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IMMEDIATE CHANGES IN ESTIMATED CARDIAC OUTPUT AND VASCULAR RESISTANCE AFTER ^{60}Co EXPOSURE IN MONKEYS

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20 ABSTRACT (Continue on reverse side if necessary and identify by block number)

Aortic blood flow velocity, blood pressure, and heart rate were recorded in 12 unanesthetized, nonperforming monkeys during exposure to 1000 rad ^{60}Co at 129-164 rad/min. The first post-radiation changes were seen within 3-4 min of the exposure's start and included tachycardia, a transient hypotension secondary to a loss in peripheral resistance, and a brief increase followed by a decrease to subnormal levels in cardiac output.

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20. ABSTRACT (Continued)

Lowest cardiac output occurred between 10-20 min postexposure while blood pressure and peripheral resistance were recovering. It was proposed that the concurrent combination of low cardiac output, low blood pressure and supranormal peripheral ~~resist~~-ance might sufficiently attenuate cerebral perfusion temporarily to account for the transient behavioral decrements often seen during this time. Histamine release was postulated as responsible for this vascular shock syndrome.

PREFACE

This work was performed as a Nuclear Effects Subtask entitled "Neurophysiological Basis of Primate Performance Decrement," funded by the Defense Nuclear Agency under Contract No. DNA-001-74-C-0098. The present report determined that the initial cardiovascular response to supralethal, wholebody irradiation is a precipitous loss of peripheral vascular resistance. The profound hypotension which follows resembles a shock-like state. This study also determined that cardiac output declines below normal levels during this early syndrome. The resulting cardiovascular balance is critically marginal for the maintenance of adequate cerebral perfusion pressure. An insufficient cerebral blood supply is the presumed basis for transient performance decrement and/or incapacitation. Histamine release was postulated as responsible for this vascular shock syndrome.

This research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences, National Research Council.

The author acknowledges the contributions to this work of the following individuals: E. A. Henderson (surgery), S. Jennings and A. Mills (technical assistance), G. K. Weiss and D. Priola (consultation).

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INTRODUCTION

Within a few minutes of exposure to high-dose, wholebody, ionizing radiation, monkeys generally exhibit a transient period of profound hypotension which is frequently followed by incapacitation and/or performance decrement.[1,2] Shortly thereafter performance accuracy may return to normal while mean arterial blood pressure gradually recovers to 80% or more of its preradiation level about 20 min postexposure. Tachycardia is also usually observed shortly after exposure as well as hyperventilation[1,3] and the appearance of slow waves in the EEG.[4]

Of main interest in such studies as the foregoing has been the search for reliable physiological predictor variables of the behavioral decrements seen. Significant associations between hypotension and performance decrement have been obtained in only two studies.[2,5] As was pointed out in both, however, severe radiation-induced hypotensions are still regularly seen without any accompanying change in the behavioral measures. Obviously the association between blood pressure and behavior here is indirect.

Among the potentially important observations missing from the complex of physiological responses to radiation are

whether cardiac output and peripheral vascular resistance are maintained in appropriate balance during the hypotensive period to support adequate cerebral perfusion, since a deficiency in the latter would be a likely basis for the behavioral impairments seen. To date, attempts to determine the adequacy of cerebral blood flow[1,6,7,8] and oxygen tension[9] after irradiation have yielded inconsistent or at least unenlightening results. And the attempts to examine for changes in cardiac output were not made soon enough following exposure to sample from the initial critical phase before recovery had partly taken place.[10,11] Consequently, the purpose of the present study was to attempt to provide on-line estimates of cardiac output and peripheral vascular resistance during and following exposure using conscious, nonperforming monkeys.

METHOD

Subjects

The subjects were 12 male rhesus monkeys (*Macaca mulatta*) weighing between 2 and 3 kg, obtained from Primate Imports Corp., New York. They were treated as necessary for enteric disorders and tuberculin tested during quarantine before entering the experiment.

Apparatus

One week prior to irradiation each subject underwent surgical implantations of an intravascular aortic flow velocity catheter* (shown in Fig. 1) and a femoral artery polyethylene catheter. Surgery was performed under halothane general anesthesia following premedication with sernylan and atropine.

The catheter flow probe was inserted through a scissor-cut in the right common carotid artery about 7 cm cephalad to the heart, and was pushed toward the heart until it extended into the ascending aorta. Blood flow velocity was monitored via an oscilloscope display of the pulsatile output of a Carolina Model 501 Flowmeter. Zero flow (flat trace) was displayed during the probe's traverse through the carotid, as the carotid was completely occluded by the catheter probe. On entering the aortic arch, the pulsatile flow waveform appeared (Fig. 1) and grew in amplitude as further passage placed the probe's electrodes fully within the aortic root. Further insertion produced either entry into the descending aorta, shown by inversion of the

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* Model EP1006, Size 6 French (2 mm diameter), Carolina Medical Electronics, P. O. Box 307, King, NC 27021.

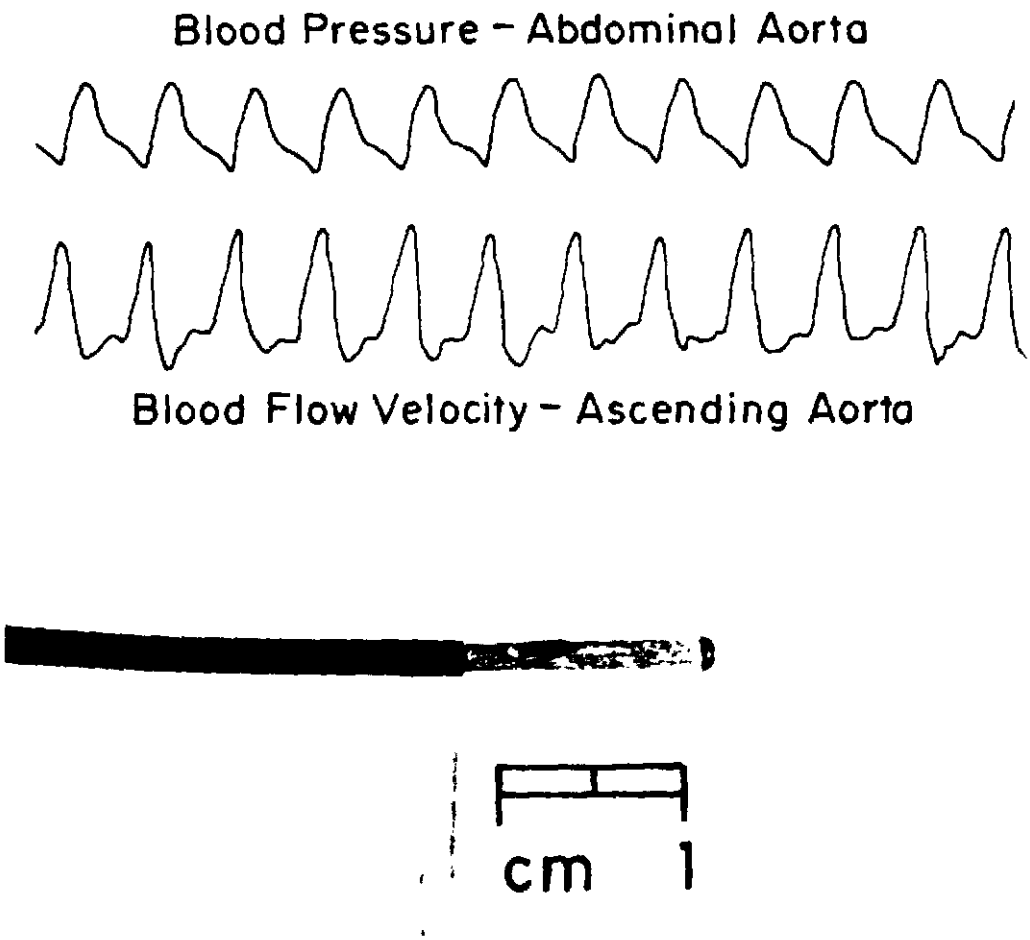

Figure 1. Polygraph Tracings of Blood Pressure and Aortic Flow Velocity, the Latter Being Recorded with the Intravascular Velocity Flow Probe Shown at the Bottom.

displayed waveform, or by protrusion through the aortic valves into the heart which was evidenced by waveform distortions as well as by resistance to insertion felt by the surgeon.

At the desired insertion point, where the largest amplitude, undistorted waveform was displayed, the catheter was secured by ties around the carotid just below the point of the catheter's entry. The distal carotid portion was tied off. Overlying connective tissue and skin were sutured closed over the exiting catheter, which was further secured outside to neck skin and to two points on the skin of the right side of the head. As the animal's head movement would be limited by a restraining chair, the slack allowed in the catheter between its exit tiedown at the neck and the anchor points on the head insured that the probe tip would not likely be displaced from its initial location within the aortic root. Actual location of the probe was determined by dissection at sacrifice after the radiation experiment, usually within one day after exposure.

The polyethylene catheter was inserted into the left femoral artery up to the level of the diaphragm for the recording of systemic arterial blood pressure within the abdominal aorta. The femoral catheter terminated outside in the

three-way Leur-lock fitting secured to the chair near the exit of the catheter at mid-thigh level. The catheter was maintained patent outside the recording periods by pulsed infusion of heparinized saline (5 U/cc/15 min).* Horizontal stocks at the neck and waist levels of the restraining chair as well as a snug-fitting nylon mesh vest prevented the monkey from reaching the catheters. The chair and head-restraint device employed are pictured in Bruner et al.[12] For blood pressure recording, a pressure transducer** was attached to the Leur-lock fitting. All recordings were written out on a Grass Model 78 polygraph.#

Flow Velocity (FV) Measurement. Cardiac output changes were inferred from the changes in blood flow velocity recorded within the ascending aorta. Initially the velocity flow probe was precalibrated under controlled flow conditions using saline with tubes of known inside diameters in order to determine the probe gain factor to be used for the experimental recordings. With the velocity probe calibrated properly, the Carolina 501 Flowmeter gives a direct dial readout

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* Model 1302 Lambda Pump, Harvard Apparatus Co., 150 Dover Rd., Millis, MA 12054.

** Model PSL 125-6, Kulite Semiconductor Products, 1039 Hoyt Ave., Ridgefield, NJ 07657.

Grass Instruments, Quincy, Mass. 02169.

in mean cm/sec. The present mean readings obtained during implantation in the anesthesized, supine monkeys ranged between 8 and 12 cm/sec. These values increased slightly in the conscious, sitting state.

Postmortem measurements of several aortas indicated that the typical internal diameter at the level of the probe's electrodes was approximately 8 mm. However, under the tension of normal blood pressure, the average internal diameter would be expected to increase as much as 3-4 mm.[13] A velocity of 9.0 cm/sec recorded with the present flow probe within a 12-mm mean diameter aorta yields a mean flow of approximately 594 ml/min.*# For a 2.2-kg monkey this value would be in agreement with the mean cardiac output of 273 ml/kg/min observed in conscious, sitting monkeys by Forsyth.[14]

---

*# Mean Flow (ml/min) = 60 x velocity (cm/sec) x effective x-sectional area of aorta in cm^2 (1)

where x-sectional area = $\pi d^2 \div 4$, and effective area amounts to the x-sectional area of the aorta minus that of the probe (probe diam. = 2 mm).

Figure 1 shows typical tracings of the aortic flow velocity (FV) and blood-pressure waveforms. An integrated "mean" flow output from the flowmeter was also recorded but is not shown. The pulsatile FV waveform, reflecting instantaneous flow velocity throughout the cardiac cycle was utilized for scoring purposes rather than the mean flow, because of the lack of dependence by the former on a baseline zero reference in the aorta, where approximately zero flow is assumed between systoles. Instabilities in the mean flow output's baseline zero reference rendered those values very unreliable, a not uncommon happening with electromagnetic flow recordings. To the extent that the integrated mean flow recordings could be corrected in retrospect for baseline drift on a minute-to-minute basis they showed the same changes postirradiation as did the pulsatile flow measure. Pulsatile flow was quantified simply by measuring the distance in millimeters between the minimum (≈zero) and maximum flow velocities recorded during a cardiac cycle. Retrograde flow, when evident in the recordings, was not excluded from the measurements for convenience, after we determined that the retrograde deflections were not differentially affected by irradiation and therefore their inclusion would not influence the flow data's interpretation. More

precise analysis was not considered necessary as only relative changes (percentage increase or decrease) were evaluated. The average pulsatile FV deflections recorded over the 5 minutes just preceding irradiation served as the preexposure standard with which the corresponding postirradiation flow measurements were compared in terms of percentage change over time following the start of the exposure.

However, since recorded FV is a function of vessel x-sectional area and as vessel lumen decreases when blood pressure does,[13] it was judged necessary to attempt to correct measured FV for varying vessel diameter. To achieve the correction, estimates of aorta diameter were made as a function of blood pressure based on the volume-pressure curves of Green for human aorta and the Laplacian tension-length diagram derived therefrom by Burton.[15] Burton's data points were fitted with the logarithmic curve shown as the lower curve in figure 2. Normal mean blood pressure was defined as 100 mm Hg for purposes of the calculations, at which tension level the aorta diameter was estimated to be 11.5 mm.

Given estimated aortic diameter as a function of blood pressure, the expected FV (for any constant cardiac output) was then calculated for the present probe using

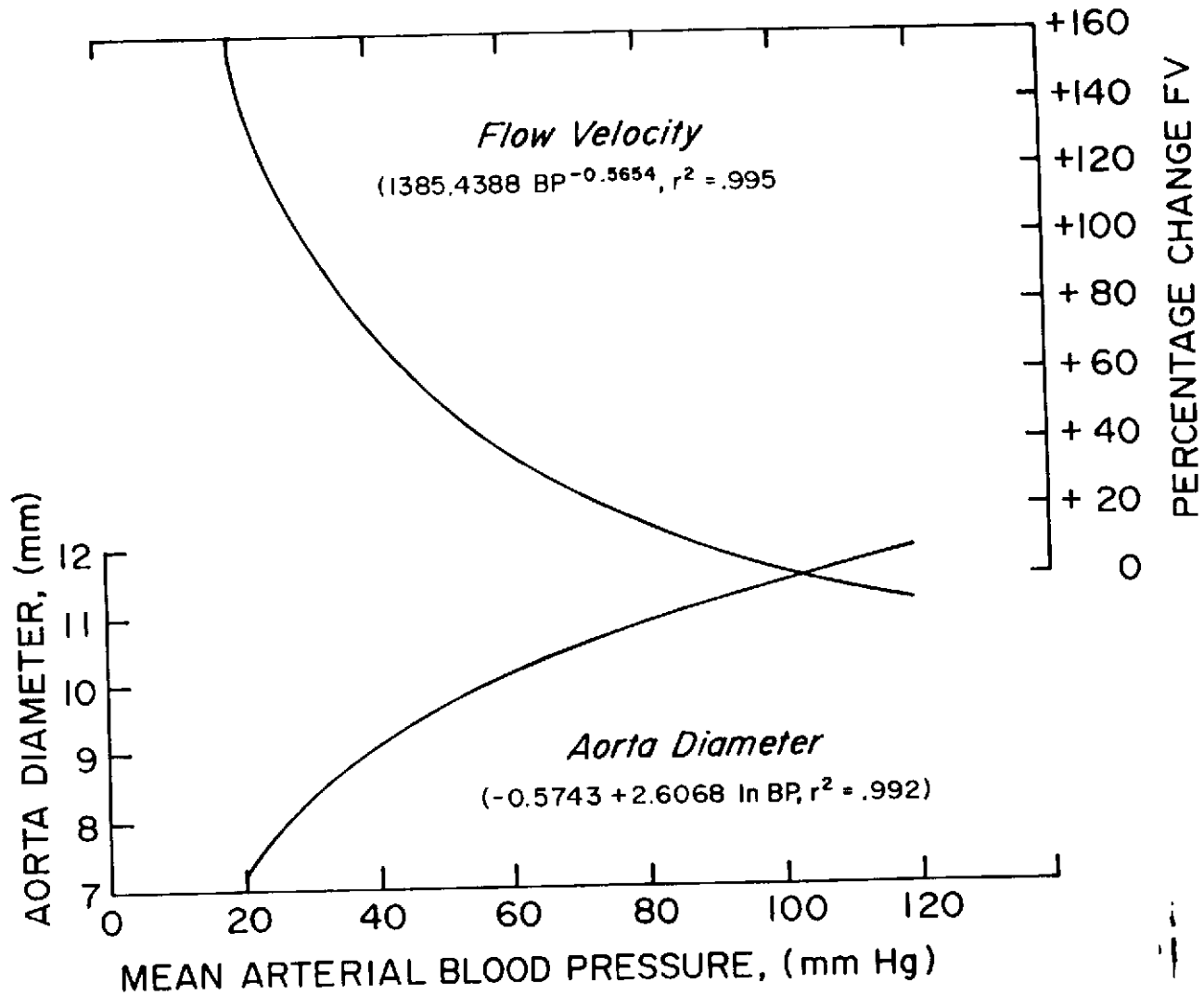

Figure 2. Estimated Aorta Diameter as a Function of Mean Blood Pressure After Burton[15] (lower curve). Flow Velocity Predicted for a Constant Cardiac Output Given Aorta Diameter as a Function of Blood Pressure (upper curve). Formula Used as Basis for Correction of Flow Velocities Measured.

formula (1). Predicted FV as a function of vessel diameter as a function of blood pressure was then derived and fitted with the power curve shown as the upper curve in figure 2, in terms of percentage change relative to 100 mm Hg. This curve reveals, for example, that a drop in pressure to 50 mm Hg (50%) should elicit a decrease in vessel lumen to 9.62 mm, which, in the absence of any change in cardiac output, would increase FV about 52% as recorded. Consequently a correction based on the functional relations shown in figure 2* was applied to all the FV data to be reported here, whereby this artifactual increase was subtracted out so as to leave estimates of cardiac output free of the presumed lumen-size effect. Otherwise FV, as measured directly, would be observed to increase as pressure decreased even with no real change in flow output. The correction applied was considered a conservative handling of the FV measurement problem--the correction tends to underestimate cardiac output changes--since some investigators have not found the degree of lumen reduction with blood pressure[13] as was

---

* $FV_{corr} = FV_{meas} - 1385.4533 \times BP^{-0.5654}$ in percentage change: e.g., for $FV_{meas} = +20\%$, and BP = 80 mm Hg, $FV_{corr} = 20 - 16.3 = 3.7\%$

incorporated into the present correction. (A comparison of FV values measured with and without the correction will be presented in the Results section.)

Blood Pressure (BP). Mean arterial blood pressure (BP) was calculated by taking one-third of the pulse pressure difference plus the diastolic pressure with reference to atmospheric pressure zero, corrected for transducer distance below the aortic arch.

Total Peripheral Resistance (TPR). Total flow resistance (or peripheral resistance) was determined as a percentage of the preirradiation value by the following formula after FV correction:

$$TPR = \frac{\text{Flow resistance post}}{\text{Flow resistance pre}} = \frac{\text{BP post}}{\text{BP pre}} \times \frac{\text{FV deflection pre}}{\text{FV deflection post}} \quad (2)$$

Procedure

The monkeys were irradiated individually, dorsoventrally while seated in a wood and plastic restraining chair. Eleven animals received 1000 rad ^{60}Co and one received 876 rad. Dose rates varied over individuals from 129 to 164 rad/min and are given in the Results section. The exposure was administered in the morning approximately 16 hr after the last feeding. Dosimetry was determined using high-sensitivity Lithium Flouride Thermoluminescent

dosimeters with live and cadaver monkeys and cardboard phantoms. Further details of the exposure and dosimetry may be found in Bruner et al.[12]

Continuous remote polygraph recordings of the cardiovascular responses were instituted approximately 30 min prior to beginning the exposure, and continued without interruption normally to 30 min or more postexposure. Exposure duration ranged from 6.1 to 7.75 min depending upon the dose rate used as will be indicated for each subject in the Results section. All present references to postexposure changes are with respect to time from the exposure's start and thus the changes to be described may have occurred while the exposure was still in progress.

RESULTS

Figure 3 presents the group mean percentage changes in the four cardiovascular response measures for the initial 30 min after the start of irradiation. The exposure was delivered over the first 6-8 min shown in figure 3, its duration depending on dose rate as specified on the individual response figures to follow. Figures 4-16 present each subject's response changes for as long as monitored up to 60 min following the exposure's start. The curves are expressed in terms of percentage of preradiation baseline value, the latter

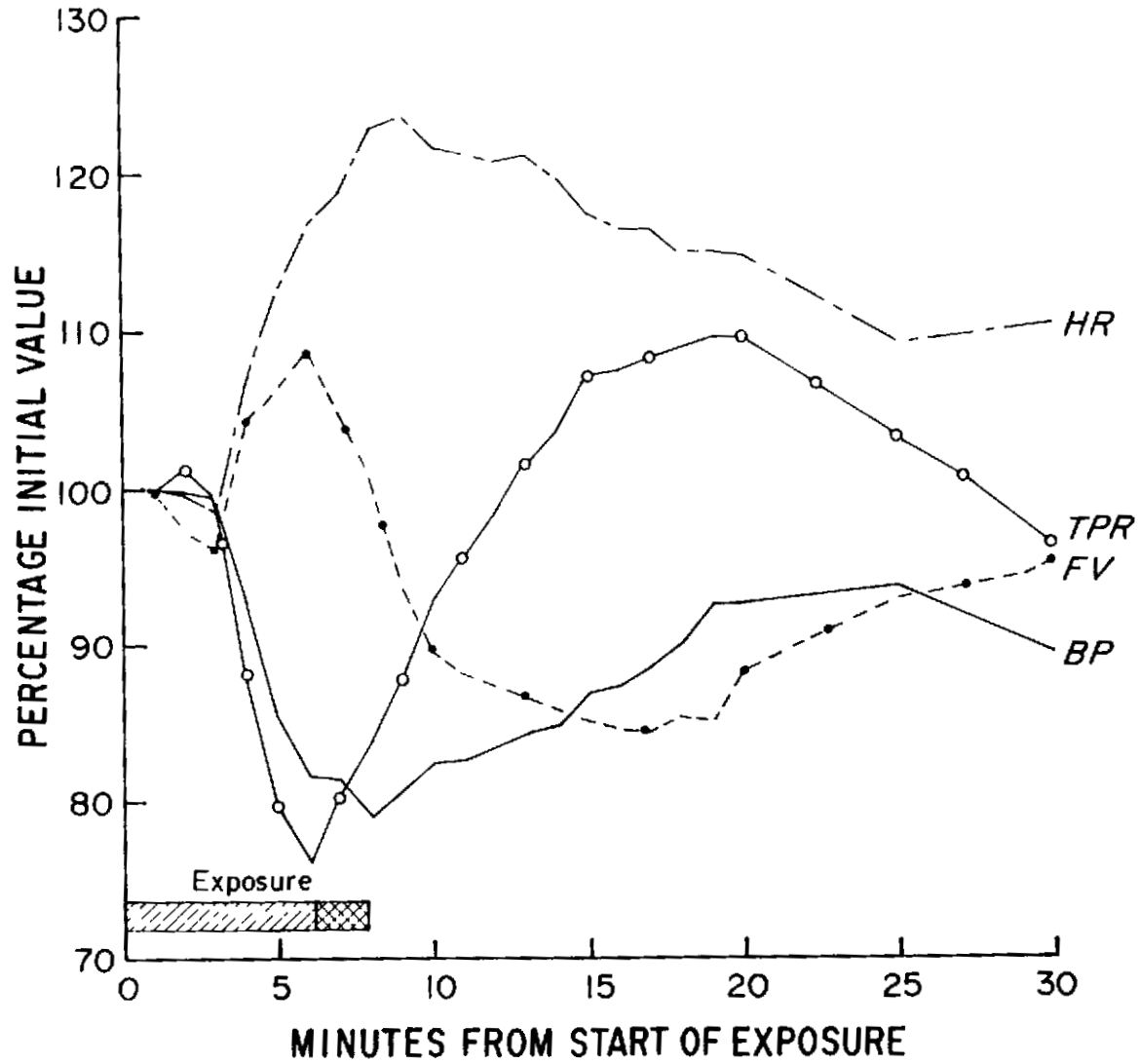

Figure 3. Group Mean Percentage Heart Rate (HR), Total Peripheral Resistance (TPR), Flow Velocity (FV), and Blood Pressure (BP) Relative to Preradiation Baseline During and After Irradiation. Exposure Duration Ranged from 6.1 to 7.75 min. N = 12 up through 20 min, N = 11 at 25 min, N = 10 at 30 min.

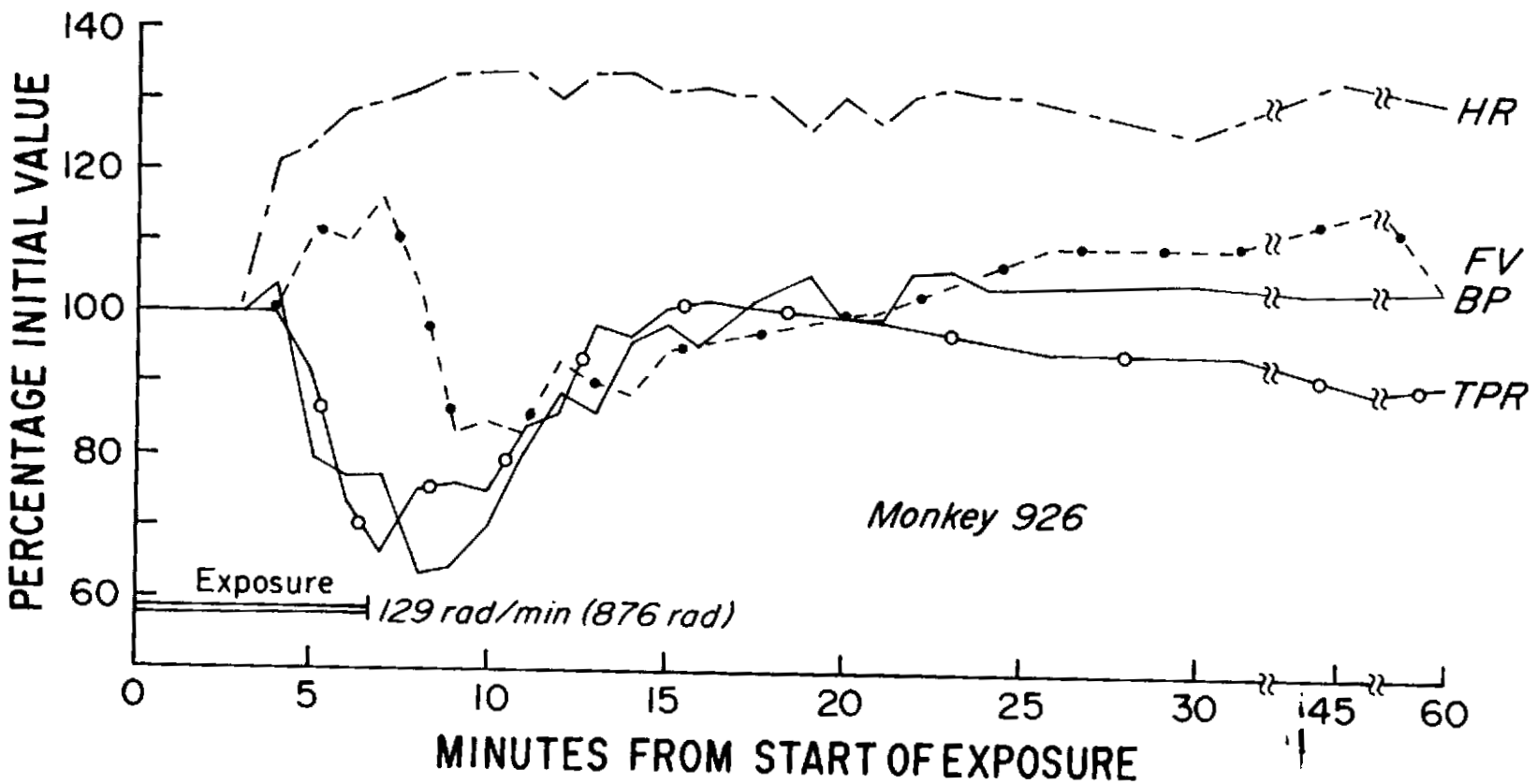

Figure 4. Percentage Relative to Baseline for Cardiovascular Responses of Monkey 926 During and Following Exposure. The Exposure Duration, Dose Rate, and Total Dose are Indicated. Values Plotted for FV and TPR are Based on FV Before Correction for Vessel Lumen Reduction Associated with Drop in BP.

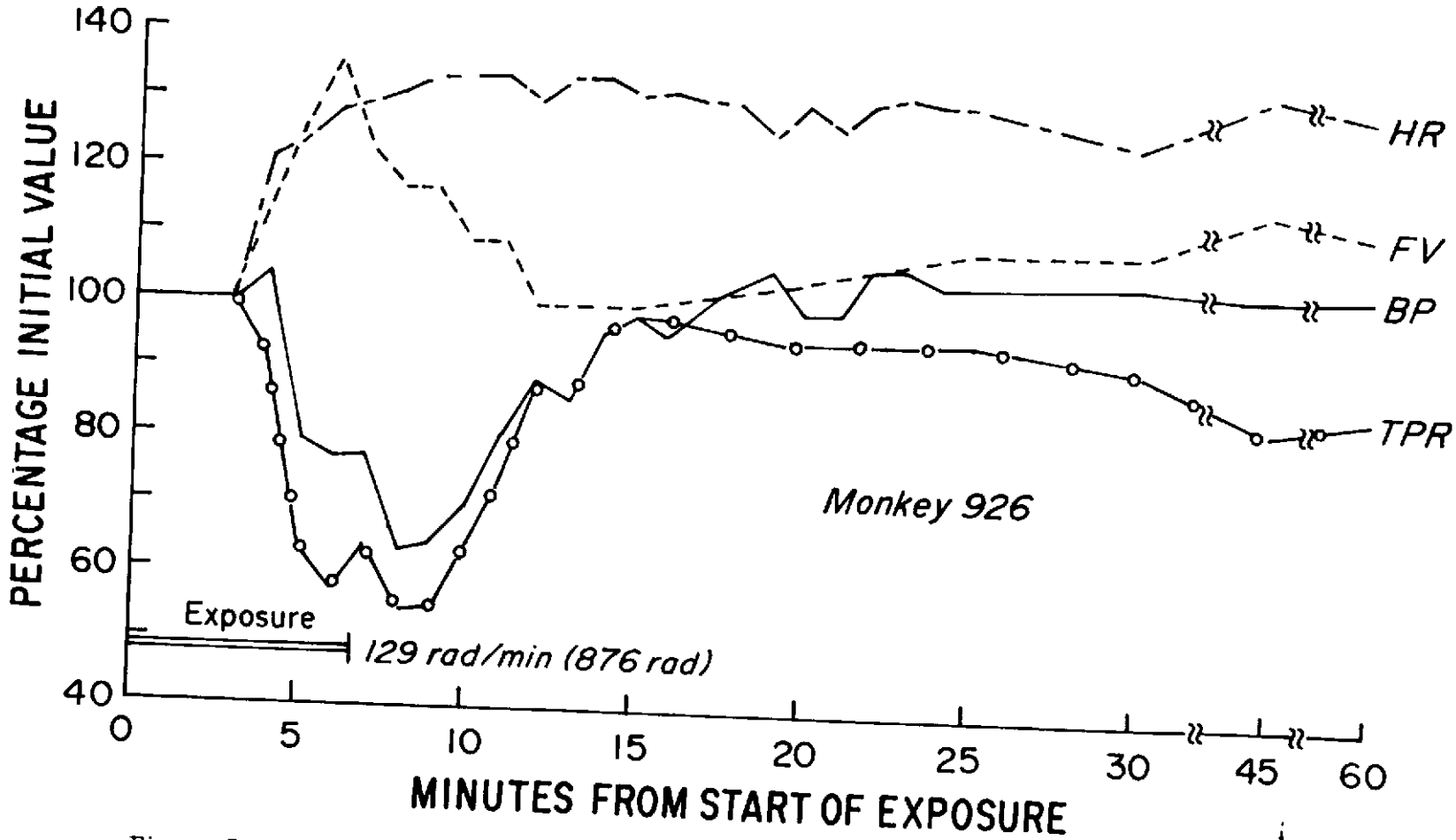

Figure 5. Percentage Cardiovascular Responses for Same Monkey (926) as Shown in Figure 4, Shown Here After Adjustment of FV for Vessel Diameter/BP Relationship. All Subsequent Figures Incorporate Only the Corrected FV Values.

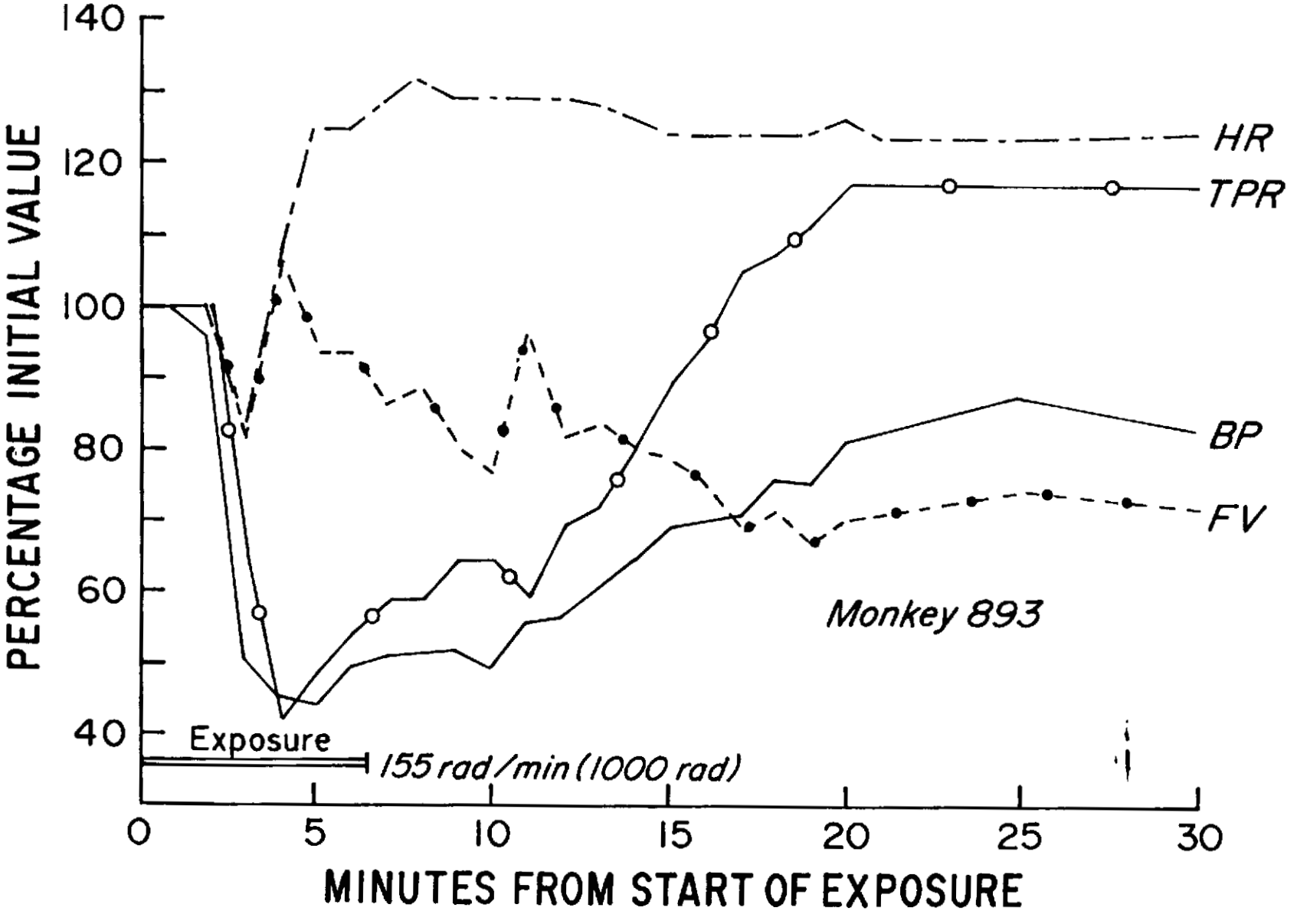

Figure 6. Postradiation Cardiovascular Responses of Monkey 893.

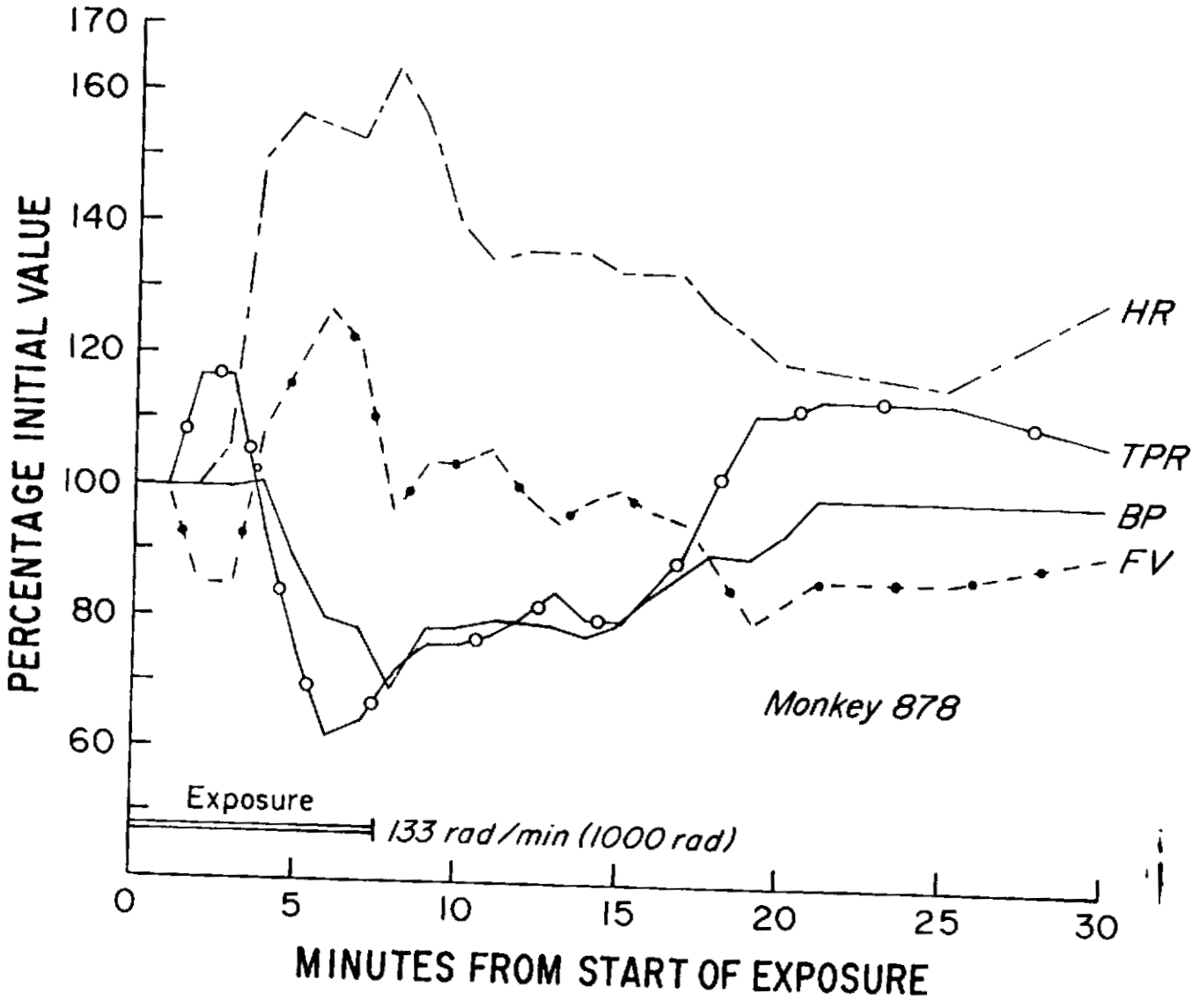

Figure 7. Postradiation Cardiovascular Responses of Monkey 878.

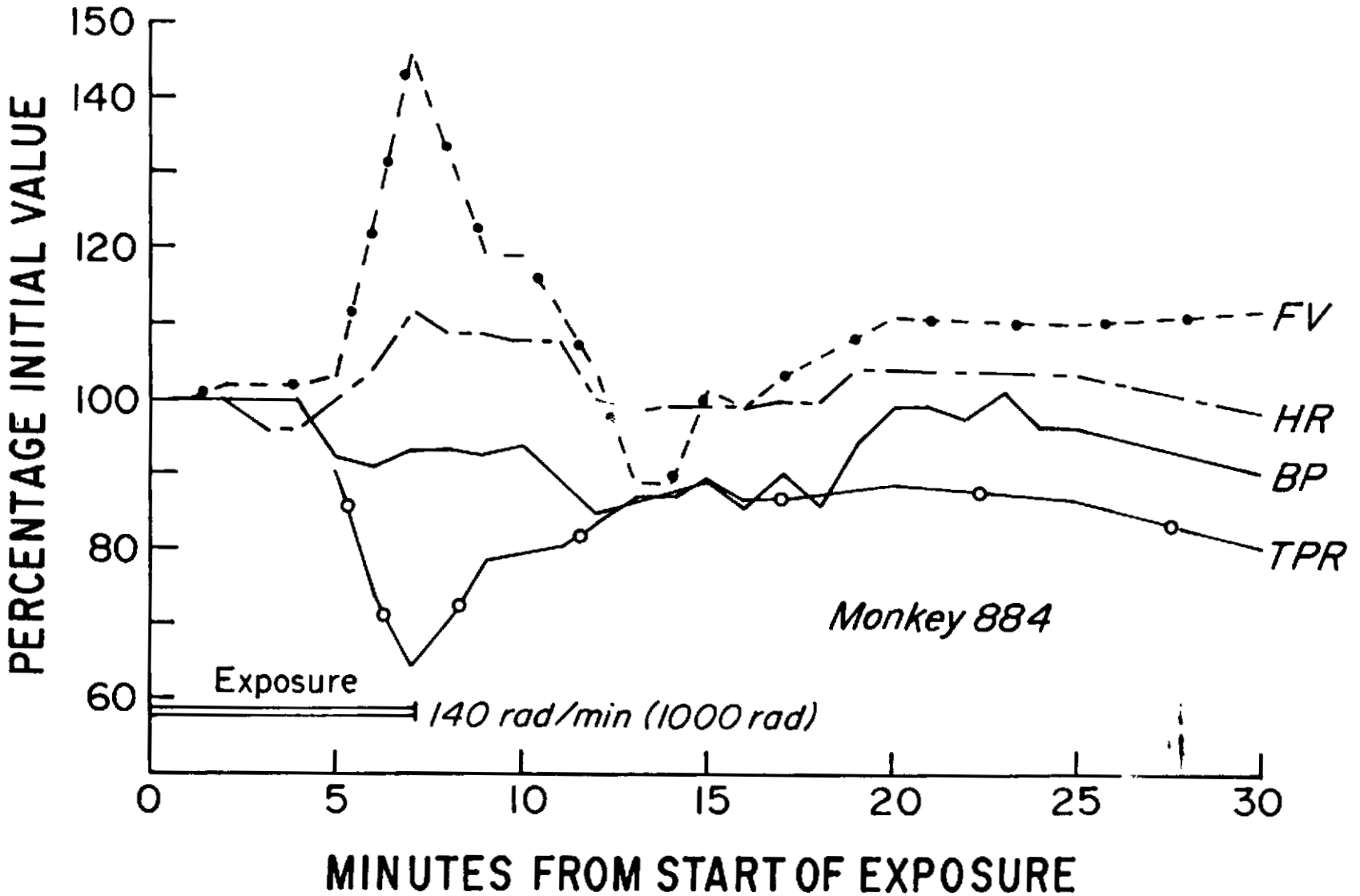

Figure 8. Postradiation Cardiovascular Responses of Monkey 884.

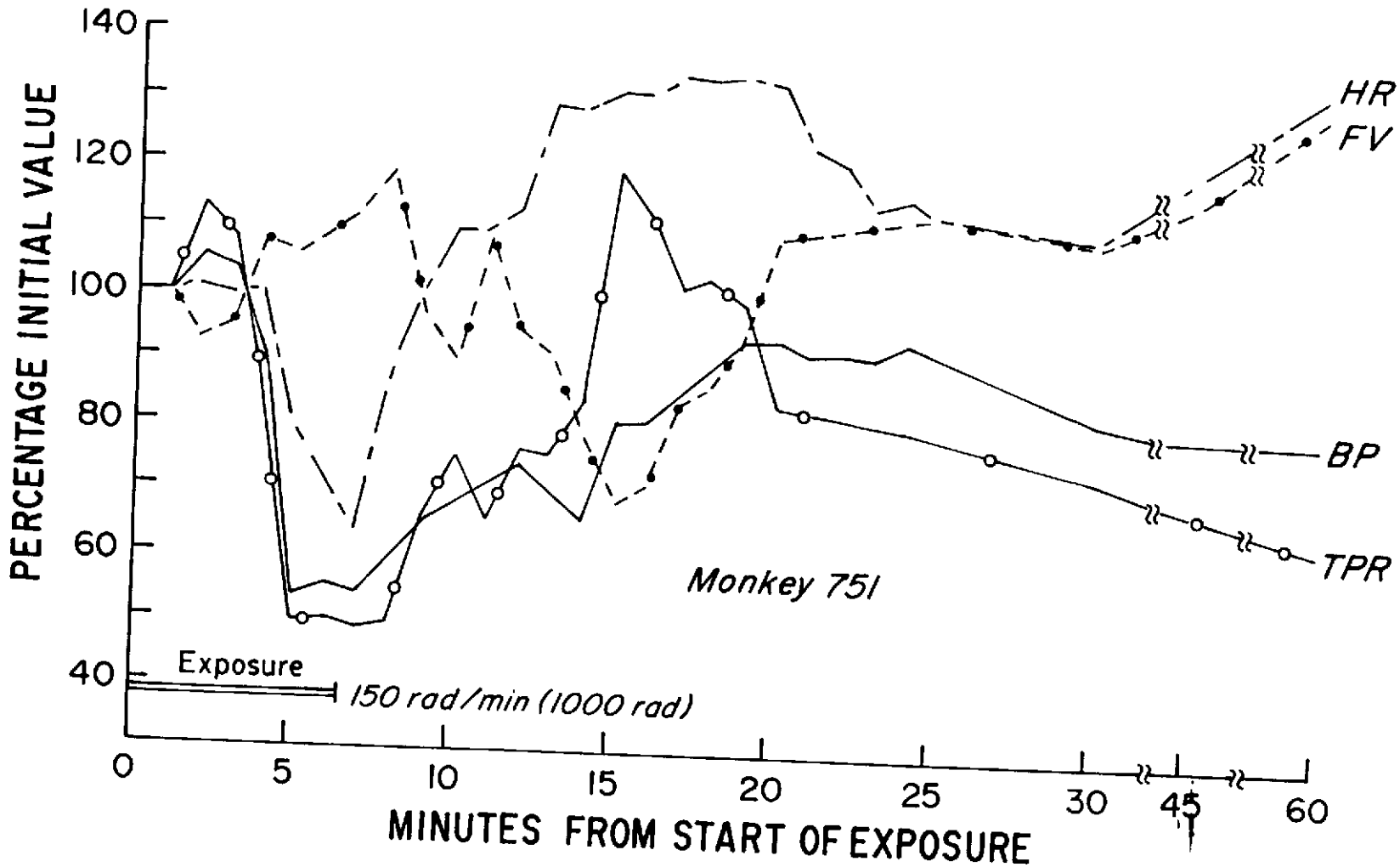

Figure 9. Postradiation Cardiovascular Responses of Monkey 751.

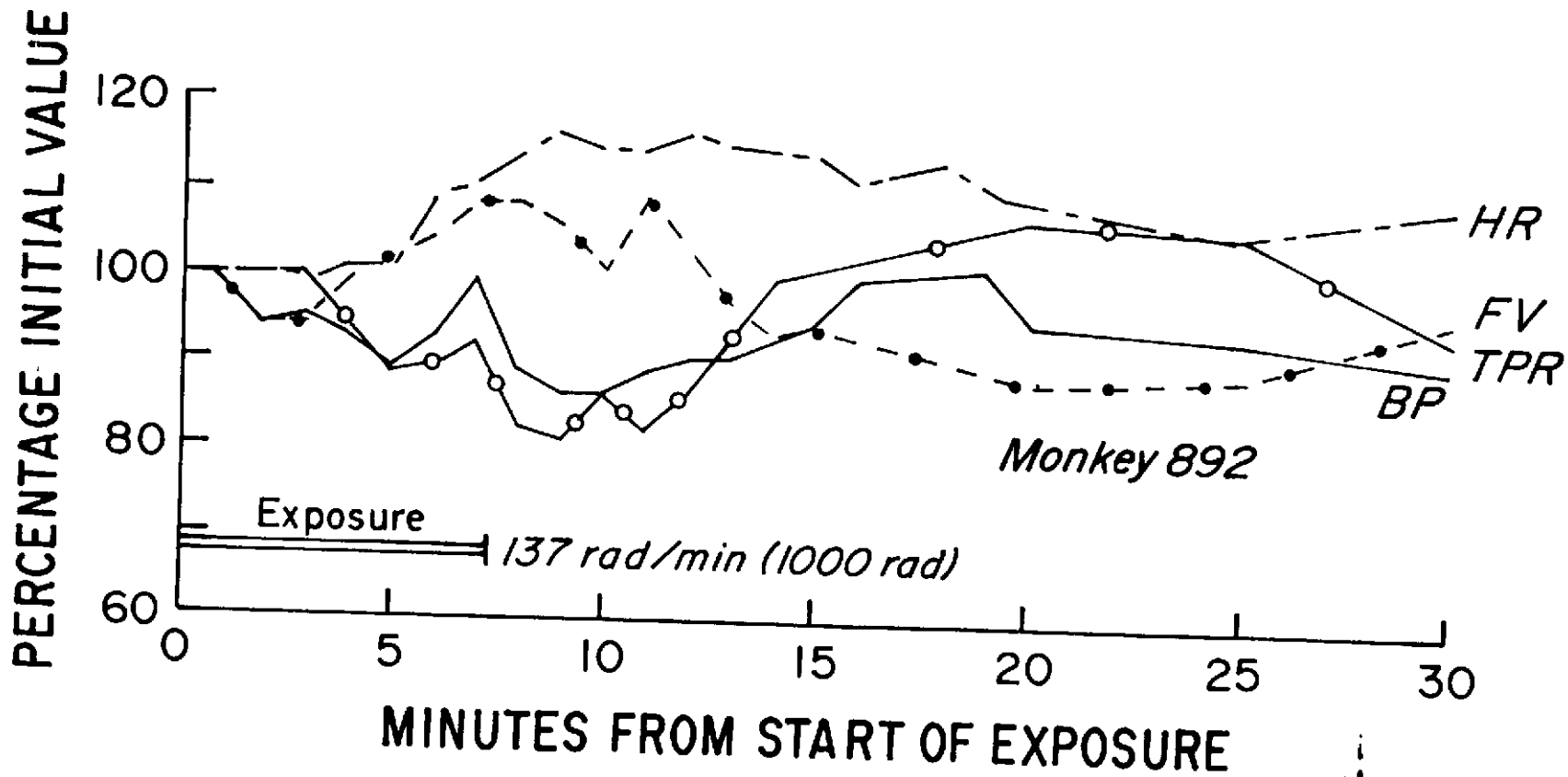

Figure 10. Postradiation Cardiovascular Responses of Monkey 892.

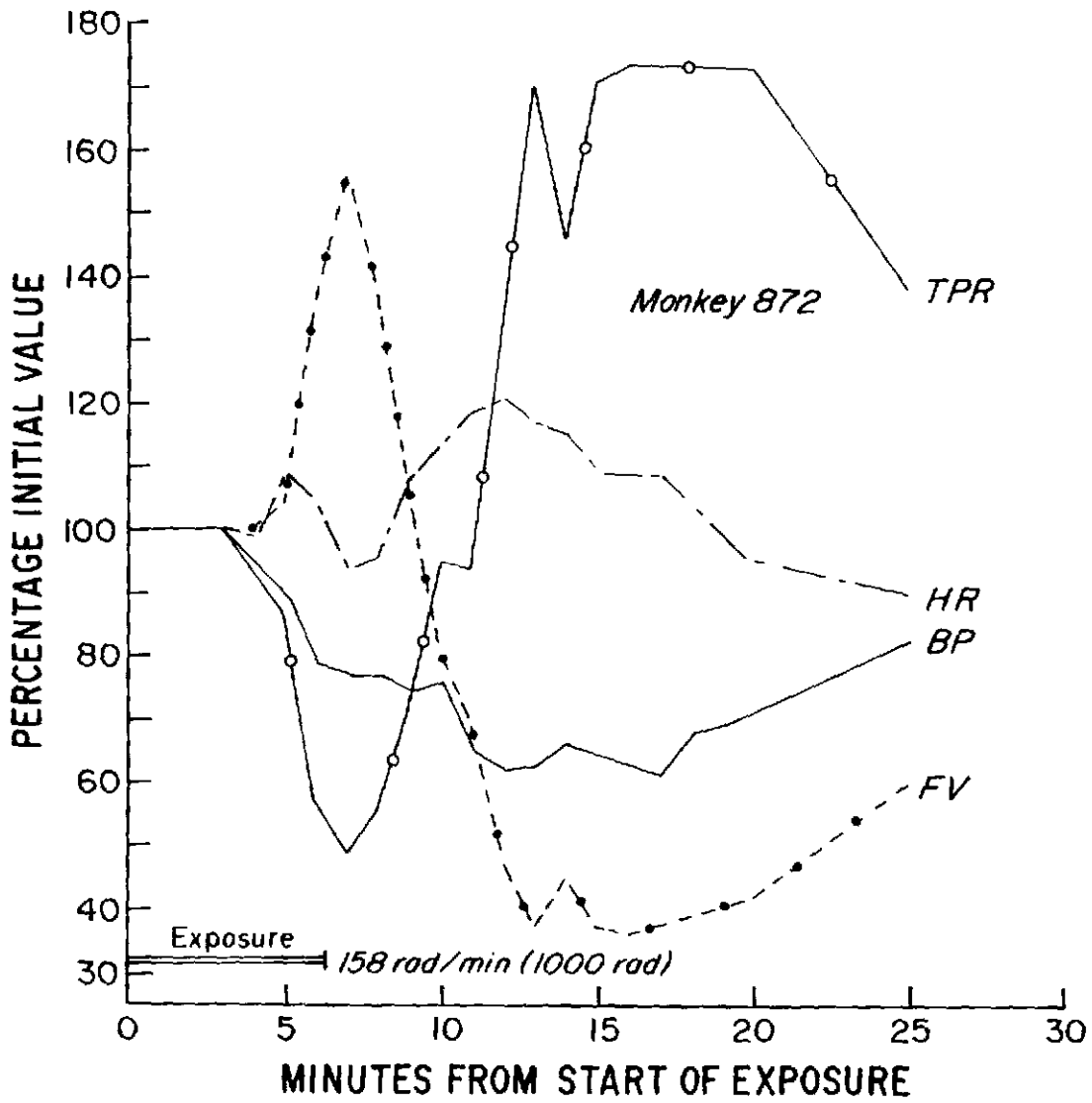

Figure 11. Postradiation Cardiovascular Responses of Monkey 872.

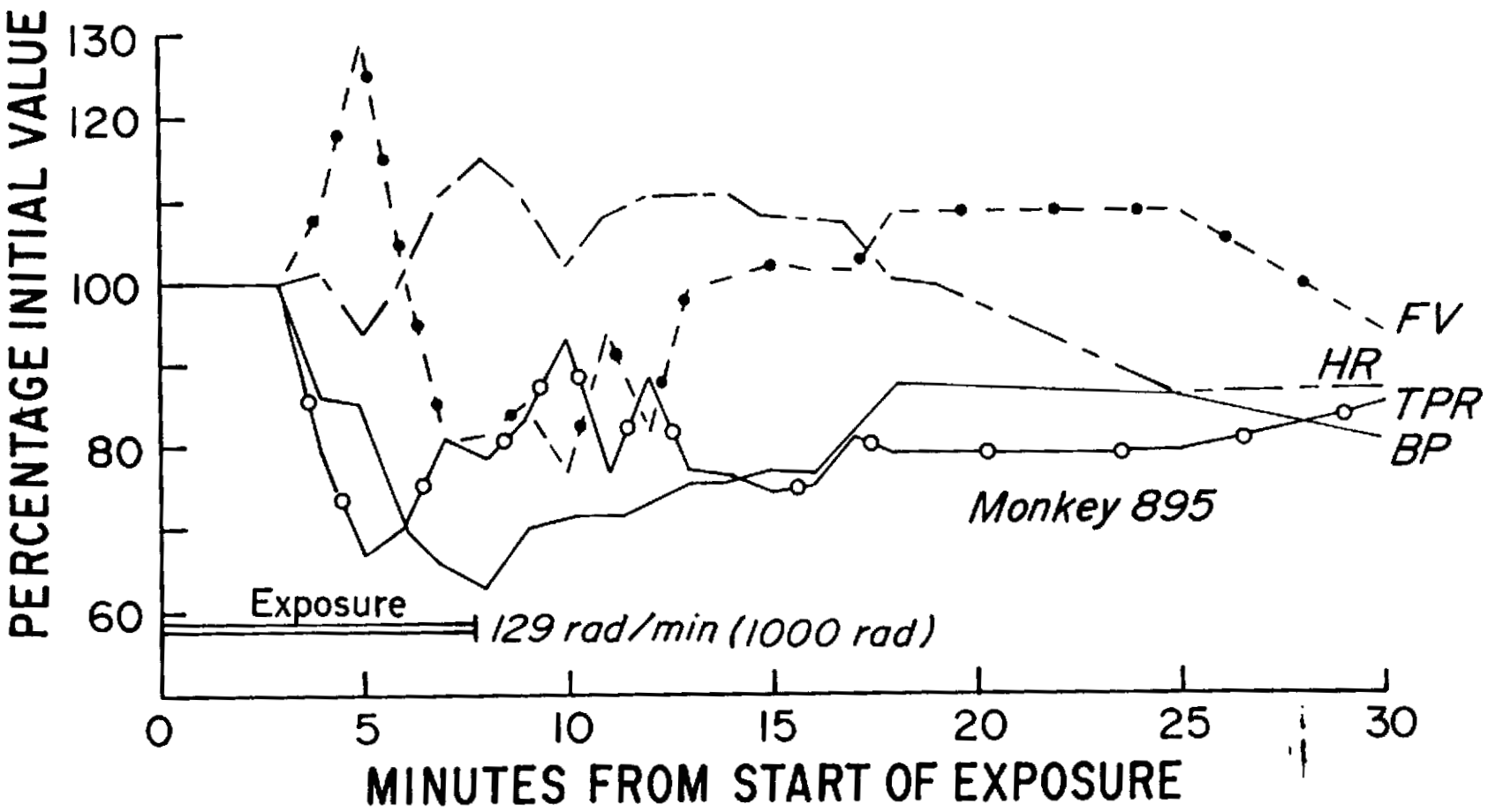

Figure 12. Postradiation Cardiovascular Responses of Monkey 895.

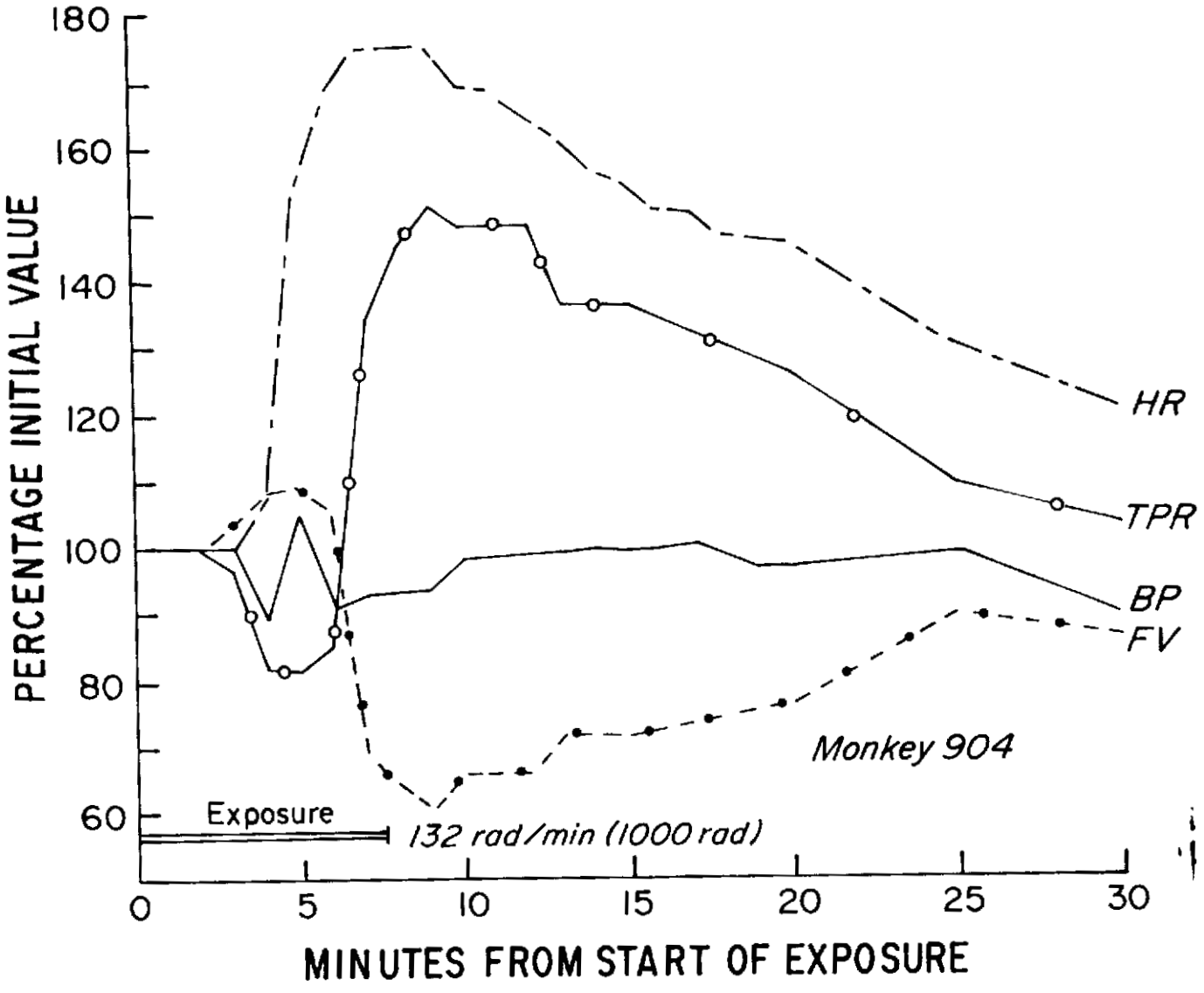

Figure 13. Postradiation Cardiovascular Responses of Monkey 904.

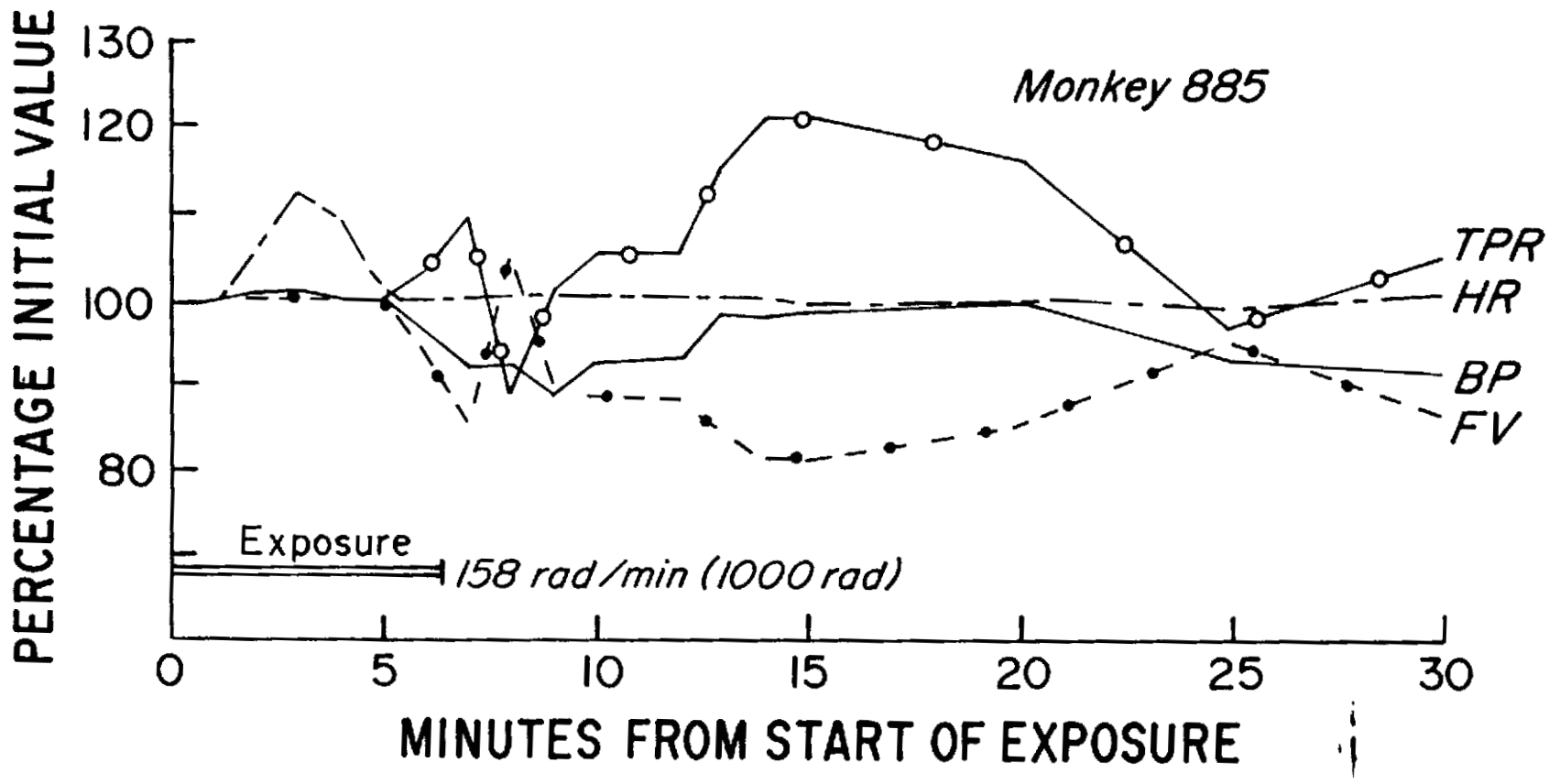

Figure 14. Postradiation Cardiovascular Responses of Monkey 885.

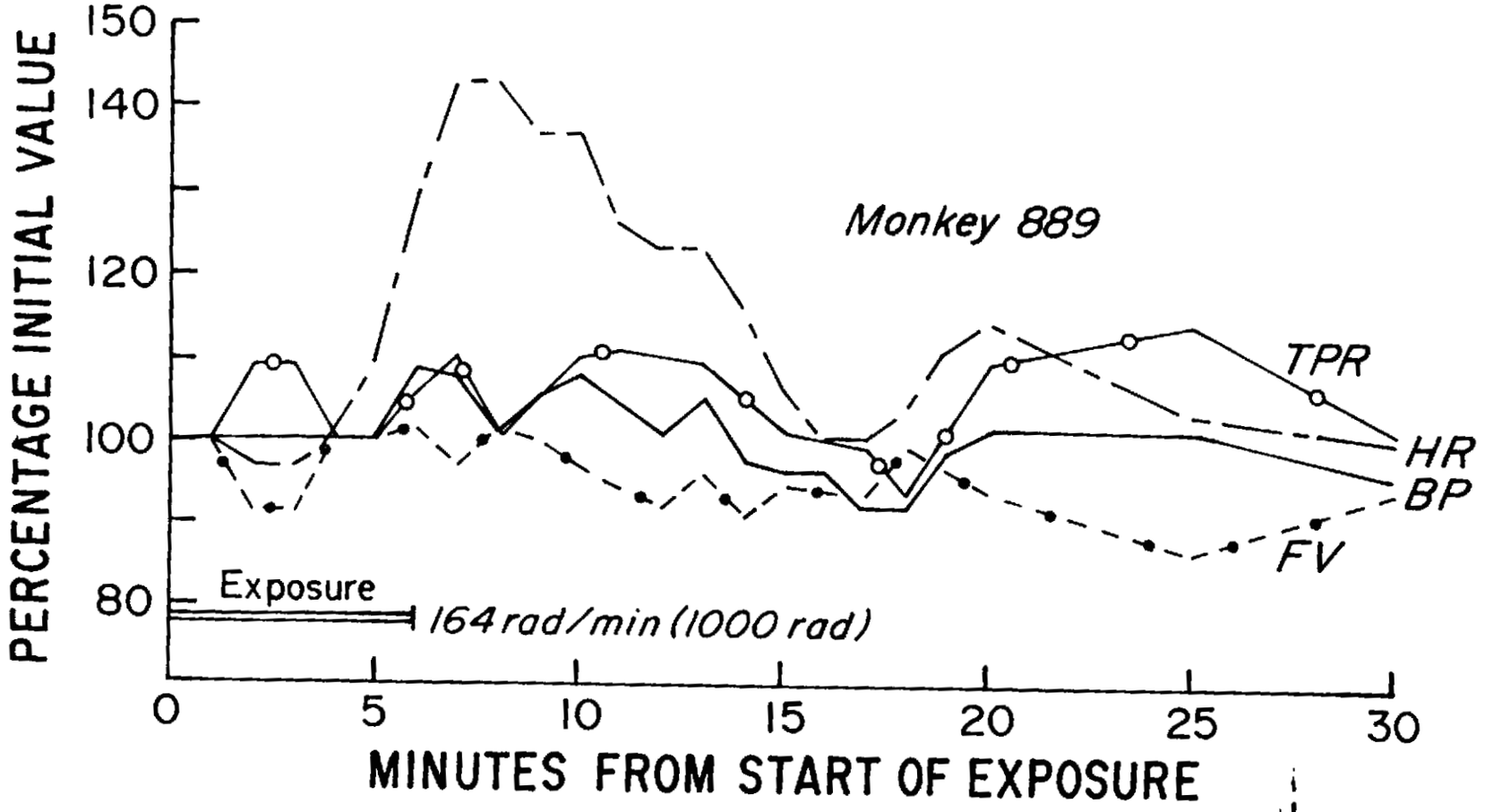

Figure 15. Postradiation Cardiovascular Responses of Monkey 889.

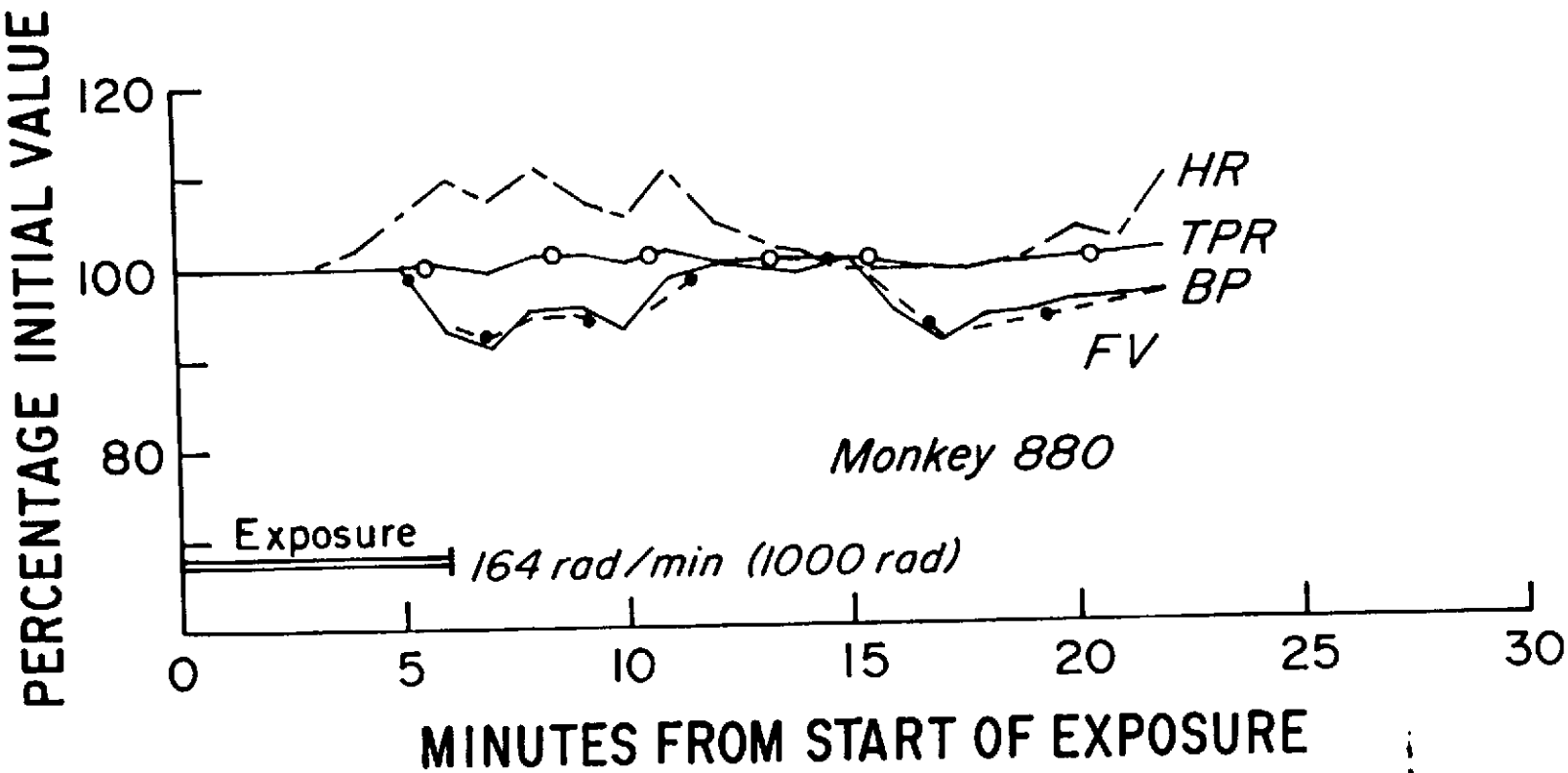

Figure 16. Postradiation Cardiovascular Responses of Monkey 880.

being the mean values observed during the 5 min just preceding exposure. The substantial individual variability so often seen in response to irradiation is evident in these figures. Figures 4 and 5 contrast the effects of the FV correction. Without correction (fig. 4) the FV changes appear somewhat higher and the TPR changes lower than with the correction (fig. 5). The remaining figures display only the adjusted FV values, and all further references to FV or its equivalent, cardiac output, will be based on the corrected FV values.

The trends shown by the HR and BP responses to irradiation are consistent with our previous findings.[2,5] For most of the animals BP generally began falling 3-4 min after the exposure's start. In some cases BP dropped precipitously within a 4 or 5 min span to its lowest observed level, while in other cases, the fall endured over 12 or more minutes. Over all subjects the deepest point of hypotension ranged from 44% to 92% of baseline value, with a mean of 79%, and occurred in most cases between 4 and 12 min (mean = 8 min) after the exposure's start. Recovery of BP to slightly below preexposure levels occurred for the group by the 20-min observation.

Heart rate (HR) generally showed an increase of 20% or more during the initial 10 min after the start of

exposure, following which it tended to drop over the next 20 min to a slightly higher rate than observed prior to exposure. A few of the animals, for example nos. 893 and 751 (fig. 6 and 9), showed an early drop in HR before the increase occurred. They also showed a relatively deep hypotension. In these and other cases we have previously observed where the HR slowed initially before accelerating the slowing was usually accompanied by a number of arrhythmias. As the individual figures show, the BP and HR curves appear reciprocally related for most of the subjects, suggesting that the normal compensatory pressoreflex adjustments were operative.[16]

Total peripheral resistance (TPR) showed a sharp drop just ahead of the BP drop and fell to a low resistance point at 6 min post for the group. TPR then began rising steadily up to 20 min post slightly overshooting its preradiation level at 13 min post.

FV showed an early increase for most of the animals while HR was accelerating and BP and TPR were falling. FV peaked at 6 min post at 108.75% for the group just opposite the lowest TPR point. Then as resistance returned gradually over the next several minutes, average FV dropped to below-normal output levels, being most noticeably subnormal

between 10 and 20 min postexposure, before regaining over 95% of its preexposure output after 30 min. The lowest average level of FV output occurred between 15 and 20 min post by which time BP had already recovered to 87% and was still climbing. Most of the animals' cardiovascular responses had returned to 80% or more of their preradiation values by the 30-min observation.

DISCUSSION

Cardiovascular Changes

The initial radiation effect measured in the present study is considered to be the precipitous loss of TPR. The rapid drop in systemic BP consequent upon this pervasive vascular shock presumably heightened sympathetic drive to the heart via the pressoreceptor reflexes, resulting in tachycardia, and possibly enhanced ventricular contractility. The interplay of these supportive cardiac responses probably accounted for the initial rise in cardiac output (CO) while TPR and BP were falling. Without such cardiac balance the hypotension might have been even more severe, perhaps to the point of cardiovascular collapse. The individual monkeys whose cardioaccelerations were delayed did in fact appear to experience deeper hypotensions. However, we

cannot assess the role of contractility in these and the other cases as it was not measured.

The maintenance of a high CO was temporary, however. A subsequent decline in CO developed after 6 min post which seemed to mirror the rebound of TPR, as if flow volume was a passive function of vessel caliber. Contributing to the diminution of CO would have been a reduction of pressoreceptor sympathetic drive to the heart signalled by the slowly increasing BP. This is suggested by the gradual slowing of HR commensurate with the recovery of BP over minutes 8 to 25. Again here it is likely that contractility (a decrease) also participated in the composite of responses resulting in the CO decline.

The fall in CO could also have been associated with a reduction in venous tone and consequent pooling, resulting in a decreased return to the heart and inadequate filling. The measurements pertinent to these possibilities were not made and therefore we can only speculate on their nature. Consistent with the notion of venous dilatation is the work of Turbyfill et al.,[8] who observed central venous pressure to show a slight increase followed by a decrease after a 4000 rad gamma-neutron pulse over the same time course as observed here for the biphasic CO response.

However, their venous pressure changes were not significantly different from preirradiation levels. But the interpretation of even significant venous pressure changes would be complicated without knowing whether venous capacitance (Δ vol. ÷ Δ pressure) and volume also changed, as these three variables are interdependent. Obviously venous return to the heart was adequate during the initial rise in CO we observed. But in the absence of more complete measurements the role of venous return for the CO decline is unclear.

An additional factor which may have been implicated in the CO decline comes from our previous observation that the baroreceptor reflex arc providing sympathetic input to the heart becomes relatively unresponsive to BP changes for a brief time during the immediate postirradiation minutes.[16] Therefore a reduced degree of sympathetic support of CO by the heart would be expected from the low BP sensed by the baroreceptors during their transient period of depression, which coincides with the period in the present study when TPR was below about 90% (minutes 4-9 in fig. 3).

In the baroreflex report[16] we found a markedly diminished capacity for vasoconstriction in response to phenylephrine injection during the early postirradiation minutes. Phenylephrine i.v. normally elicits a brief but

widespread peripheral vasoconstriction which raises BP and via the baroreceptor reflex reduces HR. Within the first 8-min postexposure (1000 rad, 170 rad/min ^{60}Co) under similar conditions to the present, we had great difficulty in eliciting any rise in BP during the deep hypotensive period, using even large doses of phenylephrine. What small BP rises we did produce, however, brought about smaller than expected reductions in HR, indicating that the baroreflex arc was generally depressed at this time, in accord with an earlier finding by Nathan and Craig who used the carotid occlusion technique.[7] After 8-15 min post, however, we observed the vasoconstrictive response to phenylephrine to return and the baroreflex became increasingly hyperreactive up to about 25 min post, as evidenced by exceptionally sharp increases in BP and parallel reflexive decreases in HR with each injection. This later development of hyperreactivity corresponds in time postexposure with the recovery and overshoot stage of TPR noted in the present study. The initially diminished vasopressor response forthcoming in the presence of an ongoing tachycardia indicates that it was the vascular component of the reflex that was rendered temporarily impotent immediately after irradiation. Thus, the period encompassing the initial loss and gradual restoration of

TPR over minutes 6-13, approximately, is considered to bracket the primary vascular shock period, that is, where the capacity for vasomotor responses was temporarily disabled.

A similar vasopressor depression was encountered during the same postirradiation critical period in a previous study where we irradiated monkeys while they were lever-pressing for electrical stimulation of the hypothalamus or other deep brain sites.[17] Transient hypotension occurred as usual and in parallel with it self-stimulation response frequency diminished and then recovered. Furthermore, the effectiveness of brain stimulation which elevated BP prior to irradiation was attenuated during the postexposure hypotensive period, whether administered manually or by self-stimulation. Like the phenylephrine failure to elicit vasoconstriction via direct chemical stimulation of the vessels, electrical stimulation through presumably normal neural pathways was also temporarily ineffective.

Results analogous to the phasic rise and fall in cardiac output observed here have been obtained in previous studies where postirradiation changes in internal carotid blood flow were recorded by means of extravascular-cuff flow probes (electromagnetic). Turbyfill et al.[1] presented

a group curve for 12 monkeys depicting mean carotid flow following a 4000-rad gamma-neutron pulse which revealed a pattern of changes over time very similar to the trend shown by the majority of the present animals. Immediately following the radiation pulse, carotid flow was observed to begin rising. Carotid flow peaked at 4 min postpulse at the same time as the point of deepest hypotension. Carotid flow then declined as BP rose in the Turbyfill study, and remained depressed at the final 60-min post observation. In another experiment, Turbyfill et al.,[8] presented a carotid flow curve for six monkeys performing a task during irradiation with a 2500 gamma-neutron pulse. That curve also depicted an early postradiation increase followed by a decrease. The flow decrease was transient, however, and the changes generally were not found to be significant.

Our own unpublished observations of changes in common carotid blood flow after 1000 rad ^{60}Co exposure at dose rates of 50 to 180 rad/min,[2] have likewise revealed the general finding of an initial increase followed by a decrease in mean carotid flow. However, because of (1) the recording instabilities of electromagnetic flow probes mechanically clasping a vessel which may shrink in circumference after irradiation, and (2) the unreliability of

zero-flow reference determinations with the chronically implanted flow transducers and vessel occluders, excessive variability occurs and obscures the results. Such difficulties as we experienced also very likely influenced Turbyfill et al.'s nonsignificant changes in carotid flow mentioned above.

The studies of Nathan and Craig,[7] and Chapman and Young[6] both employed anesthetized, recumbent monkeys having acutely implanted, electromagnetic cuff-type flow transducers on the common carotid with the external carotid ligated. Nathan and Craig also witnessed a phasic increase and sustained decrease in carotid flow following 2500 rad pulsed gamma-neutron radiation. In a separate group of monkeys receiving 10 1000-rad X-ray exposures repeated at 5 min intervals, Nathan and Craig noted only the later decrease in carotid flow.

Chapman and Young[6] administered 2500 rad ^{60}Co at 500 rad/min to 16 monkeys and noted a decline in internal carotid blood flow to 30% of its preirradiation baseline at 10 min following the exposure's start, which time was the earliest they were able to reinstitute monitoring after the exposure's completion. At the high dose rate they employed (500 rad/min), the point of deepest hypotension

should have been achieved within 2-3 min of the exposure's start based on our own dose-rate findings.[2,5] Thus by their 10-min postexposure observation BP should have been rising and flow falling by analogy to the present findings, as well as to those of Turbyfill et al.[1,8] Therefore the available reports of postirradiation changes in carotid blood flow seem generally in agreement with the changes presently seen for aorta flow (cardiac output) with respect to directional pattern and time course.

Cerebral Circulatory Insufficiency

Task performance decrement and/or frank incapacitation are often observed briefly during the early postirradiation minutes, and a continuing effort has been underway to elucidate the underlying physiological correlates. Because radiation-induced hypotension has been a reliable and easily measured concomitant, repeated attempts have been made to determine statistical correlations between BP and the behavioral measures after exposure, but these have been generally disappointing.[1,2,4,5] Although we recently demonstrated a statistically significant association between depth of hypotension and frequency of performance decrement, we also noted that a sizeable proportion (52%) of monkeys showing BP drops of 50% or more did not demonstrate any measureable performance decrement.[5]

But it is obvious that hypotension constitutes only one component of a complex composite of cardiovascular sequelae to exposure. A more direct physiological correlate of the behavioral impairments would seem logically to be cerebral circulatory insufficiency. However we still have no very direct information as to the circulatory status of the brain during the early postirradiation syndrome. The present results revealed that the first few minutes following the nadir of hypotension should have been the most critical for the maintenance of an adequate cerebral perfusion pressure, because it was during this period when cardiovascular balance resulted in a low cardiac output, a low (although rising) BP, and an increasing, perhaps supranormal vascular resistance (i.e., declining, subnormal peripheral flow). The studies cited earlier which monitored carotid blood flow suggested that a corresponding decrease in brain blood flow (BBF) might occur during this critical period.[1,2,6-8] Our recent behavioral study showed that the majority of animals exhibiting performance decrement did so about 1 to 4 min following their hypotensive nadir,[5] which time we are proposing is the critical period for the maintenance of the BBF at an adequate level for task performance.

The possibility of BBF deprivation is implied by McFarland's and Levin's recording of high amplitude, slow

wave EEG in monkeys during their performance decrement episodes shortly after 2500 rad gamma-neutron exposure.[4] Brooks, earlier, had seen EEG slowing in nonperforming monkeys immediately after 1000+ r gamma exposure.[18] We likewise have made observations (unpublished) of slow wave EEG as well as diminished sensory evoked potentials during this period of presumed marginal circulatory balance underlying performance decrement.[19]

Another influence operating to cause the secondary decrease in BBF during the critical period postexposure would be the vasoconstrictive effect on brain blood vessels of hypocapnia. A common observation has been the dramatic increase in respiration rate and volume in monkeys within minutes after irradiation in the present dose range.[1,3] Moreover, as is well known, hyperventilatory hypocapnia also induces EEG slow waves.

Also in support of phasic postexposure changes in BBF corresponding to those recorded in the carotid and aorta are the findings on brain temperature and brain lateral ventricular pressure. Virtually the same time course of directional change has been reported for brain and deep body temperature in monkeys during the early postradiation minutes. McFarland[20] recorded a slight rise in both deep and surface brain temperatures within 5 min of exposure, followed by a

decline to subnormal temperatures at 20-min post, with resumption to near-normal temperatures by 30-min post. Parallel changes were observed for body core temperature. To the extent that the temperature changes were influenced by altered blood flow rates, McFarland's findings corroborate the altered BBF notion.

Turbyfill et al.[8] observed significant increases in the brain's lateral ventricle pressure during the first few minutes following a 4000 rad pulsed exposure. There then was a rapid fall in this pressure below preirradiation levels until approximately 20 min post. A secondary minor rise occurred at approximately 30 min post. These phasic changes in intracranial pressure are also thought to have reflected BBF changes by way of the latter's impact on brain blood volume.

Nathan and Craig[7] proposed that the brain's autoregulatory mechanisms might be damaged by irradiation, since they observed BBF to ultimately decrease after exposure even before a critically low BP was achieved. In the nonirradiated animal severe hypotension alone jeopardizes autoregulation of BBF, and the mechanism appears abolished altogether below a mean arterial BP of about 50 mm Hg.[21]

However, the present conception argues that active vasomotor mechanisms, such as cerebral autoregulation of BBF, should not be expected to function normally, if at all, during the critical postirradiation period according to the vascular shock hypothesis. The cerebral vessels are similar in structure to the fine vessels elsewhere, and, for example, react with a similar sharp vasodilatation and gradual recovery after histamine injection.[22] Presumably, therefore, the cerebral vasculature may undergo the same transient loss of vasomotor competence after exposure, and during the succeeding recovery minutes the vasculature's refractoriness to ongoing neural control influences should gradually subside enabling autoregulation to resume. Therefore, concerns with whether the particular level of systemic arterial BP was sufficient to maintain adequate cerebral perfusion pressure appear inappropriate because they are based on observations of the nonirradiated animal having an operative vascular component for its autoregulatory device.

The Histamine Hypothesis

The proposition that radiation directly affects the peripheral vasculature has long been a popular and viable one.[23-27] The nature of the direct effect at the cellular level has not been fully elaborated, but has most commonly

been hypothesized to involve the injury-liberation of a vasoactive substance, for example, histamine, as the basis for the loss of vasomotor tone following exposure.[28,29] Several of the classic histamine responses seem to have been closely reproduced by the present radiation-induced cardiovascular changes, as is apparent from the following summary of histamine effects taken from Douglas.[22]

Sufficient amounts of i.v. histamine cause a profound fall in systemic BP through dilatation of the terminal arterioles and venules. Concurrent, feebler constrictive effects occur on the larger vessels. Direct heart effects are not seen, but cardiac output is augmented briefly by baroreflex-mediated tachycardia, venoconstriction and increased venous return. Subsequently cardiac output falls markedly as blood pools in the peripheral vascular bed and venous return diminishes. These effects are rapidly reversible after moderate doses as the histamine is destroyed and compensatory reflexes are activated.[22]

The histamine hypothesis has been reinforced considerably by several recent observations. Doyle and Strike[30] observed circulating blood histamine levels (which they determined to be primarily of mast cell origin) to increase to a peak eight times greater than preirradiation

levels 3 min after a 4000 rad gamma-neutron pulse. Histamine levels then decreased over subsequent 2-min measurement intervals to become near-normal at 20 min post. Doyle and Strike concluded that the amount of histamine released was sufficient to produce the observed hypotension. Watters et al.,[31] injected 50 μg/kg of histamine i.v. over a 30-sec period in lightly anesthetized, nonirradiated monkeys. BP began to drop immediately and achieved its nadir of 72% of baseline at 4-min postinjection. BP then recovered gradually to over 90% of baseline by 20 min.

Doyle, Curran, and Turns[32] were able to partially ameliorate postirradiation hypotension and performance decrement in monkeys pretreated with the antihistamine, chlorpheniramine. Their lack of complete success may have been due to the fact that chlorpheniramine is an H_1 receptor antagonist only, and the unblocked H_2 receptors, when stimulated, can still produce a depressor effect.[30] In a separate report, Doyle and Strike[33] concluded that in the monkey, both H_1 and H_2 receptors, when stimulated, have the ultimate effect of producing hypotension. Pretreatment with both H_1 and H_2 antagonists (mepyramine and burimamide) afforded significant protection against histamine-induced vasodilatation.

The directional pattern and time course of the presently observed events involving vascular shock and the subsequent recovery of vasoconstrictive capacity are clearly concordant with the time course of histamine liberation and elimination following irradiation reported by Doyle and Strike.[30] The results also concur with the timing and depth of histamine-induced BP drop and recovery observed in monkeys by Watters et al.[31] The histamine hypothesis therefore seems eminently acceptable to explain the immediate radiation effects seen in this laboratory as well as elsewhere insofar as the author's review of the literature has determined.* Its further confirmation now awaits the testing of the pretreatment efficacy of the combined H_1-H_2 receptor antagonists against performance decrement in irradiated monkeys.

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* The onset of the present complex of cardiovascular changes became visible only 3 min after the exposure's start. It follows that the absorption of some 300+ rad (2 min x 150 rad/min) was a sufficient radiation exposure to provoke the vascular shock. This threshold dose to effect has been very consistent over a range of dose rates.[5] Slower dose rates (down to 33 rad/min) systematically delay the onset of the changes and as well protract the fall time of the BP drop. The latter finding indicates that the vascular

relaxation response is graded as a function of exposure dose rate, once the 300 rad cumulative threshold has been exceeded. To align the graded vascular response result with the histamine hypothesis requires only the assumption that the rate of histamine liberation likewise is a function of dose rate. The frequent finding that recovery from hypotension may begin even while radiation exposure continues,[5] may simply mean that the available histamine stores had been depleted by that time.

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