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Original Article

Myocardial oxidative metabolism, blood flow and efficiency in rapid pacing induced heart failure in dogs

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Abstract: Purpose: Heart failure is the final common pathway for most forms of heart disease, and is characterized by a reduced energy status. Myocardial oxygen consumption (MVO_2) is closely related to the main determinants of systolic function (heart rate, pressure and contractility). The aim of the study was to compare myocardial blood flow, metabolism and mechanical efficiency in rapid pacing induced heart failure in dogs. Methods: 5 dogs were paced for 3 weeks at 240 bpm, with regular follow up of hemodynamic characteristics. Coronary blood flow and oxidative metabolism were evaluated with [^{15}O] water and [^{11}C]acetate clearance respectively, in baseline conditions (B) and after 3 weeks of rapid pacing (3 wk RP) using positron emission tomography. Results: Three weeks of rapid pacing in a dog model resulted in a severely depressed left ventricular function (LV dP/dt_{max} 3698 ± 314 mmHg (B) vs. 1365 ± 103 mmHg (3 wk RP)). On the contrary myocardial blood flow 1.29 ± 0.11 ml/min/g (B) vs. 1.05 ± 0.07 ml/min/g (3 wk RP) and oxidative metabolism 0.178 ± 0.1 min^{-1} (B) vs. 0.161 ± 0.1 min^{-1} (3 wk RP) remained essentially unchanged, indicating a reduced efficiency and a change in O_2 utilization. Conclusions: Heart failure induced by rapid ventricular pacing in dogs provokes a clearly reduced mechanical efficiency, illustrating the occurrence of a metabolic remodeling in heart failure induced by rapid pacing.

Keywords: Oxidative metabolism, mechanical efficiency, heart failure, tachycardiomyopathy

Introduction

The heart is an aerobic organ that relies nearly exclusively on aerobic oxidation for the generation of energy. This explains the close relationship between myocardial oxygen consumption (MVO_2) and the main determinants of systolic function: heart rate, contractile status and wall stress [1, 2]. Heart failure is the final common pathway for most forms of heart disease, and is characterized by a reduced energy status [3-5]. Longterm administration of inotropic agents in heart failure is detrimental [6], while treatment with vasodilating (ACE-inhibitors) and betablocking agents improves survival, possibly partially due to an energy-sparing effect [7]. This concept stresses the interest of mechanical efficiency and stimulates the need to study the myocardial metabolism in heart failure [8, 9].

The model of rapid ventricular pacing in dogs is actually a frequently used animal model to induce congestive heart failure, and it mimics the biochemical and clinical changes seen in human congestive heart failure [10, 11]. The aim of the study was to compare myocardial blood flow, metabolism and mechanical efficiency in baseline conditions and after 3 weeks of rapid pacing in conscious dogs. Myocardial energetics have been studied in the rapid pacing model [12], using pressure-volume relationships and direct measurements of oxygen consumption in isolated heart preparations. This study differs, as it was performed in vivo, in clinically more relevant circumstances, evaluating each animal in baseline conditions and during heart failure using positron emission tomography (PET) to measure oxygen consumption and myocardial blood flow.

Methods

Chronically instrumented animals

Seven *adult* mongrel dogs weighing between 20 and 36 kg underwent surgical instrumenta-

tion. All animals were sedated with droperidol-fentanyl (HYPNORM®, Janssen Pharmaceutica), and subsequently anesthetized with pentobarbital (30 mg/kg IV) (NEMBUTAL®, Janssen Pharmaceutica). A left thoracotomy was performed in the fifth intercostal space, the pericardium was incised and the heart exposed. Heparin filled silastic catheters were implanted in the aorta, left atrium, and the coronary sinus (Dow Corning Co., CA). A miniature solid-state pressure transducer P_7 (Konigsberg Instruments Inc., Pasadena, CA) was implanted in the left ventricular cavity through a stab wound in the apex. Finally pacing electrodes were sutured to the left atrium and to the left anterior wall near the apex. All transducer wires and catheters were tunnelled subcutaneously to the dorsal neck surface. Postoperatively the animals received IV antibiotics (sulfadoxine - trimethoprim) (BORGAL®, Hoechst, GE) for 10 days and were allowed to recover from surgery during at least two weeks. Animals used in this study were treated in accordance with the guidelines of the animal ethic committee of the University of Ghent and with those prepared by the Committee on the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1996).

Functional and hemodynamic measurements

LV pressure was measured with the implanted miniature pressure gauge, which was calibrated in vitro as well as in vivo during the experiments against systolic arterial pressure measured in the descending aorta and against diastolic left atrial pressure, both sampled through the fluid-filled catheters, and measured with Statham P_{23} ID strain-gauge manometers (Statham instruments, Oxnard, CA). The LV pressure derivative (dP/dt) signal was used for timing of the cardiac cycle. End-ventricular diastole was defined as the beginning of the rise of positive LV dP/dt, and end-ventricular systole was defined at 20 ms before peak negative LV dP/dt. LV DP_{40} is defined as the LV dP/dt/pressure at a developed pressure of 40 mmHg. The modified Triple product (TP) is calculated as the product of heart rate, systolic arterial pressure and LV dP/dt_{max} and used as an indirect index of myocardial oxygen demand [13].

Preparation of radionuclides

[^{15}O] Water was produced by irradiating natural oxygen with 28-MeV protons from the Cyclone 30. The irradiation time was 10 minutes with a beam current of 20-35 μA. After bombardment, the irradiated gas was transferred to an automatic processing module, in which it was mixed with hydrogen in an oven containing 2.5 g palladium (Pd) wire at 150°C. The Pd-catalyzed reaction of oxygen with hydrogen produced the [^{15}O] water and natural water vapor that is trapped by bubbling through sterile isotonic water. The nearly quantitative transformation from [^{15}O] into [^{15}O] water was realised within 3 minutes, filtration through a 0.22-μm Millipore filter included. Radionuclide purity was controlled by decay curve analysis [14].

[^{11}C] Acetate was prepared in a remote controlled, semi-automated system, using a modification of the procedure by Pike [14, 15]. The solution was sterilized through a 0.22 μm Millipore filter. Radiochemical purity, measured by high-performance liquid chromatography (Aminex HPX-87H column, 300x7.8 mm, Biorad, Richmond, CA, solvent H_2SO_4 0.008 N, flow rate 0.6 ml/min, absolute retention time 13.5 min) was more than 99%. Specific activity was > 100 Ci/mmol/l.

Experimental protocol

Hemodynamic measurements

After complete recovery from surgery a baseline evaluation was performed. Consequently heart failure was induced by rapid ventricular pacing (240 bpm) for 3 weeks [10, 11], using a homemade stimulator. The presence of heart failure signs was determined by both clinical signs, such as exercise intolerance, dyspnoe and cachexia on the one hand, and hemodynamic parameters, such as increases in baseline heart rate and LVEDP, and the decrease of LV dP/dt_{max} on the other hand. The hemodynamic parameters were measured in conscious animals laying on their right side, in baseline conditions and after 48 hours, 1 week, 2 and 3 weeks of rapid pacing. All measurements were performed in sinus rhythm with the pacemaker turned off.

PET studies

Myocardial perfusion estimates and myocardial substrate metabolism [16-18] were obtained with an ECAT III (model 911/01, CTI Inc., Knoxville, Tennessee) one ring device, the char-

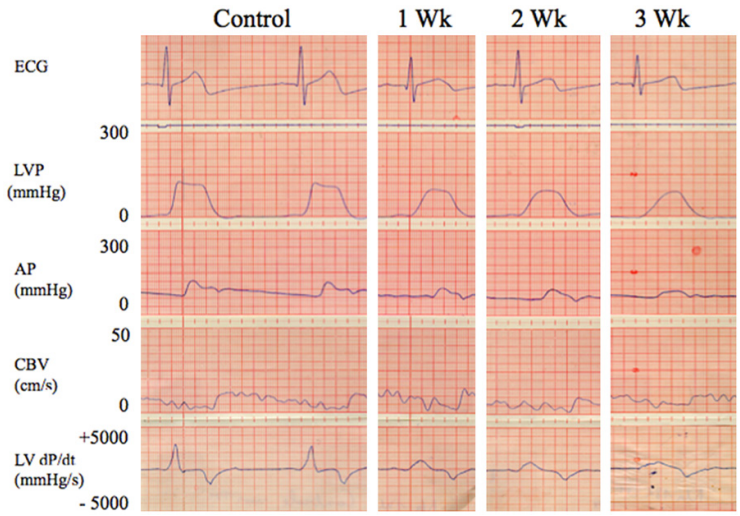

Figure 1. Hemodynamic parameters in control conditions and after 1, 2 and 3 weeks of rapid pacing. ECG, electrocardiogram; LVP, left ventricular pressure; AP, arterial pressure; CBV, coronary blood flow velocity; LV dP/dt, index of the initial velocity of myocardial contraction.

acteristics of which have been described previously [14, 19]. Measurements were performed with a stationary ring, and images were reconstructed with a Hann filter (cutoff frequency, 0.4 Hz) at a nominal in-plane resolution of 9 mm full width at half maximum 5FWHM). The collimator aperture was set at 30 mm, resulting in a slice thickness of 15 mm FWHM. The tomograph was cross-calibrated against a well counter using a uniform cylindrical phantom (diameter, 20 cm) filled with a solution of ^{68}Ge. Transmission scans - needed for attenuation correction - were obtained with an external ring of ^{68}Ge to confirm proper positioning of the dog [19].

Tomographic procedures were performed in baseline conditions and after 3 weeks of rapid pacing in five out of seven instrumented animals, with correction of partial volume effect and spillover. During the procedure the dogs were mildly sedated with propionylpromazine (Combilen®, Bayer).

Coronary blood flow: Coronary blood flow was calculated using the [^{15}O] water perfusion estimate.

15 mCi [^{15}O] water was administered as a slow bolus over a 30-second period with an infusion pump (model 351, Sage Instruments). Thirty serial cross-sectional images were acquired for 180 seconds (15 for 2 seconds and 15 for 10 seconds). [^{15}O] water kinetics were calculated using a 2-compartment model. The method was previously described in detail [14].

Oxidative metabolism: Following [^{15}O] water acquisition myocardial oxidative metabolism was estimated using the [^{11}C] acetate clearance [20, 21]. [^{11}C] acetate was injected intravenously with a pump for 30 seconds. [^{11}C] acetate clearance was measured by serial imaging following the IV administration of 5-10 mCi of [^{11}C] acetate. The turnover rate constant k1 (min^{-1}) was calculated using a monoexponential fitting (initially 30 s images were acquired 6 times followed by 60 s images 5 times, 120 s images 6 times, 300 s images 3 times and 600 s images 2 times depending on residual activity). [^{11}C] acetate clearance gives an estimate of the overall oxidative metabolism and correlates with direct measurement of oxygen consumption using the Fick method, as previously described [16, 21, 22].

Statistical analysis

Analog signals were recorded on a multichannel tape recorder (HP 3968A) (Hewlett-Packard Co., Palo Alto, CA), and were digitised and stored for processing and statistical analysis (SAS 6.03, SAS Institute Inc., Cary, N.C.). Mean ± SEM values were calculated for all parameters, and differences between responses were first tested by the analysis of variance (null hypothesis). Differences between responses versus control were analysed by the Student's paired t-test.

Results

Hemodynamic measurements

Following 3 weeks of rapid pacing the animals show clear signs of congestive heart failure (slower walking, with shortness of breath and coughing following exercise). Compared to control conditions (**Figure 1**) 3 weeks of rapid pacing induces a significant increase of left ventricular end diastolic pressure, accompanied by a significant decrease of left ventricular systolic

Table 1. Hemodynamic parameters at baseline, after 48 hours of rapid pacing (48 h RP), 1 week of rapid pacing (1 week RP), 2 weeks of rapid pacing (2 weeks RP) and 3 weeks of rapid pacing (3 weeks RP)

	Baseline	48 h RP	1 week RP	2 weeks RP	3 weeks RP
HR (bpm)	105 ± 9	118 ± 10	115 ± 18	113 ± 14	111 ± 14
LVEDP (mmHg)	11 ± 3	15 ± 4	21 ± 3*	23 ± 1*	22 ± 3*
LVSP (mmHg)	123 ± 4	113 ± 3*	102 ± 4*	102 ± 4*	102 ± 3*
MAP (mmHg)	93 ± 5	89 ± 2	77 ± 5*	76 ± 9*	74 ± 2*
LV dP/dt+ (mmHg/s)	3698 ± 314	2081 ± 157*	1705 ± 105*	1546 ± 113*	1365 ± 103*
LV dP/dt- (mmHg/s)	2685 ± 107	2415 ± 136	1887 ± 165*	1689 ± 119*	1738 ± 63*
LV DP40	65 ± 6	33 ± 3*	26 ± 2*	24 ± 2*	22 ± 3*
Tau (s^{-1})	18.5 ± 4.2	26 ± 2.7*	31.3 ± 4.7*	36.7 ± 2*	34.7 ± 4.2*
TP (10^6 x bpm x $mmHg^2$/s)	48.2 ± 7.7	28.2 ± 4.9*	19.9 ± 2.6*	18.1 ± 3.0*	15.5 ± 1.5*

HR, heart rate; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular end systolic pressure; MAP, mean arterial pressure; LV dP/dt_{max}, index of the initial velocity of myocardial contraction; LV DP40, LV dP/dt at a developed pressure of 40 mmHg; Tau, time constant of relaxation; TP, triple product: systolic arterial pressure x heart rate x LV dP/dt_{max}. Data are mean ± standard error of the mean (SEM) *P < .05.

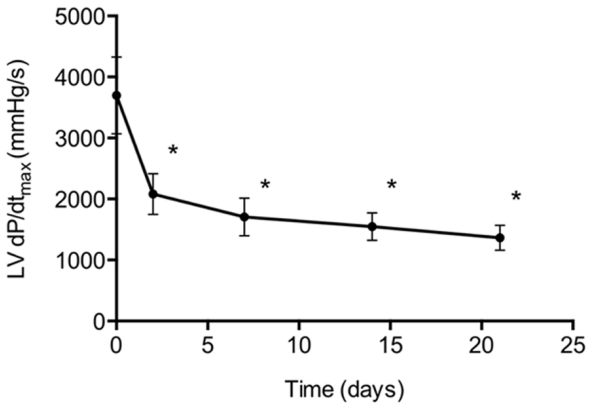

Figure 2. Progressive decrease of contractile function, expressed as LV dP/dt_{max} during 3 weeks of rapid pacing (mean ± sem) (*P < .05).

Table 2. Triple product, [^{15}O] water estimated myocardial blood flow and [^{11}C] acetate clearance in control conditions and after 3 weeks of rapid ventricular pacing

	Control	3 wk RP
TP (10^6 x bpm x $mmHg^2$/s)	47.4 ± 9.5	19.1 ± 1.9*
MBF (ml/min/g)	1.29 ± 0.11	1.05 ± 0.07
Acetate clearance (k_{-1}, min^{-1})	0.178 ± 0.10	0.161 ± 0.10

TP, triple product: systolic arterial pressure x heart rate x LV dP/dt_{max} as indirect index of myocardial oxygen demand; MBF, [^{15}O] water estimated myocardial blood flow; k_{-1}, the turnover rate constant using a mono-exponential fitting from the 1-[^{11}C] acetate clearance curve; 3 wk RP, 3 weeks of rapid pacing at 240 bpm. Data are mean ± standard error of the mean (SEM) *P < .05.

pressure, mean arterial pressure and LV dP/dt_{max} as a measure of contractility. Heart rate increased slightly but not significantly. Consequently the modified triple product (TP), an indirect index of myocardial oxygen demand - using the product of heart rate, systolic arterial pressure and LV dP/dt_{max} - was significantly decreased (**Table 1**). Significant changes in contractile parameters are already observed following 48 hours of rapid pacing (**Figure 2**).

PET results

After 3 weeks of rapid pacing myocardial blood flow (**Table 2**) measured with [^{15}O] water decreased slightly but not significantly from 1.29 ± 0.11 ml/min/g to 1.05 ± 0.07 ml/min/g, while [^{11}C] acetate clearance (**Figure 3**) decreased slightly but not significantly from 0.178 ± 0.1 min^{-1} to 0.161 ± 0.1 min^{-1}. Both parameters did not significantly change. This underscores the similar myocardial perfusion and oxygen consumption after 3 weeks of pacing, compared to baseline conditions.

However a work-metabolic index combining the modified TP and oxygen consumption (**Table 1**) is significantly altered, indicating an alteration of the O_2-utilization and a reduced mechanical efficiency.

Discussion

Three weeks of rapid pacing in dogs induces a significant decrease of left ventricular function, with clinical signs indicating congestive heart failure. Hemodynamic measurements confirm a severely depressed left ventricular function. The modified triple product, an indirect param-

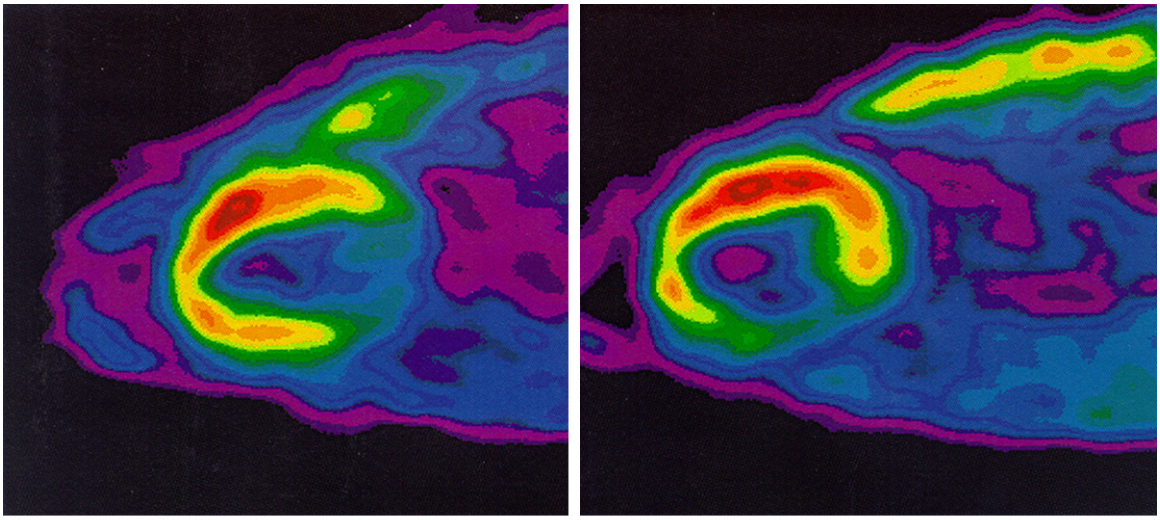

Figure 3. Selected PET images after [^{11}C] acetate injection in the same dog in control conditions (Control) and after 3 weeks of rapid pacing (RP). Radioactivity is color coded, with the highest activity in red and the lowest in dark blue.

eter of myocardial O_2 demand and work performed, and closely related to the main determinants of systolic function, is significantly decreased. We deliberately used a modified calculation of the triple product, in which formula the left ventricular ejection time was exchanged for the LV dP/dt_{max}, in order to have a more powerful impact of the contractile status of the myocardium.

In contrast to the clearly reduced contractile status, the myocardial blood flow, calculated with [^{15}O] water is preserved and the [^{11}C] acetate decay measurements - a measure for the overall myocardial oxidative metabolism - are unchanged. These findings indicate that while flow and oxidative metabolism are preserved the mechanical work is severely reduced, confirm earlier in vitro findings in this model using isolated hearts [12], and clearly illustrate a reduced mechanical efficiency, suggesting a shift of the O_2-utilization in this rapid pacing model of heart failure to other energy consuming processes in the myocardial cells, i.e. basal metabolism and excitation-contraction coupling [8].

These data also confirm the decrease of mechanical efficiency and the clear metabolic remodeling observed in human dilated cardiomyopathy and underscore the hypothesis that an increased energy expenditure relative to work is present in heart failure and may also contribute to the progression of the disease [3-5]. It was shown that drugs which provoke an oxygen sparing effect in heart failure (ACE inhibitors, beta-blocking agents) not only have a positive effect on LV function but also on survival [7, 8], while on the contrary positive inotropic drugs [6, 21, 22] which increase the energetic cost provoke an acute enhancement of LV function but with a detrimental effect on survival and induce an oxygen wasting at the cellular level. More recently cardiac resynchronisation therapy was also proven not only to have a positive effect on myocardial function, but also on survival, which was again associated with an increase of mechanical efficiency [24-29]. These observations should stimulate to study more carefully energetics during the evaluation of new therapeutic strategies in heart failure, as the effect on energetics appears to be cardinal for the impact of treatment on survival.

In addition in this animal model clear changes in the hemodynamic profile are already observed after 48 hours of rapid pacing, as illustrated by the early significant decrease of contractile function and the triple product. These observations suggest the early occurrence of major changes at the myocardial and cellular level, which may trigger the evolution unto heart failure. Therefore the focus of future work in this model should be deflected to the elucidation of the mechanism of these early changes at the cellular level.

Disclosure of conflict of interest

None.

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