The use of artificial electrical stimuli for pacing the heart in the prevention of Stokes-Adams attacks associated with complete heart block is the accepted method of treatment. This is usually accomplished by the insertion of an endocardial pacemaker into the right ventricle or the direct attachment of epicardial electrodes to the surface of the right ventricle at thoracotomy. When this is done, there is no longer synchronous atrial contraction and the transport function of the atrium is lost. Because of this, atrial-triggered pacemakers have been designed and used. The contribution of the atrium to ventricular output has been shown to be important in the isolated heart-lung preparation, during fast and slow rates experimentally and in patients with myocardial decompensation.

When the cardiovascular system is intact, however, and no disease is present, the importance of atrial contraction is still a controversial subject, but most acute physiological experiments in animals suggest that when atrial contraction is asynchronous, the cardiac output and blood pressure tend to be lower.

When an electrical stimulus is applied to the heart, depolarization of the myocardial membrane occurs, followed by contraction. This is followed by repolarization of the cell which is divided into two phases—an initial absolute refractory period, followed by a relative refractory period—and corresponds to the QT interval on the electrocardiogram. If a stimulus is applied during the absolute refractory period, no response is elicited; but outside this, depolarization can occur.

Paired pacing is where the heart is excited by two selectively spaced artificial stimuli, the first causing depolarization and subsequent mechanical contraction, the second occurring shortly after the absolute refractory period causing a second depolarization; which is mechanically ineffective. The subsequent contraction is potentiated, resulting in a more forceful ventricular contraction with better and more rapid ventricular emptying. This phenomenon is known as post-extrasystolic potentiation (PESP) and also occurs after spontaneously-occurring ectopic rhythms. It is a fundamental characteristic of mammalian cardiac muscle. The history and development of this phenomenon have been reviewed by Cranfield. When the paired stimuli are applied continuously, they act as the cardiac pacemaker and will break both normal and ectopic rhythms. Clinically this has been tried for the treatment of serious and unmanageable tachycardias. Because of the powerful positive inotropic effect, it has been used both experimentally and clinically for the treatment of heart failure. In the normal heart PESP, like digitalis, does not result in any improvement in cardiac function. PESP can be satisfactorily elicited only from the ventricle, since when two stimuli are applied to the atrium the second may be delayed by the AV node and fail to depolarize the ventricle.

This paper compares the effects of right atrial pacing and right ventricular pacing with single and paired electrical stimuli in anaesthetized dogs before and during increased stress (afterload) produced by raising the blood pressure with an angiotensin infusion. Right single atrial and right ventricular paired pacing were also compared during and after acute reversible heart failure.

METHOD

Twelve mongrel dogs weighing between 15 and 24 kg. were studied. Each dog underwent right thoracotomy under thiopentone anaesthesia. The pericardium was opened and alcohol injected into the region of the sinus node which was later crushed and sutured to achieve sinus arrest. Pacemakers were sewn to the upper part of the right atrium and the anterior surface of the right ventricle.

The dogs were allowed to recover and between 24 and 48 hours later were anaesthetized with 15 mg./kg. of pentobarbitone initially and maintained on a constant infusion of approximately 0·05 mg./kg./min. throughout the experiment. All dogs were intubated and breathed O2 spontaneously through a Manley respirator. Catheters were placed in the left ventricle and thoracic aorta for recording pressures via a Statham P23D strain-gauge with zero point at level of the mid-right atrium: the first derivative of the left ventricular pressure was recorded on a RC differentiating circuit. The pressure tracings plus the electrocardiogram were recorded photographically on a NEP (Honeywell) recorder.

Cardiac output was measured after injection of 1·25 mg. of cardiozyn into the right atrium via a catheter and a constant volume syringe (Clay, Adams, Aupette) and sampling via a femoral artery using a Waters densitometer X502 with a Sanborn computer and constant withdrawal (38·9 ml./min.) Harvard pump. All blood was reinfused. The densitometer and computer were previously calibrated using the dog's blood and a preselected dye concentration. At the end of the experiment a dog's blood was calibrated again to see if the effect of the background dye was important.

The heart was paced at 3 milliamperes using a transistorized battery-driven pulse generator capable of delivering single or paired stimuli (Metronics Inc. Model 583A). Throughout each experiment the heart rate was held constant. After 4 minutes of pacing, during which a steady state was obtained, dual cardiac output, left ventricular pressure and its first derivative (\( \frac{dp}{dt} \)) LV end-diastolic pressure and aortic mean pressure were recorded. The mode of pacing was then changed and the measurements repeated after a further 4 minutes.

When the effects of right atrial and right ventricular single and paired pacing had been measured, angiotensin had been infused to increase the afterload, and after 8 minutes, when the pressure had been increased significantly and was not varying, all measurements were again recorded during the 3 types of pacing.

Stroke volume was calculated by dividing cardiac output by heart rate. Stroke work from the formula

\[
\text{Stroke work (G/m.)} = \frac{\text{SV} \times (\text{MAP} - \text{LVED}) \times 1.36}{100}
\]

where

- SV = stroke volume ml.
- MAP = mean aortic pressure mm.Hg.
- LVED = left ventricular end-diastolic pressure mm.Hg.

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The mean aortic pressure was measured by electrical integration.

When the angiotensin had been discontinued for at least 20 minutes and the haemodynamic parameters had returned to the control state, atropine in a dosage of 0.07 mg./kg. and propranolol in a dosage of 0.4 mg./kg. were administered to produce complete autonomic nervous blockade of the myocardium. Right ventricular paired pacing and right atrial single pacing were then compared. Experimental heart failure was next induced by infusing angiotensin to raise the systemic pressure to a significant level and additional propranolol up to 2.5 mg./kg. was given intravenously. This would produce heart failure as judged by a decreased cardiac output, blood pressure and a raised left ventricular end-diastolic pressure. When this had been achieved the right atrial and right ventricular paired pacing were again compared. Lastly, the angiotensin was discontinued and isoprenaline infused to overcome the beta-blockade produced by propranolol. By this means heart failure could be reversed and the two types of pacing were again compared.

**RESULTS**

The average heart rate of 12 dogs was 116, with a range of 108-145. In all cases single right ventricular pacing could be achieved with no atrial interference, and paired

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**Fig. 1.** Values during right atrial pacing (RA) and right ventricular pacing (RV) before and during angiotensin. 1(a). Pressure. 1(b). Stroke volume. 1(c). Stroke work.

**Fig. 2.** Right atrial single pacing (RAsp) compared with (RVpp) before and during angiotensin. 2(a). Pressure. 2(b). Stroke volume. 2(c). Stroke work.
pacing was easily accomplished with a stimulus interval between 160 and 210 millisees, at 5 volts, which was usually twice the diastolic threshold. In Fig. 1a, where right atrial pacing is compared with single right ventricular pacing, the blood pressure decreases slightly with a mean drop of 7-2 mm.Hg and 8-7 mm.Hg after angiotensin. The stroke volume (Fig. 1b) is similarly compared and the average decrease of 14% is unchanged by angiotensin. The stroke work (Fig. 1c) shows a decrease of 35% and 37% with angiotensin during right ventricular single pacing. The average rise in left ventricular end-diastolic pressure with right ventricular single pacing was 0-06 mm., and 0-04 mm. when the blood pressure was raised. Percentage decline of dp/dt was 14 and 16%, respectively. Thus in all measured parameters, right atrial pacing was superior to right ventricular single pacing.

When right atrial pacing was compared with right ventricular paired pacing, before and after angiotensin, no striking differences in either the stressed or non-stressed heart were seen. Fig. 2a shows that the blood pressure is not significantly changed, while Figs. 2b and 2c show that stroke volume and stroke work are likewise unchanged. The minor variations seen are all within the limits of experimental error and are not statistically significant. However, the first differential of the left ventricular pressure pulse (dp/dt) shows a 20% increase with paired pacing, which increased to 30% when afterload was present, and the end-diastolic pressure decreased 1-1 mm.Hg during control and 1-5 mm.Hg during increased afterload. This confirmed the known observation that the velocity of contraction and the compliance of the left ventricle are altered by paired pacing but do not necessarily result in increased output or external work.

After autonomic blockade by propranolol and atropine, stroke work (which incorporates both the variables of pressure and stroke volume) again shows no significant change between right atrial and right ventricular paired pacing and is comparable to Fig. 2. The end-diastolic pressure is decreased and dp/dt is increased by paired pacing.

During experimental heart failure (Fig. 3a) significant and dramatic improvement occurs following paired pacing as shown by the increase in stroke volume, work and aortic pressure (Fig. 3b), while left ventricular end-diastolic pressure falls. This shows that the powerful inotropic stimulus of post-extrasystolic potentiation produced by

![Heart Failure Diagram](image-url)
taken show that pressure and stroke work during paired
and single pacing are the same, and once more comparable
to the results in Fig. 2.

The over-all result in comparing right atrial single
pacing with right ventricular paired pacing is shown in
Fig. 4. This demonstrates that only when heart failure is
present, is a significant increase in heart performance
produced by paired pacing.

**DISCUSSION**

The cardiac output in anesthetized dogs is known to vary
moderately.\(^1\) Pentobarbitone was the anesthetic agent
used and is known to have an anticholinergic effect\(^2\) and
in large doses a significant myocardial depressant effect.\(^3\)
Dogs were lightly anesthetized to avoid this, and a slow
continuous infusion was used to achieve this steady state
of anesthesia. Although considerable fluctuation in output
was noted initially, about 1 hour after induction of
anesthesia the output was relatively stable, and the
measurements could be commenced. A thoracotomy was
done on the previous day to allow the dogs time to recover
and thus prevent fluctuations in output.

The sinus node was obliterated, to cause a slower rate
so that paired pacing could be established at the same rate
as single pacing, and to impair atrial contraction grossly,
i.e. remove the atrial contribution to ventricular filling.
Thus the atrial pacemaker attached at the time of opera-
tion could be used to control the rate and cause a synchro-
nous atrial contraction, but when right ventricular pacing
was instituted, no significant variation in left ventricular
pressure from interfering atrial contraction could be seen.
Fig. 5 illustrates the various types of pacing used, and Fig.
6 shows how a contracting atrium may interfere with the
dynamics of right ventricular single pacing. When external
work is used as a parameter of myocardial function the
rate must be constant, otherwise spontaneous fluctuation
in rate found in the anesthetized dog plus bradycardia
caused by an increased pressure will be responsible for
variation in the stroke volume due to rate alone, and
invalidate comparisons which should depend on output
changes. Fig. 7 shows a hypothetical model illustrating
this and emphasizing why rates were constant throughout
each experiment. Angiotensin was used to increase the blood pressure (afterload) and provide significant ventricular stress.

This drug is particularly suitable because, although it has some inotropic action in the isolated muscle preparation, when the cardiovascular system is intact there is no significant myocardial or venous action. The drug is short-acting and has no significant tachyphylaxis during an acute experiment. The amount of drug varied between 4 and 14 mg per minute depending upon the weight and individual response of the dog, and the blood pressure was elevated to a single constant level in each experiment (usually about 40 mm.Hg). When increased resistance to ejection (afterload) is applied to a normal ventricle the rate slows, the heart dilates, with a rise in end-diastolic pressure, and the output falls. If the afterload is within the range of normal physiological stress, all these parameters return to normal. From serial observations it was found that after 8 minutes compensation had occurred and a steady state would be reached, and the measurements were thus taken after this time.

In the 12 dogs, in the initial experimental procedure when right ventricular single pacing was compared with right atrial single pacing, results show that in this preparation the loss of atrial contraction is significant as in all respects right atrial pacing was superior. This difference was not accentuated when an increased afterload was applied.

When right atrial pacing was compared with right ventricular paired pacing. however, no significant difference was seen in the control state and during afterload, although from Fig. 2c it would appear that it conferred a slight benefit, but this was not statistically significant. From the graphs shown it is obvious that when right ventricular paired pacing and single pacing are compared, right ventricular paired pacing, like right atrial single pacing, is superior to right ventricular single pacing. With the rapid velocity of contraction as judged by the enhanced dp/dt, and the alteration in compliance as seen from the lowered left ventricular end-diastolic pressure, it is possible for the ventricle to compensate for the loss of atrial transport function, but it will not improve the dynamics beyond this, because of the intricate regulatory system which can adjust pressures and flows in the normal preparation. As PESP causes moderate increase in oxygen consumption and as external work is not enhanced, normal rhythm with synchronous atrial contraction is more efficient. The increase in the velocity of contraction in the normal state therefore serves no useful purpose, as the external performance of the heart is unchanged and the velocity of contraction is unimportant. This is similarly seen with digitalis preparations on the normal myocardium, and, in fact, paired pacing has been termed 'electro-digitalization'.

Total autonomic blockade or pharmacological denervation has been described by Jose. Propranolol has a significant depressant action on the myocardium which could be due to quinidine-like effect as well as the effect of beta-blockade. Atropine is given in a vagolytic dose to prevent any vagal overactivity during beta-blockade, because this may cause further myocardial depression. Although some decrease of output and pressure was noted after propranolol, there was no significant difference shown between right atrial and right ventricular paired pacing.

In the anaesthetized dog, beta-blockade by propranolol may cause measurable reduction of the resting haemodynamic state, because the normal sympathetic stimulation to the myocardium is blocked. Fig. 8 shows the change after propranolol, mainly in regard to decrease of dp/dt, which reflects the velocity of contraction and its increase by paired pacing.

When acute heart failure was present, the response to paired pacing was dramatic, confirming that this is an extremely effective inotropic agent. The external work of...
the heart was greatly improved with striking reduction in LVED pressure, presumably due to decrease in heart size as well as diastolic compliance. In other experiments not detailed here, it was only possible to keep the dog alive by paired pacing. Fig. 9 shows the change in left ventricular pulse and dp/dt produced by paired pacing. Paired pacing thus exerts a very favourable effect on the circulation in the presence of abnormal dynamics such as seen in heart failure.

When heart failure is reversed, as previously described, we have seen that the striking distinction between paired and single pacing is no longer present. In the control state and during physiological stress where normal compensatory adaptation takes place, paired pacing produces no benefit and, indeed, because of the increased oxygen consumption, probably decreases the mechanical efficiency. During acute failure, however, paired pulse stimulation dramatically improves the heart failure and thus it is a further aid to our treatment of this condition.

The exact mechanism whereby paired pacing increases the force of contraction of heart muscle is unknown, but electrical events at the myocardial cell membrane influence ionic shifts. The interchange of sodium calcium and potassium ions and the proportions of such are known to influence contractility and paired electrical stimuli in some way undoubtedly alter this ionic passage.

The technique is not without hazard, as the second stimulus falls near the T waves where the vulnerable period for production of ventricular fibrillation is found. Its use, at the moment, is therefore necessarily limited to centres where both facilities for cardiac monitoring and staff with an adequate understanding of the application of artificial pacing coexist. Undoubtedly, however, this technique could afford benefit to many patients with resistant arrhythmias and intractable heart failure. It has been used also in resuscitation after prolonged heart-lung bypass surgery, prolonged and difficult defibrillation or arrest, and in severe haemorrhagic shock in conjunction with the routine measures. In all these situations, paired pacing may be life-saving, and when no response is obtained by more conventional methods of resuscitation, its use can now hardly be termed experimental or meddlesome.

**SUMMARY**

When right ventricular single pacing was compared with right atrial single pacing in the intact anaesthetized dog, right atrial pacing was superior in that a greater blood pressure stroke volume and subsequent external stroke work were recorded. The difference was due to loss of atrial contraction. When, however, paired electrical stimulation of the right ventricle was used, there was little difference between this and right atrial pacing. The powerful inotropic produced by paired pacing in the normal subject merely compensates for the loss of atrial contraction by altering the compliance of the ventricle and enhancing the velocity of contraction. This is done, however, at the expense of a greatly enhanced oxygen consumption. The haemodynamic findings in right atrial and right ventricular single and paired pacing are unaltered after increased afterload which allows physiological compensation.

When right atrial and right ventricular paired pacing are compared after total autonomic blockade, no significant difference is seen, but during acute heart failure paired pacing dramatically increases the output pressure and hence external stroke work of the heart, tending to restore the haemodynamics to normal. When the heart failure is abolished again, no difference is seen. Paired electrical stimulation with postextrasystolic potentiation is a further impressive therapeutic weapon in the treatment of heart failure.

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