Anesthesiology
52:365–369, 1980

Improved Clinical Measurement of Pulmonary Vascular Resistance

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Widespread commercial distribution of flow-directed thermodilution pulmonary arterial catheters, inexpensive pressure transducers, and portable electronic monitors has encouraged routine bedside assessment of hemodynamic variables in critically ill patients. However, despite these tools, measurement of pulmonary vascular resistance (PVR) has proven difficult to reproduce for two reasons: the inability to measure simultaneously requisite blood pressures and flows with simple instruments, and the inability to avoid misleading ventilation-induced pressure and flow excursions without compromising patient respiration. These difficulties can be overcome by using a low-cost microcomputer to make rapid, selective pressure measurements in a more intelligent fashion than is possible with conventional intensive-care monitors or time-consuming strip-chart waveform analyses. This report describes clinical studies and validation with animal experiments of a simple microcomputer-based measurement technique that is significantly more reproducible than conventional practice.

Pulmonary vascular resistance is equal to the pressure differential measured across the lungs divided by pulmonary blood flow, an equation that is wholly analogous to Ohm's law for electrical flow. In the strictest sense, to perform the calculation implied by this equation requires simultaneous instantaneous measurement of pulmonary arterial and left atrial pressures, and pulmonary arterial blood flow. Because pulmonary arterial blood flow is pulsatile, and instantaneous measurement of blood flow is generally not available clinically, time-averaged blood flow is conventionally determined by an indicator-dilution technique. Consequently, time-averaged pulmonary arterial pressures must also be used.

Pulmonary arterial pressures, compared with aortic pressures, are highly non-uniform and statistically unstable (not time-invariant). As a consequence, significant error is introduced into the calculation of PVR if the requisite pressures and flows are not simultaneously averaged over an identical time interval.[1] For example, the time-averaged or mean pressure in the pulmonary artery will vary between expiration and inspiration (fig. 1). Such fluctuations

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Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305. Accepted for publication November 7, 1979.

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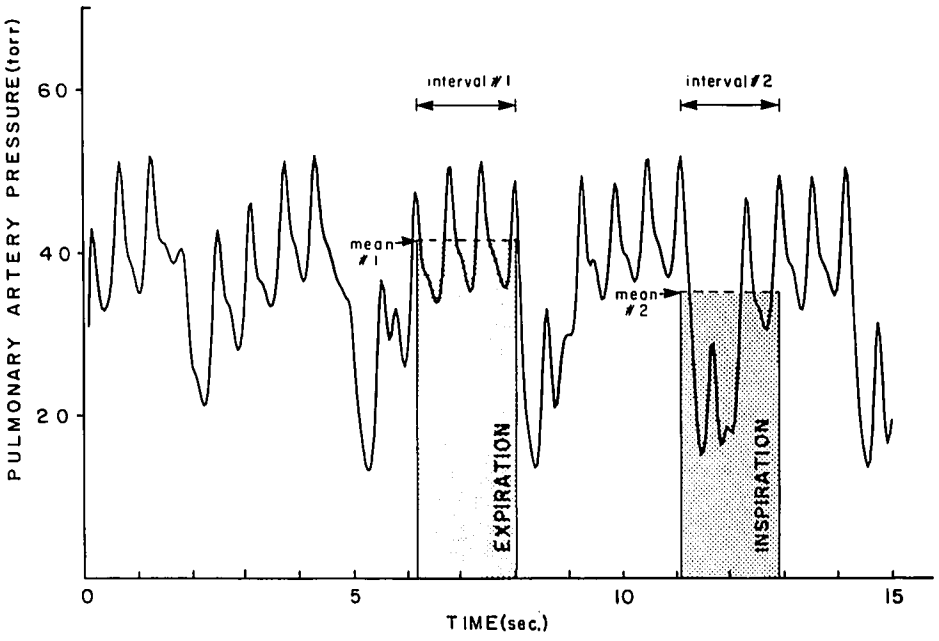

FIG. 1. Pulmonary arterial mean pressure determination. Pressure is computed by time-averaging over three heart beats. The mean for interval 1 (expiration) is significantly different from that for interval 2 (inspiration). The computer program uses only end-expiratory measurements for averaging.

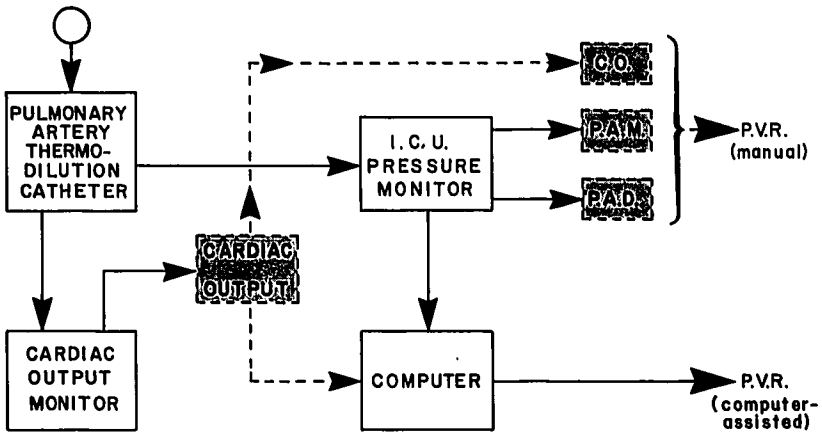

FIG. 2. Block diagram of experimental measurement apparatus.

due to ventilation are minimized by averaging only over a specific phase of the ventilatory cycle. We have elected to consider pulmonary arterial pressures for calculation of PVR during stable periods of end-expiration only.

Although open-chest surgical placement of a left atrial catheter is certainly possible, it is often impractical, and is by no means risk-free. For this reason, it is advantageous to secure a demonstrably close approximation to left atrial mean (LAM) pressure for the calculation of PVR. Both pulmonary arterial wedge (PAW) and pulmonary arterial diastolic (PAD) pressures give reproducible and well-correlated approximations to left atrial pressure in acute measurements.[2,3] In nonpathologic states, PAW and PAD pressures are both within 1–2 torr of LAM pressure.[4,5] As PVR increases, the approximately equal values for PAW and PAD pressures and LAM pressure progressively diverge[5,6]; however, even with twofold increases in PVR, both pulmonary arterial approximations remain well-correlated with LAM pressure.[7] Unfortunately, the need to obtain pulmonary arterial mean pressure and an approximate LAM pressure simultaneously through the same catheter obviates the choice of a balloon-occluded PAW pressure as the left atrial approximant. This leaves PAD pressure as the only feasible estimator of left atrial pressure.

METHODS

We tested the hypothesis that measurement of pulmonary arterial pressures and flows according to the end-expiratory stability criteria of our algorithm would yield more consistent values for PVR than by the conventional technique. Ten patients who had undergone cardiac surgery were studied in the immediate postoperative period. All routine hemodynamic, hematologic, ventilatory and fluid-balance variables were within normal limits for our institution. Some patients were receiving modest supportive infusions of either nitroprusside or dopamine, or both. Ventilation was spontaneous, assisted, or controlled. Cardiac output (CO) values were determined with an Edwards 9520 Cardiac Output Monitor® via a flow-directed pulmonary arterial thermodilution catheter. Room-temperature saline solution, 10 ml, was rapidly injected with the initiation of patient inspiration (fig. 2). A Hewlett-Packard 9825A Calculator® programmed with our algorithm and interfaced to a Hewlett-Packard 78200® ICU monitor was used for continuous digital measurement of thermo-indicator dilution and pulmonary arterial pressure during a 15-sec washout period immediately following indicator injection.

An interval period of end expiration was identified by the algorithm as stable when two successive PAD pressures were within ±2 torr of each other. The second pressure was then considered a satisfactory approximation of LAM pressure (fig. 3). Pulmonary arterial mean pressure was derived by passing the digitized pulsatile pulmonary arterial pressure through a two-pole low-pass Butterworth digital filter[8] with rolloff appropriate to yield the average pressure for the one to two cardiac cycles just prior to the stable diastolic pressure selected. After we had manually entered the cardiac output values, the computer algorithm calculated PVR for that interval by dividing cardiac output into the mean-minus-diastolic pressure differential. This computer-assisted result was immediately compared with the conventional manual calculation that simply used sequential pressure readings for pulmonary mean and diastolic pressures visually copied from the digital display of the Hewlett-Packard ICU monitor. Fifteen successful paired determinations were done in rapid succession for each patient (fig. 4). The mean and standard deviation for both manual and computer-assisted determinations were calculated for each patient. A formal Student *t* test was applied to the ten sets of paired data.

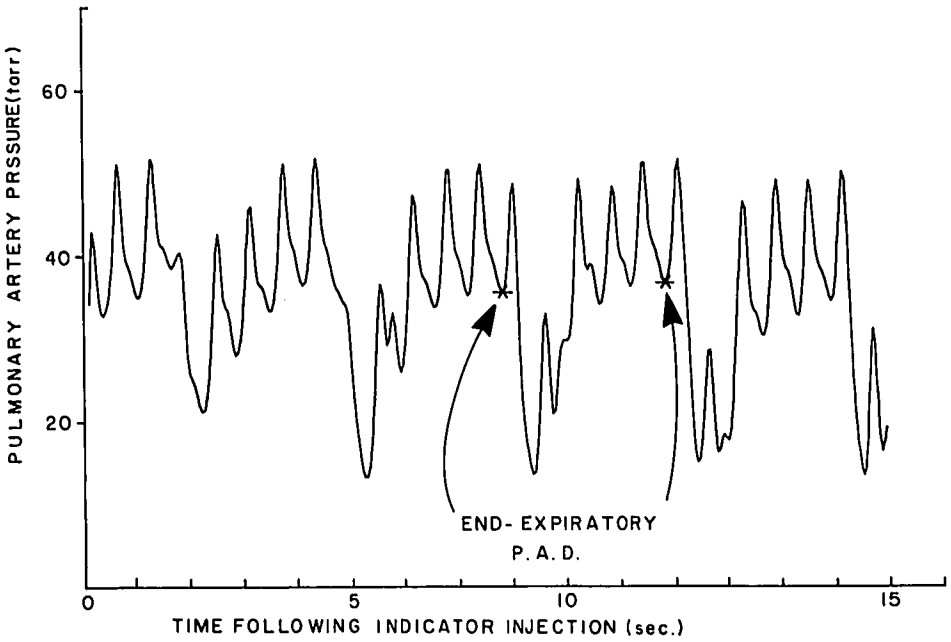

FIG. 3. Two computer-selected end-expiratory pulmonary arterial diastolic pressures at end-expiration are marked. Other end-expiratory diastolic pressures are rejected because they fail to meet stability criteria.

The computer algorithm was verified in preparations using five mongrel dogs. Following induction of general anesthesia with thiopental, initiation of mechanical ventilation and surgical instrumentation with a flow-directed thermo-dilution pulmonary arterial catheter and left atrial catheter, four hemodynamic states were sequentially obtained by selectively combined administration of vasopressor and inotropic drugs and intravenous fluid therapy. The states were defined as: I, low CO/low PVR; II, low CO/high PVR; III, high CO/low PVR; IV, high CO/high PVR. Following injection of room-temperature saline solution, 10 ml, stable intervals of end expiration during the wash-out period were extracted by the computer algorithm as previously described for the patient protocol. Simultaneous PAD and LAM pressures were compared. The PVR that was derived by using PAD pressure as an approximation of LAM pressure was compared with the PVR derived using LAM pressure. Approximately 50 sets of data points were obtained for each dog, and were evenly distributed over the following ranges: $80 \leq PVR \leq 700$ dynes cm/sec^5; $0.5 \leq CO \leq 7.2$ l/min.

RESULTS

For clarity, we have chosen to represent the averaged data for each patient as an ellipse[9] (fig. 5). The center coordinants of the ellipse represent the mean

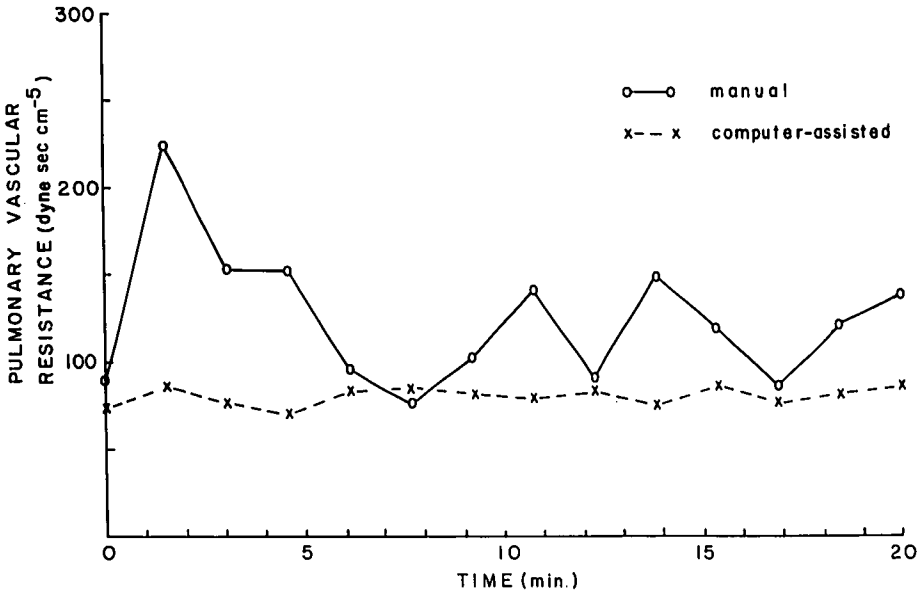

FIG. 4. Paired determinations for a sample patient.

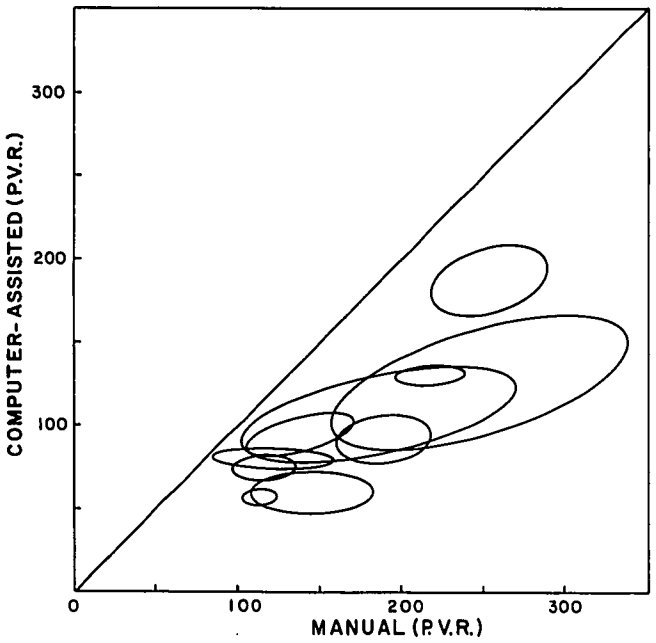

FIG. 5. Results for the ten patients studied by the two techniques (*see text*).

value, respectively, for each of the two techniques. The minor axis of the ellipse depicts the magnitude of standard deviation of the computer-assisted measurement technique; the major axis represents the standard deviation of the manual technique. The decrease in measurement scatter of the computer-assisted technique is evident: for each patient, the standard deviation of the computer-assisted technique is considerably less than that for the corresponding manual technique. The distinct flatness of the elliptic form graphically illustrates the degree of computer improvement in measurement scatter. The coefficient of variation in PVR measurement is significantly improved ($P < .001$) using the pressure-selection computer algorithm.

Linear regression analysis of the pooled results of the dog studies demonstrate that PAD pressure produces a reasonable estimation of LAM pressure (fig. 6). The computer-algorithm determination of PVR_{PAD} using PAD pressure as an estimator of LAM pressure yields a good estimation of the true PVR_{LAM} derived using LAM. Both estimations are valid over the full range of pressures and flows.

Discussion

Precise and accurate determination of PVR, using PAW pressure as an estimation of LAM pressure has been performed for years in cardiac catheterization laboratories in cases of patients having stable time-invariant pulmonary arterial hemodynamic characteristics. However, patients in the ICU are generally more critically ill, have more involved and more labile pulmonary disease, and typically have statistically unstable, time-varying pulmonary arterial hemodynamic conditions. Such hemodynamic variables defined for one time interval cannot and should not be compared with those from another time interval. Pulmonary arterial diastolic pressure has been used as an approximation to LAM pressure for this reason.

We have found, as have other investigators, that PAD pressure in dog preparations yields a biased, but linear, estimation of LAM pressure over a wide range of pressures and flows, with some statistical uncertainty. We have also demonstrated that the PVR derived from the PAD pressure used as an estimation of LAM pressure likewise yields a biased, but linear, estimation for PVR derived in the classic sense.

Because of the many influencing factors, PVR measurement reflects more than vascular tone or vascular cross-sectional area. Blood flow and pressure relationships of the right heart are demonstrably influenced by ventilatory flows and pressures within the lungs, in particular, the effects of high positive end-expiratory pressure,[10] alveolar surface tension, smooth muscle activity, and oncotic pressures.[11] A calculation of PVR that assumes static pressures (and which therefore neglects effects of kinetic and stored elastic energy) is very probably in error; however,

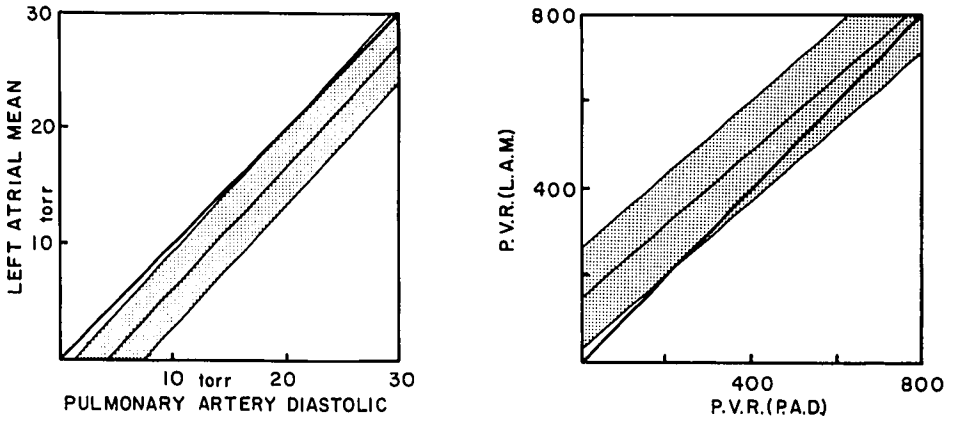

FIG. 6. Pulmonary arterial diastolic (PAD) pressure offers an estimation of left atrial mean (LAM) pressure. [LAM (torr) = 1.06795 × PAD − 4.4868, SD = 3.14 torr.] Pulmonary vascular resistance (PVR) derived using PAD pressure offers an estimation of PVR derived using LAM pressure. [PVR_{LAM} = 0.85017948 × PVR_{PAD} + 145.0436, SD = 114.9 torr.] Shaded areas represent ±1 SD.

end-expiratory pressure measurements taken at near-zero airway flows should theoretically minimize this error, since transients should have maximally settled by end-expiration. The PAD pressure values obtained just before initiation of the next ventilatory cycle would yield the most stable estimation of LAM pressure. The low-pass digital filter yields a mean value for pulmonary arterial pressure that is an exponential weighting of all previous pulmonary pressures.

The algorithm demonstrates that more reproducible determinations of PVR can be obtained in the ICU. Although the PVR so derived is surely biased, it will permit more reliable detection of changes in PVR. Stated in the most practical way, errors in determination of PVR caused by the conventional method of calculation can be larger than changes that would indicate a change in a patient's condition if accepted as real. Our approach is straightforward, easily implemented, and significantly decreases the scatter in results not due to a change in patient status.

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Anesthesiology
52:369–370, 1980

Beta-receptor Blockade Following the Use of Eye Drops

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Glaucoma is characterized by increased intraocular pressure (IOP), which, if untreated, eventually leads to blindness due to restriction of the retinal arterial blood supply and compression of the optic nerve head. In the treatment of glaucoma, use is made of autonomic drugs, usually by topical application, to decrease IOP. However, profound systemic effects have been found with the use of these drugs.[1–3] Increased IOP can also be decreased with the aid of β-adrenergic blocking agents.[4] These drugs, used topically, have met with great enthusiasm, since they do not disturb vision or cause hyperemia of the conjunctiva. Despite the potential usefulness of β-adrenergic blocking agents in the treatment of glaucoma, there is a danger that they too could exert a systemic effect following topical application because of high lipid solubility and ease of tissue penetration. This has recently been shown to occur in the case of pindolol, a β-adrenergic blocker, in healthy volunteers.[5] We now report the occurrence of systemic effects with timolol (Timoptic®), a β-adrenergic blocking agent, when used by topical application in a patient with glaucoma.

Report of a Case

A previously healthy, 73-year-old, moderately obese, 54-kg white woman, ASA 2, was admitted for vaginal repair of a cystocele and rectocele and hysterectomy. Past medical history revealed that she had glaucoma that had been first diagnosed three years prior to admission. Originally she had been treated with pilocarpine eye drops, but this had been changed, three months earlier, to timolol, 0.25 per cent, eye drops, one drop in each eye twice daily. Previous operations included uncomplicated cholecystectomy and hiatal hernia repair. She had no allergy and took no other medication. Preoperative physical examination showed no abnormality except a slow pulse, 58 beats/min. The electrocardiogram showed sinus bradycardia, but was otherwise normal.

The patient received meperidine, 75 mg, and hydroxyzine, 100 mg, im, for preoperative medication. Blood pressure immediately

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Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305. Accepted November 10, 1979.
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