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Research Article

# Hemorrhage Hypotension Influences on Plasma Glucose Concentration: A New Approach for Evaluating Baroreflex Effects on Metabolic Adjustments

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ABSTRACT

The present study shows that hyperglycemic response to hemorrhage is an easy method for evaluating metabolic adjustments in normal rats and in other models that show autonomic and metabolic imbalances. In this regard, the baroreflex control of hyperglycemic response induced by hemorrhage hypotension was evaluated by removing blood through the jugular catheter (1.2 mL/100g b.w./ 2 min). Blood samples (0.2mL) were collected immediately before hemorrhage and at 5, 10, 20 and 30 minutes after hemorrhage [1, 2]. In addition, the baroreflex control of heart rate was assessed by pharmacological test, using intravenous doses of phenylephrine hydrochloride (PE, 10 μg/mL) and sodium nitroprusside (SNP, 10 μg/mL) in random order. Heart rate and blood pressure were measured through the insertion of a polyethylene catheter inserted into the abdominal aorta through the left femoral artery. The derived variables of baroreflex control to heart rate and hemorrhage hyperglycemia response were measured according to the following equation: $Y = A_1/\{1+ exp[A_2(X - A_3)]\} + A_4$. The evaluation of a new approach for studying the baroreflex effects on metabolic adjustments was done with animals fed with a hypercaloric diet. Hypercaloric diet induced an upward shift in the baroreflex curve to heart rate ($p<0.05$) and an increased heart rate reflex due to the change in MAP during the operating range ($p<0.05$). It also shifted the baroreflex curve to a higher level of hyperglycemic response to hemorrhage ($p<0.05$), as well as, increased maximal gain ($p<0.05$) and augmented hyperglycemic response to hemorrhage hypotension during the operating range ($p<0.05$). Therefore, we propose that the baroreflex control of hyperglycemic response should be a useful tool for evaluating metabolic dysfunction related to hemorrhage in models of animals that show autonomic imbalance, such as malnutrition, hypertension, diabetes and obesity.



## Methods

It is well known that carotid body dysfunction is related not only to cardiovascular adjustments but also to metabolic regulation [3]. In this regard, we propose that baroreflex control of the hyperglycemic response to hemorrhage is a reliable tool for evaluating the integration between cardiovascular and metabolic adjustments [1, 2]. Indeed, the present study shows that such a challenge is an easy method for evaluating metabolic adjustments in normal rats and in other models that show autonomic and metabolic imbalances. Considering these aspects, the letter highlights this new approach for assessing the modulation of baroreflex on metabolic adjustments in animals fed with a hypercaloric diet using hemorrhage hypotension as a stimulus.

The baroreflex control of heart rate (HR) was evaluated by pharmacological test, using intravenous doses of phenylephrine hydrochloride (PE, 10 μg/mL) and sodium nitroprusside (SNP, 10 μg/mL) in random order. They were infused through a jugular catheter into the right atrium by bolus injections (0.1 mL). The baroreflex control

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of hyperglycemic response induced by hemorrhage hypotension was evaluated by removing blood through the jugular catheter (1.2 mL/100g b.w./ 2 min). Blood samples (0.2mL) were collected immediately before hemorrhage and at 5, 10, 20 and 30 minutes after hemorrhage [1, 2, 4]. Heart rate and blood pressure were measured through the insertion of a polyethylene catheter inserted into the abdominal aorta through the left femoral artery. Mean arterial pressure (MAP) data were acquired every 2.5 mmHg in response to SNP and PE infusion or hemorrhage hypotension [4]. A sigmoid logistic function was fit to the data using the nonlinear regression equation: $Y = A_1/\{1 + exp[A_2(X - A_3)]\} + A_4$, where Y is HR or glycemic response; $X$ is $Pa$; $A_1$ is the response range for $Y$ (maximum response minus minimum response); $A_2$ is the gain coefficient; $A_3$ is the pressure at the midrange of the curve (centering point); $A_4$ is the minimum response of $Y$ [5]. The baroreflex curves were differentiated to determine the gain of the HR and hyperglycemic components of the baroreflex across the MAP range [5, 6]. The maximum gain was determined by taking the first derivative of the baroreflex curve described by the logistic equation. Differences between groups were compared by using ANOVA followed by Newman-Keuls' Multiple range test. The differences between groups were analysed by student's t tests. $P < 0.05$ was considered statistically significant.

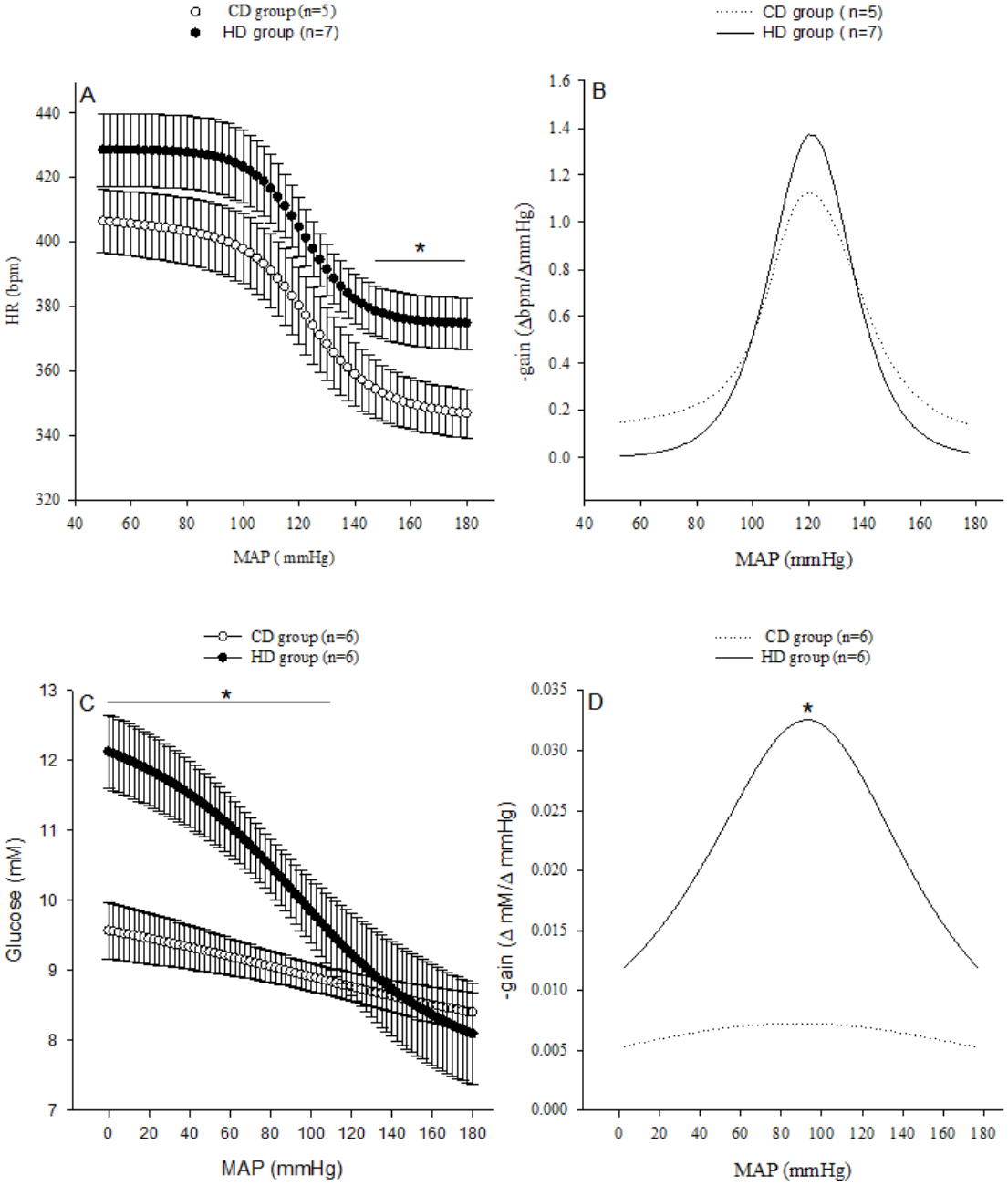


**Figure 1: A)** Averaged sigmoidal function curves derived from baroreflex test induced by phenylephrine (10µg/mL) and sodium nitroprusside ( 10µg/mL) and **B)** maximal gain to baroreflex control related to pressor and depressor drugs in animals fed with chow diet (CD group, n=5, open circles) and hypercaloric diet (HD group, n=7, closed circles). **C)** Averaged sigmoidal function curves derived from baroreflex test induced by hyperglycemia response to hemorrhage **D)** maximal gain to baroreflex control related to metabolic response in animals fed with chow diet (CD group, n=5, open circles) and hypercaloric diet (HD group, n=7, closed circles). *p<0.05 (vs CD group).

Our analyses showed that a hypercaloric diet induced an upward shift in the baroreflex curve to heart rate (Figure 1A) without any modification in the maximal gain of heart rate reflex (Figure 1B). In addition, the hypercaloric diet induced an augmentation in heart rate reflex due to the change in MAP during the operating range (CD group, 377 $\pm$ 8 bpm; HD group, 403 $\pm$ 8 bpm; $p<0.05$). Diet-induced obese rats shifted the baroreflex curve to a higher level of hyperglycemic response to hemorrhage (Figure 1C), as well as increased maximal gain (CD group, -0.0073 $\pm$ 0.004 mM/mmHg$^{-1}$; HD group, -0.032 $\pm$ 0.01 mM/mmHg$^{-1}$; $p<0.05$; Figure 1D). Furthermore, the hypercaloric diet resulted in an increased hyperglycemic response to hemorrhage hypotension during the operating range (CD group, 8.96 $\pm$ 0.21 mM; HD group, 10.13 $\pm$ 0.45 mM $p<0.05$).

The major finding of the present study is that hyperglycemic response to hemorrhage hypotension is a useful and reliable approach to evaluate the baroreflex function and its effects on metabolic adjustments in rats. We demonstrated that baroreflex function to hyperglycemia hemorrhage hypotension is shifted to a new operating range in rats fed with a hypercaloric diet compared to rats fed with chow diet. Since the mathematical equation for evaluating baroreflex function is based on the relationship between mean arterial pressure (input) and heart rate reflex (output), we support that hemorrhage hyperglycemia works as an output component of the baroreflex function, responding similarly to heart rate on baroreflex control. Therefore, the hyperglycemia response induced by hemorrhage can be considered as well-developed response for analysing the baroreflex and its influences on metabolic adjustments.

## Conclusion

In summary, this analysis is the first evidence showing that the hyperglycemic response induced by hemorrhage can be used as an approach for analysing the modulation of baroreflex control on metabolic adjustments in rats. In fact, the hyperglycemic hemorrhage responds to the output of baroreflex function in animals fed with chow diet and hypercaloric diet. Therefore, we propose that the baroreflex control of hyperglycemic response should be a useful tool for evaluating metabolic dysfunction related to hemorrhage in models of animals that show autonomic imbalance, such as malnutrition, hypertension, diabetes and obesity.

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