

Clinical Comparison of Pressure-Pulse and Indicator-Dilution Cardiac Output Determination

ROBERT M. CUNDICK, JR., PH.D., AND REED M. GARDNER, PH.D.

SUMMARY Two clinical studies of cardiac output determination using the pressure-pulse technique are presented. The Warner pressure-pulse method of estimating cardiac output was compared with the dye-dilution technique in 17 patients. Both the Warner and a variation of the Bourgeois pressure-pulse methods were compared with thermodilution in 13 patients.

The Warner vs dye-dilution comparison resulted in a poor correlation coefficient ($r = 0.61$). Values for the Warner equation calibration constant (K) were nonstationary, varying with time from -69 to 135% of the initial value in individual patients. When thermodilution was compared with the two methods, the correlation was poor ($r = 0.58$ for the Warner method; $r = 0.50$ for the modified Bourgeois method).

The Warner and a variation of the Bourgeois pressure-pulse methods for monitoring the cardiac output of critically ill patients with widely varying mean arterial pressures are not sufficiently reliable for clinical decision-making.

ACCURATE ESTIMATION of cardiac output from the central arterial pressure wave form has been widely investigated. A reliable method would offer a major advantage over other techniques in that continuous, beat-to-beat stroke volume calculations would be possible. Many methods have been proposed.¹⁻⁵ Digital computers have significantly reduced the computation time required to process pulse-pressure data, and have thus focused greater attention on the feasibility of using pulse-pressure techniques for continuous intensive care cardiac output monitoring. Investigations comparing pressure-pulse methods of cardiac output determination with other measurement techniques have produced mixed results.⁶⁻¹⁰

In this paper we present the results of two clinical studies. The first is a comparison of the Warner pressure-pulse method¹ with simultaneously performed dye-dilution curves. The second is a comparison of the Warner and Bourgeois methods with simultaneously determined thermodilution cardiac outputs.

Materials and Methods

Detailed derivations of the Warner and Bourgeois methods are found elsewhere.^{1, 5} The Warner equation used in the studies is:

$$SV = K (P_{md}) \left(1 + \frac{Sa}{Da}\right) \quad (1)$$

where SV is stroke volume, K is a calibration constant determined by making a simultaneous measurement by an independent method, P_{md} is the average increment in mean pressure, over the arterial bed, from the previous diastole to end-systole (referred to as the

mean distending pressure [fig. 1]), and Sa and Da represent the systolic and diastolic areas, respectively. In Warner's original derivation, the calculation of the mean time of transmission (t_w) of the pressure wave (from a central location to the periphery) required the simultaneous measurement of both a central and a peripheral arterial pressure. The mean time of transmission was later assumed to be constant at 80 msec,¹¹ making measurement of the peripheral arterial pressure unnecessary. The method, as published in 1966 and 1968,^{11, 12} used the square root of mean distending pressure ($\sqrt{P_{md}}$) instead of mean distending pressure. The method currently used by Warner and associates is equation 1.

The equation derived by Bourgeois and associates⁵ is:

$$SV = K_A [(P_{es} - P_d) + \frac{SA}{\tau}] \quad (2)$$

where SV is stroke volume and K_A is a calibration constant determined by simultaneously measuring stroke volume by an independent method, P_d is the diastolic pressure preceding the systolic pressure wave of the curve of interest (see fig. 2), P_{es} is the pressure at end-systole (dicotic notch), SA is the area under the curve during systole, and τ is the time constant of the exponential decay of the diastolic portion of the pressure contour. Dependent variables are the logarithms of sample points from the diastolic portion of the pressure curve from the dicotic notch to end-diastole; time is the independent variable.

The first comparative study was between the Warner pressure-pulse method and dye-dilution performed on 17 patients hospitalized for open heart surgery at LDS Hospital. One set of measurements was performed before surgery. Within the first 2 days after surgery, three to six additional sets of measurements were performed.

A set of measurements consisted of doing dye curves until two cardiac output values, within 5% of each other, were obtained and then averaged. A typical protocol included a measurement set taken 2-4 hours after surgery, with additional measurement sets

From the Department of Medical Biophysics and Computing, University of Utah, LDS Hospital, Salt Lake City, Utah.

Address for correspondence: Reed M. Gardner, Ph.D., Department of Medical Biophysics and Computing, LDS Hospital, 325 Eighth Avenue, Salt Lake City, Utah 84143.

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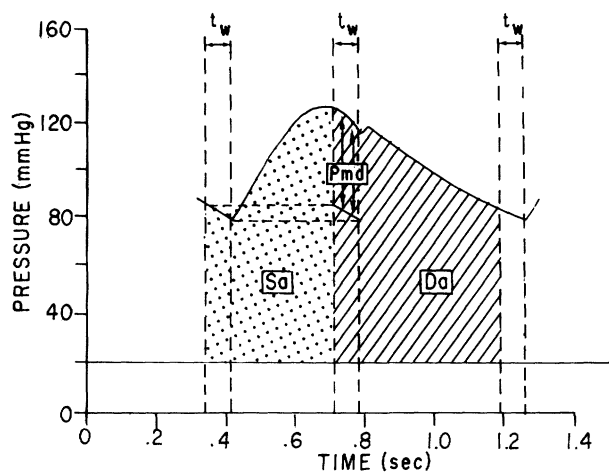


FIGURE 1. Parameters of the Warner pressure-pulse method. S_a , D_a , and P_{md} represent the systolic area, diastolic area, and mean distending pressure. The symbol t_w represents the average transmission time to the periphery.

obtained at 4-hour intervals thereafter. Indocyanine green dye (0.8 mg in 2 ml aqueous solvent) was manually injected through a central venous catheter. Withdrawal of the blood sample for dye-dilution determination was made through a cannula in the radial artery before surgery and postoperatively through a short Teflon catheter placed in the brachial artery after surgery. Dye curves were obtained with a Waters cuvette densitometer (model XC-50B). The output voltage of the densitometer amplifier was sampled for 45 seconds with a 10-bit analog-to-digital converter at 6.25 Hz and processed with the dye-dilution program on LDS Hospital's CDC 3300 computer.¹³

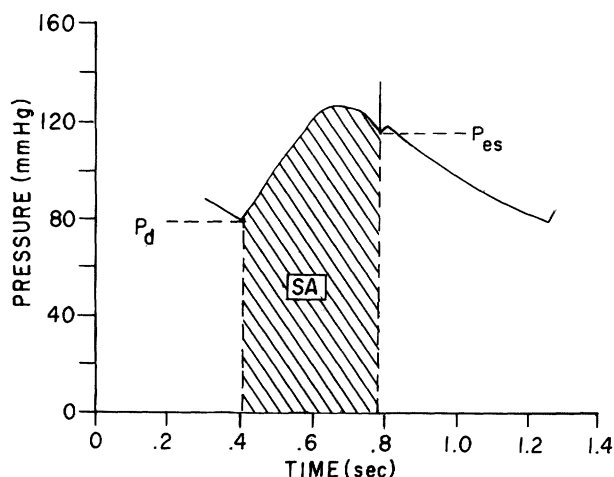


FIGURE 2. Parameters of the Bourgeois method. P_d , P_{es} , and SA represent the end-diastolic pressure, end-systolic pressure and systolic area, respectively.

A 100-cm long, 20-gauge, fluid-filled Teflon catheter (CAP INTRAFUSOR-18, Sorenson Research Company) was attached to a pressure transducer for monitoring central arterial pressure.^{14, 15} The resulting system had a natural frequency (f_n) of 20 Hz and a damping coefficient (ζ) of 0.25. Pressure transducers used were P23Db, P23ID (Statham Instruments), or Bentley 800 (Bentley-Trantec, Inc.). The catheter was inserted through the radial artery and advanced to the subclavian artery to record central arterial pressure. A continuous-flush system^{14, 15} was used to keep the catheter patent (CFS INTRAFLO, Sorenson Research Company). The transducer was connected to an amplifier system (Model 780-7C, Hewlett-Packard) that provided a continuous oscilloscopic display. The signal was conditioned using a pressure amplifier designed at LDS Hospital.¹³ The pressure wave form was sampled by a computer program at 200 samples/sec for 45 seconds. For Warner method calculations, the program selected the first 16 artifact-free pressure contours, computed the pressure-pulse parameters on each and calculated the averages. Parameters displayed included systolic pressure, diastolic pressure, mean pressure, stroke volume, heart rate, cardiac output and total peripheral resistance.

The second study made comparisons between the Warner and Bourgeois methods and the thermodilution-determined cardiac output on 13 patients in the respiratory intensive care unit (RICU) at LDS Hospital. Since thermodilution measurements and central arterial pressure monitoring were performed routinely as a part of the clinical management program, the comparison studies were performed without departing from normal patient-care procedures. One hundred forty-four sets of simultaneous pressure-pulse and thermodilution measurements were taken, with a mean of 3.5 measurements per set. A typical protocol included three to four measurement sets per day, taken at 3-4-hour intervals. Except for one patient, all were observed for at least 2 days; one of the patients was observed for 3 weeks and one for 5 weeks. Thermodilution measurements were made using 10 ml of iced normal saline injected through the right atrial port of a Model 44166 Instrumentation Laboratories Inc. #7F flow-directed thermodilution catheter. The resistance change of the catheter thermistor was measured and converted to an output voltage by an amplifier designed and built by the Department of Medical Biophysics and Computing at the University of Utah. The voltage output of the amplifier was sampled at 6.25 samples/sec for 45 seconds with an analog-to-digital converter and processed by the computer. For low-output states, a longer sampling duration was used to allow the curve to return to baseline. After the computer processed the data, both the cardiac output value and the time-temperature curve were displayed. Sampled analog data for pressure, dye-dilution and thermodilution was stored temporarily on magnetic disc; the data were later transferred to digital tape for further evaluation.

Pattern recognition of the pressure wave form used

for the Bourgeois method was accomplished by displaying the raw sampled pressure-pulse data on a computer terminal. The incisura, the beginning and end of systole for each beat, were located by adjusting a cursor under human visual control. Ten artifact-free, contiguous pressure wave forms after injection of the thermal indicator were then selected. The computer then determined P_{es} , P_d , and SA (equation 2) by averaging these values over the 10 beats. The time constant τ was determined by the computer using the method for averaging successive diastolic decays described by Bourgeois.⁵ The average diastolic decay curve was then used to determine τ as described in the original Bourgeois paper.¹⁶

Results

Five of the 17 patients in the dye-dilution study were female; average age was 47.9 years. Five of the 13 patients in the thermodilution study were female; average age was 49.0 years.

Cardiac output data from both studies were plotted against time. In most cases the pressure-pulse cardiac outputs were observed to begin diverging from the indicator dilution cardiac outputs within a few hours. Long-term drift in the pressure-pulse method had been observed before in this clinical setting and had been attributed to changes in the cardiovascular system that altered the calibration constant of the pressure-pulse equation. If the pressure-pulse methods failed as an absolute measure of changes in cardiac output, the question remained whether they could at least be useful in following trends. To reduce the effect of drifts between the pressure-pulse and indicator-dilution methods, the results of both studies were analyzed using percent change between the average of each measurement set and the average of the preceding measurement set. Thus, for each measurement set (i_n) the percent change from the previous set (i_{n-1}) would be:

$$\text{Percent change} = 100 \times \frac{i_n - i_{n-1}}{i_{n-1}} \quad (3)$$

A scatter diagram comparing percent changes in the Warner pressure-pulse method against percent changes in the dye-dilution cardiac outputs of the first study is shown in figure 3. The correlation coefficient was $r = 0.61$, with a regression equation of $y = 0.69x - 0.59$ (52 measurement sets). Scatter diagrams of the results of the second study comparing thermodilution to the Warner and Bourgeois pressure-pulse methods are shown in figures 4 and 5. The correlation coefficient for the Warner equation was $r = 0.58$, with a regression equation of $y = 0.78x + 2.0$ (144 measurement sets). The Bourgeois method yielded a correlation coefficient of $r = 0.50$, with a regression equation of $y = 0.61x + 2.14$ (144 measurement sets).

In the first study, the transition from pre- to post-thoracic surgery was often accompanied by large changes in cardiac output. Consequently, one reason for the improved correlation coefficient in the dye-dilution study over the thermodilution study was that

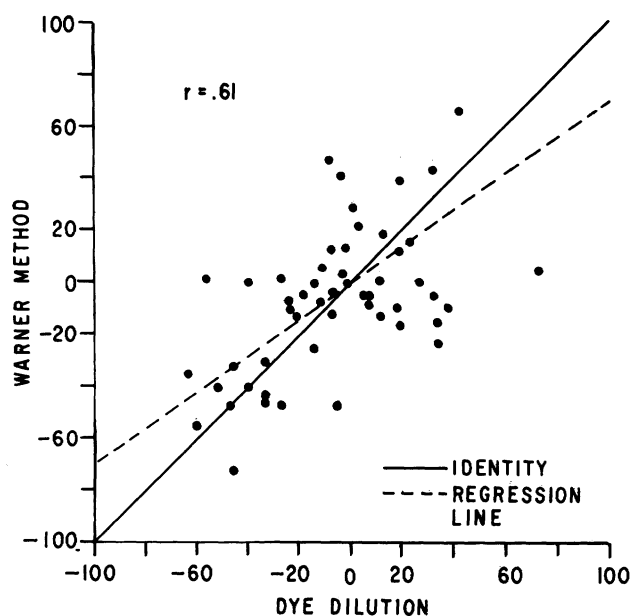


FIGURE 3. Data from the dye-dilution study comparing percent changes in cardiac outputs computed using the Warner pressure-pulse method against percent changes in dye-dilution cardiac output values. The regression equation is $y = 0.69x - 0.59$.

more data points were present at the extremes of cardiac output. When the same data were graphed and the preoperative measurements eliminated, the correlation coefficient was reduced from $r = 0.61$ to $r = 0.48$.

Considering that long-term changes in the pressure-

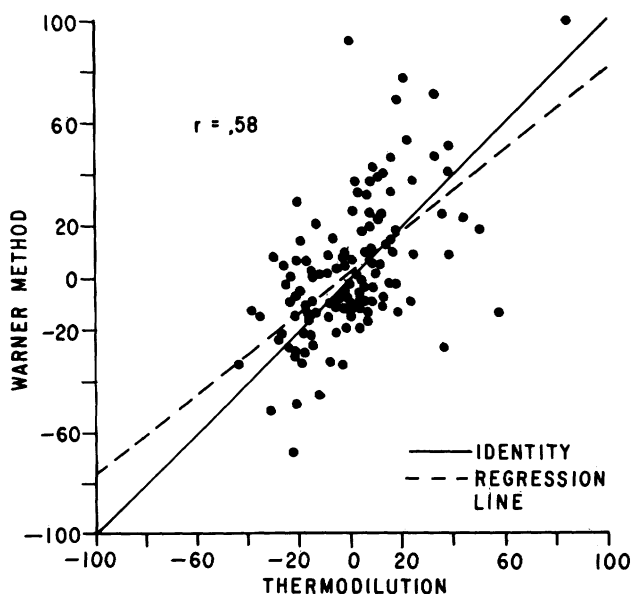


FIGURE 4. Data from the thermodilution study comparing percent changes in cardiac outputs computed using the Warner pressure-pulse method against percent changes in thermodilution cardiac output values. The regression equation is $y = 0.78x + 2.0$.

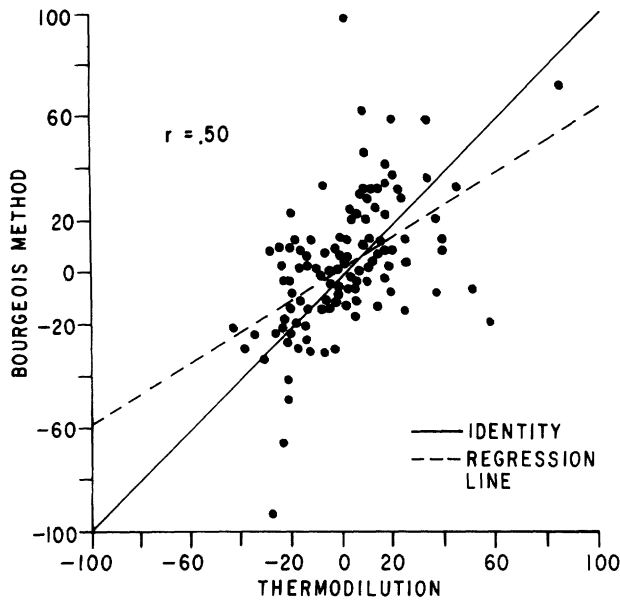


FIGURE 5. Same as figure 4, with the Bourgeois pressure-pulse method rather than the Warner method.

pulse calibration constant might cause the pressure-pulse cardiac outputs to drift away from the true values, the time between calibration and successive measurements was shortened to evaluate the effect, if any, on the agreement between thermodilution and pressure-pulse cardiac outputs. In the thermodilution study, measurements were excluded where more than 5 hours had passed since the previous set. No improvement was observed; correlation coefficients decreased to $r = 0.48$ from $r = 0.58$ for all data with the Warner method and to $r = 0.46$ from $r = 0.50$ with the Bourgeois method (59 measurement sets). Correlation coefficients decreased further when maximum time between measurement sets was reduced to 2 hours ($r = 0.32$ for the Warner method; $r = 0.24$ for the Bourgeois method; 31 measurement sets.)

Discussion

Data from the dye-dilution measurements of the first study were used to "recalibrate" the Warner equation for each measurement set to determine what changes were occurring in the calibration constant of the pressure-pulse equation. Values for the Warner equation calibration constant (K) were found to be nonstationary, varying with time; maximal errors were -69 and 135% of the initial value in individual patients. A basic assumption of the Warner pressure-pulse equation is that the relation between change in volume and the corresponding change in pressure in the arterial tree is linear. The ratio of change in volume to change in pressure is the vascular compliance, characterized by K in the Warner equation. In the derivation of the Warner equation, K is assumed to be constant in the normal physiologic pressure range. The finding that K is not constant in the clinical situation conflicted with this assumption. Further

evaluation of the data from patients in the dye-dilution study was conducted to determine if a relationship existed between change in the constant and change in the mean pressure. Plots of mean pressure vs measurement number and K vs measurement number on the same graph revealed that an inverse relationship between K and mean pressure was present in 80% of the patients. Linear regressions were performed on corresponding values for mean pressure and K in individual patients. Only two patients failed to show appreciable inverse correlation. The average correlation coefficient was $r = 0.80$. These results suggested that the vascular compliance was not constant over the mean pressure ranges of the post-operative thoracic surgery patients.

A similar analysis was made using data from the thermodilution study. New values of the K (Warner) and K_A (Bourgeois) constants were computed for each measurement set using the thermodilution cardiac output values. Constants for each method were plotted against mean pressure for the corresponding measurements. Correlation coefficients for both the Warner and Bourgeois methods are listed in table 1 for individual patients. A correlation coefficient was not obtained from one patient, in whom only two measurement sets were performed. Correlation coefficients were not as high as for the dye-dilution study.

Perhaps the high inverse correlations between mean pressure and K on the dye-dilution study were not observed in the thermodilution study because these patients were followed longer. When adjacent measurement sets were connected with lines on the mean pressure vs K and K_A plots, the majority of the lines connecting successive points were of negative slope with a similar slope value. An example for the Warner constant against mean pressure is given in figure 6 for the patient with the most data. A similar effect was noted on all patients for both the Warner and Bourgeois K values.

Bourgeois et al.⁵ based their pressure-pulse method on detecting changes in the time constant of the

TABLE 1. Correlation Coefficients for Pressure-Pulse Methods Plotted Against Mean Pressure

Patient	r (Warner)	r (Bourgeois)
1	+0.03	-0.35
2	-0.63	-0.65
3	-0.71	+0.07
4	-0.99	-0.94
5	+0.12	-0.02
6	-0.78	-0.88
7	-0.31	-0.20
8	+0.06	-0.11
9	-0.94	-0.12
10	-0.35	-0.23
11	-0.70	-0.58
12	-0.57	-0.38

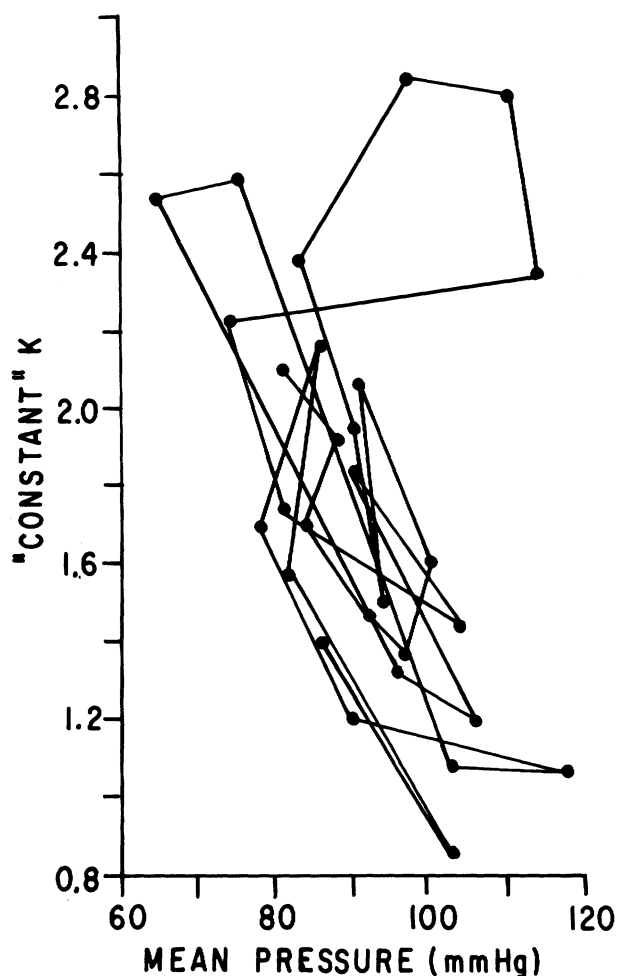


FIGURE 6. Scatter diagram showing the value computed for the Warner constant for each new measurement set plotted against mean pressure. The lines connect successive measurements.

diastolic decay of the aortic pressure wave form. They found that the best results were obtained when the tip of the arterial catheter was positioned in a segment of the thoracic aorta that gave nearly perfect exponential decay in the diastolic wave form. They found this "optimal" location about 4 cm cephalad of the dorsal insertion of the diaphragm in the dog. Dr. Edward L. Bond and Dr. Reed M. Gardner at our institution could not find the optimal location for the tip of the arterial monitoring catheter. All arterial monitoring catheters used in the present studies had their tips in the subclavian artery. Since this is not the optimal location described by Bourgeois and associates, it may be partially responsible for the poor performance of the Bourgeois method.

Although several clinical trials of the Warner and other variants of the pressure-pulse method have been reported,^{1, 7, 8, 10-12} we are unaware of other clinical reports testing the Bourgeois method. The Bourgeois method has been tested under a wide variety of physiologic conditions, but all the experimental results published have been from acute, short-term animal

models. Based on the changes in the shape of patient pressure wave forms over time in our critically ill patients, we are uncertain that the so called optimal location of the catheter will remain fixed. Only careful experimentation on several subjects will answer this question.

Conclusions

Further research on pressure-pulse methods is warranted, although these results show that the pressure-pulse methods studied were not reliable indicators of change in cardiac output. Calculation of parameters other than cardiac output may be of value. For example, in the derivation of the Warner equation from the Windkessel model, the calibration constant (K) represents the compliance of the aorta and large arteries.⁵ In these studies the arterial pressure wave form was being monitored while cardiac output was being measured by indicator dilution. The arterial wave forms and the cardiac output value were used to calculate a new value of K for each measurement procedure. If K represents arterial compliance, this protocol could provide a convenient method for monitoring arterial compliance clinically. However, the validity of this method for measuring compliance would have to be established by comparison with alternative methods.

Our data show that use of the Warner and Bourgeois pressure-pulse methods under the conditions presented do not provide sufficiently reliable data for clinical decision-making in the care of critically ill patients. Further research is required if the accuracy of the equations is to be improved or if the equations are to be adapted for monitoring variables other than cardiac output. The methods may be reliable when used on patients who have more stable mean arterial pressures than those we studied.

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Minoxidil: Right Atrial Cardiac Pathology in Animals and in Man

J. T. SOBOTA, M.D., W. B. MARTIN, M.D., R. G. CARLSON, D.V.M., PH.D.,
AND E. S. FEENSTRA, D.V.M., PH.D.

SUMMARY Minoxidil is a clinically effective vasodilator with a low order of toxicity, except for a canine-specific lesion of the right atrium of the heart of dogs after they are given daily doses of 1 mg/kg or greater for 30 days. In these experiments the canine right atrial lesion was generally located adjacent to the second of the three atrial branches of the right coronary artery and had grossly red or yellowish thickening of the atrial wall. Microscopically there was extravasation of a few intact red cells, atrophy of myocardial cells adjacent to the subepicardium, the presence of mast cells and macrophages containing hemosiderin with subsequent proliferation of angioblasts and connective tissue cells. Cytoplasmic loss in myocardial cells of the left ventricular papillary muscle identical in all respects to that seen after other hypotensive agents and β -adrenoceptor agonists was also observed in minoxidil-treated rodents and dogs. Seventy-nine of 158 patients who died secondary to severe hypertension but who received minoxidil were autopsied. Six cases had significant right atrial pathology not related to gross and histologic changes found in the right atrial lesions of dogs. A prospective study of the right atrium of normotensive and hypertensive patients not treated with minoxidil shows an increasing frequency of histologic changes, such as myocardial fibrosis and hydropic vacuolization that are related to age and the presence of hypertension.

MINOXIDIL (Loniten, Upjohn) is a chemically unique (fig. 1), orally active vasodilator drug that profoundly and consistently reduces mean blood pressure in rats, miniature pigs, rhesus monkeys, normotensive mongrel and beagle and hypertensive mongrel dogs.¹ Several clinical trials have reconfirmed its efficacy;^{2, 3} a controlled trial by Dargie et al.⁴ showed that minoxidil, in combination with propranolol and diuretics, lowers the blood pressure of hypertensive patients resistant to treatment with large doses of standard antihypertensive drugs.

The therapeutic importance of chronically administered minoxidil in man stimulated comprehensive toxicologic studies. In general, the drug has little toxicity when given intraperitoneally or orally and

causes minimal pharmacologic effects except in the cardiovascular system. The drug does produce hirsutism in humans, an annoying side effect, especially in women. Teratology studies in pregnant rats and rabbits were negative. Daily doses of 7 mg/kg of body weight in monkeys and 30 mg/kg in rats older than 1 year caused no significant organ abnormalities.⁵

Toxicity in canines is also of a low order, but a species-specific lesion of the right atrium of the heart occurs with single daily doses of 1 mg/kg or greater given for 1 month. A nonspecific myocardial lesion has also been described in rodents and dogs briefly treated with minoxidil, identical to those induced by hydralazine, other hypotensive agents and isoproterenol.^{6, 7} This lesion consists of a loss of cytoplasm in myocardial cells in the left ventricular papillary muscle.

The usefulness of minoxidil in hypertensive disease in man had to be carefully evaluated against the possible occurrence of right atrial lesions similar to those in the beagle and the nonspecific left ventricular papillary muscle change. Little information is available on gross and microscopic right atrial pathology. Infarcts and mural thrombi of the atria in humans have been studied by Cushing et al.,⁸ and by Soderstrom,⁹

From the Upjohn Company, Kalamazoo, Michigan.

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Address for correspondence: Joseph T. Sobota, M.D., The Upjohn Company, Kalamazoo, Michigan 49001.

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