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ORIGINAL ARTICLE

Oxygen deteriorates arterial function in type 1 diabetes

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Abstract
Aims Although oxygen is commonly used to treat various medical conditions, it has recently been shown to worsen vascular function (arterial stiffness) in healthy volunteers and even more in patients in whom vascular function might already be impaired. The effects of oxygen on arterial function in patients with type 1 diabetes (T1D) are unknown, although such patients display disturbed vascular function already at rest. Therefore, we tested whether short-term oxygen administration may alter the arterial function in patients with T1D.

Methods We estimated arterial stiffness by augmentation index (AIx) and the pulse wave velocity equivalent (SI-DVP) in 98 patients with T1D and 49 age- and sex-matched controls at baseline and during hyperoxia by obtaining continuous noninvasive finger pressure waveforms using a recently validated method.

Results AIx and SI-DVP increased in patients ($P < 0.05$) but not in controls in response to hyperoxia. The increase in AIx ($P = 0.05$), systolic ($P < 0.05$), and diastolic ($P < 0.05$) blood pressure was higher in the patients than in the controls.

Conclusions Short-term oxygen administration deteriorates arterial function in patients with T1D compared to non-diabetic control subjects. Since disturbed arterial function plays a major role in the development of diabetic complications, these findings may be of clinical relevance.

Keywords Augmentation index · Blood pressure · Hyperoxia · Oxygen · Pulse wave velocity · Type 1 diabetes

Abbreviations

SBP	Systolic blood pressure
DBP	Diastolic blood pressure
PP	Pulse pressure
MAP	Mean arterial pressure
AIx	Augmentation index
AIx_{HR}	Heart rate-adjusted augmentation index
AER	Albumin excretion rate
T1D	Type 1 diabetes
SI-DVP	An index of large artery stiffness (SIDVP) derived from the digital volume pulse (DVP)

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Introduction

Arterial stiffness does not only associate with but also predicts cardiovascular disease (CVD) in different patient populations [1, 2]. In patients with type 1 diabetes (T1D), the augmentation index (AIx), a measure of wave reflections, is increased, and correlates with CVD, diabetic nephropathy, diabetic retinopathy [3], and autonomic neuropathy [4]. Interestingly, the stiffening of the arteries seems to be present before clinically detectable signs of micro- or macrovascular disease [5].

Exposure to 60 min of pure oxygen increased blood pressure and AIx in healthy subjects [6]. Oxygen also decreased the coronary blood flow in patients with and without coronary artery disease [7]. Notably, in patients with T1D, 3–5 min inhalation of a hyperoxic gas mixture impaired retinal arteriolar function indicating early retinal changes [8]. These short-term changes in vascular function indicate functional arterial abnormalities. However, the mechanisms of these changes are not fully known. One player might be preexisting tissue hypoxia in patients with diabetes [9]. Hypoxia seems at least to be involved in the pathogenesis of diabetic vascular complications by disturbing the neural and the vascular function [10, 11]. Another possible player is an increase in the harmful reactive oxygen species [12].

Finally, oxygen is widely used in the treatment of a variety of different medical conditions and often administered empirically without even knowing the levels of oxygenated hemoglobin in the blood. A recent review reported possible negative effects of oxygen, not only in normoxia, but possibly even in the presence of moderate hypoxia due to its vasoconstrictive action [13]. As the effect of hyperoxia on arterial function in patients with T1D is not known, we compared the effects of acute oxygen administration on the arterial function in patients with T1D and in healthy control subjects.

Research design and methods

All subjects took part in the IDEAL (IDentification of EArly mechanisms in the pathogenesis of diabetic Late complications) study, as part of the nationwide Finnish Diabetic Nephropathy (FinnDiane) study earlier described [14]. The study protocol was in accordance with the Declaration of Helsinki as revised in 2000 and was approved by the local ethics committee. Informed written consent was obtained from each participant.

Hyperoxia

Hemodynamic recordings (blood pressure, heart rate, arterial function, and oxygen saturation) were obtained during spontaneous breathing (in ambient air) for 10 min of normoxia and thereafter, oxygen was administered at the rate of 5 l/min via a nasal cannula. Signal recordings started after the first 5 min of oxygen administration to allow stabilization of oxygen saturation and ventilation. Then a recording was obtained for 10 min during spontaneous breathing. Pulse oxymetry and carbon dioxide were monitored from the fingertips throughout the study (Cosmo, Novametrix, Wallingford, CT, USA). ECG was recorded using a bipolar precordial lead.

Arterial function by finger plethysmograph

The effect of hyperoxia on arterial function was investigated by measuring blood pressure curves with a digital plethysmograph from the tip of the finger (Finapres 2300, Ohmeda, Louisville, CO, USA) to investigate whether hyperoxia alters the peripheral pressure waveforms. We have recently validated a methodology whereby arterial function [wave reflections (AIx) and pulse wave velocity (PWV)] can be obtained by noninvasive continuous noninvasive finger pressure waveforms [15].

In brief, continuous finger pressure waveforms were monitored with a digital plethysmograph (Finapres®) from all subjects from the middle finger of the right arm held at heart level. Recorded signals were digitized with a 12-bit resolution at a sampling rate of 200 Hz using a data acquisition system (WinAcq; Absolute Aliens, Turku, Finland). The pressure wave was analyzed in a beat-to-beat manner. Using the ECG R-wave peak as a reference frame, we obtained an average pulse profile for each studied subject. From the finger pressure waveforms, two different approaches were used to characterize the arterial function. Wave reflections were estimated as the AIx and also from the comparison of the simple averaged and normalized peripheral pressure profile, whereas the PWV was calculated as its equivalent index (SI-DVP) derived from the digital volume pulse (DVP), as earlier described and validated [15]. Pulse pressure (PP) was calculated as the difference between the systolic (SBP) and the diastolic (DBP) blood pressures.

Biochemical analyses

After a light breakfast, venous blood samples were drawn for the determination of lipids, HbA_{1c}, and serum creatinine. Serum lipids were measured by automated enzymatic methods (Cobas Mira analyzer; Hoffman-La Roche, Basel, Switzerland), and HbA_{1c} was analyzed by immunoturbidimetry (MedixBiochemica, Kauniainen, Finland). Blood glucose and hemoglobin concentrations were determined using HemoCue (AB Leo Diagnostics, Helsinborg, Sweden). Serum creatinine was analyzed by routine enzymatic methods. Urinary albumin excretion rate (AER) was assessed from two overnight and one 24-h urine collection by

immunoturbidimetry. Normal AER was defined as values persistently <20 μg/min or <30 mg/24 h, microalbuminuria as AER ≥ 20 < 200 μg/min or ≥30 < 300 mg/24 h, and macroalbuminuria as AER ≥ 200 μg/min or ≥300 mg/24 h in at least two out of three timed urine collections.

Statistics

Baseline characteristics are presented as means ± standard deviation (SD) for normally distributed values and as median with (interquartile) range for non-normally distributed values or percentages. Normally distributed variables between groups were tested with the Students *t* test and non-normally distributed variables with Mann–Whitney *U* and Wilcoxon tests. To detect differences within and between the groups in response to hyperoxia, a paired samples *t* test or a two-way mixed-design ANOVA (repeated measures to test for the effect of oxygen and factorial design to test for different groups) was used. A significant interaction term indicated a different response to oxygen in the two groups. Correlation coefficients were determined using Pearson's or Spearman's correlation coefficients as appropriate.

Results

The clinical characteristics of the subjects are shown in Tables 1 and 2. The studied groups were age and sex matched.

Hemodynamic data during steady state conditions

Figure 1 shows an example of the peripheral (measured) and central (reconstructed) arterial pressure profiles. From these reconstructed central pressure profiles, the AIx was calculated. Heart rate-adjusted AIx, heart rate, or pulse pressure did not differ between patients with T1D and healthy subjects at baseline (Table 2). However, SI-DVP, SBP, DBP, and MAP were increased in patients with T1D compared to healthy subjects (Table 2). Similarly, oxygen saturation was lower in patients with T1D at baseline (97.2 ± 1.0 vs. 97.7 ± 0.8 %, $P \leq 0.05$).

Figure 1 (panel A) shows the average systolic profile of the peripheral blood pressure in the two groups. No difference between patients with T1D and healthy subjects was observed at baseline (normoxia) analyzed in a point to point manner.

Effect of oxygen on hemodynamic data

Indices of blood pressure increased during hyperoxia in patients with T1D ($n = 98$), whereas no change was observed in healthy subjects ($n = 49$) (Table 2). In contrast, heart rate decreased and oxygen saturation increased in both groups. No changes/differences were seen in carbon dioxide.

The differences in the hemodynamic indices in response to hyperoxia between the groups are shown in Table 3. The increase in SBP, DBP, and PP were larger in patients with T1D than healthy subjects and increased more in response to hyperoxia (Table 3). The interaction terms between groups and conditions were significant for oxygen saturation, SBP, DBP, and MAP (data not shown). After stratifying the data according to HbA_{1c} levels (below vs. above mean) in patients with T1D, the increase in blood pressure (SBP, DBP, and MAP), in response to hyperoxia, was higher ($P < 0.05$) in those with an HbA_{1c} above mean compared to subjects with an HbA_{1c} below mean. However, no change in the AIx elevation between the groups was observed. Moreover, there was no difference in blood pressure increase in subjects on antihypertensive treatment compared to those without.

Effect of oxygen on arterial function

Figure 1 illustrates in parallel the registered finger pressure waveforms and the reconstructed central pressure waveform both at baseline and hyperoxia from one representative subject. The figure indicates an increase in the reflected waves, which is even evident in the reconstructed central pressure profile.

Oxygen increased AIx in both T1D and controls (Table 2). Furthermore, SI-DVP increased in patients with T1D ($P < 0.05$) but not in healthy subjects in response to hyperoxia. The response in AIx to oxygen was steeper in patients with T1D than in controls, as indicated by a significant interaction term between groups and conditions ($F = 5.1$, $P < 0.05$). After correcting AIx for heart rate, it increased in response to hyperoxia in patients with T1D but not in healthy subjects. The correction for mean arterial blood pressure did not change the results in either group observed as no correlations between the change in AIx in response to hyperoxia and mean arterial blood pressure ($r = 0.20$ for patients with T1D vs. $r = 0.21$ for healthy subjects). Furthermore, after including antihypertensive drugs or smoking status into the analysis, no difference in the change in arterial stiffness in response to hyperoxia was observed. Additionally, no correlation between hemoglobin or blood glucose and the change in arterial stiffness in response to hyperoxia was found in patients with T1D.

The differences in the hemodynamic indices in response to hyperoxia between the groups are shown in Table 3. The increase in AIx was larger in patients with T1D than healthy subjects. The interaction terms between groups and conditions were significant for AIx, but not for SI-DVP.

Table 1 Clinical characteristics patients with type 1 diabetes and healthy control subjects at baseline

Data obtained in 23 control subjects*	Type 1 diabetes	Controls	*P* value
N	98	49	
Sex (men/women)	56/42	22/27	NS
Age (years)	31.9 ± 6.5	32.7 ± 8.9	NS
Duration of diabetes (years)	13.5 ± 4.9	–	
Age at onset (years)	17.9 ± 5.2	–	
Body Mass Index (kg/m^2)	25.4 ± 4.9	23.7 ± 3.9	NS
Waist/Hip ratio	0.87 ± 0.07	0.86 ± 0.08	NS
Blood glucose (mmol/l)	8.4 (4.5–13.0)	4.6 (3.9–5.0)	<0.001
Hb (g/l)	147 ± 12	–	
HbA_{1c} (%)	8.06 ± 1.15	5.24 ± 0.21*	<0.001
HbA_{1c} (mmol/mol)	65 ± 7	31 ± 1	<0.001
Total cholesterol (mmol/l)	4.54 ± 0.81	4.34 ± 0.75*	NS
HDL-cholesterol (mmol/l)	1.62 ± 0.0.50	1.64 ± 0.50*	NS
Triacylglycerol (mmol/l)	1.02 (0.76–1.30)	0.78 (0.57–1.01)*	<0.05
Urinary AER (mg/24 h)	5 (2–8)	6 (4–7)*	NS
Serum creatinine (μmol/l)	69 ± 12	72 ± 13*	NS
Insulin per body weight (IU/kg)	0.77 ± 0.3	–	
Antihypertensive treatment n (%)	22 (24)	0	<0.001
Duration of antihypertensive treatment (years)	6.0 ± 3.7	0	<0.001
ACE inhibitor or ARB, *n* (%)	19 (19)	0	<0.001
Other antihypertensive drug, *n* (%)	3 (3)	0	<0.05
Laser-treated retinopathy, *n* (%)	6 (7)	–	
Normoalbuminuria, *n* (%)	88 (93)	–	
Microalbuminuria, *n* (%)	6 (6)	–	
Macroalbuminuria, *n* (%)	1 (1)	–	
Current smokers, *n* (%)	16 (17)	3 (6)	<0.05

Data are mean ± SD, median (interquartile range), or percent

Other antihypertensive drug = Calcium channel blocker, beta blocker or diuretic

AER albumin excretion rate

Table 2 Hemodynamic variables during baseline and hyperoxia in patients with type 1 diabetes and healthy controls

	Type 1 diabetes			Controls subjects		
	Normoxia	Hyperoxia	*P* value	Normoxia	Hyperoxia	*P* value
SBP (mmHg)	131 ± 15†	137 ± 15†	<0.001	121 ± 15	122 ± 16	NS
DBP (mmHg)	63 ± 9†	67 ± 9†	<0.001	57 ± 9	57 ± 9	NS
PP (mmHg)	67 ± 12	70 ± 12	0.002	64 ± 12	65 ± 13	NS
MAP (mmHg)	86 ± 10†	91 ± 10†	<0.001	79 ± 10	79 ± 11	NS
Heart rate (beats/min)	65 ± 10	61 ± 11	<0.001	65 ± 10	61 ± 9	<0.001
O2 Saturation (%)	97.2 ± 1.0*	98.7 ± 0.7	<0.001	97.7 ± 0.8	98.8 ± 0.8	<0.001
AIx (%)	14.1 ± 8.5*	17.6 ± 8.4*	<0.001	10.9 ± 11.2	12.3 ± 9.3	0.046
AIx_{75} (%)	12.1 ± 7.3	14.1 ± 7.0*	<0.001	9.9 ± 7.8	10.4 ± 7.7	NS
SI-DVP (m/s)	5.6 ± 0.3†	5.8 ± 0.8†	0.04	5.1 ± 0.6	5.2 ± 0.5	NS

Data are presented as mean ± SD

SBP systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *MAP* mean arterial pressure

AIx, Augmentation index; AIx_{75}, Heart rate-adjusted augmentation index

* $P < 0.05$; $^\dagger P < 0.001$ for the difference between the patients with T1D and control subjects during normoxia and during hyperoxia, respectively

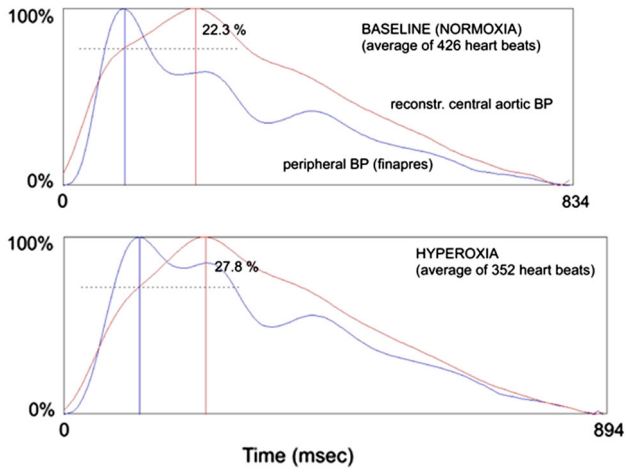

Fig. 1 Examples of central aortic pressures (*red curve*) reconstructed from the peripheral pulse pressure (*blue curve*, by Finapres) at baseline (normoxia) and during hyperoxia in one patient with T1D (color figure online)

The changes in peripheral blood pressure profile induced by oxygen are shown in Figs. 1 and 2. The simple analysis of the peripheral blood pressure profile (Fig. 2) indicated minor changes in the profile in healthy subjects in response to oxygen (panel C), whereas the change was much more evident in patients with T1D, particularly in the late systolic profile (panel B, and panel D vs. panel C). Panel B (Fig. 2) shows significant interaction terms between groups and conditions, indicating that the increase in the reflected waves in the late systole, in response to oxygen, was significantly greater in T1D than in controls.

Conclusions

The novel finding of this study was the observation that in patients with T1D acute oxygen administration caused worsening of the arterial function. Oxygen increased AIx (wave reflections) more in patients with T1D, than in healthy controls. Similarly, the hyperoxia-induced changes in blood pressure, earlier observed in healthy subjects, were enhanced in patients with T1D. Furthermore, PWV, measured as SI-DVP increased in patients with T1D but not in healthy subjects in response to hyperoxia. Finally, although heart rate decreased equally in both groups, the increase in oxygen saturation was more evident in patients with T1D in response to oxygen.

Waring et al. [6] showed in eight healthy subjects an increase in AIx during hyperoxia. They could equally observe an increase in blood pressure as well as a decrease in heart rate. Although the period of hyperoxia was shorter in this study compared to the one by Waring et al., the changes in blood pressure, heart rate, and the AIx could be observed. Notably, Ganz et al. [7] showed already in the 70s that the coronary artery blood flow decreased due to an increase in coronary resistance in response to oxygen treatment in healthy subjects as well as in patients with coronary artery disease. Similar data are also available from studies on experimental animals [16, 17]. We now extend the oxygen-induced vascular findings to patients with T1D in a much larger study sample and also broadened the arterial function evaluation by also including the PWV. These results showing that patients with T1D are more sensitive to oxygen administration than healthy subjects may have implications for the clinical practice.

Hyperoxia has been reported to be harmful in the treatment of various acute vascular conditions such as ischemic heart disease, ischemic stroke, and resuscitated patients, but rigorous randomized controlled trials are still lacking [18–20]. Sjöberg et al. [13] recently provided an interesting overview of the present knowledge of the effects of oxygen in the treatment of different acute illnesses. They summarized that oxygen administration is beneficial in subjects with definite hypoxia, but not in

Table 3 Differences in hemodynamic variables in response to hyperoxia between groups

	Type 1 diabetes	Control subjects	*P* value
ΔSBP (mmHg)	6.7 ± 12.1	1.2 ± 14.1	0.02
ΔDBP (mmHg)	3.6 ± 7.4	−0.2 ± 7.8	0.004
ΔPP (mmHg)	3.0 ± 9.5	1.4 ± 9.6	NS
ΔMAP (mmHg)	4.7 ± 8.1	0.3 ± 9.3	0.003
ΔHeart rate (beats/min)	−4.4 ± 3.8	−3.8 ± 4.0	NS
ΔO2 Saturation (%)	1.5 ± 1.0	1.1 ± 0.8	0.03
ΔAIx (%)	3.4 ± 4.8	1.5 ± 5.1	0.03
ΔAIx_{75} (%)	2.0 ± 4.4	0.5 ± 4.5	0.05
SI-DVP (m/s)	0.2 ± 0.8	0.01 ± 0.8	NS

Data are presented as mean ± SD. Data are presented as mean ± SEM

SBP systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *MAP* mean arterial pressure

AIx, Augmentation index; AIx_{75}, Heart rate-adjusted augmentation index

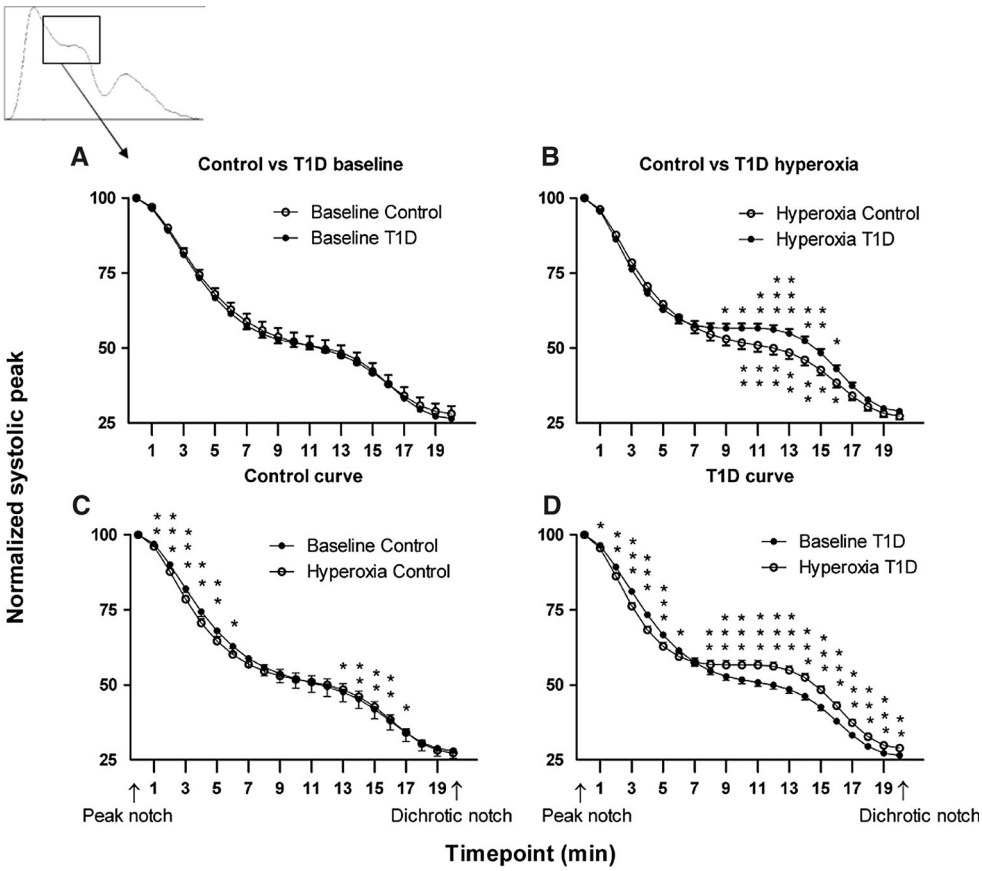

Fig. 2 The averaged peripheral pressure waves (Finapres) between the groups during baseline (*panel A*) and hyperoxia (*panel B*), as well as in response to hyperoxia in controls (*panel C*) and patients with type 1 diabetes (*panel D*). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for difference between the groups (*panel B*) versus response to hyperoxia (*panels C* and *D*) during time points. $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$ for the interaction term between groups and conditions (*panel C*) for each time point. *T1D* type 1 diabetes; Control, healthy subjects

normoxic subjects even under acute illness. The authors, therefore, questioned the use of oxygen in moderate hypoxia. Although the T1D patients in this study where hypoxic, they were not severely hypoxic, and showed an increase in arterial stiffness in response to hyperoxia in line with their theory [13].

AIx and the direct analysis of blood pressure profile showed an increase in response to hyperoxia in this study. The changes in PWV (assessed as SI-DVP) occurred in the same direction, but we could not find a significant interaction between groups and intervention. Notably, it has earlier been stated that AIx and PWV provide different information and should therefore not be used interchangeably. In a population study from the UK (Anglo-Cardiff Collaborative Trial), AIx and PWV were compared in different age groups [21]. The AIx increased steeply with age in younger individuals (<50 years), whereas aortic PWV in older people (>50 years). Hence, AIx was suggested to be a better marker of arterial function in younger, and aortic PWV in older people, although it was stressed that both indexes should be assessed to obtain a complete description of the arterial function.

The rapidity of the change in AIx favors a functional underlying mechanism. Structural changes in turn are caused by progressive transformation of elastic fibers into collagen fibers as well as arterial calcification and obviously develop over a longer period of time [22]. Acute modification of AIx might be caused by acute changes in the endothelial function and its interplay with the smooth muscle cells in the arterial wall, as well as by changes in sympathetic tone of the smaller arteries. The results may therefore indicate that the observed changes occurred rather in the peripheral vascular bed (AIx), known to be affected by diabetes, than in the large arteries (PWV) [23]. Notably, Franklin recently suggested that aortic PWV may be a better technique to measure changes over long periods of time, whereas AIx may be especially useful in short-term alterations in response to various interventions [24].

Rhee et al. [25] showed a rise in arterial stiffness after 5 min of cigarette smoking in male smokers. Unfortunately, oxygen saturation was not measured in this study. Heart rate in turn increased in parallel with arterial stiffness suggesting a sympathetic response. Conversely, we observed a decrease in the heart rate in both groups indicative of cardiac parasympathetic activity, in line with earlier findings on the effects of oxygen on autonomic function [26, 27]. Whether the parasympathetic response is an effect of hyperoxia or a secondary response to increased blood pressure is not known.

Although a lower resting oxygen saturation in patients with T1D was observed, it should be noted that hypoxia at the tissue level may not directly be paralleled by a reduction in the arterial oxygen tension [28]. Nevertheless, the reduced oxygen content in the tissues of patients with diabetes was addressed already a long time ago. Ewald et al. [29] showed delayed postischemic hyperemia as monitored by transcutaneous measurement of PO_2 ($tcPO_2$) in children with T1D without signs of vascular disease. In contrast, Haitas et al. found lower $tcPO_2$ in diabetic patients with proliferative retinopathy [30], though $tcPO_2$ was normal in newly diagnosed T1D with absence of retinopathy.

The enhanced hyperoxia-induced response may also be due to oxidative stress, a phenomenon that has been tightly linked to diabetes and its complications [11]. Oxidative stress and increased AIx have both been shown to be present in children and adolescents with T1D [31, 32]. Furthermore, as the patients with T1D are already exposed to an increased amount of oxygen free radicals at baseline, the hyperoxia could probably lead to an increased generation of ROS that exceeds the antioxidant capacity of the tissue [33]. However, also hypoxia is a known source of oxygen free radicals [34]. Accordingly, the role of oxidative stress on arterial function needs confirmation, since Thompson et al. did not find any evidence on such an effect in healthy subjects [35].

In the present study, we used the finger pressure waveform recordings (Finapres) in order to measure arterial function. It is of note that we did not compare noninvasive with invasive data that may be a limitation. However, as we recently showed in a validation study, the association between the pressure waveforms measured by arterial tonometer (considered to be the gold standard of arterial stiffness) [36] and continuous noninvasive finger pressure waveforms was very strong [15]. Moreover, this method enables long periods of recordings under unstable conditions such as hyperoxia. Furthermore, the AIx was also corrected for heart rate although it did not modify the changes observed.

A possible change in electrolyte and blood glucose concentrations may have had an impact on oxygen saturation or arterial stiffness. However, this data were not available as this study setting did not include blood sampling during hyperoxia. Anyhow, it is very unlikely that the electrolyte or blood glucose concentrations would have changed during the period of short-term hyperoxia in individual subjects and thus affected the results on arterial stiffness. Furthermore, earlier studies on a short-term hyperoxia intervention did not report such results. Thus, a study on the effect of short-term hyperoxia on metabolic changes in the blood is certainly warranted [6–8, 35]. Moreover, it is of note that a lower effect of hyperoxia on blood pressure and AIx during higher insulin concentrations (possibly mediated by nitric oxide secretion) cannot be excluded in this study.

This paper does not give a definitive answer to the question whether oxygen has a causal relationship to vascular complications in patients with T1D. However, considering the oxygen dissociation curve, it is known that even a modest change in oxygen saturation markedly alters the partial oxygen pressure in tissues that may not be a player to be neglected in this perspective. Certainly, this study gives an incentive for further long-term studies to prove the association between hyperoxia and arterial complications in T1D.

To summarize, we report that short-term oxygen administration deteriorates arterial function in patients with T1D compared to non-diabetic control subjects. Since disturbed arterial function, together with autonomic damage, plays a major role in the development of diabetic complications, these findings may be of clinical relevance.

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Conflict of interest P.-H.G. received lecture fees from Eli Lilly, Boehringer Ingelheim, Novartis, Genzyme, Merck Sharp & Dohme, and Novo Nordisk and is an advisory board member of Boehringer Ingelheim, Novartis, and Cebix. No other potential conflicts of interest relevant to this article were reported.

Human and Animal Rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2008.

Informed consent disclosure Informed consent was obtained from all patients for being included in the study.

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