Inhaled NO and Pulmonary Vasodilation

To the Editor:

Hare et al.\textsuperscript{1} concluded that inhaled nitric oxide (NO) caused selective pulmonary vasodilation in patients receiving left ventricular assist device support and that this accounted for the increase in mean left atrial pressure, which they considered a beneficial hemodynamic effect.

The evidence for pulmonary vasodilation was that pulmonary vascular resistance (PVR) decreased. However, pulmonary vasodilation (an observable quantity) and decreased PVR (a calculated quantity) are not synonymous, and either can exist in the absence of the other: PVR (dynes \cdot s \cdot cm\textsuperscript{-5}) = 80 \times (\text{Mean Pulmonary Artery Pressure} – \text{Mean Left Atrial Pressure}) / \text{Cardiac Output}.\textsuperscript{2}

In their patients whose mean pulmonary artery pressure (in mm Hg) and cardiac output (in liters per minute) were fixed, NO increased left atrial pressure and left ventricular filling pressure while it decreased stroke volume index, a negative inotropic effect.\textsuperscript{1} In the present study, the increased left atrial pressure also resulted from increased left ventricular filling pressure. The above standard equation for PVR omits Poiseuille’s factor for the radius of the tubes and calculates decreased PVR independent of the radius of blood vessels.

In other patients, assisted by left ventricular assist devices as NO was inhaled, left ventricular assist device output was increased, thereby increasing the denominator to give a lower calculated PVR, again without invoking vasodilation.

What prevents NO from dilating pulmonary blood vessels in patients who have severe heart failure is the high blood concentration of norepinephrine in this condition.\textsuperscript{4} Hare previously reported that the rise in left atrial pressure resulting from NO was greatest in the patients who had the lowest left ventricular failure.\textsuperscript{1} These were also the patients who had the highest blood levels of norepinephrine and were most susceptible to further ventricular impairment.

The observations in this article are valuable. However, instead of showing that inhaled NO dilated pulmonary blood vessels and thereby gave beneficial hemodynamic effects, this study showed that NO impaired the ventricular contractions in these patients. The authors had it right the first time.\textsuperscript{3}

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3. Hare JM, Loh E, Craeger MA, Colucci WS. Nitric oxide inhibits the contractile response to \textbeta\textsubscript{2}-adrenergic stimulation in humans with left ventricular dysfunction. \textit{Circulation.} 1995;92:2198–2203.


Response

We thank Dr Krohn for his comments. Dr Krohn’s argument that inhaled NO did not act as a pulmonary vasodilator is somewhat semantic. Although calculated vascular resistance is not synonymous with the diameter of a blood vessel,\textsuperscript{1} it is a widely used and clinically validated estimate of vascular tone. The standard equation for resistance (R) does not omit Poiseuille’s factor for the radius of blood vessels. Rather, there are two ways to calculate hydraulic resistance:

\[ R = (P_i - P_o) / \text{Flow} = 8\eta / \pi r^4 \]

where \( P_i \) and \( P_o \) are the input and output pressures, respectively, \( \eta \) is the fluid viscosity, \( l \) is the length of the tube, and \( r \) is its radius.\textsuperscript{2} Thus, fluid viscosity, length, and radius are the determinants of resistance using Poiseuille’s equation, whereas pressure gradient and flow are its determinants, using the Ohm’s law–derived formula.

Flow, therefore, is proportional to radius to the fourth power given fixed tube length and fluid viscosity, and in the absence of “vasodilation” or decreased vascular tone, flow increases must be compensated for by an increased pressure gradient. In the intact vasculature, increases in flow reflect, to a large extent, dilatation of distal arterioles, also termed resistance vessels.\textsuperscript{1,2} In some circuits, notably the pulmonary, recruitment of collapsed arterioles may also contribute to increases in flow in the proximal conduit vessels.\textsuperscript{3} This mechanism, in the absence of an increase in pressure gradient, would also be considered vasodilation because effective radius has increased.

In our study, we measured total flow and the pressure gradient across the pulmonary circuit. Although we had the unique ability to control the total blood flow in our patients using the left ventricular assist device (LVAD), we did not control pulmonary arterial or left atrial pressures. Total blood flow was maintained constant (fixed LVAD mode) or allowed to respond to changes in vascular distribution (automatic LVAD mode). The comparison in our study was between the same patients with either fixed or variable blood flow. Variables such as circulating catecholamines were controlled for in the study design because the same patients were studied consecutively.

In our study, mean pulmonary arterial pressures did not increase with either fixed or variable flow. Transpulmonary gradient narrowed only in patients with fixed flow and was due to a rising left atrial pressure. The best explanation for an increase in blood flow that is not associated with an increase in transpulmonary gradient is that pulmonary arterial pressure is vasodilation (as observed in the automatic-mode group). Similarly, transpulmonary gradient lowering with fixed pulmonary arterial pressure and blood flow also reflects vasodilation (as observed in the fixed-mode group). If ventricular impairment were the explanation for the rising left atrial pressure in patients in the fixed mode, this would have been associated with a concomitant rise in pulmonary arterial pressure and a fixed transpulmonary gradient.

Thus, we concluded, as we did in our previous study,\textsuperscript{4} that NO is a pulmonary vasodilator in patients with severe heart failure. Although selective pulmonary vasodilation is beneficial in LVAD patients who can respond with increased systemic flow, it may not be beneficial in heart failure because of the increased left atrial pressure.

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Vasopressin Deficiency and Vasodilation of Septic Shock

To the Editor:

The article by Landry et al entitled “Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock” (\textit{Circulation.} 1997;95:1122–1125) is original and provocative in its findings of apparently low plasma vasopressin concentration in septic shock, coupled with the observation that infusion of vasopressin rapidly
restored arterial pressure. Two points can be made regarding the conclusions and subsequent speculation about the reason for low vasopressin levels in this setting. First, the data obviously do not establish an actual contributing role for diminished arginine vasopressin levels in the hypotension of the syndrome, only that levels are low and infusion of vasopressin restores blood pressure. This observation may have therapeutic, not mechanistic, implications because, as noted by Dr Reid in the accompanying editorial, infusion of other peptides might have had similar effects. Second, although autonomic or baroreceptor dysfunction is postulated to account for the low arginine vasopressin levels, the explanation may in fact be due to the hemodynamics of septic shock coupled with normal baroreflex function. The sinoatrial baroreceptor is the dominant component of the afferent limb for nonosmotic arginine vasopressin secretion in humans. These receptors respond to stretch, and pukalite load may be a factor in governing their discharge frequency; although mean arterial pressure is frequently the only variable cited. There is evidence that pukalite load, especially at lower pressures, is associated with greater inhibitory effects on sympathetic activity than comparable levels of pressure with a static load; the same physiology may well apply for vasopressin secretion, because the pathways are closely related. In this regard, it is worth noting that although the arterial pressure was lower in the septic shock patients than in the subjects with cardiogenic shock (and high arginine vasopressin levels), the cardiac output was much higher in the septic shock patients. The sinoatrial baroreceptor therefore is presented with a very different load in the two syndromes. There is probably a threshold pressure below which arginine vasopressin secretion will be stimulated regardless of the mechanism of the hypotension, but even in normal humans, a moderate depression in blood pressure (if caused by vasodilation) does not stimulate arginine vasopressin. Thus, the response of arginine vasopressin in septic shock may be entirely predictable on the basis of the physiology of the reflex involved and may be teleologically understood as a protective mechanism to avoid the possible adverse vasocostrictive effects of arginine vasopressin in critical organ beds such as the coronary circulation.

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Response

We thank Dr Goldsmith for his interesting comments. Concerning his first point, that our results do not show that vasopressin deficiency is a contributor to the vasodilation of septic shock, it is worth remembering that vascular smooth muscle tone has no fixed set point and that during profound hypotension, vasopressin is normally released and constricts the vasculature. In contrast, our patients had inappropriately low levels of plasma vasopressin despite hypotension, and correction of this deficiency with exogenous vasopressin increased vascular tone. This suggests that endogenous vasopressin been appropriately elevated, the vasodilation in these patients would have been less pronounced.

His second point, that the high cardiac output of patients in septic shock may be responsible for the low vasopressin in plasma, is difficult to answer because solid data elucidating the respective roles of the different components of the cardiovascular system on the baroreflex control of vasopressin secretion are sorely lacking. However, we note that patients with cirrhosis provide a well-known clinical example of increased baroreflex-mediated vasopressin secretion in the presence of a high cardiac output.

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Lipoprotein(a) as a Determinant of Coronary Heart Disease in Young Women: A Stronger Risk Factor Than Diabetes?

To the Editor:

The age-standardized mortality rates for coronary artery disease among women is about one half to one fourth that of men, although this rate varies more than 10-fold among men as well as women worldwide. This phenomenon is due to the well-known premenopausal protection, delaying the development of coronary artery disease by 10 to 15 years in women. Coronary artery disease is considered to be premature when it occurs before the age of 65 in women, in contrast to 55 in men. Because the average age of menopause has been 50 to 51 years for centuries, coronary artery disease in premenopausal women represents the most premature form of coronary artery disease and is extremely rare, except perhaps among Asian Indians.

For example, each year only ~3000 women versus 123 000 men in the United States develop a myocardial infarction before the age of 45. This low incidence makes it difficult to identify the risk factors for coronary artery disease in premenopausal women. Therefore, I read with great interest the report by Orth-Gomér et al about the 5.1-fold higher risk of hospitalization for acute coronary artery disease in premenopausal women with serum lipoprotein(a) levels >30 mg/dL.

The risk of coronary artery disease in Swedish women with elevated lipoprotein(a) is significantly higher than the 3-fold higher risk reported in middle-aged German men with similar elevation of lipoprotein(a) and is nearly equal to the 5.3-fold risk in men with lipoprotein(a) >70 mg/dL.

Elevated serum levels of lipoprotein(a) have been associated with rapid progression of atherosclerosis, resulting in greater severity and extent of coronary artery disease as well as poor survival after myocardial infarction. Therefore, the risk of acute coronary artery disease could have been even higher if the subjects with prehospital deaths and those who died within 3 months of hospitalization were not excluded from the study.

The strong correlation of serum lipoprotein(a) levels with coronary artery disease in premenopausal women in this study adds significantly to our growing understanding of the importance of lipoprotein(a) as a powerful risk factor for premature coronary artery disease in both sexes.

Because stable lifelong levels of lipoprotein(a) are attained in infancy, the pathological processes associated with elevated lipoprotein(a) also begin in infancy (20 years earlier than other risk factors such as hypertension, cigarette smoking, and diet-related dyslipidemia). This early onset of high-risk status, along with the high atherogenicity (10 times higher than LDL) and the high thrombogenicity of lipoprotein(a), appears to explain its strong association with premature coronary artery disease.

Other investigators have focused on diabetes mellitus as the dominant determinant of coronary artery disease in premenopausal women. Diabetes is associated with a relative risk of coronary artery disease that is approximately twice as high in women as in men.

In the Rancho Bernardo Study, after a 12 year follow-up, women with diabetes had a relative risk of fatal coronary artery disease similar to that of men with or without diabetes. No other risk factor so nearly erases the female advantage. This study by Orth-Gomér et al offers a unique opportunity to ascertain if elevated lipoprotein(a) is a stronger risk factor for coronary artery disease (higher prevalence, odds ratio, or attributable risk) than diabetes in premenopausal women.

In patients with combined elevations of serum LDL and lipoprotein(a), Maher et al found a marked reduction in the angiographic progression of coronary artery disease as well as clinical event rates,
with substantial lowering of LDL without any lowering of the lipoprotein(a) level. They argue that the pathogenicity of lipoprotein(a) is modulated by concomitant LDL levels and recommend lowering the latter as the preferred treatment of the former. Solymos et al found a powerful multiplicative adverse effect of elevated serum levels of lipoprotein(a) with low levels of HDL cholesterol. In women younger than 60 years of age, the risk of coronary artery disease increased 100-fold when a lipoprotein(a) level >55 mg/dL was accompanied by a high total cholesterol/HDL ratio of 6. On the other hand, no such interaction was observed by Bostom et al in the Framingham Offspring Study.

It appears that in patients with elevated serum levels of lipoprotein(a), the interaction of lipoprotein(a) with other lipoproteins is a crucial factor affecting the choice of treatment: whether to lower lipoprotein(a) or LDL to reduce the risk of recurrent coronary artery disease. LDL levels can be lowered easily, rapidly, and markedly (by 25% increase in the Swedish women.

More importantly, estrogen replacement therapy produces a greater reduction of lipoprotein(a) in those with elevated levels. For example, estrogen replacement therapy with or without progesterone resulted in a 50% reduction in the risk of coronary artery disease in humans.

Finally, the increased risk of coronary artery disease in postmenopausal women appears to be mediated in part by a 25% increase in the serum lipoprotein(a) levels that occurs after menopause. A decrease pausal women appears to be mediated in part by a 25% increase in the lipoprotein(a) levels in subjects with baseline levels.

The combined use of such as atorvastatin. On the other hand, lowering of lipoprotein(a) or LDL to reduce the risk of recurrent coronary artery disease. LDL levels can be lowered easily, rapidly, and markedly (by 25% increase in the Swedish women.

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10. Soylmos MC, Marcol M, Woslovkska E, Griffis BM, Lesperence J, Campeau L. Relation of coronary artery disease in women 60 years of age to the combined elevation of serum lipoprotein (a) and total cholesterol to high density lipoprotein cholesterol ratio. Am J Cardiol. 1993;72:1215–1219.


Response

We acknowledged the thoughtful comments and questions from Dr Enas. We have conducted several new analyses to address some of his questions.

Although the five-fold increase (odds ratio [OR] = 5.1; 95% CI, 1.4 to 18.4) in coronary artery disease (CAD) risk associated with elevated lipoprotein(a) [Lp(a)] levels in premenopausal women appears to be higher than the increase in risk among postmenopausal women (OR=2.4; 95% CI, 1.3 to 4.5), the CIs are fairly wide, and a test of homogeneity revealed that the ORs were not statistically significantly different from each other (P=0.28). Therefore, the apparent differences in risk conferred by Lp(a) in these subgroups of women need to be interpreted cautiously.

In order to evaluate the role of Lp(a) in the absence of diabetes, we repeated the original analyses of ORs that included diabetic subjects but now restricted them to nondiabetic women. The age-adjusted

<table>
<thead>
<tr>
<th>Lp(a) &lt;0.06 g/L</th>
<th>Lp(a) &gt;0.06-0.55 g/L</th>
<th>Lp(a) &gt;0.55 g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=117)</td>
<td>(n=397)</td>
<td>(n=69)</td>
</tr>
<tr>
<td><strong>Age-Adjusted OR (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol ≤6.5 mmol/L</td>
<td>1.98 (1.16-3.39)</td>
<td>3.86 (1.70-8.74)</td>
</tr>
<tr>
<td>Total cholesterol &gt;6.5 mmol/L</td>
<td>0.90 (0.42-1.91)</td>
<td>1.41 (0.50-3.93)</td>
</tr>
<tr>
<td>LDL cholesterol ≤5.0 mmol/L</td>
<td>1.51 (0.96-2.39)</td>
<td>2.65 (1.55-4.18)</td>
</tr>
<tr>
<td>LDL cholesterol &gt;5.0 mmol/L</td>
<td>2.03 (0.65-6.33)</td>
<td>6.06 (0.91-40.45)</td>
</tr>
<tr>
<td>HDL cholesterol ≥1.5 mmol/L</td>
<td>1.79 (1.10-2.91)</td>
<td>2.86 (1.43-5.71)</td>
</tr>
<tr>
<td>HDL cholesterol ≤1.5 mmol/L</td>
<td>2.04 (0.72-5.74)</td>
<td>6.95 (0.75-64.65)</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio &lt;6</td>
<td>1.93 (1.19-3.12)</td>
<td>3.62 (1.83-7.15)</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio ≥6</td>
<td>1.87 (0.54-6.52)</td>
<td>2.16 (0.21-22.09)</td>
</tr>
</tbody>
</table>

1 mmol/L = 0.0259 x mg/dL.
Correspondence

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OR of CAD comparing the highest with the lowest quartile of Lp(a) was 2.6 (95% CI, 1.6 to 4.3), and the multivariable adjusted OR was 3.2 (95% CI, 1.8 to 5.7). In the subgroup analyses, the age-adjusted OR of CAD in the premenopausal women was 3.9 (95% CI, 1.4 to 10.8), and in the postmenopausal women, the OR was 2.2 (95% CI, 1.2 to 4.0). These results were not materially different from the results in the original analysis presented in our paper.

To evaluate whether the risk of CAD associated with high levels of Lp(a) was modified by lipids, we estimated the effect of Lp(a) among subsets of women with varying lipid levels.

As can be seen from the Table, the relative risk of CAD associated with Lp(a) >0.55 g/L appeared to be greater among women with LDL cholesterol >5.0 mmol/L or HDL ≤1.15 mmol/L than among women with lower LDL levels or higher HDL levels, respectively. However, caution is required in interpreting these subgroup analyses. Because there was limited statistical power for these analyses, the confidence limits around each of the estimated OR are wide, and the estimates are thus imprecise.

The points raised by Dr Enas are important, and further study of the determinants of CAD among young women, particularly premenopausal women, are required to better address these and other issues regarding this challenging public health problem.

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Interrelation of Hyperhomocyst(e)inemia, Factor V Leiden, and Risk of Future Venous Thromboembolism

To the Editor:

In their large, prospective cohort study published in the April 1, 1997 issue of Circulation,1 Ridker et al showed that hyperhomocysteinemia is a risk factor for venous thromboembolism (VTE) only when it coexists with factor V Leiden, which is responsible for most cases of resistance to activated protein C. Hyperhomocysteinemia alone did not increase the risk of any VTE, although it tended to increase the risk of idiopathic VTE (P=0.06). These important findings are in partial disagreement with those of previous case-control studies, which demonstrated an increased prevalence of hyperhomocysteinemia in patients with any VTE and which demonstrated that the association between hyperhomocysteinemia and any VTE was independent of the presence of activated protein C resistance2 or factor V Leiden.3 There are at least three possible explanations for these contrasting results: (1) Hyperhomocysteinemia is a consequence, rather than a risk factor, of VTE. Although this explanation can account for divergences in results of case-control studies and prospective cohort studies, it should be rejected, because Ridker et al showed in their prospective cohort study that hyperhomocysteinemia increases the risk of VTE in subjects with factor V Leiden. (2) The association between hyperhomocysteinemia and VTE is stronger in women than in men, as shown by den Heijer et al.1 If confirmed by further studies, this sex difference could account for the negative results of the study by Ridker et al, which included only men. (3) The inclusion of patients with cancer, which is a very strong risk factor for VTE, could have masked the effect of hyperhomocysteinemia, which is a relatively weak risk factor. Most epidemiological studies of hyperhomocysteinemia as a risk factor for VTE4–6 did not include cancer patients.

The demonstration by Ridker et al that the coexistence of hyperhomocysteinemia and factor V Leiden sharply increases the risk for future VTEs, particularly those considered idiopathic, agrees with two reports from our group. In a study of 111 patients with early-onset VTE,7 we found that the frequency of idiopathic episodes was higher in patients with hyperhomocysteinemia and activated protein C resistance combined (71%) than in patients with either defect alone (30% for activated protein C resistance, 44% for hyperhomocysteinemia). We consider as idiopathic those episodes not occurring in association with circumstantial triggering factors such as surgery, trauma, prolonged immobilization, pregnancy/puerperium, and use of oral contraceptives. More recently, we8 showed that the risk of VTE in carriers of both factor V Leiden and the C677T mutation of methylenetetrahydrofolate reductase, which is responsible for mild hyperhomocysteinemia,9 was greater than the expected joint effect of the two mutations, calculated by either an additive or a multiplicative model. Also in that study, the frequency of idiopathic episodes tended to be higher in doubly affected individuals than in those with either defect alone.

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Response

My coauthors and I appreciate the kind words from Dr Cattaneo and colleagues concerning our finding of a marked increase in risk of venous thromboembolism among patients affected by both factor V Leiden and hyperhomocysteinemia compared with patients with either of these abnormalities alone.1 In our prospective data, dietary-induced hyperhomocysteinemia appears to be at least as important as the presence of homozygosity for the methylenetetrahydrofolate reductase (MTHFR) polymorphism. As noted in the “Discussion” section of our article, the majority of patients in our study who had hyperhomocysteinemia did not carry the abnormal polymorphism.

We disagree somewhat with the view that there was no association in our data between hyperhomocysteinemia and venous thrombosis when hyperhomocysteinemia was considered in isolation. As described in the original manuscript, those with hyperhomocysteinemia were at significantly increased risk of developing future idiopathic venous thromboembolic events (relative risk=3.4, P=0.002). However, no such increase in risk was found for venous thromboemboli associated with cancer, surgery, or trauma, which we defined on an a priori basis as secondary events. Indeed, this difference between primary and secondary venous thromboembolic events may explain why some4–6 but not all7 prior studies evaluating hyperhomocysteinemia and venous thrombosis reported significant relationships. This distinction is additionally relevant with regard to factor V Leiden because the risk
of recurrent events associated with this mutation also appears limited to idiopathic events. Thus, our data and those forthcoming from Cattaneo and colleagues suggest that patients with idiopathic venous thromboses who carry factor V Leiden may require additional screening for other concomitant abnormalities of hemostasis, such as hyperhomocysteinemia.

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Priorities in Heart Failure Research

To the Editor:

As a student of the circulation, of aging, and of heart failure in the elderly, I was flabbergasted to read1 that the NIH “Special Emphasis Panel on Heart Failure Research” described priorities without mentioning the physical properties of the circulation and of left ventricular load in the aged. Priorities were cellular, molecular, genetic, and chemical, yet were applied to a mechanical system in which arterial stiffening with age markedly alters wave reflection and distorts the physical tuning between pulsating heart and compliant arterial tree. Though recognized as a priority area by the NIH for special funding (NIH Guide, Vol 24, No 24, June 30, 1995), this area was completely ignored in the present report, as were clinical trials. An accompanying commentary from Dr Claude Lenfant2 as NHLBI Director also concentrated on subcellular mechanisms and made no mention whatever of ventricular load in heart failure or the NHLBI’s 1995 initiative. Lenfant’s pronouncement ran counter to his own 1995 news article in *Circulation* on “Integrative Physiology: Remember the Big Picture.”

In the Louis P. Bishop lecture delivered at the 1997 American College of Cardiology annual meeting in Anaheim, Calif, a previous NIH Director, Bernadine Healy, addressed “The impact of health care reform on medical schools” and pointed out that community pressures will force researchers to tackle community problems such as the escalating problem of heart failure in the elderly. In 2 short years, the NHLBI appears to be turning from the practical problem of heart failure to the latest fashions in molecular biology. An observer from afar might be permitted to ask what American cardiology really sees as the “Big Picture” in heart failure research.

Are the priorities described in the 1997 NIH panel’s report comprehensive and potentially most fruitful? Or is something missing?

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Response

Dr O’Rourke correctly recognizes that the report of the NHLBI Special Emphasis Panel (SEP) on Heart Failure Research is not all-encompassing. His remarks concerning circulation, ventricular load, and aging are well taken. For a complex disorder such as heart failure, the ideal model would consider the various afflicted organs, neurohumoral pathways, and physiological systems, as well as the temporal alterations and interactions. Such broad consideration, though, was beyond the scope of the SEP.

The SEP’s report was not intended to review or comment on the multitudinous parameters contributing to heart failure. Such an ambitious overview was realized earlier by the NHLBI Task Force on Research in Heart Failure, which provided a detailed blueprint of suggestions for heart failure research.2 To avoid generating an exhaustive wish list, the SEP was charged with identifying and prioritizing research “gap areas” and practical, new directions to serve as a guide to the NHLBI and the community. Within the limitations imposed on it, the SEP performed admirably. With regard to Dr O’Rourke’s comments on the trendiness of the recommendations, we attempted to select SEP members with broad understanding of the nature of heart failure. I think most observers will agree a reasonable array of research and clinical ideologies was represented. Although several of the recommendations emphasize cellular and molecular approaches, other ideas, such as indicated by Dr O’Rourke, are included. For example, the third priority was to “foster studies encompassing physiological, molecular, biochemical, and multiorgan factors.” Another recommendation, to “study regression of heart failure abnormalities with left ventricular assist devices,” was included specifically to encourage investigation of the roles of ventricular load in cardiac remodeling, dysfunction, and treatment.

Finally, although this particular report may not be as broad as one would wish, the NHLBI and other institutes at the NIH do support a comprehensive battery of basic and clinical research and clinical trials addressing heart failure. The lion’s share of this work is, appropriately, investigator initiated. Where guidance appears needed, the NIH has historically sought out experts in the field to serve on advisory panels, such as this SEP, to assist in setting program priorities or inviting proposals. An example of one such priority communication, not from the NHLBI but from the National Institute on Aging, is cited by Dr O’Rourke: the 1995 program announcement, “Aging, Vascular Stiffness, and Cardiovascular Function.” We hope the recommendations of the SEP on heart failure research will prove useful as a guide to researchers and be seen as a contributing piece, if not the total “Big Picture,” in the struggle against heart failure.

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Inhaled NO and Pulmonary Vasodilation
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