engaged in the peer-review process of these journals, often distinguished as an 'elite reviewer'.

It is this breadth and depth of editorial knowledge and expertise that he brings to the role as EHJ Quality Standards Editor.

'The EHJ has a consolidated editorial quality', explained Prof. Alfonso. 'However, this is a dynamic field and quality should be perceived as a continuous, never-ending, process and paying close attention and adhering to novel editorial initiatives is of paramount importance'.

While acknowledging that the peer-review process has well-recognized limitations, he insists it remains the best means of assessing the originality, methodology, results accuracy, and clinical and scientific relevance of papers submitted for publication.

He said the best experts in the field critically scrutinize the manuscript and ascertain the value of the novel findings, confirm adequate, rigorous methods and reproducible results, and unravel all the study limitations.

However, he added: 'Papers considered for publication should also undergo a dedicated statistical review as the statistical analyses are recently becoming increasingly complex in a growing number of studies. It is interesting to see that, although reviewers not infrequently diverge, the unique insights provided by the whole process is paramount to help the Editor in the decision-making process, allowing selection of only the best papers for publication'.

Reviewers remain anonymous and academic recognition to this silent—yet fundamental—scholarly endeavour is critical to maintain the quality of the scientific process, he said.

There are also a number of issues that need to be addressed in this regard, and an array of challenges within the role of maintaining high-quality editorial standards.

'Many interesting and provocative editorial initiatives—i.e. data sharing—are difficult to implement in practice because several problems need to be resolved first such as having adequate repositories, data protection, and anonymization, allocated funding, and investigators' credit, for example', he said. 'But it is crucial to be on the frontline in helping to find solutions for the authors and the entire scientific community'.

He believes Open Access is also an important movement and an attractive target from a scientific perspective. He notes that the EHJ is moving forward in this regard and currently opens all content 1 year after publication, though he emphasizes the importance of economic issues also being taken into consideration and of the sustainability of the entire system being preserved.

Prof. Alfonso said he is very much looking forward to being a key player in maintaining the high editorial standards that the *European Heart Journal* currently enjoys and hopes to bring a new dimension and perspective to the initiative going forward.

Conflict of interest: none declared.

doi:10.1093/eurheartj/ehab108

Putting (One's) Heart into Music

Elaine Chew, PhD, FTCL[1]*, Michele Orini, PhD[2], and Pier Lambiase, PhD FRCP FHRS[3]

[1]Centre National de la Recherche Scientifique (CNRS)–UMR9912 Sciences et Technologies de la Musique et du Son (STMS) Laboratoire, Institut de Recherche et Coordination Acoustique/Musique (IRCAM), Music Representations Team, Paris, France, Department of Engineering, Faculty of Natural & Mathematical Sciences, King's College London, London, UK; [2]University College London and Barts Heart Centre, London, UK; and [3]University College London and Barts Heart Centre, Co-Director of Cardiovascular Research Barts NHS Trust, Inherited Arrhythmia Clinical Lead, UCL MRC DTP Theme Lead, BHRS Committee Research Lead, Institute of Cardiovascular Science, UCL, Department of Cardiology, Barts Heart Centre, London, UK

On links and similarities between the rhythms of arrhythmia and music, evidence showing prevalence of simple swing ratios in arrhythmia ECGs, and implications for music in medical education and for music informatics in cardiovascular science.

16 December 2020 marked the 250th anniversary of Beethoven's birth, with celebrations extending to September 2021. Apart from being one of the foremost composers of classical music, Beethoven also suffered from a litany of diseases, which some speculate included cardiac arrhythmias. This has led to the informed conjecture that Beethoven set his own ventricular early beats into the dotted rhythms of his 'Les Adieux' Sonata,[1,2] i.e. that his heart rhythm disorders may have been responsible for the distinctive rhythmic motifs in his music. Furthermore, the interoception required to turn arrhythmic heartbeats to music may have been enhanced by his deafness. *Figure 1* shows a possible inspiration for another signature Beethoven motif, one in the opening of his Fifth Symphony. The striking correspondence between the electrocardiographic (ECG) trace and the notated rhythm could be a mere coincidence or an indication of a deeper connection between music and the heart.

Noting the similarity between rhythms of arrhythmia and those found in music, Chew had independently started making music based on transcriptions of arrhythmia ECG traces. These are collage pieces made by merging music excerpts that match contiguous segments of ECG. The result is music that mirrors the arrhythmia sequences.[3,4] Supplementary material online, *Figure S1* shows a transition from normal beats to ventricular tachycardia (VT) in the ECG from the catheterization laboratory and in the matching music collaged from Holst's *The Planets*, 'Mars'. The full ECG excerpt, lasting about 3 min, showed the sequence before, during, and after VT, and formed the basis for the first of the *Arrhythmia Suite* pieces.[5] Such longer pieces were made through a semi-automatic process from ECG signal data.

The fact that arrhythmia music can be made from a collage of existing music suggests that arrhythmias are highly musical, or perhaps that music emulates physiological rhythms including, curiously, cardiac

*Corresponding author. Email: elaine.chew@ircam.fr

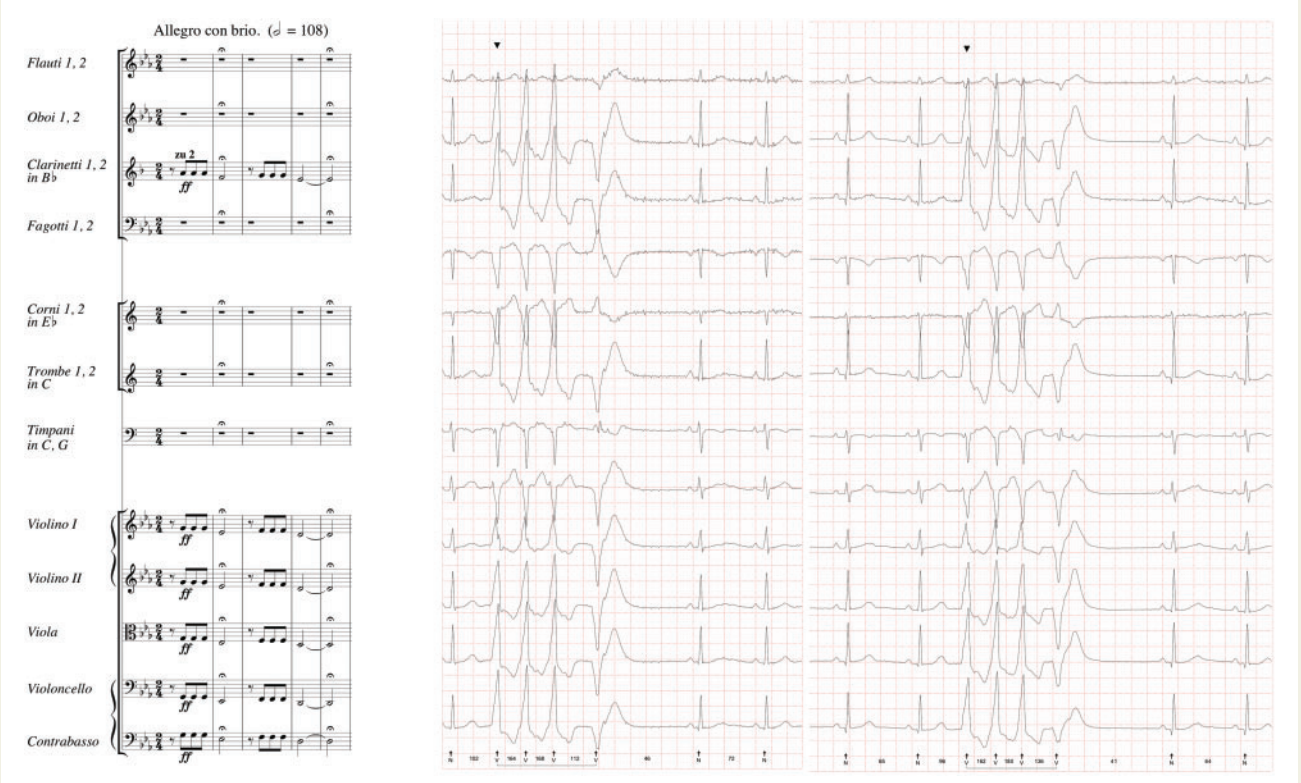


Figure 1 Opening of Beethoven's Fifth Symphony (CCARH 2008) and 12-lead Holter ECG segments showing short runs of ventricular tachycardia matching the fate motif, normal beats marking time (ECG courtesy Lambiase).

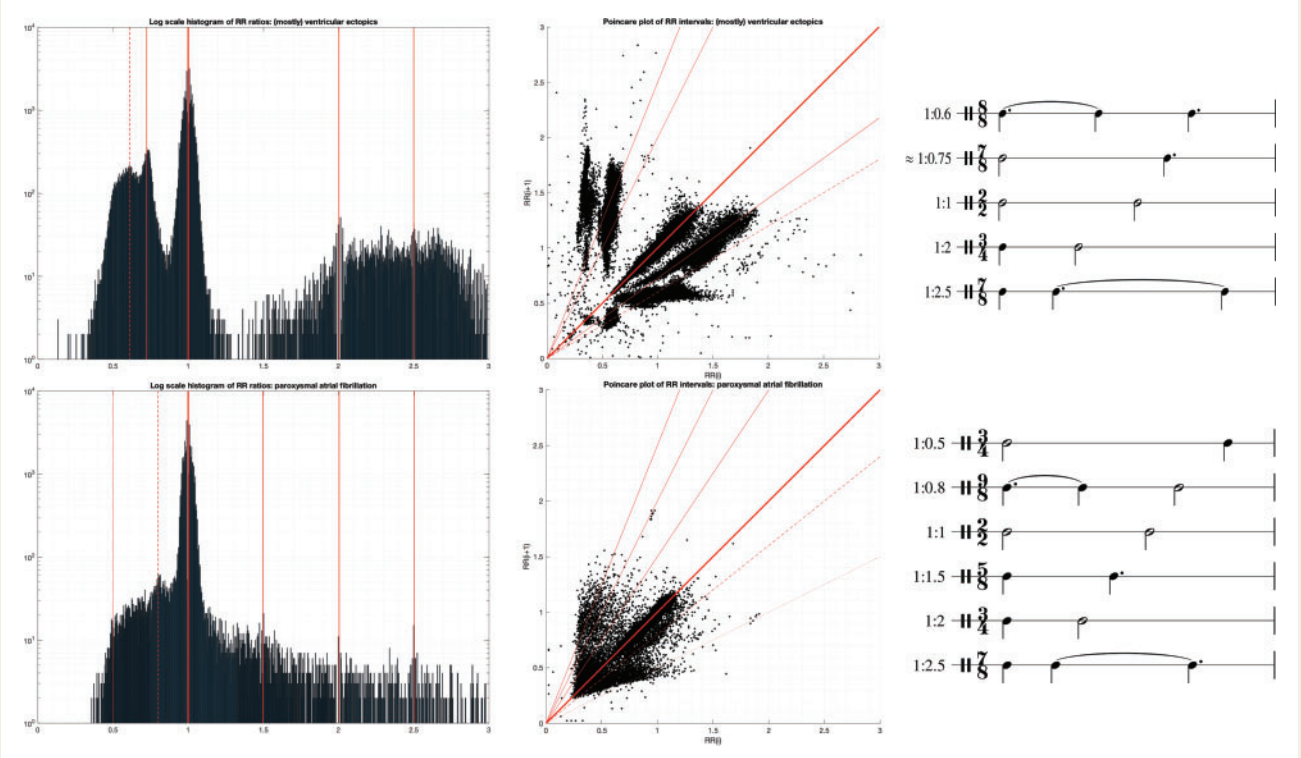
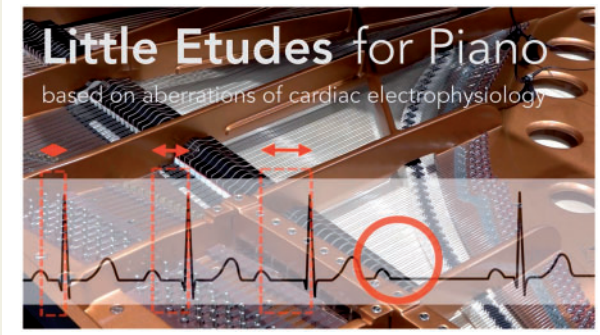


Figure 2 Log-scale histograms of RR ratios, Poincaré plots of RR intervals, and music notation for peak ratios marked (vertical lines in histograms which correspond to lines radiating from origin in Poincaré plots) for ventricular ectopics (top) and of paroxysmal atrial fibrillation (bottom) from single Holter each.



Video 1 Little Etudes for piano based on aberrations of cardiac electrophysiology–a performance by Elaine Chew of a series of short piano pieces based on cardiac electrical anomalies each described by Pier Lambiase,[10] made initially by Chew, Lambiase, Bedoya for the Ircam AIxMusic Garden at Ars Electronica 2020. The video is available at https://bit.ly/LittleEtudes-video

arrhythmic activity. Even when the heart's own natural pacemaker fails and a patient is fitted with an artificial pacemaker, the link between music and the heart persists, as the heart then starts beating like a band playing to a click track.

Why do heartbeats, even abnormal ones, map so well to music? In music with a beat, the rhythms and other musical structures unfold over an underlying grid of regular pulses which can flex with time, but are basically periodic, like a natural pacemaker. Consecutive intervals between rhythm event onsets normally form simple ratios, at least they are notated that way but the reality (performance) is slightly more complex, with respect to the underlying grid. This means that the rational numbers that express their proportional relationships are made of relatively simple numbers. An example of the importance of proportional durations lies in the quantifying of the swing ratio in jazz, where events that may be notated as even and of equal duration are actually performed off-kilter in duration ratios between 1:1 (straight) to 3:1 (hard swing).[5] This swing ratio (the ratio of consecutive RR intervals) is shown for different arrhythmias in *Figure 2* (single Holter recordings of ventricular ectopics and paroxysmal atrial fibrillation) and Supplementary material online, *Figure S2* (collections of recordings of the 1024 beats just before VT and ventricular fibrillation, respectively).

As expected, ratios around 1:1 are most prevalent. Interestingly, there are several narrow peaks showing a preponderance of simple ratios like 1:2, 1:2.5 (i.e. 2:5), 1:1.5 (i.e. 2:3), which are reminiscent musically of a light (3:2 ratio) and medium swing (2:1 ratio). Equally intriguing are the notable gaps surrounding selected peaks, most striking around 2. Distinct peak ratios are marked by vertical red lines (thickness indicating prominence of the peaks) in the histograms. These peak ratios correspond to the radial lines, although their presence is not as obvious, in the Poincaré plots. Example renderings of the duration ratios as music notation are also shown. These peaks mean that certain patterns in arrhythmia lend themselves particularly well to music representation. Why the physiology or geometry of the heart should produce such behaviours around basic ratios is a subject for further investigation.

What does it mean for arrhythmia to map naturally to music? The fact that arrhythmias can be mapped to music suggests that it is possible to describe features of an arrhythmia using musical parlance. The musical field has developed over centuries a rich and sophisticated vocabulary for describing time and frequency patterns and variations. Arrhythmias are presently classified physiologically by source, rate, and regularity. To a musician, this is tantamount to describing a piece of music (poorly) as having a fast, irregular beat and in the treble register. Musical nomenclature could offer new ways to describe arrhythmia behaviours. For example, the rhythms of arrhythmia are more than simply irregular; one may be a swing, another a tango. The parallels go well beyond rhythmic patterns. In the frequency domain, the fundamental frequency in musical pitch is like the dominant frequency in atrial fibrillation, and musical vibratos are like fibrillatory waves—they even occupy similar frequency ranges.[8] In music, large-scale (long term) time structures and their evolution are also important and rigorously studied.

Implications for this connection between music and the heart range from medical education to scientific research and communication. For example, the nephrologist Michael Field has meticulously transcribed heart murmurs using music notation for the teaching of cardiac auscultation and the diagnosis of heart valve disorders to medical students.[9] For a lay audience, the authors have created a video illustrating aberrations of cardiac electrophysiology using a set of Little Etudes for piano[10]—see Video 1. Over the past two decades, the explosion of digital music information has given rise to the burgeoning field of music information research, which is concerned with encapsulating music knowledge in computational form. These advances facilitate knowledge transfer between, and interoperability of computer algorithms for, music analysis and computational cardiology, with potential applications to disease stratification and to clinical practices and therapeutics.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data availability

The PhysioNet Spontaneous Ventricular Tachyarrhythmia Database used in Supplementary material online, Figure S2 is publicly available at https://physionet.org/content/mvtdb/1.0. Other data provided by permission in this article cannot be shared publicly for ethical and privacy reasons. The data will be shared on reasonable request to the corresponding author with permission of the owner(s).

Acknowledgements

This result is part of the COSMOS project (cosmos.cnrs.fr) that has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant agreement No. 788960). Cameryn Boyd and Cameron Elise Womack corrected the automatically derived PAF ECG beat annotations while working as associate students from Spelman College in autumn 2018. Ashwin Krishna, Daniel Soberanes, and Matthew Ybarra extracted and transcribed the VT ECG rhythms while working as Radcliffe Research Partners at Harvard University in summer 2017.

Conflict of interest: none declared.

References

1. Barnes DJ, von Herbay A, Schuhmacher F, Ditton HJ, Maiwald M, Lüderitz B, Kubba AK, Hofbauer LC, Heufelder AE, Joy M. In responses to Beethoven's final illness. *Lancet* 1996;**347**:766–767.
2. Goldberger ZD, Whiting SM, Howell JD. The heartfelt music of Ludwig van Beethoven. *Perspect Biol Med* 2014;**57**:285–294.
3. Chew E. Notating disfluencies and temporal deviations in music and arrhythmia. *Music Sci* 2018;doi:10.1177/2059204318795159.
4. Chew E. On making music with heartbeats. In: ER Miranda ed. *Handbook of Artificial Intelligence for Music: Foundations, Advanced Approaches, and Developments for Creativity*. Switzerland: Springer; 2021. https://hal.archives-ouvertes.fr/hal-03081561 (19 February 2021).
5. Chew E, Krishna A, Soberanes D, Ybarra M, Orini M, Lambiase PD. Arrhythmia Suite: I. 161122 VT before during after ECG (after Holst's "Mars" from *The Planets*); 2017–2018. https://bit.ly/ArrhythmiaSuite (28 January 2021).
6. Videos showing light (3:2 ratio), medium (2:1 ratio), and hard swing (3:1 ratio). https://en.wikipedia.org/wiki/Swing_(jazz_performance_style) (19 January 2021).
7. Goldberger A, Amaral L, Glass L, Hausdorff J, Ivanov PC, Mark R, Mietus JE, Moody GB, Peng CK, Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* 2000;**101**:e215–e220.
8. Mishra S, , Mohan S, Rajab KZ, Dhillon G, Lambiase PD, Hunter R., ChewE.Atrial fibrillation stratification via super-resolution analysis of fibrillatory waves. 2019 Computing in Cardiology (CinC), Singapore, 2019.
9. Field M. Music of the heart. *Lancet* 2010;**376**:2074.
10. Chew E, Lambiase P, Bedoya D. Little Etudes for piano based on aberrations of cardiac electrophysiology. Ircam AlxMusic Garden, Ars Electronica, 11 September 2020 https://youtu.be/42TRIL9MeOA https://bit.ly/LittleEtudes-video (30 January 2021).

doi:10.1093/eurheartj/ehab103

Exclusion of pregnant and lactating women from COVID-19 vaccine trials: a missed opportunity

Harriette Gillian Christine Van Spall [1,2,3,4]*

[1]Department of Medicine, McMaster University, Hamilton, ON, Canada; [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [3]Population Health Research Institute, 20 Copeland Avenue, David Braley Research Building, Suite C3-117, Hamilton, ON L8L 0A3, Canada; and [4]ICES, McMaster University, Canada

In the midst of a devastating pandemic with high transmissibility and case fatality, the mRNA COVID-19 vaccine trials represent hope of an end to the global burden of COVID-19 infection, hospital utilization, and death. The efficacy and safety of the vaccines have been demonstrated in adults across a range of demographics, with the exception of those who are pregnant and lactating. This systematic exclusion—common in clinical trials—represents a missed opportunity to protect a group at risk of adverse outcomes in the setting of COVID-19 infection. It has special implications on the healthcare workforce, a majority of whom are women and at high risk of COVID-19 infection.

The exclusion of pregnant and lactating women from COVID-19 vaccine trials (*Text Box 1*) reflects a historic pattern of 'protection by exclusion', representing an instance in which the estimated effect of a therapy on mother and child will rely on anecdotal and delayed reports from healthcare settings rather than the monitored setting of a clinical trial.[2] This exclusion is not justified. For example, Pfizer and Moderna excluded pregnant and lactating women from their mRNA COVID-19 vaccine trials[3,4] with no biological evidence to suggest that the vaccines are teratogenic, and no plausibility that they are transmitted in breast milk. The mRNA vaccines rapidly degenerate after injection in muscle cells, and aside from the post-vaccination immune response that can cause a fever, there is no reason to assume, *a priori*, that harm will come to pregnant and lactating women enrolled in the trials.[4]

The exclusion of pregnant and lactating women from the COVID-19 vaccine trials has implications on healthcare workers, who are among the highest risk groups for COVID-19 exposure and infection. As many as three out of four healthcare workers and four out of five nurses are women, and it is estimated that more than 300 000 health care workers in the USA alone are pregnant or immediately postpartum during vaccine implementing.[5] The dual risk posed by COVID-19 to pregnant healthcare professionals—increased workplace exposure and increased risk of adverse outcomes if infected[6]—makes it particularly concerning that the trials failed to include pregnant or lactating individuals. Furthermore, when healthcare workers are infected, they become sources of nosocomial spread thereby posing a risk to patients and to other healthcare workers.

The recommendations for use of the COVID-19 Pfizer and Moderna vaccine in pregnant and lactating women now range from avoidance of the vaccine—as recommended by the World Health Organization and some regulatory agencies—to reliance on recipients to make choices guided by their values or their clinicians' judgement.[5,7–9] Some regulatory bodies recommend against pregnancy in the weeks following the vaccine. The rationale for the recommendations of vaccine avoidance in pregnancy, pregnancy avoidance in weeks following vaccination, and decision-making regarding vaccination safety by clinicians in absence of clinical trial data is unclear.

Pregnancy and lactation are two distinct biological states that are often conflated in the eligibility criteria of clinical trials. Drugs that may have evidence of teratogenicity in biological studies may not be secreted in breast milk, and drugs secreted in breast milk with harmful effects to baby may not be teratogenic. The grouping of pregnancy and lactation into a single condition that is systematically excluded from clinical trials is often ill-conceived.[2] Indeed, the exclusions of one or both groups of patients from clinical trials is often without justification. For example, pregnant and lactating women were excluded from the COVID-19 hydroxychloroquine and

*Corresponding author. Email: Harriette.VanSpall@phri.ca