

Host: Welcome to the *ANESTHESIOLOGY* journal podcast, an audio interview of study authors and editorialists.

Dr. BobbieJean Sweitzer: Hello, I'm BobbieJean Sweitzer, professor of anesthesiology at Northwestern University and an associate editor for *ANESTHESIOLOGY*, and you are listening to an *ANESTHESIOLOGY* podcast, designed for physicians and scientists interested in the research that appears in our journal. Today we are speaking with two authors of publications that appear in the July 2020 issue of the journal. With us is Dr. Marc-Olivier Fischer. Dr. Fischer is the first author of an article titled "Individualized Fluid Management Using the Pleth Variability Index: A Randomized Clinical Trial." Dr. Fischer is professor in the anesthesiology and critical care medicine department, Normandy University, Caen University Hospital, Caen, France. Welcome Dr. Fischer.

Dr. Marc-Olivier Fischer: Hello Dr. Sweitzer and hello everybody and thank you for this invitation.

Dr. BobbieJean Sweitzer: And joining Dr. Fischer is Dr. Kamal Maheshwari, who wrote an accompanying editorial: "Goal-directed Therapy; Why Benefit Remains Uncertain." Dr. Maheshwari is professor in the departments of general anesthesiology and outcomes research, Cleveland Clinic, Cleveland, Ohio, but he's joining us today from England. Welcome Dr. Maheshwari.

Dr. Kamal Maheshwari: Thanks for the invitation. A pleasure to be here.

Dr. BobbieJean Sweitzer: So Dr. Fischer, let's start with you. And would you please tell us what you were trying to accomplish with this study?

Dr. Marc-Olivier Fischer: Sure. A lot of data is available regarding the benefit of goal related therapy to decrease the postoperative morbidity, especially for high risk surgical patients using invasive hemodynamic monitoring. And fortunately, hemodynamic monitoring is carefully used at the bedside because it could be considered as time consuming and invasive by anesthesiologists. The solution to increase its use in the operating room could be the noninvasiveness of this device. So we tested a new noninvasive (inaudible) method, the pleth variability index of hemodynamic monitoring to conduct goal-directed therapy in the operating room to decrease the hospital length of stay following surgery.

Dr. BobbieJean Sweitzer: Maybe perhaps before we get into the details of this new device in your study I want to ask Dr. Maheshwari to help us understand this phrase goal-directed therapy. I know it's become common in our medical vernacular, but can you define it for us? Tell us what it means exactly.

Dr. Kamal Maheshwari: Goal-directed therapy, as the name suggests, is trying to meet an objective hemodynamic goal over the specific interventional therapy. Administration of intravenous fluid is a universal and common intervention performed by anesthesiologists and critical care physicians. And when we give fluids how much we give, what type of fluid we give, these are important considerations to optimizing hemodynamic status. And our goal usually is to maximize oxygen delivery, which we achieve by maximizing cardiac output or stroke volume through the flat portion of cardiac pressure volume curve. And so this concept has been the central tenet of the goal-directed therapy. More recently it's been also called as individualized fluid management or individualized hemodynamic management.

Dr. BobbieJean Sweitzer: Dr. Fischer, who did you enroll in your study and what kinds of surgeries were these patients having?

Dr. Marc-Olivier Fischer: We included (inaudible) patients scheduled for hip or knee arthroplasty under general anesthesia with mechanical ventilation.

Dr. BobbieJean Sweitzer: And would you consider these patients low, intermediate or high risk patients and why?

Dr. Marc-Olivier Fischer: We included patients with low to intermediate surgical risk because the pleth variability index was not validated for high risk surgical patients, which would benefit from cardiac output monitoring and/or arterial line. In regard of the type of surgery, the surgical risk was

classified as intermediate. So we can then say that the global surgical risk was intermediate.

Dr. BobbieJean Sweitzer: Dr. Maheshwari, there has been quite a variability in outcome of various trials evaluating goal-directed therapies or individualized fluid management. What's up with that?

Dr. Kamal Maheshwari: I'm glad you asked this question. Based on an individual study when we say a certain intervention or a drug worked or did not work, by definition we are saying that we did not find any difference in a specific variable or outcome between the intervention group and the control group. In any individual study the choice of outcome variable, its definition, the extent of difference between groups, which we usually call the clinically meaningful difference, are key decisions and they also introduce the variability into different trials.

There are many systematic biases like insufficient data, different population, measurement error, selection bias, confounding and so on, which makes the interpretation of research and especially the observational research which has been done in this area very difficult. Randomized trials seems to be the cure for all these biases. And they are one of the best instruments, and I congratulate Dr. Fischer for doing this randomized controlled trial. But even with the best randomized controlled trial you have different types of technology, different treatment protocols, how people adhered to the protocols during the study period. They all introduce variability.

And finally, the confusion derived from even the best RCD, which is in one population, for example low risk, may not be applicable to a different population which is, let's say, high risk or different setting. And which is the limitation of the external validity of randomized controlled trials. So there are many reasons of variability of outcomes and conclusions of various goal-directed therapy trials.

Dr. BobbieJean Sweitzer: Dr. Fischer, was your study a single center study or not and how many patients were included in this trial?

Dr. Marc-Olivier Fischer: The (inaudible) was a randomized controlled study conducted in five French hospitals. Four hundred and forty-seven patients were randomized in this study.

Dr. BobbieJean Sweitzer: Dr. Maheshwari, what do we already know about goal-directed therapy from previous studies? I guess can you summarize does it work? Does it work in lots of populations? Are there still a lot of questions out there that we need to answer?

Dr. Kamal Maheshwari: Yes, the work on goal-directed therapy has been ongoing for the past couple of decades. One of the first studies focused on measuring and maximizing oxygen delivery in critically ill patients. That was a landmark study. And since then many smaller randomized controlled trials and many more observational studies have been done. But there's a huge heterogeneity in the studies with regards to the patient population, the inclusion criteria, what type of technology was used, what goals were used and what outcomes were studied.

I would focus on a couple of recent trials, and because they were one of the largest and in the perioperative setting, which is relevant to the current discussion. The first one which I'm going to talk is an OPTIMISE I trial. It was a more than 700 patient trial which studied the rate of postoperative moderate to serious complication at 30 days. And the technology which was used in this study was LiDCO, which is a type of a (inaudible) analysis, in moderate to high risk surgical patients.

In this trial in the control group they noticed 43% complications compared to in the intervention group they noticed 36%. So there's a seven percent absolute reduction in complications, which may sound to be great that yes it worked. But actually it was not statistically significant because at the time of planning the trial was powered to detect 12% absolute risk reduction. So it was an inconclusive trial.

Another large study which happened recently was the FEDORA trial, in which esophageal Doppler technology was used. Around 400 patients were included in this study. The complication rate in the control group was 16%. The intervention group was 8%. Again, same exact seven percent to eight

percent reduction in complication, but this study was set to be that yes reached statistical significance because they powered at the time of planning for 19% risk reduction.

So two markedly different results, but not (inaudible) many differences in outcomes which were assessed. One difference was very stark which was that in the OPTIMISE trial they studied complications at 30 days, compared to the FEDORA trial they studied complication at 180 days. So even the assessment period was different. So there's so many studies which can be discussed, but I will say that it highlights why the variability is there and why the question is not we can say solved yet.

Dr. BobbieJean Sweitzer: Thank you for those contrasting, you know, information. Which now leads me to ask Dr. Fischer about the technology that was used in his study. So I think in the treatment group you used this plethysmographic variability index to guide fluid administration. Can you tell us what a plethysmographic variability index is and how it works?

Dr. Marc-Olivier Fischer: The pleth variability index is a noninvasive technology with a specific sensor using plethysmographic variations induced by mechanical ventilation to assess fluid responsiveness. In contrast with the pulse pressure variation, or PPV, the pleth variability index, or PVI, is a noninvasive technology. The value of pleth variability index is showed in a specific monitor using a floating period of two minutes. A charted value can be used to assess the fluid responsiveness of patients.

Dr. BobbieJean Sweitzer: And was the plethysmographic variability index target achieved in your study? And what was that target that you aimed for?

Dr. Marc-Olivier Fischer: A cutoff value of 13% has been previously described. If the value is below 13, the patient is probably non fluid responsive. While if the pleth variability index is above 13, the patients could benefit from fluid loading to increase the cardiac input and so the tissue oxygenation. This cutoff value of 13 has been used in the (inaudible). The length of time that pleth variability index, or PVI, was available was 86% and the proportion of time that the pleth variability index was under the cutoff value of 13% during the awakening time was 36%.

Dr. BobbieJean Sweitzer: I want to explore more about the fluid and how that was actually managed. But before we get there, I'd like to ask Dr. Maheshwari another question. You know, you mentioned briefly these previous studies about the various invasive and noninvasive systems, I think, that were used and the variability across studies. So are all of these systems equally good? And if not, or if there's been one that has been highlighted as better, do you particularly contrast this system or device that Dr. Fischer used, the plethysmographic variability index, and tell us how that measures up against these other methods?

Dr. Kamal Maheshwari: It's true there are many invasive and noninvasive systems right now which are approved by FDA in the United States and EMA in Europe for clinical use. And yes there are differences and limitations of these models in different settings. And we should closely look into a few criteria when deciding to use these models (inaudible). One is the accuracy, which is how well the system captures the true value, for example stroke volume by comparing the low standard. The second is the precision, because we are using these models for repeat measurements and we need to know the consistency with repeat measurements. Also the effect of clinical setting. What is the effect of vasopressor use or various fluid states, various disease states? These all need to be considered.

FDA approval does not mean that models are good in all clinical settings for all purposes. We should closely examine the limitation of each system. Having said that, there are many invasive and noninvasive systems which are currently being used and they are helping in patient care. Specifically PVI, which is plethysmographic variability index, reflects dynamic changes in (inaudible) perfusion index, which was developed by the parent company. It's a noninvasive technology based on pulse oximeter. I personally have not used this thing and I cannot comment on its performance. But from the literature point of view in 2016 and meta analysis of 18 studies of 600 patients were published showing high

specificity which 80% and specificity in predicting the responsiveness in the operating room and ICU.

So I guess it can predict fluid responsiveness. I have not come across outcome studies which matters. And I, once again, congratulate Dr. Fischer who I believe did the first outcome study using PVI technology and helped improve our understanding about the usefulness of PVI.

Dr. BobbieJean Sweitzer: Thank you. So Dr. Fischer, other than this targeted index measurement that's the plethysmographic variability index, did you also have other parameters, like such as a target mean arterial blood pressure?

Dr. Marc-Olivier Fischer: Yes, we had the mean arterial pressure target was above 65 mmHg in both treatment and control groups.

Dr. BobbieJean Sweitzer: Got it. So what fluid management protocol did you use?

Dr. Marc-Olivier Fischer: On the treatment group a specific hemodynamic algorithm was designed. The first step was to achieve the pleth variability index below 13%. If it's not, the fluid loading of three millimeters per kilogram of gelatin was administered over five minutes intravenously. If the pleth variability index was in the target value, so above 13%, the intermittent mean arterial pressure was then observed. If its value was under 65 mmHg, ephedrine up to 30mg or norepinephrine then after were used. If the mean arterial pressure was above 65 mmHg and PVI below 13, no specific treatment was conducted. But we (inaudible) of both pleth variability index and mean arterial pressure was conduct continuously.

Dr. BobbieJean Sweitzer: So if I can better understand, you used as combination of vasopressors and fluid management to try to maintain the plethysmographic variability less than 13% and the mean arterial pressure greater than 65mmHg. Is that correct?

Dr. Marc-Olivier Fischer: Yes, exactly.

Dr. BobbieJean Sweitzer: Great. And so that was in the treatment group I think you described. What about the control group?

Dr. Marc-Olivier Fischer: The control group was managed using only intermittent mean arterial pressure value. When mean arterial pressure was below 65 mmHg fluid loading with three milliliters per kilogram of gelatin and/or vasopressor using ephedrine or norepinephrine, with the same dose as previously described was used.

Dr. BobbieJean Sweitzer: So the providers had very specific parameters of treatment. It was just the difference between the two groups was that the treatment group used this device and the control group did not, is that correct?

Dr. Marc-Olivier Fischer: Yes, exactly.

Dr. BobbieJean Sweitzer: Thank you. So Dr. Maheshwari, does it matter what outcomes are measured when evaluating goal-directed therapy? I guess I'm trying to understand if, you know, kidney injury, wound infection or other adverse outcomes depend on the same fluid management goals?

Dr. Kamal Maheshwari: Yes, the outcomes measured are critical for making conclusions from any observational research or randomized control trial. As an outcome researcher I'm always anxious about which outcomes to choose. There's a couple of principles which should be applied always. One is the biological plausibility that the intervention which we are doing will biologically make sense that it's going to affect a particular outcome or not.

And the second thing is the clinical importance. That if the outcomes differ between the control and intervention group, that they are really clinically important and that we will use this intervention going forward or not. So it does matter. The incident survival outcome just based on definition can change and, as I highlighted, the differing conclusion of OPTIMISE trial and the FEDORA trial, which reached to a different

conclusion despite seeing eight percent reduction in complication with the use of goal-directed therapy.

Dr. BobbieJean Sweitzer: Yes, so with that background, Dr. Fischer, can you tell us what outcomes that you were trying to determine or goals you had set to answer?

Dr. Marc-Olivier Fischer: Of course. So the primary endpoint was a postoperative length of stay in days following planned hip or knee arthroplasty. This endpoint was chosen because it was considered as a good reflection of the postoperative morbidity. If the pleth variability index use can improve the tissue oxygenation during surgery, this strategy could decrease the postoperative morbidity, therefore the hospital length of stay. The secondary endpoints were serious postoperative cardiac and noncardiac complications, postoperative troponin and lactate elevation.

Dr. BobbieJean Sweitzer: So was there a difference in the amount of fluids that each group received or how much fluid did each group on average receive?

Dr. Marc-Olivier Fischer: Fluid loading was used more often in the pleth variability index group than in the control group with a cumulative volume of fluid infused during surgery significantly larger in the pleth variability index group than in the control group, 1,088ml versus 677ml.

Dr. BobbieJean Sweitzer: And what did you find in outcome difference or length of stay?

Dr. Marc-Olivier Fischer: No differences were observed between the two groups regarding the primary endpoint and secondary endpoints.

Dr. BobbieJean Sweitzer: So why do you think this pleth variability index did not impact outcomes?

Dr. Marc-Olivier Fischer: Individualized goal-directed therapy using pleth variability index increases the amount of fluid loading compared with the control group, but did not provide any clinical benefits in terms of hospital length of stay or serious cardiac events, renal failure or postoperative lactate or troponin concentration. In this large and (inaudible) randomized control we did not observe any benefits, clinical benefits for our study population.

Dr. BobbieJean Sweitzer: You depended on the provider taking care of these patients to actually administer these medications and fluids based on the measured variabilities or vital signs in this pleth index. Did they actually do that? Did they give fluid when they were supposed to? Did they give pressors when they were supposed to? And did they achieve those goals that we had mentioned about maintaining the pleth index less than 13 and then MAP greater than 65?

Dr. Marc-Olivier Fischer: We observed effectively difficulties to achieve the target of PVI of 13%. Perhaps because the stated utilization of this device is not a good solution. Indeed, as observed for the pulse pressure variation, or PPV, actually a hemodynamic test to understand the variation of this PPV during, as example change in (inaudible) volume as an example, could better consider these parameters. But actually, no data are available in regard with changes in PVI during hemodynamic maneuver.

Dr. BobbieJean Sweitzer: So Dr. Maheshwari, there are both, I think, semi closed and closed loop fluid administration platforms that actually automate fluid management protocols and it doesn't rely on a provider to do the right thing, so to speak. Do you think these would improve compliance and have these kinds of systems been shown to improve patient outcomes in fluid directed therapy trials?

Dr. Kamal Maheshwari: Yes, you are right, protocol compliance is key for the successful implementation of goal-directed therapy. And the variation in protocol compliance as noted in this current PVI trial is a huge issue. And I believe, yes, semi closed and closed loop fluid administration will help improve compliance and take some of the decision making away from clinicians and help them during the process. And in fact, we recently completed a multicenter perspective observational evaluation of one such semi closed loop system, and looking forward to share the results with the rest of the community in the near future.

Dr. BobbieJean Sweitzer: Well we look forward to that. Dr. Fischer, you write in the manuscript that the adoption of goal-directed therapy has been slow to come about in clinical practice. What is your opinion on why this is?

Dr. Marc-Olivier Fischer: There is evidence for the benefit of perioperative goal-directed therapy, but its adoption is effectively slow at the bedside; nearly 10 or 20% of high risk surgical patients. One explanation for poor use of hemodynamic monitoring could be the invasiveness and time to use these devices. So noninvasive and (inaudible) implemented could be very interesting, but they need some rigorous validation for their accuracy before recommending their use in clinical routine.

Dr. BobbieJean Sweitzer: So Dr. Maheshwari, notwithstanding your soon to be published study, do you think we need more studies on goal-directed therapy or do you think we can put this issue to rest?

Dr. Kamal Maheshwari: Well it's going to take a long time before we put this issue to rest. Goal-directed therapy is a complex therapy based on different technology, in different clinical settings where it is implemented and different outcomes which are assessed. I'm sorry to say that, but the issue is alive and what we need is high quality randomized controlled trials with different technologies, in different settings and which show either goal-directed therapy improves outcomes which are clinically meaningful outcomes or not. And if it does show that it improves outcomes, then we should use it for all relevant patients. And if it does not improve outcomes, then we should stop wasteful spending and focus on other high value areas.

Dr. BobbieJean Sweitzer: Well said. I guess, you know, it's a multi-layered sort of question to answer, though, right, if we talk about these different devices. I mean there's even differences of opinion about how much fluid should be given based on the measured variables. And, you know, the use of vasopressors or vasoactive agents versus fluids. And then the variety of surgeries and the difference between low risk and high risk patients. And then the vast difference in outcomes that are measured. You know, is length of stay I guess the best measurement versus acute kidney injury versus, you know, major adverse cardiovascular events?

So I guess lots of great opportunities. As many things go, I hope you've stimulated folks' interest in this. And perhaps we don't have all the answers from this study or this discussion, but have raised a lot of interesting points and questions for the future.

I do hope today's discussion will interest many of our listeners and lead you to read these important articles to learn more. Thank you very much Drs. Fischer and Maheshwari for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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