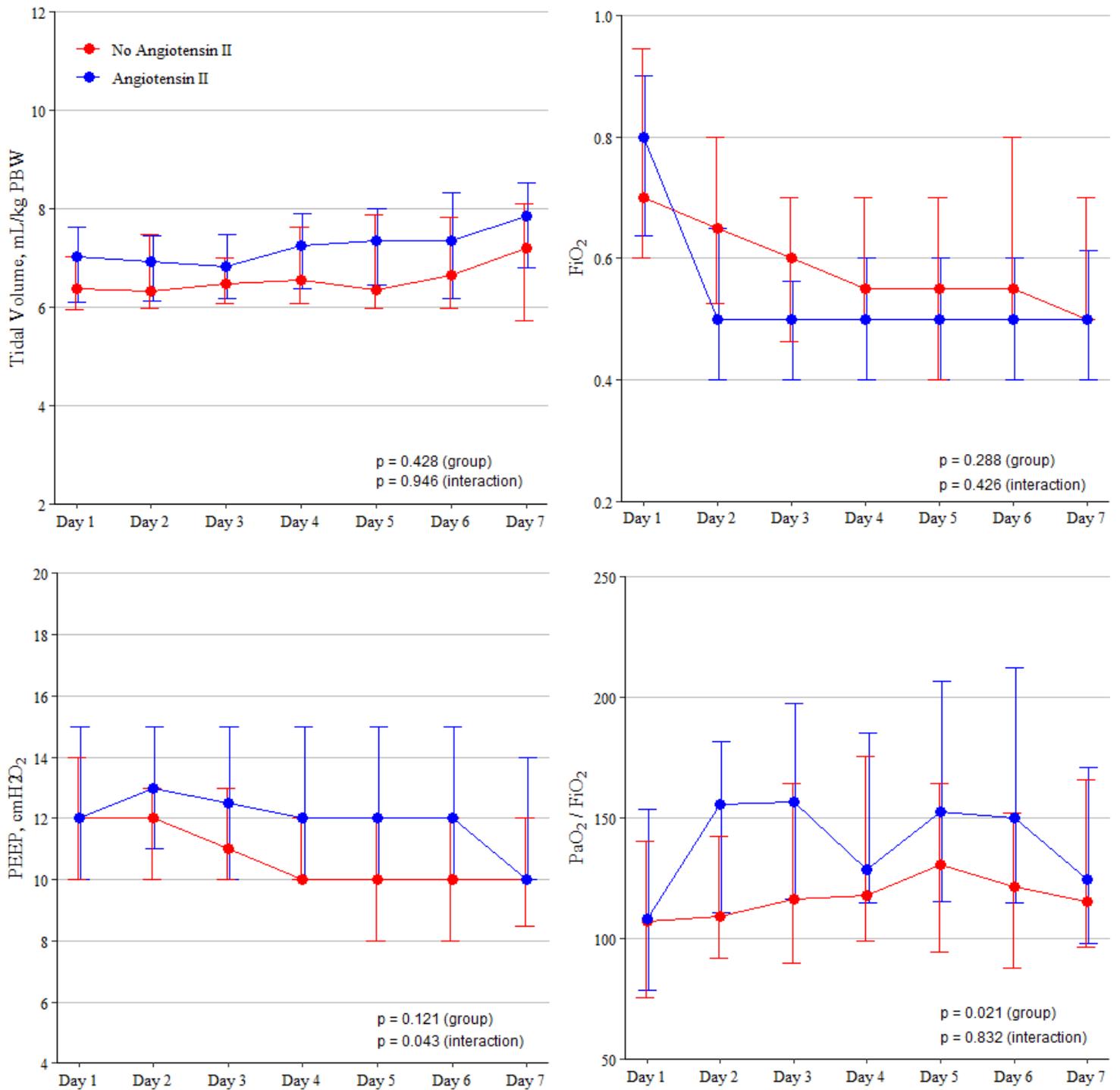


Figure 1

Daily Ventilation Variables According to Use of Angiotensin II Data are median and quartile 25% - quartile 75% p values calculated from a mixed-effect quantile model considering $\alpha = 0.50$, an asymmetric Laplace distribution and p values were extracted after 1,000 bootstrapping samplings. Overall p values from this analysis represent the overall difference among groups over time and p values from interaction represent if the trend over time differs among the groups.

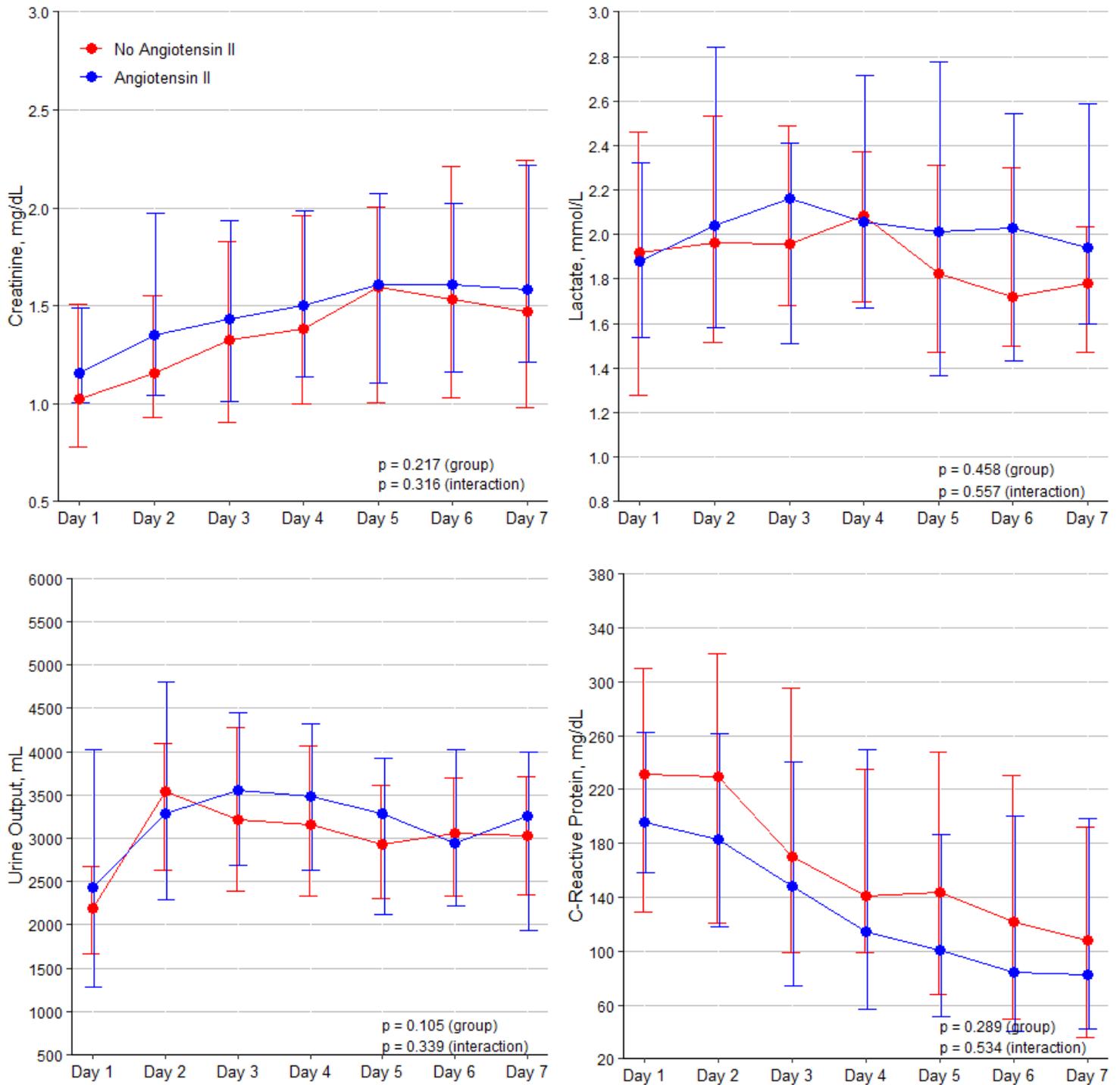


Figure 2

Daily Clinical and Laboratory Variables According to Use of Angiotensin II Data are median and quartile 25% - quartile 75% p values calculated from a mixed-effect quantile model considering $\alpha = 0.50$, an asymmetric Laplace distribution and p values were extracted after 1,000 bootstrapping samplings. Overall p values from this analysis represent the overall difference among groups over time and p values from interaction represent if the trend over time differs among the groups.

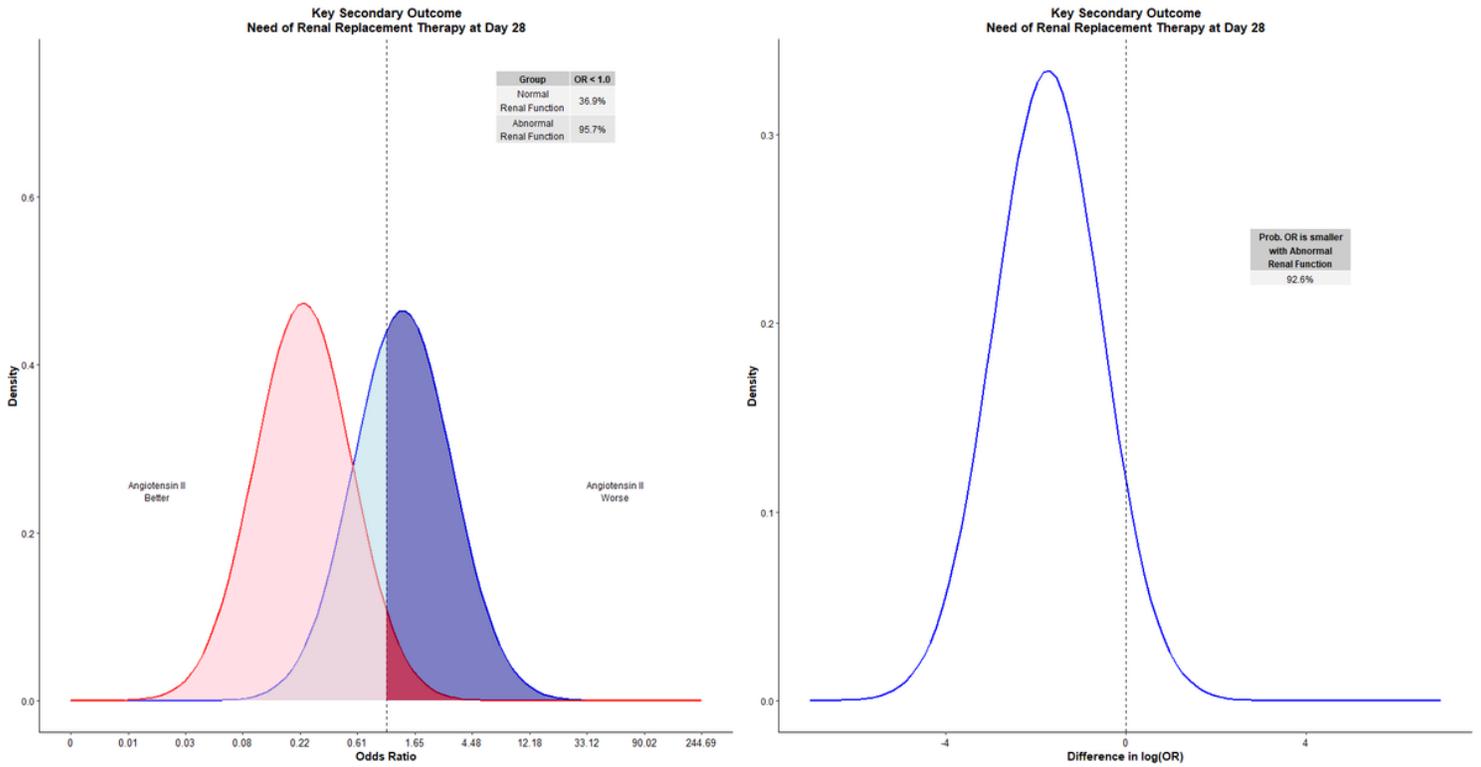


Figure 3

Heterogeneity of Treatment Effect According to Presence of Abnormal Renal Function at Admission and the Use of Renal Replacement Therapy Light red area represents where angiotensin II is beneficial while dark red area represents where angiotensin II is harmful. Abnormal renal function defined as creatinine > 1.10 mg/dL in females and > 1.20 mg/dL in males.

Supplementary Files

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- [GiovanniOnlineSupplementAng2July232020General.docx](#)