Spontaneous baroreflex control of heart rate versus cardiac output: altered coupling in heart failure

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Departments of 1Physiology and 4Surgery, Wayne State University School of Medicine, Detroit, Michigan; 2Laboratory for Applied Human Physiology, Faculty of Human Development, Kobe University, Kobe, Japan; 3Laboratory for Human Performance Research, Osaka International University, Osaka, Japan; and 5Dipartimento Medicina Interna, Università di Roma Tor Vergata, and 6Istituto di Ricovero e Curazza a Carattere Scientifico San Raffaele Pisana, Roma, Italy

Submitted 11 October 2007; accepted in final form 5 January 2008

Sala-Mercado JA, Ichinose M, Hammond RL, Coutos M, Ichinose T, Pallante M, Iellamo F, O’Leary DS. Spontaneous baroreflex control of heart rate versus cardiac output: altered coupling in heart failure. Am J Physiol Heart Circ Physiol 294: H1304–H1309, 2008. First published January 11, 2008; doi:10.1152/ajpheart.01186.2007.—Dynamic cardiac baroreflex responses are frequently investigated by analyzing the spontaneous reciprocal changes in arterial pressure and heart rate (HR). However, whether the spontaneous baroreflex-induced changes in HR translate into changes in cardiac output (CO) is unknown. In addition, this linkage between changes in HR and changes in CO may be different in subjects with heart failure (HF). We examined these questions using conscious dogs before and after pacing-induced HF. Spontaneous baroreflex sensitivity in the control of HR and CO was evaluated as the slopes of the linear relationships between HR or CO and left ventricular systolic pressure (LVSP) during spontaneous sequences of greater or equal to three consecutive beats when HR or CO changed inversely versus pressure. Furthermore, the translation of baroreflex HR responses into CO responses (HR-CO translation) was examined by computing the overlap between HR and CO sequences. In normal resting conditions, 44.0 ± 4.4% of HR sequences overlapped with CO sequences, suggesting that only around half of the baroreflex HR responses cause CO responses. In HF, HR-LVSP, CO-LVSP, and the HR-CO translation significantly decreased compared with the normal condition (2.29 ± 0.5 vs. −5.78 ± 0.7 beats·min⁻¹·mmHg⁻¹; −70.95 ± 11.8 vs. −229.89 ± 29.6 ml·min⁻¹·mmHg⁻¹; and 19.66 ± 4.9 vs. 44.0 ± 4.4%, respectively). We conclude that spontaneous baroreflex HR responses do not always cause changes in CO. In addition, HF significantly decreases HR-LVSP, CO-LVSP, and HR-CO translation.

arterial baroreflex sensitivity; parasympathetic activity; stroke volume

THE ARTERIAL BAROREFLEX is the primary short-term regulator of systemic blood pressure via modulation of parasympathetic and sympathetic nerve activity (26). Changes in arterial blood pressure result in arterial baroreflex-mediated reciprocal changes in heart rate (HR) and total peripheral resistance. Arterial baroreflex sensitivity (cardiac component) has often been assessed via techniques that analyze normally occurring spontaneous changes in blood pressure and the reciprocal changes in HR (3, 12, 21, 32). This technique has been used as an index of cardiac baroreflex function in a number of species, including humans, and in many experimental and pathological conditions (1, 3, 11, 13, 18, 21, 25, 32). Sinoaortic baroreflex denervation virtually abolishes baroreflex sensitivity assessed via this method, indicating that the spontaneous reciprocal changes in HR that occur as a result of changes in arterial pressure are indeed mediated by the baroreflex (1, 19). However, changes in HR do not necessarily dictate changes in cardiac output (CO) because stroke volume (SV) may also vary, for example, with changes in ventricular filling time (17, 35). Since pressure is the product of CO and total peripheral resistance, baroreflex-mediated changes in HR unaccompanied by changes in cardiac output would be completely ineffective in correcting the rise or fall in arterial pressure. Since the arterial baroreflex is a blood pressure regulation reflex, CO modulations are a more appropriate index of baroreflex regulation than HR. However, to the best of our knowledge, no information exists as to whether the spontaneous baroreflex-induced changes in HR do indeed elicit changes in CO. Therefore, one objective of the present study was to determine whether the baroreflex HR responses also cause changes in CO. Furthermore, no previous study has examined baroreflex regulation of CO using the sequence technique. Thus an additional aim was to characterize baroreflex control of CO using this approach and to determine whether the changes in CO were due to changes in HR versus SV.

Heart failure (HF) is characterized by an impaired cardiac performance, excessive sympathetic and reduced cardiac vagal activity, and a reduced baroreflex control of HR as assessed by a variety of techniques, including the spontaneous baroreflex-HR approach (2, 4, 5, 10, 14, 34). With the reduced baroreflex control of HR and impaired ventricular contractility in HF, we hypothesized that the ability of spontaneous baroreflex-induced changes in HR to elicit changes in CO would also be reduced. Finally, we also examined whether HF also reduces the strength of spontaneous baroreflex changes in CO and whether HF alters the relationships between CO, HR, and SV.

MATERIALS AND METHODS

Experiments were performed on seven adult, mongrel dogs (weight, ~20–25 kg) of either sex. The protocols employed in the present study were reviewed and approved by the Wayne State University Animal Investigation Committee and conform to the National Institutes of Health guidelines.

Surgical preparation and procedures. All animals were accustomed to human handling before they were surgically instrumented in two different procedures (sternotomy and left flank abdominal surgery).

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Before each surgery, the dogs received an intramuscular injection of acepromazine (0.2 mg/kg) for tranquilization. Thirty minutes later, the animals were anesthetized with thiopental sodium (25 mg/kg iv). Following endotracheal intubation, anesthesia was maintained with isoflurane gas (1–3%). Before the surgery, the animals received cefazolin (500 mg iv, antibiotic), carprofen (2.0 mg/kg iv, analgesic), buprenorphine (0.1 mg/kg im, analgesic), and a 72-h transdermal fentanyl patch (125–175 μg/h, analgesic). In addition, before the sternotomy, selective intercostal nerve block was performed with bupivacaine hydrochloride (2.0 mg/kg). Following each surgical procedure, the dogs received a second intravenous dose of cefazolin (500 mg iv), and antibiotics were continued for the length of the experimental protocol at an oral dose of cephalixin (30 mg·kg⁻¹·12 h⁻¹) to prevent infections. Moreover, after each surgical procedure, for the following 12 h, buprenorphine and acepromazine were administered through intravenous infusions (0.05 and 0.5 mg/kg, respectively) as needed to control any type of discomfort. Thereafter, carprofen was administered orally (4 mg·kg⁻¹·day⁻¹) for 10 days.

In the first surgical procedure under sterile conditions, a midline sternotomy was performed. A fully implantable telemetered blood pressure transducer (model PAD-70, Data Sciences International) was placed subcutaneously on the left side of the chest. Its catheter was tunneled into the thoracic cavity through the seventh or eighth intercostal space and located inside the left ventricle for measuring left ventricular pressure (LVP). A 20- or 24-mm blood flow transducer (Transonic Systems) was placed around the ascending aorta to measure CO. Three stainless steel ventricular pacing electrodes (O-Flexon, Ethicon) were sutured to the right ventricular free wall. For studies unrelated to the present investigation, vascular occluders were placed on the superior and inferior venous cava and two pairs of sonomicrometry crystals were placed on the left ventricular endocardium. The pericardium was reapproximated loosely, and the chest was closed in layers. After a recovery period (at least 10 days), a second surgical procedure (left abdominal retroperitoneal surgery) was performed. During this procedure, a catheter was placed through a lumbar artery on the proximal abdominal aorta to measure CO. Three stainless steel ventricular pacing electrodes were placed on the terminal aorta. All flow probe cables, pacing wires, vascular occluder tubings, and the aortic catheter were tunneled subcutaneously and exteriorized between the scapulae at the end of its corresponding surgical procedure. The animals were allowed at least 7 days for recovery before any experiments.

Experimental procedures. All experiments were performed after the animals had fully recovered from instrumentation (i.e., active, alert, afebrile, and of good appetite). Before every experiment, each animal was transported to the laboratory and allowed to roam freely for 15–30 min and then was led to adopt a resting (standing) position. The CO blood flow transducer was connected to the flow meter (Transonic System). The arterial catheter was connected to a pressure transducer (Transpac IV, Abbott), the LVP signal was checked, and HR was computed by a cardiotachometer triggered by the CO signal. All data were recorded on analog-to-digital recording systems for subsequent off-line analyses. After all hemodynamic values had reached steady state (~30 min). The pacemaker was turned back on right after the experiment was completed.

Data analysis. Each animal served as its own control. During each experiment, beat-to-beat mean arterial pressure, HR, LVP, and CO were collected continuously for 3 to 5 min so that the recording period spanned multiple respiratory cycles. Spontaneous baroreflex control of HR and CO was dynamically assessed by analyzing the beat-to-beat relationship between HR and left ventricular systolic pressure (LVSP) and between CO and LVSP (Fig. 1). Spontaneous SV-LVSP relationships were also assessed. Since LVSP is virtually identical to systolic pressure in the aortic arch, we used LVSP as the input to the arterial baroreflex. Briefly, the beat-to-beat time series of LVSP and HR or CO were searched for three or more consecutive beats in which the LVSP and HR or CO of the following beat changed in opposite directions. A linear regression was applied to each individual baroreflex HR sequence and CO sequence, and only those sequences in which r² was >0.85 were accepted, and a slope was calculated. The mean slope of the LVSP-HR and LVSP-CO relationships was obtained by averaging all slopes computed within a given test period. We examined the translation of the baroreflex HR responses into CO responses by computing the overlap between HR sequences and CO sequences. When HR and CO sequences completely overlapped (changes in LVSP are directly related to reciprocal changes in HR and CO simultaneously for every beat in the individual regression), they were defined as complete overlap sequences. When HR and CO sequences overlapped by at least two beats, they were defined as partial overlap sequences. Therefore, complete overlap sequences are included in the tabulation of the partial overlap sequences. The proportion of a complete and partial to total number of HR or CO sequences were calculated, respectively (as can be seen in Fig. 3, most of the partial overlap sequences were complete sequences). We also assessed the spontaneous changes in stroke volume by using the same technique described above and calculated the percentage of CO sequences that completely or partially overlapped with SV sequences, respectively. Since not all baroreflex HR sequences resulted in proportional changes in CO because reciprocal changes in SV occurred that limited or prevented any change in CO, we also analyzed to what extent SV changed in the opposite direction from the change in HR within each HR-LVSP relationship.

Statistical analysis. We compared the averaged responses for each animal between conditions using a paired t-test. An α-level of P < 0.05 was set to determine statistical significance. In the figures, table, and text, data are expressed as means ± SE.

RESULTS

Figure 1 shows the results from one experiment before and after the induction of HF from one animal. Table 1 shows the average values of LVSP, CO, SV, HR, and the normalized number of spontaneous HR, CO, and SV-LVSP sequences (incidence) in normal (N) and HF conditions. As expected and in agreement with previous studies (8, 9, 28) after pacing-induced HF, the animals showed a significant decrease in resting LVSP, CO, and SV, whereas HR was significantly increased compared with that in normal animals. The occurrence of spontaneous baroreflex HR sequences was significantly less in HF in accordance with a previous study from our laboratory (14). In addition, the incidence of spontaneous CO-LVSP sequences was also substantially less in HF.

Figure 2 shows the HR-LVSP (Fig. 2A), CO-LVSP (Fig. 2B), and SV-LVSP (Fig. 2C) relationships before and after the induction of HF. In HF, both HR-LVSP and CO-LVSP were decreased in the aortic arch, we used LVSP as the input to the arterial baroreflex. Briefly, the beat-to-beat time series of LVSP and HR or CO were searched for three or more consecutive beats in which the LVSP and HR or CO of the following beat changed in opposite directions. A linear regression was applied to each individual baroreflex HR sequence and CO sequence, and only those sequences in which r² was >0.85 were accepted, and a slope was calculated. The mean slope of the LVSP-HR and LVSP-CO relationships was obtained by averaging all slopes computed within a given test period. We examined the translation of the baroreflex HR responses into CO responses by computing the overlap between HR sequences and CO sequences. When HR and CO sequences completely overlapped (changes in LVSP are directly related to reciprocal changes in HR and CO simultaneously for every beat in the individual regression), they were defined as complete overlap sequences. When HR and CO sequences overlapped by at least two beats, they were defined as partial overlap sequences. Therefore, complete overlap sequences are included in the tabulation of the partial overlap sequences. The proportion of a complete and partial to total number of HR or CO sequences were calculated, respectively (as can be seen in Fig. 3, most of the partial overlap sequences were complete sequences). We also assessed the spontaneous changes in stroke volume by using the same technique described above and calculated the percentage of CO sequences that completely or partially overlapped with SV sequences, respectively. Since not all baroreflex HR sequences resulted in proportional changes in CO because reciprocal changes in SV occurred that limited or prevented any change in CO, we also analyzed to what extent SV changed in the opposite direction from the change in HR within each HR-LVSP relationship.

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Figure 2 shows the HR-LVSP (Fig. 2A), CO-LVSP (Fig. 2B), and SV-LVSP (Fig. 2C) relationships before and after the induction of HF. In HF, both HR-LVSP and CO-LVSP were significantly attenuated. HF had no effect on the SV-LVSP relationship; however, the incidence of SV-LVSP sequences was significantly greater (Table 1).
Hemodynamic values in normal animals and in the same animals after induction of heart failure.

<table>
<thead>
<tr>
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<th>Normal</th>
<th>Heart Failure</th>
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<tr>
<td>LVSP, mmHg</td>
<td>135.8±5.3</td>
<td>104.9±5.4*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>4.69±0.42</td>
<td>3.57±0.35*</td>
</tr>
<tr>
<td>SV, ml</td>
<td>44.9±4.1</td>
<td>26.1±2.8*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>105.5</td>
<td>139±6*</td>
</tr>
<tr>
<td>HR-LVSP incidence, sequences/100 beats</td>
<td>11.3±2.2</td>
<td>6.9±0.6*</td>
</tr>
<tr>
<td>CO-LVSP incidence, sequences/100 beats</td>
<td>6.6±1.0</td>
<td>3.3±0.7*</td>
</tr>
<tr>
<td>SV-LVSP incidence, sequences/100 beats</td>
<td>1.1±0.3</td>
<td>2.4±0.3*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVSP, left ventricular systolic pressure; CO, cardiac output; SV, stroke volume; HR, heart rate; HR-LVSP incidence, number of spontaneous baroreflex HR sequences; CO-LVSP incidence, number of CO-LVSP sequences; SV-LVSP incidence, number of SV-LVSP sequences. *P < 0.05, normal vs. heart failure.

DISCUSSION

To our knowledge, this is the first study to investigate to what extent the spontaneous baroreflex-induced changes in HR also cause changes in CO. Furthermore, this is the first study to examine whether the coupling between baroreflex control of HR and CO is altered in HF.

Cardiac baroreflex responses in normal animals. Several previous studies have examined spontaneous baroreflex control of HR during rapid, transient changes in blood pressure under various experimental and pathological conditions (1, 3, 11, 13, 18, 21, 25, 32). However, whether the spontaneous baroreflex HR responses functionally translate into effective blood pressure regulation has often been uncertain, since the extent to which HR responses cause changes in CO can be variable. CO responses are determined by both HR and SV changes. Previous studies (17, 35) have shown in conscious dogs with partially overlapped with HR sequences (Fig. 3B). In the same condition, the CO sequences (either partial or complete) overlapped with SV sequences were <5% (Fig. 3, E and F). In HF, HR-CO overlap and CO-HR overlap were significantly decreased. On the contrary, in HF, CO-SV overlap was significantly increased. In both conditions, the HR sequences that overlapped with the SV sequences were negligible and there was no significant difference between the two conditions (HR-SV partial overlap, 1.9 ± 0.7% vs. 4.1 ± 1.7%, N vs. HF, P > 0.05; and HR-SV complete overlap, 0.2 ± 0.2% vs. 1.9 ± 1.3%, N vs. HF, P > 0.05). Because changes in HR affect ventricular filling time and thereby can cause reciprocal changes in SV, we also analyzed during what percentage of the HR-LVSP sequences did reciprocal changes in SV occur (e.g., situations in which SV falls while HR increases or in which SV increases while HR falls). In the normal condition, 65.1 ± 3.3% of the HR-LVSP sequences had reciprocal changes in SV, which averaged −0.48 ± 0.06 ml/beat. After induction of HF, these significantly changed to 85.7 ± 2.9% and −1.16 ± 0.32 ml/beat, indicating that in HF, the larger reciprocal changes in SV with changes in HR acted to limit the ability of the chronotropic response to cause functional changes in CO. Indeed, for normal animals, in only 4.0 ± 2.5% of the HR-LVSP sequences did CO change in the same direction as LVSP (in the opposite direction to a baroreflex response). In contrast, after the induction of HF, this significantly increased to 21.0 ± 4.8%.

Figure 3 shows the percentage of partial and complete overlap of HR sequences with CO sequences (Fig. 3, A and B), of CO sequences with HR sequences (Fig. 3, C and D), and of CO sequences with SV sequences (Fig. 3, E and F) before and after HF. Importantly, one can reach the same conclusions with either partial or complete overlap. In normal animals, 44.0 ± 4.3% of HR sequences partially overlapped with CO sequences (Fig. 3A), but, on the other hand, 70.6 ± 6.1% of CO sequences

Fig. 1. Example of spontaneous heart rate (HR)-left ventricular systolic pressure (LVSP) (A), cardiac output (CO)-LVSP (B), and stroke volume (SV)-LVSP (C) relationships from 1 animal in normal (N) and heart failure (HF) conditions. Heavy line represents mean slope of HR-LVSP, CO-LVSP, and SV-LVSP relationships obtained from each individual sequence of 3 or more consecutive beats in which LVSP and HR or CO or SV changed in opposite direction, either + HR or CO or SV-LVSP or -HR or CO or SV/LVSP.
induced atrial-ventricular block that steady-state changes in HR (between 110 and 180 beats/min) do not elicit changes in CO per se due to the inverse relationship between HR and SV; that is, as HR increased, SV decreased, resulting in little net change in CO. Moreover, increases in HR above 180 beats/min caused precipitous decreases in SV, such that CO actually decreased. One cause of reciprocal changes in SV is the likely alterations in ventricular filling time associated with HR changes. Furthermore, as it has been shown in previous studies, even if SV is initially maintained, an increase in CO will decrease central venous pressure, thereby decreasing right ventricular filling pressure that would ultimately limit the ability to sustain left ventricular SV and therefore sustain the rise in CO (7, 24, 29). However, because of the capacitance of the pulmonary circulation, the fall in the ventricular filling does take time to occur, and, therefore, transient changes in HR can still cause transient changes in CO (30). In normal animals at rest, although most of the baroreflex CO responses were accompanied by HR responses, only ~50% of HR responses translated into CO responses. This suggests that only about half of baroreflex-induced HR changes are effective in restoring perturbations in arterial pressure in the resting condition but that effective changes in CO are tightly linked to baroreflex changes in HR. Thus, when the baroreflex was effective in changing CO, it was mainly via changes in HR; in contrast, baroreflex attempts to restore pressure via changes in HR were only effective about half of the time due to reciprocal changes in SV. We must mention that, even during, the other half of the HR responses, which are uncoupled with CO responses, could be beneficial in blood pressure regulation. For example, if arterial pressure was to decrease and the corresponding increase in HR did not increase CO (due to a concurrent fall in SV), then at least the baroreflex/HR response would work to attenuate a reduction in CO that may have occurred with a decreased SV and constant HR.

Fig. 2. Average values of HR-LVSP (A), CO-LVSP (B), and SV-LVSP (C) relationships in N and HF conditions. *P < 0.05, significant difference between N and HF.

Fig. 3. Proportion of overlap among HR, CO, and SV sequences. HR-CO partial overlap, proportion of HR sequences overlapped by at least 2 beats with CO sequences; HR-CO complete overlap, proportion of HR sequences that completely overlapped with CO sequences; CO-HR partial overlap, proportion of CO sequences overlapped by at least 2 beats with HR sequences; CO-HR complete overlap, proportion of CO sequences that completely overlapped with HR sequences; CO-SV partial overlap, proportion of CO sequences overlapped by at least 2 beats with SV sequences; CO-SV complete overlap, proportion of CO sequences that completely overlapped with SV sequences. *P < 0.05 between N and HF.
Cardiac baroreflex responses in HF. HF is characterized by altered neural cardiovascular regulation, including increased resting sympathetic nerve activity to the heart and vasculature, depressed vagal outflow to the heart, and attenuated baroreflex control of HR (6, 31, 33, 36, 37). Recently, Iellamo et al. (14) found that the spontaneous baroreflex control of HR in HF subjects was significantly depressed compared with normal subjects. In the present study, HF not only significantly decreased HR-LVSP but also substantially diminished the cardiac output responses as well. Furthermore, significantly fewer HR responses caused CO responses, and CO-SV overlap significantly increased. We must mention that although this overlap (CO-SV) significantly increased, it was still around the levels of the CO-HR overlap. These results suggest that, in HF, the observed changes in CO become less related to changes in HR and more related to changes in SV. Our study is in agreement with a previous study by Olivier and Stephenson (22), which demonstrated in conscious dogs that carotid baroreflex-induced changes in HR caused little changes in CO after induction of HF.

We can suggest at least three (likely interacting) mechanisms that may explain why in HF baroreflex changes in HR cause smaller changes in CO with less frequency. First is the diminished HR baroreflex sensitivity seen during HF. With a reduction in baroreflex HR sensitivity, even if SV was to remain constant, smaller changes in HR would cause smaller changes in CO. Furthermore, the impaired inotropic state of the heart and an increased afterload sensitivity in HF (15) could contribute to the smaller changes in CO in that even if baroreflex HR sensitivity were to remain at normal levels, the reduced SV would thereby generate smaller changes in CO. A third mechanism (and perhaps the most important) is that, in HF, there are greater reciprocal changes in SV related to changes in HR. After induction of HF, the percentage of HR-LVSP sequences in which SV changed in the opposite direction to the change in HR (e.g., falling SV with rising HR) increased significantly, and the extent of the change in SV per beat was over twofold greater than the normal condition (on a percent basis, the difference was even greater). In the normal animal, in only 4% of the HR-LVSP sequences did the reciprocal changes in SV result in CO changing in the same direction as LVSP. After induction of HF, far more HR-LVSP sequences were associated with CO changes in the same direction as LVSP. The increased baseline HR seen in HF may contribute to the larger reciprocal relationship. This further limits the ability of changes in HR to cause changes in CO in HF. Thus, with the decreased baroreflex HR sensitivity and depressed ability of changes in HR to cause changes in CO, baroreflex-mediated blood pressure regulation relies less on CO control and is more dependent on peripheral vascular regulation in HF (16, 22).

Limitations of the study. Our approach employed to evaluate arterial baroreflex control of HR and CO (based on spontaneous fluctuations in blood pressure, HR, and CO) has several advantages and disadvantages, which have been previously described in detail (12, 14, 27). Briefly, on one hand, the spontaneous baroreflex technique enables a qualitative and quantitative estimate of the integrated baroreceptor-cardiac response relationships during the spontaneous blood pressure fluctuations without the necessity of any pharmacological or mechanical interventions. This aspect is particularly relevant in HF conditions, in which, for example, sympathostimulatory reflexes by stretch of cardiac chambers after phenylephrine-induced increase of afterload or a direct β-adrenergic stimulation at the sinus node level by high doses of the drug may affect baroreflex sensitivity determination. On the other hand, the autonomic mechanisms mediating these rapid baroreflex-induced changes in HR and CO are likely confined to the parasympathetic component of baroreflex (20, 21). Furthermore, this approach only examines the baroreflex sensitivity over a relatively modest range of pressure, which therefore does not allow the calculation of the entire sigmoidal baroreflex stimulus-response relationship.

The finding that not all baroreflex/HR sequences translate into CO sequences should not be interpreted as indicating that the baroreflex is inactive for a prominent fraction of time or that it regulates the sinus node rate and CO only in a sequence-like fashion. This may only reflect an intrinsic limitation of the sequence technique, whereas it is likely that the baroreceptors modulate cardiac activity also by causing a single-beat change in response to a single-beat disturbance in blood pressure. Previous studies have shown that baroreflex HR sensitivity, as assessed by the spontaneous sequence method, is virtually abolished after arterial baroreceptor denervation, which shows the reflex nature of the HR responses (1, 19). In normal animals, the majority of the CO-LVSP sequences were associated with baroreflex HR responses, so we feel it is a safe assumption that these changes in CO were a result of arterial baroreflex-induced changes in HR. This relationship was less in HF, which was likely due to the larger reciprocal changes in SV that occurred with the baroreflex changes in HR. For the CO-LVSP sequences to be baroreflex in nature would dictate that the cause for the rise in pressure would be changes in resistance inasmuch as, if CO drove the increase in pressure, then the CO-LVSP relationship would be feed forward and not feed back (e.g., the slopes of the individual CO-LVSP regressions would be in the opposite direction for a baroreflex response). In the normal animal, for all the HR-LVSP individual sequences, CO changed in a nonbaroreflex (feed forward) fashion only 4% of the time. This rose to 21% in HF, likely due to the markedly greater changes in SV that occurred. The SV-LVSP sequences were unlikely of baroreflex origin inasmuch as this technique only examines rapid, dynamic changes, a time frame unlikely to be the result of autonomic neural mechanisms mediating these rapid baroreflex-induced changes in ventricular contractility. Rather, the SV-LVSP sequences more likely reflect the afterload sensitivity of the left ventricle. The incidence of these sequences was quite low, although it did increase with HF, which is consistent with the increased afterload sensitivity in this condition.

Conclusions. Our results show that, in normal conditions, spontaneous baroreflex HR responses do not always cause changes in CO. In contrast, most of the CO-LVSP sequences are related to HR changes. In addition, HF decreases not only the magnitude of the changes in HR and CO but also how often baroreflex-induced changes in HR cause changes in CO. Finally, in HF, baroreflex changes in CO are less related to changes in HR and more related to changes in SV.

ACKNOWLEDGMENTS

We thank Erin Krengel, Sue Harris, Jaime Rodriguez, and Dominic Fano for expert technical assistance and care of the animals and also Dr. Jong-Kyung Kim for assistance with the surgeries.
GRANTS

M. Ichinose and T. Ichinose are recipients of research fellowships of the Japan Society for the Promotion of Science for Young Scientists. This research was supported by a National Heart, Lung, and Blood Institute Grant HL-55473 and by a Agenzia Spaziale Italiana, Disturbi del Controllo Motore e Cardiorespiratorio project, Grant ASI I/006/06 (to F. Iellamo).

REFERENCES