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# Liver Transplantation: The University of Pittsburgh Medical Center Experience

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Wayne A. Calder

Presbyterian University Hospital  
Pittsburgh, PA

## Abstract

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**PURPOSE:** To provide the perfusion community with a literature review of liver transplantation and the four year liver transplant experience at the University of Pittsburgh Medical Center

**METHODS:**

1. define the various diagnoses associated with liver transplantation
2. describe past and present immunosuppressant therapy
3. describe the development and use of a heparinless veno-venous extracorporeal circulation system
4. describe the development and use of past and present rapid-infusion systems
5. correlate liver disease diagnosis with blood usage and survival

**CONCLUSION:** Liver transplantation is fast becoming a service operation:

1. operative mortality has decreased from 10% to less than 1%
2. operative bloodloss and blood usage has been significantly reduced
3. gastrointestinal engorgement has essentially been eliminated

## Introduction

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After 20 years as an experimental procedure, orthotopic liver transplantation has come of age. It gives the chance of excellent rehabilitation for patients with no other treatment available, and the operation is oftentimes less costly than prolonged care of a patient dying of liver disease in hospital.<sup>1</sup>

The history of liver transplantation dates back to the immediate post World War II years when early experiments, performed primarily on dogs, showed the

technical feasibility of transplanting a liver into a recipient, either heterotopically or orthotopically. The first known reported efforts at experimental liver transplantation were made by Dr. Jack Cannon of Los Angeles in 1956. This report was very brief but did note the animals did not survive operation. In June and August of 1958, programs of canine orthotopic liver transplantation research were initiated respectively at the Peter Bent Brigham Hospital in Boston by Dr. Francis D. Moore and at Northwestern University in Chicago by Dr. Thomas Starzl. The technical problems of liver transplantation and the issues of rejection in untreated canine recipients were delineated and chronic survival was achieved in mongrel dogs, of which one lived for almost 12 years.<sup>2</sup>

The history of human orthotopic liver transplantation dates back to March 1963 when Thomas Starzl and associates performed the first liver transplant at the University of Colorado in Denver. This patient died along with four other liver replacement attempts in Boston and Paris. Finally, after six consecutive failures in three institutions, the first extended survival of a human recipient was achieved on July 23, 1967. The patient, an 18 month old girl, lived for more than 13 months before dying of metastases from the hepatocellular carcinoma for which she had been treated.<sup>2</sup> Since 1963 and until 1979, the Colorado group performed 170 liver transplants with an adult survival rate of only 24%. The worldwide survival rate at this time was approximately 26%.<sup>3</sup> With these statistics it is understandable that the attitude among health care providers was that liver transplantation was a last-ditch and expensive effort. Up until 1984 this attitude was supported by the fact that there were only six centers on the North American continent that were involved in orthotopic liver transplantation. These centers were located in Pittsburgh, Minneapolis, Memphis, Sacramento, Boston, and London, Ontario.

In the last two years, this attitude has dramatically changed. In June 1983, during the National Institutes of Health's Consensus Development Conference, organized to develop guidelines on liver transplantation, Dr. Thomas Starzl reported that liver transplant

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Direct communications to: Wayne Calder, 9232 Oak Court, Pittsburgh, PA 15237

one-year survival rate at the University of Pittsburgh since 1981 exceeded 50%,<sup>4</sup> and there have been recent reports that suggest that one-year survival in pediatric patients should exceed 85% and approach 75% in adults.<sup>5</sup> This reasoning is supported by the proliferation of liver transplant programs during the last two years to 40 programs in North America and approximately 25 centers outside the United States and Canada.

The number of patients that these centers will treat is difficult to estimate. Few new centers will expect to transplant more than 15 patients per year and most likely will treat fewer than 10 per year. In Pittsburgh, the projected number of adult and pediatric transplant procedures to be performed in 1986 is approximately 400.

Although there are many variables to consider for the increased number of liver transplants performed worldwide and the tremendous increase in 1-year survival during the past 5 years, the introduction of Cyclosporin A as a potent immunosuppressant has had a dramatic impact on survival following liver transplantation, while the use of heparinless, venovenous bypass system has contributed to a number of the technical difficulties to the anhepatic phase of a liver transplant procedure.

## Materials and Methods

### 1. Diagnoses Associated with Liver Transplantation

In 1983 the American Liver Foundation estimated that 100 hospital admissions and 50,000 deaths in 1983 were attributable to liver disease. It has been estimated that only 5,000 of these patients would be suitable candidates for liver transplantation. Also during 1983, after a thorough review of the literature and oral testimony by experts in the field, an NIH panel determined which patients would be most likely to have a satisfactory result from transplantation. The panel concluded that patients most likely to benefit from liver transplantation are those with biliary atresia, chronic active hepatitis, and primary biliary cirrhosis. Other less common potential candidates include patients with alpha-1-antitrypsin deficiency, Wilson's disease, Criglar-Najjar syndrome, and some genetic disorders.<sup>4</sup> A brief synopsis of the more common liver diseases associated with adult liver transplantation is given.

a. *Primary Biliary Cirrhosis* is a chronic, progressive, and usually fatal liver disease. The etiology of the disease is unknown, however, it is widely assumed that tissue injury is mediated by immunologic mechanisms and that the pathogenesis is related in part to abnormalities of immune response. This liver disease group comprises the

largest number of liver transplants (73 patients).<sup>6,7</sup>

b. *Cirrhosis and Hepatitis* contain the second greatest number of liver transplant patients (65). Cirrhosis is a diffuse process characterized by fibrosis and a conversion of normal architecture into structurally abnormal nodules. Fibrosis is an integral part of the definition and pathogenesis of cirrhosis. Also, it is essential to the diagnosis because it differentiates cirrhosis from diffuse nodular hyperplasia.<sup>6,7</sup>

The etiology of cirrhosis is varied and may be unknown in individual cases. The major causes are listed below. Their significance and predominance varies geographically and socially. For example, alcohol is the most common cause of cirrhosis in the United States and England, whereas cirrhosis due to hepatitis B is common in Africa and many parts of Asia. In addition, cirrhosis is usually classified by its etiology; however, some causes are best grouped under a common pathogenesis, for example, biliary obstruction. In this system, cirrhosis is a stage in liver damage reached in the evolution of a particular disease.<sup>6,7</sup>

### *Etiology of Cirrhosis*

Drugs	Alcohol
Infections	Hepatitis B Hepatitis non A, non B
Autoimmune	Chronic active hepatitis Primary biliary cirrhosis
Metabolic	Wilson's disease Alpha-1-antitrypsin deficiency
Vascular	Budd-Chiari syndrome

- c. *Chronic Active Hepatitis* is a term used to describe an illness associated with prolonged and continuing inflammation of the liver following an attack of hepatitis B or arising spontaneously of unknown etiology. Alcoholic liver disease, Wilson's disease, primary biliary cirrhosis, alpha-1-antitrypsin deficiency, and drug induced chronic active liver disease may show clinical biochemical and histological features similar or indistinguishable from chronic active hepatitis. Using strict criteria, patients can be recognized who have almost no chance of survival beyond six months and these patients may be suitable for liver transplantation.
- d. *Sclerosing Cholangitis*, an uncommon disease of unknown etiology, is a chronic inflammatory fibrosing process affecting all parts of the biliary tract including the gallbladder, but may be localized to either the extra- or intrahepatic ducts.

This disease group includes the third largest number of liver transplant patients (33).<sup>6,7</sup>

- e. *Wilson's Disease* is a fatal defect in copper metabolism characterized by an accumulation of excess copper and impaired biliary excretion of the metal and is present in individuals who have inherited a specific pair of abnormal recessive genes. The underlying defect in copper homeostasis has not been determined. Patients who have undergone liver transplants have had a dramatic reversal of this abnormal metabolism, which strongly suggests that the primary defect lies in the liver.<sup>6,7</sup>
- f. *Common Adult Liver Diseases Associated with Liver Transplants*
  - 1) Alpha-1-antitrypsin deficiency
  - 2) Crigler-Najjar syndrome
  - 3) Budd-Chiari
  - 4) Hemophilia
  - 5) Hypercholesterolemia
  - 6) Wolman's disease

The preceding descriptions and listing are but a brief synopsis and the interested reader should consult his medical library.<sup>6,7</sup>

## 2. *Past and Present Immunosuppressant Therapy*

Immunosuppression for human liver transplantation is the direct result of the kidney transplant prototype. Liver transplantation is too complex to be used as a model to evaluate pharmacological agents or combinations thereof; instead all methods to prevent or reverse rejection of organs have depended upon observation after renal transplantation. Azathioprine, described and reported in 1962, was the first genuinely promising drug to be used as an immunosuppressant. However, it proved to be effective only rarely when given alone and in 1963 it was realized that Azathioprine and Prednisone have an additive or possibly synergistic effect. This double drug therapy has been the most commonly used immunosuppressant for almost 20 years. Between 1963 and 1979, alternative therapeutic programs were introduced for renal transplantation. All were modifications of or additions to the original double drug therapy. One promising approach involved lymphoid depletion with antilymphocyte globulin (ALG) derivative which was given intravenously or intramuscularly as an adjunct to Azathioprine and Prednisone during the first few weeks or months when the risk of rejection is the greatest. The triple drug therapy has been the second most commonly used technique of immunosuppression. There was, however, from 1963 to 1978, widespread discontent with all techniques with immunosuppression and there was certainly a hope for better immunosuppressive drugs to increase the success rate in organ transplantation. This hope became at least partially realistic with the advent of Cyclosporin A.

Cyclosporin had a modest beginning as a newly discovered derivative from the fungi *Cylindrocarpum lucidum* and *Trichoderma polysporum* discovered and characterized biochemically by scientists at the Sandoz Corporation of Basel, Switzerland, and noted to have immunosuppressive properties in 1972 by immunologist Jean F. Borel, Ph.D., also of Sandoz Corporation. Since 1978 in Europe and since 1980 in the United States, numerous clinical trials have shown that Cyclosporin is as good or significantly better than the previous and more conventional Azathioprine-Prednisone therapy used by most organ transplantation institutions. Cyclosporin interferes with the body's immunologic machinery in numerous but highly specific ways. Most notably is its ability to inhibit the function of helper T cells which play a crucial role in the generation of both cellular and humoral immune responses. Much helper T cell activity is mediated by lymphokines, a group of regulatory proteins secreted by lymphocytes which act on other cells. In addition, Cyclosporin seems to inhibit the synthesis of certain other T cell lymphokines, including immune interferon, interleukin-3, and several others that recruit and activate macrophages. Cyclosporin's complete action remains elusive, however. In general, patients receiving Cyclosporin retain their grafts longer and have fewer rejection episodes than patients treated with conventional therapy.<sup>8</sup>

## 3. *The Development and Use of a Heparinless Venovenous Extracorporeal Circulation System*

The use of extracorporeal circulation during liver transplantation came about primarily due to difficulty, both physiologically and at times technically, during the anhepatic phase of the procedure. During this phase of the operation, the abdominal portion of the inferior vena cava and the portal vein are cross-clamped. Because of the loss of blood return to the central venous system from the inferior vena cava, the cardiac output can be reduced as much as 20% in young, otherwise healthy patients, and as much as 50% or more in older patients or those with pre-existing cardiac ailments. Many of the latter patients develop marked hypotension, a 300% to 400% increase in systemic vascular resistance, cardiac arrhythmias, cardiac failure, and at times cardiac arrest. Patients who can tolerate the cross-clamping of the inferior vena cava and the portal vein still require large infusion volumes of crystalloid and blood product solutions resulting in severe fluid overload at the time of liver revascularization and cross-clamp removal. The portal vein cross-clamp can produce gut swelling and petechial hemorrhage with frank gastrointestinal bleeding not being an infrequent occurrence. Because of this lack of control for both the surgical and anesthesia teams, several means to reduce or eliminate these problems have

been examined, namely end-to-side portacaval shunts combined with femoral to jugular venous bypass cannula (unsuccessful both in 1960 studies by Francis Moore in Boston and T.E. Starzl in Denver and more recently by Starzl in 1982 in Pittsburgh) and extracorporeal circulation systems.

Previous to 1983 and as far back as 1963, extracorporeal circulation has been attempted during liver transplantation. Except for the Cambridge-Kings College Hospital liver transplant program, which was using a venoarterial extracorporeal system on approximately 10% of the liver transplant procedures, all other liver transplant centers abandoned bypass systems because of disappointing results, mainly due to excessive and potentially fatal bleeding caused by systemic heparinization of the recipient. During the fall of 1982, a study was performed at the University of Pittsburgh to test the plausibility of using a venovenous circuit without systemic anticoagulation during liver transplantation. The study was described by McSteen at the 1984 American Academy of Perfusion meeting and reported by Denmark et al in 1983.<sup>10</sup> Briefly, the unique components of the nonheparinized, reservoirless, filterless, extracorporeal system are the Bio-Medicus<sup>a</sup> centrifugal constrained-vortex pump and heparin-bonded 7 mm and 9 mm Gott shunts connected to short lengths (approximately 25–30 inches) of PVC tubing via a 3/8" straight and a 3/8" Y stainless steel connector. Custom tubing set-up is provided and sold by the Argyle Division of Sherwood Medical of St. Louis, Missouri. Although priming differences do exist between the two tubing systems, cannulation of the patient in preparation for the venovenous bypass is similar. The femoral vein is exposed and the Gott shunt (7 mm end with side hole) is inserted into the femoral vein to near the confluence of the common iliac veins. A 9 mm Gott shunt is inserted end-on into the transected portal vein. The portal vein and inferior vena cava cannulae provide drainage to the Bio-Pump while venous blood return is via a 7 mm Gott tubing inserted into the ipsilateral axillary vein. Extracorporeal circulation of deoxygenated blood is initiated and maintained at approximately 30 to 50 cc/kg/min with the lowest acceptable adult flow rate at 1000 cc/min (below this flow rate clots and platelet aggregates are more likely to occur and have been witnessed in the laboratory). Once bypass is established at an acceptable flow rate, the vena cava above and below the recipient's native liver is clamped, the liver is excised and removed from the field. Because the portal venous and lower caval systems are decompressed, petechial hemorrhages in the bowel or significant gastrointestinal hemorrhage has been virtually eliminated.

After revascularization of the new liver and flushing (300 to 500 cc of cold Lactated Ringers), bypass is discontinued by clamping afferent and efferent lines of the Bio Pump and the blood vessels are quickly decannulated and the extracorporeal lines are handed off the surgical field to the perfusionist. Bypass times range between 60 to 150 minutes.<sup>9</sup> As of January 1, 1986, the above-described venovenous bypass system has been utilized during 313 adult liver transplants and on 18 pediatric liver transplants.

#### 4. *The Development and Use of Rapid Infusion Systems:*

Prior to the routine use of nonheparinized venovenous bypass, the median number units of blood transfused was 28, and even in our most recent series, the median packed red blood cell usage is 9 units. Why is so much blood needed for adult liver transplant? The answer is several-fold. First, since the liver produces all but two of the clotting factors and because these patients are in end-stage liver disease, they present with preexisting coagulopathies. Also, the liver is a blood filled organ receiving approximately 300 ml/min from the hepatic artery and approximately 1,000 ml/min from the portal vein. Many of the transplant candidates have portal hypertension, a frequent complication of cirrhosis, with subsequent venous collateral circulation and an increased rate of collateral blood flow. Most of the bleeding occurs while the recipient's native liver is being removed. In addition, some patients have had previous surgery and there are problems with adhesions and large collateral blood vessels.

Because of the potential for large loss of blood and the need for replacement blood products, the use of multiple IVs, pressure infusion bags, and numerous personnel is not the most efficient means to manage the well-being of the liver transplant patient. The Perfusion Department, in cooperation with Dr. John Sassano of the Anesthesia Department, developed a system called the Rapid Infusion Pump that allows the anesthesia personnel or perfusionist to better manage the patient. This system has been used on all adult liver transplants at Presbyterian-University Hospital since the Fall of 1982. The system consists of one or two cardiotomy reservoirs, an arterial filter, heat exchanger, PVC tubing, polycarbonate or stainless steel connectors, infusion cannulae, and an optional air bubble detector to automatically shut off the roller head pump if the cardiotomy reservoirs are drained of prime. In order to maintain normal hemodynamics before, during, and following liver bypass, this system can be utilized to rapidly infuse a blood product crystalloid prime at a rate as high as 2,000 cc/min through two large infusion cannulae (10 gauge or 8 French) usually inserted through the antecubital veins or the external or internal jugular veins opposite from the venovenous bypass cannulation site.<sup>12</sup> Dr. John Sas-

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a Bio-Medicus, Inc., Minneapolis, MN 55344

sano, in conjunction with Haemonetics, Inc., is currently evaluating several prototype rapid infusion systems for production in the very near future.

#### 5. *Correlation of Liver Disease Diagnosis with Blood Usage and Survival*

Adult orthotopic liver transplants performed between January 1, 1981 and October 1, 1985 were reviewed. Patients were categorized by primary diagnosis. RBC (packed red blood cells; hematocrit approximately 70%, and unit volume of 250 to 300 cc) and survival rate (defined as discharged from the hospital) were determined. The patient population was divided into three groups. Group I is comprised of 68 patients having orthotopic liver transplants prior to the routine use of heparinless venovenous bypass. Group II contains Group I patients plus 110 additional liver transplants. Group III contains the adult liver transplant population from January 1, 1985 until October 1, 1985; all patients in this group were placed on venovenous bypass.

- a. *Group I:* In patients with primary biliary cirrhosis, a median of 15 units of packed red blood cells (RBC) with a range of 3 to 123 were used intraoperatively. The survival rate was 69%. Patients with carcinoma had an intraoperative median use of 17 with a range of 6 to 65 units and a survival rate of 67%. In contrast, patients having a diagnosis of sclerosing cholangitis used a significantly greater number of RBC units; a median of 36 with a range of 10 to 143 units and survival of 50%. The patients having a diagnosis of cirrhosis or hepatitis had a median use of 39 units and a range of 7 to 251 units and a survival rate of 49%. Overall, the median number of units transfused for the group was 28 with a range of 3 to 251.
- b. *Group II:* In patients with primary biliary cirrhosis, a median of 13 units of RBCs were used intraoperatively having a range of 1 to 123, survival 82%. Carcinoma patients had a median of 15 units with a range of 6 to 148 and a survival rate of 77%. Patients with sclerosing cholangitis had a median of 18 and a range of 3 to 143 units; survival was 79%. A cirrhosis or hepatitis primary diagnosis had a median of 25, a range of 4 to 251, and a survival of 63%. The median RBC use for Group II was 18 units—significantly less than Group I (28 units).
- c. *Group III:* Patients having a diagnosis of primary biliary cirrhosis used a median of 8.5 units of RBCs intraoperatively with a

range of 2 to 84 units and a survival rate of 85%. Cirrhosis or hepatitis brought a median of 12 with a range of 4 to 167 units and a survival of 77%. Sclerosing cholangitis patients needed a median of 10 units and a range of 9 to 28 units RBCs; survival was 100%. During the first nine months of 1985, only two primary liver carcinoma diagnoses were transplanted. As a result, they were added to a miscellaneous category along with the following diagnoses: Carolis, hepatic tumor (nonmalignant), hepatic trauma, hemangioma, hepatic failure, hemophilia, and Budd-Chiari syndrome. This category used a median of 11.5 units with a range of 4 to 26 and had a survival rate of 75%. In the metabolic liver disease category, including Wilson's disease (three patients), alpha-1-antitrypsin disease (two patients), and one hypercholesterolemia patient, the median was 15 units with a range of 10 to 84 units of RBCs and the survival rate was 67%. The overall median packed red blood cell unit usage for Group III was 9 units with a range of 1 to 167 units.

In general, the frequency distribution of intraoperative packed red blood cell usage for the first 68 adult liver transplants and the last 107 transplants show that the more blood products used the less chance of survival. Red blood cell usage correlated with diagnosis. In Groups I and II, those conditions not associated with portal hypertension or perihepatic scarring used fewer blood products. Since all patients in Group III were placed on venovenous bypass, those primary diagnoses categories which without bypass would use large amounts of blood due to portal hypertension or perihepatic scarring now need much fewer blood products and have a higher survival rate.<sup>13</sup>

#### **Conclusion**

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The liver transplantation experience at the University Health Center of Pittsburgh during the last four years has emerged from the experimental, expensive, blood devouring, oftentimes last ditch and heroic efforts into a service operation which is performed on a daily basis with efficiency and increasing success. During the first two years of the program, approximately 60 liver transplants were performed at a great cost of lives, blood, and money. Operative mortality was approximately 10%, blood requirements were quite high, as much as 250 units of packed red blood cells, and cost of the procedure could be well over \$200,000. In 1985, 175 adult liver transplant procedures were

performed with heparinless venovenous bypass. The operative mortality is now < 1%, blood usage has decreased from a median of 28 units in the first 60 patients to a median of 9 units of red blood cells in our most recent evaluation. Costs from initial evaluation to discharge from the hospital after transplantation range between \$50,000 and \$100,000 depending on the duration of time spent in the intensive care unit after the operation. More important, however, is the quality of life of patients after successful liver transplantation. They return to active life and gainful employment is achieved in as many of 85% of the adults receiving transplant, and children who have successful transplants return to school and have normal growth and pubertal development.

In the first 20 years of the liver transplantation experience, approximately 500 procedures were performed. In 1986 we expect to perform approximately 400 adult and pediatric liver transplant procedures. With the increasing regularity of liver transplantation procedures, clinical decision-making is enhanced and patient care improved. Serious data are becoming available that will serve as the basis on which modifications of existing and new programs can build. Certainly, there are many issues to be resolved, however, our efforts as health care providers at the University Health Center of Pittsburgh have been worthwhile. Because of the need for more liver transplants (in 1983 the National Institutes of Health estimated a need of 5,000 liver transplants in that year) and the great proliferation of liver transplant institutions it is inevitable that many more perfusionists will be involved in liver transplant programs.

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## Questions from the Audience

*Question—Lanier Allen:* Have you had any instance in rapid infusion where you had to have "O" bank blood, you couldn't keep up with the bank blood to the point where you had to use real old blood—and had very high potassiums in your patients?

*Answer:* No I haven't. At our institution, our anesthesia department is responsible for the rapid infusion pump. I don't have any direct knowledge of whether they have or have not. We monitor the potassium closely, plus the ionized calcium, because of the citric toxicity, a potential for the large amount of blood being given. During bypass, I do know what the ionized calciums and the potassiums are, and it's very rare that they are above 5.5. For the most part they're between 4 and 5, 5.5 max.

*Question—Lanier Allen:* At MCV we have had several instances when we have had "O" bank blood that has had tremendously high potassium levels and I used the Cell Saver and washed the blood before we put it into the rapid infusion system. Just a note that some people may be interested in. We had one 7-year-old child, that was a redo, who could not stand to have any potassium on board at all, because there was a problem with the kidneys also. So, I washed all the blood from the bank that we had to put into the patient, and we had no problems at all with high potassium levels. But we had some instances when we didn't do that. They were dead.

*Response—Calder:* Very good point. We need to have a very, very large blood bank—for the most part, for cardiac service and liver service. It's very rare that we get old blood.

*Question—Bob Emerson:* You mentioned, at the beginning, the heat loss. Have you taken any special precautions in trying to keep the liver patients warm?

*Answer:* Yes and no. Not through the circulation system. We heat all ingoing fluids, all the IVs. All the blood that is being infused is warmed to normal/thermia, the ventilating gases are warmed, and the blanket underneath the patient is put up to max. Very rarely do we even warm the room. In the majority of the patients, the temperature will drop pre-bypass because of the larger area up into the atmosphere. Usually it's about 35 degrees before bypass. When we go on bypass, our system holds about 350 or 400 cc's. You see a slight decrease of 1/10 or 2/10 of a centigrade in body temperature. Once the liver is removed, if it's a long time before the new liver is brought to the field, you'll see an even greater decrease in temperature. Then, of course, once the liver is flushed with 300–500 cc's of cold, it's usually around 4 or 5 degrees centigrade. When it's washed with lactated Ringer's solution, of course, the temperature decreases even more. By that time our temperatures are usually 34.5 to 35. In some instances, the temperature has been 33, and we have gotten down as low as 31. I'm not aware of any that have caused cardiac arrhythmias, however. I do know of other centers reporting back to us that ask about the use of and incorporation of the heat exchanger. And so the only thing that I have said is that we haven't seen the need in our particular system.