Original articles

Effect of enriched oxygen inhalation on lower limb skin temperatures in diabetic and healthy humans: a pilot study

Kwan Leong Au-Yeung[1,2], Christopher Selvaraj[1], Tajrian Amin[3], Lawrence K Ma[4], Michael H Bennett[1]

[1] *Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, Sydney, Australia*
[2] *Department of Accident and Emergency Medicine, Queen Elizabeth Hospital, HKSAR*
[3] *Department of Medicine, University of New South Wales, Sydney, Australia*
[4] *Department of Psychology, The Education University of Hong Kong, HKSAR*

Corresponding author: *Dr Kwan L Au-Yeung, 30 Gascoigne Road, Yau Ma Tei, Kowloon, HKSAR*
aedraye@yahoo.com.hk

Key words
Chronic wounds; Diabetes; Hyperoxia; Skin thermometry; Vasoconstriction

Abstract
(Au-Yeung KL, Selvaraj C, Amin T, Ma LK, Bennett MH. Effect of enriched oxygen inhalation on lower limb skin temperatures in diabetic and healthy humans: a pilot study. Diving and Hyperbaric Medicine. 2022 March 31;52(1):2–6. doi: 10.28920/dhm52.1.2-6. PMID: 35313366.)
Introduction: Measurement of skin temperature with infrared thermometry has been utilised for assessing metabolic activity and may be useful in identifying patients with ulcers suitable for hyperbaric oxygen treatment and monitoring their treatment progress. Since oxygen promotes vasoconstriction in the peripheral circulation, we hypothesised that oxygen administration may lower skin temperature and complicate the interpretation of temperatures obtained. This pilot study investigated the effect of oxygen administration on lower limb skin temperature in healthy subjects and diabetic patients.
Methods: Volunteers were recruited from healthy staff members (n = 10) and from patients with diabetic foot ulcers (n = 10) at our facility. Foot skin surface temperatures were measured by infra-red thermometry while breathing three different concentrations of oxygen (21%, 50% and 100%).
Results: Skin temperature changes were observed with increasing partial pressure of oxygen in both groups. The mean (SD) foot temperatures of diabetic patients and healthy controls at air-breathing baseline were 30.1°C (3.6) versus 29.0°C (3.7) respectively, at FiO_2 0.5 were 30.1°C (3.6) versus 28.5°C (4.1) and at FiO_2 1.0 were 28.3°C (3.2) versus 29.2°C (4.3). None of these differences between groups were statistically significant.
Conclusions: Data from this small study may indicate a difference in thermal responses between healthy subjects and diabetic patients when inhaling oxygen; however, none of the results were statistically significant. Further investigations on a larger scale are warranted in order to draw firm conclusions.

Introduction

Infrared thermometry (IRT) is an effective tool in monitoring disease progression and predicting diabetic foot ulceration.[1–5] By measuring skin surface temperature elevation, IRT allows early detection of ulceration at home by patients themselves.[6–8] Another non-invasive technology used in the management of diabetic ulcers is transcutaneous oximetry measurement (TCOM). It is used both for assessing the suitability of a problem wound for treatment with hyperbaric oxygen treatment (HBOT) and for monitoring progress during the course of a therapy.[9] Transcutaneous oximetry measures the partial pressures of oxygen in subcutaneous tissue ($PtcO_2$) immediately surrounding a wound, usually while breathing air or a high concentration of oxygen. To measure the $PtcO_2$, the intact skin surrounding the wound is warmed in order to 'arterialise' the area and facilitate diffusion of oxygen from the subcutaneous tissue for estimation by the Clarke electrode. Elevation of the $PtcO_2$ by oxygen administration under normobaric and hyperbaric conditions as measured by TCOM is associated with treatment success with HBOT.[9–12] Transcutaneous oximetry is a lengthy and technically challenging task, and prone to the production of puzzling or clearly erroneous results that require careful interpretation.[13] While well-established in hyperbaric practice, the search nevertheless continues for a more time-efficient and reliable measure of the potential success of HBOT in individual patients.

The use of IRT as an estimate of metabolic activity in skin wounds is a promising alternative to TCOM. Results are dependent on the integrity of the peripheral vasculature and the vasomotor responses which in turn have direct effects on the dermal temperature. There are, to our knowledge, no data available on the effect of inspired oxygen on skin temperature. We hypothesised that in normal individuals,

vasoconstriction at high tissue PO_2 might lower skin temperature while in diabetic patients this phenomenon might be blunted by poor vasomotor responses. Furthermore, we hypothesised the improvement of wound metabolism in poorly healing ulcers over a course of HBOT might be reflected in peri-wound temperatures.

In the present small-scale pilot study, we have embarked on a series of investigations to evaluate the suitability of IRT to both select suitable problem wounds for treatment with HBOT and to monitor wound progress. A higher temperature at a problem wound suggests either a more metabolically active wound resulting from inflammation or infection, or an impaired autonomic response with vasodilation. On the other hand, vasomotor responses to hyperoxia may reduce flow and thus temperature of a wound despite suitable healing. As a first step, this study simulated the conditions of TCOM assessment by having subjects breathe different fractions of inspired oxygen while measuring skin temperatures by IRT. The primary aim was to identify any potentially reliable signals in either normal individuals or diabetic patients during oxygen administration up to an FiO_2 of 1.0 at 101.3 kPa (1 atmosphere absolute).

Methods

Following ethics committee approval (HREC 15/255 -LNR/15/POWH/463), two groups of volunteers were enrolled: diabetic patients with chronic lower leg wounds, present for at least three months, and receiving wound care at our hyperbaric facility (n = 10); and healthy controls (members of staff of the hyperbaric facility with no established diagnoses relevant to perfusion of the lower limbs) (n = 10). Patients with clinical signs and symptoms of large vessel disease or a primary diagnosis other than an ulcer due to diabetes mellitus were excluded. Patients who were unable to provide informed consent were also not included. Volunteer staff were matched for gender with the patient group. The primary outcome was comparison of the mean wound skin temperatures in each group (healthy volunteers and diabetic foot patients) in response to breathing three different oxygen fractions at 101.3 kPa, while the secondary outcome was to compare the temperature changes between these two groups at each concentration.

Each subject was given a study information sheet and provided written, informed consent prior to commencement. Temperature measurements were taken in an air-conditioned examination room. When wounds were present on both lower legs, one leg was chosen by toss of a coin. The same applied to the choice of limb of the healthy control subjects. For the diabetic group, the selected lower legs were cleaned with soap-free pH-balanced wash by hyperbaric nurses, and were then dried and covered with sterile sheets. Staff volunteers had their legs cleansed then covered with a sterile sheet in the same manner. Body temperature was measured by tympanic membrane thermometer (Braun Pro 4000 Thermoscan, Welch Allyn) and the room temperature was recorded. Skin temperature images (STI) were captured by a handheld FLIR E6 1.0 infra-red camera (FLIR Systems, Wilsonville OR, USA) with the following settings: alignment distance of 0.3 meter; emissivity ε0.98 hu (for skin); and reflected temperature at 22°C. The camera displayed values in increments of 0.1°C and provided a thermal sensitivity of < 0.06°C. The temperature at any point selected in the image was displayed on the screen. The camera continuously auto-calibrated and was accurate to within +/-2%.

All subjects were seated on the same chair in a semi-reclined position of about 45 degrees to horizontal. After a 10-minute rest breathing room air (FiO_2 = 0.21) with the lower legs covered, the first images were taken. These were of the index ulcer and the equivalent area in the gender-matched healthy volunteer pair. Subjects then had their legs re-covered and breathed an FiO_2 of 0.5 using a calibrated Venturi mask (Hudson RCI® Teleflex medical, USA) for ten minutes before a second set of STIs of the same area were captured. The mask was removed, the legs re-covered and the mask replaced with an oxygen hood (Amron™ Oxygen Treatment Hood, Amron International, USA) supplied with 100% oxygen at 15 $L \cdot min^{-1}$ for a further 10 minutes. Previous investigation suggested this will provide a mean (95% CI) FiO_2 of 0.94 (0.14).[14] The third set of STIs was then taken. Finally, the wound patients had their dressing procedure completed as normal. The entry and exit of the dressing room was kept to a minimum to avoid producing any draft which may affect the surface temperature.

The STIs were analysed using a proprietary software program provided with the camera (FLIR Tools version 1.18.8). Skin temperatures were recorded at eight points circumferentially around the wound edge and two points over the wound on patients' legs, and at the corresponding anatomical locations in control subjects' legs according to the gender matched pair. The mean temperatures of these areas at different inspiratory concentrations of oxygen were analysed.

Average skin temperatures were compared between groups by mixed-design analysis of variance (ANOVA) using SPSS Statistics version 26.0 (IBM, Armonk, USA). Individual group measurements were expressed as mean (standard deviation). Statistically significant differences were considered to exist at $P < 0.05$.

Results

The individual baseline data for the two groups are shown in Tables 1 and 2. Independent sample t-tests failed to reveal any significant differences between the control participants and the patients in body temperature at baseline, t (18) = -0.3, P = 0.077.

Skin temperature changes with changing inspired oxygen concentrations for both groups are shown in Figure 1. The skin temperatures changed little in either group between room

Table 1
Characteristics of the healthy volunteers

Control	Sex/Age (years)	Room temp (°C)	Body temp (°C)
1	M/44	22.0	36.6
2	M/45	22.7	36.7
3	M/43	23.5	36.7
4	M/46	23.5	36.5
5	M/44	24.0	36.7
6	M/45	25.5	36.9
7	F/39	25.5	37.0
8	M/41	23.6	36.7
9	M/64	21.0	36.7
10	M/24	21.0	36.7
Mean (SD)	43.5 (9.7)	23.2 (1.6)	36.7 (0.1)

Figure 1
Mean skin temperatures (SD) with increasing inspired oxygen over the wound sites

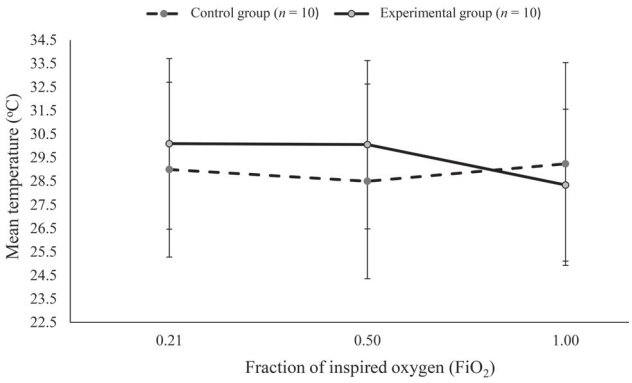

Table 2
Characteristics of the diabetic wound patients

Patient	Sex/Age (years)	Room temp (°C)	Body temp (°C)	Wound location	Wound size (mm)	Duration (months)
1	M 69	21.0	36.0	Right sole below MTPJ 1	29 x 2.5	4
2	M 58	22.0	36.3	Left lateral sole	22 x 22	7
3	M 62	23.0	36.5	Right sole medial to MTPJ 1	43 x 44	9
4	M 71	24.0	36.6	Proximal right big toe	10 x 11	6
5	M 56	23.7	37.1	Right big toe	6 x 8	4
6	M 68	25.5	37.1	Right heel	40 x 32	4
7	F 58	23.4	36.9	Left heel	60 x 52	5
8	M 67	21.8	36.7	Right shin	40 x 41	12
9	M 63	21.0	37.2	Right 5th toe amputation	6 x5	6
10	M 66	21.0	37.2	Right heel	10 x 8	12
Mean (SD)	63.8 (5.2)	22.6 (1.5)	36.8 (0.4)			

air and an FiO_2 of 0.5, but changed in opposing directions when breathing an FiO_2 of 1.0. In this small cohort, none of the observed differences were significantly different from baseline temperatures using repeated-measures ANOVA and analysing the control versus ulcerated subjects at the three levels of FiO_2 ($P = 0.089$). The mean (SD) measurements were: room air, patient group 30.1°C (3.6) versus healthy control 29.0°C (3.7); FiO_2 0.5, 30.1°C (3.6) versus 28.5°C (4.1); FiO_2 1.0, 28.3°C (3.2) versus 29.2 (4.3).

Discussion

The present study constitutes a pilot endeavour to examine the potential of IRT in providing important information on the suitability of a diabetic wound for HBOT and/or the monitoring of progress during treatment. Specifically, we intended to investigate the feasibility of the testing regimen under clinical conditions and to seek an indication that individuals with lower leg ulcers might display differences in skin/wound temperature compared to normal controls when breathing high concentrations of oxygen. We broadly simulated the TCOM testing process for this trial, with the addition of a period of 50% oxygen breathing. We measured skin surface temperatures under three conditions in two small groups of subjects, normal controls and diabetic patients with lower leg ulcers. We believe this work has generated two findings worthy of discussion and potentially helpful in guiding further investigations.

First, there were temperature changes with increasing inspired oxygen fraction above 0.5 in both normal subjects and diabetic wound patients. Second, those changes demonstrated a difference in trajectory between groups (albeit not statistically significant). Diabetic patients showed a mean drop in temperature of about 1.5°C when breathing 100% oxygen, whereas normal individuals displayed an increase in skin temperature. This may be an important observation if confirmed in more definitive studies.

Major determinants of skin temperature include blood vessels, sweat glands, endocrine glands and skeletal muscle. Vasodilation of the skin venous plexus increases blood flow which results in a rise of the skin temperature and the dissipation of heat during heat exposure or exercise and the opposite happens with cold exposure.[15] These vasomotor responses to environmental thermal stresses are controlled by

reflex innervation and neurotransmitters.[16,17] The effects of arterial oxygen tension (PaO_2) on mechanisms of vasomotor responses in human skin have been studied.[18,19] We are not, however, aware of any investigation(s) to date on the effect of hyperoxia on human skin temperature. In this small cohort there was a signal that skin temperature may vary with FiO_2 under a relatively stable environmental temperature. It was observed that in normal subjects the skin temperature may drop initially when the FiO_2 is increased from 0.21 to 0.5, followed by an unexpected rebound increase in skin temperature when the FiO_2 was further increased to 1.0. The (non-significant) observed initial drop in skin temperature was consistent with the findings of previous physiologic studies investigating vasoconstriction under hyperoxia.[15] However, the observation of a subsequent rise in skin temperature when the FiO_2 was further increased to 1.0 was not expected as hyperoxia should lead to vasoconstriction, which in turn should result in skin temperature drop. This observation suggests vasodilatation, instead of vasoconstriction, may have occurred in response to a further increase in oxygenation or under prolonged hyperoxia. The latter suggestion (that sustained hyperoxia may result in increased flow) is supported by the recent reporting of increased skin perfusion in the foot early after an initial decrease during exposure of healthy subjects to hyperbaric oxygen.[20] While our finding may simply be a Type II error attributable to our small sample size, this observation is interesting and justifies further investigation in appropriately powered studies. Definitive conclusions cannot be drawn at this stage.

As observed in this study, the corresponding skin/wound surface temperatures in the legs of diabetics did not seem to respond in the same way on exposure to increasing FiO_2. There was no indication of significant surface temperature change when the FiO_2 increased from 0.21 to 0.5; however, a drop of skin temperature at an FiO_2 of 1.0 was noted. The lack of temperature change to the initial rise in FiO_2 may reflect the blunted vasomotor response among diabetic patients and this is consistent with the findings in physiologic studies on the diabetic vasculature under different conditions.[21,22] The temperature drop when FiO_2 rose further could be a reflection of skin temperature being equilibrated with the environmental temperature given that the environmental room temperatures throughout the study period (21.0–25.5°C) were lower than the limb temperatures of either group. The baseline skin temperatures among diabetic patients were observed to be higher than normal subjects. This could be the result of the chronic inflammation associated with the ulcers and this is consistent with published observations.[23] This temperature drop may indicate the unmasking of an underlying failing of the temperature-regulating physiology during high FiO_2 breathing among the diabetic group. The observed values may be the result of a true difference between the groups or simply a random event of no importance. We believe this observation deserves further study and justifies future investigation designed to either confirm or refute our hypothesis concerning impaired responses to oxygen in the diabetic group.

Future investigations will not only require a larger study cohort but also improved environmental control of ambient temperature and careful attention to the inclusion criteria for the control group in order to more closely match the diabetic patients. In the present study our staff volunteers in the control group were an average of 20 years younger than the experimental group and this could constitute an important reason for the difference observed between groups. Senescent changes in the skin and underlying vessel may well be important in this regard.

Measurement error of the thermal camera would also need to be considered. The manufacturer claimed a thermal sensitivity of < 0.06°C, and that this camera auto-calibrates continuously and is accurate to within ± 2%. It is unlikely our observed differences represent a measurement error. Achieving a gold standard of calibration is difficult with electronic instruments and repeated measurements may help to reduce the measurement error. Nine of the ten patients recruited had wounds over the foot while only one had wound located on the lower leg. The statistical analysis was repeated with the non-pedal wound excluded and the results are similar. Having said that, we would recommend separate analyses of pedal and non-pedal wounds in future studies due to potential differences in vasomotor responses. Although it is not easy to nail down a gold standard for comparison in this area, we suggest future studies should compare the IRT with both ABI values and TCOM results under hyperoxic conditions. In regard to the demographic data collection, details on tobacco and caffeine consumption, current vasomotor medications use and documentation of presence of peripheral sensory neuropathy and/or autonomic neuropathy would also be important factors that may affect the vasomotor response of the dermal vasculature. Given the environmental temperature is likely to significantly confound any difference in response in the diabetic group, any future investigation will need to be undertaken under tight control of the room temperature for all study subjects through the study period.

Conclusions

Data from this limited pilot study may indicate a difference in thermal responses between healthy subjects and diabetic patients when inhaling oxygen. None of the results were statistically significant, and further appropriately powered investigations with better matched controls and experimental subjects under rigorous environmental temperature control are needed before any definitive conclusions be drawn.

References

1 Armstrong DG, Lavery LA, Liswood PJ, Todd WF, Tredwell JA. Infrared dermal thermometry for the high-risk diabetic

foot. Phys Ther. 1997;77:169–75. doi: 10.1093/ptj/77.2.169. PMID: 9037217.
2 Armstrong DG, Lavery LA. Predicting neuropathic ulceration with infrared dermal thermometry. J Am Podiatr Med Assoc. 1997;87:336–7. doi: 10.7547/87507315-87-7-336. PMID: 9241978.
3 van Netten JJ, van Baal JG, Liu C, van der Heijden F, Bus SA. Infrared thermal imaging for automated detection of diabetic foot complications. J Diabetes Sci Technol. 2013;7:1122–9. doi: 10.1177/193229681300700504. PMID: 24124937. PMCID: PMC3876354.
4 Sivanandam S, Anburajan M, Venkatraman B, Menaka M, Sharath D. Medical thermography: a diagnostic approach for type 2 diabetes based on non-contrast infrared thermal imaging. Endocrine. 2012;42:343–51. doi: 10.1007/s12020-012-9645-8. PMID: 22411072.
5 Houghton VJ, Bower VM, Chant DC. Is an increase in skin temperature predictive of neuropathic foot ulceration in people with diabetes? A systematic review and meta-analysis. J Foot Ankle Res. 2013;6:31. doi: 10.1186/1757-1146-6-31. PMID: 23919736. PMCID: PMC3750703.
6 Lavery LA, Higgins KR, Lanctot DR, Constantinides GP, Zamorano RG, Armstrong DG, et al. Home monitoring of foot skin temperatures to prevent ulceration. Diabetes Care. 2004;27:2642–7. doi: 10.2337/diacare.27.11.2642. PMID: 15504999.
7 Lavery LA, Higgins KR, Lanctot DR, Constantinides GP, Zamorano RG, Athanasiou KA, et al. Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. Diabetes Care. 2007;30:14–20. doi: 10.2337/diacare.27.11.2642. PMID: 17192326.
8 Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. Am J Med. 2007;120:1042–6. doi: 10.1016/j.amjmed.2007.06.028. PMID: 18060924.
9 Smart DR, Bennett MH, Mitchell SJ. Transcutaneous oximetry, problem wounds and hyperbaric oxygen therapy. Diving Hyperb Med. 2006;36:72–86. [cited 2021 Dec 26]. Available from: https://www.dhmjournal.com/images/IndividArticles/36June/Smart_dhm.36.2.72-86.pdf.
10 Grolman RE, Wilkerson DK, Taylor J, Allinson P, Zatina MA. Transcutaneous oxygen measurements predict a beneficial response to hyperbaric oxygen therapy in patients with nonhealing wounds and critical limb ischemia. Am Surg. 2001;67:1072–9. PMID: 11730224.
11 Sheffield PJ. Measuring tissue oxygen tension: a review. Undersea Hyperb Med. 1998;25:179–88. PMID: 9789339.
12 Fife CE, Smart DR, Sheffield PJ, Hopf HW, Hawkins G, Clarke D. Transcutaneous oximetry in clinical practice: consensus statements from an expert panel based on evidence. Undersea Hyperb Med. 2009;36: 43–53. PMID: 19341127.
13 Trinks TP, Blake DF, Young DA, Thistlethwaite K, Vangaveti VN. Transcutaneous oximetry measurements of the leg: comparing different measuring equipment and establishing values in healthy young adults. Diving Hyperb Med. 2017;47:82–7. doi: 10.28920/dhm47.2.82-87. PMID: 28641320. PMCID: PMC6147223.
14 Davidson G, Bennett MH. Effect of oxygen flow on inspired oxygen and carbon dioxide concentrations and patient comfort in the Amron™ oxygen hood. SPUMS Journal. 2004;34:68–74. [cited 2021 Dec 26]. Available from: https://www.dhmjournal.com/images/IndividArticles/34June/Davidson_dhm.34.2.68-74.pdf.
15 Charkoudian N. Skin blood flow in adult human thermoregulation: How it works, when it does not, and why. Mayo Clin Proc. 2003;78:603–12. doi: 10.4065/78.5.603. PMID: 12744548.
16 Wong BJ, Hollowed CG. Current concepts of active vasodilation in human skin. Temperature (Austin). 2016;4:41–59. doi: 10.1080/23328940.2016.1200203.
17 Smith CJ, Johnson JM. Responses to hyperthermia. Optimizing heat dissipation by convection and evaporation: neural control of skin blood flow and sweating in humans. Auton Neurosci. 2016;196:25–36. doi: 10.1016/j.autneu.2016.01.002. PMID: 26830064.
18 Yamazaki F, Takahara K, Sone R, Johnson JM. Influence of hyperoxia on skin vasomotor control in normothermic and heat-stressed humans. J Appl Physiol (1985). 2007;103:2026–33. doi: 10.1152/japplphysiol.00386.2007. PMID: 17885027.
19 Yamazaki F. Hyperoxia attenuates endothelial-mediated vasodilation in the human skin. J Physiol Sci. 2007;57:81–4. doi: 10.2170/physiolsci.SC011006. PMID: 17169168.
20 Yamamoto N, Takada R, Maeda T, Yoshii T, Okawa A, Yagishita K. Microcirculation and tissue oxygenation in the head and limbs during hyperbaric oxygen treatment. Diving Hyperb Med. 2021;51:338–44. doi: 10.28920/dhm51.4.338-344. PMID: 34897598.
21 Wick DE, Roberts SK, Basu A, Sandroni P, Fealey RD, Sletten D, et al. Delayed threshold for active cutaneous vasodilation in patients with Type 2 diabetes mellitus. J Appl Physiol (1985). 2006;100:637–41. doi: 10.1152/japplphysiol.00943.2005. PMID: 16210432.
22 Sokolnicki LA, Strom NA, Roberts SK, Kingsley-Berg SA, Basu A, Charkoudian N. Skin blood flow and nitric oxide during body heating in type 2 diabetes mellitus. J Appl Physiol (1985). 2009;106:566–70. doi: 10.1152/japplphysiol.91289.2008. PMID: 19056994. PMCID: PMC2644253.
23 Yavuz M, Ersen A, Hartos J, Lavery LA, Wukich DK, Hirschman GB, et al. Temperature as a causative factor in diabetic foot ulcers: a call to revisit ulceration pathomechanics. J Am Podiatr Med Assoc. 2019;109:345–50. doi: 10.7547/17-131. PMID: 30427732.

Acknowledgements

We thank the hyperbaric nurses in the Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, Sydney, Australia, and Jayne Mcgreal, chief podiatrist in the Endocrine Clinic, Prince of Wales Hospital, Sydney, Australia.

Conflicts of interest and funding: nil

Submitted: 30 May 2020
Accepted after revision: 04 November 2021