physiological data from a monitor should not be used as a surrogate for reported pain, but rather as a way to measure end-organ effects of therapies for pain.

To be more precise, this approach simply attempts to answer the question of whether and to what extent a given pain therapy (e.g. opioid, nerve blocks, N-methyl-D-aspartate [NMDA] receptor antagonist) has saturated its end-organ target. If there is evidence of saturation, then there is minimal clinical value in further use of that therapeutic approach, regardless of the patient's pain scores. In some contexts, this approach is so obvious that it has become the standard of care. For example, if a patient has a central or peripheral nerve block but still reports pain, most acute pain physicians assess whether there is a sensory loss in the intended distribution. If there is not, the block is either repeated or adjusted to provide an appropriate sensory block. If the block does cover the intended distribution, then other therapeutic agents or techniques are used to treat the pain.

We advocate the development of tools that allow expansion of this approach to new agents—for example use of opioids as the therapy and pupillary unrest as the physiologic endpoint. If a patient has a pattern of pupillary unrest consistent with a high degree of central opioid effect, then escalating doses of opioids are not advisable and other therapies should be used such as nerve blocks or ketamine.[3,4] Within this framework there are a number of drug–physiological effect pairs that could potentially prove useful.

In the anaesthetised patient, the value of nociception monitoring is different. As Ledowski[1] points out, nociception monitoring during anaesthesia could be used to tailor opioid requirements for each patient and reduce the stress response to surgery. However, many of these monitors rely on the detection of sympathetic responses that might be obtunded by commonly used antihypertensive medications. For example a recent evaluation of some of these monitors' associated indices (namely the nociception index, the surgical plethysmograph index, the pulse plethysmograph amplitude, and heart rate) eliminated 12% of enrolled patients because they were taking beta-adrenergic receptor blockers.[5]

Interestingly, many pupillary indices appear to be less affected by sympathetic tone (or sympatholytic antihypertensives) compared to cardiovascular indices. For example painful stimulus reflex dilation of the pupil *during anaesthesia* is not a sympathetic reflex.[6] Rather, it is brought about through inhibition of the Edinger–Westphal nucleus, and is therefore entirely a parasympathetic reflex. Like pupillary unrest, it is inhibited by opioids, and thus it is potentially useful for assessment of central opioid effect rather than global sympathetic tone (or blockade). Based on this and other examples, we believe pupillary indices have the potential to provide distinct and complimentary diagnostic information compared to cardiovascular indices. It is clear that there is potential for future research into the important issue of nociception monitoring.

Declaration of interest

The authors declare that they have no conflicts of interest.

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Vocal markers of preoperative anxiety: a pilot study

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Editor—Recent European guidelines in anaesthesia recommend systematic preoperative anxiety management to prevent its negative perioperative impact,[1] including impaired memory of important instructions and higher incidence of postoperative acute and chronic pain. Usual self-administered questionnaires or scales to assess anxiety in the preoperative setting are time consuming and rely on patient willingness to comply with instructions.[2] Physiological signals, such as patient voice, may provide useful information for objective, reliable, and accurate anxiety assessment before surgery.

Because of the extensive parasympathetic innervation to the larynx, pharynx, face, and head, stress modifies vocal parameters.[3,4] The effects of acute anxiety on voice are poorly explored in the preoperative context. Our objective was to describe the characteristics of patient vocal parameters related to declared anxiety level in a day-care ophthalmic surgical unit performing cataract surgery.

With approval from the Ethics Committee of the French Society of Ophthalmology (IRB 00008855 Société Française d'Ophtalmologie IRB#1), vocal conversations between patients and nurse assistants were recorded during admission interviews on the day of surgery. The standardised 5 min interview aims at validating patient identity, address, surgical indication, fasting status, and removal of all jewellery, and also assessing patient anxiety. At the outset of the interview, both patients and nurse assistants evaluated patient anxiety using a 0–10 VAS. The criteria for exclusion were age <18 yr, under guardianship, non-French-speaking patients, communication difficulties, or hearing or speaking impairment. All participants gave their written informed consent.

In each recording, patient voice was separated from the nurse-assistant voice by manual screening using Audacity software. An utterance was defined by each moment where the patient was speaking alone, surrounded by words from the nurse assistant, or by silent periods >2 s. We also excluded nonverbal sequences (background noise, coughs, etc.) using automated criteria. For each patient utterance, we then extracted a number of acoustic features traditionally associated with emotional expressivity and vocal stress,[3,4] including utterance duration; mean, maximum, minimum, and standard deviation (SD) of fundamental frequency (F_0); four standardised measures of pitch perturbation quotient (jitter), five measures of amplitude perturbation quotient (shimmer), and two measures of noise-to-harmonic ratio (NHR/HNR). Acoustic features were extracted with the Praat software (see Supplementary material for details).

To analyse the effects of patient anxiety on average vocal features, we calculated the mean of each utterance feature, weighted by utterance duration, and tested for the main effects using a one-way analysis of variance, using patient self-reported VAS anxiety as a binary factor ('low' if VAS <5; 'high', otherwise). To analyse the effect of patient anxiety on the temporal evolution of features, we controlled for differences in interview duration by normalising the utterance time location between 0 and 1, and indexed each utterance's feature with its normalised time location. We then used the generalised linear mixed models to evaluate the contribution of the anxiety factor to the linear regression of each feature's values on normalised time, using random intercepts to account for patient differences. In both procedures, we took α=0.05 as the significance threshold, and applied Bonferroni corrections for alternative measures of the same feature (F_0: α_{Bonf}=0.013; jitter: α_{Bonf}=0.013; shimmer: α_{Bonf}=0.010; NHR: α_{Bonf}=0.025; see Supplementary material for details).

Between April 1 and June 30, 2016, data for 44 patients were collected, including 29 female, with a median age of 74 (interquartile range [IQR]: 69–79). The median duration of interviews was 6 min 50s (IQR: 5 min 49s–7 min 38s), of which a median of 1 min 55s (IQR: 2 min 47s–1 min 19s) was spoken by patients. The median duration of manually segmented patient utterances was 1 min 65s (IQR: 2 min 5s–1 min 0s]). The mean F_0 was 165 Hz (SD=16 Hz) for female patients, and 143 Hz (SD=18 Hz) for male patients. The mean anxiety score in patient VAS reports was 3.5 (SD=2.6), whilst 11 (25%) patients rated their anxiety level >5. The correlation between patient self-report and evaluation by the nursing staff of anxiety level was 91%.

Whilst there was no main effect of anxiety on patient average measures of F_0 (all P-values >0.44), there was a significant effect of anxiety on how F_0 evolved along with interview time for mean F_0 (χ^2=6.85; P=0.008; α_{Bonf}=0.013), SD of F_0 (χ^2=8.52; P=0.003; α_{Bonf}=0.013), and maximum F_0 (χ^2=24.0; P<0.001; α_{Bonf}=0.013) (Fig. 1). Whilst the F_0 of low-anxiety

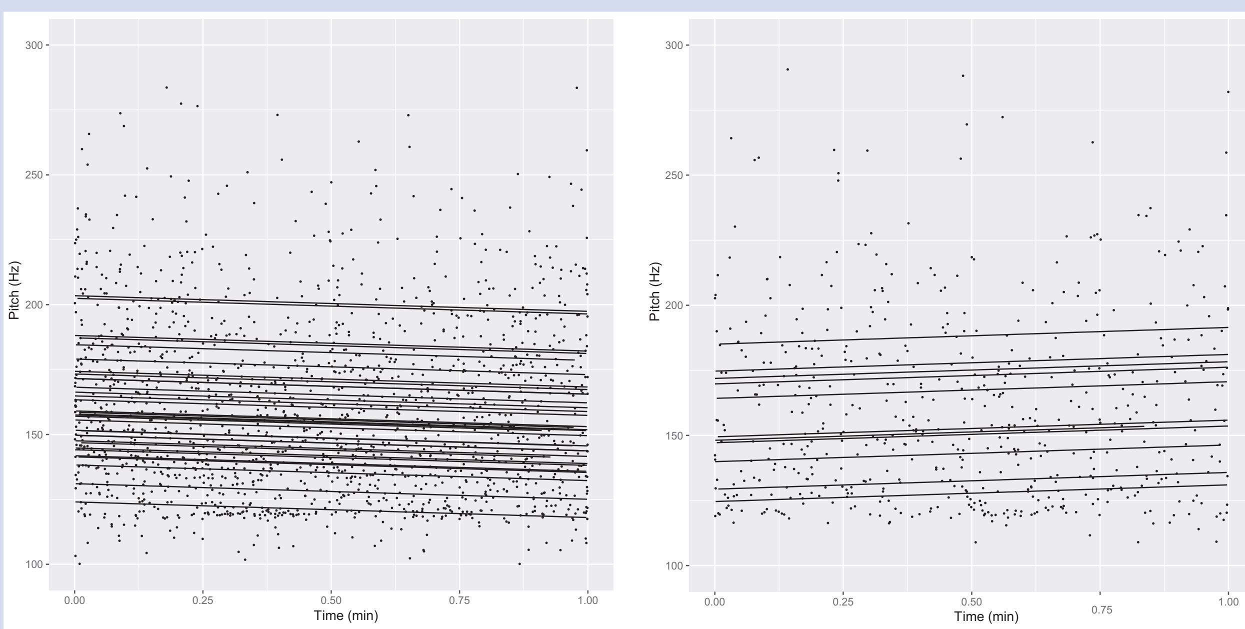

Fig 1. Values and predictions of linear mixed model for the acoustic feature 'pitch' (non-anxious patients (VAS <5) on the left and anxious (VAS ≥5) patients on the right).

patients decreased by an average 3.8% along the interview, the F_0 of high-anxiety patients increased by 4.1%. None of the other acoustic features (duration, jitter, shimmer, and NHR) appeared to be significantly associated with anxiety levels, either on average or relative to time (see Supplementary material).

To date, preoperative anxiety studies have focused on validating self-questionnaires in different surgical settings rather than identifying reliable objective biomarkers of anxiety. The main finding of our study is that a comparison between repeated F_0 measurements may be an acoustic marker for preoperative anxiety if confirmed by further study. Consistent with the literature, this relative F_0 increase in stressed patients compared with less anxious patients may be attributable to sustained sympathetic nervous system activation[3] balancing the short-term vocal fatigue observed over the course of normal conversations.[4] Contrary to other reports studying anxiety in different stressful contexts, including cognitive workload, social stress, stage fright, and during life-threatening emergencies,[5,6] we found no effect of preoperative anxiety on voice quality features, such as jitter, shimmer, or NHR. The reasons for this discrepancy may include low statistical power, linguistic characteristics of the conversations (short utterances in a question–answer mode), top-down control exerted by the patients in front of medical professionals, or lower emotional load as a result of distant time to surgery. Finally, we found a higher-than-expected correlation between self-reported anxiety level and nurse evaluation of patient anxiety. This suggests that staff's perception might be strongly influenced by patient reporting, and therefore, may lack reliability. In sum, we report a possible association between voice pitch and anxiety amongst patients awaiting cataract surgery. This result needs to be further evaluated in other surgical contexts on a broader scale and corroborated with other biomarkers involving the vagal tone response to anxiety, including HR variability.

Authors' contributions

Study design: GG, ML, CB, J-JA.
Patient recruitment: P-RR.
Data collection: ML.
Data analysis: LL, AV.
Writing of first draft: GG, LL, J-JA.
All authors critically revised the article, approved the final version to be published, and are accountable for all aspects of the work.

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Appendix A. Supplementary data

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