Fibroelastoma and Embolic Stroke
To the Editor:

Conte and Katz\(^1\) recently provided images of a mitral valve papillary fibroelastoma detected by transeosophageal echocardiogram. The patient presented with an embolic stroke, and the tumor was removed surgically. The authors postulated that a tumor fragment was responsible for the embolic event. This deserves comment because there is another possibility, potentially important for patient management.

Papillary fibroelastomas are benign cardiac tumors, usually located on valves, thought to be related to Lambli’s ex crescences. They may be incidental findings at surgery or autopsy, or clinically they have been associated with neurological events, stroke, angina, myocardial infarction, or sudden death.\(^2\)\(^,\)\(^3\) These events are thought to be related to emboli or to tumor obstruction of a coronary artery ostium.

Unlike myxoma, another common benign cardiac tumor that may be valvular and associated with similar clinical events, fragments of the tumor have only rarely been found in the arteries involved.\(^2\)\(^,\)\(^4\) It is more likely that the embolic material is fibrin or thrombus originating from the tumor surface. This probably relates to local trauma and endothelial damage at the tumor surface.\(^3\)\(^,\)\(^5\)

These tumors are composed of papillary fronds of collagen and elastin covered by endothelial cells. They are firmly attached to the valve. Pathological examination, it may be necessary to examine multiple slices of the tumor, but not uncommonly, small fragments of adherent fibrin and thrombus are found.

This is of clinical importance because some authors have proposed that as an alternative to surgical excision with valve repair or replacement, the tumors should be treated by anticoagulation.\(^3\)\(^,\)\(^5\) This may be a viable treatment option while the patient is on the waiting list awaiting surgery or in patients in whom surgery is contraindicated.

John P. Veinot, MD
Laboratory Medicine
Ottawa Civic Hospital
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Response

We thank Dr Veinot for his excellent comments concerning embolization and fibroelastomas. The association between fibroelastomas and embolic stroke is indeed controversial. The diagnosis of ischemic stroke from left-sided papillary fibroelastomas is usually made by exclusion. In a recent study, Yee and colleagues\(^1\) reported on 15 patients with papillary fibroelastomas and found 5 patients (33%) who had ischemic strokes with no other etiologic explanation. Furthermore, thrombus is occasionally superimposed on papillary fibroelastomas.\(^2\) It may have been responsible for the stroke in the patient whom we reported, although no fibrin or thrombus was observed on pathology. Anticoagulation is a viable alternative to surgical excision of the tumor, particularly when there are contraindications to surgery. In 1 case report, no recurrence of transient ischemic attack occurred in 3 years after excision of a left-sided papillary fibroelastoma. Follow-up data on patients who underwent surgical excision are rare, and we are unaware of any follow-up studies on patients treated with anticoagulation alone. The best method of management of papillary fibroelastomas, the second-most common cardiac tumor,\(^3\) awaits further observations and clinical trials.

Alan S. Katz, MD
The Miriam Hospital
Division of Cardiology
Frank J. Conte, MD
Providence, RI

Is Atherosclerosis a No NO State?
To the Editor:

A recent article in Circulation by Lüscher’s group (Oemar et al)\(^2\) has reported that in tissue derived from human atherosclerotic lesions, endothelial NO synthase (eNOS) protein expression as well as NO release are markedly reduced. They then suggested that these reductions are involved in the progression of atherosclerosis.

We would like to provide further support for their contention that an altered NO system is involved in human atherosclerosis. In a series of articles, our group has established that patients with Bartter syndrome or Gitelman syndrome, syndromes that show a peculiar picture of vascular hyporeactivity characterized by normotension/hypotension in the presence of elevated levels of pressor agents (eg, angiotensin II, norepinephrine, and aldosterone), have an anomalous calcium-dependent signaling system\(^2\) and an upregulation of the NO system.\(^3\)\(^,\)\(^4\) In particular, this upregulation is characterized by increased ecNOS mRNA levels as well as increased and correlated urinary excretions of NO metabolites (\(\text{NO}_2^-/\text{NO}_3^-\)) and cGMP, the second messenger of NO. In these same patients, we have also demonstrated a reduced susceptibility of their LDL to oxidation,\(^5\) as shown by reduced production of thiobarbituric acid–reactive substances as well as volatile lipid peroxidation products such as pentanal and hexanal. In addition, the lag phase of conjugated diene formation in the Bartter and Gitelman patients was strongly correlated with increased NO release and decreased susceptibility of their LDL to oxidation,\(^6\) as shown by reduced production of thiobarbituric acid–reactive substances as well as volatile lipid peroxidation products such as pentanal and hexanal.
It is of great interest that nature has provided a mirror image of the results reported by Oemar et al and thus provide further support for and evidence of the importance of NO in the prevention of atherosclerosis and in related conditions such as hypertension, diabetes, and smoking.

Paul A. Davis, PhD
Division of Clinical Nutrition and Metabolism
University of California, Davis
Davis, Calif

Paul A. Davis, PhD

Lorenzo Calò, MD
Institute of Internal Medicine
Division of Nephrology
University of Padova
Padova, Italy


Response

We greatly appreciate the comments by Davis and Calò related to our recently published article.1 The syndrome the authors studied, namely, Barter and Gitelman patients, is of great interest in this context. The fact that NO serves as an antioxidant and therefore a protective mechanism against oxidative stress is also in line with our recently published “Current Perspective” in Circulation.2 It is of great interest that nature has provided a mirror picture of atherosclerosis in these patients and that this mirror picture provides further support for the protective role of NO against atherosclerosis and related cardiovascular conditions.

Thomas F. Lüscher, MD
Division of Cardiology
University Hospital
Zürich, Switzerland

Barry S. Oemar, MD
Hoffmann-La Roche Inc
Department of Metabolic Diseases
Nutley, NJ


Direct Antigen Presentation and Chronic Rejection

To the Editor:

I read with interest the article by Hornick et al.1 They conclude that direct antigen presentation (donor MHC presented by donor antigen-presenting cells) is an unlikely mechanism to explain the accelerated coronary disease (CAD) that develops after cardiac transplantation. I have concerns regarding these data and conclusions.

First and foremost, the data are limited to 10 allograft recipients studied at wide time disparities, with the majority of recipients being at least 4 years past transplantation. Although the development of CAD is progressive, disease occurring later after transplantation is difficult to distinguish from traditional atherosclerosis. Furthermore, most of the alloimmune “action” occurs within the first year after transplantation. Several studies have demonstrated that those patients who develop CAD early have by far the worst prognosis. Only 2 patients were studied in this time frame. Second, only patients with CAD were studied without a control group. The appropriate comparison (assuming consistent time periods) would be those with and without CAD, not donor-specific versus third party. It is important to also point out that 5 of the 10 patients had precursor frequencies to donor-specific antigens similar to third-party antigens, with patients later after transplantation tending to have less aggressive responses.

Third, the progressive loss of donor-specific alloreactivity in stable allograft recipients, based on precursor frequency or MLR, is not a new finding.2–3 More importantly, Rabinowich et al demonstrated that an augmented MLR correlated with both acute and chronic rejection in lung transplant recipients using BAL cells as responders and donor spleen cells as stimulators. Our own data2 are somewhat more intriguing because they showed a dichotomy between the standard MLR (using donor lymphocytes as stimulators) and lymphocyte proliferation when donor endothelial cells were used. Although a hyporesponsive effect developed over the first year when the standard MLR was used, recipient lymphocyte reactivity actually increased in response to donor-specific endothelial cells. These data raise the possibility that different costimulatory signals occur in this lymphocyte-endothelial interaction compared with an MLR, or alternatively, this response is less well inhibited by immunosuppression. A subsequent study in 52 cardiac allograft recipients correlated the intensity of this response serially to the development of angiographic coronary disease by 1 year after transplantation.6

On the basis of the above, I would have to conclude that the question of direct antigen presentation as a mechanism for chronic rejection is still an open one.

Jeffrey D. Hosenpud, MD
Department of Cardiology
Medical College of Wisconsin
Milwaukee, Wis


6. Hosenpud JD, Everett JP, Morris TE, Mauck KA, Shipley GD, Wagner CR. Cardiac allograft vasculopathy: association with cell-mediated but

Response

Dr Hosenpud makes several important observations with which we agree. First, we accept that we studied only a small number of patients and that the findings we reported need to be confirmed in a larger series. We are currently accumulating prospective data in renal transplant recipients in order to extend these observations to chronic rejection in another context. Second, we agree that the direct alloresponse is maximally active during the first few weeks and months after transplantation, when the highly immunogenic donor passenger leukocytes are present. Third, we are well aware of the correlation between early transplant coronary artery disease (TxCAD) and acute rejection; this implies that the direct alloresponse sets in motion a cycle of events that manifest as TxCAD at a later time point. Fourth, not only are we familiar with previous reports of emerging donor-specific hyporesponsiveness in transplant patients, but we have described this observation ourselves in renal transplant recipients. However, this is the first description of donor-specific hyporesponsiveness in cardiac patients with established and progressive TxCAD, which is thought to be the manifestation of chronic cardiac allograft rejection.

Having identified where we agree with Dr Hosenpud, we would like to highlight where we disagree. First, as stated above, our study makes a novel observation in patients with the clinical manifestation of chronic cardiac allograft rejection. Second, we dispute the importance of a control group without TxCAD. The thrust of our findings is that a continuing strong antidonor direct alloresponse is unlikely to be responsible for continuing TxCAD. This conclusion would be uninfluenced by the study of CAD-free patients, whatever pattern of reactivity they displayed. Finally, Dr Hosenpud’s observation that hyporesponsiveness against donor peripheral blood mononuclear cells (PBMCs) may occur while reactivity against donor endothelial cells (ECs) is preserved is potentially interesting. However, until a mechanism can be identified to explain this dichotomy, it remains a somewhat puzzling phenomenon. Indeed, in our own studies, alloreactive T cells primed against allogeneic PBMCs respond to ECs expressing the same alloantigens when bystander costimulation is provided, suggesting the conservation of allantigenic epitopes, although accessory molecular interactions may differ.

Further definition of the nature of the T-cell alloresponse that drives chronic allograft rejection is clearly crucially important. Our recent data support the possibility that the indirect rather than the direct alloresponse is of greater significance.

Philip Hornick
Philip Mason
Magdi Yacoub
Marlene Rose
Richard Batchelor
Robert Lechler

Departments of Immunology and Cardiothoracic Surgery
Hammersmith and Harefield Hospitals
Imperial College School of Medicine
London, UK


Clinical Significance of Arterial Blood Gas Analysis for Detection and/or Treatment of Central Sleep Apnea in Patients With Heart Failure

To the Editor:

In a recent issue of Circulation, Javaheiri et al demonstrated that sleep-disordered breathing (SDB), including central sleep apnea (CSA) and periodic breathing (eg, Cheyne-Stokes respiration), is extremely common in patients with stable heart failure and that atrial fibrillation, ventricular arrhythmia, and low left ventricular function are associated with sleep apnea in these patients. Because the reversal of SDB by nasal continuous positive pressures and oxygen may lead to improvements in markers of cardiovascular outcome in selected patients with congestive heart failure (CHF), all cardiologists should pay attention to the recent study. However, the mechanisms of SDB in patients with CHF were not extensively discussed in the article. The same authors recently proposed that low PaCO₂ resulted in ventilatory instability and central apnea during sleep. In the previous study, the values of PaCO₂ were 37±5 and 39±4 mm Hg in patients with SDB and those without SDB, respectively. Although the differences in resting PaCO₂ in arterial blood gas between awake patients with SDB and those without SDB were very small, experimental human study suggested that central apnoea could be induced by lowering PaCO₂ 1 to 3 mm Hg below resting PaCO₂ while patients were awake. In addition, instability in the ventilatory control system might be involved in periodic breathing. The higher prevalence of CSA in patients with SDB is at least in part explained by ventilatory instability as indicated by low PaCO₂. Wilcox and coworkers also revealed that CHF patients with CSA had decreased awake end-tidal CO₂ tension (4.1±0.5 kPa), increased ventilatory response to CO₂, and eucapnic hypoxic responses in the normal range, but that CHF patients with obstructive sleep apnea had a normal awake end-tidal CO₂ tension and normal ventilatory response to CO₂. These data indicated that ventilatory instability and augmented chemosensitivity to hypercapnia were important factors in the pathophysiology of CSA in patients with CHF. In addition, it is known that oxygen effectively reduces CSA but not obstructive sleep apnea in patients with CHF. This suggests that oxygen supplementation therapy may be beneficial for both cardiac function and SDB in patients with CHF. Considered together, the assessment of arterial blood gases is particularly important for both detection and treatment of CSA in patients with CHF.

Shinji Teramoto, MD, FCCP
Yasuyoshi Ouchi, MD
Department of Geriatric Medicine
Tokyo University Hospital
Tokyo, Japan


Response

We thank Drs Teramoto and Ouchi for their interest in and comments on our work. We echo their comment, “all cardiol-
ogists should pay attention to the recent study. This was the reason for publication of our research work in *Circulation*.¹

Due to the length of the article,¹ we did not discuss the mechanisms or treatment of sleep apnea in heart failure and systolic dysfunction, but we have covered these issues elsewhere.²⁻⁴

Regarding PaCO₂, however, the values quoted (Table 2 of Reference 1) included heart failure patients without (PaCO₂=39±4 mm Hg) or with (PaCO₂=37±5 mm Hg) sleep apnea. Although these values were significantly different, the group with sleep apnea included both central (39% of all heart failure patients) and obstructive (11% of all heart failure patients) sleep apnea.

Regarding central sleep apnea, our previous data² in a relatively large number (n=59) of patients with heart failure and systolic dysfunction showed that 14 of 18 hypocapnic patients had central sleep apnea. However, 16 of 41 eucapnic patients also had central sleep apnea. In other words, out of 30 heart failure patients who had central sleep apnea, 14 (47%) were hypocapnic. Therefore, an awake low PaCO₂ is not a prerequisite for development of central sleep apnea in patients with heart failure, although it highly predicts it. Meanwhile, there are other markers associated with central sleep apnea in heart failure; these include presence of atrioventricular arrhythmias and a very low left ventricular ejection fraction,¹ which should serve as clues to the potential presence of central sleep apnea.

With regard to obstructive sleep apnea in heart failure, patients are commonly obese and have a history of loud habitual snoring,¹ features similar to those patients with obstructive sleep apnea-hypopnea syndrome without heart failure and systolic dysfunction.

The various therapeutic approaches have also been briefly reviewed elsewhere.³ However, longitudinal studies are necessary to determine whether the natural history of heart failure (particularly the mortality rate, which remains high in spite of the use of ACE inhibitors and carvedilol) is changed by administration of O₂, continuous positive airway pressure, or medications. Meanwhile, until such data are available, we recommend that the first therapeutic step is optimization of left ventricular systolic function and treatment of subtle volume overload and pulmonary congestion. If sleep apnea persists, there are several therapeutic options available.³⁻⁵ However, careful follow-up is necessary.

S. Javaheri, MD
T.J. Parker, MD
J.D. Liming, MD
W.S. Corbett, BS
H. Nishiyama, MD
L. Wexler, MD
G.A. Roselle, MD
Sleep Disorders Laboratory
Department of Veterans Affairs Medical Center
Department of Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio

Clinical Significance of Arterial Blood Gas Analysis for Detection and/or Treatment of Central Sleep Apnea in Patients With Heart Failure
Shinji Teramoto and Yasuyoshi Ouchi

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