The hemodynamic effects of ventricular pacing with and without atrioventricular synchrony in patients with normal and diminished left ventricular function

The relative hemodynamic effects of heart rate, inotropic state, and atrioventricular (AV) synchrony during ventricular pacing were evaluated in 10 patients with normal left ventricular ejection fraction (LVEF) (0.66 ± 0.07, mean S.D.) and in eight patients with a diminished LVEF (0.34 ± 0.18). Hemodynamics were measured at AV intervals of 130, 0, and −130 msec during ventricular pacing at a baseline rate that was 10 pulses/min greater than the resting heart rate, at 130 pulses/min alone, and at 130 pulses/min during continuous intravenous infusion of dobutamine. During baseline ventricular pacing and during ventricular pacing at 130 pulses/min with and without dobutamine, both groups of patients had a significant decrease in cardiac index, stroke volume index, and stroke work index when the AV pacing interval was decreased from 130 to 0 msec. The observed decrease in these three hemodynamic variables was similar when patients with diminished LVEF were compared to patients with normal LVEF. No further significant decrease in cardiac index, stroke volume index, and stroke work index occurred in either group when the AV interval was changed from 0 to −130 msec during baseline ventricular pacing or during ventricular pacing at 130 with and without dobutamine. Beneficial hemodynamic effects occur during ventricular pacing when AV synchrony is maintained at resting heart rates and during increases in heart rate and inotropic state in patients with normal and diminished LVEF. (Am Heart J 1987;114:746.)

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The hemodynamic effects of atrioventricular (AV) synchrony during ventricular pacing at rest and during exercise have been controversial.[1,2] Previous studies[3-5] have demonstrated that appropriately timed atrial contraction is important in maximizing cardiac output at rest in animals and in humans without structural heart disease. However, evaluation of cardiac performance during exercise has provided unclear results.[6-9] This may be due to several inherent limitations encountered in the evaluation of hemodynamic response to ventricular pacing during exercise. The hemodynamic response to ventricular pacing may differ depending on whether atrial contractions are absent, are dissociated from ventricular activity, or are coupled to ventricular depolarizations by constant retrograde conduction.[6] Assessment of the hemodynamic effects of AV synchrony during exercise is limited by the difficulty of separating effects of atrial contraction from changes in ventricular rate and increases in myocardial contractility. Repeated measurements of cardiac performance during a single period of prolonged exercise or during serial exercise periods may be affected by several confounding influences including conditioning effects, peripheral muscle and vasomotor tone, and respiratory rate.[10-12]

Quantitative assessment of the hemodynamic effects of varying AV relationships in humans during exercise has not been previously described. Whether the hemodynamic consequences of AV synchrony may differ when patients with normal left ventricular function are compared to patients with abnormal left ventricular function during increases in heart rate and inotropic state has not been determined. This study was therefore designed to

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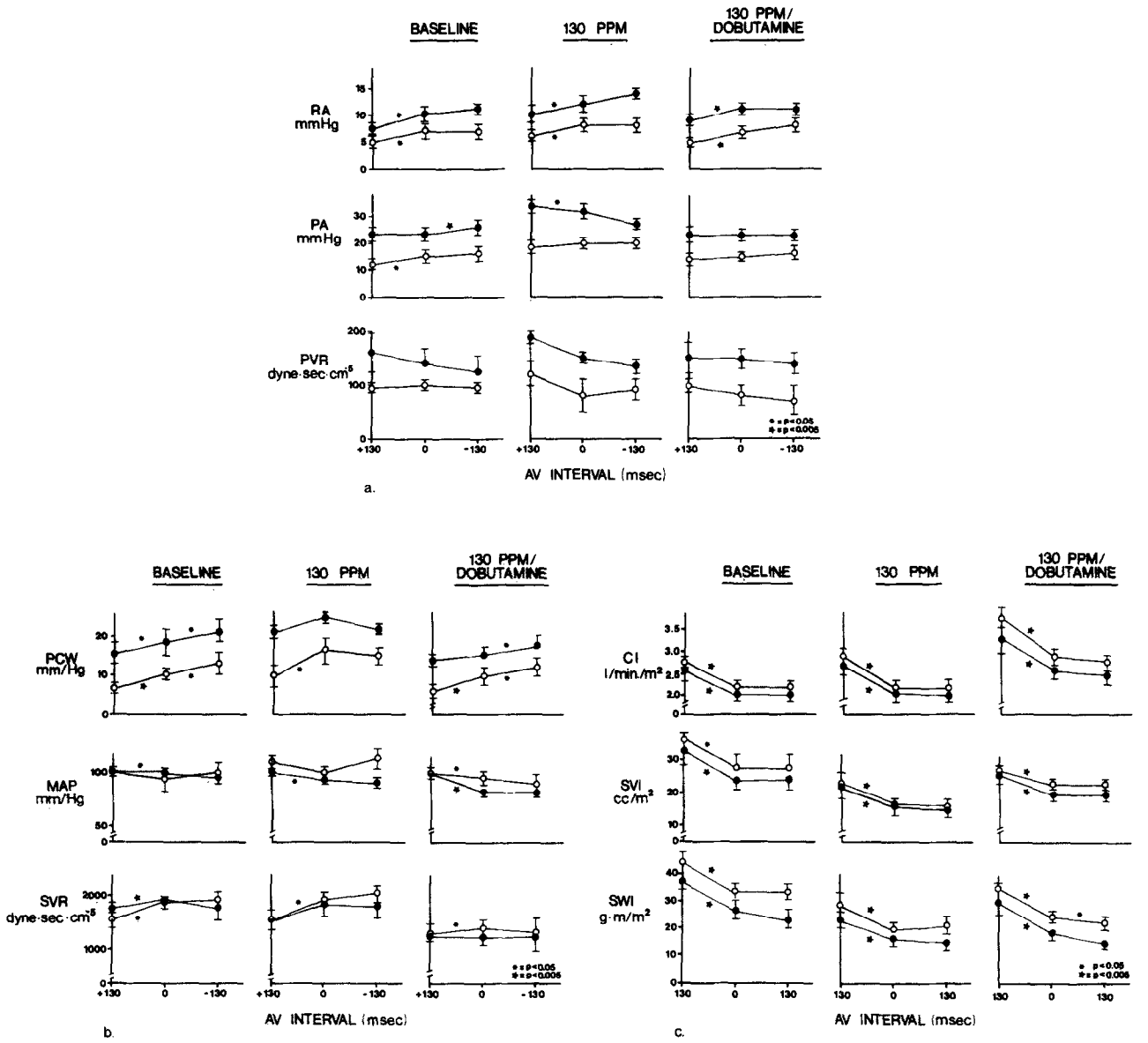

Fig. 1. Comparison of hemodynamic responses to atrioventricular *(AV)* pacing at intervals of +130 msec, 0 msec, and −130 msec during baseline ventricular pacing *(BASELINE)*, ventricular pacing at 130 pulses/min *(130 PPM)*, and ventricular pacing at 130 pulses/min during continuous intravenous infusion of dobutamine *(130 PPM/DOBUTAMINE)*. *a*, Mean right atrial *(RA)* pressure, mean pulmonary artery *(PA)* pressure, and pulmonary vascular resistance *(PVR)*. *b*, Mean pulmonary capillary wedge pressure *(PCW)*, mean arterial pressure *(MAP)*, and systemic vascular resistance *(SVR)*. *c*, Cardiac index *(CI)*, stroke volume index *(SVI)*, and stroke work index *(SWI)*. Values plotted are mean ± S.E.M. ○ = normal left ventricular ejection fraction; ● = decreased left ventricular ejection fraction. Consistently significant decreases in cardiac index, stroke volume index, and stroke work index occur when the atrioventricular pacing interval is decreased from 130 msec to 0 msec.

quantify the hemodynamic effects of varying AV relationships during ventricular pacing at rest in patients with normal and diminished left ventricular function, and to determine the importance of AV synchrony during an increase in heart rate alone when compared to a simultaneous increase in heart rate and inotropic state. Dobutamine, a synthetic catecholamine and potent beta-1 agonist,[13] was chosen in order to avoid the confounding influences imposed upon the repeated measurement of ventricular performance during prolonged or repeated exercise. While dobutamine was not intended to be a substitute for exercise itself, it provided a means of maintaining a steady state of increased inotrophy

Table I. Comparison of the hemodynamic effects of ventricular pacing with and without atrioventricular synchrony in patients with normal and diminished left ventricular function

	Baseline (RHR + 10 ppm)			*130 ppm*		
	AV 130	*AV 0*	*AV −130*	*AV 130*	*AV 0*	*AV −130*
RAP						
I	5 ± 1	7 ± 1*	7 ± 1	6 ± 1	8 ± 1*	8 ± 1
II	8 ± 1	10 ± 1*	11 ± 1	10 ± 1	12 ± 1*	14 ± 1
PAP						
I	12 ± 1	15 ± 1*	16 ± 2	19 ± 2	20 ± 2	20 ± 2
II	24 ± 3	24 ± 3	26 ± 4§	32 ± 1	31 ± 2*	27 ± 1
PRV						
I	90 ± 5	100 ± 10	93 ± 10‡	120 ± 20	80 ± 30	90 ± 20
II	160 ± 35	140 ± 30	125 ± 30	190 ± 10	150 ± 10	130 ± 10
PCWP						
I	6 ± 1	10 ± 1†	12 ± 2	10 ± 2	16 ± 3*	15 ± 2
II	15 ± 3	18 ± 3*	21 ± 3‡	21 ± 1	24 ± 1	22 ± 1
MAP						
I	100 ± 3	98 ± 5	100 ± 6	110 ± 4	100 ± 4	107 ± 5
II	100 ± 4	95 ± 4*	90 ± 6	100 ± 6	95 ± 5*	92 ± 5
SVR						
I	1530 ± 90	1850 ± 130*	1920 ± 190	1500 ± 150	1930 ± 130*	2050 ± 170
II	1660 ± 120	1870 ± 150*	1750 ± 200	1550 ± 160	1810 ± 200	1800 ± 120
CI						
I	2.7 ± 0.1	2.2 ± 0.1†	2.2 ± 0.1	2.9 ± 0.2	2.2 ± 0.1†	2.2 ± 0.2
II	2.6 ± 0.2	2.0 ± 0.2†	2.0 ± 0.2	2.7 ± 0.2	2.1 ± 0.3†	2.0 ± 0.2
SVI						
I	34 ± 1	28 ± 2*	28 ± 3	23 ± 3	17 ± 2†	17 ± 2
II	31 ± 2	24 ± 3†	24 ± 3	21 ± 2	16 ± 2†	15 ± 2
SWI						
I	43 ± 3	34 ± 3*	34 ± 3	29 ± 5	20 ± 3†	21 ± 3
II	37 ± 2	26 ± 4†	24 ± 4	23 ± 3	16 ± 2†	15 ± 2

AV = atrioventricular pacing interval (msec); CI = cardiac index (L/min/m²); MAP = mean arterial pressure (mm Hg); PAP = pulmonary artery pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); ppm = pulses per minute; PVR = pulmonary vascular resistence (dyne · sec · cm⁻⁵); RAP = right atrial pressure (mm Hg); RHR = resting heart rate; SVI = stroke volume index (ml/beat/m²); SVR = systemic vascular resistence (dyne · sec · cm⁻⁵); SWI = stroke work index (g · m/m²); I = patient groups with normal left ventricular ejection fraction; II = patient group with decreased left ventricular ejection fraction.

* = $p < 0.05$, AV 0 vs AV 130.

† = $p < 0.005$, AV 0 vs AV 130.

‡ = $p < 0.05$ AV −130 vs AV 0.

§ = $p < 0.005$, AV −130 vs AV 0.

during which the effects of pacing interventions could be assessed.

METHODS

Approval for this physiologic pacing protocol was obtained from the Institutional Review Board at the University of Michigan Medical Center. Informed consent was obtained from each patient before participation in this study. Eighteen patients (12 men and 6 women) with an age range of 34 to 82 years were recruited from among patients undergoing a diagnostic cardiac electrophysiologic study for syncope. Ejection fraction was determined by radionuclide or iodine contrast ventriculography. Ten patients had a normal left ventricular ejection fraction (LVEF) (0.66 ± 0.07, mean ± S.D.). Eight patients had stable chronic congestive heart failure with a moderately depressed LVEF (0.34 ± 0.18) and were in New York Heart Association class III. Of these eight patients, six had ischemic cardiomyopathy and two had an idiopathic dilated cardiomyopathy. No patient had myocardial ischemia during exercise treadmill testing or obstructive or regurgitant valvular disease. No patient was receiving beta-blocking agents or calcium channel antagonists at the time of this study.

All studies were performed in the cardiac electrophysiology laboratory. All patients were in sinus rhythm. A No. 6F quadripolar electrode catheter was inserted percutaneously into a femoral vein and was positioned in the high lateral right atrium. A second electrode catheter was positioned in the right ventricular apex. All pacing was performed with a standard external dual-chamber pulse generator (Model 5330, Medtronic Inc., Minneapolis, Minn.) at a current intensity of twice diastolic threshold. To perform ventriculoatrial sequential pacing, insertion of the atrial and ventricular electrode catheters into the atrial and ventricular poles of the pulse generator was

130 ppm/Dobutamine		
AV 130	*AV 0*	*AV −130*
5 ± 1	7 ± 1†	8 ± 1
9 ± 1	24 ± 2*	11 ± 1
14 ± 2	15 ± 1	16 ± 2
24 ± 3	24 ± 2	24 ± 2
100 ± 10	80 ± 20	70 ± 30
150 ± 30	150 ± 20	140 ± 20
6 ± 2	10 ± 2†	12 ± 2‡
13 ± 1	15 ± 1	16 ± 3‡
100 ± 2	95 ± 6*	90 ± 8
100 ± 6	85 ± 6†	85 ± 6
1220 ± 280	1360 ± 210*	1250 ± 250
1290 ± 160	1250 ± 130	1300 ± 180
3.6 ± 0.2	2.9 ± 0.2†	2.8 ± 0.2
3.3 ± 0.2	2.6 ± 0.2†	2.5 ± 0.0
27 ± 1	22 ± 1†	22 ± 1
25 ± 2	20 ± 1†	20 ± 1
35 ± 2	25 ± 2†	22 ± 2‡
30 ± 3	19 ± 2†	18 ± 2

reversed. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were measured with a balloon flotation triple-lumen catheter. Cardiac output was determined in triplicate by the thermodilution technique.[14] A No. 5F cannula was placed into a femoral artery for continuous monitoring of the arterial pressure. Continuous pressure and ECG recordings were made with Electronics for Medicine recording equipment (Electronics for Medicine/Honeywell Inc., Pleasantville, N.Y.) at a paper speed of 25 to 50 mm/sec.

Ventricular pacing was performed initially at 10 pulses/min greater than the resting heart rate (baseline pacing rate) with atrioventricular pacing intervals of +130 msec, 0 msec, and −130 msec. Pacing was performed at each interval until stable hemodynamics were obtained and recorded. Hemodynamics were initially determined 5 minutes after each pacing intervention and were considered stable if the average of the determinations of cardiac output, made before and after measurement of all other hemodynamic variables, differed by less than 10%. Pacing was then repeated in a similar manner at 130 pulses/min with AV intervals of +130 msec, 0 msec, and −130 msec, and hemodynamic measurements were repeated. After obtaining these measurements, dobutamine was infused at a rate of 2 μg/kg/min and was increased in a stepwise fashion until stable hemodynamics and a sinus rate of 115 to 120 bpm or 10 μg/kg/min was reached. Pacing was then repeated at 130 pulses/min with AV intervals of +130 msec and −130 msec, and hemodynamic measurements were repeated. Derived hemodynamic indices were calculated by means of standard equations.[15]

The hemodynamic data were analyzed by paired and unpaired *t* tests where appropriate. When significant variation from the mean existed for variables being compared between groups, these variables were reanalyzed with the Behrens-Fisher test.

RESULTS (TABLE I)

Hemodynamic measurements during baseline ventricular pacing (Fig. 1, BASELINE). Initial hemodynamic measurements were made at a baseline ventricular pacing rate that was 10 pulses/min greater than the resting heart rate. The baseline ventricular pacing rate was similar in patients with a normal LVEF when compared to the pacing rate used in patients with a diminished LVEF (78 ± 8 vs 85 ± 12 pulses/min, mean ± S.D., N.S.). Comparing initial hemodynamic measurements during pacing with an AV interval of 130 msec, both groups had a similar cardiac index (2.7 ± 0.4 vs 2.6 ± 0.7 L/min/m^2, N.S.), but patients with a diminished LVEF had a significantly higher mean pulmonary capillary wedge pressure (6 ± 2 vs 15 ± 7 mm Hg, $p < 0.001$).

When the AV interval was changed from 130 to 0 msec, a significant decrease occurred in cardiac index, stroke volume index, and stroke work index in both patient groups. The observed decrease in these three hemodynamic variables was similar when the two patient groups were compared. Mean right atrial pressure, pulmonary capillary wedge pressure, and systemic vascular resistance increased significantly. Mean pulmonary artery pressure increased significantly in the patient group with normal LVEF, while a significant decrease in mean arterial pressure was observed only in the patient group with diminished left ventricular function.

When the AV interval was changed from 0 to −130 msec, a further significant increase in pulmonary artery pressure and pulmonary capillary wedge pressure was observed in the patients with diminished left ventricular function. No other significant hemodynamic changes occurred.

Hemodynamic measurements during ventricular pacing at 130 pulses/min (Fig. 1, 130 PPM). When the AV interval was changed from 130 to 0 msec, significant decreases in cardiac index, stroke volume index, and stroke work index occurred in both patient groups. The observed decrease in these three hemodynamic

variables was similar when the two patient groups were compared. Mean right atrial pressure increased significantly. Mean pulmonary artery pressure decreased minimally, and pulmonary capillary wedge pressure and systemic vascular resistance increased significantly only in the patient group with normal left ventricular function. Mean arterial pressure decreased significantly only in the patient group with diminished left ventricular function. When the AV interval was changed from 0 to −130 msec, no significant hemodynamic changes occurred.

Hemodynamic measurements during ventricular pacing at 130 pulses/min with dobutamine (Fig. 1, 130 PPM/DOBUTAMINE). The mean dose of dobutamine administered to each group was similar (9.3 ± 1.5 vs 9.2 ± 1.7 μg/kg/min, N.S.). In order to assure that an increase in inotropic state occurred during dobutamine infusion, the cardiac index obtained with an AV interval of 130 msec during ventricular pacing at 130 pulses/min with dobutamine was compared to the cardiac index obtained with the same AV interval during ventricular pacing at 130 pulses/min alone. During infusion of dobutamine, cardiac index increased significantly in patients with normal left ventricular function (3.6 ± 0.6 vs 2.7 ± 0.4 L/min/m^2, mean ± S.D., $p < 0.002$) and in patients with diminished left ventricular function (3.3 ± 0.8 vs 2.6 ± 0.6 L/min/m^2, $p < 0.03$).

When the AV interval was changed from 130 to 0 msec, significant decreases in cardiac index, stroke volume index, and stroke work index occurred in both patient groups. The observed decrease in these three hemodynamic variables was similar when the two patient groups were compared. Mean right atrial pressure and mean arterial pressure decreased significantly. Mean pulmonary capillary wedge pressure and systemic vascular resistance decreased significantly only in the patient group with normal left ventricular function.

When the AV interval was changed from 0 to −130 msec, a statistically significant but minimal increase in mean pulmonary capillary wedge pressure was observed in the latter patient group. No other significant hemodynamic changes occurred.

DISCUSSION

The mean cardiac index of the patients with normal LVEFs was at the lower limit of normal and may have been due to the overnight fasting required before participation in this study. The eight patients with diminished LVEFs in this study were in New York Heart Association class III. As a group, their hemodynamic indices represented the findings of a dilated, failing ventricle having moderately diminished left ventricular function but being capable of maintaining a cardiac index within the normal range by increasing left ventricular filling pressure. Significant hemodynamic benefit was demonstrated in patients with normal and diminished left ventricular function when appropriate AV synchrony was maintained during ventricular pacing at 10 pulses/min greater that the resting heart rate. When heart rate increased alone, or when heart rate and intropic state increased together, patients with normal and diminished left ventricular function continued to derive a significant improvement in ventricular stroke work when atrial and ventricular contraction were synchronized appropriately. The mean improvement in stroke work index in both patient groups in this study was similar and exceeded 25% during ventricular pacing at 130 pulses/min with or without a simultaneous increase in inotropic state.

Importance of atrial function in maximizing left ventricular filling. Several studies[3-5, 16-18] have demonstrated that appropriately timed atrial contraction optimizes cardiac output at resting heart rates in animals and in humans with normal hearts. Maximum ventricular performance occurs when atrial contraction precedes the preejection period of the ventricle.[4] Atrial contraction during ventricular diastole increases the ventriculoatrial pressure gradient before ventricular contraction, resulting in close apposition of the AV valves before ventricular ejection. When ventricular contraction occurs without a preceding atrial contraction, significant regurgitation into the atrium occurs.[16,17] When atrial contraction occurs very late in ventricular systole—just before opening of the AV valve—there is a significant decrease in end-diastole volume and a decrease in the magnitude of ventricular contraction.[18] In patients with diminished left ventricular function and markedly elevated left ventricular filling pressures (resting pulmonary capillary wedge pressure >20 mm Hg), the atrial contribution to cardiac output is inversely proportional to left ventricular filling pressure.[19] The findings of this study demonstrate that a significant atrial contribution to the left ventricular function remains, however, during ventricular pacing at resting heart rates in patients with diminished left ventricular function and moderately elevated left ventricular filling pressure (mean pulmonary capillary wedge pressure = 14 mm Hg). This difference in observations may be explained on the basis of the Frank-Starling mechanism. When compared to patients with normal hearts and normal filling pressures or patients

with diminished left ventricular function and moderate increases in left ventricular filling pressure, patients with diminished left ventricular function and markedly elevated left ventricular filling pressure reach the steeper part of their pressure-volume curve before atrial contraction. In this latter group of patients, the markedly elevated ventricular pressure that is present before atrial contraction acts to impede further ventricular filling when atrial contaction occurs.[19]

It has been suggested by some authors that the size and function of the atrium itself also has significant effects upon left ventricular filling and cardiac output. Labovitz et al.[20] have observed an inverse correlation between left atrial size and the dependence of left ventricular output on maintenance of AV synchrony. They propose that this correlation is best explained by inability of an enlarged, increasingly compliant left atrium to generate a sufficiently vigorous systolic contraction to contribute significantly to ventricular filling.[20]

Comparison with other pacing studies. In patients with symptomatic left ventricular failure and depressed left ventricular function, cardiac index and intra-arterial pulse pressure increase significantly during acute AV sequential pacing at rest, when compared to ventricular pacing, at paced rates of 75 to 100 pulses/min. This increase appears to be independent of New York Heart Association functional class, cardiothoracic ratio, resting ejection fraction, cardiac index, or pulmonary capillary wedge pressure.[21]

The increase that occurs in inotropic state alone during exercise can augment stroke volume and increase cardiac output without an increase in heart rate. Further increases in cardiac output occur subsequently if ventricular rate is increased, even in the absence of synchronous atrial contraction.[20] An almost linear relationship has been reported between ventricular rate and patient exercise tolerance.[23-26] However, attempts at measuring the atrial contribution to ventricular function during ventricular pacing with exercise have had variable results. When limited supine bicycle exercise has been performed serially with peak heart rates less than 100 bpm, cardiac index has been 15% greater with synchronous, atrial-triggered ventricular pacing when compared to ventricular pacing alone at the same pacing rate.[6] In contrast, no substantial differences in stroke volume and blood pressure have been found when a faster pacing rate (128 bpm) has been employed during serial supine bicycle exercise when atrial-triggered ventricular pacing has been compared to ventricular pacing alone.[7]

Few studies have determined the hemodynamic effects of increasing heart rate by atrial-synchronous ventricular pacing when compared to increasing ventricular pacing rate alone during upright exercise. In patients with normal myocardial function who perform maximum upright treadmill exercise, a significant decrease in exercise performance and anaerobic threshold has been observed when ventricular pacing at a fixed rate has been compared to rate-responsive pacing in which ventricular pacing increases in rate in response to an extracardiac sensor, e.g., respiratory rate. However, aerobic and hemodynamic variables are similar in these same patients during exercise when the latter mode of pacing and atrial-synchronous ventricular pacing are compared.[8] In another study of patients with normal left ventricular function,[9] stroke volume has been reported to be similar when atrial-synchronous ventricular pacing is compared to ventricular pacing alone at the same heart rate during low-level upright bicycle exercise (exercise heart rate 95 to 120 bpm, maximum load 300 kilopoundmeters).

Differences in hemodynamics when comparing AV sequential pacing to ventricular pacing alone in previous studies may have depended upon several factors including the relative degree of random AV synchronization that may have occurred in the same patients during ventricular pacing. The design of the present study permitted demonstration of a significant atrial contribution to ventricular performance when ventricular pacing rate increased alone in patients with normal and diminished left ventricular function. Synchronous atrial contraction continued to contribute significantly to stroke work when inotropic state increased concurrently.

Limitations. Dobutamine permitted establishment of a steady state of increased ventricular contractility during various pacing interventions. However, exclusion of the hemodynamic effects of changes in peripheral muscle and vasomotor tone and respiratory rate, which occur when exercise is performed, limits the conclusions that may be drawn from this study. There was considerable variance in the magnitude of atrial contribution to ventricular performance among patients in this study. Therefore, the general relationship demonstrated between the timing of atrial contraction and left ventricular performance in this study cannot be used to predict the magnitude of atrial contribution to ventricular performance in any individual patient. The influence of atrial size upon changes in hemodynamics observed in a previous study[20] was not determined in the present study.

Continuous pacing was performed in this study

such that atrial contraction always occurred before or during ventricular contraction in order to quantify its hemodynamic effects. It is possible that adrenergic or neurohumeral responses may have occurred in response to atrial contraction during the ventricular preejection or ejection period, resulting in an overestimation of the adverse hemodynamic effects that might occur when atrial contraction occurs randomly during the ventricular preejection or ejection period. Finally, the hemodynamic findings demonstrated by this study in supine patients may differ from those that might be obtained from a similar study performed in erect patients.

Conclusions. During ventricular pacing, beneficial hemodynamic effects occur when AV synchrony is maintained at resting heart rates in patients with normal and diminished LVEF. Both groups benefit equally from AV synchrony at resting heart rates as well as when heart rate alone or heart rate inotropic state are increased.

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