Longer telomeres in PA-SMCs from iPAH patients did not correlate with age (**Figure 1B**). Strikingly, telomere lengths in iPAH positively and significantly (Spearman rank correlation $r^2 = 0.818$; $p = 0.00096$) correlated with pulmonary vascular resistance values, suggesting a strong relationship between disease severity and better telomere length maintenance. This phenomenon seems to be exclusive to PA-SMCs, because it was not found in matched endothelial cells or peripheral blood cells (data not shown).

Alterations in the proliferation capacity of the PA-SMCs have been associated with pulmonary hypertension. Recent studies have also highlighted the similarities between iPAH and cancer, 2 diseases that involve abnormal cell growth. Here, we extend these similarities to aspects related to telomere biology and show the correlation between telomere maintenance and proliferation capacity of iPAH PA-SMCs, as well as disease severity. This correlation, probably related to an increase of telomerase activity (4), seems to be exclusive to iPAH, because it was not found in chronic obstructive pulmonary disease pulmonary hypertension (5), suggesting that the mechanisms involved in the PA-SMC abnormal growth are different. In conclusion, our work suggests that in iPAH, PA-SMCs overcome the proliferation barriers that operate in normal cells through a better maintenance of telomeres.

Mohamed Izikki, PhD
Eric Hoang, BSc
Irena Draskovic, PhD
Olaf Mercier, MD, PhD
Florence Lecerf, BSc
Lilia Lamrani, MSc
Win-Yan Liu, PhD
Christophe Guignabert, PhD
Elie Fadel, MD, PhD
Peter Dorfmuller, MD, PhD
Marc Humbert, MD, PhD
Arturo Londoño-Vallejo, MD, PhD
***Saadia Eddahibi, PhD**

*INSERM U1046
Centre Hospitalier Universitaire
Arnaud de Villeneuve
371 Avenue du Doyen Gaston Giraud 34295
Montpellier Cedex 05
France
E-mail: saadia.eddahibi@inserm.fr

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Is Caffeine Abstention Necessary Before Adenosine-Induced Fractional Flow Reserve Measurement?

Caffeine antagonizes the pharmacological actions of adenosine by blocking adenosine receptor activity (1). A protocol for adenosine stress myocardial perfusion imaging recommends that caffeine-containing products be withheld for 12 h before the test (2). However, there has been no widely accepted consensus for the need of caffeine abstention before fractional flow reserve (FFR) measurement. Conflicting results have been reported in the literature concerning the effects of caffeine on FFR measurement (3,4). Thus, we designed this study to determine if caffeine abstention is required before FFR measurement and if high-dose intracoronary adenosine overcomes the caffeine antagonism.

This prospective, single-center study enrolled 76 patients who underwent clinically indicated FFR assessment. Of these patients, 19 patients in each group were asked to refrain from caffeine-containing products for 12, 24, and 48 h before the test and 19 patients were allowed to have caffeine. Exclusion criteria included acute myocardial infarction, severe arrhythmia, previous coronary artery bypass grafting, any contraindications for adenosine or papaverine, and the presence of pressure drift (>0.03) after pull-back. Hyperemia was induced by central intravenous adenosine at a dose of 140 μg/kg/min (ADN-IV), by intracoronary adenosine at varying doses (60 μg [ADN-IC60], 150 μg [ADN-IC150], 300 μg [ADN-IC300], by 600 μg [ADN-IC600]), and by papaverine (10 to 12 mg in the right coronary artery or 15 to 20 mg in the left coronary artery), as a reference standard. The

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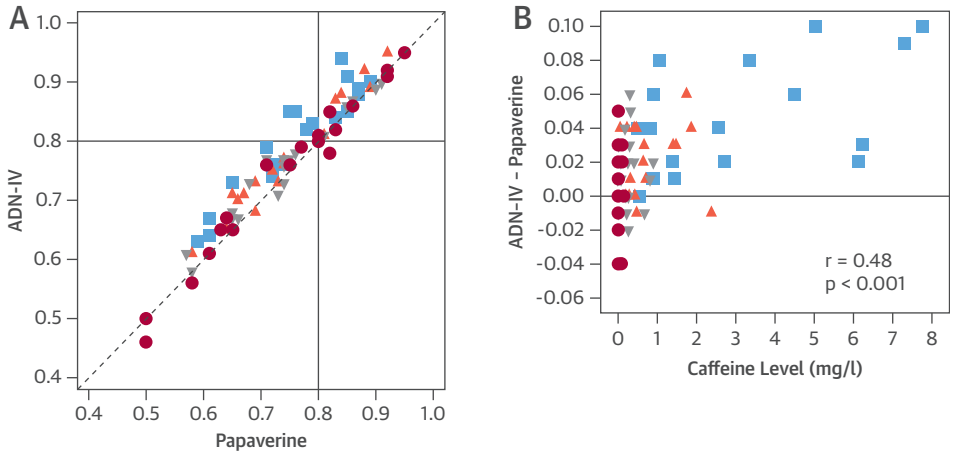
FIGURE 1 Comparisons of FFR Between Papaverine and Intravenous Adenosine



Caffeine abstention	n	ADN-IV	Overestimation (vs. papaverine)	p value
No	19	0.804 ± 0.091	0.045 ± 0.032	< 0.001
12-h	19	0.769 ± 0.096	0.023 ± 0.020	< 0.001
24-h	19	0.754 ± 0.089	0.015 ± 0.021	< 0.01
48-h	19	0.743 ± 0.141	0.003 ± 0.022	0.61

(A) Comparisons of fractional flow reserve (FFR) between papaverine and intravenous adenosine. The **dashed line** indicates the line of identity. **(B)** Scatterplots of caffeine level and difference in FFR values between intravenous adenosine and papaverine.

next higher doses of intracoronary adenosine were not administered in the event of a pause in the heartbeat of >3 seconds.

The median caffeine levels were 1.424, 0.452, 0.240, and 0 mg/l (interquartile ranges: 0.876 to 4.764, 0.291 to 1.054, 0.060 to 0.303, and 0 to 0.002 mg/l) in the no caffeine, and 12-, 24-, and 48-h caffeine abstention groups, respectively. The protocol of ADN-IV was completed in all patients. Figure 1A shows scatterplots of FFR between papaverine and ADN-IV. Compared with papaverine, ADN-IV overestimated FFR in the no caffeine group ($p < 0.001$) and in the 12-h ($p < 0.001$) and 24-h caffeine abstention ($p < 0.01$) groups, whereas the difference in FFR was not significant in the 48-h abstention group ($p = 0.61$). The overestimation in FFR by ADN-IV was correlated with caffeine levels ($r = 0.48$; $p < 0.001$) (Figure 1B). ADN-IV overestimated FFR in 91% (29 of 32) and 94% (16 of 17) of the patients who had caffeine levels of >0.5 and >1.0 mg/l, respectively.

ADN-IC600 was feasible in 84% (51 of 61) of the patients for the left coronary artery and in only 13% (2 of 15) of the patients for the right coronary artery. Incremental ADN-IC produced progressively lowered FFR values in all the groups. However, even increased doses of intracoronary adenosine up to 600 μg still overestimated FFR compared with papaverine in the no caffeine group ($p < 0.001$) and the 12-h ($p < 0.01$) and 24-h caffeine abstention ($p < 0.01$) groups. In the 48-h caffeine abstention group, the mean FFR value did not differ significantly between papaverine and ADN-IC600 ($p = 0.31$), whereas FFR was overestimated by ADN-IC60 ($p < 0.01$) and tended to be overestimated by ADN-IC150 ($p = 0.07$) and ADN-IC300 ($p = 0.05$).

We found that the currently recommended central ADN-IV overestimated FFR in the presence of caffeine in a dose-dependent manner, and the increased doses of ADN-IC up to 600 μg could not fully surmount the antagonism. A review article suggested that a caffeine level of <3 to 4 mg/l was acceptable for adenosine stress myocardial perfusion imaging (5). However, the remaining caffeine in the blood could be clinically relevant for FFR measurement even after 24 h of caffeine abstention.

The results of this study suggest prolonged caffeine abstention (>24 h) would be safer to avoid incomplete hyperemia. Otherwise, we would have to choose alternative drugs that are unaffected by caffeine, such as papaverine and nicorandil, when an FFR value obtained with adenosine stays above 0.80.

In conclusion, caffeine abstention is necessary before adenosine-induced FFR measurement, regardless of the administration route.

*Hidenari Matsumoto, MD, PhD
Shunpei Ushimaru, MD
Tetsuya Matsuda, MD, PhD
Toshihiko Shimada, MD
Mikiko Mikuri, MD
Haruya Takahashi, PhD
Nobuyuki Takahashi, PhD
Teruo Kawada, PhD
Taketoshi Yamazaki, MD, PhD

*Cardiovascular Center, Iseikai Hospital
6-2-25, Sugahara, Higashiyodogawa-ku
Osaka 533-0022
Japan
E-mail: matsumoto.hidenari@gmail.com

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Going Over LEGACY With a Pinch of Salt

Pathak et al. (1) reported that sustained weight loss ≥10% in patients with a body mass index ≥27 kg/m^2 was associated with a 6-fold reduction of atrial fibrillation (AF) recurrence during a 5-year follow-up, compared to patients without weight loss. The nonrandomized design and statistical methods used raise concerns about the extent to which the findings can be considered valid.

The study was based on a post-hoc analysis of 355 patients, allocated to groups for comparison after study completion according to the achieved weight loss. We detected several potential sources of selection bias for these groups. Most importantly, patients with the highest weight loss participated more often in the offered dietician consulting, suggesting generally better lifestyle management and drug treatment compliance, which could also possibly comprise a better control of other AF relevant comorbidities such as hypertension, obstructive sleep apnea, or diabetes. Indeed, important information on these comorbidities are missing, eliminating the potential to assess their impact on AF: 1) classes and doses of the antihypertensive drugs (rather than their number per patient); 2) changes in apnea-hypopnea index at follow-up; and 3) data on HbA1c at baseline and follow-up (rather than fasting insulin levels that do not inform about longer-term glycemic control). Furthermore, patients with the highest weight loss tended to be older than the control group. More details regarding AF treatment would also be helpful in interpreting the results, since electrocardioversion, number of ablations, and/or use of amiodarone at any time could have influenced the maintenance of sinus rhythm more robustly than sotalol or flecainide use alone. It is not clear whether the outcome was adjusted for these variables.

Another form of bias includes attrition bias: the information on the number and nature of dropouts is missing. Although the authors aimed for a 5-year follow-up, the average follow-up was 48 months for unclear reasons. Dropouts due to death—especially in older subjects (i.e., those with the highest weight loss)—would have affected the outcome. In any study, death can prevent detection of cause-specific nonfatal endpoints. Hence an analysis combining AF recurrence and death is warranted as sensitivity analysis.

In our opinion, evaluating the real effect of weight loss on AF would need a randomized controlled study. Short of this, use of case-mix adjustments, such as the propensity score matching, could provide a better control for confounding.

*Miroslava Valentova, MD
Nour Raad, MD, PhD
Stefan D. Anker, MD, PhD

*Department of Cardiology and Pneumology
University Medicine Göttingen
Robert Koch Strasse 40
Göttingen D-37079
Germany
E-mail: miroslava.valentova@med.uni-goettingen.de

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