Effects of Esmolol on Vascular Waterfall Phenomenon in Septic Shock Patients by Bedside Measurement of Critical Closure Pressure and Mean Systemic Filling Pressure: A Prospective Observational Study

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Research

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Abstract

Background

To explore the effect of esmolol on the vascular waterfall phenomenon and body oxygen supply and demand in septic shock patients by bedside measurements of critical closure pressure (Pcc) and mean systemic circulation filling pressure (Pmsf).

Methods

Enrolled in the Intensive Care Medicine Unit (ICU) of the Third People's Hospital of Chengdu City/Southwest Jiaotong University Hospital from August 2019 to January 2021, admitted to our department for infectious shock. Adults with endotracheal intubation, invasive ventilator-assisted ventilation, pulse-indicated continuous cardiac output monitoring (PiCCO) catheters and deep venous catheters placed for medical reasons.

Results

After 24 hours of initial hemodynamic optimization, 56 patients were finally enrolled. After heart rate control with esmolol, patients had a significant decrease in cardiac index (CI) (4.0 vs. 3.3 L/min/m^2, $p < 0.001$), a significant increase in stroke index (SI) (34.1 vs. 36.6 ml/m^2, $p < 0.01$), and a significant decrease in heart rate (HR) (116.8 vs. 90.6 beats/min, $p < 0.001$). After 1 hour of treatment with esmolol, patients had a significant increase in Pcc (31.4 vs 36.7 mmHg, $p < 0.01$). The difference between Pcc and Pmsf before and after treatment was statistically different (4.0 vs 10.0 mmHg, $p < 0.01$). After heart rate control with esmolol, the patients had a significant increase in the body circulation vascular resistance indices (RIs) (15.14 vs 18.25 mmHg/min/m^2-L-1, $p < 0.001$). There was an increase in ScvO2 in patients after treatment with esmolol, but the difference was not statistically significant (68.4% vs 69.8%, $p > 0.05$), while Pcv-aCO2 was significantly lower (6.3 vs 4.9 mmHg, $p < 0.001$) and patients had a significant decrease in blood lactate levels (4.0 vs 3.6 mmol/L, $p < 0.05$) .

Conclusion

Patients with septic shock whose heart rate was still greater than 95 beats/min after hemodynamic optimization were treated with esmolol, which could effectively control heart rate and reduce CI, as well as improve Pcc and increase the difference between Pcc and Pmsf, without affecting MAP, CVP, Pmsf and arteriovenous vascular resistance, and improve the balance of oxygen supply and demand in the body.

Background

The early clinical management of patients with septic shock depends on hemodynamic management and optimization. The pathophysiological characteristics of septic shock are a waterfall-like inflammatory response, which is often accompanied by sympathetic hyperactivation, continuously elevated catecholamine levels, myocardial depression, vascular hyporesponsiveness and autonomic nerve dysfunction, etc [1, 2, 3]. Among them, the continuous increase of catecholamine levels will cause myocardial ischemia, calcium overload, oxidative stress, metabolic disorders, mitochondrial dysfunction, cell dysfunction or death and so on, thereby endangering the body in many ways [3].

Therefore, blocking the side effects caused by high catecholamine levels seems to improve the prognosis of patients with septic shock [4, 5]. Esmolol is a highly selected, ultra short acting β1-receptor blocker that blocks the high metabolism caused by high catecholamines, reduces oxygen consumption, protects the myocardium, and modulates the body's inflammatory response. It seems to be a treatment for septic shock ideal drug [6]. Currently, esmolol has been reported and recommended in many studies for the treatment of heart rate control after fluid resuscitation in patients with septic shock, which can significantly improve their hemodynamic status and prognosis. However, these studies do not seem to fully explain why the systemic resistance of patients is significantly improved (increased) with esmolol and the hemodynamic mechanisms underlying the patients' improved microcirculatory perfusion and renal function remain unclear [7, 8].

The presence of "vascular waterfall" phenomenon in the vascular bed of the organism, which is similar to waterfalls in nature, has been studied since the 1960s [10–13]. The flow of the waterfall depends on the pressure difference between the upstream source (arterial blood pressure, ABP) and the top of the waterfall (critical closure pressure, Pcc), while the pressure at the bottom of the waterfall (mean systemic filling pressure, Pmsf) and the downstream resistance do not affect its flow [14]. Under these circumstances, the whole vasculature would be divided into arterial units, microcirculation units and venous units. Whereas the classic hemodynamics that compares the entire vascular system to a set of stiff ducts no longer seems to suitable [15]. Therefore, in this paper, the effects of esmolol on hemodynamics in septic shock patients were studied by bedside measurement of Pcc and Pmsf et al. Furthermore, it is speculated that esmolol does not affect systemic arteriovenous vascular resistance and can restore the body's vascular waterfall phenomenon.

Materials And Methods

Patients

The study which adopts a prospective observational method,was approved by the medical ethics review committee of The Third People's Hospital of Chengdu, Affiliated Hospital of Southwest Jiaotong University (Approval No. [2019] S-22) , and informed consent was obtained from patients or their next of kin. Enrollment occurred between August 2019 to January 2021 in Department of Critical Care Medicine (ICU), Chengdu Third People's Hospital. Patients with septic shock were admitted to our department and they were placed with endotracheal intubation, invasive ventilator assisted ventilation, pulse indicator

continuous cardiac discharge monitoring (PICCO) catheter and deep vein catheter due to their condition. Inclusion criteria were age ≥ 18 years, 24 h after ICU admission, heart rate greater than 95 bpm after appropriate hemodynamic therapy, need for norepinephrine (≥ 0.10 μg/kg/min) to maintain mean arterial pressure (MAP>65 mmHg), Global End-Diastolic Volume Index (GEDVI) > 700ml / m^2, and Intrathoracic Blood Volume Index (ITBVI > 850ml/ m^2).

Exclusion criteria were previous treatment with β blockers before or within 24h of ICU admission, severe valvular disease, congenital heart disease or cardiomyopathy, severe pulmonary bullae or spontaneous pneumothorax, need for inotropic agents or severe cardiac dysfunction (CI < 2.2L/min/m^2 and GEDVI > 700ml / m^2 and ITBVI > 850ml/ m^2), adequate sedation and analgesia for less than 36 h, length of stay in the ICU less than 48 hours, surgery or re-operation within 48 hours after admission to ICU, and pregnancy.

Measurements of Hemodynamics

Enrolled patients within 24 hours of admission to the ICU, the primary treatments were taken as follows: 1) Hemodynamic therapy: hemodynamic therapy with shock resuscitation immediately after the patient was admitted to the ICU. Hemodynamic treatment objectives were: CI>3 L/min/m^2 and GEDVI>700ml/m^2, ITBVI>850ml/m^2，MAP>65mmHg, central venous oxygen saturation （$S_{cv}O_2$）≥70%, and urine output >0.5 ml/kg/h. 2) Respiratory support therapy: Mechanical ventilation was performed in volume control mode (AVEA ,CareFusion, California, US) with a target tidal volume of 6 to 8 ml / kg or less. 3) Sedation and analgesia: Dexmedetomidine or midazolam was used for continuous intravenous infusion sedation, fentanyl or butorphanol was used for analgesia, 4) Others: Rational use of antibiotics to fight infection, insulin control of blood sugar, dynamic monitoring of blood lactic acid level, maintaining acid-base electrolyte balance, etc

24 hours after admission to ICU, patients whose heart rate was more than 95 beats / min after hemodynamic optimization and needed norepinephrine (≥0.10μg/kg/min) to maintain blood pressure began to receive intravenous esmolol (Esmolol Hydrochloride Injection, Qilu Pharmaceutical, Jinan, China) to control heart rate. The loading dose was 0.25 ~ 0.5mg/kg (intravenous injection, administration time at least 1min) and the maintenance dose was 0.05mg/kg/min, iv (intravenous pumping), which was dynamically adjusted by the doctor in charge according to the heart rate and the changes of the disease. 24 hours after the patient enters the ICU, the target heart rate was controlled at 80-94 bpm until he leaves the ICU [8].

Through continuous sedation at the bedside until the patient no spontaneous breathing and can hold his breath for 12s, steady-state CO, CVP and MAP were measured over the last 3 seconds of 12-second inspiratory hold maneuvers at plateau pressures of 5, 15, 25 and 35 cmH_2O. The ventricular output (VO) curve and venous return (VR) curve were constructed for the 4 pairs of CO, MAP values and CO, CVP values obtained from the 4 plateau pressures. A linear regression line was fitted through these data

points. When the flow velocity was zero, the cutoff values of the pressure axis were Pcc and Pmsf, respectively [16,17].

CVP, MAP, HR, GEDVI, ITBVI, extravascular lung water (EVLWI), cardiac stroke volume index (SI), CI, ScvO2, Pcc, Pmsf, VO curve slope, VR curve slope, blood lactate level (Lac), central venous-to-arterail carbon dioxide difference (Pcv-aCO_2), dosage of norepinephrine and urine output per hour were observed and recorded before and 1 hour after esmolol treatment (that is, 24 and 25 hours after ICU admission). During the observation period, the patient was no longer treated with fluid resuscitation, and only the necessary drugs were given to maintain infusion. The systemic vascular resistance index (RIs) was defined as RIs=(MAP-CVP)/CI, arterial vascular resistance index (RIa)=(MAP-Pcc)/CI, venous vascular resistance index (RIv)=(Pmsf-CVP)/CI. When Pcc > Pmsf, there is a vascular waterfall.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (IBM, Armonk, NY, US). The measurement data are presented as mean±SD (x±s). The data before and after treatment with esmolol were compared by a paired-sample *t* test. The least square method was used to fit the linear regression of Pcc and Pmsf. Differences with a *p* value of less than 0.05 were considered statistically significant.

Results

Patient's basic information

56 patients were finally enrolled, including 40 males and 16 females, their ages ranged from 29 to 88 years, with a mean of (62.6±13.7) years, 28 of them had pulmonary infections, 23 had abdominal infections, and 5 had pyelonephritis.

Effect of esmolol on haemodynamics in septic shock patients

56 patients enrolled were treated with appropriate hemodynamic therapy, had a heart rate >95 bpm 24 hours after admission to the ICU, required norepinephrine (≥0.10 μg/kg/min) to maintain MAP >65 mmHg, and had a GEDVI >700 ml/m^2 and ITBVI >850 ml/m^2. At this time, we immediately administered esmolol to control the heart rate and controlled the patient's target heart rate to 80-94 bpm. We measured hemodynamic parameters before esmolol treatment (control group) and after esmolol treatment for 1 hour (experimental group) and compared them (Table 1, Figure 1).

After heart rate control with esmolol, patient CI decreased significantly (4.0 vs 3.3 L/min/m2, P<0.001), while SI was significantly increased (34.1 vs 36.6 ml/m2, *p* <0.01). The decrease in CI was mainly due to a decrease in heart rate after esmolol treatment (116.8 vs. 90.6 bpm, *p*<0.001). Esmolol did not affect the levels of MAP (71.4 vs 72.0 mmHg, P > 0.05) and CVP (12.4 vs 12.8 mmHg, *p* > 0.05). Simultaneously, before and after esmolol treatment, patients' PiCCO volume indexes GEDVI (748.0 vs 751.9 ml/m^2,

p >0.05), ITBVI (906.1 vs 903.0 ml/m^2, p>0.05) and EVLWI (13.3 vs 13.4 ml/kg, p>0.05) were not changed either.

In summary, the results of this study suggest that esmolol was effective in controlling the elevated heart rate in patients with septic shock without affecting cardiac contraction, and even increasing SI. The decrease in CI caused by it is mainly due to a decrease in heart rate. Esmolol did not affect patients' MAP, CVP levels, or PiCCO volume indicators. Esmolol raised Pcc levels without affecting Pmsf levels and can significantly increase the Pcc to Pmsf difference. It seems to suggest that it restored vascular waterfall in more tissues and organs of the body. In contrast, there was no statistical difference in the patients' hourly urine output, although there was an increase. Patients had significantly elevated RIs, while RIa, RIv, and the sum of RIa and RIv did not change before and after, further suggesting that RIs do not truly reflect changes in vascular resistance in the presence of vascular waterfalls.

Effect of esmolol on the balance of oxygen supply and demand in septic shock patients

We also monitored the oxygen supply and demand balance indicators before and after esmolol administration in 56 patients admitted to the hospital, and the results are shown in Table 2. After treatment with esmolol, patients had an increase in $ScvO_2$, but the difference was not statistically significant (68.4% vs 69.8%, p>0.05), while Pcv-aCO2 was significantly decreased (6.3 vs 4.9 mmHg, p<0.001) and patients had a significant decrease in blood lactate levels (4.0 vs 3.6 mmol/L, P<0.05) , suggesting that esmolol improves the tissue oxygen metabolism of the body. Combined with the changes in hemodynamic indicators, the difference between Pcc and Pmsf was significantly increased, and it seems that the improvement in oxygen metabolism was associated with the restoration of vascular waterfalls and improved microcirculatory perfusion in more tissues and organs.

Discussion

According to the classic Poiseuille law, arterial blood pressure is determined by cardiac output and systemic vascular resistance, that is, the flow is proportional to the pressure gradient of the pipeline. However, an increasing number of studies have reported that there are vascular waterfalls in vascular beds [10–13]. When there is a vascular waterfall phenomenon, Poiseuille's law can not be applied to the entire vascular beds. Just like a waterfall in nature, the flow of a waterfall has nothing to do with the pressure difference between the top and bottom of the waterfall and the resistance downstream. It only depends on the pressure difference between the upstream of the waterfall and the top of the waterfall and the flow resistance of the upstream of the waterfall and there is no resistance from the top of the waterfall to the bottom of the waterfall [15]. In the vascular waterfall, the pressure at the top of the waterfall is Pcc and the pressure at the bottom is Pmsf. The specific location of Pcc and Pmsf in vascular access is not clear. Some studies suggest that Pcc may be located in the anterior capillaries. It is suggested that PCCC may be located in the anterior arterioles of capillaries and Pmsf is located in the posterior venules of capillaries [18, 19]. When Pcc is greater than Pmsf, there is a vascular waterfall phenomenon. Because the vascular waterfall is mainly located in the microcirculation, it can reflect the

tissue perfusion. Therefore, if the vascular waterfall disappears, the tissue perfusion disappears. On the contrary, if vascular waterfall exists, then there is tissue perfusion.

Therefore, monitoring Pcc and Pmsf, which can be measured at the bedside in the ICU, is an opportunity for hemodynamic management to shift from macrocirculation to microcirculation. Draw VO curve and VR curve respectively through cardiopulmonary interaction, end-inspiratory breath-holding and continuous increase of end-inspiratory airway platform pressure, and linear fitting can be used to obtain the corresponding Pcc and Pmsf when CO is zero [16, 17]. This method has been confirmed by numerous studies, and it is an accurate, reliable, repeatable, non-invasive and convenient method for measurement. However, different organs or tissues of the body have different Pcc. The perfusion pressure of tissues and organs depends on the difference between MAP and its corresponding Pcc, which determines the different distribution of blood flow in the body and ensures the perfusion of important organs. The Pcc measured in this study reflects the average Pcc of the body's tissues and organs [15].

So far, many evidence-based medical evidence recommends esmolol to control the increased heart rate of septic shock patients after hemodynamic optimization, which can improve the hemodynamic status, microcirculation perfusion and renal function and can improve the prognosis of patients [7–9]. However, these studies mainly focus on the level of the macrocirculation and the mechanism of esmolol to improve the microcirculation and tissue perfusion is still unclear. And from these research data [7, 8], it seems that esmolol can significantly increase systemic vascular resistance (CI decreased, MAP unchanged). These are phenomena that are difficult to explain in clinical work. In 2017, an animal study conducted by Liu Dawei's team at Peking Union Medical College Hospital in China found that esmolol not only restored the vascular waterfall that had disappeared in the kidneys during septic shock, but also improved the prognosis [20]. Therefore, in this study, we try to further investigate the effect of esmolol on the increase of heart rate in septic shock patients by bedside measurement of Pcc and Pmsf, and how to improve tissue perfusion and prognosis, and how to influence the changes of vascular resistance.

In this study, we found that after treatment with esmolol, as heart rate was effectively controlled, patients showed a significant decrease in CI and no statistical change in MAP. However, due to the existence of the vascular waterfall, the patient's arterial and venous resistance did not change. This finding seems to explain the problem of previous studies that the systemic vascular resistance increased significantly after the use of esmolol [7, 8]. The study also found that Pcc levels were significantly elevated after the use of esmolol and the difference between Pcc and Pmsf increased. Since the Pcc of this study was the average Pcc of the whole body, it means that more tissues or organs of the body recovered the vascular waterfall. This has also been further confirmed in the monitoring of oxygen supply-demand balance, that is, esmolol improved the body's state of oxygen supply-demand balance. Map is a key factor for tissue organ perfusion and CI is a prerequisite. In previous reports, MAP remained unchanged and CI decreased after esmolol administration in septic shock patients, whereas tissue perfusion (hypoglossal circulation and renal function) was significantly improved [7, 8]. This is a phenomenon that these studies are difficult to explain. And these findings in the present study seem to precisely explain these phenomenon. The kidney is the first organ involved when shock occurs and the last organ that recovers when shock is

corrected [20]. This seems to explain why the hourly urine output of patients did not increase significantly after esmolol use in this study.

This study still has certain limitations: First, nonrandomized controlled studies, because evidence-based medical is currently available to recommend esmolol for patients with septic shock whose heart rate remains greater than 95 bpm after hemodynamic optimization [8, 21, 22], it would be unfavorable and not ethical to perform randomized controlled studies in these patients again. Therefore, this study adopted a self controlled research method to allow enrolled patients all to receive timely treatments recommended by evidence-based medicine. Second, this study only compared hemodynamic, oxygen supply-demand balance data obtained 1 hour after the use of esmolol. No comparison was made between the use of esmolol for 6h, 12h, 24h or even longer. The main reasons for this are as follows: 1) The main reasons for this are as follows: 1. Intravenous esmolol has a rapid onset of action within 1min after initial infusion. So, the data after using esmolol for 1 hour can accurately reflect the treatment effect and there was no need to wait longer; 2) Measurements of Pcc and Pmsf required the patients to be under sedation, free of spontaneous breathing, invasive ventilator assisted ventilation and able to hold his/her breath for 12s. Thus, Measuring data for a longer period of time will cause a lot of unnecessary sedation and prolong the mechanical ventilation time, which were disadvantageous to the patients; 3) Measuring data for a longer period of time will inevitably bring many confounding factors, such as differences in the amount of infused fluid, the effect of individual different self-healing on the study data, the effect of different therapeutic drugs on the measured data, and so on. Third, this study has no data analysis on the prognosis of patients. The main reason is that this study is a self-controlled and observational study, consequently, the treatment plan is the same, so it is difficult to compare the difference in prognosis. Fourth, there is a lack of normal reference value ranges for PCC and PMSF, which is not conducive to the interpretation of the results of this study and remains to be further investigated to refine. Finally, the results of this study need to be further confirmed by multicenter large sample clinical studies.

Conclusions

Patients with septic shock whose heart rate remained greater than 95bpm after hemodynamic optimization were treated with esmolol, which effectively controlled the heart rate and reduced the CI. At the same time, it can increase the Pcc, increase the difference between Pcc and Pmsf without affect on MAP, CVP, Pmsf as well as arteriovenous vascular resistance and it can improve the body's oxygen supply-demand balance status.

Declarations

Consent for publication

Not applicable.

Availability of supporting data

The data sets supporting the results of this article are included within the article

Competing interests

None of the authors declare any conficts of interest.

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Authors' contributions

LZH was the main investigator responsible for collecting and analysing data, as well as study design and writing of the manuscript. LJP contributed to analysis of data. XH and LH were responsible for collection of data and assisted in manuscript writing. PCL contributed to all parts of the project, including study design, data interpretation, and manuscript writing. All authors read and approved the fnal manuscript.

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Conflict of interest: All authors declare no conflict of interest.

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Tables

Table 1 Comparison of hemodynamic data before and after esmolol administration in patients with septic shock

Variables	Control group		Experimental group		*p*
	Mean	SD	Mean	SD	
CI（L/min/m^2）	4.0	0.5	3.3	0.5	0.000
SI（ml/m^2）	34.1	4.9	36.6	5.6	0.008
HR（beats/min）	116.8	10.1	90.6	4.8	0.000
MAP（mmHg）	71.4	3.1	72.0	1.9	0.309
CVP（mmHg）	12.4	1.5	12.8	1.7	0.273
GEDVI（ml/m^2）	748.0	25.7	751.9	25.8	0.426
ITBVI（ml/m^2）	906.1	47.0	903.0	41.6	0.676
EVLWI（ml/kg）	13.3	4.7	13.4	3.9	0.888
Pcc（mmHg）	31.4	10.9	36.7	9.4	0.008
Pmsf（mmHg）	27.7	4.7	26.7	4.5	0.293
Slope of VO curve（L/min/mmHg）	0.109	0.040	0.104	0.044	0.511
Slope of VR curve（L/min/mmHg）	-0.294	0.136	-0.290	0.210	0.906
Pcc-Pmsf（mmHg）	4.0	12.1	10.0	10.0	0.009
Pmsf-CVP（mmHg）	15.3	4.8	13.9	5.0	0.179
RIs（mmHg·min·m^2·L^{-1}）	15.14	2.02	18.25	2.79	0.000
RIa（mmHg·min·m^2·L^{-1}）	10.14	2.98	10.80	3.04	0.264
RIv（mmHg·min·m^2·L^{-1}）	3.91	1.30	4.25	1.57	0.231
RIa+RIv（mmHg·min·m^2·L^{-1}）	14.05	3.51	15.05	3.40	0.145
Norepinephrine dosage（ug/kg/min）	0.20	0.05	0.20	0.04	0.444
Urine output per hour（ml/kg/h）	1.40	0.49	1.45	0.54	0.589

Table 2 Comparison of oxygen supply and demand balance data before and after esmolol administration in patients with septic shock

Variables	Control group		Experimental group		*p*
	Mean	SD	Mean	SD	
$S_{cv}O_2$（%）	68.4	4.7	69.8	3.2	0.063
$P_{cv\text{-}a}CO_2$（mmHg）	6.3	1.7	4.9	1.6	0.000
Lac（mmol/L）	4.0	1.0	3.6	0.9	0.012

Figures

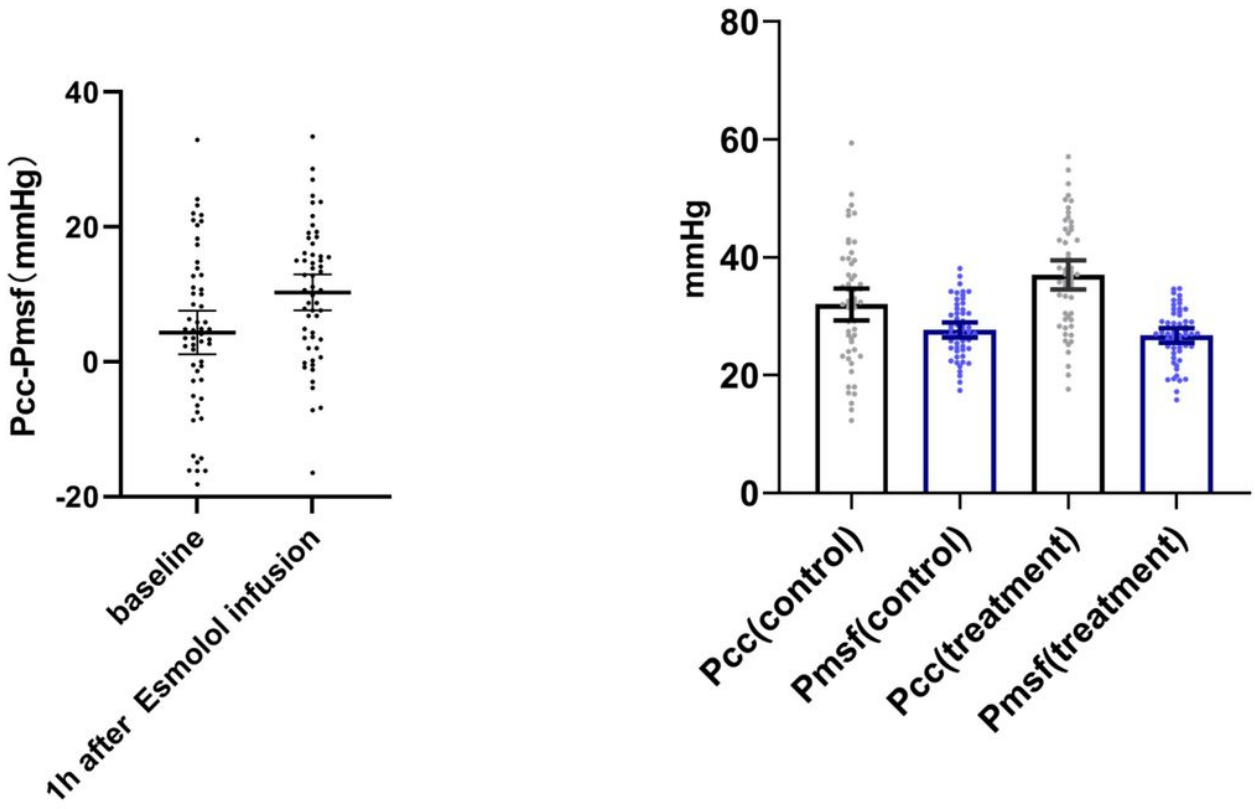

Figure 1

Esmolol raised Pcc levels without affecting Pmsf levels (p=0.293) and can significantly increase the Pcc to Pmsf difference (p=0.008).