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Hemodynamic patterns associated with activation of bradykinin-sensitive pericardial afferents

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ABSTRACT

The heart is endowed with reflexogenic areas capable of powerful blood pressure responses. Relatively little work has studied the hemodynamic mechanisms underlying these responses and whether these are sexually dimorphic. We hypothesized that activation of bradykinin-sensitive pericardial afferents would produce a sexually dimorphic cardiac output response. Male and female Sprague Dawley rats were anesthetized and instrumented with catheters for recording arterial pressure, with an aortic arch flow probe to record cardiac output and with a catheter in the pericardial sac. Mean arterial pressure (**MAP**), cardiac index (**CI**) and total peripheral resistance index (**TPRI**) responses to pericardial bradykinin injection (0.1, 1 μg/kg) were recorded. Pericardial bradykinin injection caused similar increases in MAP in male and female rats. However, the underlying hemodynamic patterns varied considerably. We identified a cluster of CI responders and TPRI responders in both male and female rats. Within CI responders, females exhibited greater CI increases than males. Conversely, in TPRI responders, males exhibited a greater TPRI increase than females. We conclude that aggregate activation of bradykinin-sensitive pericardial afferents is associated with a relatively uniform pressor response but different hemodynamic patterns with males exhibiting a more robust vascular response and females a more robust cardiac output response.

1. Introduction

Reflexogenic areas of the cardiovascular system play a crucial role in mediating both normal and pathophysiological circulatory responses. The arterial baroreceptor reflex has garnered the most research focus. Nevertheless, other reflexes also play critical roles in regulating cardiovascular homeostasis. The heart is endowed with reflexogenic areas that can elicit robust blood pressure responses (Chen et al., 2015; Fu, 2009; Hainsworth, 1991). Ventricular cardiogenic reflexes may be excitatory or depressant on the cardiovascular system. Depressant reflexes arise from cardiac vagal afferents (Hainsworth, 1991; Longhurst, 1984), which decreased sympathetic nervous system (SNS) activity, venous tone and blood pressure (Hainsworth, 1991; Longhurst, 1984; Ross et al., 1961; Tutt et al., 1988; Veelken et al., 1996; Wang et al., 1994) and ventricular filling (Nganele and Hintze, 1990). In contrast, sympathoexcitatory reflexes originate from cardiac sympathetic afferents to cause tachycardia, hypertension and arterial vasoconstriction (Hainsworth, 1995; Longhurst et al., 2001; Malliani et al., 1983). Cardiac afferents are activated by numerous stimuli including endogenous factors such as hydrogen peroxide or bradykinin released during challenges such as cardiac ischemia (Chen et al., 2015; Longhurst et al., 2001). These responses can be also be evoked experimentally by application of bradykinin to sensory afferents in the epicardium (Veelken et al., 1996; McDermott et al., 1995; Pagnani et al., 1985; Staszewska-Woolley et al., 1988).

While the blood pressure responses to cardiac afferent stimulation have been studied extensively, a significant gap remains in our understanding of the hemodynamic mechanisms underlying these responses. This is critical information as the underlying hemodynamics may determine, at least in part, cardiovascular risk since so called vascular responders show elevated risk of cardiovascular disease (Branch and Knuepfer, 1994; Christian and Stoney, 2006; Kasprowicz et al., 1990; Kline et al., 2002). Early work showed that epicardial BK elicited a decrease in renal blood flow and an increase in femoral blood flow (Staszewska-Barczak and Dusting, 1977) but did not affect coronary blood flow (Wang et al., 2001). To our knowledge, only a single study has assessed the overall hemodynamic responses to activation of cardiac afferents. This work in male rats used pericardial BK application

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localized to the region containing sympathetic afferents and reported an increased cardiac output (CO) as assessed with Millar pressure volume catheters (Wang et al., 2017). The net hemodynamic responses to overall activation of bradykinin-sensitive pericardial afferents remains to be determined.

Convincing evidence supports the view that sex plays an important role in modulating many cardiovascular control mechanisms (Maranon and Reckelhoff, 2013), including reflex control in both animals (Santa Cruz Chavez et al., 2014) and humans (Barnes, 2017). Moreover, sex differences in cardiovascular control is thought to influence cardiovascular risk (Maranon and Reckelhoff, 2013; Barnes, 2017). Yet study of sex differences in cardiac afferent regulation of the circulation is limited. Pinkham reported that estrogen modulates cardiac afferent mediated autonomic drive (Pinkham and Barrett, 2015). We demonstrated that pericardial BK injection increased venous tone, an important CO control factor, in both male and female rats (Martin et al., 2020) in a sexually dimorphic manner. Accordingly, we hypothesized that activation of pericardial bradykinin-sensitive afferents would produce a sexually dimorphic cardiac output response.

2. Methods

2.1. Surgical procedures

Male and female Sprague Dawley rats (240–400 g) were maintained in the Animal Resource Center at the University of South Dakota on a 12 h day/night cycle and allowed free access to rat chow and tap water. The Institutional Animal Care and Use committee of the University of South Dakota reviewed and approved all procedures and these conformed to the NIH Guide for the Care and Use of Laboratory Animals.

The rats were initially anesthetized with isoflurane, instrumented with femoral arterial and venous lines and then transitioned to anesthesia with intravenous urethane (800 mg/kg) and alpha chloralose (80 mg/kg). The rats were intubated via a tracheotomy and placed on a ventilator. The left chest was opened between the 3rd and 4th intercostal space to reveal the thymus gland which was reflected to expose the pericardial sac. A catheter was positioned in the pericardial sac with the ejection ports along the lateral aspects of the left ventricle and anchored with cyanoacrylic glue. Blunt dissection was used to expose the aortic arch and pass suture under the aorta. Traction was placed on the suture to temporarily collapse the aorta sufficiently to place an electromagnetic flow probe (Carolina Medical) around the aorta and the suture removed. The chest was closed, evacuated, and the rats were allowed to breathe spontaneously.

2.2. Experimental protocols

Arterial pressure (AP) and CO were monitored continuously (Biopac data acquisition system) and the animals allowed at least 30–60 min stabilization prior to any interventions. Mean arterial pressure (MAP) and CO responses to pericardial injections of saline or BK (0.1, 1 μg/kg) were assessed before and after ganglionic blockade (hexamethonium 20 mg/kg or chlorisondamine 10 mg/kg).

2.3. Data analysis

All values are expressed as mean ± SEM. Cardiac output was expressed as cardiac index (CI) to account for variation in body size. CI was calculated as the flow in ml/min divided by 100 g body weight. Total peripheral resistance index (TPRI) was calculated as MAP/CI. The rats were clustered based on sex and their CI response (greater than 2% increase in CI = CI responder) observed between 90 and 120 s after bradykinin injection when the responses appeared to be stable. Four groups were identified: female CI responders, male CI responders, female TPRI responders or male TPRI responders. Data that met the criteria of normal distribution (Shapiro Wilk test) and homogeneity of variance (Brown Forsythe test) were analyzed using parametric statistics. Data that did not meet these criteria were transformed to meet criteria and analysis was conducted on the transformed data. Two way analysis of variance (ANOVA) (factors: treatment, sex/cluster) with treatment as a repeated measure was used to compare MAP, CI and TPRI responses. Two way ANOVA was used to analyze baseline values (factors: sex, cluster). If interaction terms were not significant, one way ANOVA was used to analyze the data. Post hoc comparisons were performed using the Student Newman Keuls test to correct for multiple comparisons or unpaired *t*-test (cluster post hoc). Differences were considered significant at $p < 0.05$.

3. Results

3.1. Control values

Control values for MAP, CI and TPRI for each group are shown in Table 1. There was considerable variation in the baseline values for MAP, CI and TPRI from animal to animal. Two way ANOVA did not detect any statistically significant interaction terms. However, two way ANOVA did reveal a significant main effect of cluster. Post hoc analysis indicated that irrespective of sex CI responders has lower baseline MAP ($p = 0.004$) and TPRI ($p = 0.005$) but there was no detected difference in CI ($p = 0.07$). One way ANOVA identified a difference in MAP with female CI responders exhibiting a lower baseline MAP than female TPRI responders and male TPRI responders. There were no differences in identified in CI or TPRI.

3.2. Pericardial bradykinin injections

Pericardial injection of saline vehicle caused only minor non-statistically significant changes in MAP, CI and TPRI (Fig. 2) in each of the four groups. In contrast, pericardial BK injection was associated with rapid onset changes in AP and CO as illustrated in Fig. 1. Despite relatively uniform increases in AP, this figure illustrates the distinct hemodynamic patterns obtained. Some animals showed a rise in CO while others showed little change or even a decrease during the BK response. Fig. 2A shows that pericardial BK produced pressor responses significantly greater than vehicle saline at both doses. These responses were not statistically different amongst the four groups. Ganglionic blockade largely abolished the pressor responses (Fig. 2A).

Fig. 2B summarizes the CI responses to pericardial BK injection. Compared to pericardial saline, female CI responders exhibited significant increases in CI (ml/min/100 g) of 2.71 ± 0.51 at BK 0.1 μg/kg and 3.24 ± 0.65 at BK 1.0 μg/kg. Male CI responders also exhibited significant increases in CI in response to pericardial BK. However, these were significantly smaller than those of female CI responders averaging 1.18 ± 0.42 at BK 0.1 μg/kg and 1.70 ± 0.62 at BK 1.0 μg/kg. In contrast, female TPRI responders did not exhibit any significant changes in CI while male TPRI responders showed a slight but significant decrease in CI. Accordingly, CI responses obtained in female and male TPRI responders were significantly different than those observed in the female and male CI responders. The CI responses to pericardial BK were abolished following ganglionic blockade.

Fig. 2C shows the aggregate data for the TPRI responses to pericardial BK injection. Female TPRI responders showed increases in TPRI (mm Hg/ml/min/100 g) of 3.01 ± 0.90 at BK 0.1 μg/kg and 3.78 ± 0.92 at BK 1.0 μg/kg. Male TPRI responders exhibited increases of TPRI of 4.85 ± 1.1 and 5.4 ± 1.2 at BK doses of 0.1 and 1.0 μg/kg respectively. These responses were statistically greater than those in female TPRI responders at the lower dose of BK. In contrast, there were no significant changes in TPRI in female or male CI responder groups compared to saline injection. Thus, there were statistically significant differences in TPRI responses amongst the TPRI and CI responder groups. The TPRI responses to pericardial BK were eliminated by ganglionic blockade.

Table 1
Baseline values.

Group	MAP (mm Hg)	CI (ml/min/100g)	TPRI (mmHg/ml/min/100g)
Female CI Responders (n=10)	87±5 #,β	15.0±2.5	7.2±1.3
Male CI Responders (n=8)	93±3	14.8±2.5	7.6±1.3
Female TPRI Responders (n=9)	102±4	12.2±2.8	11.8±2.0
Male TPRI Responders (N=9)	104±6	9.3±1.0	11.9±1.4

Table Analyzed	Two-way ANOVA , not RM Baseline MAP			
Two-way ANOVA	Ordinary			
Alpha	0.05			
Source of Variation	% of total variation	P value	P value summary	Significant?
Interaction	0.7609	0.5752	ns	No
Cluster	20.26	0.0063	**	Yes
Sex	1.8	0.3902	ns	No

Table Analyzed	Transform of Two-way ANOVA not RM Baseline CI			
Two-way ANOVA	Ordinary			
Alpha	0.05			
Source of Variation	% of total variation	P value	P value summary	Significant?
Interaction	0.355	0.7209	ns	No
Cluster	11.76	0.0462	*	Yes
Sex	0.3437	0.7252	ns	No

Table Analyzed	Two-way ANOVA , not RM Baseline TPRI			
Two-way ANOVA	Ordinary			
Alpha	0.05			
Source of Variation	% of total variation	P value	P value summary	Significant?
Interaction	0.02296	0.9235	ns	No
Cluster	21.07	0.0062	**	Yes
Sex	0.06665	0.8701	ns	No

Table Analyzed	Baseline Values MAP			
Data sets analyzed	A : Female CO Responders	B : Male CO Responders	C : Female TPR Responders	D : Male TPR Responders
ANOVA summary				
F	3.38			
P value	0.0301			
P value summary	*			

Newman-Keuls multiple comparisons test	Mean Diff.	Significant?
Female CO Responders vs. Male CO Responders	-6.544	No
Female CO Responders vs. Female TPR Responders	-15.88	Yes
Female CO Responders vs. Male TPR Responders	-17.27	Yes
Male CO Responders vs. Female TPR Responders	-9.338	No
Male CO Responders vs. Male TPR Responders	-10.73	No
Female TPR Responders vs. Male TPR Responders	-1.388	No

Table Analyzed	Transform of Baseline Values CI			
Data sets analyzed	A : Female CO Responders	B : Male CO Responders	C : Female TPR Responders	D : Male TPR Responders
ANOVA summary				
F	1.528			
P value	0.2260			
P value summary	ns			

Newman-Keuls multiple comparisons test	Mean Diff.	Significant?
Female CO Responders vs. Male CO Responders	0.000406	No
Female CO Responders vs. Female TPR Responders	-0.1199	No
Female CO Responders vs. Male TPR Responders	-0.17	No
Male CO Responders vs. Female TPR Responders	-0.1203	No
Male CO Responders vs. Male TPR Responders	-0.1704	No
Female TPR Responders vs. Male TPR Responders	-0.05004	No

Table Analyzed	Baseline Values TPRI			
Data sets analyzed	A : Female CO Responders	B : Male CO Responders	C : Female TPR Responders	D : Male TPR Responders
ANOVA summary				
F	2.922			
P value	0.0489			
P value summary	*			

Newman-Keuls multiple comparisons test	Mean Diff.	Significant?
Female CO Responders vs. Male CO Responders	-0.3962	No
Female CO Responders vs. Female TPR Responders	-4.585	No
Female CO Responders vs. Male TPR Responders	-4.688	No
Male CO Responders vs. Female TPR Responders	-4.189	No
Male CO Responders vs. Male TPR Responders	-4.292	No
Female TPR Responders vs. Male TPR Responders	-0.1031	No

This table shows the baseline values for mean arterial pressure (MAP), cardiac index (CI) and total peripheral resistance index (TPRI) in separate cohorts of rats. # p<0.05 female CI responders vs female TPRI responders; β female CI responders vs male TPRI responders. * p <0.05 main effect between CI responders and TPRI responders.

4. Discussion

The present work was undertaken to address two questions: 1) does overall activation of bradykinin-sensitive pericardial afferents increase cardiac output and 2) is this response different in males and females. We hypothesized that activation of pericardial bradykinin-sensitive afferents would produce a sexually dimorphic cardiac output response. In fact, as described above, we observed two distinct hemodynamic patterns upon pericardial BK injection that consisted of either an increase in CI or an increase in TPRI. These responses were mediated via the autonomic nervous system since they were abolished by ganglion blockade. Moreover, the CI response was greater in females whereas the TPRI response was greater in males. Thus, overall activation of bradykinin-sensitive pericardial afferents elicits sexually dimorphic hemodynamic responses.

Epicardial BK application is recognized as a trigger for cardiac afferents that elicit a powerful pressor response (Chen et al., 2015; Veelken et al., 1996; Wang et al., 2017; Xu et al., 2013; Zahner and Pan, 2005; Zhang et al., 1985). In the present work, we observed pressor responses between 17 and 27 mm Hg. This compares well with other work using anesthetized open chested rat preparations, which reported pressor responses ranging between 10 and 25 mm Hg (Wang et al., 2017; Xu et al., 2013; Zahner and Pan, 2005). Thus, our findings with respect to blood pressure are generally consistent with the established literature for pericardial bradykinin-induced pressor responses.

The first goal of this work was to assess the overall blood flow responses to pericardial bradykinin injection. While the blood pressure and sympathetic drive responses to pericardial bradykinin have received considerable investigation, direct study of the hemodynamic mechanisms underlying the pressor responses is sparse. Work in dogs showed that pericardial BK application caused renal vasoconstriction but vasodilation in the femoral region (Staszewska-Barczak and Dusting, 1977). In contrast, coronary blood flow was reportedly not affected by pericardial BK(Wang et al., 2001). To our knowledge, only one study assessed the overall hemodynamic responses to bradykinin-sensitive pericardial afferents. This work in male rats using pressure-volume loop analysis indicated that localized epicardial BK application increased overall systemic flow, CO, by approximately 14% (Wang et al., 2017). Since we reported previously that pericardial bradykinin injection increased venous tone (Martin et al., 2020), we expected increased CO in response to pericardial bradykinin injection. In fact, we observed two distinct patterns of pericardial BK-induced hemodynamic responses. In one, CI was increased with little change in TPRI. In these rats, CI increased by approximately 21% in female CI responders and by 12% in male CI responders. These responses obtained in male rats by direct measurement of CO compare favorably with those reported previously using pressure-volume loop analysis (Wang et al., 2017). Thus, at least in this subset, the pressor response triggered by overall activation of bradykinin-sensitive pericardial afferents was mediated by increased CI. However, in other rats, the pericardial BK-induced pressor response was

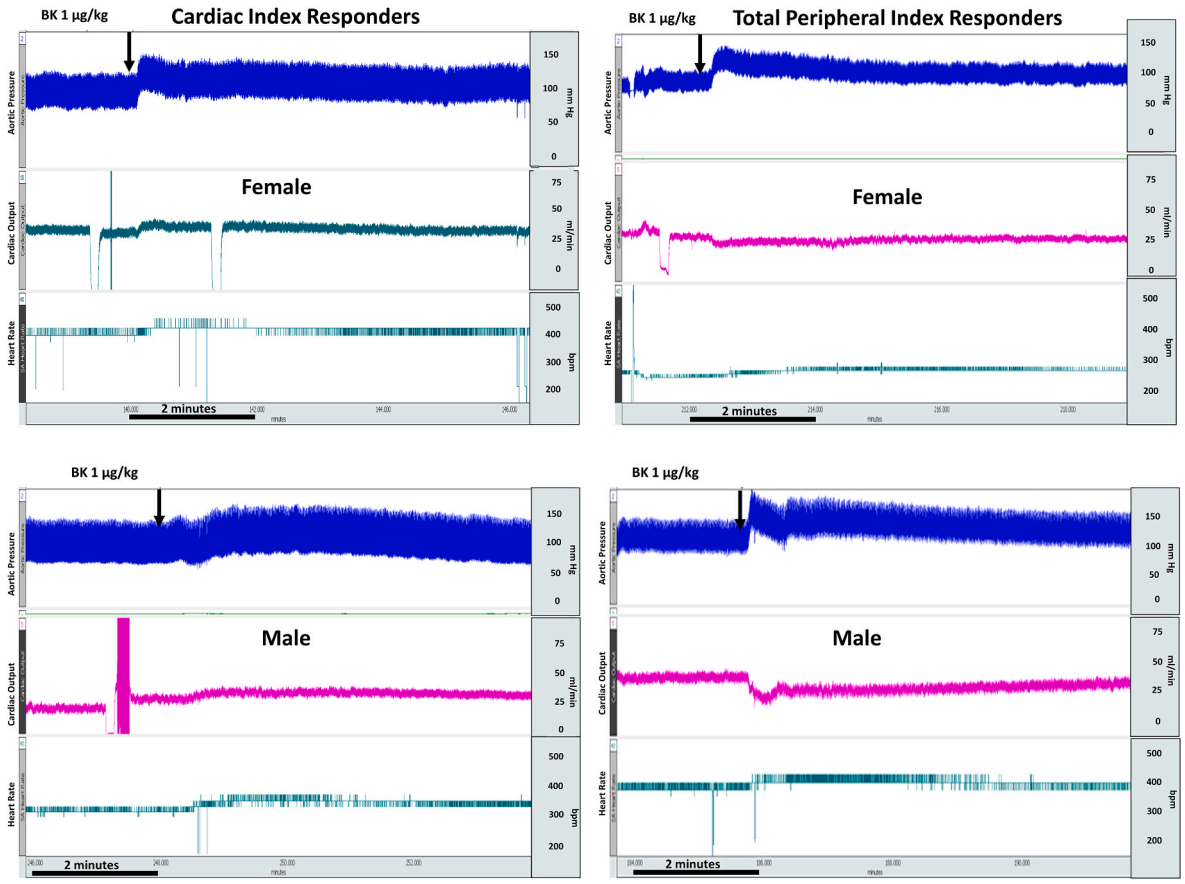

Fig. 1. This figure shows raw tracings illustrating the hemodynamic patterns associated with pericardial bradykinin injections in female (top panel) and male (lower panel) classified as cardiac index responders (left side) and total peripheral resistance index responders (right side). The arrow indicates the approximate time of pericardial injection of bradykinin at a dose of 1 µg/kg).

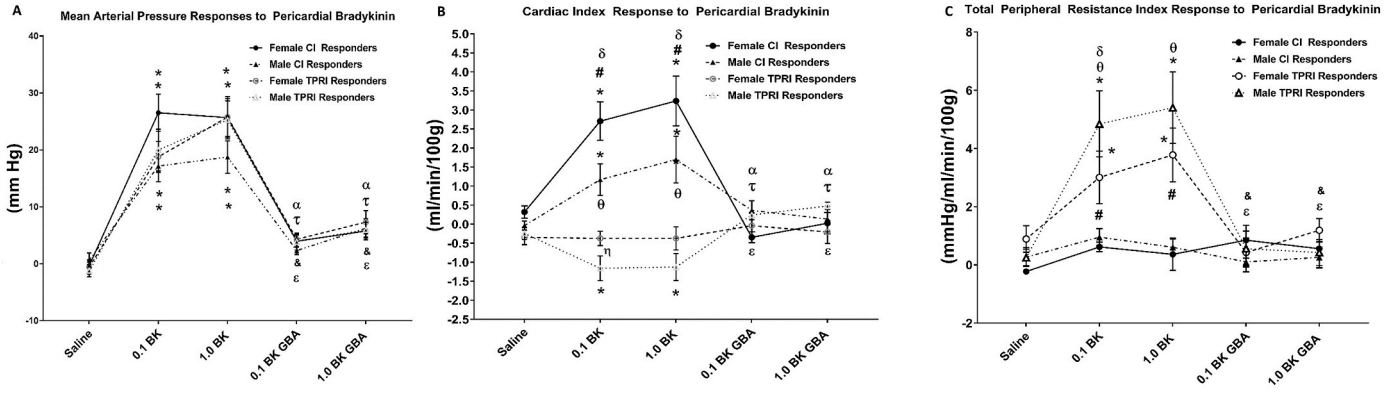

Table Analyzed	Transform of Two-way ANOVA with RM MAP	
Two-way ANOVA	Ordinary	
Alpha	0.05	
Source of Variation	% of total variation	P value
Interaction	1.628	0.6478
Trmt	70.12	<0.0001
Cluster	0.5312	0.3737

Table Analyzed	Transform of Two-way ANOVA with RM CI	
Two-way ANOVA	Ordinary	
Alpha	0.05	
Source of Variation	% of total variation	P value
Interaction	33.07	<0.0001
Trmt	4.255	0.0034
Cluster	20.59	<0.0001

Table Analyzed	Transform of Two-way ANOVA with RM TPRI calc	
Two-way ANOVA	Ordinary	
Alpha	0.05	
Source of Variation	% of total variation	P value
Interaction	16.65	<0.0001
Trmt	18.89	<0.0001
Cluster	12.84	<0.0001

Fig. 2. This figure shows the aggregate data for the mean arterial pressure (MAP), cardiac index (CI) and total peripheral resistance index (TPRI) responses to pericardial injection of bradykinin (0.1 and 1 µg/kg) in female and male rats classified as either cardiac index (CI) responders or total peripheral resistance index (TPRI) responders before and after interruption of autonomic function with a ganglion blocking agent (GBA). $P < 0.05$ * within group comparison to pericardial saline; **α** female CI responders pre post ganglionic blockade; **Ƭ** male CI responders pre post ganglionic blockade; **&** female TPRI responders pre post ganglionic blockade; **ε** male TPRI responders pre post ganglionic blockade. # female CI responders vs female TPRI responders; **Θ** male CI responders vs male TPRI responders; **δ** female CI responders vs male CI responders; **η** female TPRI responders vs male TPRI responders.

mediated by an increase in TPRI, with little change in CI. Thus, there were two distinct hemodynamic patterns triggered by mixed activation of bradykinin-sensitive pericardial afferents despite similar pressor responses. The observation of distinct hemodynamic patterns underlying similar pressor responses is not without precedent. While pressor and tachycardic responses were similar, cocaine caused increases in CO in some rats and decreases in others (Branch and Knuepfer, 1993). Similarly, air jet stress or cold stress caused an analogous dichotomy in hemodynamic responses in distinct groups of rats despite similar pressor responses (Knuepfer et al., 1993, 2001). Thus, dichotomy of hemodynamic patterns is a recognized phenomenon.

Since it was reported that estradiol modulated cardiac afferent mediated autonomic drive (Pinkham and Barrett, 2015), we predicted that there might be a sex-based difference in hemodynamic responses to pericardial bradykinin. To address this second goal, we compared responses in male and female rats. Somewhat unexpectedly, we did not observe an overall qualitative sex-based difference in hemodynamic responses since CI and TPRI responders were identified in both males and females. Nevertheless, some interesting sex-based differences were observed within these groups. Within the CI responders, females exhibited an increase in CI of 21% while males showed a 12% increase in CI. On the other hand, in TPRI responders, males exhibited a greater TPRI response than females (~45 vs 32%). Thus, in response to pericardial bradykinin injection, males could be characterized as more robust vascular responders whereas females could be characterized as more robust cardiac output responders.

The mechanisms underlying these differential hemodynamic responses remain to be elucidated. One possibility is that the dichotomous hemodynamic responses were dependent on the balance of afferent activation produced by pericardial BK injection. It is noteworthy that our approach, which mirrored that of McDermott (McDermott et al., 1995) and our previous study (Martin et al., 2020), used a pericardial catheter fixed in place along the lateral left ventricle to inject into the pericardial sac. Thus, the injectate was able to circulate within the pericardial sac and likely activated different types of cardiac afferents leading to overall activation of bradykinin-sensitive pericardial afferents. BK is somewhat non-selective since it activates both ischemia sensitive and ischemia insensitive cardia afferents (Fu, 2009). Additionally, BK may have activated cardiac vagal afferents which generally lower blood pressure and heart rate (Hainsworth, 1991) but have also been reported to increase heart rate and blood pressure (McDermott et al., 1995). Thus, the observed responses are likely an amalgam of activation of different types of cardiac afferents and would be best viewed as a mixed cardiac afferent response. This type of aggregate cardiac afferent response is important nonetheless since it may mimic that produced by endogenous release of BK during cardiac ischemia. Additionally, Pinkham reported that estradiol amplified cardiac vagal afferent responses and attenuated cardiac sympathetic afferent responses (Pinkham and Barrett, 2015). Thus, some of the divergence in hemodynamic patterns may be ascribed to differences in the extent of activation of cardiac sympathetic versus vagal afferents.

In any case, the underlying mechanisms warrant further study since they may have clinical implications. Differential cardiac output and vascular resistance responses occur in humans (Kasprowicz et al., 1990; Kline et al., 2002; Sherwood et al., 1990). Moreover, subjects (animal or human) classified as vascular responders appear more susceptible to cardiovascular disease (Branch and Knuepfer, 1994; Christian and Stoney, 2006; Kasprowicz et al., 1990; Kline et al., 2002). In the context of the present work, cardiac afferents are thought to be activated by endogenous stimuli such as hydrogen peroxide or BK released during challenges such as cardiac ischemia (Chen et al., 2015; Longhurst et al., 2001), which might be expected to result in a mixed cardiac afferent response. Since the MAP responses were similar in CI responders and TPRI responders, afterload would be similar. However, the increase in systemic flow in CI responders might provide some degree of mitigation of coronary ischemia. In contrast, TPRI responders may be rendered more susceptible to coronary ischemia by a lack of systemic flow increase. The present work showed that males had a lesser CI response and a more robust TPRI response to overall activation of cardiac afferents. Thus, the dichotomous hemodynamic response to mixed cardiac afferent activation may in part explain male sensitivity to the deleterious effects of coronary ischemia.

5Conclusion

Overall activation of BK-sensitive pericardial afferents elicits a dichotomous hemodynamic pattern consisting of increased cardiac output in some but increased vascular resistance in others. Male rats exhibit a more powerful vascular response while females exhibit a more robust cardiac output response. Thus, mixed activation of bradykinin-sensitive pericardial afferents elicits sexually dimorphic hemodynamic responses despite producing similar increases in blood pressure. The uniform pressor response masks an important potentially clinically relevant dichotomy in the hemodynamic mechanisms underlying aggregate cardiac afferent activation.

CRediT authorship contribution statement

Douglas Martin: Conceptualization, Writing – original draft. **Samuel Drummer:** data acquisition/compilation. **Jessica Freeling:** Conceptualization, Writing – original draft. **Casey Reihe:** Conceptualization, data acquisition/compilation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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