

## Catheterization of pulmonary artery in rats with an ultraminiature catheter pressure transducer

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**Deten, Alexander, Huntly Millar, and Heinz-Gerd Zimmer.** Catheterization of pulmonary artery in rats with an ultraminiature catheter pressure transducer. *Am J Physiol Heart Circ Physiol* 285: H2212–H2217, 2003. First published July 24, 2003; 10.1152/ajpheart.00315.2003.—Utilizing new materials and miniaturization techniques, an ultraminiature catheter pressure transducer for catheterization of the pulmonary artery (PA) has been developed and applied in intact, spontaneously breathing, anesthetized rats. The catheter arrangement consists of three components: 1) an SPR-671 ultraminiature pressure transducer (measuring catheter), 2) a plastic introducer (sheath) that is slipped over the measuring catheter, and 3) an external wire mounted on the outside of the introducer for bending its tip. The measuring catheter is first inserted through the right jugular vein into the right ventricle. The introducer is then slipped over it. The tip of the introducer is bent so that there is an angle of  $\sim 90^\circ$  or less to the shaft. The measuring catheter is advanced across the pulmonary valve into the PA. Measurements of pulmonary arterial pressure were made in five male Long Evans ( $364 \pm 7$  g body wt) and five female Sprague-Dawley ( $244 \pm 7$  g body wt) rats under control conditions. The effects of infusion of norepinephrine ( $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  iv for 20-min duration) were tested in Long Evans rats. Pulmonary arterial systolic pressure measurements were  $34.0 \pm 0.8$  and  $29.5 \pm 0.4$  mmHg, and diastolic pressure values were  $23.6 \pm 0.8$  and  $18.1 \pm 0.6$  mmHg in male Long Evans and female Sprague-Dawley rats, respectively. Norepinephrine induced an increase in pulmonary arterial systolic ( $40.8 \pm 0.1$  mmHg) and diastolic ( $28.6 \pm 0.4$  mmHg) pressures and an elevation in pulmonary vascular resistance from a control value of  $0.093 \pm 0.003$  to  $0.103 \pm 0.004$  mmHg  $\cdot$  kg  $\cdot$  min  $\cdot$  ml $^{-1}$ .

cardiac output; contractility; norepinephrine; right heart

IN BASIC CARDIOVASCULAR RESEARCH, the right heart and pulmonary circulation have been studied less frequently than the left heart and peripheral circulation. Also, the method for catheterization of the left ventricle in rats using ultraminiature catheter pressure transducers was established earlier (21) than that for catheterization of the right ventricle (24). Recently, catheterization of both heart chambers with microtip catheters has become feasible also in mice (3). For the characterization of experimental animal models with

alterations in pulmonary circulation and right ventricular (RV) function such as pulmonary hypertension and RV hypertrophy and failure, the measurement of pulmonary arterial pressure is needed to better understand the underlying pathophysiological processes. Some attempts have been made over the past 30 years to obtain this important parameter in small laboratory animals. However, no microtip catheter method is presently available that can be applied for measurements of pulmonary arterial pressure and pulmonary vascular resistance.

In a one-step approach, a 3.5-Fr umbilical vessel catheter prefilled with heparinized saline had a  $90^\circ$  angle to the shaft at the distal end. When it was inserted into the right jugular vein of a rat, it straightened out and then resumed its original shape once it was located in the right ventricle. It was further advanced so that the tip slipped through the pulmonary valve (16). A similar one-step technique was used thereafter by other investigators (9, 11, 13, 17, 18). Several approaches were made using an introducer or a cannula. In 1972, a method was developed that made use of a cannula-catheter assembly. A fluid-filled catheter with a pigtail shape at the distal end was contained in a well-fitting cannula. This assembly was introduced into the right ventricle. From this point, the inner tubing was pushed out of the cannula whereupon it resumed its original shape and was introduced by delicate manipulation into the PA. The tubing was filled with saline and heparin solution and was connected to a pressure transducer (6). In another technique, the tip of a catheter had a “shepherd’s crook” shape that allowed the catheter arch to press against the RV wall while the tip remained free. This catheter, with a cannula sleeve, was placed in the right ventricle, and the tip of the catheter was manipulated into the PA (5). A fluid-filled catheter was also used in an approach whereby measurements of PA were obtained in awake rats. An introducer, which was a blunted 7.5-cm, 19-gauge needle with the tip turned up  $30^\circ$ , was passed inside by a Silastic catheter that had a notched end hole. This was flushed with heparinized saline and was attached by a 25-gauge blunted needle to a pressure transducer. After the introducer had been

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placed in the RV cavity, the catheter was introduced into the PA, whereupon the introducer was removed, and the catheter was exteriorized in the back of the animal's neck (15). In a recent study, a similar technique was applied for recording of pulmonary arterial pressure in rats over 1 day (7). Several other studies that involved measurements of pulmonary arterial pressure also used this type of technique (4, 10, 12, 14).

In mice, a catheter with an outer diameter of 0.25 mm and a curved tip was straightened with an angioplasty guide wire to facilitate insertion in the right atrium under fluoroscopic control. The straight wire was removed, and the catheter with the curved tip was passed into the right ventricle. A soft-tip coronary artery angioplasty guide wire was then inserted, and the catheter was passed over the guide wire into the main PA for the measurement of pressure using a pressure transducer (2).

As to the previous attempt with an ultraminiature catheter pressure transducer, a 3-Fr Millar catheter was inserted into the right femoral vein and advanced via the inferior cava vein into the right atrium. By rotating the catheter tip, it was possible to place it in the right ventricle and then further advance it into the PA. This technique was applied in studies on the functional effects of hypoxia (20) and triiodothyronine (19). The procedure associated with this approach, however, required much time, was not always successful, and was not considered to be suitable for routine measurements (23).

Therefore, considerable effort during the past years has been put into development of a microtip catheter that can be applied in rats via the jugular vein for the measurement of pulmonary arterial pressure. With the use of new materials and miniaturization techniques, such an ultraminiature catheter pressure transducer was recently constructed and used in rats. In this report, we describe this catheter and the technique for pulmonary arterial catheterization. The first results obtained in two rat strains under control conditions and after infusion of norepinephrine (NE) are presented.

#### MATERIALS AND METHODS

The catheter consists of three components: 1) an ultraminiature pressure catheter transducer (model SPR-671, 1.4-Fr,

Millar Instruments; Houston, TX) for pressure measurements; 2) an introducer (sheath) with a deflectable tip that is slipped over the measuring catheter; and 3) a guiding wire that is mounted on the outside of the introducer for deflecting its tip. The deflectable sheath consists of a thin-walled sleeve with several parallel notches near the tip. These allow the tip to deflect in the direction of the notches when tension is applied to the tip with a pulling wire. The sheath itself is polyimide tubing of the following dimensions: inner diameter,  $\sim 0.023$  in.; outer diameter, 0.029 in.; and length, 7 cm. There is a bifurcation near the proximal end of the sheath, and a heavy-walled polyimide tubing contains the pulling wire, which exits and terminates in a deflection controller.

The deflection controller has a knurled knob that can be turned with the thumb to produce a tip deflection as required. The connection between the knurled wheel and the tip consists of a 3-mm nickel-titanium wire that was previously bonded securely to the catheter tip. This guiding wire is brought up along the outside of the sheath and fastened at the tip of the sheath with a small polyimide ring and some hard epoxy. Although it is bonded at the tip, it is free to move in the consecutive support rings down the sheath and along the handle.

The experimental procedure used conforms with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health [DHEW Publication No. (NIH) 85-23, Revised 1996, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205] and was approved by the appropriate state agency of Saxony. Male Long Evans rats ( $n = 5$ ;  $364 \pm 7$  g body wt) and female Sprague-Dawley rats ( $n = 5$ ;  $244 \pm 7$  g body wt) were used. All rats were obtained from Charles River (Sulzfeld, Germany). Rats were allowed to move freely in their cages and had access to tap water and rat chow diet (Altromin C 100, Altromin; Lage, Germany).

The animals were anesthetized with thiopental sodium (Trapanal, 60 mg/kg ip, Byk Gulden; Konstanz, Germany). A cannula was inserted into the trachea to control respiration of the spontaneously breathing animals. First, the 1.4-Fr measuring catheter was inserted through the right jugular vein into the right ventricle as evidenced by the typical RV pressure curve; the introducer was then slipped over it. The tip of the introducer was deflected to an angle of  $\sim 90^\circ$  or less to the shaft by pulling the guiding wire. The measuring catheter was advanced across the pulmonary valve into the PA. Finally, the deflection was released, and the introducer was removed. The successive steps are illustrated in Fig. 1.

After collection of the RV and pulmonary arterial data, the left ventricular (LV) catheter (model SPR-249, 3-Fr, Millar) was placed in the right carotid artery and advanced up-

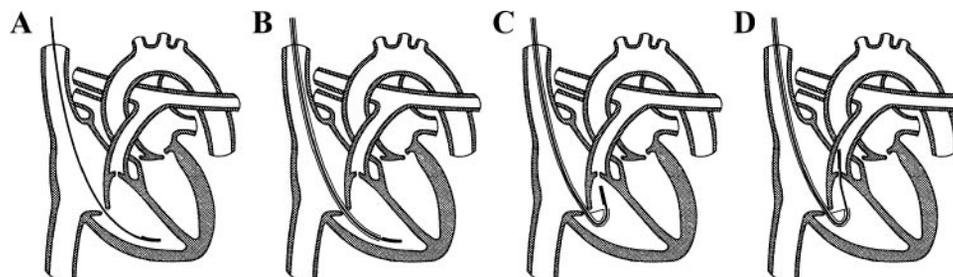


Fig. 1. Schematic view of the sequential steps that lead to pulmonary arterial catheterization. A: placement of the 1.4-Fr microtip catheter in the right ventricle via the right jugular vein. B: placement of the introducer by slipping it over the microtip catheter. C: deflection of the tip of the introducer to an angle of  $\sim 90^\circ$  or less to the shaft by pulling the guiding wire. D: placement of the measuring catheter by advancing it across the pulmonary valve into the pulmonary artery (PA).

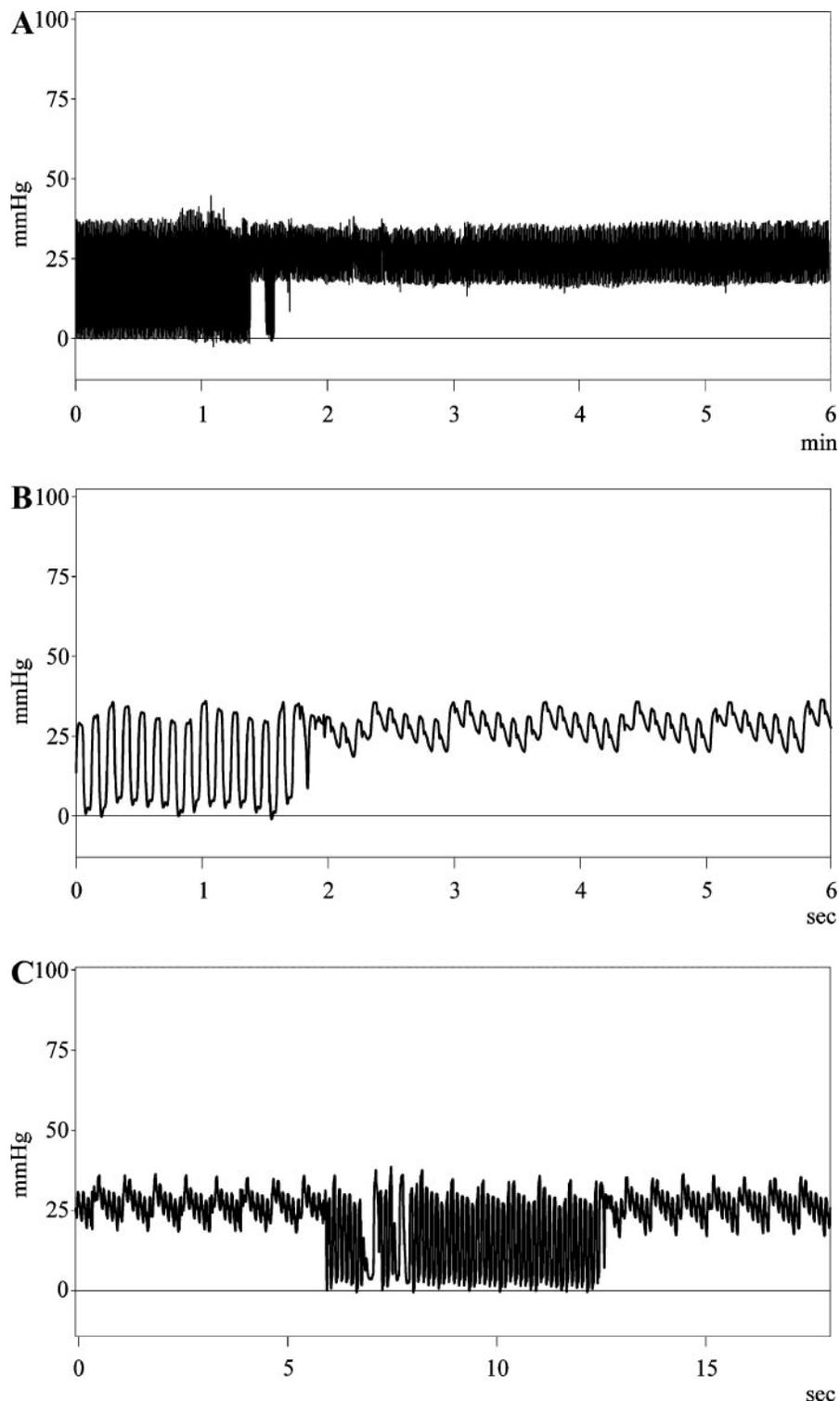


Fig. 2. Original recordings of right ventricular and pulmonary arterial pressure. *A*: overview; *B*: higher time resolution to illustrate the moment when the catheter is advanced from the right ventricle into the PA. *C*: pressure changes when the catheter is withdrawn from the PA into the right ventricle and advanced again into the PA.

stream in the aorta into the left ventricle. Thereafter, NE dissolved in 0.9% NaCl at a dose of  $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  iv was applied as a continuous infusion via a catheter (Vygon; Aachen, Germany) positioned in the left jugular vein. To prevent oxidation, 100 mg/l ascorbic acid was added. After 15 min, the pulmonary arterial catheter was withdrawn into the right ventricle to measure RV pressure under steady-state conditions of NE application. Cardiac output was measured using the thermodilution method (19) at the beginning of the

experiment (basal conditions, CTRL) and at the end of the 20-min NE infusion period using a Cardiomax II thermodilution machine (Columbus Instruments; Columbus, OH).

Heart rate (HR); RV, LV, and pulmonary arterial pressures; and the rates of rise and fall of ventricular pressures (LV and RV  $dP/dt_{\text{max}}$  and  $dP/dt_{\text{min}}$ , respectively) were recorded continuously on a personal computer at a sampling rate of 2 kHz as described previously (3). Total peripheral and pulmonary vascular resistance values were calculated by

dividing mean aortic and pulmonary arterial pressures, respectively, by cardiac output normalized to body weight.

All data are presented as means  $\pm$  SE. For statistical comparison before and after NE treatment, a paired *t*-test was used (SigmaStat 2.0, SPSS; Chicago, IL). A *P* value  $<0.05$  was considered significant.

## RESULTS

The sequential steps of the procedure that eventually led to pulmonary arterial catheterization are shown in Fig. 1. When the measuring catheter was advanced into the PA, the pressure signal changed immediately to that characteristic for the vascular system. Similar to aortic pressure, there was a typical notch during the diastolic decrease of the pressure curve. Furthermore, the respiratory movements affected the sequence of the pressure waves (Fig. 2).

Pulmonary arterial systolic pressure (PASP) values were  $34.0 \pm 0.8$  and  $29.5 \pm 0.4$  mmHg, and pulmonary arterial diastolic pressure (PADP) measurements were  $23.6 \pm 0.8$  and  $18.1 \pm 0.6$  mmHg in male Long Evans and female Sprague-Dawley rats, respectively (Table 1). RV systolic pressure (RVSP) and PASP were of the same magnitude, which indicates that no obstruction of the pulmonary valve had been induced when the measuring catheter was located in the PA (Fig. 2C). In addition, there was no change in RV end-diastolic pressure (RVEDP). Pulmonary vascular resistance (PVR) was comparable in Long Evans and Sprague-Dawley rats (Table 1). The functional parameters of the left ventricle (Table 2) were comparable to those obtained in earlier studies (3, 21).

Infusion of NE in male Long Evans rats accelerated HR and elevated RVSP, LVSP, RV  $dP/dt_{max}$ , and LV  $dP/dt_{max}$  values (Table 3). It induced an increase in both PASP ( $40.8 \pm 0.1$  mmHg) and PADP ( $28.6 \pm 0.4$  mmHg; Fig. 3 and Table 3) and an elevation in PVR from  $0.093 \pm 0.003$  to  $0.103 \pm 0.004$  mmHg $\cdot$ kg $\cdot$ min $^{-1}$ .

Table 1. Right ventricular and pulmonary artery hemodynamic parameters in male Long Evans and female Sprague-Dawley rats

	Rat Subject	
	Male Long Evans	Female Sprague-Dawley
HR, beats/min	447 $\pm$ 8	415 $\pm$ 6
RVSP, mmHg	34.0 $\pm$ 0.6	29.5 $\pm$ 0.3
RVEDP, mmHg	3.9 $\pm$ 0.1	4.5 $\pm$ 0.4
RV $dP/dt_{max}$ , mmHg/s	1,601 $\pm$ 49	1,767 $\pm$ 131
RV $dP/dt_{min}$ , mmHg/s	-1,328 $\pm$ 55	-1,285 $\pm$ 57
PASP, mmHg	34.0 $\pm$ 0.8	29.5 $\pm$ 0.4
PADP, mmHg	23.6 $\pm$ 0.8	18.1 $\pm$ 0.6
COI, ml $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$	308 $\pm$ 9	286 $\pm$ 9
SV, $\mu$ l	242 $\pm$ 2	166 $\pm$ 7
PVR, mmHg $\cdot$ kg $\cdot$ min $^{-1}$ $\cdot$ ml $^{-1}$	0.093 $\pm$ 0.003	0.084 $\pm$ 0.002

Values are means  $\pm$  SE; *n* = 5 male and 5 female rats. HR, heart rate; RV, right ventricular; RVSP, RV systolic pressure; RVEDP, RV diastolic pressure; RVEDP, RV end-diastolic pressure; RV  $dP/dt_{max}$  and  $dP/dt_{min}$ , rates of rise and fall in RV pressure, respectively; PA, pulmonary artery; COI, cardiac output index; SV, stroke volume; PVR, pulmonary vascular resistance.

Table 2. Left ventricular and aortic hemodynamic parameters in male Long Evans and female Sprague-Dawley rats

	Rat Subject	
	Male Long Evans	Female Sprague-Dawley
LVSP, mmHg	150.3 $\pm$ 3.6	140.5 $\pm$ 1.8
LVEDP, mmHg	5.4 $\pm$ 0.9	4.5 $\pm$ 0.5
LV $dP/dt_{max}$ , mmHg/s	7,906 $\pm$ 524	9,440 $\pm$ 772
LV $dP/dt_{min}$ , mmHg/s	-8,418 $\pm$ 293	-8,952 $\pm$ 255
SAP, mmHg	150.3 $\pm$ 4.8	140.0 $\pm$ 2.1
DAP, mmHg	123.8 $\pm$ 3.5	118.8 $\pm$ 2.7
TPR, mmHg $\cdot$ kg $\cdot$ min $^{-1}$ $\cdot$ ml $^{-1}$	0.44 $\pm$ 0.008	0.45 $\pm$ 0.013

Values are means  $\pm$  SE; *n* = 5 male and 5 female rats. LV, left ventricular; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; LV  $dP/dt_{max}$  and LV  $dP/dt_{min}$ , rates of rise and fall in LV pressure, respectively; SAP, systolic aortic pressure; DAP, diastolic aortic pressure; TPR, total peripheral resistance.

ml $^{-1}$  (Table 3; *P* = 0.053). Similar effects were observed when NE was administered in female Sprague-Dawley rats (data not shown).

## DISCUSSION

Catheterization of the PA in small laboratory animals poses several problems. The catheter must be directed from the jugular vein and the right atrium into the right ventricle, a procedure that was established previously (24). When the catheter is placed in the right ventricle, the catheter tip has to follow the blood stream, i.e., a diversion from the direction of inflow, that ultimately passes the pulmonary valve in an antegrade fashion. To adjust to this anatomical situation, some catheter modifications were developed in the past. All of these previous techniques involved fluid-filled catheters only. The pulmonary arterial catheterization procedure described in this study is the first using an ultraminiature catheter pressure transducer in the approach via the jugular vein.

In previous attempts, preformed catheters (16), introducers (5, 6, 15), or guide wires (2) were used that released the preformed shape of the measuring catheter.

Table 3. Changes in hemodynamic parameters after norepinephrine infusion for 20 min in male Long Evans rats

	Male Long Evans Rats	
	Control (5)	Norepinephrine (4)
HR, beats/min	447 $\pm$ 8	537 $\pm$ 9*
RVSP, mmHg	34.0 $\pm$ 0.6	40.8 $\pm$ 0.1*
RV $dP/dt_{max}$ , mmHg/s	1,601 $\pm$ 49	4,536 $\pm$ 178*
LVSP, mmHg	150.3 $\pm$ 3.6	164.9 $\pm$ 2.0
LV $dP/dt_{max}$ , mmHg/s	7,906 $\pm$ 524	21,334 $\pm$ 462*
PASP, mmHg	34.0 $\pm$ 0.8	40.8 $\pm$ 0.1*
PADP, mmHg	23.6 $\pm$ 0.8	28.6 $\pm$ 0.4*
COI, ml $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$	308 $\pm$ 9	337 $\pm$ 8*
PVR, mmHg $\cdot$ kg $\cdot$ min/ml	0.093 $\pm$ 0.003	0.103 $\pm$ 0.004

Values are means  $\pm$  SE; numbers of rats are shown in parentheses. \**P*  $< 0.05$  vs. control.

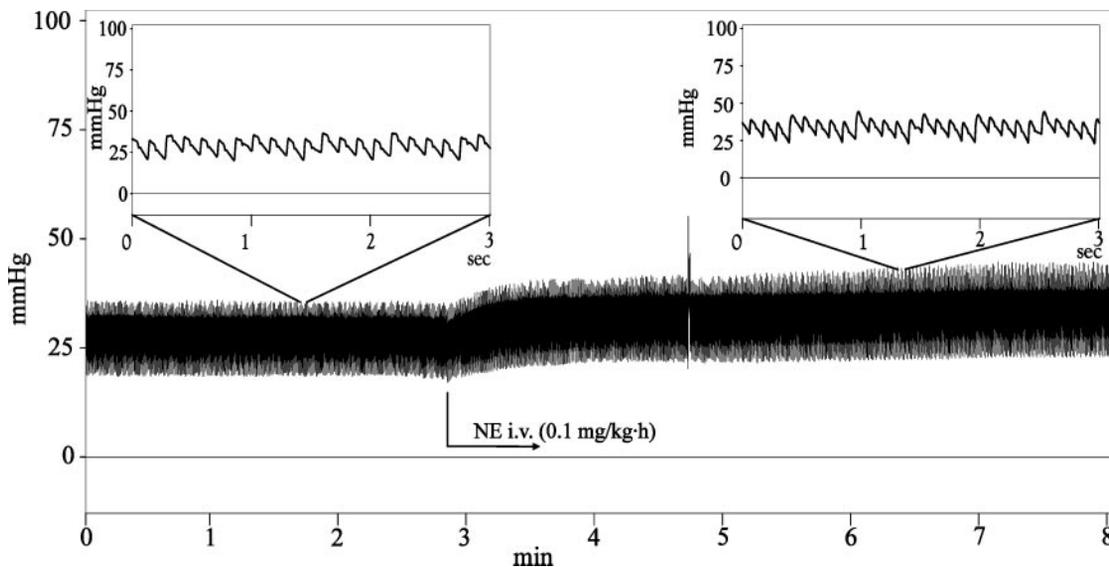


Fig. 3. Original registration of pulmonary arterial pressure under basal conditions (*left inset*) and continuous infusion of norepinephrine (NE; *right inset*) as indicated.

ter when they were removed from it. In the present approach, the tip of the introducer becomes mechanically deflected when it is placed in the right ventricle (see Fig. 1). This seems to be an appropriate and straightforward approach that is reproducible in the hands of experienced researchers and may ultimately result in a routine method. At the present stage, this catheterization procedure is successful when much experience has already been obtained with similar techniques in small laboratory animals or after extensive practice and training periods.

The shape of the PA pressure curve resembled that obtained in the aorta, although at a lower level. There was a prominent dicrotic notch during the diastolic decrease in pressure (see Fig. 2). The PASP was of the same height as the RVSP (see Fig. 2C); this is similar to the situation in LV catheterization where LVSP is the same as systolic aortic pressure (21). RVEDP did not increase when the catheter was placed in the PA as indicated by unchanged RVEDP before and after pulmonary arterial catheterization. Also in LV catheterization, LVEDP did not increase when the catheter was positioned in the left ventricle even for extended periods of time (21). Thus there is no obstruction of the pulmonary or aortic valve during these catheterization procedures. The values for PASP and PADP agree quite well with those published (5, 6, 15, 16). The rhythmic respiratory changes (see Fig. 2) were clearly seen on all records of pulmonary arterial pressure, which is in accordance with previous data published thus far for rats (5, 7, 15).

Stimulation of male Long Evans rats with NE induced the well-known positive chronotropic and inotropic effects of both heart chambers (Table 3). Also, RVSP was elevated in this rat strain, although not to the same extent as previously observed in Sprague-Dawley rats (24). The stimulation intervals with NE, however, were longer in most of the studies in which

NE had been shown to elevate RVSP (1, 8). A dose-dependent increase in pulmonary arterial pressure was observed earlier (16), whereas a variable response was reported in another investigation (5). In this study, PASP, PADP, and PVR increased in parallel with the increase in RVSP (Table 3). That the values of PVR can be obtained in all experimentally induced disturbances of pulmonary circulation is important for future studies.

It may be envisaged that the pulmonary arterial catheter that is now available for rats may be miniaturized to such an extent that it will become applicable to mice. Because transgenic and knockout mice are generated in increasing numbers, pulmonary arterial catheterization is needed to examine the effects of overexpressing or deleting a protein or physiological process on pulmonary circulation.

#### DISCLOSURES

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