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Heart Rate and Oxygen Uptake Kinetics in Type 2 Diabetes Patients – A Pilot Study on the Influence of Cardiovascular Medication on Regulatory Processes

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ABSTRACT

The aim of this pilot study was to investigate whether there are differences in heart rate and oxygen uptake kinetics in type 2 diabetes patients, considering their cardiovascular medication. It was hypothesized that cardiovascular medication would affect heart rate and oxygen uptake kinetics and that this could be detected using a standardized exercise test. 18 subjects were tested for maximal oxygen uptake. Kinetics were measured in a single test session with standardized, randomized moderate-intensity work rate changes. Time series analysis was used to estimate kinetics. Greater maxima in cross-correlation functions indicate faster kinetics. 6 patients did not take any cardiovascular medication, 6 subjects took peripherally acting medication and 6 patients were treated with centrally acting medication. Maximum oxygen uptake was not significantly different between groups. Significant main effects were identified regarding differences in muscular oxygen uptake kinetics and heart rate kinetics. Muscular oxygen uptake kinetics were significantly faster than heart rate kinetics in the group with no cardiovascular medication (maximum in cross-correlation function of muscular oxygen uptake vs. heart rate; 0.32 ± 0.08 vs. 0.25 ± 0.06; p = 0.001) and in the group taking peripherally acting medication (0.34 ± 0.05 vs. 0.28 ± 0.05; p = 0.009) but not in the patients taking centrally acting medication (0.28 ± 0.05 vs. 0.30 ± 0.07; n.s.). It can be concluded that regulatory processes for the achievement of a similar maximal oxygen uptake are different between the groups. The used standardized test provided plausible results for heart rate and oxygen uptake kinetics in a single measurement session in this patient group.

Abbreviations

τ	time constant
ACE	angiotensin-converting enzyme
BMI	body mass index
CCF_{lag}	lag between maximum of autocorrelation function and cross-correlation function
CCF_{max}	maximum in cross-correlation function
Q'	cardiac output
ECG	electrocardiography
HR	heart rate
HR_{max}	maximal heart rate
mBP	mean arterial blood pressure
PRBSs	pseudo-random binary sequences
SV	stroke volume
T2DM	type 2 diabetes mellitus
T2D	type 2 diabetes mellitus patients without treatment with cardiovascular medication
$T2D_c$	type 2 diabetes mellitus patients treated with centrally acting medication
$T2D_p$	type 2 diabetes mellitus patients treated with peripherally acting medication
$V'O_2max$	maximal oxygen uptake
$V'O_2musc$	muscular oxygen uptake
$V'O_2pulm$	pulmonary oxygen uptake
WR	work rate
WR_{max}	maximal work rate

Introduction

Type 2 diabetes mellitus (T2DM) is associated with increased cardiovascular morbidity and mortality. This presents a major challenge to healthcare systems for several aspects [1–4]. T2DM is often accompanied by comorbidities such as arterial hypertension [5, 6], lipid metabolism disorders [7], overweight or obesity [8]. This cluster of diseases is termed the metabolic syndrome [4].

Centrally acting beta blockers, affecting directly the sympathetic nervous system to decrease heart rate (HR) and consequently cardiac output (Q'), or peripherally acting drugs as angiotensin-converting enzyme (ACE) inhibitors or calcium-channel blockers, influencing the vascular tone, are commonly used to control arterial hypertension in patients with T2DM.

There are indices, that both types of drugs can improve the responses of the cardiovascular, respiratory and metabolic system to changing work rates (WR) at submaximal exercise intensities [9–12], which can be described with oxygen uptake ($V'O_2$) kinetics. $V'O_2$ kinetics give information on the adjustment of the cardiovascular and respiratory and metabolic system and therefore aspects of transport and metabolic processes to changes in WR. Slower $V'O_2$ kinetics are associated with lower exercise tolerance [13]. Using a circulatory model, considering venous volume and the $V'O_2$ as well as perfusion of the non-working part of the body, muscular $V'O_2$ ($V'O_2$musc) kinetics can be estimated from pulmonary $V'O_2$ ($V'O_2$pulm) and HR [14]. This allows for a more detailed analysis of metabolic and circulatory processes.

To the best of our knowledge, no data are available regarding HR kinetics in patients taking cardiovascular drugs. Although faster HR kinetics as indicators for kinetics of Q' have been considered as a potentially influencing factor for faster $V'O_2$pulm kinetics [10, 11], they were not yet measured in this context. It was shown that beta blockers increase RR interval variability and vagal tone in patients with former uncomplicated myocardial infarction [15].

Apparently, no data have been published that show the influence of different cardiovascular drugs on HR and $V'O_2$ kinetics in patients with T2DM. Subjects with medication were either excluded from the analysis [16–19], no detailed information was provided [20], or patients were included in the study (except patients taking beta blockers) but not analyzed seperately [21, 22].

The aim of the present pilot study is to investigate differences in HR and $V'O_2$ kinetics between T2DM patients, considering their cardiovascular medication.

The following hypotheses were tested:

1) The kinetics responses of $V'O_2$musc and HR are faster in T2DM patients taking centrally acting medication compared with T2DM patients not taking cardiovascular medication.
2) T2DM patients taking mainly peripherally acting medication show faster $V'O_2$musc and HR kinetics compared with T2DM patients not taking cardiovascular medication.

Materials and Methods

Subjects

18 male subjects participated in the study. All subjects declared that they were not diagnosed with diabetic nephropathy, retinopathy, neuropathy, and/or other cardiovascular complications other than arterial hypertension. None of the subjects performed regular physical activity, and no contraindications for participation in exercise testing were evident. The subjects were selected for 3 subgroups, according to their medication: 6 patients were diagnosed with T2DM and did not take any cardiovascular medication, 6 subjects were diagnosed with T2DM and took mainly centrally acting antihypertensive medication ($T2D_c$, 2 of these subjects had dyslipidemia); and 6 patients were T2DM patients treated with mainly peripherally acting drugs ($T2D_p$, one subject had dyslipidemia). One subject taking the calcium-channel-blocker 'verapamil' was included in the $T2D_c$ group, because this drug is known to act at heart level. Anthropometric data and differentiation of the subgroups are specified in ▶ **Table 1**.

Considering the subjects' anti-diabetic treatment, 4 of the T2D subjects took metformin and 2 did not take any medication. In the $T2D_c$ group 3 subjects took metformin, one took sitagliptin and 2 did not take anti-diabetic drugs. 5 of the $T2D_p$ subjects took metformin and one did not take any anti-diabetic medication. Subjects visited the laboratory twice: The first time, anthropometric measurements, resting electrocardiography (ECG), and a $V'O_2$max test were performed. Given that no contraindications in the ECG and during $V'O_2$max test were identified, the subjects returned to the laboratory a second time for a cardiorespiratory kinetics test.

▶ **Table 1** Anthropometric data of all subjects divided into subgroups.

Group (N = 18)		Age [years]	BMI [kg · m^{-2}]	Group of cardiovascular medication	Cardiovascular agent	Duration of type 2 diabetes mellitus since diagnosis [years]
T2D (n = 6)	Mean	60	33.0	–	–	3.5
	SD	8	5.9			3.1
$T2D_p$ (n = 6)	Mean	56	32.8	ACE inhibitors, angiotensin 1 blockers, calcium-channel blockers	Ramipril, enalapril, irbesartan, amlodipine	8.0
	SD	10	4.0			7.2
$T2D_c$ (n = 6)	Mean	61	32.6	ß-blockers or any combination of ß-blockers and other antihypertensive drugs	Bisoprolol, verapamil, combination of bisoprolol or verapamil with other antihypertensive drugs	4.3
	SD	9	8.0			3.9

BMI: body mass index; SD: standard deviation; T2D: subjects with type 2 diabetes mellitus not taking additional medication; $T2D_p$: subjects with type 2 diabetes mellitus taking peripherally acting medication; $T2D_c$: subjects with type 2 diabetes mellitus taking centrally acting medication

A positive vote of the ethics committee of the German Sport University Cologne, in accordance with the Declaration of Helsinki (1964 including the amendments until 2013), was available before the beginning of the tests. All subjects gave their written informed consent prior to the testing procedures.

V'O_2max testing

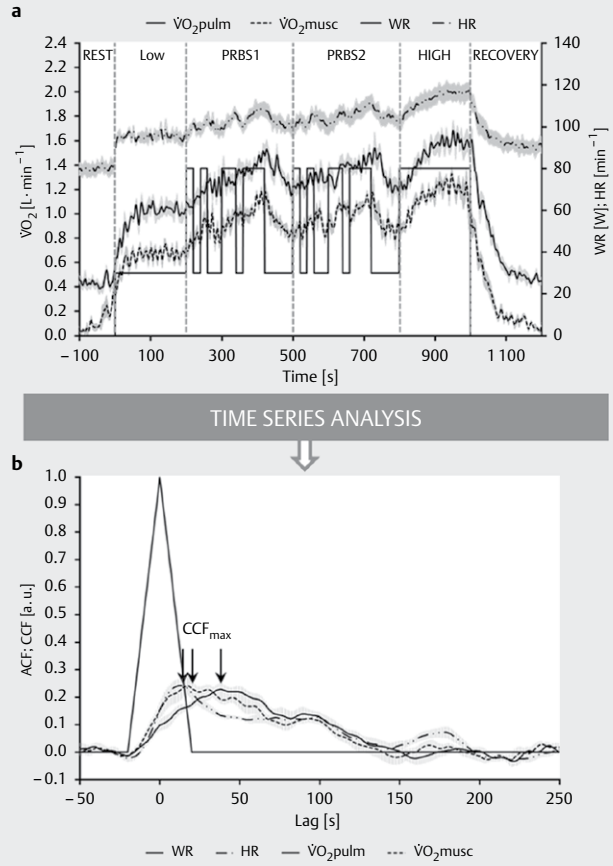
The subjects were tested using the protocol recommended by the World Health Organization in a seated position on a cycle ergometer (Ergoline ER 900, Ergoline GmbH, Bitz, Germany). WR was increased by 25 W every 2 min until subjective exhaustion or the occurrence of one of the common reasons for test termination (e. g., ST segment depression or couplets of premature heart contractions).

HR was measured continuously via 12-lead ECG (GE Medical Systems, Information Technologies, Munich, Germany) and recorded by an AMEDTEC ECGpro® V.3.66 (MedizintechnikAue GmbH, Aue, Germany). Pulmonary data were assessed breath by breath via a ZAN 600 (ZAN Messgeräte GmbH, Oberthulba, Germany) including the algorithms of Beaver et al. [23]. All instruments were calibrated according to the manufacturer's suggestions before all tests. For maximal oxygen uptake (V'O_2max) the highest 30 s averaged value of the highest achieved WR was determined as the maximum value. The Achievement of true V'O_2max was assumed, if a plateau in V'O_2 (increase in V'$O_2 \leq 2.1\ ml\ kg^{-1} \cdot min^{-1}$) despite an increase in WR (as the primary criterion) appeared. When no plateau occurred, V'O_2max was assumed when HR_{max} was higher than 200 beats min^{-1} minus the years of age [24] and the maximal respiratory exchange ratio was not lower than 1.06 [25, 26]. All subjects included in this study achieved V'O_2max according to the predefined criteria, which was then normalized to body mass.

Cardiorespiratory kinetics test

Subjects were tested on a semi-recumbent cycle ergometer (Cardiac Stress Table, Lode B.V., Netherlands; backrest at 45 °, legs at 42 °, relative to ground level). Pseudo-random binary sequences (PRBSs) were used as the WR protocol. The protocol consisted of 180 s of rest; 200 s of 30 W, as low steady state (Low); followed by two 300 s periods of PRBS (PRBS1 and PRBS2), with changing WRs between 30 and 80 W; and ended with 200 s of 80 W, as high steady state (High) (▶ **Fig. 1a**). The cadence was maintained at 60 rpm. HR was assessed beat to beat via electrocardiography; stroke volume (SV) was measured beat to beat via impedance cardiography (Task Force® Monitor, CNSystems Medizintechnik AG, Graz, Austria). Pulmonary gas exchange data were determined breath by breath (ZAN 680, ZAN Meßgeräte GmbH, Oberthulba, Germany), incorporating the algorithms of Beaver et al. [23]. From SV and HR, Q' was calculated. The instruments were calibrated before each measurement, according to the manufacturer's guidelines. For reduction of noise, data were filtered with a low-pass filter (0.1 Hz). Data were synchronized via trigger signals and interpolated to 1 s intervals for homogeneous sampling [27].

For analysis of cardiorespiratory kinetics, time series analysis was applied and V'O_2musc kinetics were estimated from HR and V'O_2pulm [14]. Briefly, the PRBS WR protocol was auto-correlated, which resulted in a triangular shape and each parameter was cross-correlated with the WR protocol (▶ **Fig. 1b**). The autocorrelation can be approximated as a WR impulse. The cross-correlation function was interpreted as the response of the respective parameter to this impulse. The kinetics of the parameters were summarized by the maximum in cross-correlation function ($CCF_{max,}$ compare ▶ **Fig. 1b**) and the related lag (CCF_{lag}). Higher CCF_{max} indicate faster response times of the particular parameter. From CCF_{max}, the time constant τ can be estimated. Further, V'O_2musc and the corresponding kinetics were calculated using the backward calculation method. This method is based on a circulatory model with 2 compartments (working and remainder part). V'O_2musc was estimated considering a certain venous blood volume between muscle and mouth, as well as V'$O_{2,}$ and perfusion of the remainder of the body (see [14] for further details on the method). This method makes it possible to distinguish between V'O_2musc and V'O_2pulm, which leads to a more detailed analysis of the cardiorespiratory and metabolic regulation considering transport processes. For kinetics comparisons, V'O_2musc and HR kinetics have been considered.



▶ **Fig. 1** Demonstration of data acquisition and analysis. **a**: Data acquisition during the work rate protocol; **b**: Data after time series analysis. The arrows indicate the respective maximum of the cross-correlation course (CCF_{max}). Lag: lag of cross-correlation function; ACF: autocorrelation function; CCF: cross-correlation function; HR: heart rate; V'O_2musc: muscular oxygen uptake; V'O_2pulm: pulmonary oxygen uptake; Rest: resting period; Low: 30 W constant phase; PRBS: pseudo-random binary sequence; High: 80 W constant phase; Recovery: recovery phase.

▶ **Table 2** Means and standard deviations of anthropometric and glycemic data, and parameters of cardiorespiratory capacities.

Group (N = 18)		$V'O_2max$ [$ml \cdot min^{-1} \cdot kg^{-1}$]	WR_{max} [Watt]	HR_{max} [min^{-1}]	Fasting blood glucose [$mg \cdot dl^{-1}$]	$HbA1_c$ [% (mmol · mol^{-1})]	Resting mBP [mmHg]
T2D (n = 6)	Mean	21.3	146	146	160	7.1 (54)	108
	SD	5.2	25	12	81	1.9 (21)	7
$T2D_p$ (n = 6)	Mean	23.0	158	153	150	7.2 (56)	105
	SD	6.7	34	25	29	1 (11)	7
$T2D_c$ (n = 6)	Mean	19.2	133	131	140	6.4 (47)	97
	SD	5.1	13	17	24	1.4 (15)	9

$V'O_2max$: maximum oxygen uptake; WR_{max}: maximum work rate; HR_{max}: maximum heart rate; HbA1c: glycosylated hemoglobin; mBP: mean arterial blood pressure; T2D: subjects with type 2 diabetes mellitus not taking additional medication; $T2D_c$: subjects with type 2 diabetes mellitus taking centrally acting medication; $T2D_p$: subjects with type 2 diabetes mellitus taking peripherally acting medication

Statistical analysis

Between-group comparisons for the factors '$CCF_{max}(V'O_2musc)$' and '$CCF_{max}(HR)$' ('Parameter x Group') were performed via 2-factorial ANOVA. The following post hoc comparisons were implemented via LSD test. For the means of HR, mean arterial blood pressure (mBP), $V'O_2pulm$, $V'O_2musc$, SV and Q' during the different steps (Low, PRBS1, PRBS2, High) of the PRBS protocol, 2-factorial ANOVA ('Step x Group') were applied. Since each group included only 6 subjects, Kruskal-Wallis tests were used to compare $V'O_2max$, HR_{max}, maximal WR (WR_{max}), body mass index (BMI), age, resting mBP, fasting blood glucose and glycosylated hemoglobin (HbA_{1c}) between the groups. When applicable, post hoc tests were adjusted via Bonferroni correction.

Results

Anthropometric data as well as cardiorespiratory and metabolic capacities are shown in ▶ **Table 2**.

No significant differences between groups were observed regarding $V'O_2max$, WR_{max}, HR_{max}, resting mBP, fasting blood glucose or $HbA1_c$.

For the absolute values of HR during the WR protocol, a significant between-group effect was found ($p = 0.01$). $T2D_c$ was significantly different to both T2D ($p = 0.014$) and $T2D_p$ ($p = 0.005$), which did not differ. These group differences for HR were found for all analyzed phases. For all other parameters, no statistical group differences were found, as listed in ▶ **Table 3**.

Static linearity, as a prerequisite for the application of time series analysis, was analyzed and proved for all groups. The respective regression functions for HR and $V'O_2pulm$ (during Low, PRBS1, PRBS2 and High; n=4) for each group are shown in ▶ **Table 4**.

ANOVA Parameter x Group with repeated measures on $CCF_{max}(HR)$ and $CCF_{max}(V'O_2musc)$, presented in ▶ **Fig. 2**, showed a significant main effect on the Parameter x Group ($p = 0.004$, partial; $\eta^2 = 0.515$) and Parameter ($p = 0.005$, partial; $\eta^2 = 0.424$). Post hoc tests revealed significant differences between $CCF_{max}(V'O_2musc)$ and $CCF_{max}(HR)$ for T2D ($p = 0.001$) and $T2D_p$ ($p = 0.009$) but not for $T2D_c$. Between groups, no significant differences were identified following ANOVA.

For comparisons with data from other publications, CCF_{max} values of $V'O_2musc$, $V'O_2pulm$ and HR were converted into time constants (τ) (see [14]). These time constants should be regarded as rough estimates, since they were obtained from CCF_{max} values ▶ **Table 5** .

Discussion

The aim of this study was to investigate differences in HR and $V'O_2musc$ kinetics between groups of patients with T2DM, considering their cardiovascular medication. For comparisons between the groups, a standardized WR protocol was used and $V'O_2musc$ kinetics were estimated from HR and $V'O_2pulm$ applying a circulatory model.

1) Descriptively, HR kinetics, represented by CCF_{max}, were faster in $T2D_c$ patients, compared with T2D patients not taking cardiovascular medication. $V'O_2musc$ kinetics seemed slower in $T2D_c$ subjects, but the results were not significant.
2) $V'O_2musc$ kinetics of the $T2D_p$ patients were slightly faster compared with the T2D patients without cardiovascular medication, but this was not significant. HR kinetics of the $T2D_p$ were slightly faster compared with the T2D groups, but this difference was also not significant.

Although no statistical differences regarding direct group comparisons were identified, a significant main effect for Parameter x Group including $V'O_2musc$ and HR kinetics was found. $V'O_2musc$ kinetics were significantly faster than HR kinetics within the $T2D_p$ and T2D groups, but not within the $T2D_c$ group. For the $T2D_c$ group, $V'O_2musc$ kinetics seemed slower than HR kinetics. For comparison, HR kinetics have been shown to be faster than $V'O_2musc$ kinetics in healthy young subjects [14, 28]. In sedentary aged subjects, $V'O_2musc$ kinetics were faster (but not significantly) than HR kinetics [29]. This is in line with the results of the $T2D_p$ and T2D group, in the present study. Taniguchi et al. [10] showed a positive effect of beta blockers (after one year of treatment) and Dayi et al. [11] for ACE inhibitors (administered shortly before the exercise test) on $V'O_2pulm$ kinetics in hypertensive subjects and in patients with dilated cardiomyopathy. They explained this effect by improved cardiac function (improved left ventricular ejection fraction). Descriptively, the results of this study show this positive effect of the cardiovascular medication on HR kinetics compared with the group not taking cardiovascular medication (▶ **Fig. 2**). Never-

▲ **Table 3** Analyses of cardiorespiratory parameters of all WR steps.

Group (N = 18)	WR step	HR [min^{-1}]		V'O_2pulm [L · min^{-1}]		V'O_2musc [L · min^{-1}]		mBP [mmHg]		SV [mL]		Q' [L · min^{-1}]	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T2D (n = 6)	Low	96	8	1.0	0.1	0.7	0.1	115	11	85.0	24.8	8.1	1.8
	PRBS1	103	8	1.3	0.1	0.9	0.1	117	10	86.8	21.7	8.7	2.0
	PRBS2	105	9	1.4	0.1	1.0	0.1	116	6	86.2	19.4	8.9	2.0
	High	116	10	1.6	0.2	1.2	0.2	122	11	84.4	12.6	9.8	2.4
T2D$_p$ (n = 6)	Low	98	10	1.1	0.1	0.7	0.1	112	8	85.7	28.0	8.4	2.0
	PRBS1	106	11	1.3	0.1	1.0	0.1	114	10	86.7	26.7	9.1	2.1
	PRBS2	108	11	1.3	0.1	1.0	0.1	112	10	89.7	32.6	9.2	2.1
	High	119	15	1.6	0.1	1.3	0.1	117	12	90.8	35.4	10.2	2.2
T2D$_c$ (n = 6)	Low	80 *	12	1.1	0.2	0.7	0.1	106	9	101.6	16.5	8.1	1.9
	PRBS1	86 *	12	1.3	0.2	0.9	0.1	111	7	99.7	12.2	8.6	1.9
	PRBS2	88 *	11	1.3	0.2	1.0	0.1	111	8	98.1	14.3	8.8	2.0
	High	96 *	12	1.6	0.2	1.2	0.1	114	8	98.0	22.3	9.7	2.1

HR: heart rate; V'O_2pulm: pulmonary oxygen uptake; V'O_2musc: muscular oxygen uptake; mBP: mean arterial blood pressure; SV: stroke volume; Q': cardiac output; SD: standard deviation; T2D: subjects with type 2 diabetes mellitus not taking additional medication; T2D$_c$: subjects with type 2 diabetes mellitus taking centrally acting medication; T2D$_p$: subjects with type 2 diabetes mellitus taking peripherally acting medication; Low: 30 W low steady state; PRBS1: 53.3 W, mean value of first pseudo-random binary sequence; PRBS2: 53.3 W, mean value of second pseudo-random binary sequence; High: 80 W high steady state; WR: work rate; * indicates significantly different from T2D and T2D$_p$ ($p < 0.05$)

▶ **Table 4** Static linearity for HR (heart rate) and V'O_2pulm (pulmonary oxygen uptake) during the PRBS WR protocol.

Group (N = 18)	HR			V'O_2pulm		
	Slope	Intercept	R^2	Slope	Intercept	R^2
T2D (n = 6)	0.40	83.46	0.98	0.017	0.7	0.99
TD2$_p$ (n = 6)	0.43	84.76	0.99	0.011	0.74	0.99
TD2$_c$ (n = 6)	0.32	70.43	0.98	0.011	0.71	0.99

HR: heart rate; V'O_2pulm: pulmonary oxygen uptake; T2D: subjects with type 2 diabetes mellitus not taking additional medication; T2D$_p$: subjects with type 2 diabetes mellitus taking peripherally acting medication; T2D$_c$: subjects with type 2 diabetes mellitus taking centrally acting medication

▶ **Fig. 2** Means and standard errors for CCF_{max} of HR and V'O_2 in the T2D, T2D$_c$ and T2D$_p$ group. CCF_{max}(V'O_2musc) was significantly different from CCF_{max}(HR) in T2D ($p = 0.001$) and T2D$_p$ ($p = 0.009$) but T2D$_c$ was not. CCF_{max}: maximum of cross-correlation function; CCF_{lag}: lag of cross-correlation function; HR: heart rate; V'O_2musc: muscular oxygen uptake. * Significantly different.

theless, the effect was insignificant and did not result in faster V'O_2musc kinetics compared with the T2D group.

Overall, the disease status of the T2D$_c$ group might have been worse, since some of them were treated with more than one cardiovascular medication (▶ **Table 1**). Between the 3 groups, no obvious differences in V'O_2max were evident. Hence, regulatory processes to achieve the same V'O_2max seem to be different and influenced by cardiovascular medication and/or disease status.

The very slow HR kinetics in the T2D patients (no cardiovascular medication) in the present study were also observed in other studies, comparing T2DM patients with healthy controls [19, 21, 22]. It has been shown, that T2DM influences cardiac mechanoenergetic efficiency and cardiac hypertrophy [30–33]. The respective medication in the T2D$_c$ and T2D$_p$ group might have improved cardiac function, as has been supposed in previous studies [9–11]. However, as can be observed in ▶ **Fig. 2** this did not lead to faster V'O_2musc kinetics compared to the T2D group.

The patients analyzed in this study were selected for the subgroups, considering the group of cardiovascular medication they were taking (▶ **Table 1**). The possiblity of the underlying disease to influence the obtained results cannot be excluded. Anyway,

▲ **Table 5** Time constants of HR, $V'O_2$musc and $V'O_2$pulm kinetics and model parameters.

Group (N = 18)	τHR		τ$V'O_2$musc		τ$V'O_2$pulm		V_v		Q'_{rem}		$V'O_2$rem	
	[s]		[s]		[s]		[ml · min^{-1}]		[ml · min^{-1}]		[L · min^{-1}]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T2D (n = 6)	69.5	28.2	49.7	23.8	66.4	20.3	2816.7	892.0	3111.1	1294.0	0.38	0.06
$T2D_p$ (n = 6)	53.8	12.7	41.8	10.5	50.9	15.4	2308.3	1081.9	3219.8	1676.5	0.34	0.04
$T2D_c$ (n = 6)	52.1	17.6	57.1	18.3	58.0	16.9	3100.0	834.9	2386.0	536.8	0.35	0.07

HR: heart rate, $V'O_2$musc: muscular oxygen uptake; $V'O_2$pulm: pulmonary oxygen uptake; V_v: venous volume; Q'_{rem}: perfusion of the remainder of the body; $V'O_2$rem: oxygen uptake of the remainder of the body; τ: time constant; SD: standard deviation; T2D: subjects with type 2 diabetes mellitus not taking additional medication; $T2D_p$: subjects with type 2 diabetes mellitus taking peripherally acting medication; $T2D_c$: subjects with type 2 diabetes mellitus taking centrally acting medication

the applied method showed that differences can be detected between the analyzed patient groups even in a small sample size. Regulatory processes between $T2D_c$ and the other 2 groups were different.

To be comparable with other studies, time constants were calculated as rough estimates from CCF_{max}. The time constants calculated in this study were within the given ranges from the literature, where values for $\tau V'O_2$musc (in the literature represented by the phase 2 τ of $V'O_2$pulm) as a response to WRs vary from 41 s to 58 s and values for HR vary from 51 s to 81 s for T2DM [16, 17, 19–22, 34]. Since the applied test delivers plausible results within a single test session, without the need to adjust WR ranges or the need to fit data to an explicit model, the applied test might be relevant for clinical routine.

Conclusion

Even though this study can only be treated as a pilot study, the different effects of the peripherally and centrally acting medication and/or disease conditions on HR and $V'O_2$musc kinetics without any obvious differences in $V'O_2$max are worth being considered. In the T2D and $T2D_p$ group, but not the $T2D_c$ group, $V'O_2$musc kinetics were significantly faster than HR kinetics. This shows that regulatory processes for the achievement of a similar $V'O_2$max are different between the groups. Future, larger studies analyzing T2DM patients should consider the influence of cardiovascular medication on HR and $V'O_2$musc kinetics, rather than excluding those patients from analysis.

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Conflict of Interest

None.

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