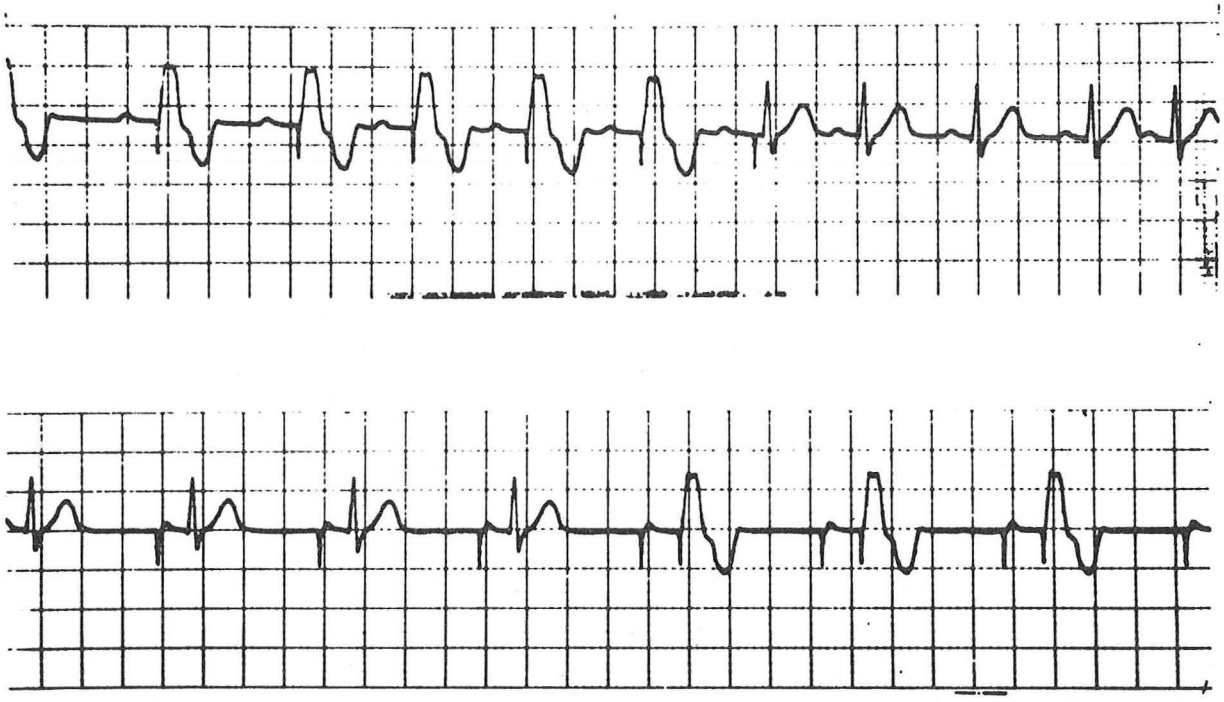
Cardiol

PHYSIOLOGIC PACING



MEDICAL GRAND ROUNDS

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WHY DISCUSS PACEMAKERS?

In the four years since permanent cardiac pacemakers were discussed at these grand rounds (Narahara, 1979), startling technologic advances have led to a proliferation of different pacemakers available for permanent implantation. It is now possible to implant small, reliable units which pace either the atrium or the ventricle or both, sense one or both chambers, and respond variously to sensed events. Miniaturized computer chips and programming devices allow the physician to select multiple pacing function parameters (such as rate, energy output, sensitivity to cardiac stimuli, refractory period), and to change them, as clinically indicated, by non-invasively delivering information to the implanted unit through the intact skin. Different pacing modes have produced a multiplicity of confusing electrocardiograms ("pseudoarrhythmias"), and some units have been associated with real iatrogenic arrhythmias which are at times dangerous to patients. There is widespread confusion about which patients might benefit from these "new" pacemakers, and physicians' reactions have ranged from what can be described as overenthusiasm to unfounded conservatism. At a time when widespread understanding of available technology and its application is wanting, there is every indication that the rapidity of change in pacemaker technology is still accelerating.

Although one could select many pacing subtopics for detailed consideration, the one which seems to be of most practical and immediate significance is that which has come to be known as "physiologic" pacing. Although there is no agreement on a definition of this term (Furman, 1980), several major symposia and published articles have discussed its merits and applications (Sutton et al., 1980). Although the term has obviously positive connotations, only recently have data appeared supporting the chronic efficacy of some "physiologic" pacing applications. My definition of physiologic pacing is the individualized application of a permanent pacing mode in such a way as to minimize a patient's hemodynamic and electrophysiologic abnormalities, particularly at times of stress.

In this presentation we will review some recent developments in pacemaker technology, and demonstrate how they might be applicable to some patients requiring permanent pacemaker implantation.

PACEMAKER CLASSIFICATION

In 1974, Parsonnet, Furman and Smyth proposed a three letter code to facilitate communication among those dealing with pacemakers. Although two further terminal letters have been added to reflect programmability and tachyarrhythmia functions (Table 1), the simpler three letter designation is more commonly used. The code is easily mastered and serves as a constant reminder of the basic functions of each type of unit.

Table 1 Five-Position Pacemaker Code

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Mode of response(s)	Programmable functions	Special tachyarrhythmia functions
Letters used	V—Ventricle	V—Ventricle	T—Triggered	P—Simple programmable (rate and/or output)	B—Bursts
	A—Atrium	A—Atrium	I—Inhibited	M—Multi-programmable	N—Normal rate competition
	D—Double	D—Double	D—Double*	C—Multi-programmable with telemetry	S—Scanning
			O—None		
		O—None	R—Reverse†	O—None	E—External
Manufacturer's designation only	S—Single Chamber‡	S—Single Chamber‡	[Comma optional here]		

* Atrial triggered and ventricular inhibited.
† *Activated* by tachycardia and (usually) bradycardia.
‡ Can be used for atrial *or* ventricular pacing; a manufacturer's designation.

First Letter = chamber paced
- A = atrium
- V = ventricle
- D = dual (both atrium and ventricle)

Second Letter = chamber sensed
- A = atrium
- V = ventricle
- D = dual
- O = none

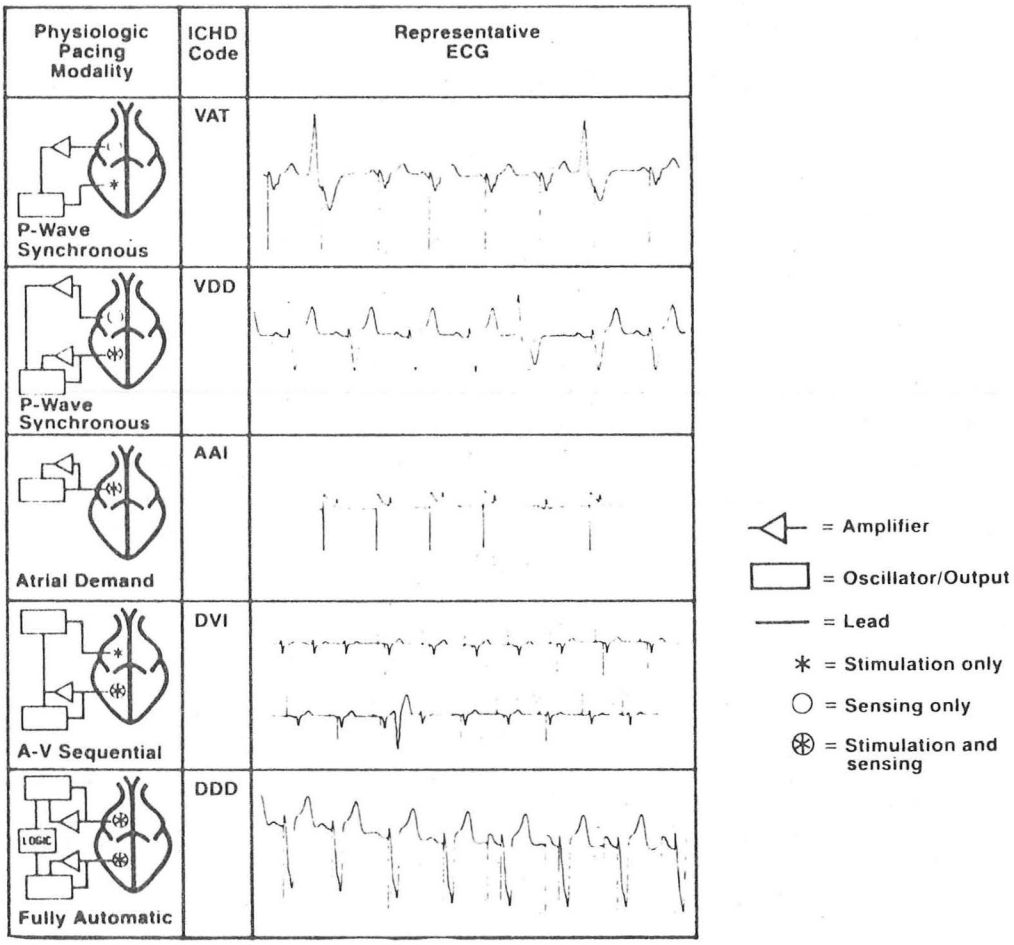
Third Letter = mode of response to sensed event
- I = inhibited
- T = triggered
- D = dual (two modes of response, e.g. inhibited in atrium and triggered in ventricle)
- O = none

Thus, the "ventricular demand" or "R-wave inhibited" pacemaker used most commonly for treatment of a wide variety of bradyarrhythmias is classified as VVI in the above scheme. Such a pacemaker, when functioning properly, paces only the ventricle (first V), senses only ventricular electrical activity (second V), and its output is inhibited (I) for a specified period after ventricular sensing. Application of a magnet to most VVI units converts operation to a ventricular asynchronous pacing mode which is known as VOO. During such operation, the pacemaker paces the ventricle, and is incapable of sensing (first O) or of responding (second O) to spontaneous cardiac activity. Historically the first pacemakers used for life support in bradyarrhythmias were VOO units.

The four pacing modes most commonly considered "physiologic" are AAI, DVI, VDD, and DDD. An atrial demand pacemaker (AAI) functions analogously to the VVI unit, except that the single pacing and sensing electrode is positioned in the atrium. Thus, only atrial pacing (first A), atrial sensing (second A), and

inhibition of atrial output (I) following sensing can result. The classic indication for such a unit is sinus bradycardia without compromised atrioventricular conduction.

FIGURE 1



A DVI pacemaker, also sometimes referred to as an "AV sequential demand" unit, paces in both chambers (D), senses only in the ventricle (V), and responds to ventricular sensing by inhibiting both atrial and ventricular output (I). Such a unit requires two pacing electrodes, one in the atrium and one in the ventricle.

A VDD pacemaker is also a dual chamber unit, and is frequently referred to as a "P-wave synchronous" or "atrial synchronous, ventricular inhibited [ASVIP]" pacemaker. Such a unit paces only in the ventricle (V), but is capable of sensing in both atrium and ventricle (first D), and has two modes of response (ventricular pacing triggered in response to atrial sensed event; ventricular output inhibition in response to ventricular sensed event) (second D).

The forerunner of the VDD mode was VAT; this unit also paced only the ventricle (V), sensed in the atrium (A), and triggered ventricular pacing (T) in response to atrial sensing. Note that this pacemaker was not inhibited by ventricular events, and it was thus capable of competitive ventricular pacing.

A DDD unit, sometimes referred to as a "fully automatic" or "universal" pacemaker, is the most flexible and complicated mode currently available. This

unit paces in both chambers (first D), senses in both chambers (second D), and responds in a dual fashion (third D): ventricular pacing triggered in response to atrial sensing; ventricular or atrial output inhibited in response to sensing in the same chamber.

The three letter codes, although quite helpful in remembering basic normal function of pacemakers, are not detailed enough to describe all the programmable features which may be selected for each unit (heart rate, atrioventricular pacing delay between the two chambers, pulse width and voltage output, sensitivity levels in one or more chambers, refractory periods in one or more chambers, hysteresis). Some units are even programmable as to mode, so that a DDD unit might be reprogrammed to function in a DVI or VVI mode. Most VDD units spontaneously function in a "VVI backup" mode when atrial bradycardia occurs.

WHAT IS WRONG WITH VVI PACING?

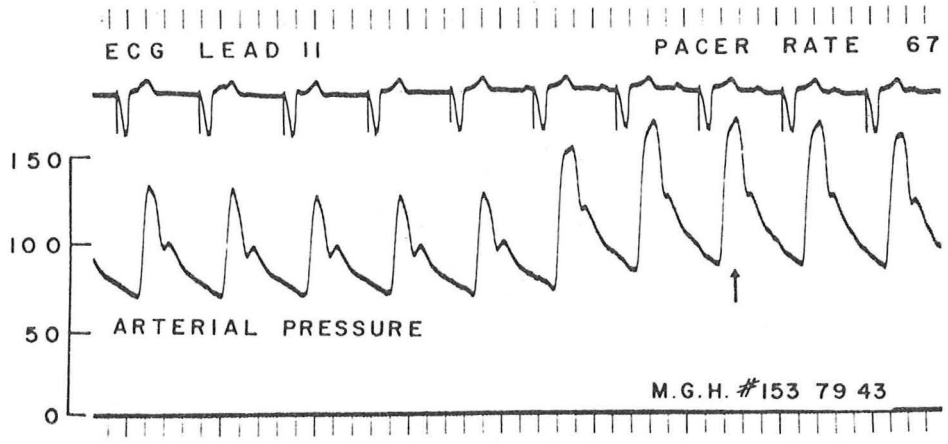
Treatment of severe and life threatening bradyarrhythmias with the ventricular demand pacemaker (VVI) has prevented severe disability from Stokes-Adams attacks and in most physicians' opinions has resulted in prolongation of life in many patients with fixed bradyarrhythmias and in some with intermittent bradycardias and conduction blocks. Such VVI pulse generators have performed reliably up to a decade after implantation (Parsonnet, 1982). Physicians in most specialties are now accustomed to electrocardiographic interpretation of VVI pacing, with only occasional ECG artifacts, non-sensed VPB's, and hysteresis producing apparent pacemaker malfunction.

Although there is little doubt that VVI pacemakers are quite effective in eliminating symptoms of severe bradycardia, hemodynamic problems attributable to the pacing mode or not corrected by it may still hamper the quality of life in some paced patients. The most commonly cited problems are those of the absence of atrioventricular synchrony and the lack of rate responsiveness to increases in metabolic demands, e.g., exercise.

Atrioventricular Synchrony

During VVI pacing, normal atrioventricular synchrony (both electrical and mechanical) occurs only as a random event. In the situation of complete or high grade antegrade atrioventricular block, atrial activity is often independent of ventricular pacing and P waves "march through" paced QRS complexes and the intervening RR intervals (Figure 2). In patients with intact ventriculoatrial conduction, ventricular pacing may lead to atrial depolarization immediately after or during ventricular systole, thus causing atrial contraction to occur against a closed atrioventricular valve.

FIGURE 2: From Leinbach et al., 1969.

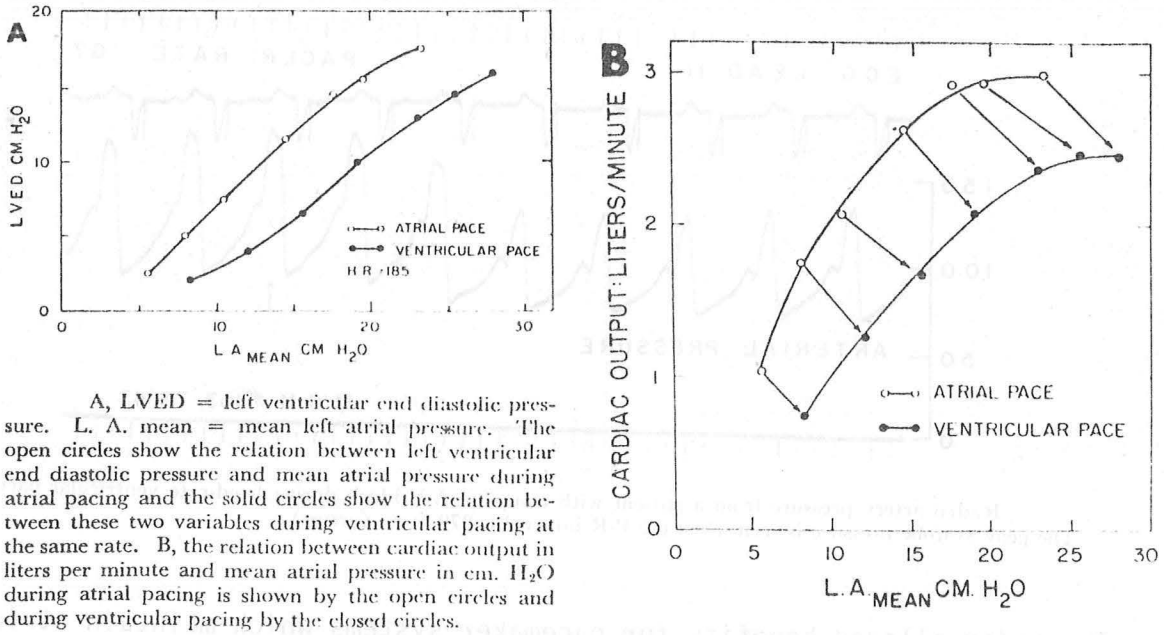


Radial artery pressure from a patient with complete A-V block during fixed-rate ventricular pacing. The peak systolic pressure is seen when the P-R interval is 270 msec. (arrow).

The major alleged benefits for pacemaker systems which maintain atrioventricular synchrony are 1) an increase in stroke volume, and thus cardiac output, because of an intact "atrial kick" mechanism, and 2) avoidance of symptomatic hemodynamic sequelae of atrioventricular asynchrony (the "pacemaker syndrome").

It seems relatively well established in experimental studies in animals and in human subjects that hemodynamic comparison of the most deleterious circumstance (ventricular pacing with atrial depolarization following ventricular activation, resulting in a situation where the atria and ventricles contract and fill simultaneously) to atrial pacing or spontaneous sinus rhythm with normal atrioventricular synchrony, demonstrates an approximately 20% greater stroke volume and cardiac output in the latter situation (Samet et al., 1966; Ogawa et al., 1978: El Gamal and Von Gelder, 1981). Precise hemodynamic characterization of the events was established in a series of classic investigations from the NIH in the early 1960's. Mitchell et al (1962) compared the hemodynamics of atrial and ventricular pacing at constant ventricular rates in anesthetized dogs, and demonstrated that mean left atrial pressure was higher in relationship to left ventricular end diastolic pressure (LVEDP) during ventricular pacing than during atrial pacing at the same rate (Figure 3).

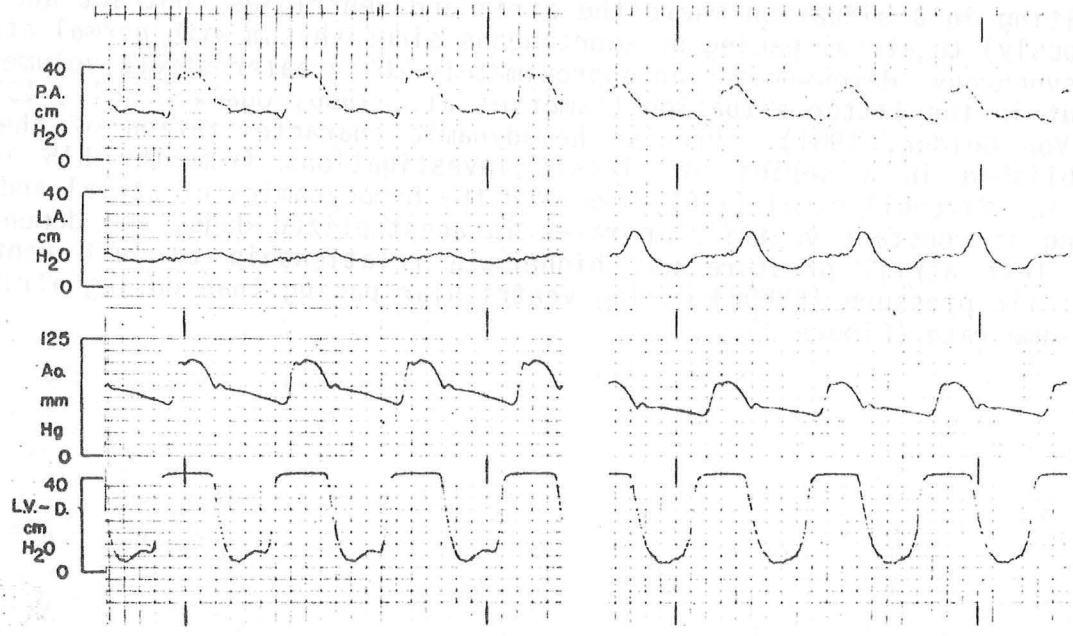
FIGURE 3: From Mitchell et al., 1972.



A, LVED = left ventricular end diastolic pressure. L. A. mean = mean left atrial pressure. The open circles show the relation between left ventricular end diastolic pressure and mean atrial pressure during atrial pacing and the solid circles show the relation between these two variables during ventricular pacing at the same rate. B, the relation between cardiac output in liters per minute and mean atrial pressure in cm. H_2O during atrial pacing is shown by the open circles and during ventricular pacing by the closed circles.

Elevation of mean left atrial pressure was largely due to a high "a" wave produced by atrial contraction against a closed mitral valve (Figure 4A).

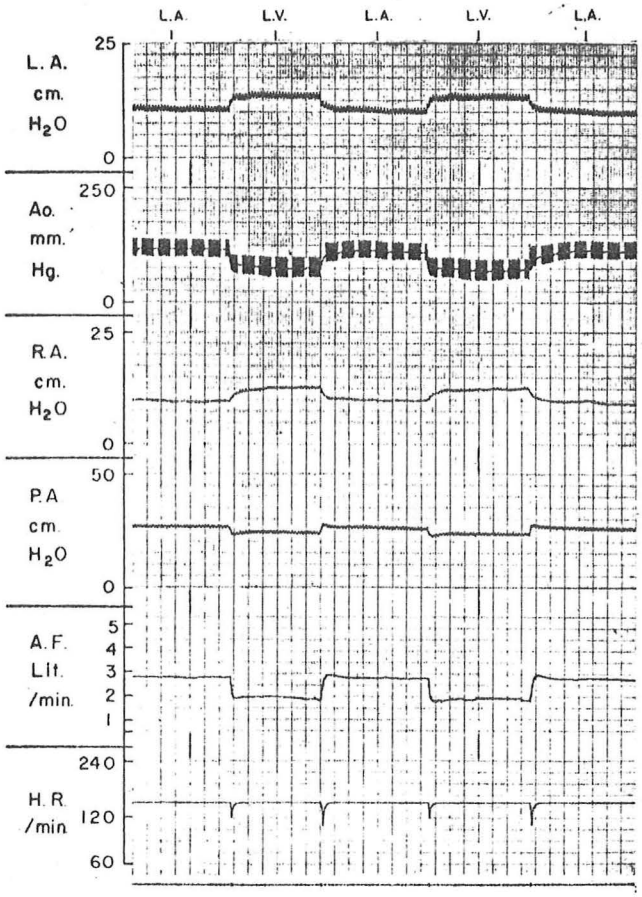
FIGURE 4A: From Gilmore et al., 1963.



—P.A.=pulmonary arterial pressure; L.A.=left atrial pressure; Ao=aortic pressure; and L.V.-D.= left ventricular diastolic pressure. Left panel taken during left atrial stimulation; right panel taken during left ventricular stimulation. Heart rate=162. Bilateral cervical vagotomy and left stellate ganglionectomy. Chart speed=100 mm./sec.

Gilmore et al (1963) demonstrated an abrupt decrease in cardiac output and aortic pressure, and a rise in left ventricular stroke work and mean left atrial pressure when atrial pacing was suddenly changed to ventricular pacing at the same rate in anesthetized dogs (Figure 4B).

FIGURE 4B: From Gilmore et al., 1963.



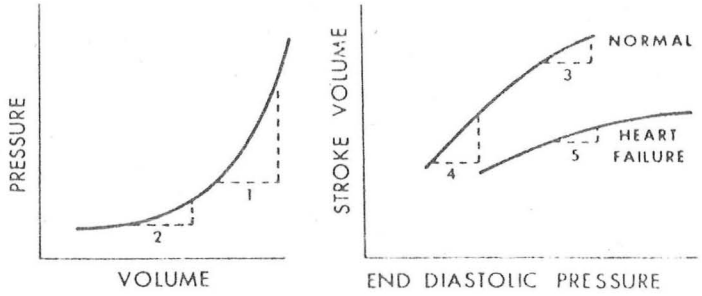
—L.A.=mean left atrial pressure; Ao=aortic pressure (full pulse pressure alternating with electricity integrated mean pressure); R.A.=mean right atrial pressure; P.A.=mean pulmonary artery pressure; A.F.=aortic flow (cardiac output minus coronary flow); H.R.=heart rate. L.A. and L.V. at top of tracing indicate periods during which the left atrium or left ventricle were stimulated. Bilateral stellectomy and bilateral cervical vagotomy. Chart speed=0·5 mm./sec.

Such studies have been performed in animals with relatively normal left ventricular function, a circumstance which is, of course, not always present in patients who are candidates for pacemaker implantation. Braunwald and Frahm (1961) studied the hemodynamic functions of the left atrium in patients with disturbances of left ventricular function and in normal subjects in sinus rhythm. They found that LVEDP and mean left atrial pressure were similar in patients without heart disease, but that LVEDP averaged 9 mm Hg higher than mean left atrial pressure in subjects with heart disease (usually valvular aortic stenosis); the "atrial kick" at the end of diastole allowed elevation of the LVEDP, thus increasing fiber stretch and presumably enhancing left ventricular performance, while maintaining left atrial mean pressure at a lower value than LVEDP. These and other studies have suggested major importance of left atrial systole in

maintaining cardiac output (through elevation of end-diastolic pressure) without undue elevation of left atrial mean pressure in patients with left ventricular hypertrophy but without conspicuous left ventricular dilatation (Braunwald, 1964). Such conditions with prominent "stiffness" (decreased compliance) of the left ventricle are quite common in clinical medicine, and include hypertensive heart disease, ischemic heart disease, valvular aortic stenosis, restrictive cardiomyopathies, and idiopathic hypertrophic subaortic stenosis.

Clinical studies have demonstrated that there is an inverse relationship between the atrial contribution to cardiac output and the absolute level of pulmonary capillary wedge pressure (Greenberg et al, 1979). In other words, patients with advanced heart failure and marked elevation of mean pulmonary capillary wedge (left atrial) pressure at rest have less augmentation of stroke volume and cardiac output with AV synchrony than do those with lower mean left atrial pressures. Such patients with marked left atrial pressure elevation usually have smaller "atrial kicks" in their left ventricular diastolic pressure tracings, and have dilated, hypocontractile left ventricles. These data are explained by the left ventricular pressure - volume relationship (Figure 5).

FIGURE 5: From Greenberg et al., 1979.



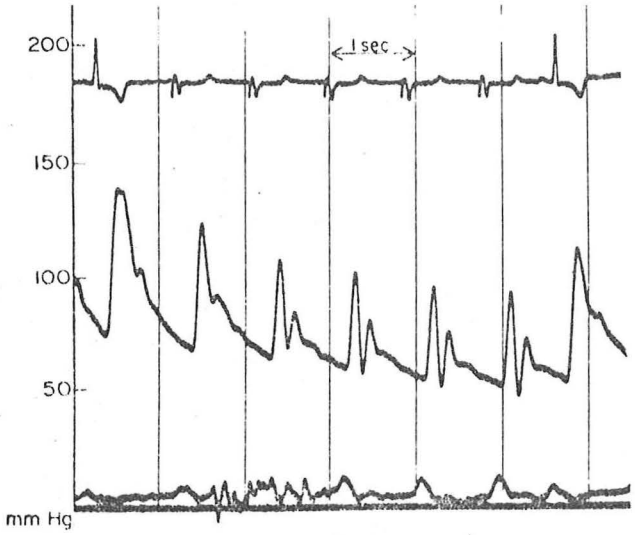
Left panel, Left ventricular pressure–volume relationship. *Right panel*, Left ventricular function curve. In subjects with elevated filling pressure, increase in ventricular volume can be accomplished only by a large increase in pressure *(point 1)*; at lower initial pressure, a similar increase in volume is accommodated with much less rise in pressure *(point 2)*. In addition, the same increment in pressure in a subject with high end-diastolic pressure *(point 3)* results in less increase in stroke volume than would occur with lower end-diastolic pressure *(point 4)*. In heart failure, this same increment in pressure might be expected to have even less of an effect on stroke volume *(point 5)*, as the curve is flatter.

Thus, it would seem that the preponderance of experimental and clinical data suggest that beneficial effects of maintenance of atrioventricular synchrony (and conversely, deleterious effects of its absence) are more likely to be demonstrated in conditions where left ventricular function is normal or where "heart failure" is manifest primarily by decreased left ventricular compliance than by marked left ventricular dilatation. This is yet another situation where careful direct hemodynamic assessment of "heart failure" is helpful in the optimal management of this common clinical syndrome (Rude et al, 1981).

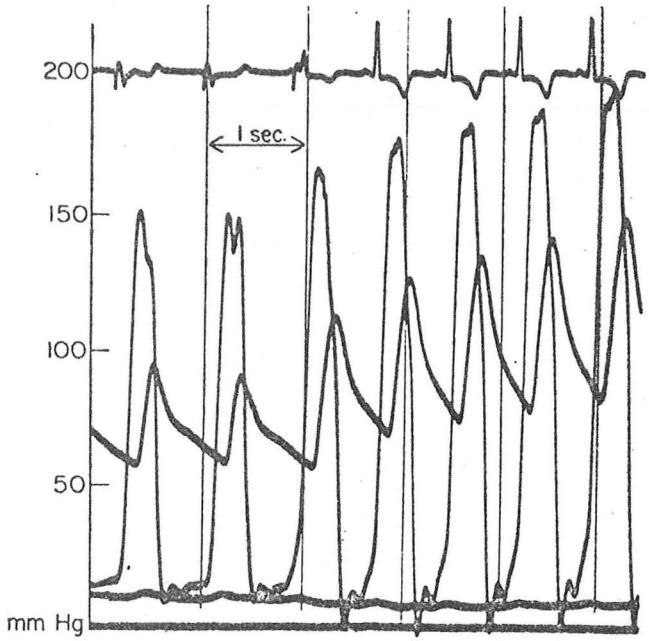
The pacemaker syndrome, characterized by symptoms of fatigue, dizziness, venous pulsations in the neck, or near syncope is most commonly seen in patients with ventricular demand pacing in accompaniment with either sinus rhythm and variable degrees of heart block, or intact ventriculoatrial conduction (Haas and Strait, 1974; Patel et al., 1977; Lewis et al., 1981; Miller et al., 1981). The symptoms are caused by variations in left ventricular stroke volume and/or

arterial pressure which occur due to altered relationships of atrial and ventricular systole. Figure 6 demonstrates the exaggerated swings in systolic arterial pressure which can result from intermittent placement of spontaneous non-conducted sinus beats before or during paced ventricular complexes. Although the symptoms of the pacemaker syndrome are usually minor in comparison to those of the bradycardia which led to pacemaker insertion, there are occasional patients whose preimplantation symptoms are only replaced by equally severe symptoms post operatively. Because the symptoms are non-specific, usually not progressive or markedly severe, and usually occur in elderly patients with multiple medical problems, many physicians fail to recognize the presence of pacemaker syndrome.

FIGURE 6: From Patel et al., 1977.



Aortic systolic and diastolic (A, s/d) pressures in millimeters of mercury in response to change from normal sinus rhythm (N) to paced beats (P).



Simultaneously recorded left ventricular systolic/end-diastolic (LV, s/ed) and aortic systolic/diastolic (A, s/d) pressures in millimeters of mercury. Numbers at bottom indicate hemodynamic changes in response to paced (P) and normal sinus rhythm (N). Grad, Peak pressure gradient between left ventricle and aorta; and F, fusion beat.

Nishimura et al (1982) studied 50 patients with recently implanted permanent units which were programmable to either VVI or DVI modes, thus affording them the opportunity to measure arterial blood pressure in the presence or absence of atrioventricular synchrony. Patients with intact ventriculoatrial conduction during ventricular pacing had a much greater fall in systolic blood pressure with VVI pacing (24±11 mmHg) than those with ventriculoatrial dissociation (mean fall of 4±15 mmHg) during the same pacing mode, ($p<0.005$), and these differences were present in both the supine and standing positions. Patients with clinical congestive heart failure had lesser drops in systolic blood pressure with ventricular

pacing alone than did those without heart failure, and most patients with congestive heart failure lacked ventriculoatrial conduction. Ten patients had symptomatic dizziness during VVI pacing, and this was much more common (9 of 23 patients) in patients with ventriculoatrial conduction than in those without (1/27), (p=0.003) (Figure 7). Their study suggests that patients most likely to have pacing-induced hypotension with VVI units are those who have 1) intact ventriculoatrial conduction during ventricular pacing, and 2) relatively well preserved left ventricular function. Thus, patients with sinus bradycardia and varying degrees of antegrade atrioventricular block who do not have severe heart failure would seem to be the most likely candidates for development of the pacemaker syndrome; such patients might include those with congenital complete heart block and otherwise normal hearts or heart block after cardiac surgery.

FIGURE 7: From Nishimura et al., 1982.

	Symptomatic (no. of pt)	Nonsymptomatic (no. of pt)	
Ventriculoatrial conduction			
Present	9	14	$P = 0.003$
Absent	1	26	
Congestive heart failure†			
Present	0	14	$P = 0.04$
Absent	10	26	

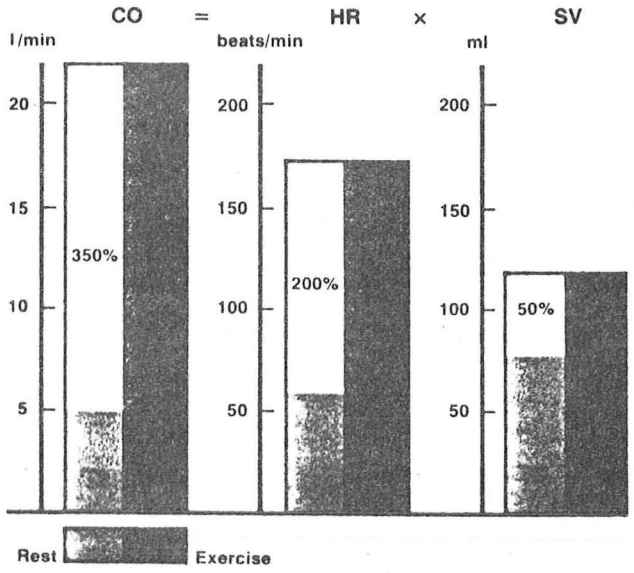
*Symptomatic hypotension was defined as the occurrence of symptoms of near syncope associated with a decrease in blood pressure with pacing from the right ventricle.
†NYHA Class 2 or higher.

These studies, as well as other reports (Miller et al., 1981; Fananapazir et al., 1983)), strongly suggest that many symptoms of pacemaker syndrome can be alleviated with pacing modes which promote atrioventricular synchrony (VDD, DVI, DDD). Satisfactory management of the pacemaker syndrome may also be possible with a programmable VVI unit: a lower ventricular demand rate may allow more frequent spontaneously conducted beats and less atrioventricular asynchrony.

Rate Responsiveness

A second disadvantage of VVI pacing is that there is no mechanism by which ventricular rate can be accelerated at times of increased metabolic demands for enhanced cardiac output, such as during physical exercise. Thus, unless the patient's underlying ventricular rate accelerates above the demand rate of the pacemaker with exercise, any cardiac output response to increased metabolic demands must be through an increased stroke volume. It should be recalled that in a normal untrained subject, cardiac output may be increased with maximum physical exercise by four or five-fold; such a response is mediated by a near tripling of heart rate (from resting values of 60-70 to exercise values of 180-200 beats per minute), and by an approximately 50% increase in stroke volume (Hermansen et al., 1973).

FIGURE 8:
Cardiac output (CO) during exercise is increased mainly by an increase in heart rate (HR) and to a lesser extent by an increase in stroke volume (SV).



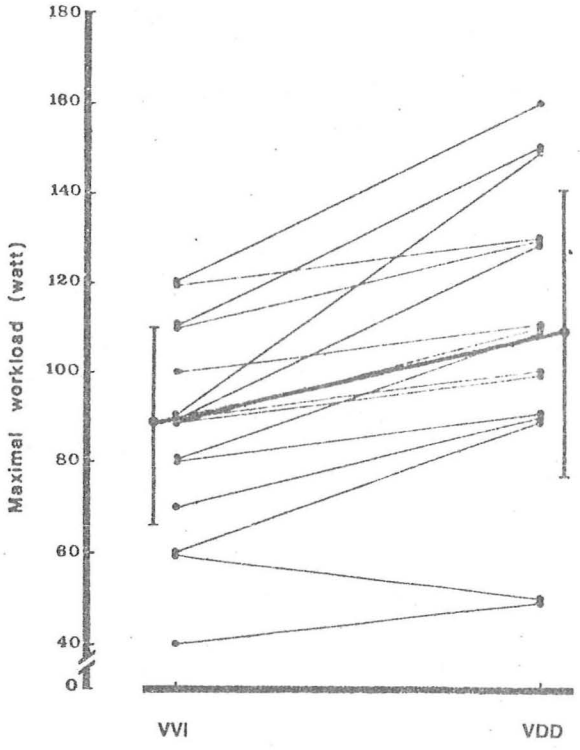
Thus, approximately two-thirds of the cardiac output increase is due to rate responsiveness and only about one-third to increases in stroke volume (Figure 8). Pacemaker patients may be even more limited in their ability to summon an increased stroke volume, because of myocardial dysfunction which limits the end-systolic volume which can be attained. Dependence on enhanced stroke volume as the major mechanism of an exercise response explains why patients with non-rate responsive pacemakers may be severely limited in their exertional capacity. Based on the above figures, patients with fixed rate pacing during exercise would be expected to be limited to approximately 50% increases in cardiac output, as opposed to the 300-500% increases which might be attained if an increase in ventricular rate were possible. Reported studies in small numbers of patients confirm the relative inability of patients with fixed heart rates to increase cardiac output with exercise. Eimer and Witte (1974) found an average 34% increase in cardiac output with exercise in patients with fixed-rate ventricular pacemakers, and concluded that such patients were likely to exhaust their maximum exercise capacity with ordinary daily activities.

These data, as well as clinical observations by physicians involved in early pacemaker clinics, led to interest in designing a pacemaker which allowed cardiac output enhancement with exercise. Early efforts were directed at design of a pacemaker which could sense spontaneous increases in atrial rate and provide isorhythmic ventricular pacing. Atrial synchronous ventricular pacing was first suggested over two decades ago, and the atrial synchronous, ventricular-triggered mode (VAT) was introduced in 1962 (Center et al., 1963). Such units sensed spontaneous P-waves, and paced the ventricles at a fixed atrioventricular interval after the atrial sensed event. Because no ventricular sense amplifier was present, competitive ventricular pacing could result (Kruse et al., 1980). These units were the forerunners of more modern VDD and DDD units, and the ability of these three pacing modes to maintain rate responsiveness during moderate exercise is essentially identical. All three modes depend upon a response of the patient's intrinsic atrial rhythm to the metabolic demands of exercise, and thus the maintenance of atrioventricular synchrony and rate-responsiveness are inextricably linked.

Two recently reported clinical studies strongly suggest that rate responsive pacing modes allow a greater increase in cardiac output during exercise than is attained with fixed rate ventricular pacing (Kruse et al., 1982; Fananapazir et al., 1983). Kruse, in Sweden, performed extensive exercise and exercise-hemodynamic studies in 16 patients with non-invasively programmable pacemakers which could be changed from VVI to VDD modes. Maximal work capacity was determined by bicycle ergometry, and catheterization allowed measurements of ateriovenous oxygen difference, cardiac output, and pulmonary arterial pressures. Non-invasively monitored exercise tests after prolonged periods (usually 3 months) of VVI and VDD pacing demonstrated a 24% higher maximal work load during VDD pacing; all but one of the 16 patients increased maximal work load in the VDD mode (Figure 9). In the invasive limb of the study, resting cardiac output was 25% higher with VDD pacing than with VVI pacing at a very similar heart rate, and cardiac output was also higher at two levels of submaximal exercise in the VDD mode. As one would expect, heart rate was fixed during submaximal exercise with VVI pacing, but increased during both submaximal exercise tests in the VDD mode. The arteriovenous oxygen difference was higher during both levels of exercise during VVI pacing (Figure 10), and arterial blood lactate levels were significantly higher during exercise with VVI pacing than during exercise during VDD pacing. There was no further hemodynamic inprovement with VDD pacing after two hours as compared to three months. Although the patients could not be blinded with regard to their chronic pacing modes (because of their ability to detect changes in heart rate with activity), 14 preferred the VDD pacing mode, and 2 did not have a preference (Figure 11).

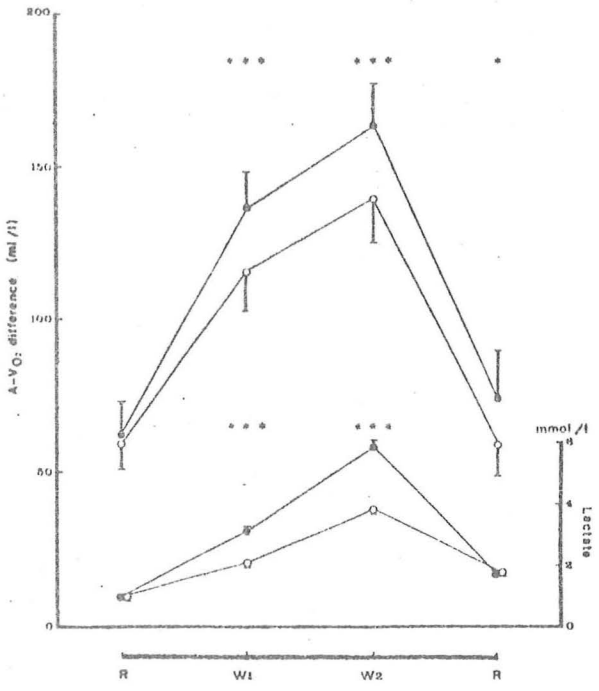
FIGURES 9-11: From Kruse et al., 1982.

Fig. 9



Maximal work capacity with ventricular inhibited (VVI) and atrial synchronous ventricular inhibited (VDD) pacing. Individual data and the mean ± SD for the group (heavy line) are shown.

Fig. 10

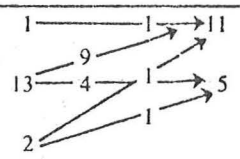


*Arteriovenous oxygen difference ($A\text{-}VO_2$) and blood lactate during ventricular inhibited (VVI) (●) and atrial synchronous ventricular inhibited (VDD) (○) pacing. Group values are mean ± SD. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. R = rest; W1 = 32 ± 8 W; W2 = 65 ± 13 W.*

Fig. 11

General Condition on Ventricular Inhibited and Atrial Synchronous Ventricular Inhibited Pacing

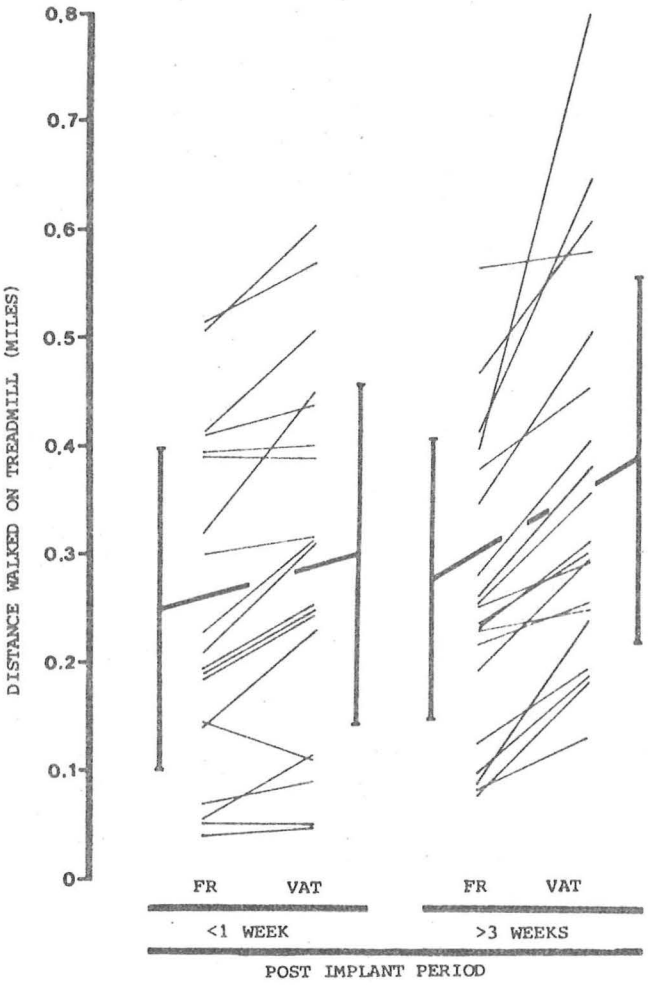
Class	General condition	Pacing mode: VVI	Pacing mode: VDD
I	Fine (no physical restriction)	1	11
II	Fair (some physical restriction)	13	5
III	Bad (very restricted)	2	



Abbreviations: VVI = ventricular inhibited pacing; VDD = atrial synchronous ventricular inhibited pacing.

Fananapazir et al. (1983), in the United Kingdom, studied 35 patients with implanted pacemakers which could be externally programmed to asynchronous ventricular pacing (VOO) or an atrial synchronized (VAT) mode. Resting cardiac output averaged 22% higher during VAT as compared to VOO pacing. Maximal exercise performance was assessed using the Bruce treadmill exercise protocol and the investigator utilized a blinding technique whereby the supervising physician, who controlled the termination of exercise for subjective complaints of fatigue, was unaware of the pacing mode (a second physician monitored the ECG, heart rate and blood pressure, and could terminate the test if arrhythmia or hypotension developed). There was significantly higher systolic blood pressure response at each level of the Bruce protocol in VAT pacing, and atrial rates were lower during VAT pacing at each level of exercise tested. Exercise tolerance was improved by VAT pacing in 30 of 35 patients, and this improvement in calculated work performed was at least 33% in 23 of the 35 patients. The improvement in exercise tolerance with VAT pacing was shown to be maintained in the 20 patients who had repeat exercise tests several weeks later (Figure 12). Finally, exercise induced hypotension was found to be an important limiting factor in 11 patients during VOO pacing, but occurred in only 3 of the same patients during VAT pacing.

FIGURE 12: From Fananapazir et al., 1983.



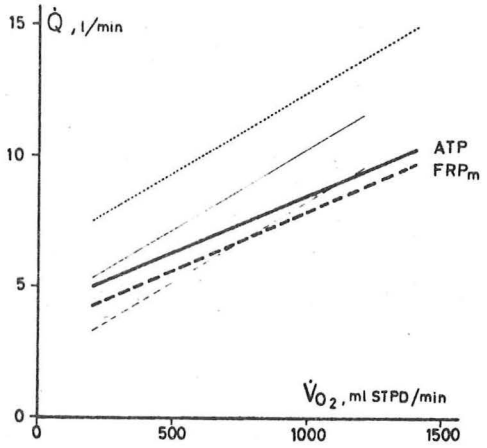
Comparison of distances walked during VOO and VAT pacing modes, in the 20 patients who had two sets of exercise tests, separated by several weeks. Individual data and mean ± 1 SD for the two sets of tests (thick line).

Thus, it seems relatively well established that objective measurement of exercise performance characteristics demonstrates a tendency for improved exercise hemodynamics during atrial synchronous pacing. The subjects of both studies had high degree antegrade atrioventricular block, and their atria retained the ability to increase their sinus rates with the metabolic demand of physical exercise. Because of the atrial synchronous pacemaker design, the favorable hemodynamic improvement during the "physiologic" mode may have been due to the presence of atrioventricular synchrony or to the rate responsiveness of the ventricles, or to both.

Of particular pertinence to the relative roles of atrioventricular synchrony and ventricular rate responsiveness in mediating cardiac output responses to exercise are the studies of Karlof (1975) and Snell (1982). Karlof (1975) designed an ingenious study to investigate the potential significance of atrioventricular synchrony in response to exercise. During an initial exercise test during VAT pacing, the attained cardiac rate was noted; then, during exercise to an equivalent load, the patients were paced at the same ventricular frequency without the benefit of atrial synchrony, and hemodynamic measurements were made. The increased stroke volume characteristic of an exercise response during fixed rate ventricular pacing was not seen during ventricular pacing which increased in rate with exercise. When adjusted rate ventricular pacing (non-AV sequential) was compared to atrial synchronous pacing at the same rate, a very similar relationship between cardiac output and oxygen consumption was documented, suggesting only a minor enhancement of cardiac output with atrial synchrony at a given oxygen uptake(Figure 13).

FIGURE 13: from Karlof, 1975.

Cardiac output ($\dot{Q}$) in relation to oxygen uptake ($\dot{V}O_2$) at rest and during exercise with atrial synchronous (ATP) and ventricular asynchronous (FRP_m) pacing at similar peak exercise rates.



Snell et al (1980) studied a subject who was dependent on a ventricular pacemaker following surgically induced heart block for uncontrollable ventricular response to idiopathic atrial fibrillation. With the use of an externally activated programmer, the subject or the investigator could increase ventricular pacing rate; with chronic atrial fibrillation, there was of course no opportunity to provide atrioventricular synchrony. In this patient with normal left ventricular function, it was demonstrable that increases in cardiac output at each fixed heart rate were slightly less than in normal subjects, and that they were attained at the expense of marked elevation of pulmonary capillary wedge pressure at low heart rate (70 beats per minute) and widened arteriovenous oxygen differences (Figures 14 - 16). Increases in the pacemaker rate led to a greater work capacity and a more favorable left ventricular pressure-volume relationship.

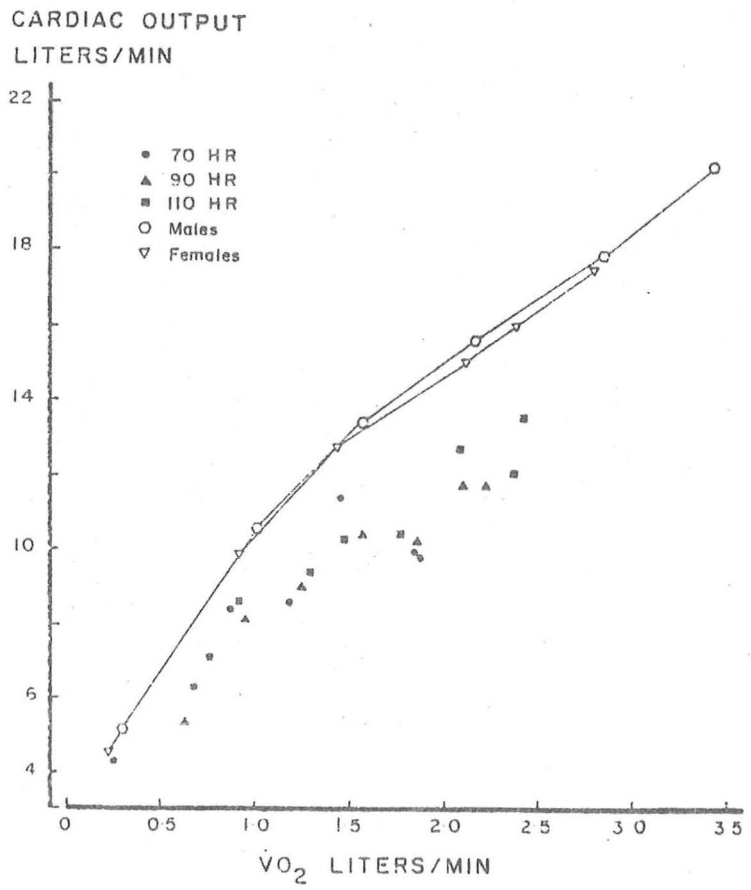


FIGURE 14: From Snell. Cardiac output as a function of oxygen uptake during exercise. Mean values for normal subjects, and individual values for pacemaker subject at different fixed ventricular rates.

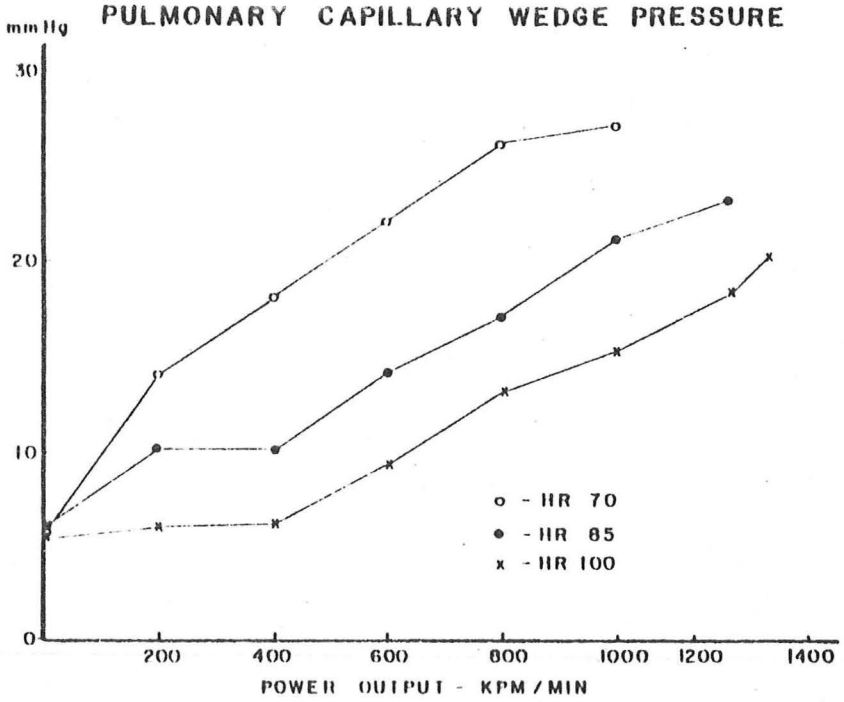


FIGURE 15: From Snell. Pulmonary capillary wedge pressure during exercise in same patient at 3 separate fixed ventricular rates, without A-V synchrony.

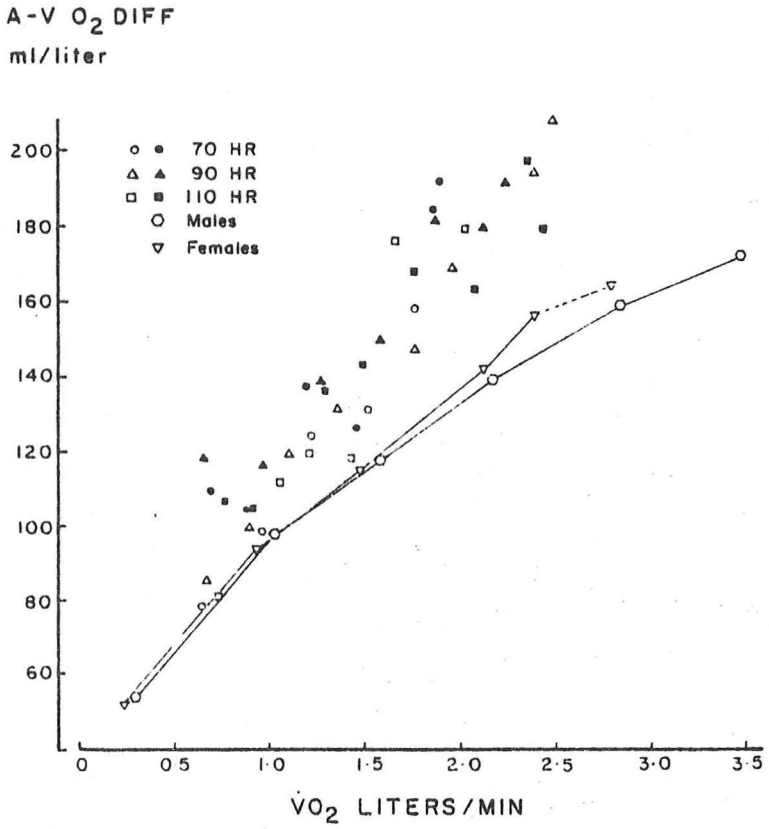


FIGURE 16: From Snell. Arteriovenous O_2 differences as a function of O_2 uptake during exercise. Mean values for normals and individual values for pacemaker subject at different ventricular rates.

The studies of Karlof (1975) and Snell et al (1980) both suggest that increases in ventricular rate alone can allow a more physiologic response to exercise than is seen at a lower fixed heart rate. The additional benefits of atrioventricular synchrony during exercise are demonstrable but are not of the same magnitude as increases in ventricular rate. This important physiologic point is often ignored in discussions of "physiologic pacing", and will likely assume more importance as methods are developed to provide ventricular "rate responsiveness" to patients whose atrial rates do not appropriately accelerate with exercise and sympathetic stimulation, thus making atrial synchronous ventricular pacing ineffective in mediating a significant increase in heart rate during exercise.

PRACTICAL POINTS REGARDING THE COMPLEXITY OF "PHYSIOLOGIC" PACING

Before assimilating the information reviewed above concerning both the available pacemaker modes and the data which imply that application of these pacing modes may be beneficial to some patients, it is appropriate to review some of the complexities and potential adverse effects of these pacemakers. No portion of this grand rounds is likely to become out of date faster than this section, because of the constant changes in pacemaker technology which have been stimulated by these issues. Many of these problems are rare and should not be considered of sufficient magnitude to dissuade the physician from ever considering a "physiologic" pacing mode; knowledge of them will allow, however, better estimation of risk/benefit ratios for particular patients being considered for a "physiologic" pacing mode.

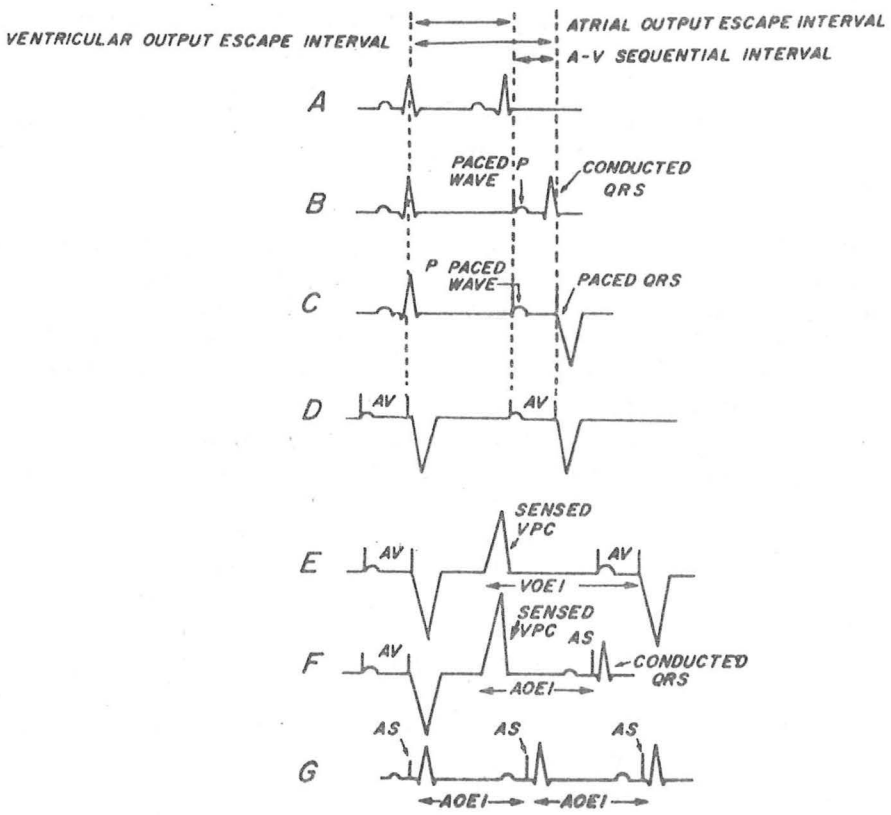
An important issue regarding the complexity of these pacemaker systems is the increased difficulty of performance of the implantation procedure. Implantation of a standard VVI pacing unit requires successful placement of an electrode in the right ventricular apex, confirmation of adequate pacing and sensing thresholds, and connection of the lead to the implanted pulse generator. Implantation of most "physiologic" units involves placement of a ventricular electrode as well as an atrial electrode for pacing and/or sensing. Atrial leads have been traditionally difficult to insert and have had higher rates of dislodgement and pacing/sensing problems than their ventricular counterparts, but recent advances in atrial lead technology and transvenous insertion techniques of one or two leads have greatly reduced these obstacles to dual chamber pacing. Rather than previous approaches such as combined cephalic and subclavian or internal jugular venous cutdowns, access for dual lead insertion is now most commonly obtained by a single subclavian venipuncture and insertion of two permanent electrodes through a peel-away dilator-introducer (Parsonnet et al., 1980). Stability of atrial leads has been enhanced by development of tined "J" loop electrodes which are rather easily positioned in the right atrial appendage; furthermore, active fixation electrodes, such as the "screw-in " atrial lead have also gained popularity and are particularly useful in post operative patients who have no atrial appendage. Thus, in centers where surgeons and/or cardiologists have a sustained interest in the techniques of implantation, proper use of a number of options and implantation techniques usually results in successful insertion of both atrial and ventricular leads. Slightly greater risk is involved with use of the subclavian technique which may be associated with pneumothorax and central venous air embolism. Another added complexity to insertion of some "physiologic" pacemakers is that more elaborate electrophysiologic measurements must be made at the time of pacemaker implantation to assure successful operation of the unit. Namely, sensing and pacing thresholds may be required in the atrium as well as the

ventricle, and tests for the presence or absence of retrograde (ventriculoatrial) conduction during ventricular pacing are appropriate if an atrial-sensing unit is implanted (Hayes and Furman, 1983). Commercially available pacing systems analyzers (PSA) are now available which make these measurements possible without much more difficulty than proper testing of a single ventricular lead. Ventriculoatrial conduction testing has been more readily accepted in centers with some electrophysiologic expertise.

A second complexity of the use of physiologic pacing modes is that of "pseudomalfunction" (Parsonnet and Bernstein, 1983), defined as an electrocardiographic finding that looks like pacemaker malfunction but is not. These are particularly frustrating to electrocardiographers who may have to attempt to interpret ECG's of paced patients in the absense of knowledge of what pacemaker model, mode, and programmable features are present; in the 1980's, proper interpretation of ECG's of paced patients is impossible without such information being provided. Dissemination of information about such pseudomalfunction to the general medical community is important because of the great levels of concern which may develop about a particular pacemaker system and lead to uninformed treatment, even including needless pulse generator replacement.

The most common pseudomalfunctions occur with atrioventricular sequential demand (DVI) units, and have been reviewed extensively by Barold et al (1980, 1981) and Parsonnet and Bernstein (1983). Figure 17 is a necessarily detailed review of the different sensing and pacing intervals which control function of most of the "non-committed" DVI units. The key to most pseudomalfunctions is to remember that the pacemaker is DVI, and that it only senses in the ventricle; thus, the atrial output capacitor is reset and a new atrial output escape interval (AOEI) begins when a ventricular event is sensed or when the ventricle is stimulated, and atrial output is inhibited only when a ventricular event is sensed. Thus, the V-atrial spike interval is constant, regardless of atrial events.

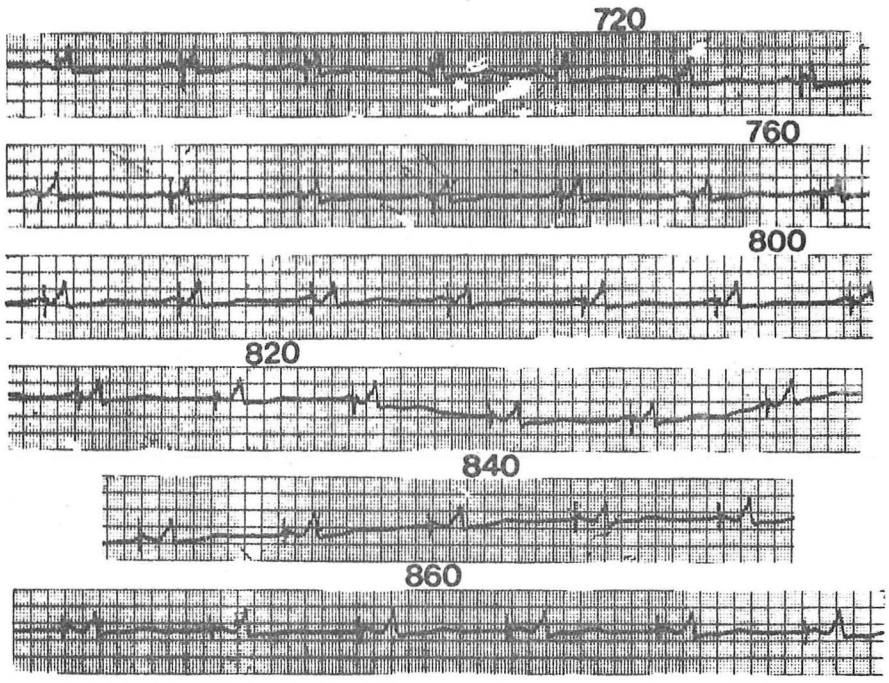
FIGURE 17: From Barold et al., 1980.



Function of AV sequential demand pulse generator. A) When the patient's spontaneous R-R interval is shorter than the atrial output escape interval (AOEI) of the pulse generator both atrial and ventricular outputs are inhibited by sensed ventricular depolarization and the pulse generator produces no stimuli. B) When the R-R interval exceeds the AOEI, an atrial output is emitted. If the patient's PR interval is shorter than the AV sequential interval the patient's conducted R wave inhibits the pulse generator's ventricular stimulus and only the atria will be stimulated. C) After an atrial output pulse, if the patient's PR interval exceeds the pulse generator AV sequential time (difference between VOEI and AOEI) the ventricular output pulse will also be emitted. D) If there is no underlying rhythm, regular AV sequential pacing with atrial and ventricular spikes will occur. E) A sensed ventricular premature beat (VPC) occurring during the AOEI initiates a new VOEI and no atrial output occurs. F) A sensed VPC initiates a new VOEI and a new AOEI. If the sinus rate is relatively fast, the atrial spike may occur within the PR interval because the pulse generator does not sense atrial activity, i.e., the sensed VPC from the ventricular electrode determines both the AOEI and VOEI. G) When the patient's intrinsic RR interval is very close but slightly slower than the programmed AOEI, atrial spikes may fall consistently within the PR interval of normally conducted beats causing an apparent increase in the rate of atrial pacemaker emission.

A particularly common and confusing situation simulating pacemaker malfunction with DVI units is illustrated in Figure 17G, wherein the spontaneous sinus rate is faster than the programmed ventricular rate but slower than the atrial output escape interval (V-A spike interval). In this situation, the spontaneous ventricular activity initiates a new atrial output escape interval and an atrial spike falls within the succeeding P-wave or PR interval, creating confusion about why the pacemaker is not "turned off" by the spontaneous ventricular rate which is greater than the programmed demand rate. Confusion may also result because slight variations in sinus rate may produce different interatrial spike intervals (Figure 18).

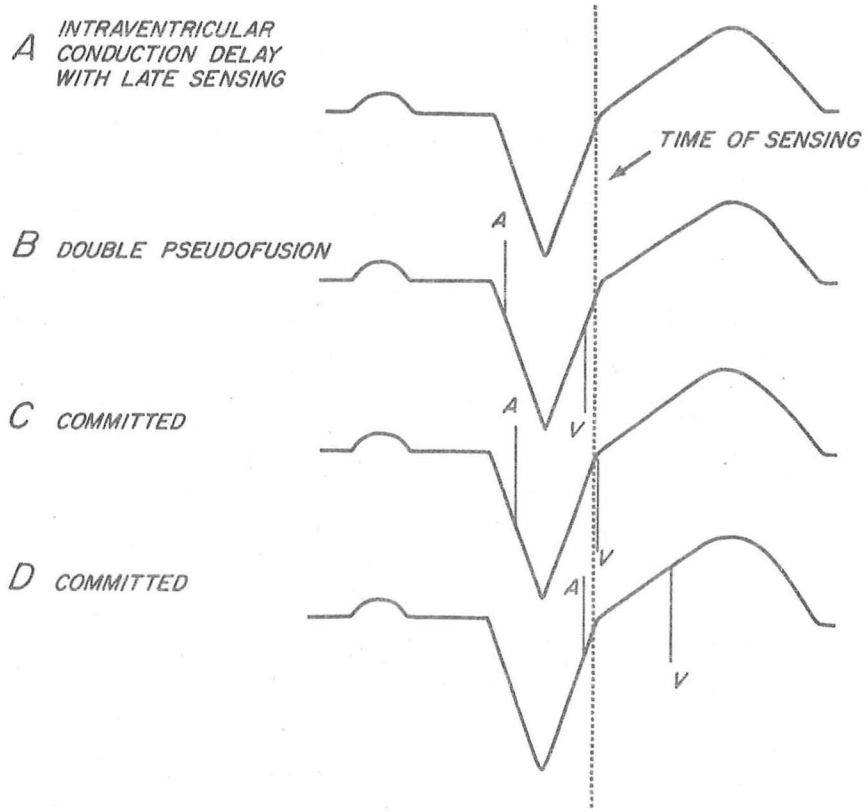
FIGURE 18: From Barold et al., 1980.



Paper speed 50 mm/s. Normally functioning Byrel DVI pulse generator showing an increase in atrial pacemaker rate. AOEI = 700 ms, AV sequential time = 250 ms, VOEI = 950 ms (free-running AV sequential rate = 63/min). The spontaneous PP interval exceeds the AOEI but is shorter than the VOEI. Consequently the pulse generator senses ventricular depolarization and emits only atrial spikes according to its fixed V-atrial spike interval (AOEI). Gradual slowing of the sinus rate from top to bottom causes progressive prolongation of the AA cycle length from 720 to 860 ms. The atrial spike progressively moves away from the QRS complex into the isoelectric portion of the PR interval and through the P wave until it precedes it whereupon it begins to pace the atrium. The spontaneous and the atrial paced PR intervals measure 140 ms. The V-atrial spike interval measures 720 ms, slightly longer than the AOEI (700 ms) because sensing of the ventricular electrogram occurs a brief but finite time after the onset of the surface QRS complex (see Figure 4 for explanation). All AA intervals are expressed in milliseconds.

In general, there are two types of DVI pacemaker design, called "committed" and "non-committed" based on whether ventricular output can be inhibited by a ventricular sensed event after the emission of an atrial stimulus. Patients with non-committed DVI units may have electrocardiograms on which only atrial spikes appear (Figure 17B,G and 18); sensing of a ventricular event before the end of the programmed atrioventricular delay inhibits ventricular output and allows the normally conducted beat or the ventricular escape beat to occur. In a "committed" DVI unit, however,atrial pacing will occur at predictable intervals after either ventricular sensing or pacing, and once an atrial spike is emitted, a ventricular spike will always follow. The committed DVI unit is thus an "all or none" emitter of pacing stimuli, and lack of two pacing stimuli in the same cycle is indeed a malfunction. Apparently inappropriate pacemaker output is most common when, because of intraventricular conduction delay, there is late sensing of ventricular activity, well within the QRS complex. When such a condition exists, pacing spikes or a spike may occur as demonstrated in Figure 19.

FIGURE 19.



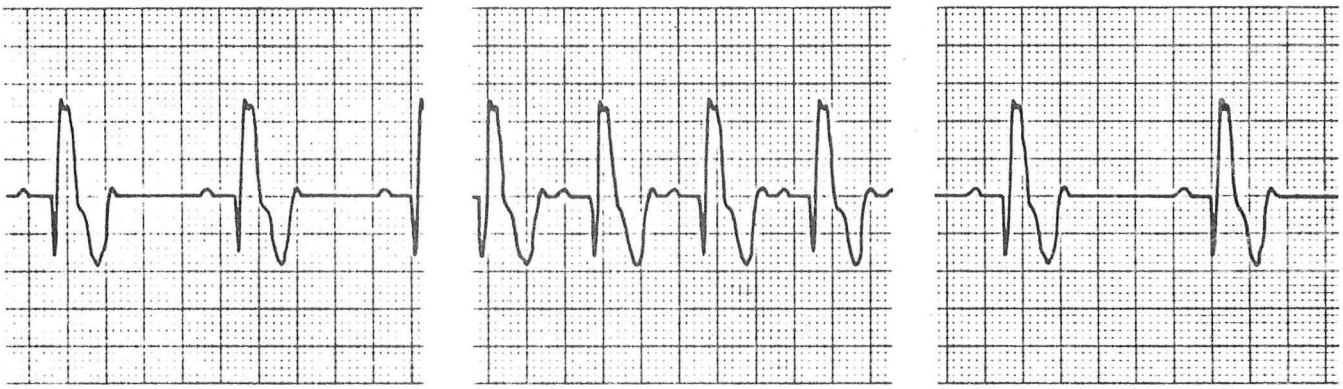
From Barold, et al, PACE 3: 712, 1980

Diagrammatic representation of intraventricular delay with late sensing. The ventricular electrogram inhibits the pulse generator only at the dotted line on the surface QRS complex. A: Inhibition of both atrial and ventricular output circuits. B: Double pseudofusion (combined pseudopseudofusion and pseudofusion beats). If the AV sequential time is relatively short (≲ 0.15 s) and the QRS is considerably widened both atrial and ventricular spikes can occur within the same QRS complex. The ventricular spike occurs just before the dotted line because ventricular depolarization has not yet generated sufficient intracardiac voltage to inhibit the sensing circuit. C: Double pacemaker spikes within the QRS complex with Intermedics DVI pulse generator. There is a pseudopseudofusion beat with delivery of the atrial spike on the initial descending limb of the QRS complex. This initiates a refractory period so that the ventricular spike occurs after the dotted line. Although the occurrence of double pacemaker spikes within the QRS complex resembles a double pseudofusion beat, the mechanism is different because the ventricular spike must always occur after the delivery of the atrial spike regardless of ventricular events. D: Intermedics DVI pulse generator. Late sensing may also cause "late" pseudopseudofusion beats and delivery of the ventricular spike near the apex of the T wave.

Although complete understanding of these principles can only be obtained by careful analyses of an ECG with calipers in the clinical setting, it should be easily understandable how pacemaker spikes may fall within spontaneous P-waves, PR intervals, QRS complexes, ST segments and ascending limbs of T-waves, during completely normal function of various DVI pulse generators.

The most common ECG pseudomalfunction observed with VDD pacing is much simpler to understand. The uninitiated observer may note that on serial electrocardiograms, the pacemaker rate is different, and in instances of abrupt changes in sinus rate, as may be observed with sinus arrhythmia, it may vary on a short ECG strip. Such findings are to be expected if the pacemaker is indeed sensing and "tracking" spontaneous atrial activity. Careful attention to the fact that pacemaker spikes follow spontaneous P-waves at constant intervals, and that there are never any atrial spikes observed, will be the key to the diagnosis of both the mode and the propriety of pacemaker function (Figure 20).

FIGURE 20: Normally functioning VDD (or DDD) pacemaker. Although ventricular pacing rate varies, atrioventricular synchrony and a constant A-V interval are maintained at atrial rates between the programmed upper and lower rate limits.



It must also be remembered that VDD units function in a "VVI backup" mode when the atrial rate falls below a programmed lower rate limit. This affords the added safety of ventricular pacing in the event that a patient's atrial rate is not always sufficient, usually because of changing clinical conditions after pacemaker implantation. Thus, in a patient with known VDD pacing who develops AV dissociation and VVI pacing at the lower rate limit, it should be obvious that the atrial rate is lower then than of the programmed lower rate limit. Upper rate limit responses of VDD units are similar to those of DDD units, and will be considered below.

DDD pseudomalfunctions are, in general, also easier to recognize and understand than those of DVI units. Figure 21 demonstrates a smooth transition from AV sequential pacing to atrial synchronous pacing with gradual acceleration of the atrial rate. The emergence of a spontaneous P-wave after the second ventricular complex, and the fact that it was appropriately sensed, explains the absence of atrial spikes during the remainder of the tracing. A common apparent pseudomalfunction is the response to sensed retrograde atrial electrical activity, which is sometimes not obvious from the surface ECG. Figure 22 represents such an instance where an early VPD is followed by a retrograde P-wave, which is sensed and which initiates an AV delay and ventricular pacing. There are at least three different responses to VPD's which vary among available DDD units. In some manufacturer's units the sequence of events in Figure 22 would indeed be malfunction.

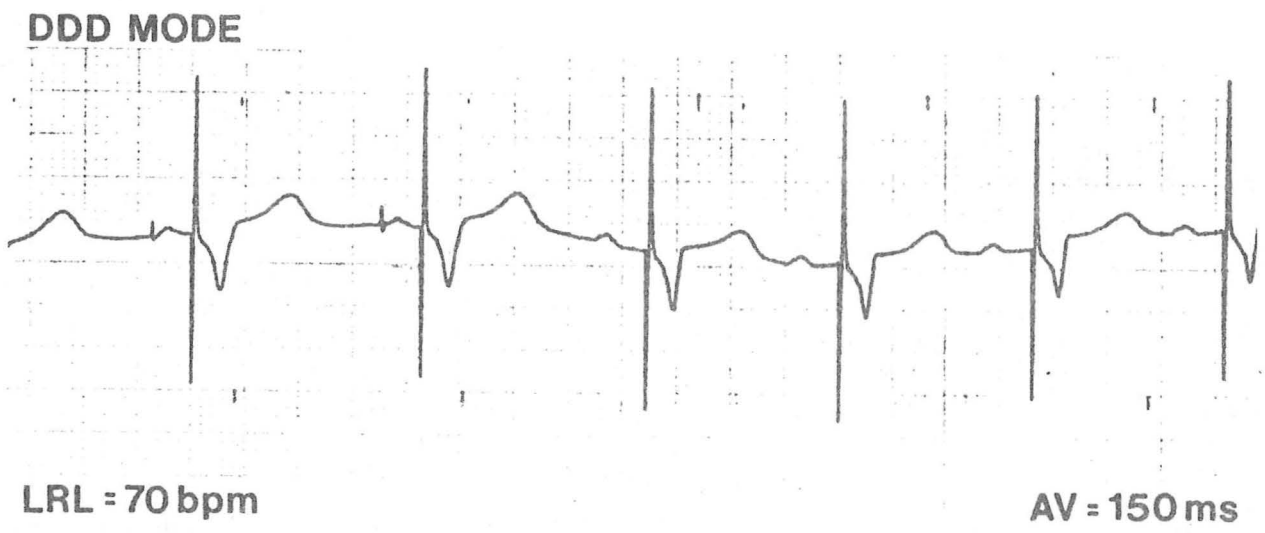
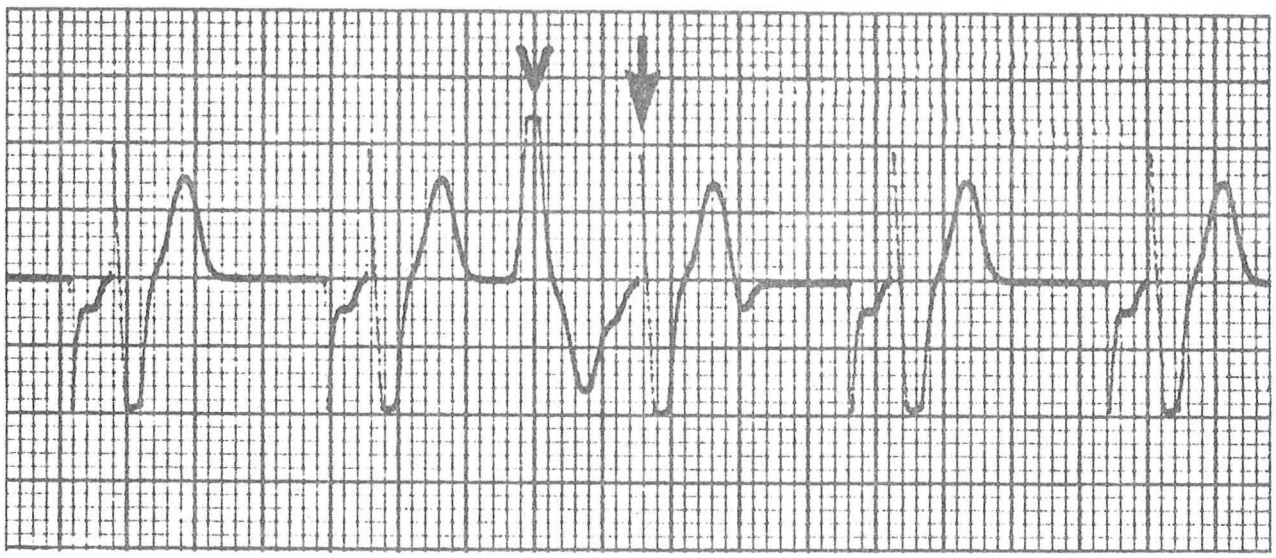


FIGURE 21: From Hauser, 1983. Smooth transition from A-V sequential pacing (first 2 complexes) to atrial synchronous ventricular pacing with gradual acceleration of the sinus rate. Programmed lower rate limit is 70/min; A-V delay = 150 msec.

FIGURE 22: From Hauser, 1983.

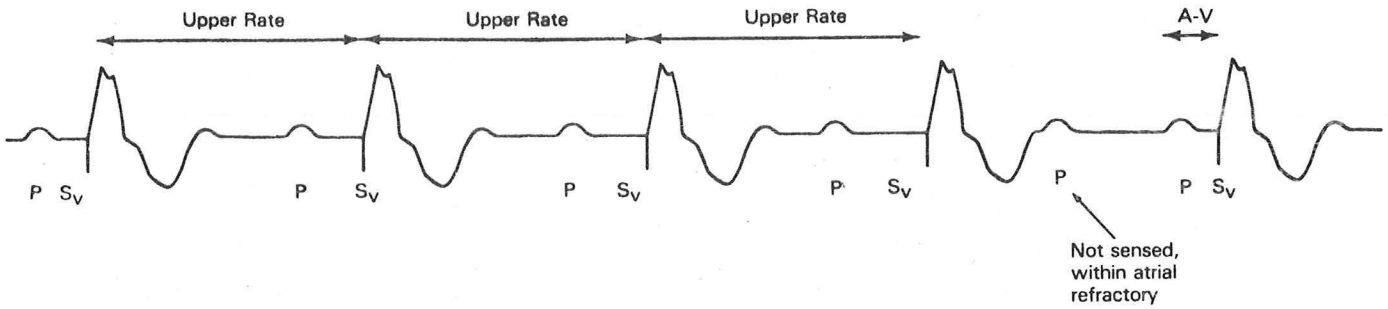


During DDD pacing, a VPC (V) is followed by an early atrial depolarization which triggers a ventricular stimulus. This R on T phenomenon may be avoided by extending the atrial refractory period after consecutive ventricular events.

It is important to understand the concept of an upper rate limit with atrial synchronous pacing modes (VDD and DDD). This is an obviously necessary feature to prevent life-threatening rapid ventricular pacing in response to atrial tachyarrhythmias (particularly atrial flutter). Upper rate limits are usually programmable up to values of approximately 175 beats per minute. When sinus tachycardia exceeds the upper rate limit, there are various "fall back responses" which determine the rate of ventricular pacing. Some units employ a rate smoothing method in which the unit shifts to a VVI mode at a rapid rate when the upper rate limit is exceeded, and the ventricular pacing rate is gradually decremented to a

lower rate over a period of minutes. Some units can be programmed to respond in a 2:1 AV block fashion in response to rapid atrial rates; this is much more useful when dealing with spontaneous ectopic atrial tachycardias than with exercise-induced sinus tachycardia. A popular and very ingenious upper rate limit response is a pseudo-Wenckebach pattern in which the AV interval successively prolongs until eventually a sinus beat is not sensed because it occurs during the atrial refractory period, and is thus blocked (Figure 23); ventricular pacing occurs after the next sensed sinus beat.

FIGURE 23: Wenckebach-like response to atrial sensed events which exceed the upper rate limit in a DDD unit.



Upper rate delays ventricular stimulus causing A-V prolongation.
5 P-waves → 4 ventricular stimuli
5:4 Block

True arrhythmias may also be caused by "physiologic" pacemakers which are functioning properly. Furman and Cooper (1982) have documented that atrial stimulation at a critical point after a spontaneous sinus beat may fall in the "vulnerable period" of the atrial cycle and initiate atrial fibrillation (Figure 24). Their retrospective review of 31 patients with recently implanted DVI units found that 5 who had not had previous atrial fibrillation or atrial flutter developed such an arrhythmia soon after pacemaker implantation. Obviously, appropriate atrial sensing in a DDD or VDD unit would obviate this occurrence.

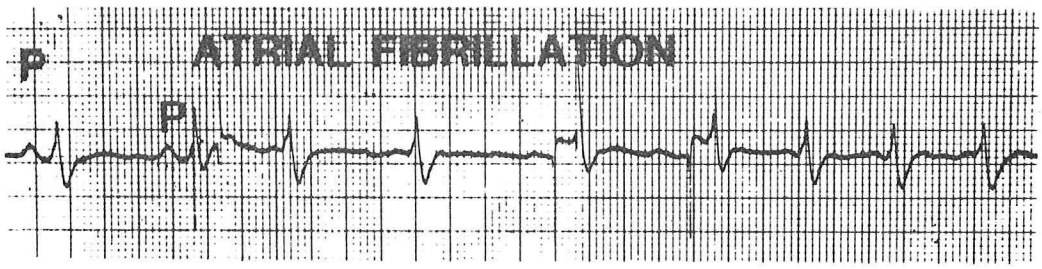


FIGURE 24: From Furman and Cooper, 1982. Induction of atrial fibrillation by competitive atrial pacing by a normally functioning "committed" DVI unit. An atrial spike falls in the "vulnerable period" of the second P wave.

Luceri et al. (1983) have reported an even more disastrous arrhythmia, occurring with a committed DVI unit in which "late" sensing of a VPB allowed a ventricular stimulus in the vulnerable period of the cardiac cycle, initiating sustained ventricular tachycardia (Figure 25).

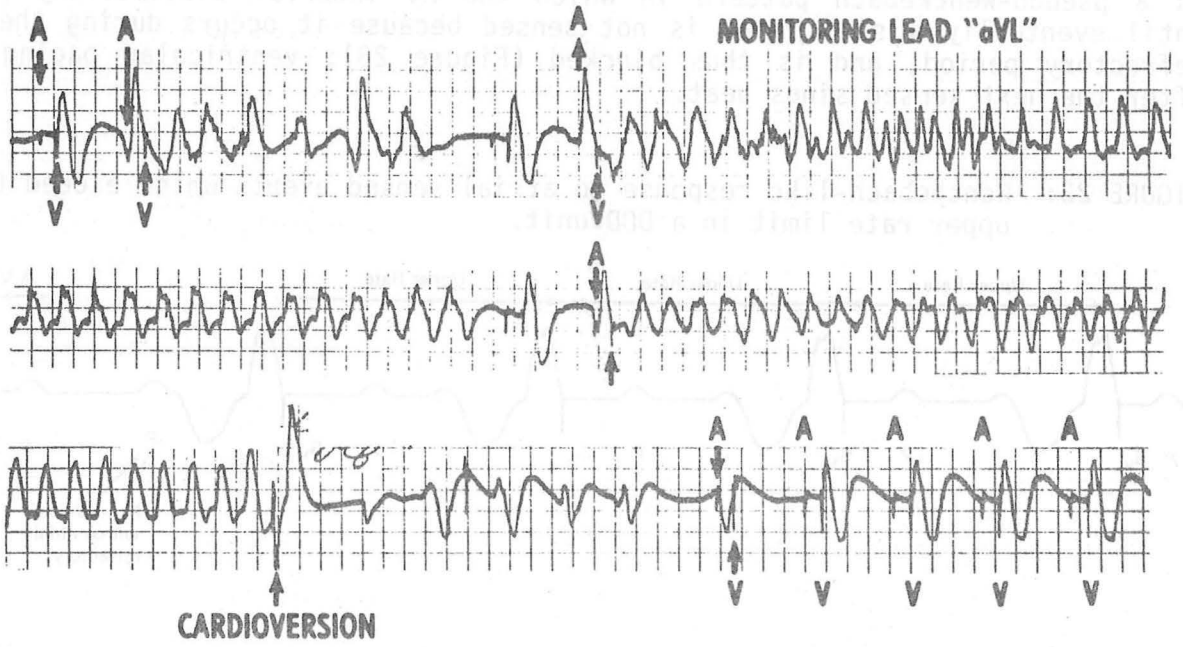
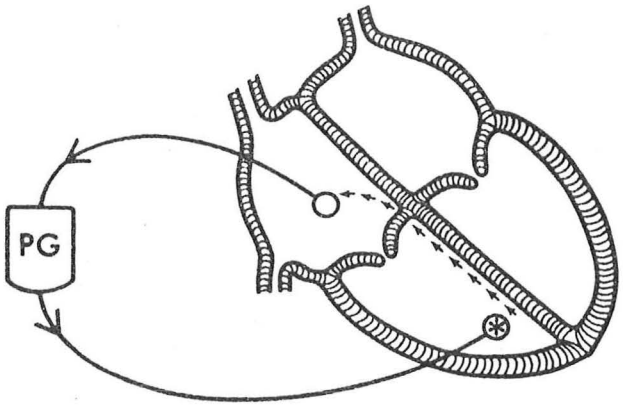


FIGURE 25: From Luceri et al., 1983. Continuous strips showing several episodes of similarly coupled non-sensed premature ventricular complexes resulting in ventricular (V) stimulation causing repetitive responses and ventricular tachycardia. Cardioversion terminated one episode of ventricular tachycardia in the bottom strip.

A much more common and truly "new" arrhythmia has also been described in some patients with atrial sensing dual chamber units (VDD, VAT and DDD). The arrhythmia has been called "pacemaker-induced tachycardia" (Tolentino et al., 1982), "endless loop tachycardia" (Furman and Fisher, 1982), and probably most appropriately, "pacemaker-mediated tachycardia" (PMT) (Furman, 1982). In this arrhythmia, intact retrograde ventriculoatrial conduction results in an atrial electrical event which is sensed, and which therefore initiates a new A-V delay which is followed by ventricular pacing (Figure 26); each subsequent paced ventricular beat produces another retrograde atrial depolarization, which is sensed, initiating another A-V delay and ventricular pacing. The pulse generator essentially acts as a "bypass tract" which links retrograde P-waves to paced QRS complexes.

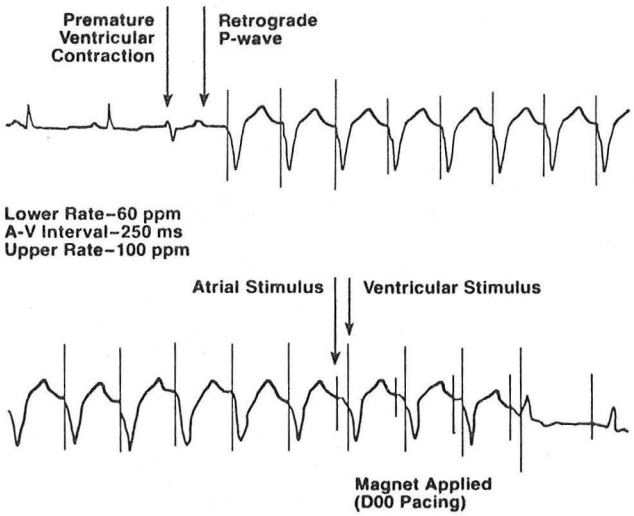
FIGURE 26: From Tolentino et al., 1982.



Each time the ventricle is depolarized by the pacer stimulus, the impulse is retrogradely conducted (arrows) into the right atrium which is subsequently detected by the atrial electrode. The pulse generator then triggers the next stimulus into the ventricle and the cycle is repeated. Therefore, as long as the retrogradely conducted impulses reach the atrium after the pacemaker ventricular refractory period of 140 ms has elapsed, tachycardia will persist at a rate equivalent to the programmed atrial rate limit of 100, 125, 150 or 175/min.

Pacemaker mediated tachycardias commonly begin after spontaneous ventricular premature beats which are conducted retrogradely to the atria. They may also be initiated by any form of asynchronous or non-AV sequential ventricular pacing, such as that which might occur at the end of magnet application, after transient failure of atrial sensing, during the VVI backup response in a VDD unit, or with post-ventricular premature beat responses in some pacemakers. The tachycardias characteristically produce a ventricular rate equal to the programmed upper rate limit of the pacing system. They may be terminated by any intervention which eliminates either retrograde conduction or the capacity for atrial sensing at the time of such conduction. Magnet application, which eliminates atrial and ventricular sensing, is the easiest way to terminate such a pacemaker mediated tachycardia (Figure 27). Also, reprogramming of an implanted unit from an atrial sensing mode (VDD, DDD, or VAT) to either DVI or VVI will eliminate the tachycardia.

FIGURE 27: Initiation of pacemaker mediated tachycardia in a patient with a DDD unit. A premature ventricular contraction during normal sinus rhythm is followed by ventriculoatrial conduction which initiates the tachycardia. The tachycardia is terminated by application of a magnet, which produces asynchronous AV sequential pacing (DOO). When the magnet is removed atrial pacing at the lower rate limit begins (last complex).



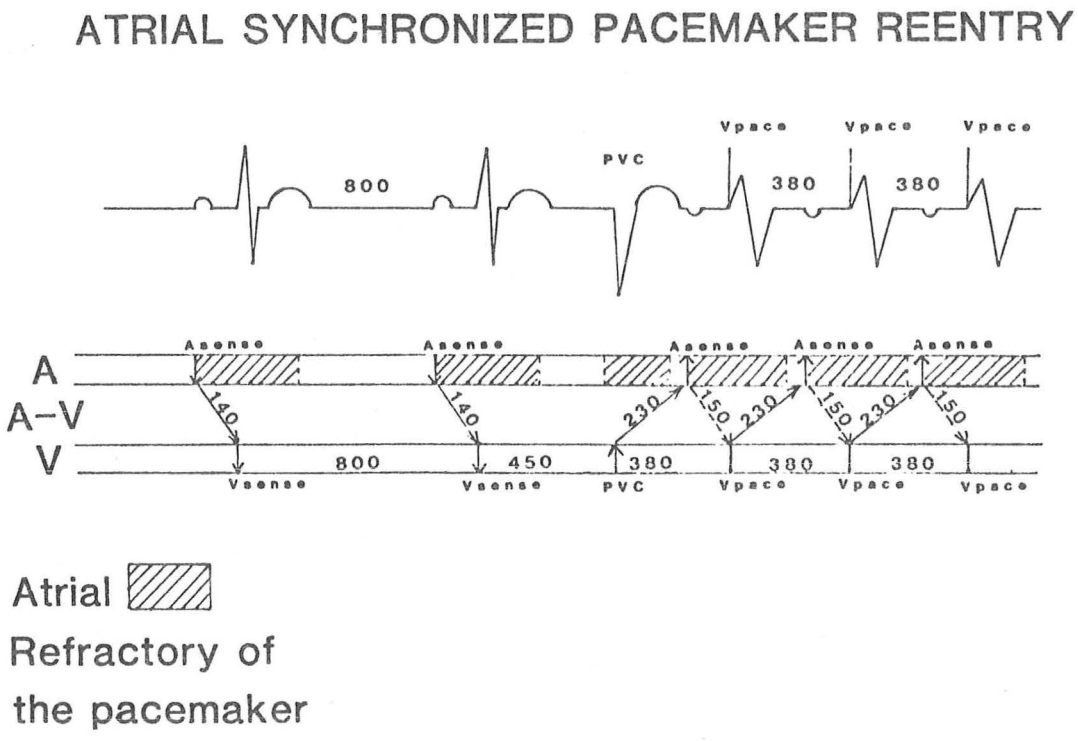
The occurrence of such arrhythmias has sparked renewed interest in limited electrophysiologic study before or during pacemaker implantation in patients with symptomatic bradycardias and conduction blocks and obvious clinical indications for permanent pacemaker implantation. Hayes and Furman (1983), and Levy et al., (1983), have found intact ventriculoatrial conduction in one third of patients with abnormal antegrade conduction, including an incidence of 25% of patients with complete antegrade atrioventricular block (Figure 28). The incidence of 1:1 VA conduction in patients with sinus node disease was 67% in the study by Hayes and Furman (1983). The mean ventriculoatrial conduction time was 235 msec, although it ranges widely from 110 to 380 msec (Hayes and Furman, 1983).

FIGURE 28: From Hayes and Furman, 1983.
Incidence and characteristics of ventriculoatrial conduction in patients undergoing permanent pacemaker insertion.

		1:1 VA Conduction		VA Conduction Time At Lowest Rate
Primary DX	**No.**	**Pts**	**%**	**ms**
Sick Sinus Syndrome	6	4	67	222
Sinus Brady/Arrest	16	11	69	214
Incomplete AV Block	14	5	36	293
Complete AV Block	16	4	25	210
Ventricular Tachycardia	1	1	100	NA
TOTAL	53	25	47%	235 ms

A primary determinant of whether retrograde P-waves can be sensed in the atrium is the duration of the pacemaker's atrial refractory period, or that time after a sensed or paced atrial event or sensed VPB during which the atrial sensing amplifier is disabled. Only when retrograde P waves occur after the atrial refractory period can pacemaker mediated tachycardia be sustained (Figure 29).

FIGURE 29: From Messenger et al., 1983.



Atrial refractory periods in various DDD pacing units vary from 155 to 500 msec, and are sometimes externally programmable. Thus, for a retrogradely conducted P-wave to sustain a reciprocating pacemaker mediated tachycardia, it must occur "late", that is after the end of the existing atrial refractory period. The advantage of a programmable atrial refractory period is that one can usually select a value which renders the first retrograde P-wave unsensed, thus making initiation of PMT impossible. The disadvantage of long programmed atrial refractory periods is that it infringes upon the available upper rate limit for atrial synchronous pacing which provides rate responsiveness during sinus tachycardia. For instance, if the atrial refractory period is 500 msec, and the programmed atrioventricular interval is 150 msec, the maximum heart rate achieved during atrial sensing cannot be greater than $\frac{60}{0.650}$ = 92.3 beats per minute. Other potential ways of preventing sustained pacemaker mediated tachycardias are programming the upper rate limits or A-V intervals to either very low or high values, pharmacologic therapy (verapamil or digitalis) to block retrograde A-V nodal conduction, and programming atrial sensitivity so as to detect higher amplitude sinus P-waves but not lower amplitude retrograde P-waves. It is very likely that other means will be available in the future to eliminate unwanted sensing of retrograde P-wave activity.

For the present time, the practical implications of pacemaker mediated tachycardia are:

1. Patients being considered for atrial sensing dual chamber pacemakers should be tested at the time of pacemaker implantation, or at a separate electrophysiologic study, for the presence of 1:1 V-A conduction during ventricular pacing at various heart rates. Knowledge of the presence or absence of ventriculoatrial conduction, and the ventriculoatrial conduction time may allow programming of a permanent pacing system to prevent pacemaker mediated tachycardia, and may lead to selection of one available model over another.

2. All patients with atrial sensing pacemakers should be monitored (either Holter monitoring or inpatient telemetry monitoring) for spontaneously occurring pacemaker mediated tachycardia after permanent pacemaker insertion.

3. In patients at particular risk of major sequelae of an unexpected pacemaker mediated tachycardia (e.g., ischemic heart disease patients with angina), it is probably wise to program the upper rate limit to a low value until it is determined whether spontaneous PMT will occur.

INDICATIONS FOR PHYSIOLOGIC PACING

The above apparent advantages and potential disadvantages of "physiologic" pacing systems, and the fact that long term follow-up of many of the units is not available, make it obvious that there can be disagreement among reasonable physicians as to the indications and contraindications for the use of available pacing modes other than VVI. The following indications and contraindications to the use of such modes are general rules which have evolved at Parkland Memorial Hospital over the last two years. Insofar as possible, they are based on data from the literature that there is at least moderate chance of improvement in patient well-being attributable to the use of a specific mode other than VVI. Doubtlessly, these indications will change as further evidence of long term efficacy or inefficacy of "physiologic pacing" modes becomes available, and as technologic improvements occur.

AAI units are classically indicated for patients with fixed or intermittent atrial bradyarrhythmias such as sick sinus syndrome (sinus bradycardia, SA block, sinus arrest) sinus bradycardia due to drug therapy, and as chronic "overdrive" treatment for various arrhythmias. Contraindications to this mode of pacing are atrial inexcitability (e.g., atrial fibrillation) and overt atrioventricular block. It is problematic as to how extensively one should look for occult atrioventricular block before also implanting a ventricular lead. Some authors (Sutton and Citron, 1979) have advocated electrophysiologic study, to include measurement of the H-V interval during rapid atrial pacing, to define patients "at risk" of developing manifest A-V block in the future. Our approach has usually been to implant non-committed DVI units in such patients, and to program the AV interval beyond the existing PR interval (e.g., to 250 msec). In this fashion, the noncommitted DVI unit functions quite similarly to an atrial demand unit, and does not pace the ventricle unless at least first degree A-V block develops. In the absence of chronic ventricular pacing, battery drain is similar to that with an AAI unit; and the capacity for immediate ventricular pacing exists if the patient suddenly develops heart block. Competitive atrial pacing is not a major problem in this patient population if fixed sinus bradycardia is present.

VDD units are most commonly used in patients with chronic or intermittent atrioventricular block with normal sinus node function. The advantage of the unit, of course, is that both atrial synchrony and rate responsiveness, within programmed limits, are possible, as long as sinus node function remains normal. Contraindications to such units are sick sinus syndrome, atrial fibrillation or flutter, and intact ventriculoatrial conduction at such intervals as to make pacemaker mediated tachycardia likely. We do not implant such units to maintain AV synchrony in patients who have only very intermittent A-V block with normal sinus rhythm; such patients are treated with VVI units which give them adequate "rate back-up", unless it thought that their atrioventricular conduction problems are progressive. VDD units should be particularly considered in younger patients who are more active, and in those patients with relatively normal left ventricular function or left ventricular diseases with decreased ventricular compliance, which make them more susceptible to the pacemaker syndrome with VVI pacing.

DVI units are classically indicated in patients with sinus bradycardia, SA block or sinus arrest in conjunction with various degrees of or risk for atrioventricular block, especially when maintenance of atrioventricular synchrony is considered important. They are also quite useful in the carotid sinus syndrome, particularly in patients with a vasodepressor response, in which hypotension may occur even with ventricular pacing; the enhanced stroke volume due to an "atrial kick" in this situation may improve the blood pressure enough to lessen the patient's symptoms during a vasodepressor response. The major contraindication to DVI units is atrial inexcitability, particularly atrial fibrillation. Because of the reported incidence of induction of atrial fibrillation by these units, they should be used carefully in patients with paroxysmal atrial fibrillation, and they are relatively contraindicated in patients who have the capacity to develop sinus tachycardia with ventricular rates below the demand rate of the unit (e.g., sinus tachycardia with second degree AV block). Such a situation is a perfect milieu for competitive atrial pacing and induction of atrial fibrillation.

DDD units are indicated in patients who have combinations of atrioventricular block and the sick sinus syndrome, particularly if maintenance of atrioventricular synchrony and/or rate responsiveness is thought to be of importance in their management. The units may also be of help in carotid sinus syndrome, as are DVI

units. DDD units provide all the advantages of VDD units with the added capacity for atrial pacing should it ever become necessary, and have therefore almost eliminated the use of VDD units in some centers. The major contraindication to these units is atrial fibrillation or flutter, which results in atrial inexcitability and potentially non-physiologic atrial synchronous pacing. A relative contraindication is the presence of retrograde ventriculoatrial conduction with V-A intervals which are very likely to result in sustained pacemaker mediated tachycardia. Most DDD units are programmable as to mode, and if PMT is an incurable problem after pacemaker insertion, it can be eliminated by programming to the DVI mode. This function also allows temporary control of the arrhythmia while other programming and/or pharmacologic maneuvers are carried out in an attempt to prevent PMT.

Of major importance in the evaluation of patients for physiologic pacing modes is some common sense assessment of the level of the patient's expected activity, and the frequency of the bradyarrhythmia being treated. Pacemaker candidates vary in extreme from very inactive octogenarians with infrequent but severe sinus bradycardia to extremely active children with congenital heart block and normal exercise capacities during rate responsive pacing. Selection of pacing modes is relatively easy for these extreme examples, but is sometimes more difficult for patients who fall in between. A further complicating factor is that when the need for permanent pacing becomes obvious, the patient is usually not considered stable enough to perform normal exercise testing which might define the responsiveness of the atrium to autonomic stimuli. Resting hemodynamic evaluations are also not routinely performed, particularly if the patient is dependent on the presence of a temporary pacemaker which might be dislodged by further catheterization. Thus a careful history of the patient's ordinary activities, hopefully including that period before the onset of the symptomatic bradyarrhythmia, is the best, although certainly imperfect guide to deciding which pacemaker mode might be indicated.

FUTURE DIRECTIONS IN RATE RESPONSIVE PACING

Significant numbers of patients paced for bradyarrhythmia have sinoatrial disease with inappropriate sinus bradycardia. Rickards and Donaldson (1983) reported that of 13,000 patients undergoing pacemaker implantation during the last 23 years in the United Kingdom, 32% had an obvious sinus node abnormality or atrial arrhythmia (e.g., atrial fibrillation) and estimated that another 22% of patients were likely to develop sinoatrial disease within a short time. They calculated that about 54% of pacemaker candidates would not benefit from atrial synchronous pacemakers which require a normally responsive sinus node to mediate an increase in ventricular rate. Thus, a large number of patients might be helped by pacemakers which increase ventricular pacing rate during exercise and activity in the absense of normal atrial responses to such stimuli.

Potential indicators of increased metabolic demand which might be used as "markers" to mediate an increased ventricular pacing rate are listed in Table 2.

TABLE 2: From Rickards and Donaldson, 1983.

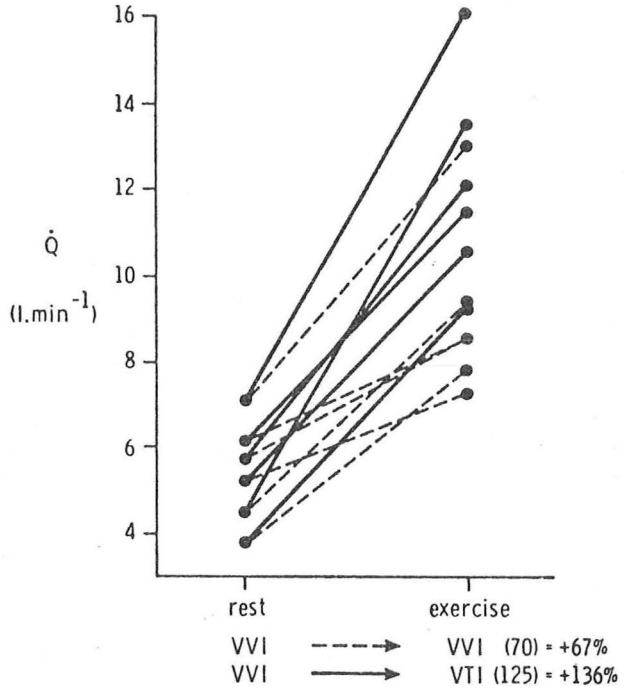
	Sensor	Pacemaker
Metabolic Demand		
Primary indicators		
Catecholamines	N/A	—
Sympathetic drive	N/A	—
Secondary indicators		
Atrial rate	atrial electrode	VAT, VDD, DDD
QT interval	none	C.E.
Stroke volume	RV electrodes	EXT
Pacing threshold	none	—
QRS time	none	—
Exercise		
O_2 saturation	RV oximeter	EXT
pH	RV pH electrode	C.E.
Temperature	RV thermistor	EXT
Respiration rate	Thoracic dipole	C.E.
Stroke volume	RV electrodes	EXT

Sensor implies additional device needed other than a ventricular electrode; EXT = implemented as an external test device; C.E. = implantable device in clinical evaluation.

There are no reports of pacing systems which respond to primary indicators of metabolic demand such as circulating catecholamines and sympathetic nerve traffic, but rate responsive pacemakers are in development which might respond to secondary indicators of metabolic demands such as shortened QT interval and increased stroke volume. Similarly, preliminary data suggest that it might be possible to design pacing systems which respond to exercise-induced changes in central venous oxygen saturation, venous pH, central body temperature, and respiratory rate.

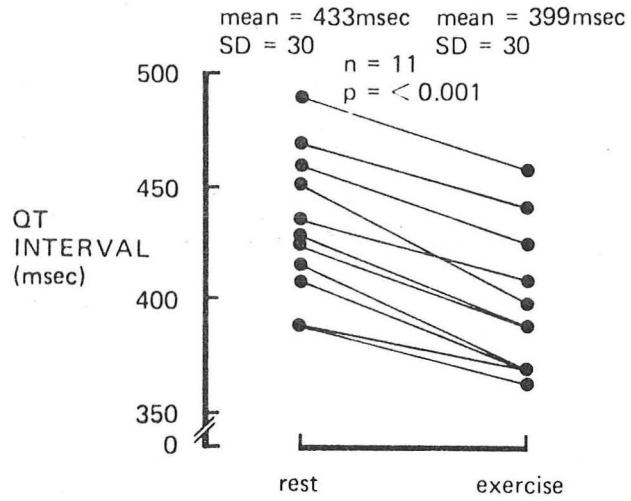
Rickards and Norman (1981), have described a pacing system which senses the physiologic shortening of QT interval which occurs with an increase in circulating catecholamines during exercise or emotional stress (Figure 30). By the end of 1982, 13 permanent units had been implanted. Preliminary reports (Rickards and Donaldson, 1983) demonstrate greater increases in cardiac output during maximal treadmill exercise with such "evoked QT pacing" than during fixed rate VVI pacing (Figure 31). The investigators feel that the technical design of the device is sound, but that more experience is required in larger numbers of patients in view of possible responses to biologic changes in QT interval which might occur (drug effects, effects of myocardial ischemia, etc.).

FIGURE 30: From Milne et al., 1982.



Cardiac output (Q) measurements in six patients by paired thermodilution during rest and maximal treadmill exercise during VVI pacing and QT pacing (VTI) with upper rate limited to 125 ppm. % indicates mean increase in cardiac output during the two modes of pacing.

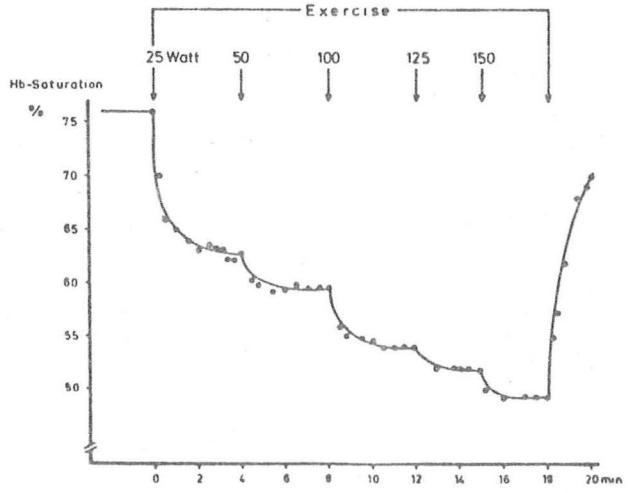
FIGURE 31: From Rickards and Donaldson, 1983.



Effect of exercise on the QT interval at identical ventricular paced rates.

Wirtzfeld has pioneered studies of an implantable optical sensor of mixed venous oxygen saturation which might serve as the basis for a rate responsive pacemaker. As patients exercise at fixed heart rates, central venous oxygen saturation is decreased; detection of this change by a phototransistor detector mounted on a pacing electrode in the central venous circulation is possible (Wirtzfeld et al., 1982, 1983); (Figure 32). These investigators are currently attempting to derive an algorithm which links sensed changes in oxygen saturation to appropriate changes in pacemaker rate, and have preliminary data with external pacing devices to suggest that this is feasible. Unlike the evoked QT sensing unit, the central oxygen saturation unit requires a sophisticated implanted sensor which may have more inherent instability. Furthermore, algorithms to deal with changes in oxygen saturation from other causes, particularly pulmonary diseases and non-bradycardia related heart failure, will be necessary.

FIGURE 32: From Wirtzfeld et al., 1982.
Sensed decrease in central venous oxygen saturation with increasing exercise load and duration, and return toward baseline at end of exercise.



Like central venous oxygen saturation, venous pH falls with sustained exercise. Cammilli et al. (1978) have reported a pH sensor constructed of iridium oxide which senses right atrial venous pH and causes a gradual increase in firing rate of a ventricular pacemaker. Stability of the pH electrode, relatively long time constants in changes in venous pH, and problems in distinguishing acidosis due to other causes have been limiting factors to date in the development of a pH-triggered pacemaker.

Griffin et al (1983) have suggested that a pacemaker system might increase heart rate in response to the sensed increase in body temperature which occurs with exercise. Although the required sensors (thermistors) are relatively well developed and appear to be stable, the technique may be limited by the relatively slow (several minutes) increase in blood temperature after the onset of exercise.

Rossi et al (1983) have used a respiratory rate responsive pacemaker successfully in two patients. The device takes advantage of the relationship between increases in respiratory rate and heart rate during exercise in individual patients. Respiratory rate is sensed by dipole changes between an extra subcutaneous lead and the pacemaker itself(Figure 33). Because the mathematical relations between respiratory rate and desired heart rate vary between individuals, a programmable algorithm of pacing rate response is necessary. This device is technically straightforward, but its adequacy is as yet unproven in significant numbers of patients.

FIGURE 33: From Rossi et al., 1983.

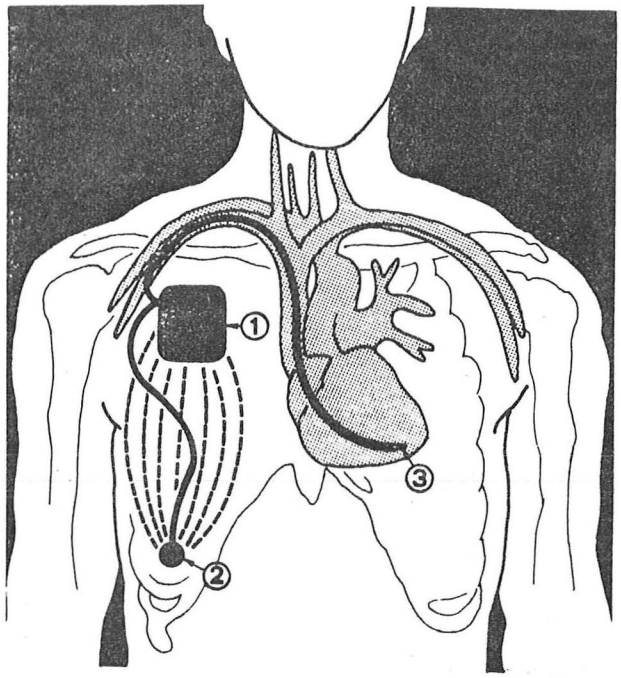


Diagram of the respiration-dependent pacemaker system. (1) Pacemaker, (2) Auxiliary lead, (3) Pacing lead.

Although no published data exist, Knudson (Rickards and Donaldson, 1983) has applied for a patent on a pacing system which incorporates an algorithm to alter ventricular pacing rate based on sensed right ventricular stroke volume. Additional electrodes on a ventricular pacing catheter would determine changes in right ventricular stroke volume by an electrical impedance principle. When venous return is increased at the onset of exercise, a sensed increase in right ventricular stroke volume would mediate an increase in heart rate. The system attempts to maintain a constant right ventricular stroke volume by altering heart rate as necessary.

Although extensive research and development will be necessary before widespread clinical testing and availability of such pacing systems, it is very likely that research will lead, within this third decade of cardiac pacing, to devices which are capable of improving rate responsiveness to stress in significant numbers of patients who are currently limited to fixed heart rates during exercise.

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