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Review

High heart rate: a cardiovascular risk factor?

Stéphane Cook[1], Mario Togni[1], Marcus C. Schaub[2], Peter Wenaweser[1], and Otto M. Hess[1]*

[1] *Department of Cardiology, Swiss Cardiovascular Center, University Hospital, Freiburgstrasse, 3010 Bern, Switzerland and* [2] *Institute of Pharmacology, University of Zurich, Zurich, Switzerland*

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De battre mon coeur s'est arrêté—Movie by Jacques Audiard.

Resting heart rate (RHR) is one of the simplest cardiovascular parameters, which usually averages 60 to 80 beats per minute (b.p.m.), but can occasionally exceed 100 b.p.m. in unconditioned, sedentary individuals and be as low as 30 b.p.m. in highly trained endurance athletes. Epidemiological evidences demonstrate that RHR, or its corollaries, namely post-exercise heart rate recovery, which is mediated primarily by vagal tone, and heart rate variability (HRV, beat-to-beat variability also mediated by autonomic nervous system, especially parasympathetic) correlates with cardiovascular morbidity and suggests that RHR determines life expectancy. Multiple studies have identified RHR as an independent risk factor for cardiovascular disease (comparable with smoking, dyslipidemia or hypertension). However, it is often overlooked.

Heart rate: an independent cardiovascular risk factor

Since 1980, it is known that resting heart rate (RHR) is a prognostic factor in coronary diseased patients.[1,2] Data from the Coronary Artery Surgery Study (CASS) published last year underline the prognostic importance of RHR for morbidity (time to rehospitalization), as well as total and cardiovascular mortality.[3] Heart rate proves to be the best predictor after myocardial infarction,[4,5] in patients with congestive heart failure, as well as in patients with diabetes mellitus or hypertension.

In addition, it was found that elevated RHR is also strongly associated with mortality in the general population. For instance, in the Framingham Study, in a cohort composed of 5070 subjects who were free from cardiovascular disease at the time of entry into the study, cardiovascular and coronary mortality increased progressively with RHR[6] (*Figure 1*). In a subset of 4530 untreated hypertensive (>140 mmHg systolic or >90 mmHg diastolic) patients included in this study, using 36-year follow-up data, odds ratio (OR) for each increment in heart rate of 40 b.p.m. were 1.68–1.70 (CI: 1.08–2.67) for cardiovascular mortality and fascinatingly also 2.14–2.18 (CI: 1.59–2.88) for all-cause mortality. This latter study, however, also underlines a key concept: because high RHR is associated with elevated sympathetic activity, it is also frequently related to arterial hypertension. A crucial step is therefore to know whether high RHR is also associated with cardiovascular mortality when controlling for potential confounding cardiovascular risk factors, such as arterial hypertension or age.[7] Subsequent analysis demonstrated that rapid RHR was not an indicator of pre-existing illness, but was rather an independent risk factor.[8] Moreover, four studies involving hypertensive subjects demonstrated that this effect was sustained in this subset of patients.[7–11] This abundant literature was further incremented by data also demonstrating this effect in elderly.[12–14]

Multiple follow-up studies confirmed these data, as the Cordis trial, the Paris Prospective Study or the MATISS project: Kristal-Boneh *et al*. (CORDIS)[15] found that RHR was strongly associated with both all-cause (RR: 2.23, CI: 1.4–3.6, RHR >90 vs. <70 b.p.m.) and cardiovascular mortality after controlling (in various statistical models) for manifold recognized risk factors. Filipovsky *et al*. (PPS)[16] found that mortality could be predicted by resting heart frequency in 4907 middle-aged males followed during 17 years. Seccareccia *et al*. (MATISS)[17] verified that in a low-risk Italian population, heart rate increment was associated with a relative risk increase from 1.52 (CI: 1.29–1.78) for all-cause mortality, 1.63 (CI: 1.26–2.10) for cardiovascular mortality, and 1.47 (CI:1.19–1.80) for non-cardiovascular mortality.

As with cholesterol levels, the risk is graded;[9,18] i.e. the risk rises with increasing RHR. In the French IPC trial, Benetos *et al*.[9] evaluated the prognostic value of RHR on mortality in more than 19 000 healthy subjects and found a continuous, graded effect of RHR during a mean follow-up duration of 18.2 years. In men, the relative risk for cardiovascular death was 1.35 (CI: 1.01–1.80) in the group with RHR 60–80 b.p.m. to 2.18 (CI: 1.37–3.47) in the group with RHR >100 b.p.m. Data from the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic follow-up study confirmed this association in white men (RR: 1.37, CI: 1.02–1.84, RHR >84 vs. <74 b.p.m.) and extended this observation to black men and women.[19] This is an important finding because it has been considered that high RHR was only a weak predictor in the female gender. The key studies on the topic are listed on the *Table 1*.[13,20–27]

On the basis of this evidence, it has been proposed that, as in animals, life span could be predetermined using allometric scales based on RHR.[28] Longevity determination is a key element in biogerontology. Within the animal kingdom, the mammalians' heart rate represents an inverse semi-logarithmic relation to life expectancy: small

* Corresponding author. Tel: +41 31 632 96 53; fax: +41 31 632 47 71.
E-mail address: otto.hess@insel.ch

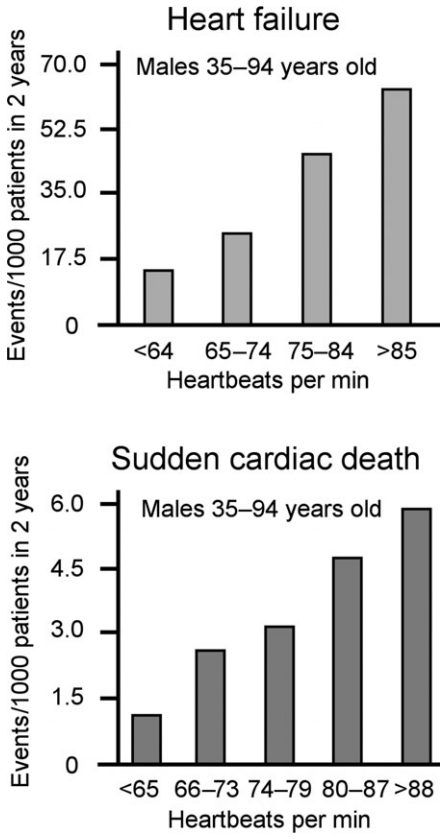

Figure 1 Dependency of heart failure events and sudden cardiac death on RHR divided in quartiles or quintiles. Included are men in a 36-year follow-up in the Framingham Heart Study.[6,8]

animals have a higher heart rate and shorter lifespan than do larger[28–30] (*Figure 2*). The average number of heart beats per lifetime in mammalians is unexpectedly constant within one order of magnitude, $7.3 +/- 5.6 \times 10^8$ despite a >40-fold difference in longevity (*Figure 3*). As a corollary, the basal energy consumption per heart beat and heart mass may be the same for all animals. This suggests that the life span is predetermined by the basic energetics of the living cells, and that the apparent inverse relation between life span and heart rate reveals the heart rate to serve as a marker of the metabolic rate. This may be exemplified by considering the vast range of physiological cardiac parameters between one of the smallest, the shrew weighing 2 g, and the largest extant mammalian, the blue whale of 100 000 kg (*Table 2* with data compiled from Dobson[31]). Despite a difference of many millions in body weight, heart weight, stroke volume, and total blood pumped per lifetime, the total oxygen consumption and ATP usage per unit mass and lifetime are almost identical together with the total number of the heart beats per lifetime.

Only humans make an exception to the rule by living longer and thus accumulating a larger mean number of heart beats of around 30×10^8 per lifetime (*Figure 3*). One might speculate how modern humans have stretched the biological boundaries by pushing the life expectancy to 80 years and beyond. The most likely explanations may be changes in life-style, drugs (in particular, antibiotics), prevention, and nutrition.[28] However, the question should still be raised: does the RHR causally determine the life span, or is it only an epiphenomenon?

Table 1 Main studies on high RHR as cardiovascular risk factor

Reference	Study population subset(s)	Study name	Year
CAD			
Wong *et al.*[20]		Framingham	1989
Disegni *et al.*[4]		SPRINT	1995
Copie *et al.*[1]			1996
Hathaway *et al.*[5]		GUSTO-I	1998
Diaz *et al.*[3]		CASS	2005
General population			
Dyer *et al.*[2]		Chicago	1980
Kannel *et al.*[6]		Framingham	1985–87
Gillum *et al.*[19]		NHANES I	1991
Filipovsky *et al.*[16]		Paris Prospective	1992
Shaper *et al.*[21]		British Men Study	1993
Goldberg *et al.*[22]		Framingham	1996
Benetos *et al.*[9]		French IPC	1999
Jouven *et al.*[23]		Paris Prospective	1999
Kristal-Boneh *et al.*[15]		CORDIS	2000
Seccareccia *et al.*[17]		MATISS	2001
Hypertensive individuals			
Benetos *et al.*[9]		French IPC	1999
Gillmann *et al.*[8]		Framingham	1993
Thomas *et al.*[10]		French IPC	2001
Female gender			
Perk *et al.*[25]		Jerusalem 70-year-old Longitudinal Study	2003
Diaz *et al.*[3]	+CAD	CASS	2005
Diaz *et al.*[3]	+diabetes	CASS	2005
Chang *et al.*[26]	+elderly	Women's Health and Aging Study I (WHAS I)	2003
Gillman *et al.*[8]	+arterial hypertension	Framingham	1993
Palatini *et al.*[11]	+elderly +arterial hypertension	Syst-Eur	2002
Elderly			
Aronow *et al.*[27]			1996
Palatini *et al.*[14]		CASTEL	1999
Menotti *et al.*[13]		FINE	2001
Benetos *et al.*[12]		French IPC	2003
Palatini *et al.*[11]	+arterial hypertension	Syst-Eur	2002

High RHR: genetics vs. environmental factors?

The last decade has witnessed key discoveries on mechanisms leading to isolated high RHR. Singh *et al.*[32] highlighted

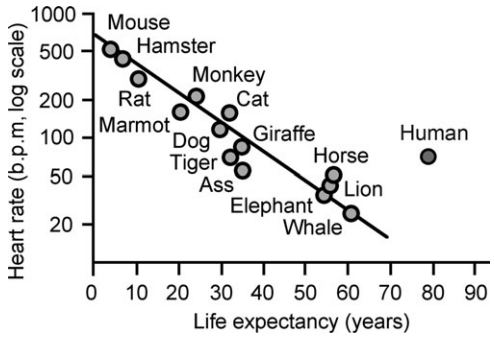

Figure 2 Inverse linear relation between RHR and life expectancy in mammals and humans. Redrawn from Levine[28] with permission from American College of Cardiology Foundation.

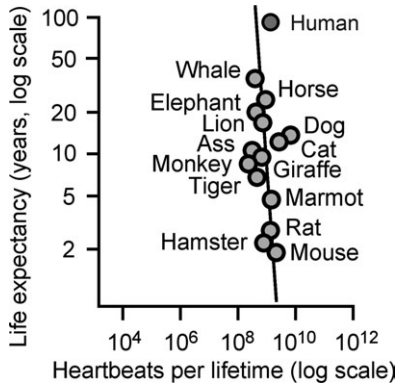

Figure 3 Relation between life expectancy and total heart beats per lifetime in mammals and humans. Redrawn from Levine[28] with permission from American College of Cardiology Foundation.

Table 2 Cardiac parameters of one of the smallest and one of the largest living mammalians

Parameter	Shrew	Blue whale	Fold difference
Body weight	2 g	100 000 kg	50 000 000
Heart weight	12 mg	600 kg	50 000 000
Heart weight over body weight	0.006	0.006	1.0
Heart rate per minute	1000	6	170
Life span (years)	1	118	118
Heart beats per lifetime	6.6×10^8	11×10^8	1.7
Stroke volume (litres)	1.2×10^{-6}	350	300 000 000
Cardiac output (litres per min)	0.001	2098	2 200 000
Total blood pumped per lifetime (litres)	800	1.3×10^{11}	163 000 000
Blood pumped (litres) per lifetime per kg heart	6.7×10^7	22×10^7	3.3
Total oxygen consumption (litres per kg per lifetime)	35 000	39 300	1.1
Moles ATP per kg per lifetime	7813	8771	1.1

Data of column one and two were collected from Dobson.[31]

the contribution of genetic factors as a substantial determinant of RHR. Heritability analyses have been done by studying correlations between siblings and between spouse pairs after adjusting for important covariates within the Framingham Heart Study. They estimated the heritability of RHR to be 21%, which was similar to the subsequent report by Martin *et al.*'s[33] estimate of 26%. Using a candidate gene approach for looking at the genetic determination of RHR, Ranade *et al.*[34] found a ser49-to-gly (S49G) polymorphism in the beta-1 adrenergic receptor (ADRB1) associated with RHR. Serine homozygotes subjects had the highest mean RHR. A finding, which was supported by results from a genome scan study by Wilk for quantitative trait loci influencing RHR in about 1000 Caucasians and 1000 African Americans. Wilk *et al.*[35] (Hypertension Genetic Epidemiology Network-HyperGEN) also demonstrated that the highest logarithm of the odds (LOD) score was detected on chromosome 4. Further investigations by Martin *et al.*[33] from the Metabolic Risk Complications of Obesity Genes project, obtained significant evidence of linkage (LOD = 3.9) for RHR on chromosome 4q, in the same region as for long QT syndrome 4 and within the 1-LOD unit support interval of two candidates: ankyrin-B and myozenin.

So is it only genetics? The response is clearly NO. Singh *et al.*[32] demonstrated (apart from the genetic factors) that environmental causes (body mass index, systolic and diastolic blood pressure, smoking, and alcohol consumption) play at least such a large role in the determination of the RHR/HRV (13–40% vs. 13–23%). Martin *et al.*[33] observed that individuals (especially females) with elevated RHR exhibited significantly elevated insulin and glucose levels, waist circumference, BMI, and diastolic blood pressure and suggestively elevated triglyceride levels and systolic blood pressure, all different clusters from the well known insulin resistance syndrome.[36,37] The question is, therefore, whether high RHR also represents a member of this family. In line with these findings, recent studies have contributed importantly to generate the new concept that a defect in 'bioavailability' of nitric oxide (NO) plays a central role in the pathogenesis of this disorder. Interestingly, NO has been implicated in autonomic regulation of various aspects of cardiovascular system and could, thus, be the missing link between metabolic syndrome and high RHR (for review, see Sartori *et al.*[38]). In the coronary arteries, NO participates in parasympathetic vasodilation[39] and inhibition of its sympathetic vasoconstriction.[40] NO also modulates myocardial contractility in response to both cholinergic[41,42] and beta-adrenergic stimulation.[43] More importantly, NO is considered to modulate the autonomic control of heart rate, and, thus, RHR. Studies in humans suggest that NO augments cardiac vagal control in healthy subjects, as well as in patients with heart failure.[44] Studies in animals established that this effect was mediated by the neuronal isoform of NO synthase (nNOS): mice (intact animals or isolated atria harvested from such animals) with complete deletion of

the gene display impairment in the parasympathetic control of heart rate.[45,46] So, is high RHR an epiphenomenon of the same spectrum of disease, yet known as metabolic syndrome?[47] The answer is probably affirmative.

Because virtually all widespread 'common' diseases, such as diabetes or hypertension, result from the complex interaction of genetic susceptibility factors and modifiable environmental factors, one should postulate that this is also the case for the pathogenesis of elevated RHR. In line with this concept, animals fed with high-fat diet (unfortunately a not-so-infrequent diet in humans) rapidly develop a loss of nocturnal dipping of both blood pressure and heart rate[48,49] and then all the pattern of metabolic syndrome. This effect is exaggerated in animal with NO deficiency,[36,37,50] but could also happen with other gene deficiency, as demonstrated by $PPAR_{\gamma}$ conditional E-null mice.[51]

HR-lowering therapy on the myth of eternal youth

If heart rate conditioned the fate of basal energy consumption and that the total energy per life is predetermined, life span should depend on heart rate (as in everyday chassis battery): average (battery) life has become shorter as energy requirements have increased. Taking advantage of this theory, techniques aiming to lower RHR should increase the life span. In wildness, hibernation acts in this way: hibernation markedly lowers RHR and prolongs life. For example, hibernating bats' heart rate decrease by 45-fold to 10–20 b.p.m. Hibernating bats live 70% longer (39 vs. 23 years) than its non-hibernating counterparts.[52] In humans, modification of coronary heart disease risk factors play a key role in the control and alteration of the atherosclerotic process. Because hibernation is hardly possible (although some failed attempts have been reported[53]), we should know whether artificial lowering of an abnormally high heart rate (resting and non-resting) will aid primary and secondary prevention of coronary heart disease and, thus, decrease its related mortality. Exercise is a well-known intervention to lower RHR and increase survival. In the long term, endurance training increases parasympathetic activity and decreases sympathetic activity in the human heart at rest. These two training-induced autonomic effects, coupled with a possible reduction in intrinsic heart rate, decrease RHR. Interestingly, regular exercise training and RHR were strongly correlated with late survival in elderly patients from the French IPC-Study.[12]

In CAD patients, reducing heart rate is a generally accepted treatment modality; it directly minimizes the myocardial oxygen demand and enhances its supply by improving subendocardial blood flow.[54,55] Moreover, it may reduce the risk of plaque rupture[56] and decrease the risk of sudden cardiac death after myocardial infarction. In both animal and human, the anti-ischaemic benefits of beta-blockade can be abolished by atrial pacing,[57,58] which argues for an important role of heart rate control in the positive effects of this class of drug. In addition, the favourable effects of beta-blockers (BB) on mortality in CAD patients are at least partially mediated to their HR-lowering effects.[59–61]

In patients with chronic heart failure (CHF), rate-lowering therapies have shown to reduce both the morbidity (risk of hospitalization) and the mortality.[62–66] Multivariate analysis of CIBIS II showed that under beta-blockade, larger the discard of RHR was associated with, higher the survival and freedom of hospital admissions.[67]

Should we prescribe HR-lowering drugs to patients with high RHR, but without known CAD or CHF?

In the general population, a pulse rate higher than 90 b.p.m. may be harmful. So, should we treat it with the same strength as other components of the metabolic syndrome (hypercholesterolemia, arterial hypertension, or obesity)? To date, no human study has been performed to demonstrate the efficacy, the risk-benefit ratio, or even less, the cost-effectiveness of heart-rate lowering treatment in patients without cardiac disorders. Few evidences exist, however, based on animal studies. In monkeys, heart rate reduction by sinoatrial node ablation[68,69] or administration of propranolol[70] is associated with a noticeable reduction of atherogenesis. In mice, administration of digoxin slowed the heart rate and prolonged the life span.[71]

In humans, how should we currently manage high RHR? Since it could unmask hypoxaemia, anaemia, alcoholism, chronic stress or depression, or be the consequence of already prescribed drugs, a careful investigation should be done to exclude and, if necessary, treat secondary causes. Furthermore, lifestyle changes should be recommended with special emphasize on preventing anxiety, stress and toxics (caffeine, alcohol, nicotine, amphetamines, or cocaine), screen for drugs (hydralazine, thyroid hormones, catecholamines, aminophylline, etc.), and prescribe exercise or rational behaviour therapies. For instance, one should consider that pet ownership can lower RHR.[72]

Besides the BB, some of the calcium channel blockers (CCB), such as diltiazem and verapamil (non-dihydropyridines), also potently reduce the heart rate. BB reduce both RHR and the response of the heart rate to exercise. The reduction of heart rate by BB is accompanied by a decrease in peripheral blood pressure with consequently reduced cardiac oxygen consumption and a longer diastolic filling time allowing for increased coronary perfusion. BB have consistently been shown to reduce cardiovascular mortality, sudden cardiac death, and reinfarction in patients recovering from previous infarction[61,73,74] (*Figure 4*). In common with BB, the CCB of the non-dihydropyridine type also lower the heart rate and blood pressure as well as the risk of reinfarction. In principle, both classes of drugs operate by lowering the intracellular calcium signalling (although by different mechanisms), reduce conductance velocity and cardiac inotropism.[73,74] Since it is known that the heart rate is primarily determined by the hyperpolarization-activated cation current, termed If (f stands for funny because of its unusual activation by hyperpolarization at voltages in the diastolic range), Ih or Iq, the search for drugs that reduce the heart rate without the aforementioned unwanted effects of BB or CCB is going on. In the heart, the pacemaker current is carried by a family of hyperpolarization-activated, cyclic adenosine monophosphate (cAMP)-mediated cation channels (HCN1–HCN4, cloned in the late 1990s) in the sinoatrial node.[75] HCN4 is the main isoform in the heart with smaller amounts of HCN1 and HCN2.

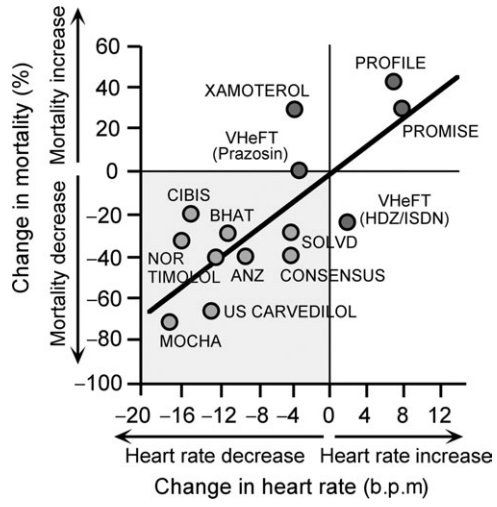

Figure 4 Effect of variations in RHR on cardiovascular mortality in several studies on heart failure. Generally, those studies with an increase in heart rate (positive inotropic substances) augment mortality, whereas those with a decrease in heart rate (ACE-inhibitors or BB) reduce mortality. PROFILE, Prospective Randomized Flosequinan Longevity Evaluation Study; XAMOTEROL, Xamoterol in Severe Heart Failure Study; PROMISE, effects of oral milrinone on mortality in severe chronic heart failure; VHeFT, Vasodilator-Heart Failure Trials; CIBIS, Cardiac Insufficiency Bisoprolol Study; BHAT, Beta-blocker Heart Attack Trial; SOLVD, effect of enalapril on mortality and development of heart failure in asymtomatic patient with reduced LV ejection fractions; NOR, Norwegian Study Group: TIMOLOL, induced reduction in mortality and reinfarction; ANZ, Australia–New Zealand Heart Failure Research Collaborative Group; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; US CARVEDILOL, United States Carvedilol Heart Failure Trials; MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment. Redrawn from Kjekshus[77] with permission.

These channels carry either an inward current (mainly Na^+) at strongly negative (−80 mV) or an outward current (mainly K^+) at mildly positive voltage (+5 mV) inducing membrane depolarization following the action potential. By mediation of cAMP their activity is subject to beta-adrenergic regulation. Mutations in HCN4 have recently been found in patients with idiopathic sinus node dysfunction.[76] Of several drugs tested, ivabradine proved to be the most specific without almost any noticeable side effects. Ivabradine specifically inhibits the HCN4 channel in the open state displaying pronounced 'use dependence'.[77] This latter property supports its therapeutic effectiveness, since with higher heart rate more channels are open and might, thus, become inhibited by the drug. Ivabradine is presently in phase-III clinical tests and may soon become available.

In conclusion, because current evidences are enough to demonstrate its efficacy, drugs that lower heart rate should be prescribed in patients with myocardial infarction, diabetes mellitus, and/or heart failure. In hypertensive patients, an approved consensus has been published recently by Palatini *et al*.[7] This publication presents a comprehensive review of clinical significance and prognosis of RHR as independent cardiovascular risk factor, especially in subsets of patients, such as women and elderly, its measurement and its management.

Lastly and because, to date, it is not known whether any drug-induced diminution of heart rate will efficiently extend life expectancy, heart rate reduction should be left to physician's discretion, hoping that large-scale, multicentre, double-blinded, placebo-controlled clinical studies will address this issue.

Conflict of interest: none declared.

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Clinical vignette

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Incidental finding of a ruptured thin-cap fibroatheroma by optical coherence tomography

Owen Christopher Raffel and Ik-Kyung Jang*

Cardiology Division, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, GRB 800, Boston, MA 02114, USA

*Corresponding author. Tel: +1 617 726 9226; fax: +1 617 726 7419; *E-mail address*: ijang@partners.org

A 61-year-old male with stable exertional angina presented for elective percutaneous treatment of a left anterior descending (LAD) coronary artery stenosis. Following successful stent deployment, [left coronary angiogram with position of stent demarcated by the two white arrows (Panel A)], optical coherence tomography (OCT) imaging of the LAD artery was performed (LightLab Imaging Inc., Westford, MA, USA). OCT imaging in a region free of significant angiographic stenosis (Panel A, black arrow) revealed a thin-cap fibroatheroma with a ruptured fibrous cap. Panel B shows an OCT image of the plaque with a thin fibrous cap (arrow) measured at 40 μm overlying a central lipid core (L). Another magnified image of the plaque in Panel D clearly illustrates rupture of the thin fibrous cap (arrow). Intravascular ultrasound imaging at the same position (Panel C) demonstrates the plaque (P), but is unable to distinguish any further morphological detail.