University of Groningen

Response to Letter to the Editor

Canu, Letizia; Van Hemert, Janna A W; Kerstens, Michiel; Hartman, Robert P; Khanna, Aakanksha; Kraljevic, Ivana; Kastelan, Darko; Badiu, Corin; Ambroziak, Urszula; Tabarin, Antoine

Published in:
Journal of Clinical Endocrinology and Metabolism

DOI:
[10.1210/clinem/dgaa472](https://doi.org/10.1210/clinem/dgaa472)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Canu, L., Van Hemert, J. A. W., Kerstens, M., Hartman, R. P., Khanna, A., Kraljevic, I., Kastelan, D., Badiu, C., Ambroziak, U., Tabarin, A., Haissaguerre, M., Buitenwerf, E., Visser, A., Mannelli, M., Arlt, W., Chortis, V., Bourdeau, I., Gagnon, N., Buchy, M., ... Timmers, H. J. L. M. (2020). Response to Letter to the Editor: "CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma". *Journal of Clinical Endocrinology and Metabolism*, 105(10), [472]. <https://doi.org/10.1210/clinem/dgaa472>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Response Letter to the Editor from Sweeney AT: "CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma".

Authors

Letizia Canu^{1,2}, Janna A.W. Van Hemert¹, Michiel Kerstens³, Robert P. Hartman⁴, Aakanksha Khanna⁵, Ivana Kraljevic⁶, Darko Kastelan⁶, Corin Badiu⁷, Urszula Ambroziak⁸, Antoine Tabarin⁹, Magalie Haissaguerre⁹, Edward Buitenwerf³, Anneke Visser¹⁰, Massimo Mannelli², Wiebke Arlt¹¹, Vasileios Chortis¹¹, Isabelle Bourdeau¹², Nadia Gagnon¹², Marie Buchy¹³, Francoise Borson-Chazot¹³, Timo Deutschbein¹⁴, Martin Fassnacht^{14,15}, H. Alicja Hubalewska Dydejczyk¹⁶, Marcin Motyka¹⁶, Ewelina Rzepka¹⁶, Ruth T. Casey¹⁷, Benjamin G. Challis¹⁷, Marcus Quinkler¹⁸, Laurent Vroonen¹⁹, Ariadni Spyroglou^{20,21}, Felix Beuschlein^{20,21}, Cristina Lamas²², William F. Young⁵, Irina Bancos⁵, Henri J.L.M. Timmers¹.

1 Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands

2 Department of Experimental and Clinical Biomedical Sciences University of Florence, Florence, Italy

3 Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

4 Department of Radiology, Mayo Clinic, Rochester, Minnesota

5 Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota

6 Department of Endocrinology, University Hospital Center Zagreb, Zagreb, Croatia

7 National Institute of Endocrinology "C. I. Parhon", Bucharest, Romania; "Carol Davila" University of Medicine and Pharmacy, Chair of Endocrinology, Bucharest, Romania

8 Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland

9 Service d'Endocrinologie Hôpital Haut-Lévêque, CHU de Bordeaux, Pessac, France

10 Department of Applied Health Research, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

11 Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom

12 Division of Endocrinology, Center hospitalier de l'Université de Montréal (CRCHUM), Montreal, Quebec, Canada

13 Fédération d'Endocrinologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron F-69677, France

14 Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Wuerzburg, Wuerzburg, Germany

15 Comprehensive Cancer Center Mainfranken, University of Wuerzburg, Wuerzburg, Germany

16 Chair and Department of Endocrinology, Jagiellonian University, Collegium Medicum, Krakow, Poland

17 Addenbrooke's Hospital, Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge and NIHR Biomedical Research Center, Cambridge, United Kingdom

18 Endocrinology in Charlottenburg, Berlin, Germany

19 Department of Endocrinology, Center Hospitalier Universitaire de Liège, Liège, Belgium

20 Medizinische Klinik und Poliklinik IV Ludwig-Maximilians-Universität München, Munich, Germany

21 Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, UniversitätsSpital Zürich, Zurich, Switzerland

22 Endocrinology Department, Hospital General Universitario de Albacete, Albacete, Spain

Correspondence: Letizia Canu

Department of Experimental and Clinical Biomedical Sciences University of Florence

50139, Florence, Italy

T +39 0552751241

Email letizia.canu@unifi.it

The authors have nothing to disclose.

We gladly respond to the interesting letter by Sweeney and Blake (1) regarding our recent paper on CT characteristics of pheochromocytoma with relevance for the evaluation of adrenal incidentaloma (2). Our findings suggest that a low unenhanced attenuation of an adrenal lesion (≤ 10 HU) has a high negative predictive value ($>99\%$) for pheochromocytoma (3). On the other hand we found that a high absolute or relative washout of an adrenal lesions with an unenhanced attenuation of >10 HU by no means rules out this disease, since the latter was the case in as many as 29% of evaluable pheochromocytomas. This is in line with a previous meta-analysis of 10 studies which indicated a rate of pheochromocytomas with a high washout pattern of 35% (4).

In their letter, the authors point out that rather than washout, portal venous phase (PVP) CT attenuation, *i.e.* the maximum attenuation at 60-75 seconds after the injection of contrast, could be used to facilitate the distinction between pheochromocytoma and adrenocortical adenoma. Based on two publications (5,6) they emphasize that pheochromocytomas have a higher PVP attenuation than adenomas. In the first study, comparing 43 histologically proven adrenal adenomas with 34 pheochromocytomas, applying a cut off of >85 HU to diagnose pheochromocytoma yielded a sensitivity of 88% (5). In the setting of evaluation of adrenal incidentalomas, however, it is of the utmost importance to rule out pheochromocytoma with a high level of certainty, since obviously, missing this diagnosis potentially has deleterious consequences for the patient. When using the suggested approach to apply contrast enhance attenuation for lesions with an unenhanced attenuation of >10 HU, in fact 12% of pheochromocytomas would be missed. The sensitivity of PVP attenuation is therefore clearly inferior to that of plasma free metanephrines, established at 98% (7). In the second study, again in pheochromocytomas versus adenomas, applying a PVP threshold of >130 HU resulted in a specificity of 100%, but this was at the cost of a sensitivity of only 38% (6). To find out whether this parameter is truly specific for pheochromocytomas as suggested, adrenocortical carcinomas and other malignant adrenal lesions should also be investigated.

Prompted by the authors' interesting suggestions, we reanalyzed our data regarding PVP values. Among 76 pheochromocytomas with unenhanced HU >10 and available washout data, PVP was available from the radiology reports only in six cases. And among those lesions, only two exhibited a PVP of >85 HU. This could be related to differences in contrast protocols among different centers.

Taking into account these considerations, it is our strong opinion that, until PVP attenuation is systematically evaluated in a larger population of patients with a mix of different adrenal tumor types, any adrenal lesion with an unattenuated HU >10 should prompt biochemical evaluation to rule out pheochromocytoma by the measurement of catecholamine metabolites.

1. Sweeney AT, Blake MA. Letter to the Editor: "CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma". The Journal of Clinical Endocrinology & Metabolism 2020.
2. Canu L, Van Hemert JAW, Kerstens MN, Hartman RP, Khanna A, Kraljevic I, Kastelan D, Badiu C, Ambroziak U, Tabarin A, Haissaguerre M, Buitenwerf E, Visser A, Mannelli M, Arlt W, Chortis V, Bourdeau I, Gagnon N, Buchy M, Borson-Chazot F, Deutschbein T, Fassnacht M, Hubalewska-Dydejczyk A, Motyka M, Rzepka E, Casey RT, Challis BG, Quinkler M, Vroonen L, Spyroglou A, Beuschlein F, Lamas C, Young WF, Bancos I, Timmers HJLM. CT Characteristics of

Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma. *J Endocrinol Metab.* 2019;104(2):312-318.

3. Buitenwerf E, Korteweg T, Visser A, Haag CMSC, Feelders RA, Timmers HJLM, Canu L, Haak HR, Bisschop PHLT, Eekhoff EMW, Corssmit EPM, Krak NC, Rasenberg E, van den Bergh J, Stoker J, Greuter MJW, Dullaart RPF, Links TP, Kerstens MN. Unenhanced CT Imaging Is Highly Sensitive to Exclude Pheochromocytoma: A Multicenter Study. *Eur J Endocrinol.* 2018;178(5):431-437.
4. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Pheochromocytoma as a Frequent False-Positive in Adrenal Washout CT: A Systematic Review and Meta-Analysis. *Eur Radiol.* 2018;28(3):1027-1036.
5. Mohammed MF, El Banna KY, Ferguson D, Harris A, Khosa F. Pheochromocytomas Versus Adenoma: Role of Venous Phase CT Enhancement. *AJR Am J Roentgenol.* 2018;210(5):1073-1078.
6. Northcutt BG, Trakhtenbroit MA, Gomez EN et al. Adrenal Adenoma and Pheochromocytoma: Comparison of Multidetector CT Venous Enhancement Levels and Washout Characteristics. *J Comput Assist Tomogr.* 2016;40(2):194-200.
7. Eisenhofer G, Prejbisz A, Peitzsch M, Pamporaki C, Masjkur J, Rogowski-Lehmann N, Langton K, Tsourdi E, Pęczkowska M, Flidner S, Deutschbein T, Megerle F, Timmers HJLM, Sinnott R, Beuschlein F, Fassnacht M, Januszewicz A, Lenders JWM. Biochemical Diagnosis of Chromaffin Cell Tumors in Patients at High and Low Risk of Disease: Plasma Versus Urinary Free or Deconjugated O-Methylated Catecholamine Metabolites. *Clin Chem.* 2018;64(11):1646-1656.

Accepted Manuscript