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APPENDIX

Institutions/Investigators

Brigham and Women's Hospital, Boston, Massachusetts: Gregory S. Couper, M.D., Lawrence H. Cohn, M.D.

Cleveland Clinic Foundation, Cleveland, Ohio: Patrick McCarthy, M.D.

Columbia Presbyterian Medical Center, New York, New York: Eric Rose, M.D., Mehmet Oz, M.D., Howard Levin, M.D.

Fairfax Hospital, Falls Church, Virginia: Nelson Burton, M.D., Edward A. Lefrak, M.D., Quentin Macmanus, M.D.

Henry Ford Hospital, Detroit, Michigan: Norman Silverman, M.D.

Loyola University Medical Center, Maywood, Illinois: Alvaro Montoya, M.D.

Lutheran Hospital, Fort Wayne, Indiana: Alan Peterson, M.D., Joseph Ladowski, M.D.

Ochsner Foundation, New Orleans, Louisiana: Cliff Van Meter, M.D., John Ochsner, M.D.

Sacred Heart Medical Center, Spokane, Washington: Timothy B. Icenogle, M.D.

Sharp Memorial Hospital, San Diego, California: Walter Dembitsky, M.D.

St. Joseph's Hospital, Atlanta, Georgia: Douglas Murphy, M.D.

St. Lukes Medical Center, Milwaukee, Wisconsin: Alfred Tector, M.D.

St. Paul Medical Center, Dallas, Texas: Christian Montcrief, M.D., Steves Ring, M.D.

Temple University Hospital, Philadelphia, Pennsylvania: Val Jeevanandam, M.D.

The Texas Heart Institute, Houston, Texas: O. H. Frazier, M.D., Denton Cooley, M.D.

University of Alabama Medical Center, Birmingham, Alabama: William Holman, M.D.

Washington Hospital Center, Washington, DC: Paul Corso, M.D., Jorge Garcia, M.D.

Discussion

DR. KEITH REEMTSMA (New York, New York): It is a pleasure for me to discuss this paper by Dr. Frazier and his colleagues. This work is an outstanding contribution to the important and evolving field of mechanical circulatory support.

This study demonstrates major changes both in concept and in technology since the earlier, much publicized work with the total artificial heart. The conceptual change involves the use of a mechanical device as an auxiliary or parallel pump rather than as a replacement for the heart, thus permitting the use of

the native heart in case of mechanical failure. The technological advances alluded to by Dr. Frazier include the development of surfaces that actually encourage the replacement of endothelium by the patient's own tissues. And the low incidence of thromboembolism in this series testifies to the effectiveness of this approach.

The success reported by Dr. Frazier has stimulated interest in the use of these devices for permanent implantation as opposed to bridges to transplantation. My colleague, Dr. Eric Rose, who succeeded me as Chairman of Surgery at Columbia, together with Dr. Frazier and Dr. McCarthy, now is planning a randomized prospective trial of this device in nontransplant candidates, comparing the left ventricular assist system with medical treatment. Their proposed study would compare medical outcomes as well as cost-effectiveness and quality-of-life measurements. We believe that such studies are important when the widespread application of these things may become possible.

Again I would say that this will be a landmark study during the next decade as we hear more and more about mechanical circulatory support. And, Dr. Frazier, again I congratulate you and your colleagues on this remarkable achievement.

DR. DENTON A. COOLEY (Houston, Texas): I also would like to congratulate Dr. Frazier on this remarkable report combining experience from 17 centers in the United States. I find such cooperation among institutions today extremely important, as the data and analyses that result do more to encourage progress in the field than the individual reports of aggressive and spectacular cardiac surgical procedures that were once the norm. I am pleased that Dr. Frazier, from our institution, has been a leader in the field of mechanical circulatory support.

Our early interest in bridges to transplantation reached a clinical level in April 1969, when we used a total artificial heart (TAH) as a bridge. During the 1980s, use of a TAH as a bridge was applied again in this country and abroad. The results did not encourage further clinical application at that time, although research and device development continued in the laboratories of the Texas Heart Institute and elsewhere.

Pulsatile support devices have now been shown to function effectively as left ventricular assist devices and may provide 80% to 90% of cardiac output. Mechanical pulsatile devices, however, usually produce some continued patient discomfort.

Dr. Frazier, will you give information regarding the physiologic need for pulsatile flow and predict the future prospects for continuous flow support devices?

DR. HOOSHANG BOLOOKI (Miami, Florida): Dr. Frazier and Dr. Rose are to be congratulated for a very fine study, which has been done, as was indicated already, by 17 centers. And in my opinion, it is a very difficult task to get them all together to follow the protocol.

The left ventricular assist device, the HeartMate, I think is the only device that works well and will be the device of the future. It causes a profound effect on cardiac output, and peripheral resistance. The high survival rates that were reported are a great deal better than the results in the past and indicate how good this device works and how dedicated the investigators are. I have two interrelated comments and questions.

First, if survival is this high, is it ethical to proceed with randomization? Is there another device with results similar to this one? The only other device perhaps would be an intra-aortic balloon pump, which is being used in most patients prior to placement of HeartMate. Along that line, at what point do you decide that we should go on now and use the HeartMate? Are there criteria or objective data that you follow or the criteria are based on subjective evidence, such as New York Heart Association Class?

My second question is related to the long waiting time of patients who are on HeartMate to get a heart transplant. Is that intentional? Are you waiting to get an optimal donor and this possibly is resulting in better survival results? Furthermore, because the patients are on this device for a longer period of time than the usual status I patients, it is possible that a long period of circulatory assist is causing a change in the immunological competence of these patients, to a point that when they get transplanted, the donor heart is less frequently rejected.

Once again I congratulate Dr. Frazier and his colleagues for a fine piece of work and thank the Association for the privilege of discussing it.

DR. ROBERT M. MENTZER, JR. (Madison, Wisconsin): I congratulate Dr. Frazier and his colleagues on their results and for providing us with important new information regarding the role of left ventricular assist devices in the management of patients with end-stage heart disease. It certainly appears that this particular device dramatically alters outcome in the severely debilitated heart failure patient awaiting transplantation.

A potential criticism, however, is the fact that the study was nonrandomized and performed at 17 different study sites with potentially different patient selection criteria, not only for a bridge to transplant, but heart replacement in general.

Although the investigators have compensated for this by adhering to strict criteria for use, the variability in patient referral patterns and philosophy regarding the treatment of patients with end-stage heart disease make it difficult for small programs or growing programs to project the number of patients at a given site that should have access to this device.

At the University of Wisconsin, there has been a steady increase in the number of patients transplanted between 1990 and 1994. The program has grown from 9 transplants in 1990 to 57 in the past year.

Although the number of patients transplanted in the past 2 years is nearly twice that of the previous 3 years, the frequency of use of the left ventricular assist device for both time periods has remained the same; that is, at the level of 5%. This is despite the fact that over the past 2 years, there has been a marked increase in the number of patients that have been referred with advanced end-stage heart disease and listed as United Network for Organ Sharing (UNOS) status 1 patients.

The same frequency of use during these two time periods is due in part to the fact that we have been able to increase our organ utilization rate from 41% to 70% and thus, have in part obviated the need for a bridge to transplant. This improvement in organ utilization began in 1992.

With this single-center experience in mind, I would like to ask Dr. Frazier, first, can you provide some insight into the percentage of patients at a given transplant site that might be

expected to need or use the assist device? Secondly, with Food and Drug Administration approval of this device, are these strict criteria that you have relied on going to be relaxed? If so, does this mean that the device should be used earlier and more frequently?

Finally, I would like to ask Dr. Frazier's opinion regarding underutilization of available organs and his recommendations, if any, for minimizing the need for a bridge to transplant.

I compliment the authors on their dedication and commitment to this extremely important area of clinical research.

DR. O. HOWARD FRAZIER (Closing Discussion): I appreciate the discussants' comments. In particular, I thank Dr. Reemtsma for his encouraging remarks.

In Europe, a randomized study has already been undertaken to address the question of older or otherwise disqualified transplant candidates. Within the next year, I hope that a similar study, comparing medical therapy and patients treated with the left ventricular assist system (LVAS), will be undertaken in the United States. Because of the safety of long-term implantable left ventricular assist systems, such a study seems almost mandatory. We hope to obtain support for such a study through the National Heart, Lung and Blood Institute.

Dr. Cooley alluded to his pioneering work in this field. Of course, he has been my mentor and has given me a great deal of support in this endeavor. His allusion specifically referred to the optimistic research regarding the continuous-flow pump. In contrast to pulsatile pumps, which do not have a suitable compliance chamber and, therefore, must be vented to the outside, the continuous-flow pump does not require either a compliance chamber or valves. As more experience is gained in using long-term ventricular unloading to improve the function of the native heart, it may become possible to operate this pump at lower levels of flow, in which case 2 to 3 L of continuous flow would be augmented by the improved native heart function and resulting pulsatility. We are doing research in this area and hope that our efforts can be continued. This approach offers great promise for cardiac support and for giving patients maximal freedom and mobility.

Dr. Bolooki mentioned randomization. A control group is necessary under current federal requirements for device approval. So this issue must be dealt with from a statistical standpoint, and I believe that such an approach is possible. Dr. Kurt Dasse of Thermo CardioSystems was integrally involved in our obtaining a satisfactory control group for our study. I think that the problem will be simplified, however, when the LVAS is electively implanted, rather than when patients are near death.

The device's success is indeed likely to increase the length of hospitalization in the bridge-to-transplant patient. One simply does not want a questionable donor heart for a patient who is doing well on a safe, effective device. With earlier assist devices, which were more subject to complications, the goal frequently was to perform transplantation as soon as possible. In contrast, this system is safe and reliable, and, therefore, allows optimal timing of transplantation. If the patient can be sent home, however, the length of stay and the cost of care will be reduced. In addition, the outcome will be improved as demonstrated in this study, probably because the patients will be in much better physical condition at the time of transplantation.

Dr. Mentzer spoke of the control group. Actually, this group was quite suitable from a statistical standpoint. This was not a prospective, randomized trial, but a nonrandomized trial with concurrent controls. The control group was obtained from a group of patients who met all of the requirements for implantation, but who did not receive an LVAS for various reasons.

I do not know how many patients could potentially benefit from this system. However, patients continue to die awaiting transplantation. In 1993, United Network for Organ Sharing (UNOS) recorded 762 deaths; the percentage of deaths is even higher in large patients with type O blood, who wait much longer for a heart (median 319 days in 1993) than other patients. Estimates of need for mechanical circulatory support range as high as 60,000 patients per year in the United States. Currently, the LVAS is being used to support 51 patients in the United States.

Like other new devices, this one will probably be used much more widely once researchers have gained more experience with it and more confidence in its safety and effectiveness.