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p25
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ETHICS

# A Harvard study on newborns draws fire

## Doctors faulted for limiting life-saving treatment

By Richard A. Knox
Globe Staff

A Harvard University study involving mortally ill newborns is being challenged as unethical in a debate that raises important questions about how to do research on promising new therapies.

Critics around the country are raising two kinds of objections to the still-unpublished Harvard study.

The study was unethical in the first place, some charge, because it involved withholding from some infants with lung damage potentially life-saving therapy that earlier, less scientifically rigorous data had indicated was probably superior to conventional treatment.

Four infants with potentially reversible lung damage died on conventional respirator therapy before the researchers stopped assigning babies to that alternative.

Second, critics say it was improper for the researchers not to seek consent from parents of the infants assigned to conventional therapy. Parents of 10 conventionally treated infants were not told their children were part of a randomized trial in which some babies would get the promising but possibly risky new treatment.

Parents of nine babies randomly assigned to the new treatment, called extracorporeal membrane oxygenation, or ECMO, were asked for their consent. All ECMO-treated babies survived.

"The clear expectation was that more patients would die on conventional therapy," statistician Donald A. Berry of the University of Minnesota, one of the study's harshest critics, said in a telephone interview. "So the question is whether having an excess of deaths balances the worth of information gained. Since I believe such information is available without randomizing, my answer is a resounding no."

Prof. Richard M. Royall of the Johns Hopkins School of Public Health charged in an interview that once the Harvard researchers decided a randomized clinical trial was necessary, they had to "cut corners" on informed consent in order to proceed. "It's clear to me they did not ask consent because it would be hard to get a control group otherwise," Royall said. "Properly informed parents would say 'No thank you.' "

However, not all agree the study was unethical at the outset.

A second group, represented by Colin B. Begg of Memorial Sloan-Kettering Cancer Center in New York and Paul Meier of the University of Chicago, lambastes the Harvard researchers from the diametrically opposite side. They say the researchers were so preoccupied with ethical problems that they stopped assigning babies to conventional therapy too soon, before

NEWBORNS, Page 27

# ECMO: a temporary artificial lung for seriously ill newborns

*ECMO, or extracorporeal membrane oxygenation, takes over the lungs' function of supplying oxygen to the blood and removing carbon dioxide, allowing the infant's damaged lungs to recover. Tubes inserted in the neck shunt blood from the baby's heart to the pump oxygenator. That machine adds an anti-clotting drug (heparin) to the blood and creates an exchange of oxygen and carbon dioxide in the blood, then returns it to the infant's aorta to be circulated through the body.*

## Harvard study results

*The following are survival rates of patients in study. Phase 1 was randomized to ECMO and conventional medical therapy (CMT) . In Phase 2 only ECMO was used.*

**Phase 1: Randomized trial**

| | ECMO | CMT |
|---|---|---|
| Lived | 9 | 6 |
| Died | 0 | 4 |

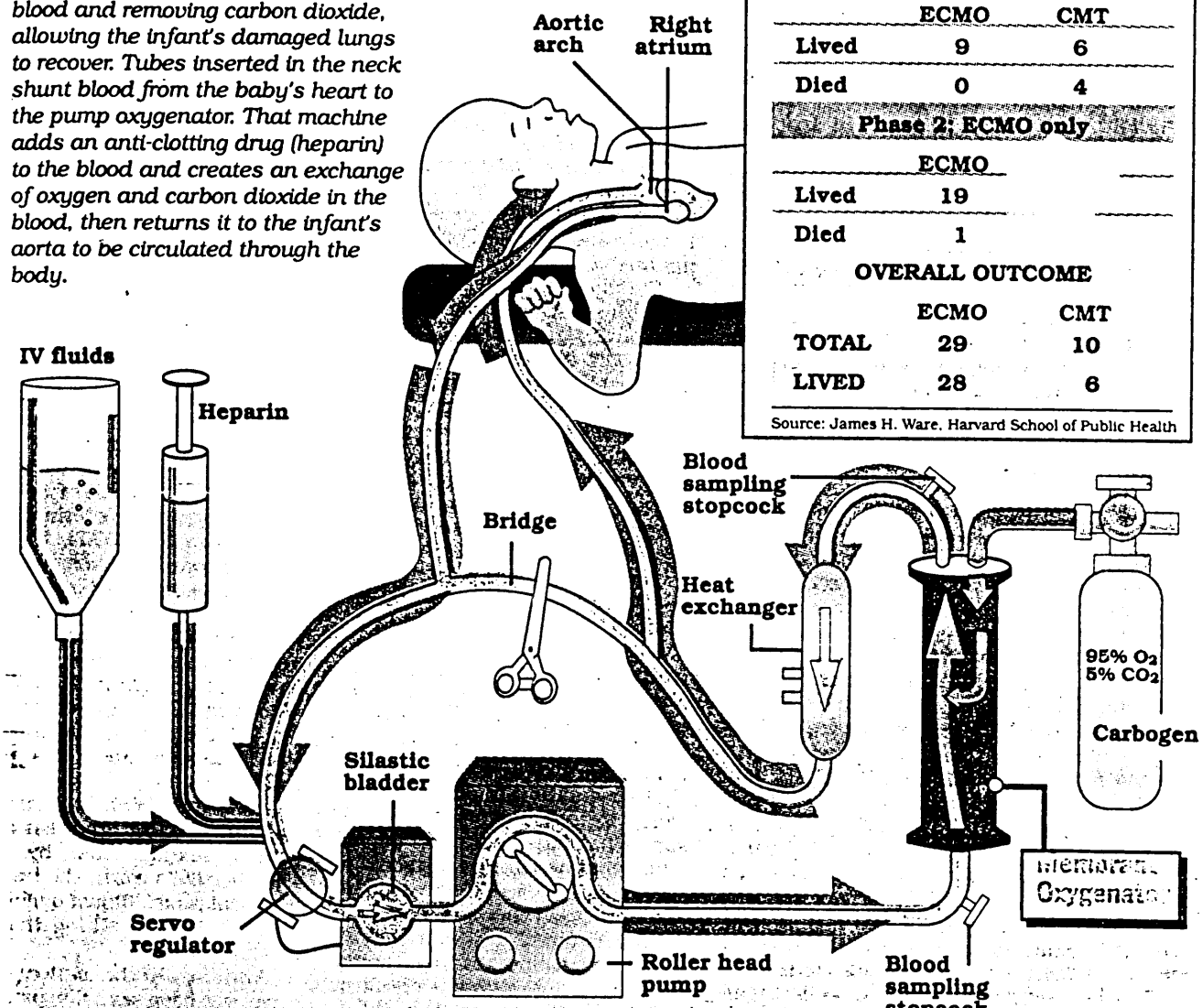
**Phase 2: ECMO only**

| | ECMO |
|---|---|
| Lived | 19 |
| Died | 1 |

**OVERALL OUTCOME**

| | ECMO | CMT |
|---|---|---|
| TOTAL | 29 | 10 |
| LIVED | 28 | 6 |

Source: James H. Ware, Harvard School of Public Health




Source: Dr. Michael Epstein Children's Hospital, and James H. Ware, Harvard University

Globe staff graphic / Neil C. Pinchin

# Harvard newborn study raises ethics question

■ **NEWBORNS**

Continued from Page 25

they really clinched the case for the experimental treatment.

"The Harvard study was informed by the slightly hysterical view that we must immediately stop [a study] as soon as we have an idea which treatment might be better," said Meier. "If we're not careful, we will soon have a system in which we can establish nothing."

The Harvard researchers say the controversy is no surprise.

Dr. Michael Epstein of Children's Hospital in Boston and biostatistician James H. Ware of the Harvard School of Public Health, who led the Harvard study, said in a joint interview they anticipated ethical objections. They said they tried to design the project to circumvent such problems while still gathering data to settle whether ECMO was truly better.

"We saw this as a departure from business as usual, and we thought we had been sensitive to the ethical concerns," Epstein said. "But we expected a lot of controversy and criticism."

Expected or not, "it's been a little more lively than I thought it would be," Ware added.

The storm is sure to intensify. Up to now the argument has been behind the scenes, but an unusual public debate on the study is scheduled for Thursday in Washington at the annual meeting of the American Statistical Association.

The Harvard study is already being cited as an important case study in a growing debate about the conduct of clinical research. "The questions are entirely generic," Royall asserts. "The Harvard case is an extreme one, but you need an extreme one to dramatize the problem."

The ECMO case comes at a time when AIDS activists have already won the attention of establishment scientists with their criticisms of clinical research, such as the randomized clinical trial – the "gold standard" of medical research.

In such a trial, patients are selected at random to receive one or another treatment. As in the ECMO study, there is often ethical tension between halting randomization when one treatment appears better and pressing on until the evidence is statistically robust.

Epstein and Ware launched the ECMO trial out of a need to settle a long-running controversy over the therapy, first used 12 years ago to save infants with several kinds of lung damage. The technique is in essence nothing more than the 35-year-old heart-lung bypass technology that made open-heart surgery routine, but in this case it is applied for up to two weeks to infants whose lungs cannot support life.

The focus has been not on premature infants with immature lungs but on full-term babies with lungs damaged at or before birth.

Babies with damaged lungs can have what is called persistent fetal circulation, in which not enough blood flows through their lungs to sustain life. Even with the aid of a respirator, more than 80 percent of such infants died before the advent of ECMO.

At Harvard and approximately 60 other US centers where ECMO is now routine, at least 80 percent of these infants now live, but many neonatologists refuse to accept such data because the outcome can be biased by how sick the treated babies were, and because there is no comparison with comparably ill babies treated at the same time with conventional therapy.

Persistent fetal circulation is not a rare condition, though it is much less common than the respiratory distress syndrome suffered by preemies. One or two full-term babies in every 5,000 has the condition, and about one a month is treated at Children's Hospital or the Brigham and Women's Hospital.

"These babies are the sickest of the sick," Epstein explained. "They are among the most difficult patients in any neonatal intensive care unit because, unlike preemies, these are kids who 'should have been fine.' "

Such infants are the focus of intense effort because the lung damage is potentially reversible. If caregivers can buy enough time for the lungs to recover – generally five days to two weeks – the problem can resolve itself, and the infant has the same prospects as any born healthy.

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Early results with ECMO were encouraging, but skeptics abounded because ECMO had not worked in adults with lung problems. Moreover, ECMO imposes serious risks, especially of hemorrhage into the brain or other vital organs.

In 1983, Dr. Robert H. Bartlett of the University of Michigan, decided to mount a randomized trial in the hope of settling the issue. But his group felt uncomfortable assigning patients totally at random because earlier results with ECMO had seemed so promising.

Instead, they used an innovative method called "play-the-winner" randomization, in which the odds of a baby's assignment to ECMO or conventional therapy depended on what happened with the previous baby. For instance, if

a baby got ECMO and survived, the chances increased for the next baby to get ECMO. If a baby got conventional therapy and died, the next baby's chances of getting ECMO also would increase. The idea is to minimize the number of deaths from whichever treatment turns out to be inferior as the trial progresses.

While fine in theory, the Michigan experiment resulted in the assignment of only one infant out of a total of 12 to conventional therapy, and that infant died. All 11 ECMO babies survived.

Ware and Epstein decided to do a more conclusive study.

"To me, the idea we should accept a new treatment based on that kind of thin, scanty information was irresponsible," Ware said. "I can cite example after example of 'breakthroughs' that didn't pan out."

The Harvard researchers faced an even bigger ethical problem than the Michigan team had, because the evidence favoring ECMO had continued to accumulate.

When the Harvard study began, a national registry of ECMO cases contained about 200 babies. The registry showed 80-85 percent survival in babies whose expected survival was only 20 percent.

In a paper scheduled for publication in the journal Statistical Science in November, Ware acknowledges that the Harvard group believed in advance "there was a strong possibility that a randomized trial would show large differences in survival" between ECMO and conventional therapy.

To minimize unnecessary deaths among the conventionally treated infants, they decided they would stop assigning babies to conventional therapy after four infants died from either treatment. Ware calculated this would be barely enough to demonstrate a significant difference in survival.

As expected, the study came out in favor of ECMO. All nine babies randomly assigned to ECMO survived without evidence of side effects. Six of 10 treated conventionally survived.

After they stopped randomizing, the group treated another 20 babies with ECMO using the same selection criteria, and 19 survived. Thus, ECMO had a 97 percent overall survival rate compared with 60 percent for conventional therapy.

Like the Michigan group, the Harvard group decided not to seek consent from parents of infants assigned to conventional treatment. The decision was controversial among the team. "We had several weeks of discussion over autonomy versus paternalism," said Epstein. "I'd prefer to call it openness versus compassion," Ware interjected.

Epstein and Ware said they did seek consent from parents of conventionally treated infants to protect them from the burden of having to decide whether to participate in a randomized trial and then worry if their child were being shortchanged. They felt ethically justified, they said, because the infants were getting "the best conventional therapy we have to offer" and because doctors were still divided on ECMO's merits.

They also worried what would happen if the parents of conventionally treated infants knew there was an alternative.

"We might have faced a situation in which a baby randomized to conventional therapy was doing worse and there would be tremendous pressure from the parents to cross over [to ECMO], and we felt we could not," Epstein said. "We were trying to relieve parents of the burden of thinking there was an alternative treatment available if only they said the magic word."