Non-invasive assessment of myocardial contractility from force–frequency relationship in patients with implanted pacemakers: first results

Hansjuergen Bondke1*, Adrian-Constantin Borges1, Sven Petersen2, Thomas Walde3, and Gert Baumann1

1Department of Internal Medicine Cardiology and Angiology, Charité Universitätsmedizin Berlin, CC13, 10098 Berlin, Germany; 2Biotronik SE & Co. KG, Hartmannstr. 65, 91052 Erlangen, Germany; and 3Department of Cardiology, Sana Clinic Berlin-Lichtenberg, 10098 Berlin, Germany

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Aims
In the normal heart, myocardial contractility is augmented at elevated heart rates. This effect is known as force–frequency relationship (FFR). The FFR is altered in failing hearts and may be used to detect myocardial function impairment. Force–frequency relationship measurements usually require invasive techniques and have therefore rarely been used in clinical practice. We studied the feasibility of FFR determination by implanted pacemakers as a non-invasive method in pacemaker patients.

Methods and results
During follow-up visits in 30 patients with implanted pacemakers and normal heart function, the intracardiac impedance (IZ) was recorded by the pacemaker during incremental pacing at 80, 100, and 120 bpm. The time interval between the ventricular pacing pulse and IZmax (tIZm) and the maximum acceleration of the IZ change during myocardial contraction (IZacc: d²Z/dt² max) were determined. Isovolumetric acceleration (IVA) was measured in parallel by tissue Doppler echocardiography at the right free wall, the left free wall, and the septum. With increasing pacing rates, the time interval tIZm shortened significantly and maximum acceleration IZacc increased significantly, consistent with the FFR. The best correlation was achieved between IZacc and IVA septal.

Conclusion
Permanent pacemakers offering intracardiac IZ measurements can be used for monitoring FFR changes and, possibly, for low-effort first-line monitoring of myocardial disease.

Keywords
Force–frequency relationship (FFR) • Heart failure • Intracardiac impedance (IZ) • Isovolumetric acceleration (IVA) • Pacemaker • Myocardial contractility

Background
Intrinsic augmentation of cardiac contractility at elevated heart rates in the normal heart is termed positive force–frequency relationship (FFR). Bowditch1 described this inherent property of the heart muscle in 1871 as the staircase (‘Treppen’) phenomenon. The FFR is blunted or otherwise altered in failing hearts and may therefore be used to monitor the progression or regression of myocardial disease.2–9 Typical FFR study objects are invasively obtained muscle strip preparations.5,6 By FFR determination in vivo, the methods of stimulation and/or contractility assessment are usually invasive.2–4,7–9 The aim of our study was to test the feasibility of FFR recording by implanted pacemakers. Knowing that a group of implantable pacemakers can increment pacing rate and simultaneously measure intracardiac impedance (IZ) as a surrogate for contractility changes,10 it is reasonable to hypothesize that FFR may be monitored noninvasively in pacemaker patients.

Methods
Patients
Thirty consecutive recipients of the Inos2+CLS pacemaker (Biotronik SE & Co. KG, Berlin, Germany) were enrolled in the present study.
The mean age of the patients was 70.2 ± 9.5 years (19 male and 11 female). Indications for pacemaker implantation were symptomatic atrio-ventricular block II/III alone or in combination with sick sinus syndrome. Noninvasively the patients had a normal heart function without underlying heart disease. Only patients with normal transthoracic echocardiogram (left ventricular ejection fraction 57.3 ± 11.3%) were included. The standard treadmill exercise tests were negative in all patients. The study protocol was approved by the responsible ethics committee. All patients provided written informed consent, and the study complied with the Declaration of Helsinki.

Impedance measurements

The Inos2+CLS pacemakers use intracardiac IZ parameters to regulate the pacing rate according to the closed-loop stimulation (CLS) rate response principle. In the present study, we recorded IZ but did not use CLS mode, since pre-determined fixed pacing rates were applied. During a follow-up control, the beat-to-beat IZ curves were recorded in resting patients at incremental pacing rates: 80, 100, and 120 bpm (each rate for 3 min, with 1 min adaptation time). The pacemaker was set to the DDD mode, with an atrio-ventricular delay of 100 ms. To measure IZ, the pacemaker delivered an alternating sub-threshold current between the right ventricular lead tip and the pacemaker housing.10,11 Due to the difference in the surface area of the tip electrode and the pacemaker housing, this method assesses the voltage drop and thus IZ in a volume of maximal 5 cm³ around the tip of the ventricular lead.10

The recorded signal was transmitted to the pacemaker programming unit by telemetry, and stored in a computer for later analysis. With the aid of Mat Lab tools, the time interval between the ventricular pacing pulse and IZmax (tIZm) and the maximum acceleration of the IZ change during myocardial contraction (IZacc: d²IZ/dt² max) were determined from beat-to-beat IZ curves averaged over one minute.

Echocardiographic measurements

To verify whether tIZm and IZacc correlate with the relative contractility changes, in parallel with the IZ measurements, we determined isovolumetric myocardial acceleration (IVA) at the right free wall, the left free wall, and the septum. Isovolumetric myocardial acceleration is known to be a suitable noninvasive parameter of myocardial contractility function independent of preload and afterload.8,12,13 To determine IVA, standard transthoracic tissue Doppler echocardiography was performed with the Vivid 7 echo system (GE Vingmed, Horton, Norway) and the M3S transducer (1.5–4.0 MHz). The guidelines of the American Society of Echocardiography were followed. The images were stored digitally and analysed off-line (Echo Pac PC, GE Vingmed, Horton, Norway). The frame rate was > 100 per s for all loops. Tissue Doppler echocardiography measurements were assessed in the apical four-chamber view.

Statistical methods

Data are reported as mean ± standard deviation. The Wilcoxon test was used to compare differences between measurements. The P-value < 0.05 was considered statistically significant. Linear correlation (Pearson’s r) between IVA and IZ variables was tested.

Results

With increasing pacing rates, the time interval tIZm shortened significantly and maximum acceleration IZacc increased significantly (Table 1). Also septal, right lateral, and left lateral ventricular wall IVAs, as determined by echocardiography, rose significantly (Table 1). The changes were most pronounced for septal IVA. Among IZ parameters, IZacc only showed a significant correlation with IVA septal (Figure 1) but weak, not significant, correlations with right lateral and left lateral ventricular wall IVAs.

Discussion

In this work, we propose a concept for noninvasive FFR recording using implanted pacemakers, as they can increment heart rate and measure intracardiac IZ as a surrogate for contractility changes. Both pacemaker-mediated IZ measurements and contractility changes determined by tissue Doppler echocardiography (for verification) depended strongly on the pacing rate, according to a positive FFR. A noninvasive regular recording of FFR and, therefore, the monitoring of changes in myocardial contractility by permanent pacemakers or implantable cardioverter–defibrillators (ICDs) that are capable of specific IZ measurements seem feasible.

Today, a positive FFR is understood to be related to an increase in the intracellular Ca²⁺ transient, mainly due to an enhanced sarcoplasmatic reticulum Ca²⁺ content at higher stimulation frequencies, resulting from an increase in Ca²⁺ influx per unit time and reduced Ca²⁺ efflux between beats. An increased activity of Ca²⁺/calmodulin-dependent protein kinase, enhanced myofilament

| Table 1 Frequency dependence (pacemaker stimulation rate 80/100/120 bpm) of the intracardiac impedance (IZ) parameters evaluated by pacemakers and in parallel by echocardiographic (IVA) parameters in the sense of a positive force–frequency relationship (FFR) |
|---------------------------------|---------|---------|---------|
|                                | 80 bpm  | 100 bpm | 120 bpm |
| tIZm (ms)                       | 2.64 ± 0.87 | 2.36 ± 0.87* | 1.98 ± 0.72* |
| IZacc (kOhm/s²)                 | 3.82 ± 0.29 | 6.00 ± 0.53* | 6.67 ± 0.56* |
| IVA (septal) (m/s²)             | 1.23 ± 0.074 | 1.67 ± 0.066* | 2.14 ± 0.105* |
| IVA (right lateral) (m/s²)      | 2.33 ± 1.10 | 2.14 ± 0.82 | 2.87 ± 1.51* |
| IVA (left lateral) (m/s²)       | 1.86 ± 1.12 | 1.92 ± 1.14 | 2.32 ± 1.22* |

IZ, intracardiac impedance; tIZm, time interval between the ventricular pacing pulse and IZmax; IZacc, d²IZ/dt² max, maximum acceleration of the IZ change during myocardial contraction; IVA, echocardiographic isovolumetric acceleration from the ventricular areas-septal/right lateral/left lateral, bpm, beats per minute.

*P < 0.05 in comparison to 80 bpm.
Weser21 was able to show that epinephrine release from the sympathetic nerve endings does not play a role in the fundamental FFR. Other results indicate that the positive FFR is preserved in rabbit after sarcoplasmatic reticulum inhibition, while such intervention reverses the positive FFR to a negative one in the rat.17 Modifications of the FFR may produce a mixture of adrenergic influenced contractility and intrinsically positive FFR. However, they do not mention a method to differentiate this share under load. Force–frequency relationship (FFR) determination was necessary in methods of FFR measurement.2–9

Studies have shown that changes in the myocardial state occurring in connection with heart failure can be characterized through the FFR.14–19,20 Force–frequency relationship is the intrinsic or basal force–frequency reaction of the myocardium.1,21 Koch-Weser21 was able to show that epinephrine release from the sympathetic nerve endings does not play a role in the fundamental FFR. On the other hand, Brack et al.22 demonstrated that β-adrenergic stimulation increases the contractility independent of the heart rate. According to Higginbotham et al.,23 up to 40% of the cardiac minute output is under normal conditions regulated by the intrinsically positive FFR. However, they do not mention a method to differentiate this share under load. Force–frequency relationship can be influenced by the β-adrenergic regulation, which operates during exercise and other forms of stress.24 All methods that utilize physical stress to increase heart rate produce a mixture of adrenergic influenced contractility and intrinsic FFR.25,26 To date, the clinical use of the FFR as a diagnostic tool was not relevant since at least one invasive component of FFR measurement was necessary in methods of FFR measurement.2–9

The opportunity to increase pacing rate of the implanted pacemakers or ICDs allows assessment of myocardial contractility changes noninvasively in situ and without an influence from adrenergic factors. Incremental pacing and offline echocardiographic examination have been used for FFR determination.19,20 In abstracts, we proposed parameters from the IZ curve recorded by a permanent pacemaker as a surrogate for offline echocardiographic myocardial contractility examination.27–29 The IZ-based method seems particularly well-suited for long-term monitoring of FFR in patients with permanent pacing or defibrillation devices. Force–frequency relationship determination from the transventricular IZ measured between the right and the left ventricular leads of a cardiac resynchronization system is a future possibility.30 Implantation of a pacemaker or an ICD is, of course, an invasive intervention. But in many patients that may benefit from FFR monitoring, pacemaker or ICD implantation is indicated anyway. The implanted device might then be used for FFR recording to monitor the progression or regression of myocardial diseases without any further invasive intervention, as long as the battery lasts.

Study limitations

The voltage drop for presented IZ measurements is limited to maximal 5 cm2 of the right ventricular lead tip10 and can therefore reflect only relative contractility changes in this area. Since all myocardial fibres are electrically coupled via gap junctions, the entire normal myocardium behaves as a single unit or functional syncytium. The characterization of myocardial diseases presupposes an even distribution of the myocardial pathologic changes. We suggest that in spite of the limited access of the proposed method to a small area of the myocardium, the results may still be representative regarding relative myocardial contractility changes.

IVA-based contractility determination methodology is not undisputed. Lyseggen et al.31 showed that IVA was of limited significance when evaluating regional myocardial function. On the other hand, Dalsgaard et al.13 have proven that IVA was unchanged following significant increases in preload in healthy subjects and is a potentially useful parameter of global left ventricular contractility. In order not to endanger patients by the application of excessively high pacing rates in the present study, the FFR was not recorded over a broader frequency range. The critical stimulation frequency of the FFR, above which there is no further contractility augmentation, was not determined for the same reason.

The patients were examined in the DDD pacing mode with short atrio-ventricular delay, resulting in right atrial and right ventricular pacing during the measurements. Due to the indication for permanent pacemaker therapy, some patients have been under chronic right ventricular pacing since pacemaker implantation. The unfavourable impact of chronic right ventricular pacing on the myocardial condition of the studied patients could not be assessed.

Conclusion and clinical implications

With increasing pacemaker stimulation rates, the intracardiac IZ parameters time interval between the ventricular pacing pulse and IZmax (tIZm) shortened significantly and the maximum acceleration of the IZ change during myocardial contraction (IZacc: d2Z/dt2 max) increased significantly, consistent with the positive FFR principle. Besides, there was a strong correlation between IZacc and echocardiographic isovolumetric acceleration (IVA)-septal.

**Figure 1** Correlation of the maximum acceleration of the IZ change during myocardial contraction (IZacc: d2Z/dt2 max) evaluated by the pacemakers vs. echocardiographic isovolumetric acceleration (IZVA septal) in reaction to the pacemakers stimulation rate increase 80/100/120 bpm in the sense of a positive force–frequency relationship (FFR). Correlation: IZacc vs. IVA (septal) (r = 0.82, P = 0.0005). IZ, intracardiac impedance; IZacc: d2Z/dt2 max, maximum acceleration of the IZ change during myocardial contraction; IVA, isovolumetric acceleration from the ventricular septal area; bpm, beats per minute.

responsiveness to Ca2+, an increase in intracellular Na+, or the Na+/Ca2+ exchanger may also play a role.14,15 Ca2+ homeostasis must be altered at several levels to explain the deterioration of the FFR observed in the failing heart.16 Other results indicate that the positive FFR is preserved in rabbit after sarcoplasmatic reticulum inhibition, while such intervention reverses the positive FFR to a negative one in the rat.17 Modifications of the FFR may be more sensitive to intracellular Ca2+ dynamics.18

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![Figure 1](https://academic.oup.com/europace/article-abstract/12/7/968/586048/970)

![Figure 2](https://academic.oup.com/europace/article-abstract/12/7/968/586048/970)
Permanent pacemakers and ICDs capable of specific IZ measurements can be used to monitor FFR without additional invasive action, except for device implantation that is indicated anyway. Since the FFR is generally known to be sensitive to impairment of myocardial function, the proposed method may be useful for a low-effort first-line monitoring of myocardial disease.

Conflict of interest: none declared.

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