Cardiac pacing constitutes an efficient treatment for bradycardias, while it has also been used recently in the therapy of dilated and hypertrophic cardiomyopathy. At the dawn of the pacing era, our interest was focused on ensuring stable, permanent pacing. Now, that our knowledge of the pathophysiology of the paced beat has deepened, our interest in the identification of more "physiological" pacing sites and explanation of the effect of pacing on the treatment of heart failure and hypertrophic obstructive cardiomyopathy (HOCM) is renewed.

Thus, myocardial innervation and perfusion along with their acute and long-term alterations have been the objective of a number of studies, that used different pacing sites.

Myocardial perfusion

It is well known that right ventricular apex (RVA) pacing leads to alterations in regional workload and finally influences the systolic and diastolic left ventricular (LV) function. In a recent study, Tse et al. demonstrated that LV perfusion defects existed in 65% of chronically paced patients for complete heart block (CHB). These regional defects were associated with wall motion abnormalities in the same areas. They also found that perfusion defect development tends to increase with the duration of pacing. Their findings were reconfirmed in a more recent study, which compared RVA and right ventricular outflow tract (RVOT) pacing. The authors showed that, after 6 months of pacing, the regional wall motion and perfusion abnormalities were similar in these two pacing sites, but after 18 months of continuous pacing these disturbances were more prominent in the RVA pacing group. This group also had significantly lower ejection fraction in comparison with the RVOT pacing group.

In our research centre we have found similar results. Forty six per cent of chronically (32 ± 19 months) paced patients with CHB had reversible defects in Tc99m scintigraphy. These defects can possibly be attributed to an impairment of the microvascular circulation in the early activated regions, according to the findings of a study by Skalidis et al., that showed reduced flow reserve in the defect related coronary artery. However, we could not establish a relationship between pacing duration and perfusion defect formation, in patients paced for sick sinus syndrome (SSS) or trifascicular block. Nielsen et al. have also reported that in SSS patients chronically paced (22 months), septal, inferior and global myocardial blood flow (MBF), as well as left ventricular ejection fraction (LVEF) are reduced. Interestingly, the latter reverted
to baseline right after the restoration of a normal activation sequence.

Furthermore, we have recently found that LV contractility and ventriculoarterial coupling, both assessed by conductance catheters, improve after restoration of the normal ventricular activation sequence. The blood flow in the dominant coronary artery increased, whereas the flow reserve in the same artery was found to decrease. These findings suggest that it is likely that LV function changes are unrelated to changes in coronary circulation and that they are both consequences of the altered activation sequence.

There is a discrepancy in the results between human and animal studies. Redistribution of the MBF is found in the latter during acute ventricular pacing, but in long term ventricular pacing, MBF tends to be equally distributed within the LV wall. This finding can be attributed to the regional differences in myocardial growth due to the pacing-induced redistribution of the myocardial workload. The authors suggested that these differences between humans and animals could be explained by the inability of the patient’s myocardium to grow proportionately to the regional workload differences, possibly because of preexisting heart disease.

Although the clinical significance of the pacing-induced perfusion abnormalities needs further elucidation, they provide yet another purpose for the search for more “physiological” pacing sites. Perfusion abnormalities for example, can worsen myocardial ischaemia in patients with coronary artery disease and further deteriorate their clinical outcome.

Left ventricular based pacing has been found to improve LV systolic function, quality of life, and possibly decrease mortality in patients with dilated cardiomyopathy and intraventricular conduction disturbances. In such patients, myocardial blood flow and myocardial perfusion has also been investigated. Biventricular pacing improves septal oxidative metabolism, but does not significantly alter myocardial perfusion. This finding leads to the conclusion that the haemodynamic and clinical benefits of biventricular pacing are not associated with an increase in oxygen consumption.

In patients with HOCM, the antianginal effects of pacing however, could not be explained by the pacing-induced alterations in the preexisting abnormalities in myocardial perfusion, as the study results were inconsistent. Fananapazir et al found that the perfusion defects were normalized or improved in 65% of DDD paced patients with HOCM while they worsened in 17%. In a study by Posma et al, the global perfusion reserve remained unchanged, whereas myocardial reserve became more homogeneously distributed. In three out of six patients perfusion reserve increased, while it decreased in two, during DDD pacing. Additionally, the authors could not establish a relation between individual pacing effects on myocardial perfusion reserve and the clinical haemodynamic response to pacing.

**Myocardial adrenergic innervation in paced patients**

Both branches of the autonomic nervous system innervate cardiomyocytes and coronary vessels. The pathogenetic role of sympathetic nervous system dysfunction is proven in arrhythmias, cardiomyopathies and congestive heart failure. Nowadays, non-invasive assessment of the adrenergic innervation is feasible using radionuclide tracers and single photon or positron emission tomography. I-123-metaiodobenzylguanidine (I123-MIBG) is usually used as a tracer. The drug is a guanethidine analogue that shares the same uptake, storage and release pathway with nor-epinephrine. Nakata et al were the first to show that pacing causes I123-MIBG scintigraphic abnormalities, more prominent during VVI than DDD pacing, probably as a result of the deteriorated haemodynamics during VVI pacing. Fukuoka et al did not find systemic sympathetic activity alterations despite the increase of the cardiac sympathetic activity, caused by chronic DDD pacing. The left ventricular adrenergic activity in some groups of patients, as well as its regional disturbances, has also been investigated in our department. Firstly, we found that in patients chronically paced for CHB, the I123-MIBG uptake was lower than in normal age and sex matched subjects. Moreover, 90% of these patients had increased sympathetic activity in the early-activated regions, which could not be associated with co-existing perfusion abnormalities. The increase occurs as a compensatory mechanism to the regionally reduced workload in the pacing area. The more profound the innervation abnormalities, the more probable the co-existence of perfusion defects. We have also studied myocardial innervation and perfusion in patients with SSS and trifascicular block. Thallium201 and I123-MIBG scintigraphic studies were performed before and 3 months after continuous DDD pacing. The myocardial perfusion was not altered during that period, but the
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adrenergic innervation showed significant redistribution. The regional adrenergic disturbances and the global sympathetic activity increase found, could contribute to the appearance of supraventricular and/or ventricular arrhythmias, by increasing automaticity and dispersion of refractoriness\textsuperscript{26,27}.

In a recent, as yet unpublished study, we examined adrenergic innervation and myocardial perfusion in biventricularly paced patients with atrial fibrillation, who had undergone ablation to control heart rate. Although chronic RV apical pacing negatively affects adrenergic innervation, the effect is reversible and cardiac adrenergic activity returns to baseline when the heart is paced from the LV free wall or from both ventricles. These findings indicate that LV-based pacing ensures a more synchronous contraction. This in turn, could have a positive impact on the up-regulation of \( \beta \)-adrenoreceptors by reducing noradrenaline concentration in myocardial tissue\textsuperscript{28}.

Conclusions

The possible positive or negative implications of pacing-induced alterations in ventricular activation sequence depend on the patient’s disease and kind of alteration. Findings to date have certainly enriched our knowledge concerning the pathophysiology of the paced beat. Nonetheless, more studies are necessary to elucidate the mechanisms and clinical significance of myocardial perfusion and adrenergic innervation changes.

References

18. Dehaas T, Arts T, Prinzen FW, Reneman RS: Regional fibre stress-fibre strain area as an estimate of regional blood


