



Advantage of recording single-unit muscle sympathetic nerve activity in heart failure

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Elevated sympathetic activation is a characteristic feature of heart failure (HF). Excessive sympathetic activation under resting conditions has been shown to increase from the early stages of the disease, and is related to prognosis. Direct recording of multiunit efferent muscle sympathetic nerve activity (MSNA) by microneurography is the best method for quantifying sympathetic nerve activity in humans. To date, this technique has been used to evaluate the actual central sympathetic outflow to the periphery in HF patients at rest and during exercise; however, because the firing occurrence of sympathetic activation is mainly synchronized by pulse pressure, multiunit MSNA, expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats), may have limitations for the quantification of sympathetic nerve activity. In HF, multiunit MSNA is near the maximum level, and cannot increase further than the heartbeat. Single-unit MSNA analysis in humans is technically demanding, but provides more detailed information regarding central sympathetic firing. Although a great deal is known about the response of multiunit MSNA to stress, little information is available regarding the responses of single-unit MSNA to physiological stress and disease. The purposes of this review are to describe the differences between multiunit and single-unit MSNA during stress and to discuss the advantages of single-unit MSNA recording in improving our understanding the pathology of increased sympathetic activity in HF.

Keywords: sympathetic nerve activity, heart failure, exercise, arrhythmia

INTRODUCTION

Augmented sympathetic nerve activity is a characteristic feature of heart failure (HF). Excessive sympathetic activation under resting conditions has been shown to increase from the early stages of the disease, and elevated levels of sympathetic nerve activity are correlated with a poor prognosis (Cohn et al., 1984; Francis et al., 1990; Grassi et al., 1995; Barretto et al., 2009). Sympathetic activity plays an essential role in maintaining blood pressure in acute HF, but excessive sympathetic activity in chronic HF has deleterious effects on the heart, including beta receptor downregulation (Bohm et al., 1997), cardiac myocyte apoptosis (Communal et al., 1998), and calcium overload (Chaudhri et al., 2002).

Although sympathetic nerve activity is difficult to assess in clinical settings, the assessment of sympathetic nerve activity is considered important in human HF. Although it has been 40 years since Vallbo and Wallin (Sundlof and Wallin, 1977; Vallbo et al., 1979) developed microneurography to record multiunit efferent muscle sympathetic nerve activity (MSNA) directly, it is still considered the best method for quantifying sympathetic nerve activity in healthy human subjects and in those with diseases associated with cardiovascular risk. Since the first report of the use of microneurography in human HF in 1986 (Leimbach et al., 1986), many groups have applied this technique to evaluate the actual central sympathetic outflow to the peripheral vascular bed in HF patients at rest and during exercise. However, as the firing occurrence of sympathetic activation is mainly synchronized by pulse pressure, multiunit MSNA may have limitations in the quantification of

sympathetic nerve activity. Single-unit MSNA analysis in humans was refined by Macefield et al. (1994). This technically demanding method requires adjustment of the tungsten electrode until a large unitary discharge is observed in a raw nerve action potential signal to discriminate a single-unit action potential. Although a great deal is known about the response of multiunit MSNA during stress, little information is available regarding the response of single-unit MSNA to stress. The purpose of this review is to describe the differences between multiunit and single-unit MSNA during stress and to discuss the advantages of single-unit MSNA recording.

DIRECT RECORDING OF MUSCLE SYMPATHETIC NERVE ACTIVITY IN HUMAN SUBJECTS

ASSESSMENT OF MULTIUNIT MSNA AND ITS LIMITATIONS

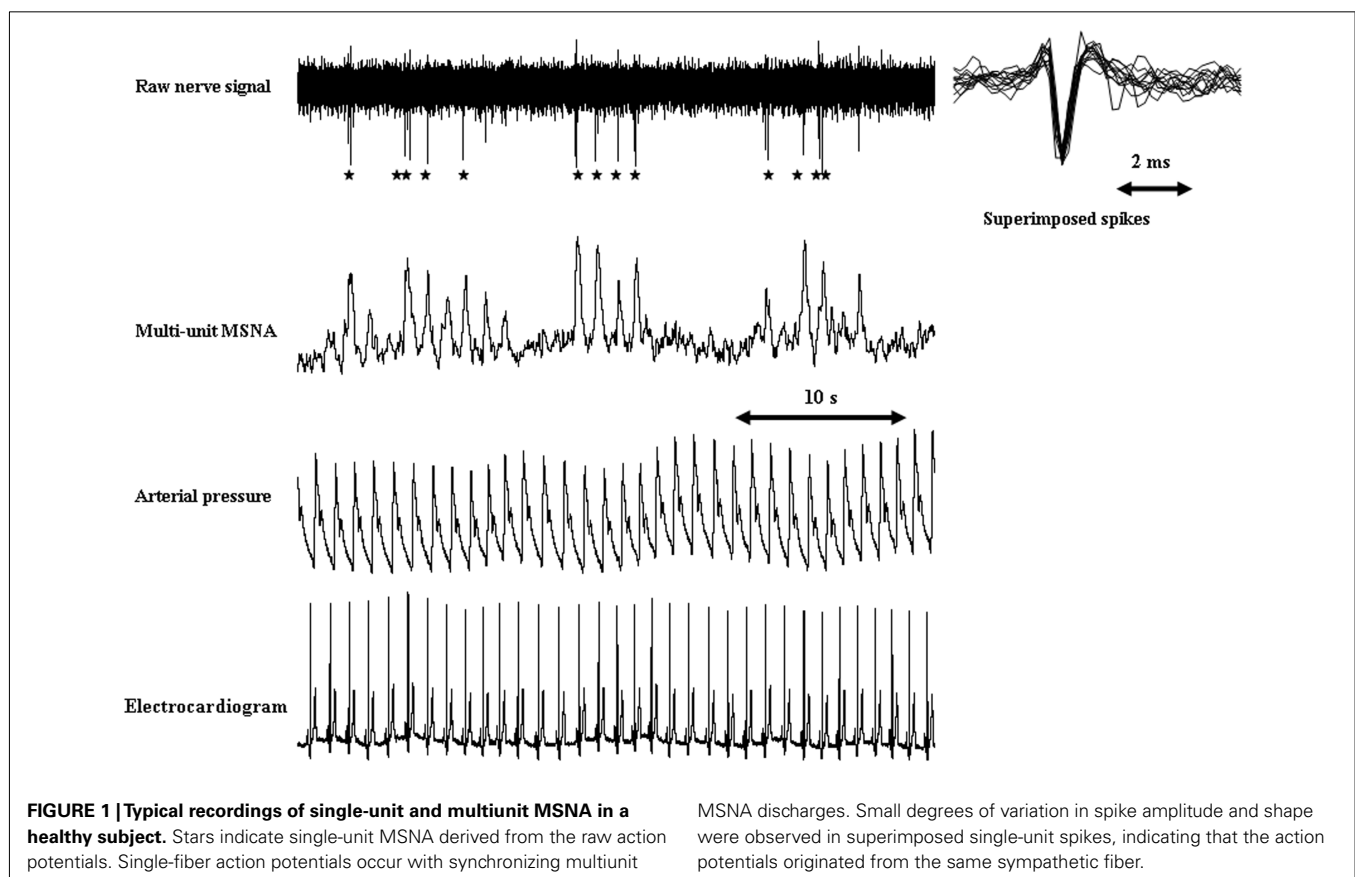
Traditionally, multiunit MSNA is quantified by counting the number of bursts during a specified period of time and 100 heart beats (Sundlof and Wallin, 1977). As multiunit MSNA is mostly regulated by arterial baroreceptors, burst occurrence is synchronized with the cardiac interval (**Figure 1**). Pulse synchronous bursts are a specific feature of MSNA, which is different from skin sympathetic nerve, sudomotor nerve, or motor nerve activity. However, under conditions of augmented sympathetic excitation, including HF, essential hypertension, or obstructive sleep apnea, the frequency of synchronized MSNA is near the maximum response level to sympathoexcitatory stimulation (i.e., 100 bursts per 100 heart beats). To break through this limitation, total MSNA and/or normalized

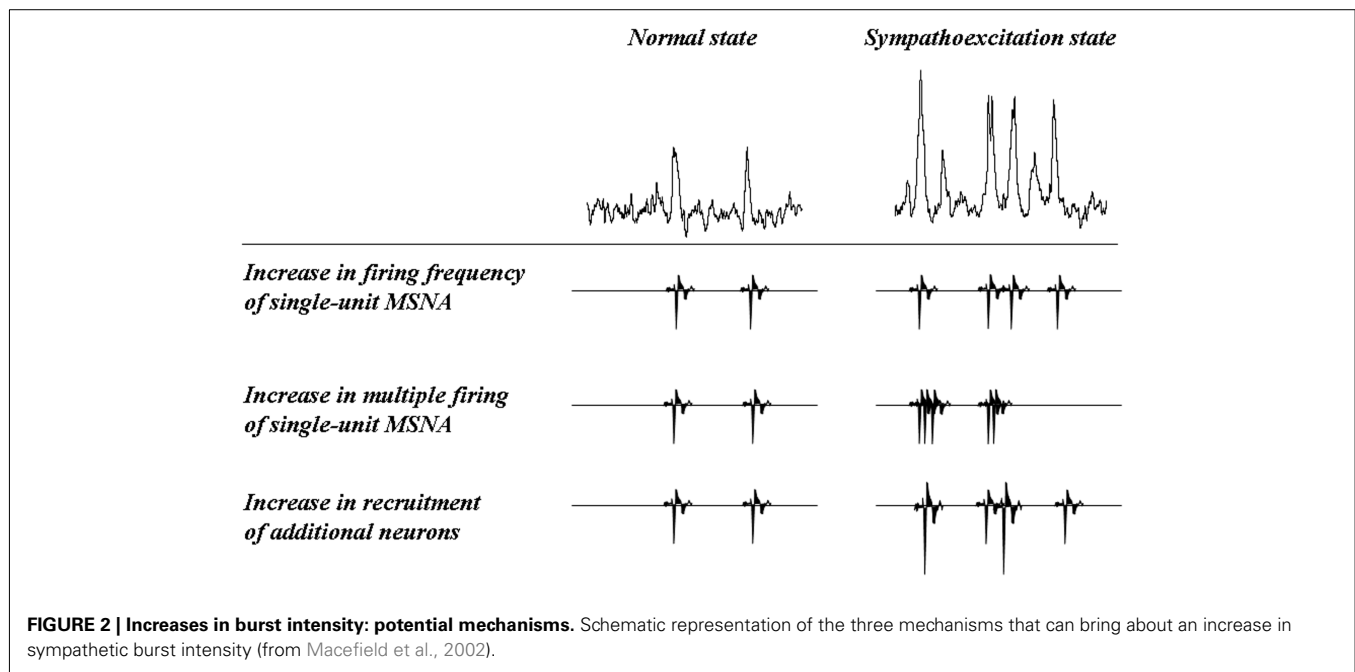
amplitude measurements have been utilized. Total MSNA is calculated as the product of the burst rate and the burst amplitude per minute, with all amplitudes normalized to the maximum amplitude (Sundlof and Wallin, 1977). The normalization process of absolute burst amplitudes has been shown to be a reproducible variable (Kimmerly et al., 2004). This approach assumes that the burst of greatest amplitude reflects maximal recruitment of active neurons for that particular recording site. However, this approach cannot be used to compare subjects or to compare the same subject on different occasions, when the intervention changes the burst amplitude (i.e., shifts the distribution), because the normalization procedure will eliminate the change (Burke et al., 2011). In addition, total multiunit MSNA cannot distinguish between changes in sympathetic nerve firing due to the recruitment of additional single-unit vasoconstrictor neurons and that due to an increase in firing rate of already active single-unit fibers.

SINGLE-UNIT MSNA ANALYSIS IN HEALTHY HUMANS AND IN VARIOUS DISEASE STATES

Macefield et al. (1994) refined single-unit MSNA analysis. This technically demanding method requires adjustment of the tungsten electrode until a large unitary discharge can be observed in a raw nerve action potential signal to discriminate a single-unit action potential (Figure 1). However, the technique provides an estimate of single-unit firing properties in relation to the number of active firings and/or the recruitment of fibers from central or reflex effects. Using this technique, additional measurements

can be obtained with regard to the mean firing frequency, the firing probability (the percentage of cardiac intervals in which a unit fires), and the percentage of spikes a unit generates per cardiac interval. Single-unit MSNA describes three possible scenarios to explain an increase in sympathetic outflow: (1) an increase in overall mean spike firing frequency without an increase in the rate of multiple firings per cardiac interval; (2) an increase in the firing frequency by multiple spike firing within one cardiac interval; and (3) the recruitment of additional neurons (Macefield et al., 2002; Figure 2). Macefield et al. (1999) demonstrated that single-unit MSNA tends to fire only once per cardiac interval even under conditions associated with elevated sympathetic nerve activity such as HF, suggesting that single-unit MSNA has the capacity to increase multiple spike firing within one cardiac interval in a state of intense sympathoexcitation. We demonstrated that single-unit MSNA can also be recorded during periods of physiological stress [e.g., handgrip (HG) exercise and the Valsalva maneuver] and that reflex sympathoexcitation could be attributed to changes in the frequency of single-unit spike firing within each multiunit sympathetic burst in healthy subjects. In particular, the firing of multiple spikes within one cardiac interval was significantly augmented during the Valsalva maneuver (Murai et al., 2006). The firing of these instantaneous multiple spikes is thought to influence strong effector organ responses. In fact, acute irregular and rapid nerve stimulation has been shown to evoke a greater effector organ response than regular stimulation through increased norepinephrine release in anesthetized rats (Dibona and Sawin, 1999).





Lambert et al. (2011) reported that the incidence of multiple firing was positively correlated to cardiac norepinephrine spillover in humans. These results suggest that an instantaneous increase in the frequency of single-unit firing during one cardiac interval provides additional and accurate information on efferent sympathetic firing, which cannot be determined by multiunit MSNA analysis. The multiple firing frequency of single-unit MSNA may be related to disease progression. Recent research has shown that a resting high firing frequency or incidence (percentage) of multiple spikes is related to cardiovascular risk factors, including hypertension (Lambert et al., 2008), type 2 diabetes mellitus (Huggett et al., 2005), obstructive sleep apnea (Elam et al., 2002), panic disorder (Lambert et al., 2006), myocardial infarction (Graham et al., 2004), and congestive HF (CHF; Macefield et al., 1999; Murai et al., 2009).

ASSESSMENT OF MUSCLE SYMPATHETIC NERVE ACTIVITY DURING EXERCISE

ROLE OF SYMPATHOEXCITATION DURING EXERCISE

At low levels of exercise, cardiac output is increased by the withdrawal of parasympathetic nerve activity, contributing to an increase in heart rate. However, the reflex response of parasympathetic withdrawal to low levels of exercise cannot meet the demand for rapid delivery of oxygen to exercising skeletal muscle during intense exercise. Exercise-induced sympathetic activity plays a key role in the redistribution of cardiac output toward active skeletal muscle (Mitchell, 2012). The reflex response of sympathetic nerve activity to exercise is evoked by central command, mechanical deformation of afferent receptive fields (muscle mechanoreflex), and metabolic byproducts during contraction (muscle metaboreflex) in thin fiber muscle afferents (Kaufman and Hayes, 2002; Williamson et al., 2006; Mitchell, 2012).

In healthy subjects, the sympathetic nervous system effectively adjusts to intense exercise at the cardiac and peripheral levels to meet the metabolic demands of exercising muscle. However, in HF

patients, heart rate and sympathetic nerve activity are already augmented at rest. The failing heart is left with limited inotropic and chronotropic reserves to respond to the demands for increased cardiac output. In a microneurographic study, Notarius et al. (1999) reported that the resting level of multiunit MSNA was negatively correlated with the peak VO_2 in HF, suggesting that sympathetic nerve activity in HF contributes to exercise intolerance as well as a poor prognosis. In fact, during exercise in HF, augmented sympathoexcitation and sympathetically mediated excess peripheral vasoconstriction were observed (Zelis et al., 1974; Lejemtel et al., 1986; Middlekauff et al., 2000; Momen et al., 2004). These factors are thought to contribute to a reduced exercise capacity in HF (Piepoli et al., 1996; Crisafulli et al., 2007).

MULTIUNIT AND SINGLE-UNIT MSNA RESPONSE DURING STATIC EXERCISE IN HF

Since the development of microneurography, the increased response of multiunit MSNA was considered to indicate elevated central sympathetic nerve activity to the peripheral vascular bed. Augmented response of multiunit MSNA to handgrip exercise and its mechanism were reported previously in healthy human subjects (Mark et al., 1985). However, there was controversy with regard to the differences in reflex response of multiunit MSNA to HG exercise between HF patients and age-matched healthy controls.

Notarius et al. (2001) reported the response of multiunit MSNA to HG exercise in chronic HF (EF = 19%). They examined the multiunit burst frequency during 2 min of 30% isometric HG and post-HG ischemia in 14 chronic HF patients compared to 10 healthy subjects, and found an augmented response of MSNA, expressed as burst frequency and incidence, to HG exercise in chronic HF.

Sterns et al. (1991) compared the response of multiunit MSNA between nine chronic HF (EF <20%) patients and eight healthy subjects. They demonstrated that the percent change in total

MSNA expressed as the multiunit MSNA frequency multiplied by the burst amplitude during 2 min of 30% HG exercise tended to be decreased in chronic HF patients compared to healthy subjects. In addition, they found significant blunting during post-HG ischemia, indicating that muscle metaboreceptor responses were blunted in chronic HF.

In addition, Negrao et al. (2001) examined multiunit MSNA frequencies using the same method and performed a comparison between 24 severe HF patients (EF = 29%), 24 mild HF patients (EF = 35.6%), and 10 healthy controls. Their results indicated that the response of multiunit MSNA did not differ between the three groups.

It is likely that the responses of multiunit MSNA are dependent on disease severity, race, sex, and intensity of exercise. However, these controversial results may be attributable to the limitations of multiunit MSNA. In CHF, the level of multiunit MSNA is nearly maximal at rest, so the frequency of pulse synchronized MSNA cannot increase further. That is, burst incidence cannot increase above 100 bursts/100 heartbeats because of pulse synchrony.

Thus, single-unit MSNA analysis is useful for determining actual sympathetic neural firing within one cardiac interval. In HF at rest, despite the elevated level of multiunit MSNA, the incidence of multiple firing of single-unit sympathetic spikes was not different, but the firing frequency of single-unit MSNA was significantly increased compared to healthy subjects (Macefield et al., 1999). However, we recently demonstrated that the percentage of multiple single-unit spikes within one cardiac interval was increased during HG exercise in chronic HF patients compared to healthy subjects, although the response of multiunit MSNA was not significantly different between the two groups (Murai et al., 2009; **Figure 3**). In particular, there was a decrease in the percentage of cardiac intervals that contained one spike (from 74 ± 2 to $61 \pm 2\%$, $P < 0.05$) and an increase in the proportion of cardiac intervals that had two and three spikes (from 20 ± 2 to $28 \pm 2\%$ and from 5 ± 1 to $10 \pm 1\%$, respectively, $P < 0.05$) between baseline and HG exercise in CHF patients (**Figure 4**). These results suggest that single-unit MSNA responses contributed

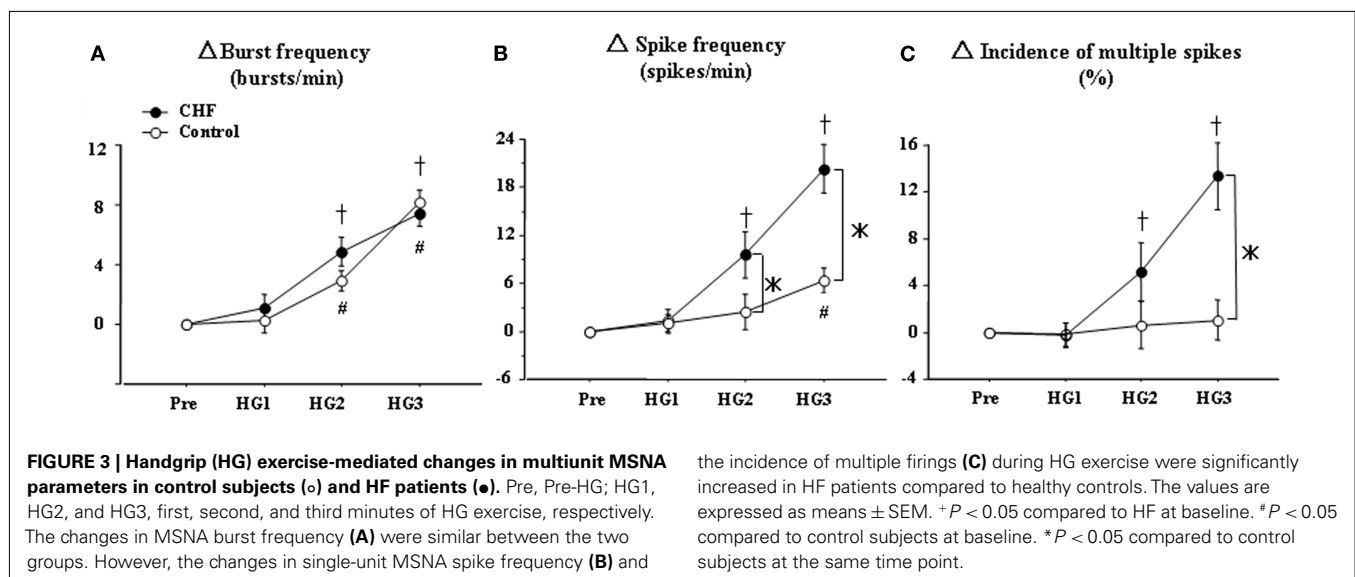
to the exaggerated sympathoexcitation measured during exercise in chronic HF patients. The instantaneous firing frequency within one cardiac interval may increase peripheral vascular tone, contributing to exercise intolerance.

ASSESSMENT OF MUSCLE SYMPATHETIC NERVE ACTIVITY DURING IRREGULAR VENTRICULAR RESPONSES IN HF LIMITATIONS OF MULTIUNIT MSNA IN ARRHYTHMIA

Arrhythmia is a common complication of chronic HF caused by arrhythmogenic substrates (Braunwald, 1997). Several studies indicated that a large multiunit MSNA burst occurred during premature ventricular contraction (PVC; Ando et al., 1997; Grassi et al., 2002) and atrial fibrillation (AF; Grassi et al., 2003; Wassmund et al., 2003) in HF patients. The low diastolic pressure induced by these arrhythmic conditions unloads arterial baroreceptors and evokes a larger and longer multiunit MSNA burst (Welch et al., 1989; Smith et al., 1995). However, only counting multiunit MSNA could cause the actual level of sympathetic nerve activity to be underestimated, because a large sympathetic activity burst could produce prolonged sympathetic inhibition. In a human study, frequent PVC and AF were recognized as exclusion criteria for evaluating sympathetic outflow by multiunit MSNA analysis. As mentioned above, total activity and/or the normalized amplitude may be useful for interindividual comparisons, but the burst amplitude and area are markedly affected by the position of the tungsten microelectrode tip. Thus, multiunit data can be difficult to compare between groups.

RECORDING OF SINGLE-UNIT MSNA IN HF WITH PVC

The mechanism underlying augmentation of the SNA in HF has been assumed to involve a disorder of arterial baroreceptors. However, recent observations indicated that arterial baroreceptor function is preserved, maintaining appropriate blood pressure in HF (Floras, 2009). Elam and Macefield (2001) demonstrated the instantaneous augmentation of multiple single-unit firing following PVC in HF patients. They reported that PVC was associated with an increase in average firing probability from 61% [in sinus



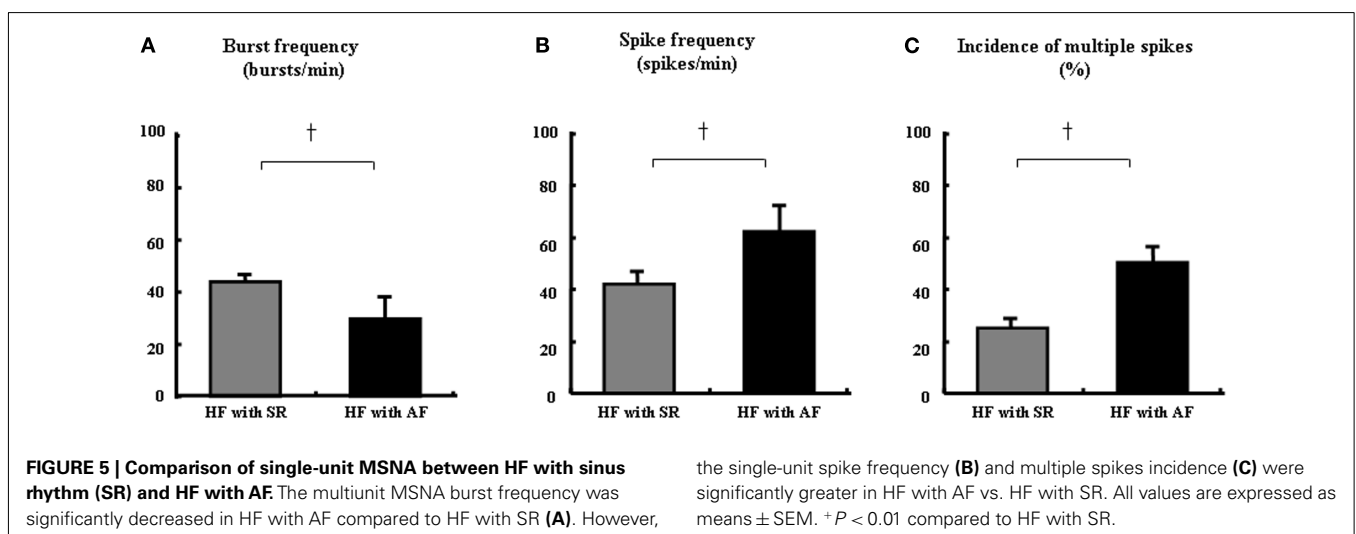
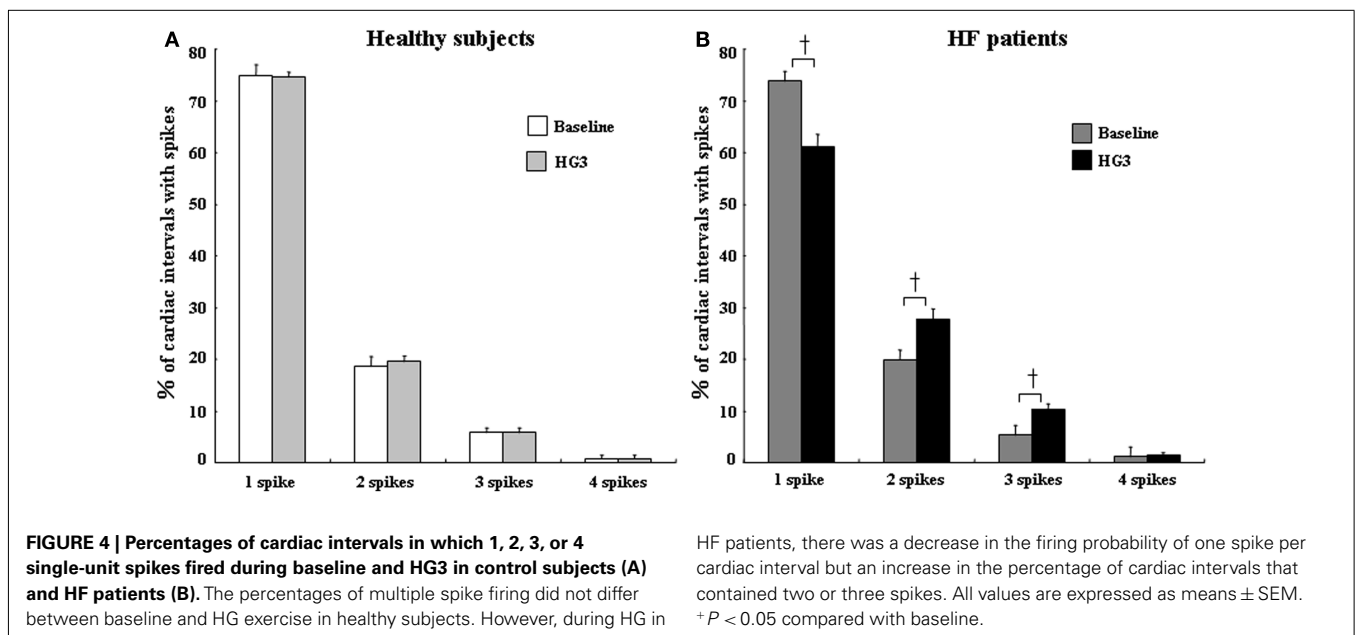
rhythm (SR)] to 80%, and that the firing pattern within one cardiac interval changed to more multiple firing spikes (from 38 to 61%). Frequent PVC is thought to induce moderate and severe left ventricular dysfunction (Baman et al., 2010). Elimination of PVC with catheter ablation has been reported to improve cardiac dysfunction (Taieb et al., 2007).

Cardiac norepinephrine spillover was reported to be related to multiple spike firing of single-unit MSNA within one cardiac interval (Lambert et al., 2011). Although the mechanisms of reduced left ventricular contraction induced by PVC remain unclear, multiple spike firing of single-unit MSNA is considered to cause the progression of heart dysfunction by instantaneous norepinephrine release to the heart.

RECORDING OF SINGLE-UNIT MSNA IN HF WITH AF

As mentioned above, the analysis of multiunit MSNA in AF is not without limitations in that a prolonged irregular ventricular

response would cause a large burst followed by prolonged sympathetic inhibition. The results of previous assessments of sympathetic nerve activity in acute paroxysmal AF patients using multiunit MSNA are controversial. Grassi et al. (2003) used multiunit MSNA to assess sympathetic nerve activity during AF and SR in patients with paroxysmal AF and observed a reduction in SNA during AF. In contrast, Wasmund et al. (2003) found significant augmentation of multiunit MSNA during AF, which was induced by right atrial pacing. Recently, we analyzed the single-unit MSNA frequency in HF patients with AF (Ikeda et al., 2012). Multiunit MSNA, expressed as burst frequency, in HF patients with AF was decreased compared to that in HF patients with SR. However, the single-unit MSNA in HF patients with AF was significantly greater than that in HF patients with SR (62 ± 9 vs. 42 ± 4 spikes/min, $P < 0.05$, Figures 5A,B). Moreover, the incidence of multiple firing of single-unit MSNA within one cardiac interval was augmented in HF + AF patients compared to HF + SR



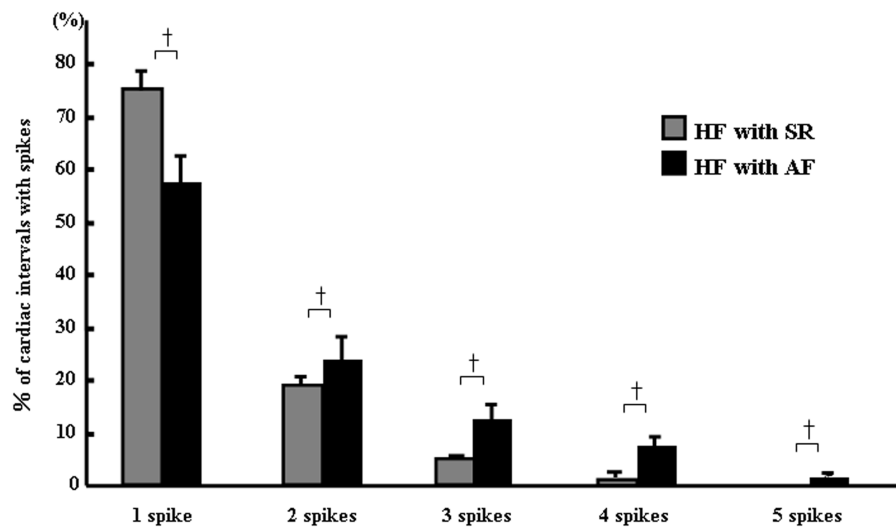


FIGURE 6 | Percentages of multiple spikes in HF with SR and AF. In HF with AF, the percentages of one to five spikes per cardiac interval were

significantly decreased for one spike and increased for two to five spikes. All values are expressed as means \pm SEM. $^*P < 0.05$ compared to HF with SR.

patients (48 ± 8 vs. $26 \pm 3\%$, $P < 0.01$, **Figure 5C**), and it shifted toward multiple firing spikes of single-unit MSNA in HF patients with AF (**Figure 6**). It has been suggested that not only does HF lead to a predisposition to AF, but AF may also facilitate and worsen the development of HF. The coexistence of these cardiac disorders produces a vicious cycle, which leads to advanced pump failure in HF patients (Ehrlich et al., 2002). The data obtained in that study suggest that the instantaneous augmentation of single-unit MSNA within one cardiac interval may be attributed to the progression of heart dysfunction in HF patients with AF.

CONCLUSION

Augmented sympathetic nerve activity plays an important role in dysfunction of the heart. However, modalities for the assessment of sympathetic nerve activity in humans are limited. Moreover, the underlying differences in central sympathetic neural firing

between diseases remain unclear. Compared to the traditional recording of multiunit MSNA, the assessment of central sympathetic nerve activity to the periphery with single-unit MSNA provides additional information regarding the underlying mechanisms of sympathetic firing in chronic HF patients. In particular, the firing spike frequency and multiple spike firing within one cardiac interval are thought to contribute to disease progression and exercise intolerance in chronic HF. Therefore, these advantages of evaluation for detailed sympathetic firing pattern could improve our understanding the pathology of increased sympathetic nerve activity in clinical situation and disease progression in HF.

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