Sympathovagal Balance

To the Editor:

A letter is inadequate to rebut fully Eckberg’s destructive and selectively referenced polemic against sympathovagal balance,1 which ignored many prior contributions constructively addressing the same points now raised.

Because RR low frequency (LF) is much reduced by atropine, its relation to sympathetic outflow was questioned. De Boer et al2 explained the origin of LF oscillations as the interaction of fast vagal and slow sympathetic responses, validated by the LF oscillations that follow a single stimulus to the human carotid sinus.3

Eckberg states that there is no evidence that LF power is related to sympathetic nerve traffic. We4 showed that sympathetically reinnervated hearts in transplanted hearts was associated with nonrespiratory LF. Exact quantitative correlations between different sympathetic measures would be surprising.

It was stated by Eckberg that respiratory RR interval variability (high frequency, or HF) “reflects primarily respiratory gating of vagal-cardiac motor neurone responses,” whereas there is much evidence that in conscious humans it represents baroreceptor-driven responses to respiratory blood pressure swings.5,6 During increasing exercise, and also with denervation, nonneural mechanisms, such as sinus node stretch from increasing respiratory fluctuation in venous return, become important contributors to RR HF.7

Fluctuations in nerve traffic were not thought important compared with absolute levels; the widely reported ATRAMI8 studies contradict this view.

The concept of reciprocal changes in sympathetic and vagus nerve output was questioned by citing the diving reflex, in contrast to more physiological states such as standing, arousal, or emotion, in which there is clear reciprocity.

Both HF and LF RR variability are greatly influenced by the gain of the baroreflex.3,5 It is not surprising that LF is paradoxically reduced in exercise and heart failure (despite increased sympathetic drive), because baroreflex sensitivity gain for heart rate control is markedly reduced in these conditions.5,7

Eckberg’s own study showed a “pivotal, largely ignored role for respiration as a determinant of HF spectral power,” but earlier, similar contributions were not quoted.7,10

We agree that heart rate variability (HRV) is complex and highly influenced by respiration7,10 but believe it more productive to explore the causes of HRV and its anomalies rather than attempt to destroy Malliani and Pagani’s early work while ignoring their later contributions.

Finally, despite this quasi-mathematical review, we notice repeated confusion over the units for spectral power (units^2) with spectral power density (units^2/Hz), eg. Figures 2 and 4.

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Sympathovagal Balance: A Reappraisal

To the Editor:

The article by D.L. Eckberg1 will surely promote a florid discussion. Its structure is based on a number of arguments about which our disagreement is substantial.

The term “sympathovagal balance,” belonging to traditional physiology, was introduced by us in the study of heart rate variability (HRV) when we wrote in 1983 that upright posture “is expected to shift the sympathovagal balance toward a sympathetic predominance.”2 Two years later, Pomeranz et al3 wrote that “autonomic control of the heart in response to postural movements strikes a balance between the activities of the parasympathetic and sympathetic nervous system.” After the emphasis provided by Pagani et al4 the term became widely used.

A hypothesis is a highly democratic entity, and its acceptance cannot be imposed. In our mind, like a horizontal beam pivoted at its center, “sympathovagal balance” refers to a reciprocal functional relationship, implying that when 1 of the 2 components of the autonomic outflow is excited, the other is inhibited, according to a central push-pull pattern of organization.

We shall now analyze the major issues of disagreement in the sequence in which they appear in Eckberg’s article.1
Beginning from Figure 1, reproduced from our own work, Eckberg writes: “My integration of the two [low-frequency] spectral powers in this figure suggests that sympathetic spectral power is ≈15% greater than vagal spectral power” and, subsequently, “sympathetic contributions to 0.1 Hz spectral power are only marginally greater than vagal contributions.”

It is hard to understand how this comparison was made. In that experiment, the impulse activities of 2 distinct nerve filaments, unlikely to contain an equal number of active units, were simultaneously recorded with different amplifications, providing 2 variability signals with different variance. In the frequency domain, considering in the Figure the much greater scale of the sympathetic power spectrum density (16×10^4 vs 8×10^4) and the larger area of the sympathetic low-frequency (LF) component, it follows that the sympathetic LF power is at least 1 order of magnitude greater than vagal LF power. Most important, however, is that this comparison of absolute power is not only erroneous but deprived of physiological meaning and, in short, is not a brilliant overture for a “critical appraisal” article.

The Figure was intended by us to show that LF and high-frequency (HF) components are simultaneously present in both sympathetic and vagal discharges, which suggests that both LF and HF components of RR variability are likely to have a mixed origin and that “a rhythm, being a flexible and dynamic property of neural networks, should not necessarily be restricted to one specific neural pathway to carry a functional significance.”

Regarding the subsequent issue raised by Dr Eckberg, the work by Introna et al is also misquoted. Spinal anesthesia, when the spread of spinal block reached the highest thoracic segments (above T3), induced a remarkable abatement of total power of the spread of spinal block reached the highest thoracic segments and the larger area of the sympathetic low-frequency (LF) component, it follows that the sympathetic LF power is at least 1 order of magnitude greater than vagal LF power. Most important, however, is that this comparison of absolute power is not only erroneous but deprived of physiological meaning and, in short, is not a brilliant overture for a “critical appraisal” article.

The next issue is of paramount importance. The article by Pagani et al reporting, as the main finding, a very tight correlation between LF normalized units (nu) of RR and LFnu of muscle sympathetic nerve activity (MSNA) variability was discounted by Eckberg largely because individual regressions were not reported. We had introduced a nonparametric statistical analysis in a previous article in which individual regressions were included. In the article by Pagani et al this was omitted “according to accepted practice” as stated by Koh et al and applied to their own article (see Figure 3 in Reference 9). Saul et al calculated group and individual regressions, presenting only part of the data “for simplicity.”

The Table reports the individual regressions, according to Theil (\(P\) is the probability that regression does not exist), computed from some of the data collected by Pagani et al. In A, regressions are calculated using LF absolute power of RR variability and bursts per minute of MSNA; as in Saul et al, very little correlation is present. In B, regressions are computed using LFnu for both RR and MSNA variability (data reported in the right inferior panel of Figure 6 in Reference 7); a significant correlation is present in 7 of 8 subjects, whereas a clear trend is observed in the remaining subject. Moreover, in B, all \(b\)-coefficients are positive and of similar magnitude, supporting the average correlation \(P<10^{-6}\). In addition, coherence analysis was used to ascertain, individually, the statistical link between oscillations of MSNA, RR, systolic arterial pressure (SAP), and respiration (Figure 7 in Reference 7).

In respect to other differences between the studies by Pagani et al and Saul et al, the following should be stressed: (1) Saul et al normalized their data in the time domain, whereas Pagani et al normalized their data in the frequency domain; (2) as in other studies, we verified that the spontaneous respiratory frequency was clearly separated from LF (see Figure 4 in Reference 7) (metronome breathing does not occur in normal life and, indeed, when the controlled frequency is close to the spontaneous cycle, it substantially increases the HF power, shifting the balance); (3) fast Fourier transforms (FFTs) and autoregressive algorithms do not provide identical results, because only with the latter approach is it possible to perform a spectral decomposition, usually resulting in an LF component greater than that obtained with FFT (see Figure 5 in Reference 11).

The example of the “diving reflex” is not well taken because spectral analysis of HRV seems quite well suited to explore this peculiar interaction between vagal and sympathetic excitatory components. In our hands, cold stimulation of the face or water immersion most often induced a shift of the balance toward vagal predominance, in spite of the emotional arousal that, when prevailing, produces an opposite effect.

Concerning the reciprocal relationship of sympathetic and vagal outflows, we had demonstrated that stimulation of sympathetic afferents reflexly induces, respectively, an excitation or an inhibition of impulse activity of single sympathetic or vagal efferent fibers isolated from the same nerve impinging on the heart. An opposite effect was obtained by stimulating cardiac vagal afferents.

The limitations of spectral analysis of HRV in several physiological and pathophysiological states have always been recognized by the proponents of this approach; however no mention is made of their caution.

Concerning heart failure patients, it is astonishing that Dr Eckberg did not quote the paper by van de Borne et al, companion of Reference 7, in which it was shown that the patients who had no LF component in RR variability also did not present this spectral component in MSNA.

Concerning the effects of graded tilt, why does LFnu or LF/HF correlate better with tilt angle than HF in absolute values?

The remaining issues to be analyzed are still quite numerous. Thus, we shall rather attempt to incorporate them in a more general perspective. In our opinion, what prevails in Eckberg’s view of cardiovascular rhythmicity is a reductionistic model attempting to equate a rhythm to 1 or few reflexes, the sovereign of which is obviously the baroreflex (see, for example, Figure 5 in Reference 1). This view should address the following facts (none of them mentioned by Eckberg): (1) conscious dogs, when quiet and acquainted with the laboratory, most often present only an HF component in RR variability, although an LF component is present in SAP variability, and even though the baroreflexes are known to be extremely active in this species; (2) transient coronary occlusion in the same model elicits a marked increase in LF, probably as a result of an excitatory cardiac sympathetic reflex, which can occur in the absence of arterial pressure changes and which is known to acutely reduce the baroreflex gain; (3) exercising dogs increase their LFnu RR component while abating the baroreflex gain; and (4) some
tetraplegic patients have an LF RR component in the absence of an LF SAP component.\(^\text{16}\)

We think that these are not just details but almost insurmountable barriers against the rigid interpretation of a baroreflex-dependent and vagally mediated LF RR component.

We obviously recognize the possibility that baroreflex mechanisms might participate substantially in the genesis of cardiovascular rhythmicity\(^\text{17}\) but have always questioned\(^\text{8}\) the exclusiveness attributed to them in the genesis of the LF component of RR variability.

In the attempt to contribute to a new way of thinking more adequate to neural complexity, we have advanced a hypothesis based on the interaction of patterns, subserved by multiple reflexes. It is a fact that major neural patterns, like wakefulness and sleep, are characterized by distinct and recognizable rhythmic activities.

What we propose is that in closed-loop conditions\(^\text{5}\), 2 main rhythms, 1 marker of excitation and linked to sympathetic excitation (LF) and 1 marker of inhibition and quiet linked to vagal predominance (HF), would be organized, in physiological conditions, in a reciprocal manner. The recent article by Jasson et al\(^\text{18}\) provides a remarkable demonstration of this hypothesis. Its Figure 4 shows, in the time and frequency domains, a perfect coincidence between an increase of LF, a decrease of HF, a shift of the instant center frequency of the whole spectrum, and an increase of heart rate at the beginning of and during tilt. With this technique, no normalization procedure is necessary, and therefore we think that the reciprocal relationship between LFnu and HFnu might reflect only a simplistic mathematical model\(^\text{1}\) should be removed. This could be an example of how the 2 rhythms constantly interact.\(^\text{5}\)

However, it is also of paramount importance to realize how diffuse these rhythms are. Both LF and HF components were found in the variability of the discharge of single medullary neurons recorded in sinoaortic denervated cats.\(^\text{19}\) In addition, acute spinal cats have an LF component in sympathetic cardiac nerve activity in RR and SAP variability after thoracic dorsal root section, suggesting the existence of an intrinsic spinal rhythmicity, independent even of the spinal afferent input (Montano et al, unpublished data, 1997). In Eckberg’s view, although a sympathetic modulation of the Mayer waves is likely to exist in tetraplegic patients, the LF RR oscillations are due to a vagally mediated baroreflex.\(^\text{1,9}\) Would a simpler hypothesis not be that the LF rhythmicity, intrinsic to the pattern of sympathetic excitation, affects both RR and SAP variability? In this case, the increase in the LF RR component, induced by phenylephrine in quadriplegic patients,\(^\text{1}\) could be due to a sympathetic spinal excitatory reflex\(^\text{20}\) released from baroreceptor restraint.

The similarities between the somatic and the autonomic nervous system have become progressively more evident, especially regarding spinal mechanisms. On this basis, a revision of the somatic integrative properties was recently attempted.\(^\text{20}\) Thus, the comparison with somatic reflexes does not derive from the concept, as criticized by Eckberg,\(^\text{1}\) but from physiology.

The sympathovagal balance is nothing but a concept. Although it is not totally quantifiable (like other useful concepts, such as homeostasis or intelligence), it should be judged for its heuristic value. The normalization procedure was not the result of serendipity but rather a result of this concept. Similarly, LF/HF ratio was proposed\(^\text{3,5,11}\) to assess the fractional distribution of power especially when simpler algorithms were used, such as FFT. The new approach was tested not only with subtractive strategies (ie, atropine administration)\(^\text{14}\) but with observational studies, which usually constitute the main path to the study of neural complexity. We selected patterns well known to exist, such as the sympathetic excitation and the vagal withdrawal during standing, comprising a cohort of reflexes and modified gains. Circadian rhythmicity was another pattern that could be assessed clearly by spectral analysis of recordings obtained with either high-fidelity measurement of arterial pressure or usual Holter devices\(^\text{21}\) (another topic ignored by Eckberg’s article).\(^\text{1}\)

In our last publication,\(^\text{22}\) we demonstrated that body posture (supine or upright) can be predicted in \(\approx 85\%\) of the cases by using 10 spectral variables extracted from short-term series of RR intervals. However, similar results were also obtained using only 3 variables, ie, RR, LFnu, and HFnu. Inconsistent results were provided when only 2 variables were used, including RR and HF in absolute units (ie, the 2 variables considered by Eckberg to carry the relevant information). This accomplishment is probably the best answer to Eckberg’s skepticism.

Regarding our language (an aspect analyzed throughout 42 lines of text), we think that the metaphor comparing “RR-interval fluctuations” to “ripples on a sea of varying depths”\(^\text{1}\) is more remote from physiology than the flexor-extensor interaction.\(^\text{5}\) But it is a fact that any new way of thinking has to generate its own language.

To the warning that “calculations of sympathovagal balance may obscure rather than illuminate human physiology and pathophysiology”\(^\text{1}\) we would like to reply that this concept might instead have furnished the Rosetta stone that made decipherable the puzzle of the rhythmic components of HRV.

Finally, because the Task Force article\(^\text{11}\) still represents the only document on HRV endorsed by an international panel of experts in the various fields, its complete disregard requires some reliable explanation for the scientific community.

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**Sympathovagal Balance: A Critical Appraisal**

*To the Editor:*

With interest, I read Dr Eckberg’s review,1 but some of his views need clarification. There are 2 principal methods for spectral analysis of heart rate variability (HRV) that differ in the determination of spectral components. Either integrals of power spectrum density over specific bands or automatic determination of spectral components. Either integrals of power or automatic autoregressions. The assumption that spectral frequency components as integrals of specific bands are equal to their automatic autoregressions is an unsound speculation; I would be very surprised if it were not wrong. Consequently, the claims that some results by Dr Pagani et al (Reference 4 and others) are unreproducible are unfounded. Dr Eckberg compares these studies with investigations (Reference 5 and others) that used data obtained under similar circumstances but analyzed them differently.

There are numerous difficulties in the interpretation of any spectral analysis of biological data. These technologies were mathematically and technically developed for different purposes, and we conveniently ignore the mathematical premises of spectral methods that are very frequently, if not always, unfulfilled. Therefore, it is not too extreme to speculate that the high- and low-frequency components obtained with 1 method have, in some cases, different physiological interpretation than the results of the other method. Indeed, the discrepancy pointed out by Dr Eckberg points precisely in this direction.

Dr Eckberg will surely agree that it is more important to realize the unknown rather than dismiss it because it does not fit our theories. A study comparing the 2 approaches and studying the effects of ignoring some presumptions of spectral methods is very much needed. Only when we understand what the differences in technology mean will the comparisons attempted by Dr Eckberg be possible.

Finally, I find it difficult to understand why Dr Eckberg (for whom I have a high regard) proposes that the study by Pagani et al was not conducted properly. Such an approach to criticism will not help us obtain a consensus between research groups that is badly needed.

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**Response**

I thank my friends for their thoughtful responses to my article. The legend to Figure 5 of the article by Malliani et al1 states that “A predominant low frequency (LF) characterizes RR and SND [sympathetic neural discharge] autospectra, whereas a greater respiratory high-frequency (HF) component is present in VND [vagal nerve discharge].” Introna et al2 showed that high spinal anesthesia does not reduce absolute LF RR-interval spectral power, and van de Borne et al3 showed that normalized LF RR-interval spectral power is low notwithstanding high sympathetic nerve activity in heart failure patients. Both studies undermine the view that LF RR-interval fluctuations reflect sympathetic-cardiac nerve traffic.

I did not cite literature critical of “sympathovagal balance”4–6 because I focused on physiology. The observation by Brown et al7 that tidal volumes and breathing rates are rarely controlled in
heart rate variability studies is unique. I cited more recent than old studies from the Milan group. Highly variable, positive, synchronous, or negative systolic pressure–RR-interval phase relations \(^8\) and reductions of arterial pressure fluctuations by fixed-rate atrial pacing \(^9\) argue against a baroreflex explanation for respiratory frequency autonomic rhythms. Badilini et al. \(^10\) reported good correlations between autoregressive and fast Fourier transform power spectra during upright tilt.

Malliani’s criticism that I made no mention that his group has recognized limitations of "sympathovagal balance" is unfair. In my review, \(^11\) I said that "The sympathovagal-balance literature is replete with assertions that spectral power reflects fluctuations, not absolute levels of autonomic nerve traffic."

Use of models imposes philosophy on physiology. The “sympathovagal balance” model holds that baseline LF/LF \(^1\) arrhythmia. \(^14\) In this case, the model is wrong in positing shifts from vagal to sympathetic; however, this shift is due entirely to reductions of vagally mediated respiratory sinus arrhythmia. \(^14\) In this case, the model is wrong in positing proportionality between LF RR-interval fluctuations and sympathetic nervous traffic. The model implicitly requires that reciprocal vagal and sympathetic changes be expressed equally; however, any vagal activity may prevent expression of sympathetic responses. \(^15\)

For my part, I prefer actual measurements to calculations based on theories about how the autonomic nervous system works. For example, if I were given some measure of absolute respiratory frequency RR-interval fluctuations, I could draw my own conclusions about whether the higher levels of LF/LF + HF reported in hypertensive \(^16\) and postinfarction \(^17\) patients reflect “sympathetic predominance,” as proposed, or merely reduced vagally mediated respiratory sinus arrhythmia.

I disagree that it is wrong to criticize science; debate of scientific issues is integral to the process of doing science. Scientific debate has intrinsic merit, independent of outcome. Authors who advance new ideas deserve great credit; the ideas themselves deserve close scrutiny.

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A Call for Professional Stenting: The Balloon Is Dead and Buried! To the Editor:
We read with interest the article by Narins et al entitled “A Call for Provisional Stenting: The Balloon Is Back!” but do not agree with their faint-hearted view about primary use of coronary stents.

First, in-stent restenosis is not a malignant disease. In a prospective study, Bauters et al. demonstrated, in addition to a very low (25%) restenosis rate after stenting, that most patients (64%) with in-stent restenosis could be effectively and easily treated with repeat percutaneous intervention, with a very low (22%) angiographic restenosis rate and a target- vessel revascularization rate of 17% at 6 months.

Next, the efficacy of stenting in lesions that, by design, were excluded from the STRESS and BENESTENT trials, namely, in restenotic lesions (REST), venous bypass grafts (SAVED), chronic total occlusion (SICO), and acute myocardial infarction (PAMI Stent Pilot), is being demonstrated. Evaluation of stenting in small vessels, long lesions, and other subsets is under way.

Third, the economic costs of stenting can be reduced by many methods (eg, market competition, generic stents, and homemade stents). We believe that a small piece of metal should be more cost-effective than sophisticated adjunctive equipment, such as intravascular ultrasound probes or Doppler flow wires, and than expensive drugs such as glycoprotein IIb/IIIa blockers.

Fourth, long-term data exist to confirm the lack of late sequelae associated with permanent implantation of metallic devices in the coronary wall. Late improvement in luminal diameter appears to occur even as much as 6 months to 3 years after implantation. The first self-expanding and balloon-expandable stents were implanted >10 years ago without any reported late sequelae.

Finally, even if the strategy of planned stent placement has not yet been documented to be superior to one of aggressive balloon angioplasty with provisional stenting in all patient or lesion subsets, coronary stenting, a revolutionary breakthrough, has already become the predominant means of coronary revascular-
ization at the end of this century. Waiting for early recoil for 30 minutes after balloon dilation is certainly a good idea, but because restenosis after balloon angioplasty is mainly due to late remodeling, an alternative and more scientific option would be to leave the patient in the catheterization room for 6 months!

In this era of cost containment, environmentally friendly materials, and low-fat, cholesterol-free, and sugar-free foods, metal-free coronary intervention is certainly politically and ecologically correct, but stent implantation is probably the best way to get a “stentlike” result.

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**Response**

In general, the field of interventional cardiology has distinguished itself from other procedurally based disciplines in demanding that new devices, pharmacological therapies, and strategic approaches be subjected to properly controlled clinical trials before entering into widespread use. We therefore remain intrigued by the seemingly zealous fervor with which many practitioners, apparently on the basis of the allure of the immediate angiographic results and the ease of implantation, support a policy of universal stent implantation. Corcos et al, in their appeal for universal stenting, appear to have misinterpreted and overlooked several important recent studies.

First, in-stent restenosis does indeed remain a highly problematic entity. Despite the study of Bauters et al in which only 22% of 103 patients treated for in-stent restenosis developed recurrent restenosis,1 among 10 other series involving >600 patients who underwent percutaneous recanalization for in-stent restenosis, recurrent restenosis occurred in 44% (range, 30% to 72%).2 It is ironic, in light of the claim by Corcos et al that in-stent restenosis is “not a malignant disease,” that we have been forced to enlist the aid of radiation oncologists to approach this condition.

Second, in-stent restenosis remains all too common in the setting of complex (non-STRESS/BENESTENT) lesion types, which constitute the majority (≈80%) of lesions encountered in clinical practice. In the SAVED trial,2 routine stent implantation for vein graft lesions was not associated with a significant reduction in the primary end point of angiographic restenosis compared with balloon angioplasty. In the REST trial of restenotic lesions, patients in the balloon angioplasty arm in whom “stent-like” results were achieved had an identical low rate of clinical restenosis as patients treated with stent implantation.4 Recently reported 30-day results from the PAMI stent trial demonstrated a trend toward more frequent restoration of TIMI-3 flow in balloon angioplasty versus stent-treated patients in the setting of acute myocardial infarction. Furthermore, among >2000 patients reported in several series of long stents (>15 mm) or multiple stent implantation, in-stent restenosis developed in 36.7%.2

Additionally, contrary to the supposition of Corcos et al, 30-day data from the 2399-patient EPILOG-stent trial strongly favors a strategy of provisional stenting with adjunct IIb/IIIa receptor antagonists. Compared with patients assigned to planned stent placement with placebo, the strategy of balloon angioplasty with abciximab was associated with significant reductions in myocardial infarction (5.3% versus 9.6%, P = 0.001) and major adverse cardiac events at 30 days (6.9% versus 10.8%, P = 0.007) despite a remarkably low (19%) use of provisional stenting. Restenosis and cost-effectiveness data are forthcoming.

As practicing interventional cardiologists, we are aware of the angiographic allure of stent implantation, especially in the presence of long stenoses or diffuse coronary disease. However, given clear improvements in the results of balloon angioplasty, with the availability of stents as backup devices, the presence of provocative early randomized data suggesting that a strategy of provisional stenting may yield short- and long-term results equivalent to universal stenting, and the still unsolved issues of in-stent restenosis and the costliness of stenting, we hope, in the proud tradition of interventional cardiology, that the optimal strategy for stent use is determined by properly designed trials rather than passionate hyperbole.

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**On the Relationship Between Cholesterol Lowering and Coronary Disease Event Rate**

*To the Editor:*

Dr Grundy’s editorial published in the April 21, 1998, issue of this journal1 provides an insightful summary of the reevaluations of the databases from the major statin trials (CARE, 4S, and WOSCOPS). These studies provide apparently divergent interpretations of the relationship between cholesterol lowering and coronary benefits experienced by study subjects. In his review, Dr Grundy elaborates on all 3 possible scenarios on the relationship between cholesterol lowering and clinical benefits: a linear model, a threshold model, and a curvilinear model. Whereas data from 4S seem to support the concept of a curvilinear relationship between cholesterol reduction and relative risk reduction, the analyses of the CARE3 and the WOSCOPS4 trials support the notion of a linear relationship up to a threshold level beyond...
which no further benefits are detected for further reductions in plasma cholesterol.

Advocates of the possibility of a linear relationship between cholesterol reduction and relative risk of coronary heart disease are not based on biologically plausible bases. If the relationship were indeed linear, there would be a degree of plasma cholesterol reduction that would eliminate the risk of coronary heart disease almost completely. This is not expected to be the case with a multifactorial intervention (ie, cholesterol lowering), which, although effective, is bound to have a limited power in situations in which the global coronary risk is contributed by more than just hypercholesterolemia (eg, hypertension, diabetes, smoking, family history, and age). The 2 other models both are biologically plausible, and possibly both are biologically true. Perhaps the apparently divergent results of 4S and WOSCOPS are both valid and can be unified in a single system. We propose that the beneficial effects of cholesterol lowering are a function of baseline event rate of coronary heart disease in the population studied and of the differential between baseline rate and the ideal event rate for the average patient enrolled in the study. For example, in a primary prevention trial like WOSCOPS, in which the event rate in the placebo group was on the order of 8% in 5 years, the outstanding initial effects of cholesterol lowering may rapidly reduce the patient’s risk to a minimum level set by the presence of other modifiable or nonmodifiable risk factors. In the case of WOSCOPS study subjects, this level could be ≈1% per year. Conversely, when the rate of major coronary events is much higher, as was the case in the 4S study (5% per year), the benefits of cholesterol lowering will not be masked by the threshold effect because of the large distance between baseline risk and minimum risk. Thus, the shape of the curve may be determined by the baseline risk in the population being studied.

Although we agree with Dr Grundy that post hoc analyses must be evaluated with caution, it is also true that when these analyses provide us with results that are in line with our expectations, we accept them less critically than when they challenge us with unexpected information. We believe that the subanalyses of major statin trials provide us with an additional point of practical relevance in our dealing with patients: it is possible that a 25% reduction in LDL will produce the maximum benefits in low-risk patients, whereas aggressive reductions in LDL to the levels recommended by the National Cholesterol Education Program Adult Treatment Panel II guidelines, or beyond, would be beneficial in high-risk hypercholesterolemic patients.

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**Response**

Drs Fazio and Linton raise interesting and important issues about the subgroup analyses of the major statin trials. They speculate that progressive lowering of serum LDL-cholesterol levels must reach a point of diminishing returns in coronary heart disease (CHD) risk reduction, otherwise the complete elimination of LDL from the circulation would drop risk to zero. On the other hand, it is possible that progressive lowering of LDL could produce a continuous lowering of risk such that when LDL levels approach zero, an irreducible baseline of risk is reached. Therefore, the linear model cannot be rejected out of hand. Importantly, logic alone or review of existing literature cannot determine the shape of the relationship between LDL-cholesterol levels and CHD risk reduction, whether linear, curvilinear, or threshold. On the basis of analogy to large epidemiological studies, I speculated that a curvilinear (log-linear) relationship is the most likely, but the final answer must await new clinical trials that are designed to specifically address this issue. It is my view that the accumulated evidence from recent clinical trials, angiographic trials, and epidemiological studies makes a strong case for a target goal for LDL cholesterol in secondary prevention of ≤100 mg/dL. Implementation of therapy to achieve this goal will ensure that most patients with established CHD will receive aggressive cholesterol-lowering therapy; the recent statin trials also make a good case for using statins (or other cholesterol-lowering drugs) in most CHD patients, regardless of baseline LDL-cholesterol levels. Because of the striking risk reduction achieved from statin therapy in patients with established CHD, the major concern at present must be that of inadequate cholesterol management, either from failure to initiate cholesterol-lowering therapy or from insufficient LDL lowering.

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Sympathovagal Balance: A Critical Appraisal
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