Whole Body Vascular Reactivity during the Development of Deoxycorticosterone Acetate Hypertension in the Pig

KATHLEEN H. BERECZEK AND DAVID F. BOHR

SUMMARY A change in vascular reactivity was characterized in the pig during the development of deoxycorticosterone acetate (DOCA) hypertension. Pigs, 8-12 weeks of age, were subjected to unilateral nephrectomy and instrumented with an electromagnetic flowprobe on the ascending aorta and with Tygon catheters in the aorta and thoracic vena cava. Approximately 2 weeks after surgery, Silastic strips impregnated with DOCA (100 mg/kg) were implanted subcutaneously. Within the first 3 days after implantation, mean arterial pressure (MAP) began to rise and reached levels approximately 40% greater than control during the 4th week. Graded intravenous infusions of norepinephrine or angiotensin II were given to unanesthetized pigs before, and at intervals during, the development of hypertension. Changes in total peripheral resistance were calculated from recordings of MAP and cardiac output. Comparison of pre-DOCA response curves with those obtained at intervals following DOCA implantation demonstrated a significant increase in vascular smooth muscle sensitivity (decrease in threshold infusion rates) to both drugs post-DOCA. There also was a shift to the left in the dose-response curves. These changes in systemic vascular reactivity occurred at the time the arterial pressure began to rise. The temporal relationship suggests that the increase in vascular reactivity may initiate the increase in mean arterial pressure.

VASCULAR reactivity, evaluated as the magnitude of an increase in flow resistance produced by a vasoconstrictor stimulus, is enhanced in chronic hypertension in man1,2 and animals.3,4 There is little agreement as to the nature of the changes in the blood vessel responsible for this increase in reactivity. Furthermore, it is not certain whether the change in vascular reactivity is the cause or the consequence of hypertension. In the current study, the temporal relationship between the development of hypertension and the increase in vascular reactivity was studied in the DOCA hypertensive pig. Whole body vascular reactivity was evaluated to give information about the net change in all vascular beds. This is the first study in which the time course of changes in whole body vascular reactivity have been monitored in a single animal as it develops hypertension. The study permits inferences about the cause and effect relationship between vascular reactivity and hypertension.

Methods

Surgical Preparation

All studies were carried out on young male feeder pigs (Chester White or Yorkshire boars) housed in individual cages and given Purina Pig Chow and tap water ad libitum. Two surgical procedures were required for chronic instrumentation of the pigs.3 The first consisted of implantation of an electromagnetic flowprobe (Zepeda Instruments) around the ascending aorta to monitor cardiac output and insertion of a Herd-Barger Tygon catheter into the aorta just distal to the probe to measure arterial pressure. The following procedures were performed approximately 1 week later: right nephrectomy, complete ligation of the left external iliac artery, and implantation of catheters into the vena cava (advanced from the abdominal region to the central venous pool) and left femoral artery. All catheters and electrodes were exteriorized, tied to a heavy wire loop implanted on the pig's left side, and protected with a heavy canvas jacket. Approximately 2 weeks after the second surgery, animals received subcutaneous implants of Silastic strips (silicone rubber, Dow Corning) impregnated with deoxycorticosterone acetate; 100 mg/kg (DOCA, Sigma Chemical Co.). Control pigs received Silastic implants without DOCA. Cardiac output and pressures were monitored daily. Pigs were maintained on conventional pig chow and tap water. This diet provided a sodium intake of approximately 3-5 mEq/kg per day.

Experimental Protocol: Infusion Studies

Prior to and at intervals after the implantation of DOCA, the pigs were subjected to graded intravenous infusions of norepinephrine (NE) (Levophed Bitartrate, Winthrop Laboratories) and angiotensin II (A II) (Hypertensin, Ciba Laboratories). All studies were performed on unanesthetized pigs restrained on their right side. The study room was kept as quiet as possible and lights were dimmed. The pigs tolerated the procedure well and usually doze during the 60- to 90-minute procedure.

Infusion rates of both drugs were varied from subthreshold rates to those producing an increase of 50-70 mm Hg in mean arterial pressure (MAP). Infusions were carried out with a Harvard infusion pump (model 975); drug doses were varied by changing the rate of infusion.
During the experiments the following parameters were monitored: (1) MAP, (2) cardiac output (CO), and (3) heart rate. Total peripheral resistance (TPR) was calculated as the quotient of MAP divided by CO. In the figures to follow, CO and therefore TPR are expressed in arbitrary units (mm pen deflection/kg for CO and mm Hg/mm pen deflection per kg × 10^(-10) for TPR) because the flowprobe had not been calibrated. Subsequent in vitro flowprobe calibration indicated that a deflection of 1.0 mm represented flows ranging from 0.25 to 0.35 liter/min.

Each dose of NE and AII tested was infused for 3 minutes. The response to each dose was found to reach a plateau within 2.5 minutes. The infusion was then followed by a rest period adequate to allow parameters to return to baseline (3–5 minutes) before the next dose was tested. An average of 12 infusions was administered in one session. Different infusion rates were randomly sequenced and each rate was repeated twice. In order to prevent any interaction between the drugs, infusions of NE and AII were not given on the same day. If the pig became uncomfortable or agitated during the study, the experiment was terminated and the data discarded.

Statistical Methods

Results are presented as the mean of the hemodynamic response ± the standard error (SE) at specific times following the intervention with DOCA or Silastic (control) implantation. Differences in responses to a given dose of the drug administered before, and at a specific time interval after the implantation, were tested by a paired r-statistical analysis.

Results

Development of Hypertension

All pigs implanted with DOCA demonstrated elevations in MAP within the first 3 days. By the end of the 1st week, MAP was approximately 20% greater than the pre-DOCA level (Table 1) and, during the 4th post-DOCA week, the MAP had plateaued at approximately 36% above the pre-DOCA values.

Infusion Studies

Systemic Response to NE in Control Pigs

Intravenous infusion of NE in unanesthetized normotensive pigs produced the following hemodynamic changes: (1) a rise in MAP, (2) an increase in TPR, (3) a decrease in heart rate, and (4) a decrease in CO. The rise in MAP in response to NE is therefore due to widespread vasoconstriction as evidenced by the increase in calculated TPR. The average threshold infusion rate of NE required to produce an elevation in MAP in five of five control pigs tested was: 0.122 µg/kg per min. The mean rise in MAP at this rate was 7.0 ± 1.3 mm Hg. Two out of five pigs responded to a rate of 0.073 µg/kg per min, the mean rise in MAP for those responding being 4.8 ± 0.88 mm Hg. The average threshold infusion rate was therefore considered to be between 0.073 and 0.122 µg/kg per min.

Comparisons of MAP, TPR, and CO changes in control pigs (n = 5) at various time intervals during their experimental life (i.e., before Silastic implantation and 2 weeks and 1 month after) demonstrate that there was not much variability in dose-response curves over time. Furthermore, the threshold infusion rate of NE required to produce a response remained constant during this period (Fig. 1).

Systemic Response to NE in DOCA Hypertensive Pigs

In contrast to the control animals, the DOCA hypertensive pigs demonstrated changes in systemic cardiovascular responses to NE infusions. The changes in reactivity occurred early in the development of hypertension. Following the administration of DOCA, a given infusion rate of NE produced a greater rise in MAP and TPR than it
Systemic Response to AII in Control Pigs

The pattern of hemodynamic changes elicited by intravenous infusion of AII was found to be similar to that obtained for NE. Infusion of AII produced the following circulatory changes: (1) a rise in MAP, (2) a rise in TPR, (3) a fall in heart rate, and (4) a fall in CO. Figure 3 shows a comparison of MAP, TPR, and CO changes in control pigs (n = 5) before Silastic implantation and at 2 weeks and 1 month after Silastic implantation. Like the findings for NE, the systemic response to AII in control pigs was not subject to much variability over time. The threshold infusion rate of AII required to elicit a response in five of the five pigs was 0.023 µg/kg per min. The average rise in MAP at this rate was 12.5 ± 0.85 mm Hg. Four out of five of the pigs responded to a rate of 0.012 µg/kg per min; the mean rise in MAP for those responding was 6.2 ± 0.76 mm Hg. Threshold at 1 month post-DOCA was considered to be between 0.023 and 0.051 µg/kg per min. Therefore, considered to be between 0.023 and 0.051 µg/kg per min.

Systemic Response to AII in DOCA Hypertensive Pigs

DOCA hypertensive pigs demonstrated marked changes in systemic vascular reactivity to AII. Paralleling the changes in response to NE, the onset of changes in reactivity to AII also occurred very early in the develop-

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**Figure 1.** Systemic reactivity in normotensive pigs (n = 5). Results are given for graded NE infusions in unanesthetized pigs during the pre-Silastic stage and 2 weeks and 1 month after Silastic implantation. Data are expressed as mean change ± SE. A = Δ MAP; B = Δ TPR; C = Δ CO. CO and TPR are expressed in arbitrary units (CO = mm pen deflection/kg; TPR = mm Hg/mn pen deflection per kg x 10³).

**Figure 2.** Changes in MAP, TPR, and CO at (A) 1 week (n = 8), and (B) 1 month (n = 6) after DOCA implantation compared to values obtained the same pigs during the pre-DOCA, normotensive stage. Paired r-analysis of the differences in the NE dose-response curves obtained in the pre-DOCA stage and at the two intervals after implantation of DOCA demonstrates that the magnitude of change in MAP and TPR elicited by NE is significantly greater after DOCA implantation. No significant changes were found in the decrease in CO between pre-DOCA and post-DOCA stages. An increase in systemic vascular reactivity is indicated by shifts to the left of the MAP and TPR response curves. Response curves obtained at both 1 week and 1 month after DOCA implantation demonstrated a significant decrease in the threshold infusion rate of NE required to elicit a response. In the pre-DOCA stage, the average minimal NE infusion rate at which 100% of the pigs showed a response was 0.125 µg/kg per min. The mean rise in MAP at this rate was 6.4 ± 0.9 mm Hg. No pig responded to an infusion rate lower than 0.125 µg/kg per min. At 1 week post-DOCA, eight out of eight of the pigs tested responded to an average NE infusion rate of 0.057 µg/kg per min with a mean rise in MAP of 7.1 ± 1.06 mm Hg. Four out of eight pigs responded to an infusion rate of 0.03 µg/kg per min and the rise in MAP for those responding was 6.2 ± 0.76 mm Hg. Threshold at 1 week post-DOCA was considered to be between 0.03 and 0.057 µg/kg per min. At 1 month post-DOCA, six out of six pigs responded to an average NE infusion rate of 0.051 µg/kg per min with a mean rise in MAP of 12 ± 2.7 mm Hg. Three out of five pigs responded to a rate of 0.023 µg/kg per min and the mean rise in MAP for those responding was 4.5 ± 1.07 mm Hg. Threshold at 1 month post-DOCA was considered to be between 0.023 and 0.051 µg/kg per min.

To ascertain whether there was any difference in the dose-response curves to norepinephrine at 1 week and 1 month post-DOCA, we compared equieffective infusion rates of norepinephrine producing a 30 mm Hg rise in MAP. The mean infusion rate of norepinephrine required to produce a 30 mm Hg change in MAP decreased from 0.46 ± 0.04 (SE) µg/kg per min pre-DOCA to 0.23 ± 0.03 µg/kg per min 1 week post-DOCA and 0.195 ± 0.02 µg/kg per min 1 month post-DOCA. The decrease in the infusion rate at 1 month post-DOCA was not significantly different from that obtained at 1 week post-DOCA (P > 0.10). There appears to be little further increase in systemic vascular reactivity between 1 week and 1 month following DOCA implantation.
VASCULAR REACTIVITY IN DOCA HYPERTENSION/Serece*

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FIGURE 2 Systemic reactivity in DOCA hypertension; comparison between pre-

DOCA norepinephrine response curves and curves obtained at two intervals after

DOCA implantation. A = 1 week post-

DOCA (n = 8); B = 1 month post-

DOCA (n = 6). Data are expressed as

mean change ± SE. 1A and IB A MAP;

2A and 2B = A TPR; 3A and 3B = A CO.

Paired t-analysis was carried out to deter-

mine the significances of the differences

between pre- and post-DOCA results. CO

and TPR are expressed in arbitrary units

(mm pen deflection/kg and mm Hg/mm

pen deflection per kg x 10², respectively).

NOREPINEPHRINE (µg/Kg/min)

ment of hypertension. Figure 4 shows the changes in

MAP, TPR, and CO at (A) 1 week (n = 9) and (B) 1

month (n = 6) after DOCA implantation compared to

changes in these parameters in the pre-DOCA period. 

Paired t-analysis demonstrated that the magnitude of

change in MAP and TPR elicited by A II is significantly 

greater after DOCA implantation. Like the findings for 

NE, no significant changes were noted in the magnitude 

of the decrease in CO. MAP and TPR curves were shifted 

to the left, indicating significant increases in systemic 

vascular reactivity. A significant decrease in the threshold 

infusion rate of A II was observed both at 1 week and 1 

month post-DOCA. In the pre-DOCA stage, the average 

A II infusion rate at which nine out of the nine pigs 

showed a response was 0.0285 µg/kg per min. The mean 

rise in MAP was 18.4 ± 1.8 mm Hg. At 0.014 µg/kg per 

min, six out of nine pigs responded; the mean rise in MAP 

for those responding was 7.5 ± 1.3 mm Hg. Threshold in 

the pre-DOCA stage was, therefore, considered to be 

between 0.014 and 0.0285 µg/kg per min. At 1 week 

post-DOCA, nine out of nine pigs responded to an 

average A II infusion rate of 0.0077 µg/kg per min with a 

mean rise in MAP of 13.7 ± 1.2 mm Hg. At an A II 

infusion rate of 0.0052 µg/kg per min, seven out of nine 

pigs responded; the mean rise in MAP for those respond-

ing was 7.35 ± 1.2 mm Hg. Threshold at 1 week was 

considered to be between 0.0052 and 0.0077 µg/kg per 

mm Hg. At 1 month post-DOCA, six out of six pigs 

responded to an average A II infusion rate of 0.0049 µg/ 

kg per min with a mean rise in MAP of 8.8 ± 1.1 mm Hg. 

Five out of six pigs responded to a rate of 0.0024 µg/kg 

per min; the mean rise in MAP for those responding was 

5.9 ± 0.55 mm Hg. Threshold at 1 month post-DOCA 

was considered to be between 0.0024 and 0.0049 µg/kg 

per min.

In six DOCA-hypertensive pigs, systemic vascular reac-

tivity to A II was assessed at 2 and 4 days post-DOCA 

implantation. Figure 5 compares the changes in MAP 

before and 2 and 4 days after DOCA implantation. As 

early as 2 days post-DOCA, a lowering of the threshold 

dose of A II required for response was apparent, as well 

as a shift to the left of the response curve. These changes 

in vascular reactivity were found to occur at a time when 

the mean arterial pressure was starting to rise.

Discussion

Evaluation of Changes in Vascular Reactivity

Vascular reactivity is measured by the magnitude of an 

increase in flow resistance in response to a vasoconstrictor 

stimulus. Three types of responses have been used to 

evaluate alterations in vascular reactivity in hypertension:
whole animal vascular resistance increase, isolated vascular bed resistance increase, and isolated vascular smooth muscle contraction. Each of these responses makes its special contribution to the understanding of vascular changes in hypertension.

Whole animal studies in which a vasoconstrictor is infused intravenously and simultaneous measurements are made of MAP and CO permit calculation of a change in TPR. They allow a more direct interpretation of the effect of changes in vascular reactivity on MAP than do studies on the isolated vascular bed. However, with this method, the magnitude of a constrictor response depends on the sensitivity of the vascular smooth muscle and on the thickness of the walls of the resistance vessels, but also on all extrinsic factors (neural and humoral) which participate in the complex vascular regulation during a pressor response.

In perfusion studies of the isolated vascular bed, extrinsic neurogenic factors can be eliminated by denervation and extrinsic humoral factors can be eliminated by perfusion with a physiological salt solution. Unique aspects of the reactivity of specific vascular beds can be identified. Still it is difficult to differentiate functional alterations in vascular smooth muscle from structural changes in vessel wall thickness as a cause of arterial vascular reactivity. Studies of isolated vascular smooth muscle strips are not biased by structural changes (i.e., the changes in wall thickness-lumen diameter ratio) that alter vascular reactivity in any vascular resistance study. Therefore, a more direct study of vascular smooth muscle function can be made. Specific assessment can be made of vascular smooth muscle sensitivity and its maximum force-generating ability (contractility). These studies are limited to large arteries (carotid, femoral, aorta), and it is not known how well changes in muscle from these large arteries reflect changes in the smooth muscle of resistance vessels.

The present study of whole animal reactivity in the pig is the first longitudinal study of changes in vascular reactivity in the same animal during the development of hypertension. These studies done before and after DOCA implantation permit inferences concerning the mechanisms underlying the development of changes in reactivity and the temporal relationship between changes in reactivity and the rise in MAP. Although only results at 1 week and 1 month post-DOCA are reported, studies were run at weekly intervals. The magnitude of the changes observed at 2 and 3 weeks post-DOCA did not differ from data obtained at 1 week.

General Mechanisms underlying Increased Vascular Reactivity in the Initial Stages of Hypertension

Evidence of enhanced whole body vascular reactivity in the DOCA hypertensive pig agrees with previous findings in hypertensive human subjects.1,2 The observed decrease in threshold and increase in reactivity to NE and A II are not merely reflections of the greater initial resistance after DOCA. Studies from numerous laboratories4-9 have demonstrated that an increase in initial resistance per se tends to decrease the magnitude of a pressor response. In the DOCA hypertensive pig, vascular reactivity does not become further enhanced beyond that found at 1 week post-DOCA in spite of the continuing increase in MAP. There is much evidence that vascular reactivity may be increased merely by increasing vessel wall thickness.2,9 This structural change confers a mechanical advantage to vascular smooth muscle so that a given shortening produces a greater decrease in lumen size and therefore an enhanced constrictor response to a given concentration of a vasoconstrictor. This structural change produces an enhanced constrictor response without altering the threshold dose of the vasoconstrictor.

We have interpreted an increased vascular smooth muscle sensitivity as indicative of a functional alteration in vascular smooth muscle. We have evaluated the sensitivity of this muscle in terms of the threshold dose of a vasoconstrictor required to produce a response. The rapid development in the hypertensive pig of changes in vascular reactivity, particularly decreases in the threshold dose of NE and A II, cannot be attributed to structural changes in the blood vessels. Structural changes are secondary adap-
VASCULAR REACTIVITY IN DOCA HYPERTENSION/Berecek and Bohr

FIGURE 4. Systemic reactivity in DOCA hypertension; comparison between pre-DOCA angiotensin response curves and curves obtained at two intervals after DOCA implantation. A = 1 week post-DOCA (n = 9); B = 1 month post-DOCA (n = 6). Data are expressed as mean change ± SE. IA and IB = ΔMAP; 2A and 2B = ΔTPR; 3A and 3B = ΔCO. Paired t-analysis was carried out to determine the significances of the differences between pre- and post-DOCA results. CO and TPR are expressed in arbitrary units (mm Hg/mm pen deflection per kg × 10^2, respectively).

ANGIOTENSIN (μg/Kg/min)

Development of changes in vascular reactivity prior to the rise in arterial pressure has been seen in other animal models of hypertension and in humans. Odgen et al. using renal hypertensive rabbits, found that increased vascular reactivity to pitressin occurred before the animals developed a rise in arterial pressure. McQueen showed that increased reactivity to NE in the perfused tail artery of a one-kidney renal hypertensive rat was evident within 2 days after clipping the sole kidney. In two-kidney renal hypertensive rats, he found that increased reactivity to NE paralleled the rise in arterial pressure for up to 2 weeks. At this time the increase in vascular reactivity was fully established and there was no further relationship between blood pressure and vascular reactivity. This is similar to findings for the pig in which there appears to be no further increase in vascular reactivity beyond that found 1 week post-DOCA. Doyle and Fraser found that infusion of

FIGURE 5. Systemic reactivity in DOCA hypertension. Results are expressed as mean changes in MAP ± SE in response to graded infusions of angiotensin. A comparison is made between responses obtained at the pre-DOCA stage to those obtained at 2 days and 4 days post-DOCA (n = 6). * = P < 0.025; ** = P < 0.005.
NE into the brachial artery induced greater vasoconstriction in the forearm in normotensive offspring of hypertensive patients than in a control group with parents that had normal blood pressures. In essential hypertension as well as in numerous animal models of hypertension, it appears that a change in vascular reactivity precedes the rise in blood pressure and could therefore be an important factor in the pathogenesis of hypertension. The distinct lowering of threshold doses of both A II and NE was found to parallel the alterations in vascular reactivity in the DOCA hypertensive pig. This parallelism supports the hypothesis that alterations in vascular smooth muscle sensitivity may be the primary vascular defect occurring in the genesis of hypertension. Since there is increased sensitivity to more than one agonist, it does not appear to be a receptor-specific phenomenon. Alterations in vascular smooth muscle sensitivity may have a primary role in the rise in arterial pressure.

Possible Mechanisms underlying the Increase in Sensitivity of Vascular Smooth Muscle

Current speculations about the mechanisms underlying the increase in sensitivity of vascular smooth muscle in DOCA hypertension include the following: (1) altered ion distribution in the vascular smooth muscle cell, both active and passive, (2) indirect humoral influence producing a chronic change in the vascular smooth muscle cell, (3) total body vascular autoregulation in response to increased cardiac output and tissue perfusion, (4) direct or indirect myogenic effect of mineralocorticoids, and (5) altered neurogenic influence producing chronic functional alteration in vascular smooth muscle.

The mechanism of altered neurogenic influence recently has received much attention and merits further consideration. Haeusler et al. demonstrated that intracerebroventricular injection of 6-hydroxydopamine prior to carrying out procedures which normally induced one-kidney and DOCA hypertension or prior to the development of spontaneous hypertension in the SHR strain, prevented the development of hypertension in these animals. The same drug was found to be ineffective in altering blood pressure when administered during the phase of established hypertension. These findings have been confirmed in other laboratories and strongly suggest that there is a centrally located neural "trigger" mechanism that initiates these types of hypertension. It is tempting to speculate that there occurs in hypertension an alteration in peripheral sympathetic activity set in motion by a central "trigger" mechanism and that this alteration in neural input causes an intrinsic change in the sensitivity of vascular smooth muscle. Comparatively few studies have been made of the trophic interactions between vascular smooth muscle and its innervation, particularly in the adult animal. Bevan has given in vivo evidence that adrenergic neurons exert a trophic influence on vascular structure and function during growth. There also is evidence that nerve-dependent changes in the sensitivity of vascular smooth muscle are consistent with those seen in other excitable tissue. Nerve-induced alterations in vascular smooth muscle sensitivity do not appear to be due to changes in specific receptors, but involve alterations in membrane electrical properties, binding of and permeability to ions, and possibly other biochemical changes.

It may be hypothesized that an initial alteration in neural input to vascular smooth muscle produces intrinsic functional alterations in the muscle detected by other investigators, such as alterations in electrogensis and ion permeability. Alteration in functional properties of vascular smooth muscle in the current study was detected as an increase in sensitivity. This alteration may underlie the initial rise in resistance and the enhanced vascular reactivity seen in hypertension.

References

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Continuous Assessment of Regional Myocardial Perfusion in Dogs Using Krypton-81m

Andrew P. Selwyn, Terry Jones, J. Harvey Turner, Tim Pratt, John Clark, and Peter Lavender

SUMMARY  Krypton-81m has been continuously eluted in 5% dextrose from a cyclotron-made rubidium-81 generator. The unique physical properties of this inert freely diffusible gas (half-life 13 seconds) have allowed the development of a technique for the constant infusion of this tracer into the aortic sinuses of 25 dogs. Theoretical considerations suggest that an equilibrium of 81mKr activity in the myocardium is principally dependent on blood flow. Experiments have tested the delivery of this indicator and have recorded quantitative high spatial resolution images of the heart with a gamma camera and digital computer. The systematic error was determined by comparing changes in regional blood flow (in ml/g per min, using an electromagnetic flow probe) and changes in calculated flow (ml/g per min) using the regional activity of 81mKr (P = < 0.001; r = 0.97; y = 908 X + 0.105; n = 60). The random error and uncertainties concerning mixing and streaming of the indicator were tested by repeating measurements (reproducibility, P = 0.001, r = 0.982; y = 0.982x + -0.257, n = 100 observations). Any quantification of changes in the myocardial activity of 81mKr must consider the stability of the arterial concentration of this indicator and washout of 81mKr at high values of myocardial blood flow. This ultra-short-lived radionuclide will, however, provide an assessment of changes in the distribution of regional myocardial perfusion.

IN 1968, Yano and Anger first suggested that ultrashort-lived radionuclides such as krypton-81m could be used to visualize blood vessels and organs. 1 Krypton-81m generators were designed to allow the intermittent elution of this gas tracer from its parent compound, rubidium-81 (81Rb). 2-3 This was used initially for ventilation and perfusion studies of the lungs and later for studies of cerebral blood flow. 4,5 Krypton-81m (half-life 13 seconds) allowed the introduction of a technique for continuous observation and assessment of the distribution of regional myocardial reactivity in man. Fed Proc 33: 143-149, 1974


Methods

Theoretical Considerations

If 81mKr is infused constantly into the aortic sinuses, the arterial concentration of this indicator will fluctuate with pulsatile blood flow. If the pattern of mixing and streaming of this freely diffusible gas is stable, then the effect, over minutes, will be that a constant quantity of 81mKr will reach the coronary circulation per unit of blood flow. Accumulation of 81mKr in the myocardial water space will
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K H Berecek and D F Bohr

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