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Vasoconstriction Seen in Coronary Bypass Grafts During Handgrip in Humans

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Abstract

In animal studies, sympathetically mediated coronary vasoconstriction has been demonstrated during exercise. Human studies examining coronary artery dynamics during exercise are technically difficult to perform. Recently, noninvasive transthoracic Duplex ultrasound studies demonstrated that: 1) patients with left internal mammary artery (LIMA) grafts to the left anterior descending artery can be imaged; and 2) the LIMA blood flow patterns are similar to those seen in normal coronary arteries. Accordingly, subjects with LIMA to the left anterior descending artery were studied during handgrip protocols as blood flow velocity in the LIMA was determined. Beat-by-beat analysis of changes in diastolic coronary blood flow velocity (CBV) was performed in six male clinically stable volunteers (60 ± 2 yrs) during two handgrip protocols. Arterial blood pressure (BP) and heart rate (HR) were also measured and an index of coronary vascular resistance (CVR) was calculated as diastolic BP/CBV. Fatiguing handgrip performed at (40% of maximal voluntary contraction; MVC) followed by circulatory arrest did not evoke an increase in CVR ($P = \text{NS}$). In protocol 2, short bouts of handgrip (15 s) led to increases in CVR ($18 \pm 3\%$ at 50% MVC and $20 \pm 8\%$ at 70% MVC). BP was also increased during handgrip. Our results reveal that in conscious humans, coronary vasoconstriction occurs within 15 s of onset of static handgrip at intensities at or greater than 50% MVC. These responses are likely to be due to sympathetic vasoconstriction of the coronary circulation.

Keywords

muscle reflexes; left internal mammary artery; autonomic nervous system

INTRODUCTION

In humans, cardiac output rises by a factor of 5 during maximal dynamic exercise (20). This is accomplished by increasing heart rate (HR) and stroke volume. This increase in cardiac work leads to a large increase in myocardial oxygen consumption. The magnitude of this increase in oxygen consumption is determined primarily by the magnitude of the rise in HR, the aortic pressure and myocardial contractility. Since the ability of the heart to increase O_2 uptake by augmenting oxygen extraction is limited (19,29), the ability to consume additional oxygen as exercise progresses must be met by an increase in coronary blood flow. However, as intraventricular pressures rise, so do intramyocardial compressive forces and this tends to reduce myocardial perfusion; this is particularly important in the subendocardium where the

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pressures due to contraction are highest (2). Thus, one would expect that exercise would be associated with a relative reduction in subendocardial blood flow. This does not occur.

Although not established in humans, prior canine studies demonstrate that sympathetic vasoconstriction occurs in coronary arteries during exercise (3,5,15). It has been suggested that this vasoconstriction helps maintain perfusion throughout the myocardium by shunting blood from the outer to the inner layer (5,15).

There have been relatively few human studies examining if coronary vasoconstriction occurs during exercise. This is largely because methods to measure coronary blood flow are invasive (7,30) and/or have poor time resolution. In this report we examine coronary blood flow velocity (CBV) to graded levels of static handgrip exercise. Static handgrip exercise evokes large increases in muscle sympathetic nerve traffic (10,22) and blood pressure (BP) (17) without evoking large increases in HR. This relative flat HR response would lead to only modest increases in myocardial oxygen consumption and coronary blood flow. We hypothesize that measurements of coronary blood flow during static handgrip would better afford us the opportunity to determine coronary vasoconstriction in human subjects.

Flow velocity was measured with transthoracic Doppler echocardiography. This method has recently been utilized in humans to measure internal mammary artery bypass graft blood flow velocity under a variety of conditions.

The results of the studies presented in this report suggest that coronary vasoconstriction occurs within seconds of initiating high intensity static forearm exercise.

METHODS

Study Population

Six male subjects (age, 60 ± 2 yrs, BMI, $28 \pm 1 \text{ kg/m}^2$) who were <3 years status post left internal mammary artery (LIMA) graft surgery were recruited from the Penn State Heart and Vascular Institute at the Hershey Medical Center. Patients with diabetes and renal failure were excluded from the study. The volunteers were nonsmokers with total cholesterol values of <200 mg/dl. All LIMA recipients were clinically stable. All subjects had normal left ventricular ejection fractions. Recent records from the LV ventriculography stress echo and/or perfusion scan depicted no signs of wall motion abnormalities or infarction within the LAD territory. They suggest that scar tissue was supplied by the LIMA graft. Medications used by the subjects include the following: β_1 -blockers ($n = 4$), α -blocker ($n = 1$) angiotensin-converting enzyme inhibitors ($n = 1$), calcium channel blocker ($n = 2$), and statins ($n = 6$). Medications were withheld on the morning of the study. Each subject signed an Institutional Review Board approved informed consent document. A physical examination was then performed.

Coronary blood flow velocity

LIMA graft blood flow velocity was measured with Duplex ultrasound (HDI 5000, ATL Ultrasound, Bothell, WA, USA). A linear-array high frequency transducer (7–10 MHz) with a 6 MHz pulsed Doppler frequency was used for these studies. The LIMA was scanned along the left sternal border in the second or third intercostal space while the subjects were lying supine (24). The probe insonation angle to the artery was $<60^\circ$. The LIMA was first identified with color flow mapping and the focal zone was then set at the depth of the LIMA. The velocity range was set 0–30 cm/s. The sample volume of the pulsed wave was adjusted according to the size of the vessel. Care was taken to ensure that the subject did not perform Valsalva maneuvers during the handgrip protocols. Each cardiac cycle (diastolic component) Doppler tracing was analyzed using HDI 5000 ATL software to obtain mean coronary diastolic blood flow velocity. Beat-to-beat recordings of blood pressure were also obtained and recorded with

a Power Lab data acquisition system (AD Instruments Inc) and analyzed using the Power Lab Chart software suite. Therefore, for each diastolic period a diastolic velocity value and a corresponding blood pressure value was obtained. Subsequently, coronary vascular resistance index (CVR) was calculated by dividing corresponding diastolic pressure by CBV (cm/sec). CVR is expressed in arbitrary units.

CBV velocities were obtained during the two handgrip protocols (see below). Continuous recordings of HR (electrocardiogram) and BP (Finapres; Ohmeda, Madison, WI) were also obtained throughout the protocols. An automated sphygmomanometer (Dinamap; Critikon, Tampa, FL) was used to determine resting BP. A force transducer (Stoelting, Wood Dove, IL) was used to measure the force of muscle contraction. Maximal voluntary contraction (MVC) of the nondominant arm was determined in each subject.

Study Protocols

Protocol 1. Fatiguing static handgrip followed by post handgrip circulatory arrest (PHG-CA): In this protocol, we measured coronary artery flow velocity during fatiguing exercise at 40% maximal voluntary contraction (MVC). Baseline HR, BP and CBV data were obtained over a 5 min period at rest before beginning the protocol. At the end of exercise, the subjects graded their perceived level of exertion as 20 (maximum effort) on the Borg scale (4). Immediately prior to discontinuing exercise, PHG-CA was initiated by inflating a previously placed BP cuff around the arm to ~250 mmHg. The cuff remained inflated for two min. This maneuver traps muscle metabolites generated during muscle contraction and activates metabolite sensitive muscle afferent nerves. Thus, the effects of muscle metaboreflex engagement evoked during handgrip could be examined.

Protocol 2. Static handgrip exercise performed at graded intensities: This protocol was designed to examine the relationship between tension generated during short bouts of handgrip and CVR. The temporal relationship between coronary vascular responses and BP responses was also determined.

Baseline HR, BP and CBV data were collected over 5 min. Each subject completed 15 s bouts of static handgrip exercise at 10%, 30%, 50%, and 70% MVC, respectively. The same sequence was maintained in all subjects. Each 15 s contraction was preceded by an ~1 min rest period. The subject rested for at least 15 min between the two protocols.

Data analysis and statistics

Beat-by-beat sequential analysis of HR, BP, CBV and CVR were performed for all subjects.

In the fatiguing static handgrip protocol, variables were measured at 10%, 20%, 40%, 60%, 80% and 100% (peak) of the time to fatigue. Data from the last 15 s time period during circulatory arrest is presented. In the second protocol, data were analyzed in 5 s time periods of the respective 15 s bouts of handgrip. Statistical analyses were performed separately on each 5 s period (i.e. 1–5, 6–10 and 11–15 s).

Data are presented as mean $\pm$ SE. Repeated measures one-way ANOVA and post hoc analysis with a Bonferroni adjustment were performed to compare variables at each point to the baseline. A $P < 0.05$ was considered significant.

RESULTS

Protocol 1. Responses to fatiguing handgrip and PHG-CA (Table 1)

Fatiguing handgrip at 40% MVC lasted for 156 ± 26 s. At the end of handgrip, HR and BP increased by 24 and 28% respectively ($P < .001$ for both). Coronary flow resistance did not change during this intervention. During PHG-CA, BP was higher than baseline but HR, flow velocity and resistance were not different than baseline.

Protocol 2. Responses to static handgrip at graded intensities (Figure 1, Table 2)

During protocol 2, BP rose within 5 s at workloads as low as 10% MVC.

HR and coronary vascular resistance rose within 10 s at the highest workload tested, 70% MVC. During 11 and 15 s of handgrip, a rise in HR was noted at an intensity of 50% MVC, BP rose at a tension of 30% MVC and resistance rose above baseline values at a tension of 50% MVC. This rise in resistance represented 18 and 20% respectively at 50% and 70% MVC. The respective changes in BP at 50% and 70% were 12 and 18%.

DISCUSSION

The principal new finding in this study is that coronary vasoconstriction occurs during handgrip at tensions of 50% and greater. Specifically, this response is seen within 10 s of 70% MVC and 15 s at 50% MVC. These human findings are consistent with prior animal studies that showed intensity dependent coronary vasoconstriction during exercise (1,9). No changes in coronary resistance were noted during fatiguing handgrip at 40% MVC. Interestingly, the rise in BP at the end of the this paradigm was greater than the BP seen at 10 and 15 s of 70% and 50% MVC.

The time courses of the vasoconstrictor responses noted in the present report indicate that certain neural mechanisms, possibly muscle mechanoreflexes and/or central command, may have been engaged during the bouts of handgrip. Prior animal studies also suggest that muscle reflex responses can evoke coronary vasoconstriction (3). Our findings (Protocol 2) are also consistent with those of Matsukawa et al. Matsukawa et al. (23) demonstrated that engagement of muscle mechanoreflexes play an important role in the initial increases in cardiac sympathetic nerve activity during muscle contraction in anesthetized cats.

As in fatiguing handgrip, no significant changes in CVR were noted during PHG-CA. On the other hand, blood pressure was higher than baseline at the end of fatiguing handgrip (27%) as well as during PHG-CA (14%). This suggests that activation of muscle metaboreflex did not elicit coronary vasoconstriction. Similar observations were found in a prior animal report by Ansorge et al. (1). In the studies by Ansorge et al., metaboreflex activation was evaluated using a graded partial hindlimb occlusion model in dogs. The authors observed no significant coronary vasoconstriction during dynamic exercise at sub maximal workloads in the normal dog. A significant vasoconstriction, however, due to muscle metaboreflex activation occurred at maximal dynamic exercise. The reason why we did not observe coronary vasoconstriction during fatiguing handgrip or during PHG-CA is not entirely clear. Possible explanations include differences in the models (human vs. canine), differences in exercise paradigms (static handgrip vs. the running dog) and differences in muscle mass (small muscle mass vs. large muscle mass).

It must be noted that significant increases in BP were also noticed during 15 s of handgrip. Previous work from this lab have demonstrated acute myogenic vasoconstrictor responses can be observed in the forearm vasculature within ~10 s of initiating a rise in transmural pressure (21). Thus, the observed increases in CVR within 10–15 s of initiation of handgrip could also

have been due to a pressure dependent autoregulatory myogenic vasoconstriction and/or sympathetic constriction. However, if this were the case, we would have anticipated a rise in CVR during fatiguing handgrip since the rise in BP was relatively pronounced. Thus we do not believe the increases in coronary contraction noted in protocol 2 were due to myogenic constriction.

Study limitations

None of our subjects had recent angina or myocardial infarctions and the flow patterns seen in LIMA grafts are reflective of flow patterns seen in normal coronary arteries (6). Moreover, Katz et al. has performed human studies examining LIMA vascular responses to vasodilators (16). The magnitude of the responses in the LIMA graft were found to be similar to the responses repeated by Kern et al. within native coronary arteries (18). Thus we believe these findings are reflective of normal coronary physiology.

Our study volunteers had LIMA grafts placed to bypassed coronary arteries with blockages in native coronary arteries and almost all of them were on statins and/or beta-blocker therapy. Recent reports have shown that statin therapy normalizes excess sympathetic nervous system activity in heart failure rabbits (12,25). However, the responses were seen only with higher doses of statin therapy (≥ 1.5 mg/Kg/d) (25). It is necessary to mention that in our study patient population, all subjects were taking lower doses (< 1.0 mg/Kg/d) of statin medication. Moreover, unpublished observations from our laboratory suggest that statin (Pravachol 40 mg/day) therapy does not lower resting plasma NE concentration in humans. Plasma NE before and after statin therapy was found ($2.00 \pm .19$ and $2.14 \pm .3$ nM, respectively; $P = \text{ns}$).

Other studies have shown that beta-blocker therapy increases resting coronary vascular resistance (28). Interestingly, another report observed no effect of intracoronary administration of beta-blockade on epicardial coronary vasoconstriction during exercise (11). It is noteworthy to mention that currently there is a study under way in this lab examining coronary blood flow velocity in native coronary arteries of healthy humans. Preliminary (unpublished data) observations suggest no coronary constriction occurs at 10% MVC. At 70% MVC is observed and the magnitude of constriction is similar to that seen in this report. These observations lead us to believe that the medications in the LIMA patients did not have a large impact on the observed findings.

Another study limitation is that we could not measure LIMA diameter due to the limited spatial resolution of the technique. However, previous studies documented that coronary flow velocity measurements were closely related to the measurement of coronary blood flow (8,13,26,27). Although, in most of these studies the method used to measure coronary flow velocity was the invasive Doppler guidewire technique, recent studies have shown excellent correlation between the two measurements of blood flow velocity obtained by Transthoracic Doppler and the Doppler guidewire technique in the LIMA graft (24) as well as in native coronary artery (14).

In conclusion, we observed coronary vasoconstriction in human subjects during handgrip. This effect was intensity dependent and appeared to be linked to central command or stimulation of mechanically sensitive afferents. This response was not likely to be due to myogenic constriction. Our current findings, do not allow us to speculate as to whether this exercise induced coronary vasoconstriction is beneficial (15). Future studies are essential to evaluate the consequences of coronary vasoconstriction during exercise in humans.

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Figure 1.

% Change from baseline data in coronary vascular resistance index (CVR; Y-axis) during 15 s bouts of static handgrip at 10, 30, 50 and 70% of maximum voluntary contraction (X axis) in LIMA subjects ($n = 6$). Data presented as mean $\pm$ SEM. Data examined separately for 1–5, 6–10 and 11–15 s. (*) indicates P value < 0.05 , significant difference from the baseline values during each five second time frame. Note significant greater increases in CVR responses during 6–10 s and 11–15 s at 50% and 70% MVC.

A. Baseline **B. Handgrip at 70% MVC** **Figure 2.**

The original blood flow velocity profile in a left internal mammary artery graft to the coronary artery. The wave signals are shown during rest (A; baseline) and during handgrip exercise at 70% MVC (B). Note, that during handgrip the diastolic blood flow velocity was lower than during baseline.

Cardiovascular Including Coronary Hemodynamics During Fatiguing Static Handgrip and Post Handgrip Circulatory Arrest (PHG-CA; Protocol 1)

Table 1

	Baseline	% Time to Fatigue					100%	2 min
		10%	20%	40%	60%	80%		
$\Delta\%$ HR		12 $\pm$ 3	11 $\pm$ 1	16 $\pm$ 4*	21 $\pm$ 5*	23 $\pm$ 6*	24 $\pm$ 5*	4 $\pm$ 0
HR	66 $\pm$ 4	72 $\pm$ 4	72 $\pm$ 4	75 $\pm$ 4	79 $\pm$ 4	80 $\pm$ 5	81 $\pm$ 4	68 $\pm$ 4
$\Delta\%$ BP		5 $\pm$ 3	10 $\pm$ 3	12 $\pm$ 4	18 $\pm$ 5*	24 $\pm$ 6*	27 $\pm$ 6*	14 $\pm$ 4*
BP	92 $\pm$ 8	93 $\pm$ 7	100 $\pm$ 7	102 $\pm$ 6	108 $\pm$ 8	112 $\pm$ 4	115 $\pm$ 4	104 $\pm$ 6
$\Delta\%$ CBV		-6 $\pm$ 6	-2 $\pm$ 7	7 $\pm$ 6	12 $\pm$ 8	17 $\pm$ 11	7 $\pm$ 9	5 $\pm$ 7
CBV	13.1 $\pm$ 3	13.4 $\pm$ 3.3	13.5 $\pm$ 3.5	14.9 $\pm$ 4	15.3 $\pm$ 4.2	16.6 $\pm$ 5.1	15 $\pm$ 4.6	13.8 $\pm$ 3.4
$\Delta\%$ CVR		13 $\pm$ 8	15 $\pm$ 12	5 $\pm$ 8	6 $\pm$ 6	9 $\pm$ 9	21 $\pm$ 10	10 $\pm$ 11
CVR	9.84 $\pm$ 2.57	10.5 $\pm$ 3.96	12.33 $\pm$ 4.35	11 $\pm$ 3.64	10.41 $\pm$ 2.79	11.12 $\pm$ 3.23	11.9 $\pm$ 3.11	10.61 $\pm$ 2.9

Fatiguing static handgrip protocol data presented as $\Delta\%$ from baseline (bold print) as well as raw data for heart rate (HR; beat/min), blood pressure (BP; mmHg), coronary blood flow velocity (CBV; cm/sec) and coronary vascular resistance index (CVR; mmHg/cm/sec). PHG-CA data (the last 15 s of 2 min) for HR, BP, CBV and CVR are shown on the right side. Data are presented as mean $\pm$ SEM.

* indicates $P < 0.05$, significant changes from corresponding baseline values at each time point.

Table 2
Cardiovascular Including Coronary Hemodynamics During Short Bouts of Static Handgrip (Protocol 2).

<i>1–5 seconds</i>					
	<i>Baseline</i>	<i>10%</i>	<i>30%</i>	<i>50%</i>	<i>70%</i>
% MVC					
Δ% HR	65 ± 3	2 ± 2	4 ± 1	2 ± 1	7 ± 4
HR					
Δ% BP	88 ± 8	67 ± 3	68 ± 3	66 ± 3	70 ± 4
		4 ± 1*	7 ± 1*	6 ± 1*	11 ± 2*
BP					
Δ% CBV	12.7 ± 2.6	91 ± 8	94 ± 09	93 ± 8	97 ± 9
		-5 ± 3	-4 ± 6	7 ± 4	-2 ± 5
CBV		11.8 ± 2.2	12.6 ± 2.7	13.3 ± 2.5	12.6 ± 2.5
<i>6–10 seconds</i>					
	<i>Baseline</i>	<i>10%</i>	<i>30%</i>	<i>50%</i>	<i>70%</i>
% MVC					
Δ% HR	65 ± 3	-1 ± 2	3 ± 2	3 ± 2	9 ± 3*
HR					
Δ% BP	88 ± 8	64 ± 2	67 ± 2	67 ± 4	71 ± 4
		4 ± 1	9 ± 2*	9 ± 2*	16 ± 1*
BP					
Δ% CBV	12.7 ± 2.6	91 ± 8	95 ± 8	95 ± 7	101 ± 9
		-3 ± 3	0 ± 8	-1 ± 2	1 ± 5
CBV		12.5 ± 2.6	13.4 ± 3.5	12.6 ± 2.6	12.9 ± 2.8
<i>11–15 seconds</i>					
	<i>Baseline</i>	<i>10%</i>	<i>30%</i>	<i>50%</i>	<i>70%</i>
% MVC					
Δ% HR	65 ± 3	1 ± 1	4 ± 2	4 ± 1	7 ± 1*
HR					
Δ% BP	88 ± 8	66 ± 3	68 ± 3	68 ± 3	70 ± 3
		6 ± 1	7 ± 1*	12 ± 3*	18 ± 3*
BP					
Δ% CBV	12.7 ± 2.6	92 ± 8	93 ± 8	98 ± 7	104 ± 9
		-4 ± 4	1 ± 7	-6 ± 3	-1 ± 6
CBV		12.5 ± 2.7	12.9 ± 3.1	12.2 ± 2.7	12.7 ± 2.8

Graded handgrip protocol data for heart rate (HR; beat/min), blood pressure (BP; mmHg), coronary blood flow velocity (CBV; cm/sec) and coronary vascular resistance (CVR; mmHg/cm/sec). Format for these data as in Table 1

* indicate $P < 0.05$, significant differences from corresponding baseline values at each time point.