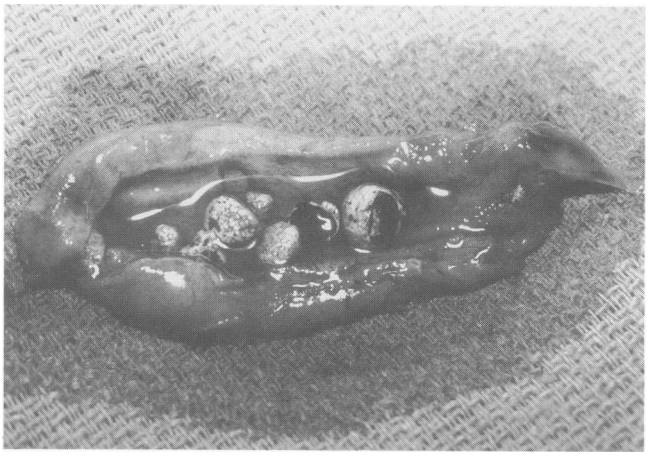

Figure 4. Example of a "coated" or "mixed" gallstone from a pediatric heart transplant patient who underwent cholecystectomy. The black core is composed of breakdown products of bilirubin and it is covered by cholesterol deposits.

ral course. Available surgical treatments, namely cholecystectomy and endoscopy, are tolerated well by heart transplant patients after transplantation. Recognition of such observations is important for physicians who follow these patients in the setting of the heart transplant center, and especially for general surgeons and other physicians who are increasingly involved with their care in community-based practices. Awareness of which patients are at higher risk—*e.g.*, through routine screening and early recognition of symptoms when they develop—will help initiate prompt and effective treatment.

Acknowledgments

The authors thank Ms. Debbie Monyak for assistance in preparation of the manuscript, Mr. George Katsones for the statistical calculations, and the Heart Transplant Program coordinators at Emory University.

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Discussion

DR. JOAQUIN S. ALDRETE (Birmingham, Alabama): Dr. Thompson, Dr. Copeland, Members, and Guests. I wish to express my appreciation to Dr. Amerson and Dr. Ricketts for inviting me to discuss this important contribution and for making their manuscript available to me several weeks ahead of the meeting.

They have carefully analyzed a field that has been emerging in the past 10 years. As more heart transplants have been done and these patients have survived longer periods of time, it has become evident that they have a number of illnesses affecting their digestive system. Some of them with presentation, incidence, and evolutions that are quite different from the nontransplant population and, in fact, different, I think, from patients similarly immunosuppressed because of kidney or liver transplants.

The careful analysis of the incidence, evolution and presentation of the biliary lithiasis to the symptoms and complications in the heart transplant patients certainly deserve special attention to improve their survival.

They found a very high incidence of biliary lithiasis in this selected group of patients. Furthermore, they noticed that in a significant proportion of these patients who initially were asymptomatic subsequently became symptomatic and others in whom the pretransplant ultrasound revealed no biliary lithiasis, a few months after the transplant, the repeat ultrasound showed calculi.

These findings have prompted the authors to recommend careful monitoring, routine ultrasounds—pretransplant and post-transplant—and, in fact, they are proposing prophylactic cholecystectomies. I completely agree with their aggressive treatment as soon as the patient develops symptoms. However, I have difficulties agreeing with screening everybody with heart transplants for biliary tract disease. And mainly, I am not certain that prophylactic cholecystectomy should be done in the patients who have stones but have no symptoms.

The reasons for this skepticism: It is our own experience at the University of Alabama, from the inception of our heart transplant program in 1981, I have had the privilege to be an integral part of the team that monitors and follows these patients. And, in fact, I get called to see in consultation most of these patients as soon as they develop symptoms of their digestive system.

There have been 413 heart transplants performed since 1981 in 377 patients in our institution. When we review some years back our initial study of the gastrointestinal complications in these patients, we analyzed 151 patients undergoing 169 transplants and found that only 4 had required operations in the biliary tract.

When I reviewed last week our experience from 1989 to date, there were 244 other patients that underwent heart transplantation. And in these patients, only 11 of them require an operation in their biliary tract, mostly cholecystectomy.

I must add that these patients are very carefully monitored by a group of cardiac surgeons, cardiologists, transplant cardiologists, and nurses, and that our team gets called to see all of these patients with even faint question of abdominal pain. Therefore, I think we have an honest discrepancy in the incidence of biliary lithiasis in this very selective group of patients.

I have no doubt whatsoever of the validity of the data presented by the authors. But in our own experience, the incidence of biliary lithiasis in heart transplant patients has been 4% in contrast to 30% that they are showing.

I also think that it is hard to establish cyclosporine as the etiological factor. Since cyclosporine became available, approximately 2500 patients have received a kidney transplant in Dr. Diethelm's program. And there were only 25 patients, only about 1.3%, who had operations for biliary lithiasis. These patients, again, are very carefully monitored. So I do not think that cyclosporine has really a significant influence in the etiology of the biliary lithiasis.

I completely agree that in the patients with heart transplants, if they develop any symptoms in the gastrointestinal tract, a diagnostic survey should be done and if any condition correctable by an operation becomes evident, the operation should be done promptly. But we have an honest discrepancy in opinion in regard to prophylactic cholecystectomy. And I think that is exactly the purpose of meetings like this, that we can compare our data and try to see what is the best treatment for our patients.

I hope that down the road 4 or 5 years from now we will be able again to compare our results, our experience, and come to a more conclusive recommendation that will be helpful for these patients.

Thank you very much.

DR. THEODORE N. PAPPAS (Durham, North Carolina): Dr. Thompson, Dr. Copeland, Ladies, and Gentlemen. This is a very interesting paper and even more interesting manuscript that I had an opportunity to review.

I have some comments and three questions. The comments relate to our experience at Duke with the same patient population. Early in the experience with heart transplantation at Duke, the transplant team decided to monitor these patients with ultrasound. And, unfortunately, at that time they were only referring patients for cholecystectomy who had symptoms. They had one patient early on who developed terrible pancreatitis and it took him about a year to recover. We eventually got him out of the hospital. But being soured by that experience, the transplant team began referring all patients with gallstones for elective cholecystectomy.

Since that time, we have done approximately 40 elective cholecystectomies; we have done no emergent cholecystectomies. The vast majority have been done laparoscopically, and we have had one patient who had a complication. That was an arrhythmia that required an extended hospital stay of approximately 4 days. The current management includes same-day admission for laparoscopic cholecystectomy and discharge within 24 hours. So we treat the laparoscopic cholecystectomies on heart transplants essentially very similar to all the other laparoscopic cholecystectomies. So I think our experience has been similar to the experience that was just reported from Emory. I am certainly not a zealot and am willing to hear other opinions about how to manage these people. But we feel comfortable with this approach for the time being.

We have a similar experience with the incidence of gallstones, and approximately a third of patients in fact have formed gallstones, be it due to cyclosporine or not.

I have three questions. Have you had trouble in Atlanta with patients who have been referred from a long distance away and have had stones detected and then require cholecystectomy away from Emory? In other words, occasionally do patients develop symptoms and have to have intervention away from the transplant center? And how do you deal with this problem?

In the manuscript, there appeared to be a couple of patients who were operated on emergently. In retrospect, could some of these emergent operations have been avoided with more careful scrutiny?

And I have this ongoing problem that was just mentioned about renal transplant patients, why this discussion about prophylactic cholecystectomy goes on in heart transplant patients but does not seem to enter into the discussion with renal transplant patients. And I would like to hear your comments about why the two patient populations are different.

Thank you very much.

DR. MARY MANCINI (Shreveport, Louisiana): Dr. Thompson, Dr. Copeland, Members, and Guests. I would like to take this opportunity to compliment the authors on an excellent review of a topic of growing importance as the transplant recipient population increases and our long-term survival rates improve.

It is only by reviewing large clinical series of this nature that we are able to begin to formulate treatment strategies for these highly selected patient populations that develop general surgical problems. This paper reiterates three important points.

First, that the transplant recipient population develops general surgical problems often at an accelerated rate than the general population. Secondly, that these patients can undergo general surgical procedures quite safely. And, most importantly, that once these patients become symptomatic with biliary tract disease, they should be approached with an aggressive tactic.

Experience has taught the thoracic transplant surgeon that an ounce of prevention is worth a pound of cure. And, in fact, in our program, we routinely survey all of our potential candidates for biliary tract disease. This has allowed us to detect potential problems and complications and take an aggressive tact in treating the symptomatic patient post-transplant.

I have a little bit of difficulty with proposing prophylactic cholecystectomy in this patient population. I congratulate the authors on their lack of complications in this patient population postoperatively. However, as one continues, one will begin to see increasing difficulties.

I have several questions for the authors, and I would like their opinions on this because I really do not have answers as to the exact approach to this patient population.

Characteristically, during the first year after transplant, the immunosuppressant regimen in this patient population is not static. And, in fact, cyclosporine levels are adjusted chronically and gradually reduced. Also, I have difficulty with blaming cyclosporine for the entire biliary tract problem. Have the authors been able to correlate any of their symptomatology in their patient population with cyclosporine levels with decreasing or increasing cyclosporine or immunosuppression treatment correlated with rejection episodes in that first year?

Also, after the first year, have you noticed a decreasing incidence in your symptomatic biliary tract disease?

Were cultures routinely obtained of the bile in these patients? And, if so, I would be interested to know the profile of the organisms found.

The authors address the aspect of hemolysis or at least imply that this may be a problem. One should recall that in routine cardiac surgery, we do have a slight increased incidence in biliary tract difficulty postoperatively; however, it is very difficult to document hemolysis in that population as well as in the heart transplant population. Was an attempt made to address hemolysis in these patients or laboratory values obtained in the post-transplant period? I know we routinely do not do this.

One aspect to consider, is the contribution of cytomegalovirus infection to this problem. It always seems that when these patients develop cytomegalovirus infection, we always have a gastrointestinal problem that follows it.

Lastly, I would like the authors opinions, again, on the renal transplant population and what their speculation is as to why we do not see this problem in other transplant populations where the gallbladder is still present. I have my own biases, but I am interested in their opinion.

Again, I congratulate the authors on a fine presentation and thank the Association for the privilege of reviewing this paper.

DR. HARVEY J. SUGERMAN (Richmond, Virginia): President Thompson, Secretary Copeland, I rise just to question the possibility of prevention. In a randomized multicenter prospective study in an unrelated population of patients with morbid obesity, we found that the incidence of gallstone formation after rapid weight loss was approximately 32%. With prophylactic ursodeoxycholic acid, that incidence was cut to 2%, and it was only needed to be prescribed over a period of 6 months.

So, again, back to the last question by the last discussant: When did these stones form in the post-transplant period? Is it early? Is it late? And if it is only early, perhaps one ought to consider a multicenter study to evaluate whether you could prevent the development of these stones in the early post-transplant period.

DR. FREDERICK R. BENTLEY (Louisville, Kentucky): I would like to congratulate the authors on a very good paper. I support their approach to prophylactic management of these patients in the postoperative period.

We, too, have noticed an increased incidence of *de novo* stone formation after a cardiac transplant. I looked this up a few years ago, and found it to be 15% of new stone formation within the first 12 months after a cardiac transplant. These were in patients who all had pretransplant ultrasounds.

Early in the cardiac transplant experience, there was a policy of doing pretransplant cholecystectomies, which was the ultimate bad idea. It was accompanied by a very high mortality rate in those patients and was rapidly abandoned.

Two questions for the authors. Were lipid profiles followed in these patients in the first 12 months after their cardiac transplant? If so, were any attempts made to correlate stone formation in patients with high cholesterol and triglyceride levels?

If there is any correlation, do the authors feel that an aggressive approach to decreasing cholesterol and triglyceride levels in cardiac transplant patients may reduce the incidence of stone formation?

I thank you.

DR. MIRA MILAS (Closing Discussion): Thank you, Dr. Thompson, Dr. Copeland, Members, and Guests. I appreciate very much the thoughtful comments of the discussants. They bring about some common themes which I hope to address, either together or individually.

I would first like to respond to Dr. Aldrete's discussion. His question regarding the need to screen everybody is, I think, in our study answered by the observation of a high incidence of disease and that a high percentage of patients do in fact become symptomatic. It would be valuable to identify those patients who are at risk for developing more serious complications, and screening is one method of doing that.

His next question addressed prophylactic cholecystectomy or doing the cholecystectomy in patients who have not yet manifested symptoms. And this was also echoed by several other discussants.

I think it is fair to say that the cardiac transplant patients comprise a very select group of patients. In them, the patterns of management that are typically applied to the normal population may not be appropriate.

Our study and several others that have been reported in the literature show that there is an accelerated natural course. Normal patients typically may develop symptoms after 15 years; but even then, only 18% of them do so. It is safe to observe them during the time that they are asymptomatic.

In our study, a high percentage (40%) develop symptoms within the first year, which is clearly different. Also well documented is the very high rate of morbidity and a 37% rate of mortality in patients who have urgent surgery. On the other hand, none of the patients in the studies that have been reported before, nor in ours, have died when elective surgery was performed.

To answer these questions and also some of the honest differences in the rates that are observed, a prospective study would be very welcome. This would probably require a multi-institutional study to gain the high numbers of patients required.

I would like to proceed to Dr. Pappas's questions. There are a few patients who over the years have gone to their hometown to have the cholecystectomy performed. We did not review their records, and none of those patients were symptomatic. I think they were referred after stones were identified.

Your question regarding whether some of the emergent operations could have been avoided. Yes, they probably could have been. A few patients have had one to two prior episodes of mild symptoms. I think a point to recognize is that in these patients, we have to be very vigilant to recognize the symptoms early, because they may be something that in a normal patient we could attribute to minor causes but in heart transplant patients could lead to a more complicated illness.

I can only speculate on what several discussants asked about. Why do renal transplant patients not have the same pattern that cardiac transplant patients do? At Emory University, the renal transplant patients are also regularly screened. They have ultrasound studies both pretransplant and post-transplant, and the same high incidence is not noticed. They, too, use cyclosporine as the main immunosuppressant agent. Perhaps it has something to do with the organ in question causing perturbation on the liver, either because of low cardiac output or congestion. It would be very interesting for other studies to address this issue further.

I appreciate Dr. Mancini's comments very much. And if she will allow me, I think I could summarize them under the theme of wondering about the multifactorial nature of gallstones. Our study was not designed to answer what in particular causes the high incidence. As we study our patients more and review the literature, we have found that there really are no good answers yet, and there are several speculations, all of which were summarized in our presentation. We did not correlate cyclosporine levels with gallstone development.

Cultures were not routinely obtained, and it was very difficult, in a chart review type of study, to identify and look for evidence of hemolysis. But I, for one, find it very curious as to what would be the cause of this high incidence of gallstones in heart transplant patients, and I would be very excited if there were studies out there that address this on a more basic level of investigation.

Choleretic agents as applied to the heart transplant population is a very interesting idea and probably also would be well analyzed in a prospective study. As I mentioned earlier, the stones in our group of patients developed within the first year after heart transplant. And, clearly, this is probably the time that those choleretic agents might become useful.

Dr. Bentley's question regarding lipid profiles: at the Emory heart transplant center, patients have yearly lipid profile levels obtained, and we did not find any correlation between the lipid levels and the high incidence of gallstones.

In summary, I would like to thank my co-authors and particularly Dr. Ricketts and Dr. Amerson, who are here, for the opportunity to perform this study, and also the Association for the honor of discussing this paper today.

Thank you.