

White Paper: Diversity of Cells and Signals in the Cardiovascular System

Eleonora Grandi, Manuel F Navedo, Jeff Saucerman, Don M. Bers, Nipavan Chiamvimonvat, Rose E. Dixon, Dobromir Dobrev, Ana Maria Gomez, Osama F Harraz, Bence Hegyi, David K Jones, Trine Krogh-Madsen, Walter Lee Murfee, Matthew A. Nystoriak, Nikki Gillum Posnack, Crystal M Ripplinger, Rengasayee Veeraraghavan, and Seth H. Weinberg
DOI: 10.1113/JP284011

Corresponding author(s): Eleonora Grandi (egrandi@ucdavis.edu)

The following individual(s) involved in review of this submission have agreed to reveal their identity: Robert S Kass (Referee #1)

Review Timeline:

Submission Date:	28-Oct-2022
Editorial Decision:	03-Jan-2023
Revision Received:	16-Jan-2023
Accepted:	19-Jan-2023

Senior Editor: Laura Bennet

Reviewing Editor: Brian Delisle

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Ele,

Re: JP-WP-2022-284011 "White Paper: Diversity of Cells and Signals in the Cardiovascular System" by Eleonora Grandi, Manuel F Navedo, Jeff Saucerman, Don M. Bers, Nipavan Chiamvimonvat, Rose E. Dixon, Dobromir Dobrev, Ana Maria Gomez, Osama F Harraz, Bence Hegyi, David K Jones, Trine Krogh-Madsen, Walter Lee Murfee, Matthew A. Nystoriak, Nikki Gillum Posnack, Crystal M Ripplinger, Rengasayee Veeraraghavan, and Seth H. Weinberg

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 1 expert referee and I am pleased to tell you that it is considered to be acceptable for publication following satisfactory revision.

Please advise your co-authors of this decision as soon as possible.

The reports are copied at the end of this email. Please address all of the points and incorporate all requested revisions, or explain in your Response to Referees why a change has not been made.

NEW POLICY: In order to improve the transparency of its peer review process The Journal of Physiology publishes online as supporting information the peer review history of all articles accepted for publication. Readers will have access to decision letters, including all Editors' comments and referee reports, for each version of the manuscript and any author responses to peer review comments. Referees can decide whether or not they wish to be named on the peer review history document.

I hope you will find the comments helpful and have no difficulty returning revisions within 4 weeks.

Your revised manuscript should be submitted online using the links in Author Tasks Link Not Available.

If you have any queries please reply to this email and staff will be happy to assist.

Best wishes

Professor Laura Bennet
Senior Editor
The Journal of Physiology
<https://jp.msubmit.net>
<http://jp.physoc.org>
The Physiological Society
Hodgkin Huxley House
30 Farringdon Lane
London, EC1R 3AW
UK
<http://www.physoc.org>
<http://journals.physoc.org>

REQUIRED ITEMS:

-Please include an Abstract Figure file, as well as the figure legend text within the main article file. The Abstract Figure is a piece of artwork designed to give readers an immediate understanding of the Review Article and should summarise the main conclusions. If possible, the image should be easily 'readable' from left to right or top to bottom. It should show the physiological relevance of the Review so readers can assess the importance and content of the article. Abstract Figures should not merely recapitulate other figures in the Review. Please try to keep the diagram as simple as possible and without superfluous information that may distract from the main conclusion of the Review. Abstract Figures must be provided by authors no later than the revised manuscript stage and should be uploaded as a separate file during online submission labelled as File Type 'Abstract Figure'. Please ensure that you include the figure legend in the main article file. All Abstract Figures will be sent to a professional illustrator for redrawing and you may be asked to approve the redrawn figure before your paper is accepted.

-Your MS must include a complete "Additional information section" with the following 4 headings and content:

Competing Interests: A statement regarding competing interests. If there are no competing interests, a statement to this effect must be included. All authors should disclose any conflict of interest in accordance with journal policy.

Author contributions: Each author should take responsibility for a particular section of the study and have contributed to writing the paper. Acquisition of funding, administrative support or the collection of data alone does not justify authorship; these contributions to the study should be listed in the Acknowledgements. Additional information such as 'X and Y have contributed equally to this work' may be added as a footnote on the title page.

It must be stated that all authors approved the final version of the manuscript and that all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding: Authors must indicate all sources of funding, including grant numbers. If authors have not received funding, this must be stated.

It is the responsibility of authors funded by RCUK to adhere to their policy regarding funding sources and underlying research material. The policy requires funding information to be included within the acknowledgement section of a paper. Guidance on how to acknowledge funding information is provided by the Research Information Network. The policy also requires all research papers, if applicable, to include a statement on how any underlying research materials, such as data, samples or models, can be accessed. However, the policy does not require that the data must be made open. If there are considered to be good or compelling reasons to protect access to the data, for example commercial confidentiality or legitimate sensitivities around data derived from potentially identifiable human participants, these should be included in the statement.

Acknowledgements: Acknowledgements should be the minimum consistent with courtesy. The wording of acknowledgements of scientific assistance or advice must have been seen and approved by the persons concerned. This section should not include details of funding.

-Author profile(s) must be uploaded via the submission form. Authors should submit a short biography (no more than 100 words for one author or 150 words in total for two authors) and a portrait photograph of the two leading authors on the paper. These should be uploaded, clearly labelled, with the manuscript submission. Any standard image format for the photograph is acceptable, but the resolution should be at least 300 dpi and preferably more. A group photograph of all authors is also acceptable, providing the biography for the whole group does not exceed 150 words.

EDITOR COMMENTS

Reviewing Editor:

Overall, the referee thinks this is an excellent white paper that will be a valuable resource to understanding the state of the fields for the diversity of the cells and signals in the cardiovascular system. The authors are to be congratulated and collating and succinctly summarizing a large amount of information from a wide variety of areas is a succinct and easy to understand manuscript. In addition to referee 1's suggested changes outlined in their review, I also suggest the authors limit the total number of abbreviations when possible. Also, please use standardized nomenclature regarding channel genes and protein names. Some phrases need to be more clearly defined, and a few areas could be complimented by additional references. Lastly, a stylistic suggestion, write out what "they" and "this" are referring to in sentences that might cause ambiguity for some readers.

Comments:

P9. 3rd sentence. Clarify what is meant by "This safety mechanism..."

P9. Clarify what a "Ca²⁺-release unit" is.

P9. "Functional LTCCs are located in the Sarcolemma." - is this the complete thought here? What are the authors trying to convey here?

P10. Second complete paragraph- do the authors want to mention gap junctions as the mechanism for transmission of the electrical impulse? It seems odd they are not included in this section but are mentioned elsewhere discussing vasculature.

P10. Clarify what is meant by "This represents a safety mechanism..."

P11. "The LTCC regulation by B-ARs is mediated by the small GTP-binding Protein Rad", can the authors also include the initial reference PMID: 31147441?

P17. What is meant by "electronic load"?

P18 Change "potassium" to "K+" for consistency.

P21. "According to recent reports" please include additional citation(s) or make singular.

P21. Define NO

P22. What is meant by "In this issue, Chowkwale et al., developed..."? This wording is confusing.

P22. What is meant by the sentence "Adipose tissue is required for normal tissue function."? Also clearly define the tissue in "This tissue" in the following sentence.

P26. Can you clarify what "Ca²⁺-mediated voltage instabilities" are? Are these EADs DADs?

P28-29. Is there a way to edit the sentence "In a similar manner, biochemical cues (e.g., oxygen levels (Neary et al., 2014), glucose/fatty acid availability (Burrige et al., 2014; Yang et al., 2019), glucocorticoid or thyroid hormone signaling (Yang et al., 2014b; Rog-Zielinska et al., 2015; Parikh et al., 2017)) and biophysical cues (e.g., e.g., electromechanical conditioning (Ronaldson-Bouchard et al., 2018), micropatterning (Heidi Au et al., 2009; Kim et al., 2010), or substrate stiffness (Bakunts et al., 2008; Bhana et al., 2010; Feaster et al., 2015; Herron et al., 2016)) also help to guide CM development." to make it easier to read? I recognize this is because of the Journal's referencing style, but as is, it is challenging for the reader.

P33. Should "BK-channel activity" should be "BK channel activity" for consistency?

P34. "Na⁺ & Ca²⁺", the & should be written out.

P34. What does "ensures appropriate conduction velocity" mean?

P34. KCNQ1/hERG1 and KCNE nomenclature is non-standard usage especially when referring to protein. Can the section be modified to adopt the standardized nomenclature for these channel proteins- perhaps as outlined in <https://www.guidetopharmacology.org/targets.jsp> ?

P36. "...distinct potassium channel..." should be "...distinct K⁺ channel..." for consistency.

P37. "(e.g., Kv, Kir, Nav) should conform to style used for K_V and Na_V

P37. "...voltage and calcium..." should be "voltage and Ca²⁺"

P38. Can the authors clearly define what they mean by "omics"

P38. Please do not start to abbreviate CV or HF here. These are used unabbreviated in earlier sections. Alternatively abbreviate when first defined, but the large number of abbreviations already used in the manuscript makes it challenging to read.

P40. The sentence "Thus, a combination of models that represent important subgroups of HFpEF patients may lead to a better understanding of disease biology and excel at therapeutic testing." is unclear. What do the authors mean by "models represent...subgroups of...patients"? Can you clarify or state more explicitly?

P41 Spell out "3"

P41 The section "Action potential and ionic current variability" seems out of place under the heading "Technical innovations to assess biological diversity" what is the technical innovation highlighted in this subsection? Can this be emphasized more clearly, or the section moved to another place where it might flow better in the white paper?

P41. The statement "IKr...channels are not functionally expressed..." when referring to small animal models is not completely accurate. IKr can be recorded from the CMs in small animal hearts (see PMID: 10681594, but numerous published references are available), however it is true the functional role of IKr in small animal cardiac electrophysiology is not clear and does not appear to be the same as guinea pigs, larger animals or humans.

P42. Does having 22,000 out of 500,000 genomes/phenomes outside of Europe really allow for quantification of ancestry diversity at scale? Please clarify.

P44. If Brm is referring to the gene, should this be italicized?

P45. Add references to support the statement "Importantly, these results were

validated with complementary proteomics methods and replicated in other studies such as the

Multi-Ethnic Study of Atherosclerosis."

P47. Should iPSC-CMs be hiPSC-CMs?

P51. Please put space between "...data(Levet..."

Suggested changes for clarity.

- P4. Define they in "They also contribute to (inter)cellular..."
- P11. Clarify this in "This leads to a gain of ICa_L function..."
- P13. Pink box. Clarify what "this occurs" is specifically referring to.
- P14. Define or write out "myosin-P"
- P15. Define they in "how they could influence"
- P15. Define they in "They are genetically, morphologically..."
- P15. Define they in "They may also originate..."
- P16. Define they in "they are secreted" - is this specific for paracrine?
- P16. Define these in "Among these, TGF-B1..."
- P17. Pink box, what is meant by these in "To address these..."
- P18. Define they in "They are critical regulators of the..."
- P20. Define this in "This will facilitate..."
- P22. Define they in the sentence "They termed this cascade..."
- P28. Define what this process is in Zhao et al., provided insight into this process..."
- P31. Clarify this in "This was demonstrated..."
- P32. Define "this" in "but this remains to be experimentally explored."
- P36. Please define this in "This provides the potential..."
- P41. Pink box - what is this referring to in "...and whether this is cell-specific..."
- P42. What is this referring to in "This turned a \$3.8 billion..."
- P46. Is "..., on their own..." needed here?
- P46. Please clarify what they is referring to in the sentences "... but they are not sufficient..." and "They are outstanding..."
- P45. Who are they in the sentence "they identified a distinct..."
- P48. Can you clarify what this is in "this could ultimately help"

REFeree COMMENTS

Referee #1:

This white paper is an excellent overall review that will be helpful to many both in the cardiovascular field and those outside of the field. The organization is outstanding and areas are covered in great detail. My only suggestions to the authors is to edit the manuscript such that all section headers include definitions of abbreviations used such as Cardiomyocytes (CMs) on page 12; vascular smooth muscle cells (VSMCs) on page 16; Fibroblasts (FBs) on page 15.

On page 41 the discussion of small animals that do not express IKr and IKs really should be altered to note that guinea pig is a good small animal model in which these two channels are expressed however the usefulness of guinea pig is compromised because alteration of guinea pig genetics fall far behind the use of mice in genetically altering experiments.

Overall, however the paper is excellent.

END OF COMMENTS

EDITOR COMMENTS

Reviewing Editor:

Overall, the referee thinks this is an excellent white paper that will be a valuable resource to understanding the state of the fields for the diversity of the cells and signals in the cardiovascular system. The authors are to be congratulated and collating and succinctly summarizing a large amount of information from a wide variety of areas is a succinct and easy to understand manuscript. In addition to referee 1's suggested changes outlined in their review, I also suggest the authors limit the total number of abbreviations when possible. Also, please use standardized nomenclature regarding channel genes and protein names. Some phrases need to be more clearly defined, and a few areas could be complimented by additional references. Lastly, a stylistic suggestion, write out what "they" and "this" are referring to in sentences that might cause ambiguity for some readers.

Thank you for the positive assessment, and for the constructive suggestions and detailed feedback. We addressed all comments and hope to have improved clarity.

Comments:

P9. 3rd sentence. Clarify what is meant by "This safety mechanism..." **Wording was modified:** "These intracellular Ca^{2+} gradients ensure that RyR2 are closed during diastolic periods..."

P9. Clarify what a "Ca²⁺-release unit" is. **Wording was modified:** "i.e., domains including the LTCC and the SR membrane with RyR2s, which openings can be visualized with fluorescent dyes and confocal microscopy as localized, rapid, and brief elevations in $[Ca^{2+}]_i$; termed Ca²⁺ sparks (Cheng & Lederer, 2008)."

P9. "Functional LTCCs are located in the Sarcolemma." - is this the complete thought here? What are the authors trying to convey here? **We removed this sentence and added the notion of LTCC localization elsewhere.**

P10. Second complete paragraph- do the authors want to mention gap junctions as the mechanism for transmission of the electrical impulse? It seems odd they are not included in this section but are mentioned elsewhere discussing vasculature. **Thank you, we have done so.**

P10. Clarify what is meant by "This represents a safety mechanism..." **We removed this sentence.**

P11. "The LTCC regulation by B-ARs is mediated by the small GTP-binding Protein Rad", can the authors also include the initial reference PMID: 31147441? **Done, thank you.**

P17. What is meant by "electronic load"? **Done, we added:** "through effectively increasing the cardiac cell capacitance and altering the resting membrane potential"

P18 Change "potassium" to "K+" for consistency. [Done](#)

P21. "According to recent reports" please include additional citation(s) or make singular. [Done](#)

P21. Define NO [We removed the abbreviation](#)

P22. What is meant by "In this issue, Chowkwale et al., developed..."? This wording is confusing. [The wording was changed to clarify that we referred to this issue of the Journal of Physiology.](#)

P22. What is meant by the sentence "Adipose tissue is required for normal tissue function."? Also clearly define the tissue in "This tissue" in the following sentence. [The wording was changed to "Adipose tissue regulates cardiovascular health by producing and releasing...."](#)

P26. Can you clarify what "Ca²⁺-mediated voltage instabilities" are? Are these EADs DADs? [We specified that these are DADs](#)

P28-29. Is there a way to edit the sentence "In a similar manner, biochemical cues (e.g., oxygen levels (Neary et al., 2014), glucose/fatty acid availability (Burrige et al., 2014; Yang et al., 2019), glucocorticoid or thyroid hormone signaling (Yang et al., 2014b; Rog-Zielinska et al., 2015; Parikh et al., 2017)) and biophysical cues (e.g., e.g., electromechanical conditioning (Ronaldson-Bouchard et al., 2018), micropatterning (Heidi Au et al., 2009; Kim et al., 2010), or substrate stiffness (Bakunts et al., 2008; Bhana et al., 2010; Feaster et al., 2015; Herron et al., 2016)) also help to guide CM development." to make it easier to read? I recognize this is because of the Journal's referencing style, but as is, it is challenging for the reader. [Thank you, we rearranged the text and references to improve clarity.](#)

P33. Should "BK-channel activity" should be "BK channel activity" for consistency? [Done](#)

P34. "Na⁺ & Ca²⁺", the & should be written out. [Done](#)

P34. What does "ensures appropriate conduction velocity" mean? [We clarified as follows: "as while I_{K1} upregulation is expected to lower excitability and conduction velocity, reciprocal modulation leads to I_{Na} enhancement and consequent increase in conduction velocity"](#).

P34. KCNQ1/hERG1 and KCNE nomenclature is non-standard usage especially when referring to protein. Can the section be modified to adopt the standardized nomenclature for these channel proteins- perhaps as outlined in <https://www.guidetopharmacology.org/targets.jsp> ? [We changed to K_v and minK/miRP.](#)

P36. "...distinct potassium channel..." should be "...distinct K⁺ channel..." for consistency. [Done](#)

P37. "(e.g., K_v, Kir, Nav) should conform to style used for K_{_V and Na_{_V [Done](#)}}

P37. "...voltage and calcium..." should be "voltage and Ca²⁺" [Done](#)

P38. Can the authors clearly define what they mean by "omics" [Done in Fig. 5 legend](#)

P38. Please do not start to abbreviate CV or HF here. These are used unabbreviated in earlier sections. Alternatively abbreviate when first defined, but the large number of abbreviations already used in the manuscript makes it challenging to read. [We removed CV and HF abbreviations.](#)

P40. The sentence "Thus, a combination of models that represent important subgroups of HFpEF patients may lead to a better understanding of disease biology and excel at therapeutic testing." is unclear. What do the authors mean by "models represent...subgroups of...patients"? Can you clarify or state more explicitly? [We clarified as follows: "creating and investigating multiple different disease models that recapitulate specific sub-phenogroups of HFpEF patients, with distinct phenotypical characteristics and underlying pathological mechanisms, may deepen our understanding of HFpEF biology and improve therapeutic testing".](#)

P41 Spell out "3" [Done](#)

P41 The section "Action potential and ionic current variability" seems out of place under the heading "Technical innovations to assess biological diversity" what is the technical innovation highlighted in this subsection? Can this be emphasized more clearly, or the section moved to another place where it might flow better in the white paper? [We moved this section to chapter 2.3.](#)

P41. The statement "IKr...channels are not functionally expressed..." when referring to small animal models is not completely accurate. IKr can be recorded from the CMs in small animal hearts (see PMID: 10681594, but numerous published references are available), however it is true the functional role of IKr in small animal cardiac electrophysiology is not clear and does not appear to be the same as guinea pigs, larger animals or humans. [Thank you, we edited the sentence to indicate that the physiological significance of I_{Kr} and I_{Ks} in small mammals is unclear, and added a note about the use of guinea pig, as suggested by Reviewer 1.](#)

P42. Does having 22,000 out of 500,000 genomes/phenomes outside of Europe really allow for quantification of ancestry diversity at scale? Please clarify. [The wording was changed to "greater scale". While this is clearly not fully representative, it is larger than previous studies.](#)

P44. If Brm is referring to the gene, should this be italicized? [Yes, this has been corrected.](#)

P45. Add references to support the statement "Importantly, these results were validated with complementary proteomics methods and replicated in other studies such as the Multi-Ethnic Study of Atherosclerosis." [The reference to Katz et al. 2022 was added to clarify that the validation was performed in the same study discussed above.](#)

P47. Should iPSC-CMs be hiPSC-CMs? [Done](#)

P51. Please put space between "...data(Letev..." [Done](#)

Suggested changes for clarity.

P4. Define they in "They also contribute to (inter)cellular..." [They refers to extracellular matrix \(ECM\), perivascular macrophages, and perivascular FB-like cells. We removed it.](#)

P11. Clarify this in "This leads to a gain of ICa,L function..." [Done](#)

P13. Pink box. Clarify what "this occurs" is specifically referring to. [Done](#)

P14. Define or write out "myosin-P" [Done](#)

P15. Define they in "how they could influence" [Done](#)

P15, Define they in "They are genetically, morphologically..." [Done](#)

P15. Define they in "They may also originate..." [Done](#)

P16. Define they in "they are secreted" - is this specific for paracrine? [Correct, removed autocrine](#)

P16. Define these in "Among these, TGF-B1..." [Clarified sentence](#)

P17. Pink box, what is meant by these in "To address these..." [Done](#)

P18. Define they in "They are critical regulators of the..." [Done](#)

P20. Define this in "This will facilitate.." [Clarified sentence](#)

P22. Define they in the sentence "They termed this cascade..." [Done](#)

P28. Define what this process is in Zhao et al., provided insight into this process..." [Clarified sentence](#)

P31. Clarify this in "This was demonstrated..." [Clarified sentence](#)

P32. Define "this" in "but this remains to be experimentally explored." [Done](#)

P36. Please define this in "This provides the potential..." [Done](#)

P41. Pink box - what is this referring to in "...and whether this is cell-specific..." [Done](#)

P42. What is this referring to in "This turned a \$3.8 billion...." [Done](#)

P46. Is "...., on their own,..." needed here? [Removed](#)

P46. Please clarify what they is referring to in the sentences "..., but they are not sufficient..." and "They are outstanding...." [Done](#)

P45. Who are they in the sentence "they identified a distinct...." [Done](#)

P48. Can you clarify what this is in "this could ultimately help" [Done](#)

REFEREE COMMENTS

Referee #1:

This white paper is an excellent overall review that will be helpful to many both in the cardiovascular field and those outside of the field. The organization is outstanding and areas are covered in great detail. My only suggestions to the authors is to edit the manuscript such that all section headers include definitions of abbreviations used such as Cardiomyocytes (CMs) on page 12; vascular smooth muscle cells (VSMCs) on page 16; Fibroblasts (FBs) on page 15. [Done, thank you.](#)

On page 41 the discussion of small animals that do not express I_{Kr} and I_{Ks} really should be altered to note that guinea pig is a good small animal model in which these two channels are expressed however the usefulness of guinea pig is compromised because alteration of guinea pig genetics fall far behind the use of mice in genetically altering experiments. [Thank you. We included the following note about the use of guinea pig as a good animal model for studying \$I_{Kr}\$ and \$I_{Ks}\$: "Guinea pig has been a highly useful small animal model in which cardiac repolarization mechanisms are more alike those in larger mammals. However, the use of guinea pig has decreased due to the rise of much more sophisticated tools for genetic manipulation of mice."](#)

Overall, however the paper is excellent.
[Thanks for the positive feedback!](#)

Dear Ele,

Re: JP-WP-2023-284011R1 "White Paper: Diversity of Cells and Signals in the Cardiovascular System" by Eleonora Grandi, Manuel F Navedo, Jeff Saucerman, Don M. Bers, Nipavan Chiamvimonvat, Rose E. Dixon, Dobromir Dobrev, Ana Maria Gomez, Osama F Harraz, Bence Hegyi, David K Jones, Trine Krogh-Madsen, Walter Lee Murfee, Matthew A. Nystoriak, Nikki Gillum Posnack, Crystal M Ripplinger, Rengasayee Veeraraghavan, and Seth H. Weinberg

We are pleased to tell you that your paper has been accepted for publication in The Journal of Physiology.

TRANSPARENT PEER REVIEW POLICY: To improve the transparency of its peer review process The Journal of Physiology publishes online, as supporting information, the peer review history of all articles accepted for publication. Readers will have access to decision letters, including Editors' comments and referee reports, for each version of the manuscript, as well as any author responses to peer review comments. Referees can decide whether or not they wish to be named on the peer review history document.

The last Word (or similar) version of the manuscript provided will be used by the Production Editor to prepare your proof. When this is ready you will receive an email containing a link to Wiley's Online Proofing System. The proof should be thoroughly checked and corrected as promptly as possible.

Authors should note that it is too late at this point to offer corrections prior to proofing. The accepted version will be published online, ahead of the copy edited and typeset version being made available. Major corrections at proof stage, such as changes to figures, will be referred to the Editors for approval before they can be incorporated. Only minor changes, such as to style and consistency, should be made at proof stage. Changes that need to be made after proof stage will usually require a formal correction notice.

All queries at proof stage should be sent to: TJP@wiley.com

Are you on Twitter? Once your paper is online, why not share your achievement with your followers? Please tag The Journal (@jphysiol) in any tweets and we will share your accepted paper with our 30,000 followers!

Best wishes

Laura

Professor Laura Bennet
Senior Editor
The Journal of Physiology
<https://jp.msubmit.net>
<http://jp.physoc.org>
The Physiological Society
Hodgkin Huxley House
30 Farringdon Lane
London, EC1R 3AW
UK
<http://www.physoc.org>
<http://journals.physoc.org>

P.S. - You can help your research get the attention it deserves! Check out Wiley's free Promotion Guide for best-practice recommendations for promoting your work at www.wileyauthors.com/eeo/guide. You can learn more about Wiley Editing Services which offers professional video, design, and writing services to create shareable video abstracts, infographics, conference posters, lay summaries, and research news stories for your research at www.wileyauthors.com/eeo/promotion.

IMPORTANT NOTICE ABOUT OPEN ACCESS: To assist authors whose funding agencies mandate public access to published research findings sooner than 12 months after publication The Journal of Physiology allows authors to pay an Open Access (OA) fee to have their papers made freely available immediately on publication.

The Corresponding Author will receive an email from Wiley with details on how to register or log-in to Wiley Authors Services where you will be able to place an order.

You can check if your funder or institution has a Wiley Open Access Account here: <https://authorservices.wiley.com/author-resources/Journal-Authors/licensing-and-open-access/open-access/author-compliance-tool.html>

REVIEWING EDITOR COMMENTS:

As noted by the referee, the authors have written a broad, up to date, and highly influential white paper that will have a significant impact on the field.

REVIEWER COMMENTS:

I think this is an excellent paper and will have a significant impact on the field. Overall the review covers multiple physiological mechanisms in the heart and thus will be wide read and helpful to a large segment of the field.

1st Confidential Review

16-Jan-2023
