



Antihypertensive Effects of Total Gastrectomy on Spontaneous Hypertensive Rats

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Abstract

Backgrounds: Total gastrectomy (TG) played an important role in DM improvement after curative surgery for gastric cancer (W J Surgery 2014, 58, 451-0458). The aim of the present study was to establish the effects of TG on weight loss and cardiovascular (CV) parameters in spontaneous hypertensive rats (SHR). **Methods:** Male SHR rats were used in the present studies. Rats were randomly assigned to either total gastrectomy (TG) or sham (Control): We measured blood pressure, heart rate, body weight and renin-aldosterone from postoperative 1 week to 12 weeks once a week for TG and Control group. **Results:** Systolic and Diastolic Blood Pressure: TG is significantly lower compared to Control. Body Weight: TG is significantly lower compared to Control. But, there is no relationship between systolic blood pressure and body weight in TG. Renin and Aldosterone Renin and aldosterone in TG were significantly lower compared to those in control from 3 to 12 weeks. **Conclusion:** We demonstrated that TG lowered BP in SHR rats. Our data also showed that the beneficial effect of TG for BP was independent of weight loss in SHR rats. Our mechanistic evidence suggests that this CV benefit is likely to be the result of decreasing Renin-angiotensin-aldosterone system activities.

Subject Areas

Emergency & Critical Care

Keywords

Spontaneous Hypertension Rat (SHR), Blood Pressure, Body Weight, Renin-Aldosterone, Sympathetic Nervous System (SNS), Total Gastrectomy (TG)

1. Introduction

Bariatric surgery is currently the most effective long-term treatment for obesity

and results in high rates of remission for type 2 diabetics and hypertension [1] [2]. Furthermore, bariatric surgery produces a greater reduction in arterial blood pressure (AP) than medical management alone [3]. However, the mechanism by which this occurs remains elusive. Bariatric surgery has been adapted as a metabolic surgery that can not only reduce body weight but also improve symptoms of metabolic syndrome, such as hypertension, hyperlipidemia and Diabetic Mellitus (DM). Different types of bariatric surgery have been adapted, including R-Y gastric bypass, sleeve gastrectomy and adjustable gastric band.

The resolution of DM after bariatric surgery results from not only body weight loss itself but also changes in gut hormones, which are now being thoroughly investigated by many researchers [4] [5]. Kange *et al.* [6] suggested that forgut-bypass was the key factor that led to improvements in type 2 DM rather than body weight loss alone. The DM improvement rates in patients who underwent B-I, B-II and R-Y surgeries were 45.2%, 85.2% and 88.2%, respectively. In that study, R-Y reconstruction was used when a patient received total gastrectomy, and B-I and B-II reconstructions were applied in patients who received subtotal gastrectomies.

The aim of the present study was to establish the effects of total gastrectomy on weight loss and cardiovascular parameters in spontaneous hypertensive rats (SHR).

2. Material and Methods

Male SHR rats were used in the present studies. All procedures were conducted in accordance with the guidelines for the Care and Use of Laboratory Animals of the National Institutes of Health and were approved by the Ethical committee for Animal Experimentation of the University of Kindai (KAME-28-024).

Eight weeks male SHR rats were obtained from Kindai Life Science Institute, Osaka Japan. Rats were randomly assigned to either total gastrectomy (TG) or sham (Control).

Surgical procedures

The rats were permitted to acclimate for 4 weeks before surgery. Prior to surgery, the animals were fasted for 24 hours. Total gastrectomy and sham ope were performed under general anesthesia (somnolently 50 mg/kg body weight intraperitoneal injection) through an upper middle incision on 12 weeks.

Total gastrectomy (TG) (n = 12) (**Figure 1**): The gastroesophageal junction was ligated and the distal esophagus was transected 2mm above the ligature. Moreover, the gastroduodenal junction was also ligated, and the proximal duodenum was transected 3mm distal to the pylorus. A total gastrectomy was performed with the removal of the entire stomach, and end-to-end anastomosis of the esophagus and duodenum.

Sham group (Control) (n = 8). Sham operation was performed.

We measured blood pressure, heart rate, body weight and renin-aldosterone from postoperative 1 week to 12 week once a week for TG and Control group.

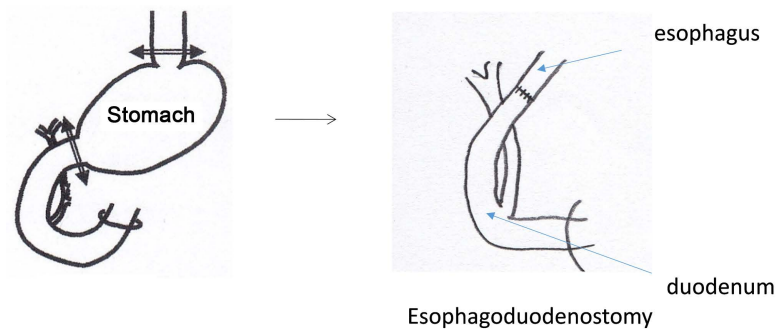


Figure 1. Total gastrectomy (Surgical procedure).

Measurement of Blood pressure and Heart rate

Blood pressure values as well as heart rate (HR) were recorded in conscious, resting animals by non-invasive tail-cuff plethymography (BP-98A-L Soltron, Tokyo, Japan).

After a 3 hour fast, the tail artery was dilated by placement of the animal into a thermostatically controlled plastic holder heated at 32°C for 20 min. Tail pulse was detected by passage of the tail through a tail-cuff sensor attached to the amplifier.

All measurements were carried out between 10:00 and 12:00, and an average of a least three readings was taken for each animal after they became used to the environment.

Plasma level of Renin and aldosterone

Peripheral blood was drawn from tail vein for the measurement of renin and aldosterone at postoperative 1, 2, 3, 4, 7 and 10 weeks for TG and Control.

The determination of plasma aldosterone activity and renin activity was determined by radioimmunoassay.

Statistics

Comparisons between groups were made by the Mann-Whitney test. A difference between groups of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the Stat View 5.0-J program (Abacus Concepts, Berkeley, CA, USA).

3. Results

1) Changes of Systolic Blood Pressure in SHR rat (**Figure 2**).

TG was significantly lower compared to Control at postoperative 1 week. But TG gradually increased from postoperative 3 to 4 weeks. There is no difference between TG and Control from postoperative 2 to 4 weeks. But thereafter TG gradually decrease from postoperative 5 to 12 weeks. TG is significantly lower compared to Control from postoperative 5 to 12 weeks.

2) Changes of Diastolic Blood Pressure in SHR rat (**Figure 3**).

TG is significantly lower compared to Control from postoperative 1 to 12 weeks. Especially, TG in Blood pressure gradually decrease from postoperative 4 to 12 weeks.

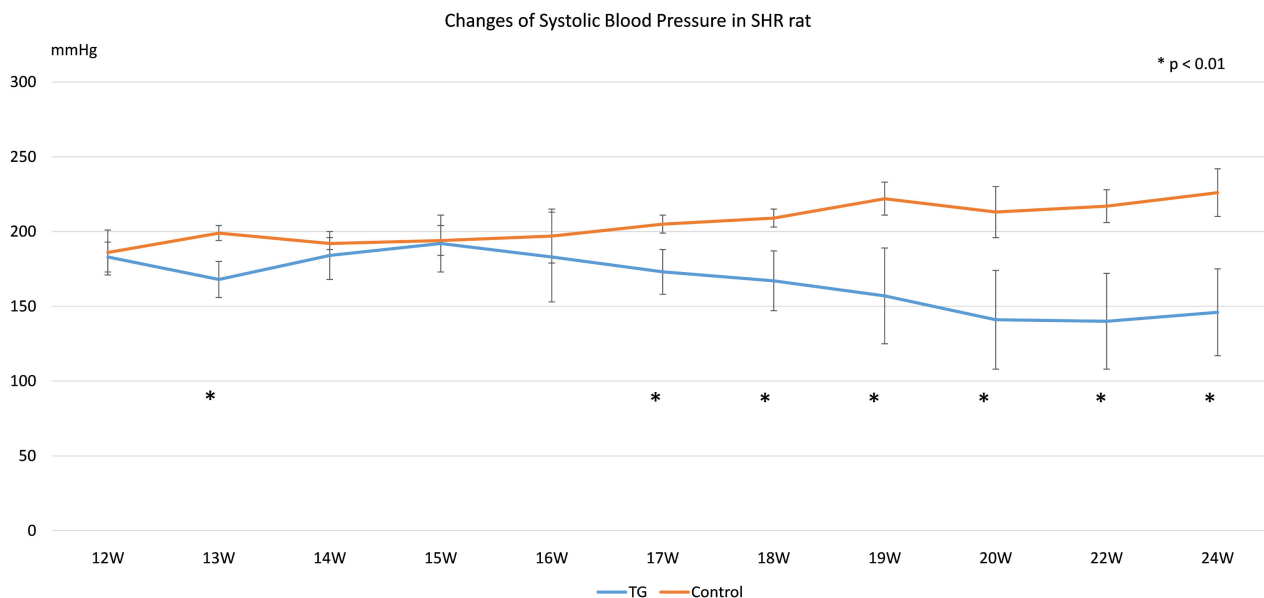


Figure 2. Changes of systolic blood pressure in SHR rat.

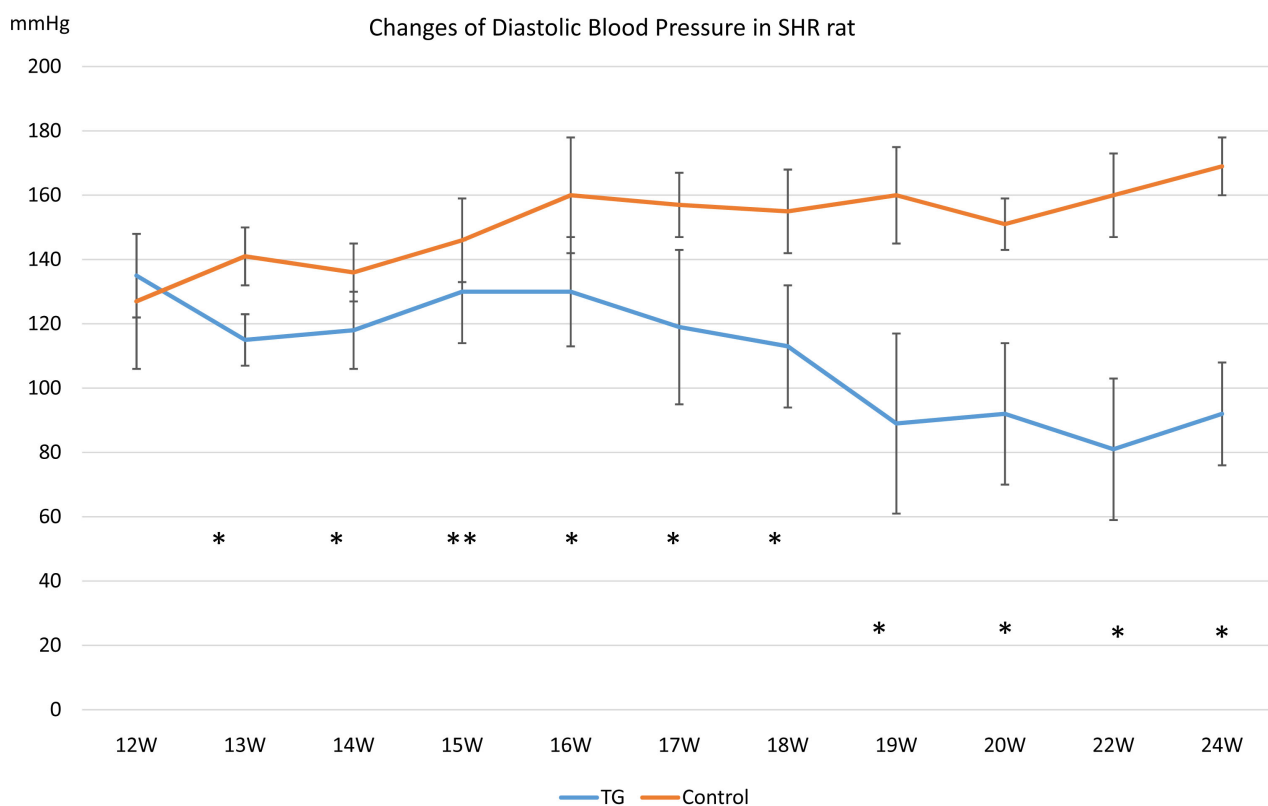


Figure 3. Changes of diastolic blood pressure in SHR rat.

3) Changes of Body Weight in SHR rat (Figure 4).

TG is significant lower compared to Control from postoperative 1 to 12 weeks.

4) Relationship between Body Weight and Systolic Blood Pressure in SHR rat (Figure 5).

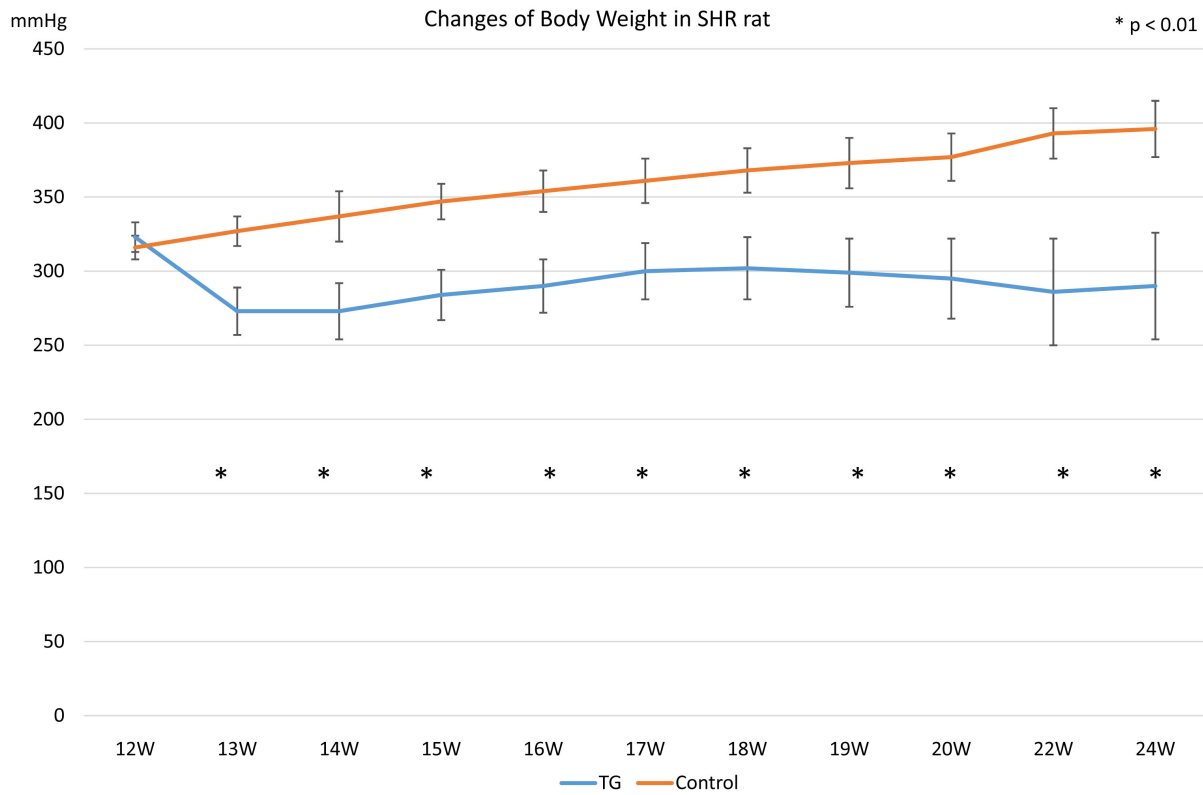


Figure 4. Changes of body weight in SHR rat.

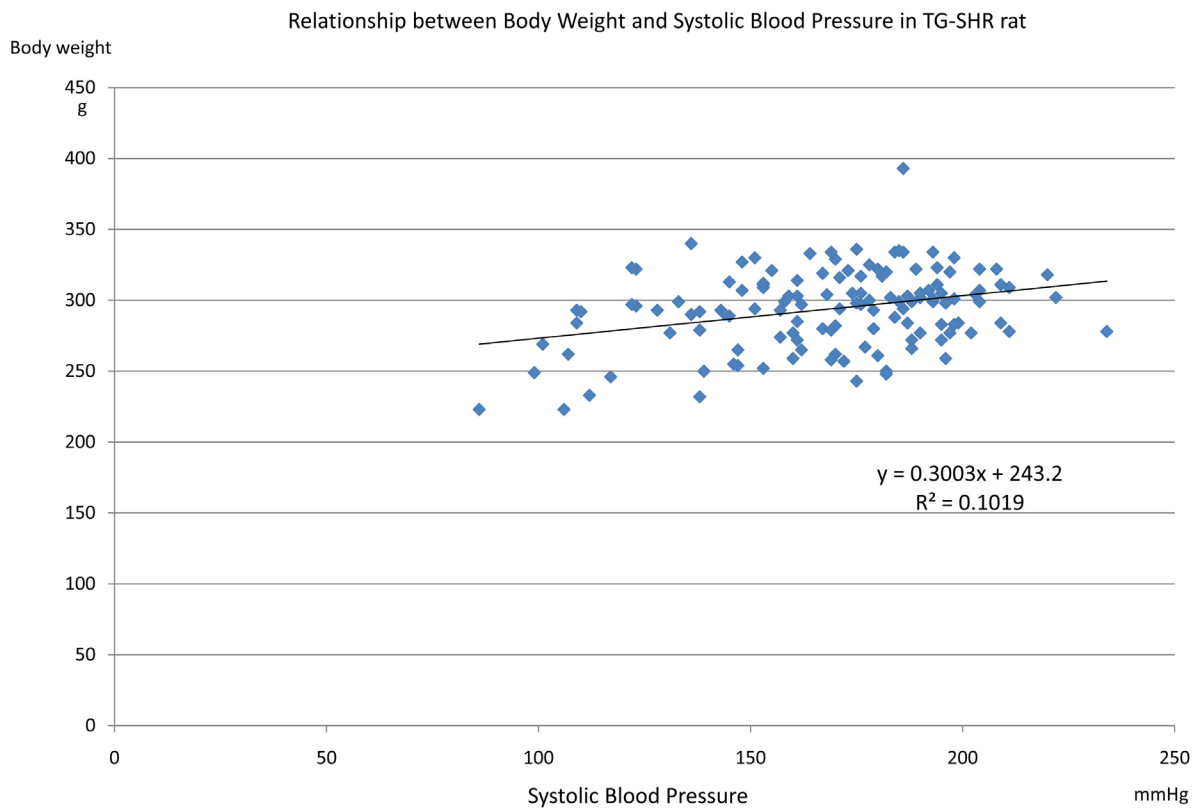


Figure 5. Relationship between body weight and systolic blood pressure in SHR rat.

There is no correlation between body weight and Systolic Pressure in SHR rat. Therefore, we are not likely to believe that the decrease in blood pressure in TG is due to weight loss.

5) Plasma level of Renin and Aldosterone in SHR rat (**Figure 6, Figure 7**).

There is no difference between TG and Control for the postoperative 2 weeks.

Renin and aldosterone in TG were significantly lower compared to those in Control from postoperative 3 to 12 weeks.

4. Discussion

The present study provides evidence for the beneficial effect of TG on hypertension and cardio-metabolic risks. Our studies confirmed that gastrointestinal (GI) surgical intervention can significantly inhibit the overdrive of sympathetic nervous system (SNS) in genetic hypertensive rats [7], which results in reducing blood pressure and improvement of cardiovascular remodeling and dysfunction. Metabolic Surgery is currently the most effective treatment option for obesity and diabetes [8] [9]. In addition, metabolic surgery can effectively ameliorate hypertension over the long term [10] [11], however, the underlying mechanism remains elusive. Several studies suggest that the reduction in BP could be related to metabolic surgery-induced weight loss [12]. However, clinical trials and experimental studies indicated that a quick reduction in BP occurred before the

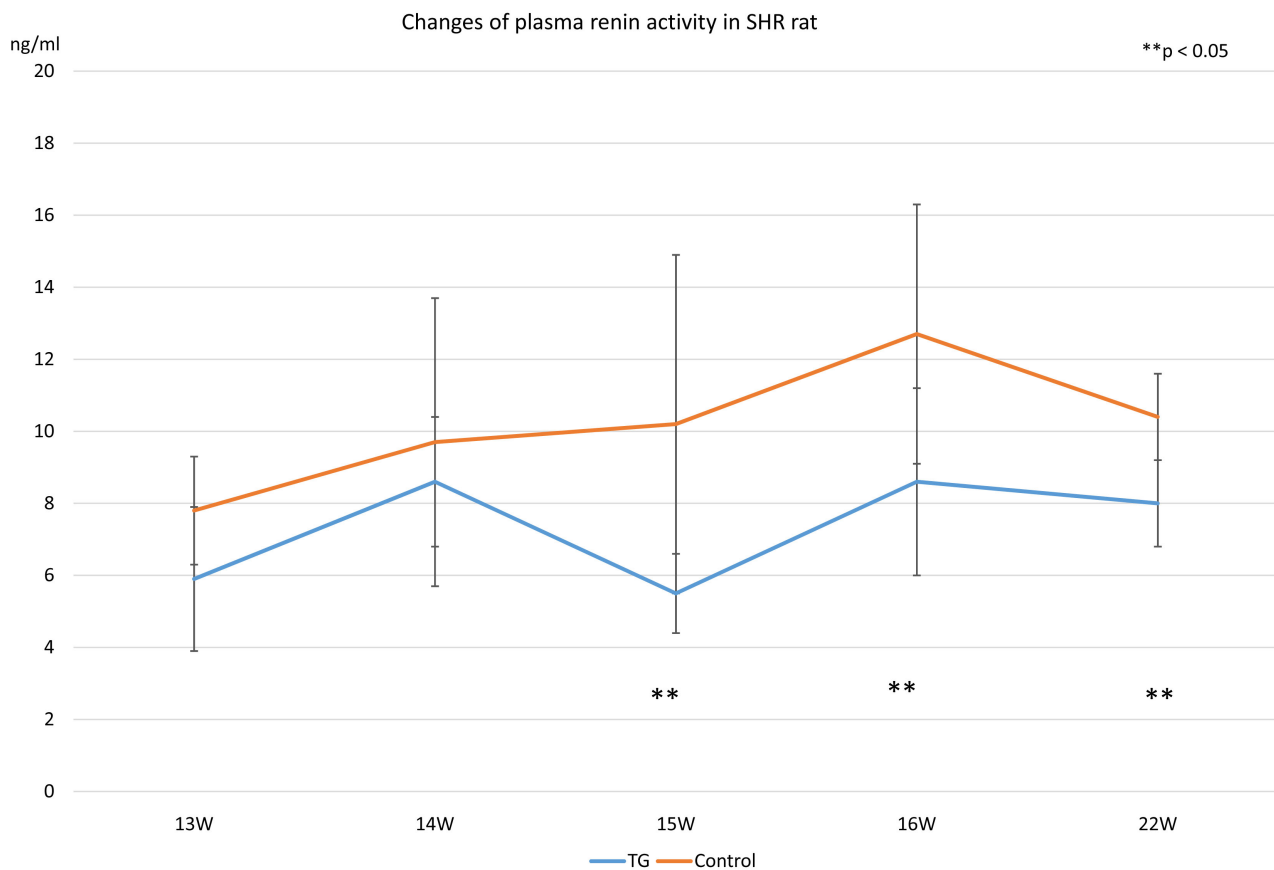


Figure 6. Plasma level of Renin in SHR rat.

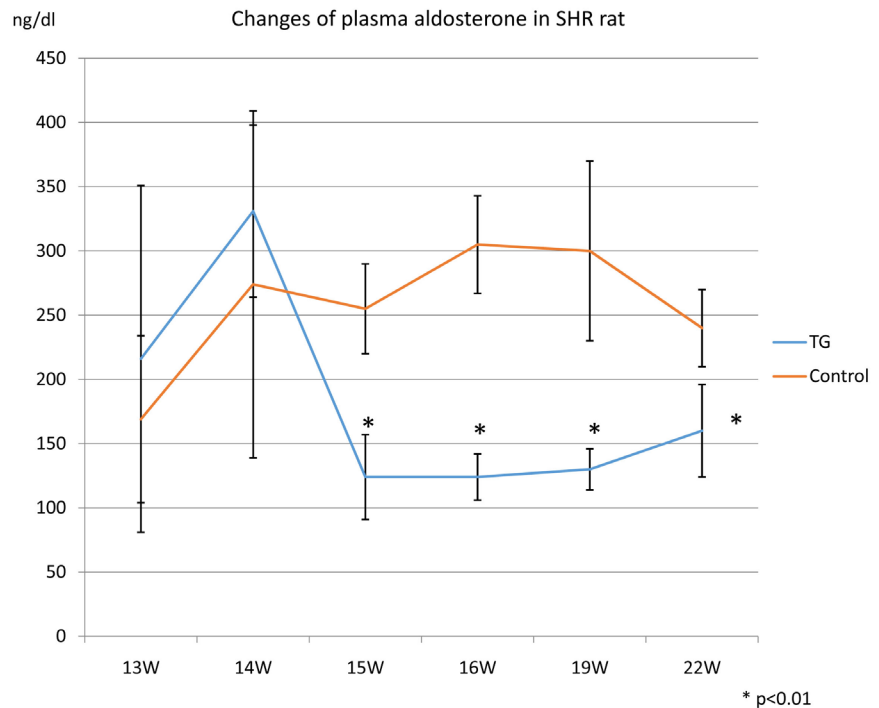


Figure 7. Plasma level of Aldosterone in SHR rat.

metabolic surgery mediated weight loss [13]. A meta analysis reported that there was resolution of hypertension in 61.7% of patients and resolution or improvement of hypertension in 78.5% of patients after metabolic surgery [14]. Antihypertensive therapy was reduced or discontinued in 70% of patients receiving metabolic surgery [15]. Our data also showed that the beneficial effect of TG for BP was independent of weight loss in surgically treated hypertensive rats. However, the mechanism underlying the metabolic surgery mediated antihypertensive effect remains unknown. Although the precise mechanism mediating hypertension remission after metabolic surgery remains poorly understood, it is apparent that rearrangement of GI anatomy can exert several discrete antihypertensive effects beyond those related to reduce sodium intake and body weight. Proposed multiple factors include the change in gut hormones, renin-angiotensin-aldosterone system and intestinal microbial flora [16] [17] [18]. Ruano *et al.* [19] proposed that the obese state is associated with raised levels of plasma renin activity, aldosterone, an angiotensin-converting enzyme leading to sodium retention and that after bariatric surgery these abnormal hormone levels tend to normalize. Our data also showed that TG decreases renin-aldosterone level compared to control. Sugerman [20] speculates a reduction in visceral fat and intraabdominal pressure after bariatric surgery might reduce renin-angiotensin-aldosterone activity, increases natriuresis and thus decrease arterial blood pressure. I agree with his opinion. Our findings provide insights into the mechanism of total gastrectomy in the regulation of BP. GI intervention may represent a promising intervention in resistant hypertension with metabolic disturbances.

5. Conclusion

We demonstrated that TG lowers BP in SHR rats. Our mechanistic evidence suggests that this CV benefit is likely to be the result of decreasing Renin-aldosterone system activities. Our findings provide insights into the mechanism of metabolic surgery in the regulation of BP. GI intervention may represent a promising intervention in resistant hypertension with metabolic disturbances.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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