CF-LVAD support, and BMI did not correlate with exercise parameters or CRP levels. Furthermore, no relationship was found between the length of CF-LVAD support and peak $\dot{V}o_2$ and percentage predicted $\dot{V}o_{2max}$.

Our study has limitations. Because of the small sample size, we cannot make definitive conclusions in this population. In addition, although patients received different models of CF-LVAD, peak $\dot{V}o_2$, percentage predicted $\dot{V}o_{2max}$, chronotropic responses, and CRP were not significantly different among patients who were supported with HeartMate II (Thoratec, Pleasanton, CA), HeartWare (HeartWare International Inc, Framingham, MA), or DuraHeart (Terumo Heart Inc, Ann Arbor, MI) devices.

Another limitation is that the length of support varied among the CF-LVAD recipients; however, the length of support did not have an effect on exercise capacity. In addition, β-blockers may affect exercise capacity and chronotropic responses, and BMI may be related to inflammation and exercise capacity. However, this study found no differences between patients who were and were not taking β-blockers, and BMI did not correlate with exercise capacity or CRP levels. In terms of the small proportion of patients taking β-blockers at baseline, clinicians at our institution titrate RAAS inhibitors first, followed by β-blockers. Accordingly, with longer CF-LVAD support, a higher proportion of patients may use β-blockers.

The presence of diabetes may affect chronotropic response; however, only 2 patients had diabetes, and therefore, we could not control for the effect of diabetes on HR reserve.

Finally, we recognize that only 11 of 15 heart failure patients were able to complete the exercise testing before CF-LVAD. However, $\dot{V}o_{2max}$ in these patients was probably extremely low because they were not able to exercise. Thus, the improvement in peak $\dot{V}o_2$ from before to after CF-LVAD may be underestimated. Nevertheless, exercise capacity after CF-LVAD remained impaired.

In conclusion, although not normalized, chronotropic responses were higher after CF-LVAD implantation compared with before CF-LVAD implantation. In our study, chronotropic responses were below 80%, confirming that chronotropic incompetence persisted after CF-LVAD implantation. Because HR recovery was <12 beats at 1 minute after exercise cessation, the increase in HR recovery from before CF-LVAD to after CF-LVAD suggests that autonomic responses improved. Our results also suggest that impaired exercise capacity may be associated with inflammation in CF-LVAD recipients. Future studies should elucidate mechanisms that contribute to chronotropic incompetence and impaired exercise capacity in patients supported with CF-LVADs.

Disclosure statement

The authors are grateful to the study participants, whose time and effort are critical to the success of our research program.

D.Z.C., co-senior author, is supported by a Canadian Diabetes Association-Kidney Research Scientist Core Education and National Training Program (KRESCENT) Program Joint New Investigator Award and receives operating support from the Heart and Stroke Foundation of Canada.

V.R., co-senior author, is a consultant to Terumo, CorMatrix, and HeartWare. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

References

1. Myers J. Principles of exercise prescription for patients with chronic heart failure. Heart Fail Rev 2008;13:61-8.
2. Haft J, Armstrong W, Dyke DB, et al. Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. Circulation 2007;116:I8-15.
3. Jakovljevic DG, George RS, Nunan D, et al. The impact of acute reduction of continuous-flow left ventricular assist device support on cardiac and exercise performance. Heart 2010;96:1390-5.
4. Leibner ES, Cysyk J, Eleuteri K, El-Banayosy A, Boehmer JP, Pae WE. Changes in the functional status measures of heart failure patients with mechanical assist devices. ASAIO J 2013;59:117-22.
5. Dimopoulos S, Diakos N, Tseliou E, et al. Chronotropic incompetence and abnormal heart rate recovery early after left ventricular assist device implantation. Pacing Clin Electrophysiol 2011;34:1607-14.
6. Nessler J, Nessler B, Kitlinski M, Gackowski A, Piwowarska W, Stepniewski M. Concentration of BNP, endothelin 1, pro-inflammatory cytokines (TNF-alpha, IL-6) and exercise capacity in patients with heart failure treated with carvedilol. Kardiol Pol 2008;66:144-51: discussion 152–3.
7. Huang PH, Leu HB, Chen JW, et al. Comparison of endothelial vasodilator function, inflammatory markers, and N-terminal pro-brain natriuretic peptide in patients with or without chronotropic incompetence to exercise test. Heart 2006;92:609-14.

Pulmonary meningothelial-like nodules are of donor origin in lung allografts

Alyssa Luvison, BS, Carol Sherer, MS, and Samuel A. Yousem, MD

From the Department of Pathology, University of Pennsylvania Medical Center, Presbyterian Shadyside Campus, Pittsburgh, Pennsylvania

Minute pulmonary meningothelial-like nodules (MPMNs) are asymptomatic small nodules representing incidental microscopic findings in lung specimens.[1,2] The majority of MPMNs are seen in women and in some studies they appear more often in the right lung than the left.[1] Recent studies have suggested that these lesions tend to present in patients with pulmonary vascular disease, especially pulmonary hypertension and thromboembolic disease/infarcts and in smoking-induced respiratory bronchiolitis–associated interstitial lung disease.[2] Microscopically, the lesions consist of nests or whorls of moderately sized epithelioid cells centered on small veins with the cells being elongated or spindled with oval nuclei, fine granular chromatin and inconspicuous nucleoli, with abundant eosinophilic cytoplasm showing poorly defined cell borders. Historically, MPMNs were thought to have an oxygen-monitoring function as chemoreceptors, but subsequent electron-microscopic studies failed to show neuroendocrine differentiation and instead showed ultrastructural features suggesting

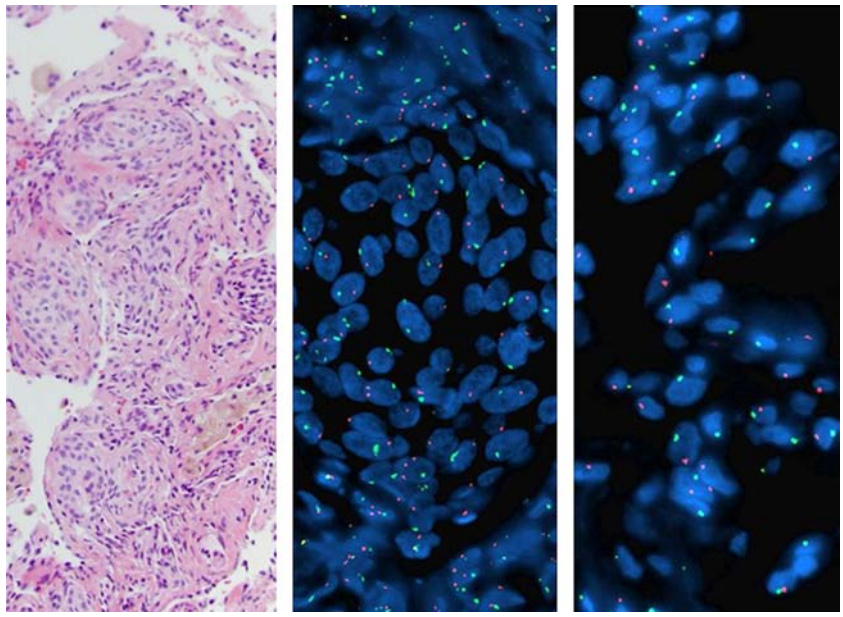

Figure 1 In this case, a female recipient received a male allograft. At left, one can identify the whorls of epithelioid cells within the interstitium characteristic of MPMNs. In the center panel, the cells comprising the MPMN have both an orange signal (X chromosome) and a green signal (Y chromosome), indicating a male genotype. At far right is the normal allograft lung with alveolar pneumocytes, endothelium and smooth muscle, displaying a male genotype.

meningothelial differentiation. On the basis of immunohistochemical stains, primarily positivity for epithelial membrane antigen and vimentin, and negative studies for cytokeratin, actin, S100 protein, CD34, chromogranin and synaptophysin, Gaffey et al suggested labeling these lesions "minute pulmonary meningothelial-like nodules" because of their similarity to meningiomas.[1]

As noted in a prior correspondence in this journal, MPMNs can be seen as an incidental finding in surveillance transbronchial biopsies performed on lung allograft recipients.[3] Agozzino et al[3] believed, based on clinical and radiographic findings, that MPMNs were probably of donor origin. Although their study relied exclusively on clinical information, no further studies of MPMNs in lung allograft recipients have been performed to further document their observations. In this brief correspondence we support their impression by utilizing XY chromosome in situ hybridization in gender-mismatched patients who were noted to have MPMNs in surveillance transbronchial biopsies of their lung allografts.

The patient files of the University of Pittsburgh Medical Center-Presbyterian Hospital were reviewed for all lung allografts where MPMNs were noted at transbronchial biopsy and there was a recipient and donor gender mismatch. Although 6 patients fulfilled the criteria, only 2 of them had sufficient formalin-fixed paraffin embedded tissue to perform chimerism assays. Dual-color fluorescence in situ hybridization for the sex chromosomes was performed using an X/Y direct labeled probe (Abbott Molecular, Des Plaines, IL), as described elsewhere.[4,5] Positive and negative controls for the XY chromosomes were performed using lung tissues from non-allograft male and female recipients: 2 orange signals (X chromosomes) in female cells, and an orange and a green signal (X and Y chromosomes) in male cells. Ninety-seven percent of cells had an appropriate signal constellation in these controls. Areas of MPMN on hematoxylin–eosin sections were matched to hybridized slides and were evaluated using a series of filters that enabled viewing of only the X or Y chromosomes (single bandpass filters), as well as both the X and Y chromosomes (dual bandpass filters). Digital images were taken of every diagnostic cell. Immunostains showed the MPMN cells to stain for epithelial membrane antigen and vimentin and to not express CD68, a histiocytic marker.

Two cases comprised the study group. One woman (Case 1) received a male lung allograft for idiopathic pulmonary fibrosis and had MPMN identified at 1.1 years post-transplant; the other (Case 2) was a male recipient of a female lung allograft for severe smoking-induced bronchiolitis obliterans and had MPMN identified 10.5 years post-transplant. In each case, the cells comprising the meningothelial-like nodules showed the donor phenotype (Case 1: 7 cells; Case 2: 40 cells) (Figure 1).

This limited study of 2 cases of lung allografts containing MPMNs demonstrates that the cells comprising the proliferation of these benign nodules are of a donor rather than recipient origin. This is of interest in that there is a continuing evolution of understanding with regard to non-alloreactive pathologic processes and stem cell colorizations occurring in the allograft lung. These processes have demonstrated, for example, that the histiocytes in the granulomas of recurrent sarcoid are of recipient origin, the proliferating lymphocytes in post-transplant lymphoproliferative disorders are most commonly of recipient origin, and the proliferating cells in recurrent lymphangioleiomyomatosis are of recipient etiology. MPMNs are incidental findings and, in our assessment of $>$ 4,800 transbronchial

biopsies performed, only 42 cases of MPMNs were identified in allograft lungs. Because of their small size and the need to recut paraffin blocks to perform chimerism studies, only 2 of our 6 gender-mismatched recipients were available for study, but they provided convincing evidence that this cellular proliferation arises from the donated graft.[4] This observation confirms earlier studies published in this journal that utilized primarily clinical data to arrive at this conclusion.

Disclosure statement

The authors have no conflicts of interest to disclose.

References

1. Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 1988;12:167-75.
2. Mukhopadhyay S, El-Zammar OA, Katzenstein AL. Pulmonary meningothelial-like nodules: new insights into a common but poorly understood entity. Am J Surg Pathol 2009;33:487-95.
3. Agozzino M, Inzani F, Cavallero A, et al. Minute pulmonary meningothelial-like nodules in the transbronchial biopsy of a lung transplant recipient. J Heart Lung Transplant 2006;25:148-50.
4. Ionescu DN, Sasatomi E, Aldeeb D, et al. Pulmonary meningothelial-like nodules: a genotypic comparison with meningiomas. Am J Surg Pathol 2004;28:207-14.
5. Kubit V, Sonmez-Alpan E, Zeevi A, et al. Mixed allogeneic chimerism in lung allograft recipients. Hum Pathol 1994;25:408-12.

Heterotopic heart transplantation for elevated pulmonary vascular resistance in the current era: Long-term clinical and hemodynamic outcomes

Angelina Vassileva, MD, Orazio Valsecchi, MD, Roberta Sebastiani, MD, Alessandra Fontana, MD, and Amando Gamba, MD

From the Diagnostica e Interventistica Cardiovascolare, Ospedali Riuniti di Bergamo, Bergamo, Italy.

The International Society of Heart and Lung Transplantation (ISHLT) Registry shows that approximately 20% of early deaths after heart transplantation is attributable to right heart failure.[1,2] Heterotopic heart transplantation (HHT), with anastomosis of the donor pulmonary artery to the recipient right atrium, is a potential solution to avoid this complication. This report updates our prior results with the use of this technique.[3]

From July 1995 to August 2007, 18 patients (9 males) with irreversibly high pulmonary vascular resistance (PVR) underwent HHT with anastomosis of the donor pulmonary artery to the recipient right atrium. All patients signed the informed consent for the treatment according to the local Ethics Committee.

The indication for HHT was based on the following parameters obtained in the presence of adequate pulmonary vasodilatation:

1. pulmonary vascular resistance (PVR) $>$ 6 units/m^2,
2. transpulmonary gradient $>$ 15 mm Hg, or
3. pulmonary systolic pressure $>$ 60 mm Hg.

All patients had a degree of pulmonary hypertension to satisfy at least two of the given criteria (Table 1). The etiologic indication for HHT was restrictive cardiomyopathy in 8, idiopathic dilated cardiomyopathy in 3, and ischemic cardiomyopathy in 2. In addition, 1 patient each presented with cardiomyopathy arising after anthracycline chemotherapy; severe left ventricular dysfunction after resection of a sub-aortic membrane, corrected transposition of great arteries with right isomerism; ventricular septal defect (with a left-to-right shunt partially reduced by a mild pulmonary stenosis), left superior vena cava draining into the left coronary sinus, previous pacemaker implantation, and severe ventricular dysfunction; severe mitral restenosis and complete calcification (porcelain-like) of the left atrium; and severe left ventricle dysfunction and severe aortic insufficiency 7 years after myectomy for hypertrophic obstructive cardiomyopathy. Twelve patients were in New York Heart Association functional class III or IV, and 6 patients were hospitalized (1 intubated) with continuous infusion of inotropic drugs.

Recipient mean age was 32 $\pm$ 19 years (range, 8–65 years), and donor age was 24 $\pm$ 16 years (range, 7–57 years), with a body weight, respectively, of 50 $\pm$ 15 kg and 54 $\pm$ 16 kg.

HHT has been performed with the technique previously described,[7] with the following associated surgical procedures on the recipient heart, including mitral (4 cases) and/or tricuspid (4 cases) valve repair; aortic root replacement with homograft (1 case); ventricular septal defect closure (1 case); and pacemaker implantation in 5 cases to synchronize the 2 hearts.

The mean duration of extracorporeal circulation was 97 $\pm$ 38 minutes, aortic cross-clamp was 58 $\pm$ 32 minutes, and total ischemic time was 122 $\pm$ 55 minutes.

One patient died on the 30th post-operative day of multiorgan failure after 6 days of circulatory support with extracorporeal membrane oxygenation for severe allograft rejection.

One patient, with a restrictive cardiomyopathy, gradually developed a few weeks after the HHT recurrent pleuropericardial effusion accompanied by protein-loosing syndrome. As shown at autopsy, the complication was caused by a remarkable hypertrophy with a very small cavity of the native right ventricle unable to bear the increased cardiac output determined by the transplant. The patient died 82 days later of a severe edema of the glottis and complete heart block after bronchoscopy.

One patient with very high pulmonary pressure required a prolonged period (40 days) of intubation for persistent post-operative pulmonary hypertension, despite nitric oxide inhalation.

In the remaining group, the mean period of invasive ventilatory support was 34 $\pm$ 27 hours, the average stay in