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# Controlled Adverse Environment Chambers in Dry Eye Research

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**ABSTRACT**

Dry eye disease (DED) is a common condition with signs and symptoms that vary depending on a wide range of environmental factors to which people are exposed in their daily lives. Factors such as variable temperature, airflow velocity, relative humidity, seasonality, and pollutants can alter the rate of tear film evaporation, improving or exacerbating symptoms of DED. Results from currently available clinical tests do not always correlate well with patient-reported symptoms, and the continually changing environment and variability in DED symptoms present challenges for the design and conduct of clinical trials. Controlled adverse environment chambers allow standardization of temperature, humidity, and airflow and may minimize potential confounding factors in clinical investigations. Their use can promote accurate study of the pathophysiology of DED, discovery of disease biomarkers, and assessment of the effect of various therapeutic approaches on patients' symptoms. Controlled adverse environment chambers have been used to simulate indoor surroundings such as airplane cabins and to test their effects on contact lens wearers. This review summarizes how these chambers may be useful for the development, approval, and differentiation of potential new treatments for DED.

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## Introduction and overview of dry eye disease

The components of the ocular surface (tear film, cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal gland, and interconnecting innervation act together as a functional unit.[1] Dry eye disease (DED) is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear instability, with potential damage to the ocular surface.[2] It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[2] Most symptoms of DED are due to chronic inflammation of the lacrimal functional unit resulting in a loss of tear film integrity and normal function, leading to a reduction in the ability of the ocular surface to respond to environmental challenges.[3]

The signs and symptoms in patients with DED can vary depending on the wide variety of environmental conditions to which they are exposed in daily life, including artificially controlled environments in buildings, vehicles, and airplanes, and particularly air pollution in urban and metropolitan areas.[4–10] In corroboration, levels of air pollution in Paris can cause short-term increases in ophthalmology emergency visits.[11] Factors such as variable temperature, airflow velocity, relative humidity, seasonality (which affects all three), levels of ozone and nitrogen dioxide, and passive cigarette smoke exposure can alter the rate of tear film evaporation, improving or exacerbating symptoms of DED.[4,7,9,10,12–17] Indeed, a newly proposed classification system for tear dysfunction has highlighted the leading role played by evaporative underlying mechanisms that are likely affected by fluctuations of temperature, humidity, and airflow.[18] Such a wide variety of symptoms and the lack of a single universal test for DED magnify the difficulty in diagnosing and classifying patients, as well as hindering monitoring of disease progression and accurate determination of patients' response to treatment.[19] Results from currently available diagnostic tests for DED do not always correlate well with patient-reported symptoms, particularly in mild-to-moderate disease.[19,20] In addition, low correlations have been found between different objective tests.[19,20] As well as the implications for clinical practice, the continually changing environment and variability in symptoms present challenges for the design and conduct of clinical trials in DED. The "background noise" of daily environmental and behavioral differences among study participants complicates the establishment of valid baseline measures and accurate assessment of treatment effects.[21] The present review article considers the role of controlled adverse environment chambers, specialized units in which the conditions surrounding the eye can be artificially manipulated, in addressing some of the above issues.

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## Development of controlled adverse environment chambers

Controlled adverse environment chambers—in which temperature, humidity, airflow, and lighting are regulated, and can be kept constant or varied—have been developed for use in studies of animals[22–24] and human subjects.[4,25–28] These chambers can allow accurate studies of the pathophysiology of DED, discovery of disease biomarkers, and assessment of the efficacy of different therapeutic approaches. The use of an adverse environmental chamber can help to control and minimize potential confounding factors such as seasonality, and to a certain extent pollution, although the variety and complex reactions of pollutants in the atmosphere, and therefore their distribution and exposure, may be difficult to replicate fully.[11,29] Despite obvious ethical constraints of exposing human subjects to harmful levels of environmental pollutants, some previous research has investigated their effects in volunteers as well as in animal experiments.[11]

## Current commercially available adverse environment chambers

A number of adverse environment chambers have been built and used in ophthalmologic research worldwide (Table 1). A chamber produced by Weiss Gallenkemp (Loughborough, UK) located at Glasgow Caledonian University, UK, has been used in several studies of DED.[27,28] This is an isolated room approximately 2 × 2 × 2 m in size. Inside the room, temperature can be controlled between 5°C and 35°C, and relative humidity between 5% and 95%.[27,28] The temperature variation and fluctuation in the chamber are ±2°C and ±1°C, respectively, and relative humidity fluctuation is ±3%.[30]

The commercially available Controlled Environment Laboratory (CELab) Vision R & D located at the Institute for Applied OphthalmoBiology (IOBA) at the University of Valladolid, Valladolid, Spain, comprises an exposure chamber and an evaluation chamber. Temperature and relative humidity can be controlled in both rooms simultaneously. Additionally, airflow (blower exit velocity: range 0.6–3.6 m/s), illuminance (range, 10–1000 lux; 1 lux steps), and atmospheric pressure (range: 930–450 mbar; 1 mbar steps) can be controlled in the exposure chamber. Environmental conditions are monitored using a control panel located exteriorly.[4]

Another chamber that has been used in various animal and human studies is Ora Inc's CAE$^{R}$, located in Andover, MA, USA.[21] This chamber regulates humidity, temperature, airflow (constant, non-turbulent), and lighting conditions, and has integrated diagnostic equipment.[21] Another chamber located in Keio University School of Medicine in Tokyo, Japan, is equipped with a closed air circulation system consisting of a circular duct with propellant and return vents. In addition, an environmentally controlled goggle system has been designed at Baylor University College, Houston, TX, USA, that delivers a constant flow of dehumidified air pumped at a flow rate of 2–5 L/min to maintain a relative humidity of 15–25% (mean, 21%).[31] Relative humidity, temperature, and airflow are measured by sensors in the goggles, and blink rate is monitored by electrodes embedded in the goggles.[31]

A selection of published research conducted in patients with DED at the above chamber facilities is presented in Table 2.[4,12,21,25,30,31]

**Table 1.** Controlled adverse environment chambers (Baylor University College = goggles system) located worldwide.

| | Settings (range) | |
|---|---|---|
| Name/location | Temperature | Humidity |
| Glasgow Caledonian University, UK | 5–35°C | 5–95% |
| CELab, Vision R & D, University of Valladolid, Spain | 15–30°C | 5–80% |
| CAE$^{R}$, Andover, MA, USA | 76 ± 6°F | <10% |
| Keio University School of Medicine, Tokyo, Japan | 0–50°C | 0–100% |
| Baylor University College, Houston, TX, USA | Ambient | 15–25% |

## Application of controlled adverse environment chambers in ophthalmologic research

### *Animal models*

Various animal models for DED exist[32] but they are affected by environmental influences on tear secretion and ocular surface conditions. A controlled adverse environment chamber was used to induce DED in mice.[22,23] The typical characteristics of these mice are loss of conjunctival goblet cells and diminished lacrimation leading to ocular surface damage (detected by corneal fluorescein staining), with features that mimic human DED.[22,23,33] This mouse model has been used to study the pathogenesis of DED and to test potential new therapies, such as topical omega-3 and omega-6 fatty acids.[33–35] Another recent study used a commercial chamber (Ora Inc's CAE$^{R}$) to demonstrate the potential efficacy of treatment with thymosin β4, a naturally occurring molecule that can reduce tissue damage and promote corneal healing, in mice with induced moderate-to-severe DED.[36] Therefore, considerable potential exists for the use of adverse event chambers to further basic research on DED in animal models.

### *Effects of desiccating environmental stress*

Controlled adverse environment chambers provide adjustable, reproducible sets of conditions that challenge research subjects' eyes isometrically and for the same length of time.[21] Exposure to adverse environmental conditions induces rapid changes to the ocular surface; these changes are reversible, suggesting that the chambers provide a safe ambience in which to standardize diagnostic tests for DED and evaluate novel therapeutics.[13] Studies can be designed to evaluate patients' responses in a harmless controlled environment (for example, to investigate biomarker-based predictive models),[37,38] to expose patients or healthy controls to desiccating environmental stress,[12,13,25,30] or to investigate contact lenses and their effect on the ocular surface.[14]

Low relative humidity can increase tear evaporation and result in elevated tear film osmolarity, which in turn may induce stress in ocular cells through a hyperosmolar mechanism.[13,25,30] One investigation performed at Glasgow Caledonian University showed that low relative humidity (5%) adversely affects tear evaporation rate, lipid-layer thickness, ocular comfort, and tear stability and production in healthy volunteers, with 1-hour exposure producing tear film parameters similar to those of a DED patient.[30] Adult patients with mild-to-moderate DED and age-matched asymptomatic subjects can experience acute exacerbation in

**Table 2.** Selection of published research using controlled adverse environment chambers in patients with DED.

| Facility/reference | Environmental conditions | Subjects | Results |
|---|---|---|---|
| Ophthalmic Research Associates, Boston, MA, USA | | | |
| Ousler et al[21] | RH: <10%; T: 24.4 ± 3.4°C<br>Airflow: constant, non-turbulent<br>Visual task: TV watching, computer use<br>Duration: 90 minutes | 33 DED patients | Adverse exposure decreases break-up area and palpebral fissure size and increases corneal staining and redness |
| Controlled Environment Laboratory (CELab), Vision R & D, IOBA, University of Valladolid, Valladolid, Spain | | | |
| López-Miguel et al[12] | RH: 5%; T: 23°C<br>Airflow: 0.43 m/s<br>Visual task: TV watching<br>Duration: 120 minutes | 20 healthy subjects<br>19 DED patients | Corneal staining increases and tear stability decreases in both groups, symptoms and conjunctival hyperemia in DED<br>Tear MMP-9 increases and EGF decreases in both groups, IL-6 increases in healthy subjects |
| López-Miguel et al[25] | RH: 5% vs 45%; T: 23°C<br>Airflow: 0.1 m/s<br>Visual task: TV watching<br>Duration: 120 minutes | 14 DED (Sjögren's syndrome) | Corneal staining, conjunctival hyperaemia, tear osmolarity increase<br>Tear IL-1RA, IL-6, IL-8, and MMP-9 increase |
| Tesón et al[4] | In-flight vs standard conditions<br>RH; 5% vs 45%; T: 23°C<br>Atm pressure: 750 vs 930 mb<br>Airflow: 0.43 m/s<br>Visual task: TV watching<br>Exposure: 120 minutes | 20 DED patients | Tear production and stability decrease, conjunctival hyperemia, corneal staining increase |
| Glasgow Caledonian University, Glasgow, UK | | | |
| Abusharha et al[30] | RH: 5%, 40%; T: 21°C<br>Airflow: not specified<br>Duration: 60 minutes | 12 healthy subjects | Low RH increases tear evaporation rate and decreases tear production and stability, lipid layer thickness, and ocular comfort |
| Environmental goggles, Baylor College of Medicine, Houston, TX | | | |
| Alex et al[31] | RH: 5%, 40%, 70%; T: 22°C<br>Airflow: not specified<br>Duration: 190 minutes | 10 healthy subjects<br>10 DED | Low RH increases tear evaporation rate in DED; no intergroup difference at 70% RH |

an environmental chamber (low relative humidity, desiccating settings) that resembles the sudden worsening that patients with DED experience daily.[12,25] Two hours' exposure to a controlled adverse environment leads to significant deterioration of the lacrimal functional unit in patients with Sjögren's syndrome-associated dry eye; the often unnoticed exposure to these conditions during daily life may increase inflammatory activity rapidly, triggering ocular surface deterioration.[25]

Airplane cabins are an example of a controlled indoor environment, characterized by low humidity (ranging from 5% to 25%), constant temperature, and reduced barometric pressure.[4] Maintenance of level cabin temperature and pressure requires high air exchange rates, which are generated using increased air flow that can lead to DED symptoms.[4] The IOBA CELab was used to simulate an in-flight airplane cabin, with a temperature of 23°C, 5% relative humidity, localized airflow, and 750 mbar of barometric pressure. DED patients exposed to this environment for 2 hours had more symptoms, a significant decrease in tear stability and volume, and a significant increase in corneal staining, whereas those exposed to a standard condition (23°C, 45% relative humidity and 930 mbar pressure) showed only a mild increase in corneal staining—possibly due to their performing near vision tasks during the assessment period.[4] These findings suggest that DED patients should take additional precautions to prevent exacerbation of their symptoms during flights.

Contact lens wear is frequently associated with DED symptoms, including discomfort and corneal sensitivity.[26,39] DED symptoms may arise in the majority of soft contact lens wearers,[40–44] and can lead to discontinuation of wear.[41,45] Dehydration of contact lenses starts rapidly after placement on the eye, and is influenced by multiple factors including the surrounding environmental conditions, lens thickness, and manufacturing materials.[14,46] Controlled adverse environment chambers provide a useful tool for investigating tear function and ocular surface alterations associated with new contact lens materials, enabling wearers to select a contact lens appropriate for their local conditions.[26] The abovementioned chamber in Tokyo, Japan, set to a temperature of 18°C, 18% relative humidity and wind velocity of 1.2 m/s, found marked tear instability and increased tear osmolarity and tear evaporation with DED and visual symptomatology in non-adapted versus silicone hydrogel contact lens wearers, suggesting that newly designed test silicone hydrogel lenses may be more suitable for people who live and work in cool, low humidity, and windy environments.[26] An in vitro comparison of three hydrogel and four silicone hydrogel contact lenses under different relative humidities and airflow rates in the IOBA CELab showed that varying environmental conditions and different chemical composition of contact lenses had considerable impact on contact lens' dehydration rate.[46]

## Evaluation of DED therapeutics in clinical trials

Controlled adverse environment chambers provide a useful tool for evaluating potential clinically significant protective effects of drugs against ocular surface damage that occurs during conditions of environmental stress. The model can be adapted according to the mode of action of each therapeutic compound, and to

evaluate and compare pharmaceutical agents intended for the treatment of DED.[21] Judicious selection of subjects is critical, as is the requirement to establish subjects' baseline response to the model challenge, ensuring a symmetrical and reproducible reaction to adverse stimuli.[21]

For example, Ora Inc's CAE$^R$ was used to evaluate the safety and efficacy of ophthalmic solutions of the tyrosine kinase TrkA receptor agonist MIM-D3 in a randomized, placebo-controlled phase II clinical trial in patients with DED.[47] Key eligibility criteria included exacerbation of corneal staining and ocular discomfort in the chamber on two visits, separated by 1 week of twice-daily dosing with artificial tears. Outcomes were measured before and after a 90-minute adverse environment exposure at baseline and after 14 and 28 days' treatment. Findings showed protection against the effects of adverse environment challenge on DED signs and reduced patient-reported diary symptoms, with a favorable safety profile.[47] A similar approach was used more recently in a US phase II clinical trial that assessed the safety and efficacy of SkQ1 (a small molecule antioxidant with topical application for DED) for reduction of signs and symptoms in subjects with mild-to-moderate DED, using Ora Inc's CAE$^R$ chamber.[29] In this randomized, double-masked, placebo-controlled trial, SkQ1 was effective as a treatment for DED, reducing post-adverse environment symptoms of ocular discomfort, dryness, and grittiness, fluorescein and lissamine green staining in the corneal central region, and lid margin redness. SkQ1 topical application before adverse environment exposure appears to protect the ocular surface from oxidative stress and provides a novel approach to the treatment of DED.[29]

Controlled adverse environment chambers may also provide a useful means to test new therapeutic applications of known drugs. For instance, a phase III, randomized, vehicle-controlled trial corroborated that topical 0.1% fluorometholone was more effective than artificial tears in diminishing dry eye signs after 3 weeks' treatment, as expected.[48] However, experiments performed in a chamber facility showed that following 2 hours' desiccating stress, patients pre-treated with this anti-inflammatory drug displayed reduced ocular surface alterations compared with control patients, demonstrating that adverse environment chambers provide useful information on preventing environmentally induced exacerbations of DED, which otherwise would be difficult in an orthodox clinical setting.[48]

Another study using the Glasgow chamber looked at differences in performance between DED treatments.[27] In this three-way, crossover, double-masked study, DED and control subjects used three different eye drop formulas for 2 weeks each, with a minimum 1-week washout period between treatments. Patients' symptoms and tear evaporation, tear break-up time, and osmolarity were assessed in conditions of 20% relative humidity and 22°C. Significant differences in tear evaporation rates were seen between treatments.[27] In another study using the same chamber, the effectiveness of emulsion eye drops in reducing tear evaporation rate was equivalent to increasing environmental humidity by 30%.[28]

A clinical trial using the environmentally controlled goggle system showed that corticosteroid eye drops mitigate the acute adverse effects of an experimental low-humidity challenge in DED patients, compared with artificial tears.[49]

## Identification of biomarkers

Identification of specific inflammatory mediators with an increased concentration in tears of patients with DED offers the opportunity for the identification of potential biomarkers for the disease. For example, a previous study found that tear levels of interleukin (IL)-6 and matrix metalloproteinase (MMP)-9 significantly increased and tear epidermal growth factor (EGF) significantly decreased after exposure to simulated air cabin conditions.[4] Another study conducted at IOBA CELab found increased tear levels of MMP-9 after exposure (23°C, 5% relative humidity, 0.43 m/s airflow velocity) in DED patients and controls; tear levels of IL-6 increased and EGF decreased in the control group.[12] A study in patients with Sjögren's syndrome-associated DED found increased tear concentrations of IL-1 receptor antagonist, IL-6, IL-8, and MMP-9 after exposure to a desiccating environment (23°C, 5% relative humidity, 0.10 m/s airflow velocity) compared with control environment in the IOBA CELab.[25] A study using goggles found an increase in HLA-DR following an initial low-humidity challenge, which was decreased by corticosteroid treatment.[49]

The IOBA CELab was used to study the effect of environmental conditions on the concentration of tear inflammatory mediators during contact lens wear.[14] EGF levels were significantly lower under AEC (5% relative humidity, 23°C, 750 mbar atmospheric pressure) than under standard conditions (50% relative humidity, 23°C, 930 mbar), whereas IL-1β, IL-2, IL-6, and tumor necrosis factor (TNF)-α were significantly elevated. In addition, the observed change in IL-1β differed between contact lens types. These findings may help in understanding the differential effects of environmental conditions and contact lens materials on the ocular surface of wearers.[14]

Controlled adverse environment chambers can also be used to study patients in controlled normal healthy environments, in an attempt to reduce variability due to influences of different conditions in experiments. For example, this method has been used to study potential biomarkers in graft versus host disease (GvHD). After 20 minutes under standard environmental conditions (23°C, 45% relative humidity), EGFR, IL-6, IL-9, and nicotinamide phosphoribosyltransferase (NAMPT) were found to have high potential as diagnostic biomarkers, with excellent sensitivity, specificity, and clinical relevance to the ocular surface status of GvHD.[37] The same group showed that a predictive model based on tear levels of IL-8/chemokine (C-X-C motif) ligand 8 (CXCL8) and interferon gamma-induced protein 10 (IP-10)/CXCL10 resulted in optimal sensitivity and specificity, revealing their potential as biomarkers for GvHD.[38]

## Considerations and opportunities for use of controlled adverse environment chambers

Controlled adverse environment chambers offer valuable opportunities to study the pathophysiology of DED, identify potential disease markers, and assess and compare different treatments. They provide an excellent resource that can be used, along with environmental studies, by various stakeholders including

researchers and pharmaceutical companies. However, adverse environment chambers have certain limitations. For example, only relatively few researchers with access to them can perform the experiments, making the research findings largely non-reproducible. In addition, with chambers available only at a few specialist centers, patients may have to travel long distances to participate in trials, taking up more of their time in addition to that spent in the chamber. Despite these limitations, however, adverse environment chambers have produced a wealth of useful research findings and have the potential to elucidate many more future roadblocks to our understanding of the effects of different environmental conditions on DED and its treatments, contact lens wear, air travel, and any number of simulated settings in which temperature, humidity, and air flow may be controlled.

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## Notes on contributors

Margarita Calonge defined the concept and scope of the review. Marc Labetoulle, Elisabeth M Messmer, Sunil Shah, Yonca A Akova, Kostas G Boboridis, Jesús Merayo-Lloves, Pasquale Aragona, José Benítez-del-Castillo, Gerd Geerling, Maurizio Rolando, and Christophe Baudouin provided critical review of the manuscript. All of the authors were involved in the finalization of the manuscript.

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