

## Higher Sympathetic Nerve Activity During Ventricular (VVI) Than During Dual-Chamber (DDD) Pacing

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**Objectives.** We determined the short-term effects of single-chamber ventricular pacing and dual-chamber atrioventricular (AV) pacing on directly measured sympathetic nerve activity.

**Background.** Dual-chamber AV cardiac pacing results in greater cardiac output and lower systemic vascular resistance than does single-chamber ventricular pacing. However, it is unclear whether these hemodynamic advantages result in less sympathetic nervous system outflow.

**Methods.** In 13 patients with a dual-chamber pacemaker, we recorded the electrocardiogram, noninvasive arterial pressure (Finapres), respiration and muscle sympathetic nerve activity (microneurography) during 3 min of underlying basal heart rate and 3 min of ventricular and AV pacing at rates of 60 and 100 beats/min.

**Results.** Arterial pressure was lowest and muscle sympathetic nerve activity was highest at the underlying basal heart rate. Arterial pressure increased with cardiac pacing and was greater with AV than with ventricular pacing (change in mean blood pressure  $\pm$  SE:  $10 \pm 3$  vs.  $2 \pm 2$  mm Hg at 60 beats/min;  $21 \pm 5$

vs.  $14 \pm 2$  mm Hg at 100 beats/min;  $p < 0.05$ ). Sympathetic nerve activity decreased with cardiac pacing and the decline was greater with AV than with ventricular pacing (60 beats/min  $-40 \pm 11\%$  vs.  $-17 \pm 7\%$ ; 100 beats/min  $-60 \pm 9\%$  vs.  $-48 \pm 10\%$ ;  $p < 0.05$ ). Although most patients showed a strong inverse relation between arterial pressure and muscle sympathetic nerve activity, three patients with severe left ventricular dysfunction (ejection fraction  $\leq 30\%$ ) showed no relation between arterial pressure and sympathetic activity.

**Conclusions.** Short-term AV pacing results in lower sympathetic nerve activity and higher arterial pressure than does ventricular pacing, indicating that cardiac pacing mode may influence sympathetic outflow simply through arterial baroreflex mechanisms. We speculate that the greater incidence of adverse outcomes in patients treated with single-chamber ventricular rather than dual-chamber pacing may be due in part to increased sympathetic nervous outflow.

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Atrioventricular (AV) synchronous cardiac pacing has distinct hemodynamic advantages over fixed rate ventricular pacing. Dual-chamber AV (DDD) pacing yields a larger cardiac output (1-4) and a smaller systemic vascular resistance (5) than does single-chamber ventricular (VVI) pacing. Although short-term AV synchronous pacing may not differentially affect arterial pressure (3,6), long-term pacing in this mode results in a higher and more stable arterial pressure with fewer episodes of hypotension (7). It is unclear whether these hemodynamic advantages are translated into less sympathetic nervous system

outflow. Estimates of overall sympathetic nervous activity have shown both less (6) and equal (3,8) sympathetic outflow with AV synchronous pacing than with fixed rate ventricular pacing. However, these estimates of sympathetic activity were derived from plasma norepinephrine and cyclic adenosine monophosphate (AMP) concentrations, which are not solely determined by the rate of norepinephrine release (9,10). Establishing the degree of sympathoexcitation during AV and ventricular pacing is clinically relevant because of the known deleterious effects of long-term elevations in sympathetic activity (11,12). Atrial fibrillation is more likely to develop (13,14) and the mortality rate is higher (15-18) in patients treated with VVI pacing than in patients treated with DDD pacing; conceivably, the detrimental effects of single-chamber pacing are mediated in part by relatively higher levels of sympathetic activity. However, indirect measures of sympathetic nervous system activity have not documented any autonomic advantages of AV synchronous pacing.

The purpose of this study was to compare muscle sympathetic nervous activity measured directly from the peroneal nerve during short-term dual-chamber AV pacing and single-chamber ventricular pacing. Beat by beat muscle sympathetic nervous outflow to the vasculature is controlled primarily by

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**Abbreviations and Acronyms**

AV	=	atrioventricular
DDD	=	dual-chamber atrioventricular
ECG	=	electrocardiogram
VVI	=	single-chamber ventricular

arterial baroreflex responses to arterial pressure; increases in pressure result in baroreflex-mediated decreases in sympathetic outflow (19). We hypothesized that DDD pacing produces less sympathetic nerve activity as a result of greater arterial pressures than those associated with VVI pacing. To determine whether this effect is rate dependent, we compared sympathetic nerve responses during dual- and single-chamber pacing at both 60 and 100 beats/min.

**Methods**

**Study patients.** Thirteen male patients (mean age  $\pm$  SE  $62 \pm 3$  years) with a dual-chamber cardiac pacemaker participated in this study. Indications for permanent pacing included complete heart block in eight patients, sick sinus syndrome in four and carotid sinus hypersensitivity in one patient (Table 1). Four patients had New York Heart Association class III or IV congestive heart failure; no other patients had evidence of clinical congestive heart failure. Ejection fraction was determined previously by echocardiography in all patients (mean  $43 \pm 3\%$ ). The study protocol was approved by the Institutional Review Boards of the Hunter Holmes McGuire Department of Veterans Affairs Medical Center and the Medical College of Virginia. All patients gave verbal and written informed consent.

**Study measurements and protocol.** Surface electrocardiographic (ECG) lead II, continuous noninvasive arterial pres-

sure (Finapres Ohmeda 2300) and respiratory excursions (pneumbelt connected to a strain gauge transducer) were recorded throughout the study. Multiunit postganglionic muscle sympathetic nerve activity was measured with use of a tungsten microelectrode inserted into the right peroneal nerve near the fibular head, as previously described (20). The raw nerve signal was amplified, rectified and integrated before recording (Nerve Traffic Analyzer, Model 662c-3, University of Iowa Bioengineering). Recordings of muscle sympathetic nerve activity were confirmed by the relation of nervous activity to the cardiac cycle and to respiratory activity and by the increase in activity during Valsalva straining.

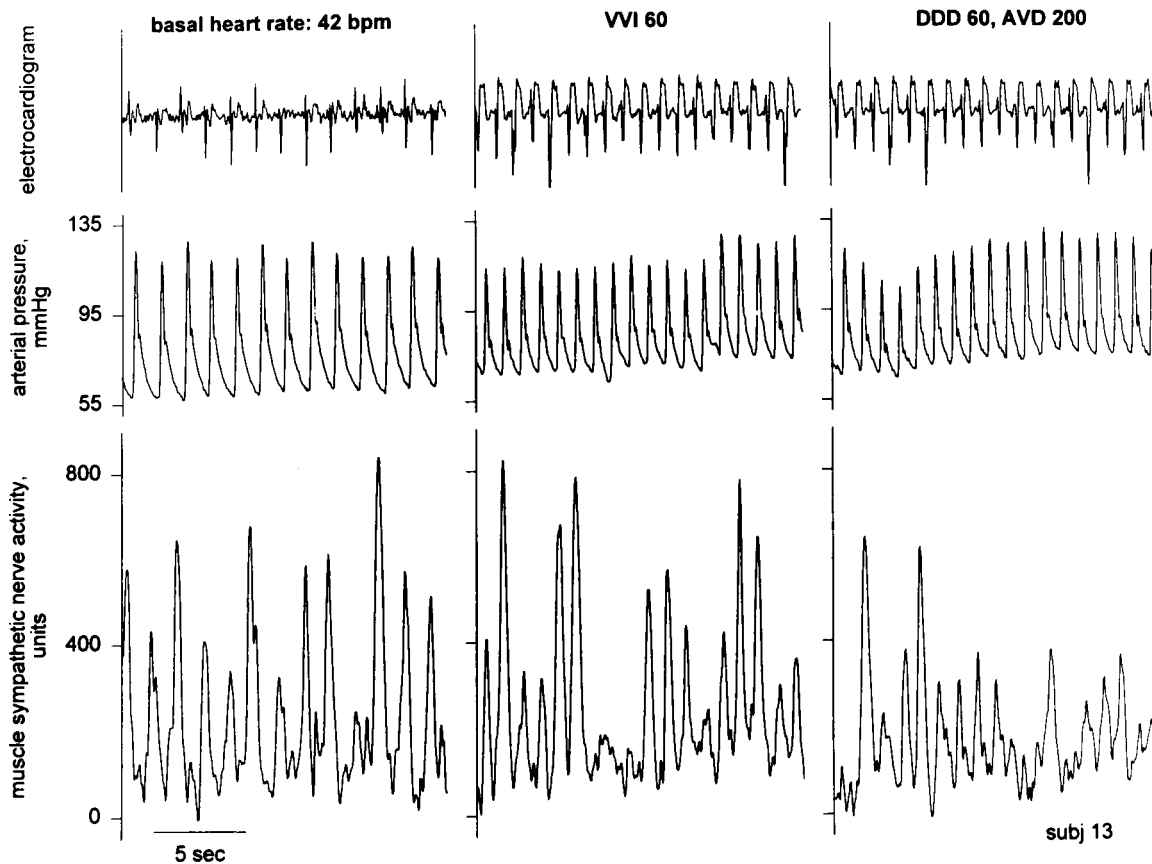
Patients were studied in the fasting state in the supine position. All cardioactive medications were withheld 24 h before the study. After the location of an adequate nerve recording, measurements were made during the last 3 of 5 min in each pacing mode. Initial measurements of sympathetic activity were made at the underlying basal heart rate ( $52 \pm 3$  beats/min) in 11 of 13 patients (7 patients had sinus rhythm, 3 had a junctional rhythm and 1 patient had atrial flutter; 2 patients with no underlying escape rhythm were not included in comparisons with basal heart rate). Subsequently, measurements were made with VVI pacing at rates of 60 and 100 beats/min and with DDD pacing at AV delays of 150, 200 and 250 ms and rates of 60 and 100 beats/min. In patients with AV node conduction, pacing was not performed at those AV delays that allowed nonpacemaker-dependent ventricular activation; therefore, not all patients underwent pacing at each delay in the DDD pacing mode.

**Data analysis and statistics.** The ECG, arterial pressure, respiration and muscle sympathetic nerve activity waveforms were recorded on FM tape and subsequently digitized at 250 samples/s for off-line analysis with signal-processing software (CODAS, Dataq Instruments). Average heart rate and average systolic and diastolic pressures were calculated from the beat

**Table 1.** Clinical Characteristics of the 13 Study Patients

Pt No.	Age (yr)/ Gender	Ejection Fraction (%)	Basal Heart Rate (beats/min)	Heart Disease	Pacing Indications
1	75/M	45	55	CAD, CABG	Complete heart block
2	70/M	55	59	CAD, HTD	Complete heart block
3	58/M	45	—	CAD	Complete heart block
4	61/M	50	40	CAD, AF	Sick sinus syndrome
5	75/M	35	58	CAD, NYHA III	Complete heart block
6	62/M	45	46	CAD	Complete heart block
7	58/M	45	41	CAD, AF	Sick sinus syndrome
8	54/M	65	58	None	Carotid sinus hypersensitivity
9*	53/M	28	—	DCM, NYHA III	Complete heart block
10*	80/M	25	52	DCM, NYHA IV	Complete heart block
11*	55/M	30	57	CAD, NYHA III	Sick sinus syndrome
12	53/M	48	58	CAD	Complete heart block
13	57/M	45	42	CAD, AF	Sick sinus syndrome

\*Data excluded from final analysis (see text). AF = atrial fibrillation; CABG = coronary artery bypass graft; CAD = coronary artery disease; DCM = dilated cardiomyopathy; HTD = hypertensive disease; M = male; NYHA III and NYHA IV = New York Heart Association functional class III and IV, respectively; Pt = patient.



**Figure 1.** Experimental record from one patient during basal heart rate, single-chamber (VVI) pacing at 60 beats/min and dual-chamber (DDD) pacing at 60 beats/min with an atrioventricular delay (AVD) of 200 ms.

to beat values. Nerve activity was quantified by custom-made programs designed to identify sympathetic bursts above baseline noise with the appropriate delay from the R wave of the ECG (~1.3 s [21]). Only bursts with a signal to noise ratio >3:1 were included for analysis of sympathetic activity. Burst amplitude was normalized by assigning a calibration value of 1,000 to the largest sympathetic burst during single-chamber ventricular pacing at 60 beats/min in each subject. This procedure allowed quantitation of sympathetic activity with units that could be compared among subjects. The area under each burst was measured and the average burst area was derived for each subject at each pacing condition. Total activity was calculated for each subject at each pacing condition both as a function of time (average burst area × bursts/min) and as a function of heart rate (average burst area × bursts/100 heartbeats). The results did not differ with either calculation; therefore, we present only total sympathetic nerve activity as a function of time.

We tested the hypothesis that changes of arterial pressure during pacing provoke inverse changes of sympathetic nerve activity. Therefore, we assessed the relation between systemic hemodynamic variables and sympathetic outflow in each patient by performing regression analyses between average systolic and diastolic pressures and muscle sympathetic nerve activity across all pacing modes. To make comparisons between pacing modes and rates, we used the optimal DDD pacing for each subject, defined as that AV delay with the

lowest sympathetic activity (60 beats/min: 150 ms, n = 3; 200 ms, n = 2; 250 ms, n = 5; 100 beats/min: <250 ms in 9 of 10 patients). To determine differences between 1) basal conditions and each pacing mode at each rate, and 2) basal conditions and each AV delay during DDD pacing, independent Student paired *t* tests were used with a Bonferroni adjustment to avoid a type I error. Two-way analyses of variance were used to determine the effects of mode and rate on arterial pressures and sympathetic activity. A *p* level of 0.05 was considered significant. All data are presented as mean value ± SE.

## Results

A representative tracing of the ECG, arterial pressure and sympathetic nerve activity from one subject at basal heart rate, ventricular pacing and AV pacing is shown in Figure 1. With the basal heart rate, arterial pressure was lowest ( $147 \pm 4$  and  $68 \pm 5$  mm Hg) and muscle sympathetic nerve activity was highest ( $5,105 \pm 805$  U/min, Table 2). Most patients had significant inverse relations between systolic or diastolic pres-

**Table 2.** Arterial Pressures and Muscle Sympathetic Nerve Activity During Intrinsic Rhythm and During Single- and Dual-Chamber Pacing

	Intrinsic Rhythm	VVI Pacing	DDD Pacing		
			AVD 150 ms	AVD 200 ms	AVD 250 ms
Systolic/Diastolic Arterial Pressure (mm Hg)					
Basal rate	147 ± 4/68 ± 5				
Pacing rate 60 beats/min		146 ± 5/73 ± 4*	159 ± 7/74 ± 4	163 ± 8*/73 ± 3*	157 ± 7/73 ± 2*
Pacing rate 100 beats/min		158 ± 6/83 ± 3*	170 ± 10*/85 ± 4*	173 ± 9*/87 ± 4*	174 ± 11*/86 ± 4*
Sympathetic Nerve Activity (U/min)					
Basal rate	5,105 ± 805				
Pacing rate 60 beats/min		4,390 ± 632	4,245 ± 723	3,006 ± 590*	2,961 ± 570*
Pacing rate 100 beats/min		2,914 ± 587*	2,316 ± 413*	2,383 ± 413*	2,396 ± 540*

\*p < 0.05 versus intrinsic rhythm. Data presented are mean value ± SE. AVD = atrioventricular delay; DDD = dual-chamber atrioventricular pacing; VVI = single-chamber ventricular pacing.

sure and muscle sympathetic nerve activity across the various modes of pacing (average  $r = 0.76$ ). However, three patients had no significant relation between any measure of arterial pressure and sympathetic activity (Fig. 2). These patients had severe congestive heart failure (ejection fraction  $\leq 30\%$ ) and consistently higher sympathetic activity than that of the remaining patients (average of all pacing conditions  $6,752 \pm 1,157$  vs.  $3,358 \pm 494$  U/min,  $p < 0.05$ ). Because severe congestive heart failure impairs arterial baroreflex function (22,23), and thus compromises the link between hemodynamic alterations and sympathetic outflow, the data of these patients were eliminated from all further analyses.

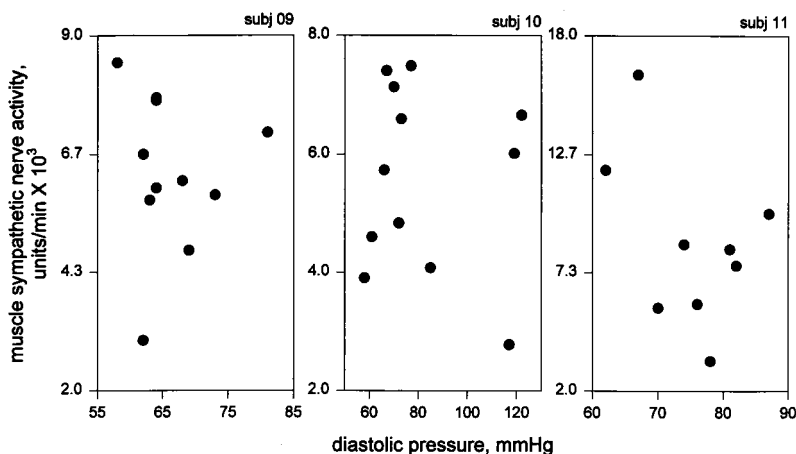
VVI pacing at 60 beats/min increased diastolic pressure above that during basal heart rate but had no significant effect on muscle sympathetic nerve activity (Table 2, Fig. 3). VVI pacing at 100 beats/min also increased diastolic pressure but, in contrast, reduced sympathetic nerve activity below that during basal heart rate by 48% on average. DDD pacing at 60 beats/min increased arterial pressures most at an AV delay of 200 ms (diastolic and systolic pressures  $p < 0.05$  vs. basal), whereas it decreased sympathetic activity at AV delays of both 200 and 250 ms. DDD pacing at 100 beats/min resulted in greater diastolic and systolic pressures than those measured

during the basal heart rate and in slightly higher arterial pressures with longer AV delays. However, sympathetic activity declined similarly at all AV delays and was on average less than half that recorded during the basal heart rate.

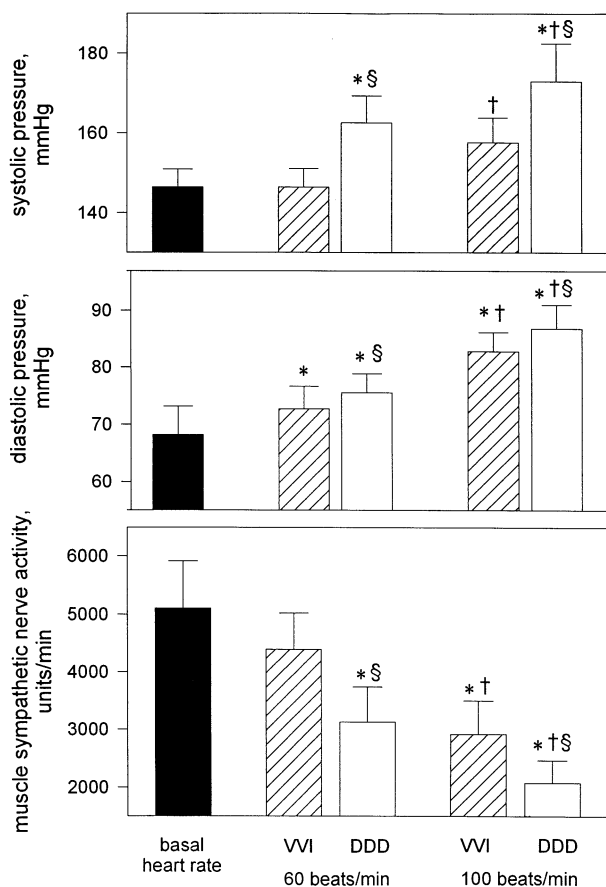
There were significant differences in arterial pressure and muscle sympathetic nerve activity in relation to pacing rate and pacing mode (Fig. 3). Arterial pressures were higher and muscle sympathetic nerve activity was lower during both VVI and DDD pacing at 100 than at 60 beats/min. Moreover, DDD pacing resulted in higher systolic and diastolic pressures and in lower sympathetic nerve activity than did VVI pacing at both pacing rates. There was no interaction between the effects of pacing rate and mode. These results indicate that the effects of both cardiac pacing rate and mode on sympathetic nerve activity were inversely related to their effects on arterial pressure.

## Discussion

Our results are the first to document an autonomic advantage of dual-chamber pacing, on the basis of direct measurements of sympathetic nervous outflow to the muscle vasculature. Several studies (1-3,5) have documented the



**Figure 2.** Muscle sympathetic nerve activity with each pacing mode in relation to diastolic blood pressure for the three patients with heart failure who showed no relation between arterial pressure and muscle sympathetic activity.



**Figure 3.** Average arterial pressures and sympathetic nerve activity during basal heart rate, ventricular (VVI) pacing and optimal dual-chamber (DDD) pacing at each rate in the 10 patients with inverse relations between arterial pressure and sympathetic nerve activity. \* $p < 0.05$  versus basal heart rate; † $p < 0.05$  versus same pacing mode at 60 beats/min; § $p < 0.05$  versus VVI at same pacing rate. Values are mean value  $\pm$  SE.

hemodynamic benefits of DDD versus VVI pacing, suggesting that DDD pacing may be the optimal pacing mode for most patients. AV synchrony increases cardiac output (1,3), which can lead to higher arterial pressures; increases in arterial pressure result in baroreflex-mediated decreases in sympathetic outflow. Our findings indicate an association between the hemodynamic benefits of dual-chamber pacing and the resultant greater arterial pressures and lower sympathetic activity.

VVI pacing generated lower arterial pressures and higher sympathetic activity than did DDD pacing. The lack of AV synchrony during VVI pacing may reduce average stroke volume and cardiac output (4), necessitating greater sympathetic vasomotor tone to maintain arterial pressure. Furthermore, ventricular pacing increases atrial natriuretic factor, possibly by increasing atrial stretch during retrograde conduction (24). Because of its potent vasodilator effects (25), increased atrial natriuretic factor may further reduce arterial pressure, resulting in even greater sympathetic nervous out-

flow. However, regardless of the mechanism, lower arterial pressure during VVI pacing would result in higher baroreflex-mediated sympathetic outflow.

Concerns about the long-term effects of VVI pacing have recently been raised on the basis of retrospective uncontrolled studies (13-18, 26-28) that suggest an increased risk of atrial fibrillation and higher mortality with ventricular pacing than with DDD pacing. Similarly, in the only prospective randomized study reported to date (29), atrial pacing was associated with a lower incidence of both atrial fibrillation and thromboembolic events when compared with VVI pacing. The present findings may provide further insight into the mechanism of the increased risk. For example, the deleterious effects of increased sympathetic activity in the presence of structural heart disease have been well documented (30). Thus, it is possible that in patients with a VVI pacemaker, increased sympathetic activity triggers lethal tachyarrhythmias leading to ventricular tachycardia and fibrillation, which may be responsible for the twofold greater mortality in these patients than in patients with a DDD pacemaker (14,27,28). Furthermore, greater sympathetic outflow with ventricular pacing may decrease the atrial refractory period, creating a milieu for increased atrial arrhythmogenesis (31).

A poor correlation between arterial pressure and muscle sympathetic nerve activity was observed in the three patients with marked congestive heart failure. This effect may be attributable to the markedly decreased arterial baroreflex sensitivity observed in patients with overt heart failure (22,23). Thus, cardiac pacing in patients with severe congestive heart failure may be ineffective in decreasing sympathetic outflow; however, our present data are insufficient to elucidate this issue.

**Study limitations.** Our study patients demonstrated heterogeneous pacing indications and varying severity and etiology of structural heart disease. Therefore, these results may not be indicative of responses in patients with particular disease states. Our measurements of sympathetic activity do not reflect the long-term effects of VVI and DDD pacing modes on sympathetic outflow, and we did not evaluate the effects of pacing mode on systemic hemodynamic variables other than arterial pressure. However, muscle sympathetic nerve activity is strongly correlated with plasma norepinephrine levels (32) and is tightly controlled by the arterial baroreflex (33). Thus, it is reasonable to conclude from these data that higher arterial pressures with cardiac pacing result in lower sympathetic activation.

**Conclusions.** DDD pacing resulted in greater declines in sympathetic activity than did VVI pacing. Decreased muscle sympathetic nerve activity was related directly to greater arterial pressure, implicating a baroreflex link between the hemodynamic effect and the autonomic consequence of cardiac pacing. These findings suggest that the DDD pacing mode may be safer and more physiologic than the VVI pacing mode by decreasing sympathetic outflow and thereby reducing the risk of adverse outcome.

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