The early diagnosis of corneal ectasia is a major concern for both the refractive surgeon and the corneal specialist. Even if the rate of ectasia after a refractive procedure due to a preexisting subclinical keratoconus is low, it is a feared occurrence because it leads to vision-threatening problems in a patient who previously had a satisfying corrected visual acuity. Unfortunately, cases of ectasia have been reported after LASIK even in the presence of low-risk scores on standard screening tests.1,2 On the other hand, some patients with documented risk factors for the development of ectasia have remained stable many years after LASIK.

One of the main concerns of the corneal specialist dealing with ectasia is early diagnosis. Keratoconus usually is diagnosed in adolescence or childhood3-5 and the more the diagnosis is delayed, the higher is the risk of corneal transplant.6 Early diagnosis and, as a consequence, its prompt treatment

**ABSTRACT**

**PURPOSE:** To present a case series of patients with subclinical keratoconus with normal topometric (anterior curvature) and tomographic findings in one eye who showed abnormalities detected by Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany) in vivo biomechanical assessment.

**METHODS:** All patients had a complete ophthalmic examination, including the Corvis ST biomechanical measurements, optical tomography, and pachymetry with Pentacam (Oculus Optikgeräte GmbH), and Placido-based topography with either the Nidek (OPD III Nidek, Gamagori, Japan) or CSO platform (Costruzione Strumenti Oftalmici, Florence, Italy). Inclusion criteria were a clinical diagnosis of ectasia in one eye and normal topometric and tomographic findings in the fellow eye (subclinical keratoconus), including a Belin/Ambrósio Enhanced Ectasia total deviation index from the Pentacam with less than 1.6 standard deviations from normative values and a Corvis Biomechanical Index score of greater than 0.5 in both eyes.

**RESULTS:** Tomographic and topographic analysis was normal in one eye and abnormal in the fellow eye in 12 patients. The biomechanical results with the Corvis Biomechanical Index were shown to be abnormal in both eyes of all patients and aided the diagnosis.

**CONCLUSIONS:** Biomechanical analysis showed abnormalities, whereas tomography and topography were normal. Basing on these findings, the authors suggest the use of biomechanics as an additional diagnostic tool.

with corneal cross-linking at the first sign of progression can halt keratoconus at a stage where visual acuity is still high.

Topography or tomography maps can aid the detection of minimal alteration in the shape of the cornea, such as thinning and increased curvature. However, they are not able to measure the biomechanical stability, which is thought to be the initiating event of the disease, even before notable changes in corneal morphology take place.\(^7\)\(^8\)

We previously published a study that evaluated the Dynamic Corneal Response parameters provided by the Corvis ST (Oculus Optikgeräte GmbH; Wetzlar, Germany) most highly correlated with biomechanics and less affected by intraocular pressure (IOP), and provided normative values for each of them.\(^9\) Subsequently, we created a new Corvis Biomechanical Index (CBI) to separate normal from keratoconic patients.\(^10\)

The aim of this article was to present a case series of 12 patients with a diagnosis of subclinical keratoconus in which the CBI score was abnormal in both the diseased eye and the topographically and tomographically normal fellow eye.

**PATIENTS AND METHODS**

The patients were enrolled at the Vincieye Clinic in Milan, Italy. The institutional review board ruled that approval was not required for this record review study and it was conducted according to the tenets of the Declaration of Helsinki. However, patients provided informed consent at the time they were seen in clinic, before their data were used in the study. All patients had a complete ophthalmic examination, including the Corvis ST biomechanical measurements, optical tomography, and pachymetry with Pentacam and Placido-based topography with either the Nidek (OPD III Nidek, Gamagori, Japan) or CSO platform (Costruzione Strumenti Oftalmici, Florence, Italy).

The inclusion criteria of this study were the presence of a subclinical keratoconus diagnosis, defined as the fellow eye of a patient with clinically diagnosed keratoconus without any previous ocular procedures, with the eye with subclinical keratoconus having normal topometric (anterior curvature) and tomographic findings. These were defined as a Belin/Ambrósio Enhanced Ectasia total deviation index (BAD-D) from the Pentacam with less than 1.60 standard deviations from normative values. The BAD-D cut-off of 1.60 standard deviations was used because it is described as the best performing screening parameter with values of 1.60 and 1.88 associated with 95% and 97.5% confidence intervals, respectively, and an acceptable false-negative rate below 1%.\(^11\)

All eyes were also considered normal with Placido-based topography. The second inclusion criterion was a CBI score of greater than 0.5 in both eyes. One patient with a BAD-D score of 1.65 was included because it was thought to be an interesting asymmetric case (case 2).

Exclusion criteria included any previous ocular surgery or disease, myopia greater than 10.00 diopters (D), and any concomitant or previous glaucoma or hypotonic therapies. Only Corvis ST examinations with good quality scores that enabled calculation of all deformation parameters were included in the analysis. All measurements with the Corvis ST were taken by the same experienced technician and captured by automatic release to ensure the absence of user dependency. Additionally, a second manual, frame-by-frame analysis of the examination, made by an independent masked examiner, was performed to ensure quality of each acquisition. The main criterion was good edge detection over the whole deformation response, with the exclusion of alignment errors (x-direction). Similarly, blinking errors were omitted.

The Corvis ST uses an ultra high-speed Scheimpflug camera that captures 4,330 images per second and covers 8 mm of the central cornea in a single horizontal meridian. The instrument’s light source is an LED light of 455-nm wavelength. The instrument applies an air impulse with a maximum pressure of 25 kP. A quality score is available just after the measurement is taken for assessing the reliability of the measurement. This is based on a series of parameters so that a quality score is also available for the pachymetry and IOP data. The Corvis ST output parameters from each measurement using research software were exported to a spreadsheet and analyzed.

**RESULTS**

We report a case series of 12 patients. Patients’ topographic, tomographic, and biomechanical analyses are summarized in Table 1. Also included in this table are the values of biomechanically corrected IOP (bIOP).\(^12\)

**CASE 1**

A 67-year-old man with a diagnosis of keratoconus in the right eye, a minimum central corneal thickness of 454 µm, and a BAD-D score of 2.44 had a CBI score on the Vinciguerra Screening Report (VSR) equal to 1.0. In the fellow eye, even though the BAD-D score was negative (1.20), the CBI score was clearly abnormal, with a value of 1.0.
Case 2

A 19-year-old man had a BAD-D score of 7.27 in the right eye (diagnosed as keratoconus) (Figure AA, available in the online version of this article) and 1.65 in the fellow eye. Even with a borderline value of the BAD-D (slightly higher than 1.60), the 4 Maps Refractive display of the left eye was not clearly abnormal (Figure AB). Conversely, the VSR showed an abnormal examination (Figures AC-AD) in both eyes, also confirming the diagnosis of at-risk cornea in the left eye. The Belin/Ambrósio Enhanced Ectasia displays of the right and left eyes are shown in Figure B (available in the online version of this article).

Case 3

A 27-year-old man had a diagnosis of keratoconus in the left eye and a normal right eye. Neither the 4 Maps Refractive display (Figures 1A-1B) nor the BAD-D score (0.74) showed any signs of ectasia in the right eye. Furthermore maximum keratometry was 43.40 D and minimum central corneal thickness was 529 µm. However, the biomechanical analysis with the CBI showed abnormal examinations in both eyes, with values of 0.86 and 1, respectively (Figures 1C-1D). The Belin/Ambrósio Enhanced Ectasia displays of the right and left eyes are shown in Figure C (available in the online version of this article).

Case 4

A 19-year-old man with a normal topography and tomography in the right eye showed clear signs of ectasia in the left eye (Figures 2A-2B). The BAD-D score was 1.5 in the right eye and 6.16 in the left eye. However, the biomechanical evaluation presented bi-
lateral abnormal corneas (Figures 2C-2D). The Belin/ Ambrósio Enhanced Ectasia displays of the right and left eye are shown in Figure D (available in the online version of this article).

**CASE 5**

A 47-year-old man had a diagnosis of unilateral keratoconus at another institute. He presented with a borderline BAD-D score of 1.57 in the right eye and 5.76 in the left eye. The diagnosis of bilateral abnormal corneas was made with the aid of the VSR, which displayed a CBI score of 1 in both eyes.

**CASE 6**

A 25-year-old man with clear ectasia in the left eye and bilateral thin corneas had a BAD-D score of 0.85 in the contralateral eye and was referred to the Vinci-eye Clinic in Milan. The topography of the right eye showed an asymmetric astigmatism with increased inferior elevation that looked suspicious. The VSR confirmed the diagnosis of bilateral biomechanically risky corneas even in this case, with a CBI score of 1 in both eyes.

**CASE 7**

A 33-year-old man had a normal thickness cornea with asymmetry in the anterior elevation and a “cone like pattern,” but the BAD-D score was normal (0.86). Conversely, the contralateral eye was ectatic. Likewise, both eyes showed a bilateral CBI score over the 0.5 cut-off (1.0).

**CASE 8**

This 45-year-old man is an example of biomechanically progressing ectasia. He presented with an initial diagnosis of keratoconus in the right eye in 2012 (Figure 3A). Results of his tomography and topography were abnormal, with a BAD-D score of 3.40. Conversely, the left eye showed a thick cornea (582 µm of minimal thickness) (Figure 3B) and a BAD-D score of 0.73.
Surprisingly, both eyes had a normal CBI score on that occasion (0.12 and 0.03, respectively; Figures 3C-3D). However, in the right eye many corneal deformation parameters were outside normative values, such as deformation amplitude ratio and highest concavity radius (Figures 3C-3D). The Belin/Ambrósio Enhanced Ectasia displays of the right and left eyes are shown in Figure E (available in the online version of this article). We observed this patient for 2 years, repeating tomographic and biomechanical examinations at each follow-up visit. In 2014, even though the tomography and topography results remained stable, the biomechanical analysis of both the right eye (CBI score of 1) and the left eye (CBI score of 0.84) became abnormal (Figures 4A-4B).

**CASE 9**

A 44-year-old man had a diagnosis of asymmetric ectasia. His right eye was abnormal with a BAD-D score of 6.37 and a CBI score of 1. Similarly, the left eye displayed a VSR with a CBI score of 0.98, even though the BAD-D score was below the 1.6 cut-off of abnormality (1.20 in particular).

**CASE 10**

A 28-year-old woman presented with central keratoconus in the right eye (Figure FB, available in the online version of this article). At the tomographic analysis, the fellow eye exhibited a normal thickness cornea, with no inferior steepening and an unremarkable posterior elevation (Figure FA). The BAD-D score was 1.57 in the right eye. The VSR with the CBI aided the diagnosis, showing bilateral abnormal examinations (Figures FC-FD). The Belin/Ambrósio Enhanced Ectasia displays of the right and left eyes are shown in Figure G (available in the online version of this article).

**CASE 11**

A 35-year-old man was also referred for unilateral ectasia in the left eye (Figure 5B). The fellow eye did
not show clear signs of ectasia (BAD-D score of 0.68) and could be diagnosed as normal (Figure 5A) without the presence of a clear ectasia in the left eye (Figure 5B). Similarly to the other presented cases, the biomechanical analysis with CBI of this patient assisted in the diagnosis, displaying a right and left eye with abnormal examinations and a bilateral value of 1.0 on the CBI (Figures 5C-5D). The Belin/Ambrósio Enhanced Ectasia displays of the right and left eyes are shown in Figure H (available in the online version of this article).

**CASE 12**

A 27-year-old man had a diagnosis of asymmetric ectasia, with the left eye more advanced than the right eye. The BAD-D scores were 1.18 in the right eye and 6.69 in the left eyes. The biomechanics analysis revealed bilateral CBI scores of 0.99 and 1 in the right and left eye, respectively.

**DISCUSSION**

It is known that keratoconic corneas are significantly “softer” or have lower tangent modulus values than normal corneas.\(^ {13,14} \) It has been argued whether this should be considered as the initiating event of the pathology or a consequence of the increased curvature and reduced thickness.

Recently, a theory was introduced that ectasia is characterized by a focal weakening rather than a global weakening,\(^ {15} \) which was later confirmed by Scarcelli et al.\(^ {8} \) It was further proposed that the focal reduction in biomechanical properties would actually be the primary initiating event in ectatic disease, resulting in tissue thinning because the softer area strains more than the surrounding stiffer areas. This focal reduction in tangent modulus induces greater deformation under the same load (IOP) over time, producing focal thinning with augmented stress and consequent increase of curvature. The
corneal bulging is associated with focal stress reduction as a compensatory mechanism, which supplies an overall stress rearrangement. This reorganization induces a negative cycle of biomechanical decompensation propelled by the discrepancy in corneal properties.
A consequence of these findings is that it might be possible to identify an “at-risk” cornea in a “biomechanical stage” before the resulting secondary changes in thickness and curvature profiles become evident and ectasia progresses. For this reason, there has been increasing interest in developing instruments to measure the in vivo biomechanical properties of the cornea to aid the diagnosis of the at-risk cornea in this earliest stage.

Both the previously introduced Ocular Response Analyzer (ORA; Reichert Inc., Depew, NY) and the newest Corvis ST demonstrated the ability to separate normal patients from patients with keratoconus. In the recently published study by our group, the CBI was shown to be highly sensitive and specific (without the aid of topography or tomography) to separate healthy from keratoconic eyes. To our knowledge, this was the first time that an index based on biomechanics alone has been able to produce such an efficient separation.

However, the distinction between normal and keratoconic eyes does not require biomechanics; standard topography or tomography would diagnose the ectasia. For this reason, patients with subclinical keratoconus (also called unilateral ectasia or form fruste keratoconus) would be the best population to test the capability of an instrument to diagnose sub-tomographic ectasia. Indeed, patients with subclinical keratoconus might have bilateral soft corneas with only one topographically abnormal eye.

In the presented case series, 12 patients with a diagnosis of subclinical keratoconus were demonstrated to be normal with tomography and topography but abnormal with the biomechanical analysis. These patients, and particularly case 8, show that the biomechanical changes inside the cornea may be present, even when the tomography and topography are normal. Furthermore, this confirms the hypothesis that keratoconus should always be considered as a bilateral disease and that the biomechanical abnormalities anticipate the shape changes such as increase curvature or elevation and thinning.

A consequence of these findings is the possibility of an early diagnosis of suspected ectasia when both eyes are tomographically normal but show early signs of biomechanical decompensation. More studies will be needed to confirm this last hypothesis.

We deliberately decided not to show the sensitivity and specificity of the CBI in subclinical keratoconus because we strongly believe that biomechanical evaluation should ideally be integrated with tomographic analysis. This was demonstrated at the 2016 European Society of Cataract and Refractive Surgery annual meeting in Copenhagen by our group, which showed that the area under the curve of the BAD-D and CBI in the diagnosis of subclinical keratoconus were similar because each can evaluate only one part of the problem, either shape or biomechanics. Other studies are also in progress to show patients with bilateral normal shape but abnormal biomechanics.

Several patients were presented in whom biomechanical analysis showed abnormalities, whereas tomography and topography were normal. Based on these findings, we recommend the use of biomechanics as an additional tool to diagnose not only ectasia, but also the biomechanically weak cornea at risk of developing ectasia.

AUTHOR CONTRIBUTIONS
Study concept and design (RV, PV); data collection (RV); analysis and interpretation of data (RV, RA, CJR, CA, PV); writing the manuscript (RV); critical revision of the manuscript (RA, CJR, CA, PV); supervision (PV)

REFERENCES


Figure A. (A-B) The 4 Maps Refractive Displays and (C-D) the Vinciguerra Screening Report of the right and left eyes of case 2. The Corvis Biomechanical Index score is 1.0 (N/A because too high) in the right eye and 0.98 in the left eye.

Figure B. The Belin/Ambrósio Enhanced Ectasia display of the right and left eyes of case 2.
Figure C. The Belin/Ambrósio Enhanced Ectasia display of the right and left eyes of case 3.

Figure D. The Belin/Ambrósio Enhanced Ectasia display of the right and left eyes of case 4.
Figure F. (A-B) The 4 Maps Refractive Displays and (C-D) the Vinciguerra Screening Report of the right and left eyes of case 10. The Corvis Biomechanical Index score is 0.89 in the right eye and 1.0 in the left eye.
Figure G. The Belin/Ambrósio Enhanced Ectasia display of the right and left eyes of case 9.

Figure H. The Belin/Ambrósio Enhanced Ectasia display of the right and left eyes of case 11.