Effect of Chronic Rapid Ventricular Pacing on Total Vascular Capacitance

Richard Ian Ogilvie, MD, FRCPC, FACP, and Danuta Zborowska-Sluis, MD

Background. Rapid right ventricular pacing (RRVP) at 250 bpm for 3–6 weeks produces chronic heart failure manifested by a reduction in cardiac output and increases in right atrial, pulmonary artery, and capillary wedge pressures.

Methods and Results. One week after splenectomy and pacemaker placement, vascular capacitance, unstressed volume, and compliance were determined in 19 anesthetized dogs from pressure–volume curves using transient circulatory arrests induced by acetylcholine. Nine dogs were restudied 31±1 days later without RRVP, and 10 dogs underwent RRVP at 250 bpm and were restudied at 23±8 and 38±8 days in cardiac failure and after 1 and 2 weeks of postpacing recovery. Control animals had no changes in vascular capacitance or compliance. Dogs undergoing RRVP exhibited a marked increase in mean circulatory filling pressure (5.4±0.4 to 10.5±1.5 mm Hg) during the development of cardiac failure with a reduction in unstressed volume (81.9±5.7 to 43.9±8.1 ml·kg⁻¹) without changing total vascular compliance. Total blood volume decreased (95.4±6.2 to 66.7±6.5 ml·kg⁻¹) primarily due to a reduction in packed cell volume. The pressure gradient for venous return and overall venous resistance was unaltered. Central blood volume as a proportion of total blood volume increased (9.3±1.7% to 16.0±2.7%). Arterial compliance and capacity and pulmonary vascular compliance were reduced. In the 2-week postpacing period, except for a reduced cardiac response to a volume load, all of these parameters returned to baseline values.

Conclusions. Chronic RRVP induced cardiac failure with a marked reduction in total vascular capacitance due to a reduction in unstressed volume without altering compliance. The rise in mean circulatory filling pressure was limited by a reduction in total blood volume. (Circulation 1992;85:1524–1530)

Key Words • heart failure • vascular capacitance • vascular compliance • blood volume

Chronic rapid right ventricular pacing (RRVP) produces severe heart failure in dogs characterized by a low cardiac output and abnormal systolic and diastolic left ventricular function with increased right and left heart filling pressures. Although a great deal is known about some of the mechanisms involved in the production of heart failure by RRVP, including the development of myocardial substrate depletion without left ventricular hypertrophy or myocardial ischemia, peripheral manifestations have not been well studied.

Alterations in skeletal muscle perfusion in vivo and peripheral and coronary artery responsiveness to α-adrenoceptor agonists and nitroglycerin in vitro have been reported, but there have been no investigations of total vascular capacitance or compliance in animals with heart failure induced by RRVP. The neuroendocrine response with the development of failure is profound and closely resembles that observed in patients. Since heart failure is also characterized by alterations in total vascular capacitance and compliance as well as distribution of the circulating volume, we embarked on a study of the effects of chronic RRVP on these parameters.

Methods

Nineteen conditioned dogs free of heartworms and parasites and weighing 18–25 kg (mean, 23 kg) premedicated with acepromazine (0.5 mg·kg⁻¹) were anesthetized with isoflurane and subjected to a splenectomy through a midline abdominal incision. A unipolar pacemaker lead was advanced through the external jugular vein to the right ventricle under electrocardiographic control and a programmable pulse generator (SX 5940, Medtronic, Richmond, B.C., Canada) was placed in a subcutaneous pocket between the scapulae with the pulse set at 60 bpm. The animals underwent a baseline study 7–10 days after surgery. Subsequently, nine animals were used as sham controls with the pacemaker continuing at 60 bpm for 4 weeks before a second study, and 10 underwent chronic rapid right ventricular pacing (RRVP) at 250 bpm for 6 weeks or until severe heart failure had developed as indicated by rapid weight gain, ascites, or marked respiratory distress. The animals were scheduled to be restudied at approximately 3 and 6 weeks of chronic pacing. The pulse generator was then reset to 60 beats per minute and the animals restudied after 1 and 2 weeks of recovery.
For each study, the fasting animal was premedicated with acepromazine (0.5 mg · kg\(^{-1}\) i.m.) and lightly anesthetized with sodium pentobarbital (12 mg · kg\(^{-1}\) i.v.). Atropine (1.0 mg i.v.) was given. The animals were not ventilated but provided with supplemental oxygen at 5 1 · min\(^{-1}\) using a cone nasal mask. Supplemental pentobarbital requirements rarely exceeded 3.0 mg · kg\(^{-1}\) for the entire experimental period. Vascular sheaths (7F, 10 cm; Cordis Corp.) were inserted into a femoral artery and a femoral vein. A Swan-Ganz pulmonary artery catheter was positioned via the femoral vein sheath for measurement of pulmonary artery pressure (Ppa), pulmonary capillary wedge pressure (Ppcw), right atrial pressure (Pra), core temperature, and cardiac output (CO) by thermodilution. The femoral artery sheath was used for arterial pressure (Psa) monitoring, blood sampling, and volume administration. Another pulmonary thermistor catheter was temporarily inserted via the femoral arterial sheath and advanced to the aortic root just above the aortic valve for subsequent determination of central blood volume (CBV).\(^{18,19}\) Cardiac output was measured by thermodilution using a Gould cardiac index computer (SP 1435) and recorder (SP 20909). Outputs were measured in triplicate using 5 ml ice-cold glucose in water injected into the right atrium and monitoring temperature changes in the pulmonary artery. Mean transit times for calculation of CBV composed of pulmonary and left heart volumes were separately measured in duplicate by injecting 10 ml ice-cold glucose in water into the pulmonary artery and estimating the mean transit time to the thermistor in the aortic root by using trapezoids and the Stewart Hamilton technique. The dog was positioned on its side for all measurements. Pressures were measured using Statham transducers with the vertebral column as zero reference point and recorded on a Grass Physiograph (7D) instrument. A surface ECG was registered to measure heart rate (HR). Body temperature monitored with the thermistor in the pulmonary artery catheter was kept constant with a warming pad.

Total blood volume (TBV) was calculated from the hematocrit and plasma volume estimated by an Evans blue dye dilution technique. The disappearance rate of Evans blue dye in the failure state paralleled that in the baseline state. Mean circulatory filling pressure (Pmcf) was determined by using transient cardiac arrest with bolus doses of acetylcholine (15 mg) into the right atrium followed by a recuperation time of 15 minutes. Repeated measurements of arterial blood gases were done to ensure maintenance of adequate oxygenation and acid-base balance following acetylcholine. No interventions were required. To determine vascular capacitance and compliance, Pmcf was determined at different circulating volumes.\(^{19,20}\) For the compliance measurement, the circulating volume was increased by a 5 ml · kg\(^{-1}\) infusion of 6% dextran (MW, 70,000) in saline (dextran 70) warmed to body temperature completed in 30 seconds. The acetylcholine arrest was repeated. The additional 5 ml · kg\(^{-1}\) circulating volume was then removed, added to 5 ml · kg\(^{-1}\) of dextran 70, and kept in a warming bath. Fifteen minutes later, the entire 10 ml · kg\(^{-1}\) mixture of blood and dextran 70 solution was infused over 30 seconds, and the acetylcholine arrest was repeated. The following calculations were made.

Mean circulatory filling pressure (mm Hg):

\[
P_{\text{mcf}} = V_P + \frac{(A_{\text{P}} - V_P)}{30}
\]

where VPP and APP are venous and arterial pressures at plateau 7 seconds after arrest, and 30 is the venous/arterial compliance ratio.\(^{19,20}\)

Pressure gradient for venous return (mm Hg):

\[
P_{\text{GVR}} = P_{\text{mcf}} - P_{\text{ra}}
\]

Overall venous resistance (mm Hg · min · kg · ml\(^{-1}\)):

\[
R_{\text{V}} = \frac{P_{\text{GVR}}}{\text{CO}}
\]

Total peripheral resistance (mm Hg · min · kg · ml\(^{-1}\)):

\[
T_{\text{PR}} = \frac{P_{\text{sa}} - P_{\text{ra}}}{\text{CO}}
\]

Total vascular compliance (ml · mm Hg · kg\(^{-1}\)):

\[
\Delta V/\Delta P_{\text{mcf}}
\]

where \(\Delta V\) is the change in total circulating volume in milliliters per kilogram.

Arterial compliance (ml · mm Hg\(^{-1}\) · kg\(^{-1}\)):

\[
C_a = \frac{T}{\text{TPR}}
\]

where T is the time constant in minutes derived from the arterial pressure decay curve following the last beat after acetylcholine infusion.\(^{21}\)

Arterial bed volume transfer (ml · kg\(^{-1}\)) was calculated from the differences in arterial capacity (arterial compliance) multiplied by Psa between each experimental condition.

Central blood volume (pulmonary artery to aortic root) (ml · kg\(^{-1}\)):

\[
\text{CBV} = \frac{\text{MTT} \cdot \text{CO}}{60}
\]

where MTT is mean transit time in seconds between the distal pulmonary artery and aortic root using the Stewart Hamilton technique and separately measured CO by thermal dilution (right atrium to pulmonary artery). We assumed that the loss of thermal indicator in the lungs and the heart was proportionately the same in all pathways.

Effective pulmonary (central) vascular compliance was estimated from the plot of Ppcw against CBV at baseline blood volume and after the 10-ml · kg\(^{-1}\) increase in circulating volume using the inverse of the slope of the Ppcw/CBV relation.\(^{22}\) Unstressed central vascular volume was estimated from the volume intercept when Ppcw was 0.

Stressed vascular volume (ml · kg\(^{-1}\)) = Pmcf · total vascular compliance.

Unstressed vascular volume (Vo) (ml · kg\(^{-1}\)) = TBV − stressed vascular volume.

Total vascular compliance was calculated by determining Pmcf at baseline blood volume and after increasing circulating volume by 5 and 10 ml · kg\(^{-1}\). The inverse
Hemodynamic improvement

Psa, marked
alterations

pacing

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blood

at

beats

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arterial

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blood volume.

marked increases in Ppa, Ppcw, and Ppa during failure with improvement during the 2-week postpacing period. The response in CO with the 10 ml · kg⁻¹ dextran 70 volume load used to measure compliance was markedly depressed with the development of heart failure. With the volume load, CO increased from 187±15 to 299±26 ml · min⁻¹ · kg⁻¹ at baseline, from 96±11 to 150±23 ml · min⁻¹ · kg⁻¹ with failure, and from 158±17 to 231±28 ml · min⁻¹ · kg⁻¹ at 1 week after pacing. Total peripheral resistance was increased with failure but returned to baseline values at 1 week after pacing. The pressure gradient for venous return and overall venous resistance were unaltered.

Total Vascular capacitance and Compliance

TBV, Pmcf, unstressed and stressed vascular volumes, and total vascular compliance were unaltered after 30.5 days in the control animals (Figure 2). In the animals subjected to chronic RRVP at 250 bpm, Pmcf increased while total blood volume was reduced with the development of heart failure so that the pressure–volume relation was shifted leftward (Figure 3). With recovery after pacing, the pressure–volume relation was shifted rightward toward baseline with a reduction in Pmcf and increase in blood volume (Figure 4).

Total vascular compliance was slightly but insignificantly reduced with failure, 2.08±0.28 versus 2.58±0.28 ml · mm Hg⁻¹ · kg⁻¹ at baseline, and increased to 3.6±0.37 ml · mm Hg⁻¹ · kg⁻¹ at 2 weeks of recovery (Figure 5). Unstressed vascular volume decreased and stressed volume increased with the development of failure (Figure 6). Total vascular capacitance at a theoretically constant Pmcf of 6 mm Hg was reduced from 97.4±6.3 ml · kg⁻¹ at baseline to 59.9±9.9 ml · kg⁻¹ with failure (p<0.01) with recovery by 2 weeks postpacing to 86.1±5.1 ml · kg⁻¹. TBV was decreased mainly due to a reduction in packed cell volume, which measured 46.9±1.7%, 39.9±2.3%, 36.3±2.0%, and 39.6±1.5% at baseline, early failure, failure, and 2 weeks recovery, respectively.

Results

The nine control animals were restudied 30.5±1.2 days after the baseline study. Of the 10 animals chronically paced at 250 beats per minute, three were not studied at midpoint (early failure), two died suddenly in late failure after the early failure study, and one animal died in the early recovery period after pacing had been terminated. Thus, seven animals were studied in early failure (23.1±8.1 days), seven in failure (38.3±8.4 days), and seven animals during recovery at 1 and 2 weeks after stopping pacing at 250 beats per minute.


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Hemodynamic Alterations

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of the slope of the Pmcf versus total blood volume relation gave an estimate of total vascular compliance. The line extrapolated to the volume intercept at a Pmcf of 0 gave an estimate of unstressed vascular volume. Total vascular capacitance was determined by the magnitude of the unstressed volume and the product of compliance and a Pmcf of 6 mm Hg. It is the volume of blood held in the system at a hypothetical Pmcf of 6 mm Hg. The baseline Pmcf averaged 5.4 mm Hg.

All values are reported as mean±SEM. Paired Student’s t tests or ANOVA was used to examine changes, with a level of p<0.05 considered statistically significant. The protocol was approved by the Animal Care Committee of The Toronto Hospital (Western Division).

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**Figure 1.** Mean systemic arterial pressure (Psa), cardiac output (CO), mean pulmonary artery pressure (Ppa), pulmonary capillary wedge pressure (Ppcw), and right atrial pressure (Pra) in anesthetized splenectomized dogs at baseline, and after chronic rapid right ventricular pacing (RRVP) at 250 bpm for 23.1±8.1 days (early failure), after 38.3±8.4 days (failure), and after 1 and 2 weeks of recovery after pacing.

**Figure 2.** Mean circulatory filling pressure (Pmcf) during transient circulatory arrest with acetylcholine plotted against total blood volume at baseline and after 5, then 10, ml · kg⁻¹ increases in volume with dextan 70 for nine anesthetized splenectomized dogs at baseline (○) and after sham rapid right ventricular pacing (RRVP) (●) for 30.5±1.2 days. The inverse of the slope gives total vascular compliance and the extrapolated volume intercept at a Pmcf of 0 give unstressed blood volume. Neither compliance nor unstressed volume was altered by sham RRVP in these control dogs.
Arterial compliance was reduced (0.066±0.008 to 0.033±0.007 ml · mm Hg⁻¹ · kg⁻¹) with failure but returned to baseline values at 2 weeks after pacing. As a consequence, arterial capacity was reduced (6.1±0.8 to 2.6±0.6 ml · kg⁻¹) with failure and some recovery by 2 weeks after pacing (4.6±0.6 ml · kg⁻¹). The reduction in arterial capacity and total vascular capacitance with the development of heart failure was associated with a significant increase in CBV (Figure 7). By 2 weeks after pacing, CBV as a proportion of TBV had returned to baseline values.

Effective pulmonary (central) vascular compliance was reduced with the development of failure (Figure 8). Thus, failure was associated with a reduction of central vascular capacitance largely due to a reduction in central vascular compliance. In the 2-week postpacing period the compliance of this bed was increased toward baseline values.

**Discussion**

This is the first demonstration that the development of heart failure with chronic RRVP was associated with a profound reduction in total vascular capacitance (Figure 3). The reduction in capacitance was accompanied by a reduction in unstressed vascular volume as total vascular compliance was unchanged (Figures 3, 5, and 6). Pmcf was increased as a consequence of the reduced capacitance. However, the increase in Pmcf was limited by a marked reduction in TBV as failure developed, primarily by a reduction in red cell mass (Figure 6). As failure developed, the stressed blood volume, which is the hemodynamically active portion, was increased. However, oxygen-carrying capacity would have been decreased by the reduced red cell mass. Only one other investigation has commented on the development of anemia after 3 weeks of RRVP as a possible mechanism for skeletal muscle underperfusion. Systemic arterial capacity was reduced from 6.1 to 2.6 ml · kg⁻¹ with the development of failure, translocating an average of 3.5 ml · kg⁻¹ of blood from the arterial to the venous side of the circulation. The reduction in total vascular capacitance from 97.4±6.3 to 59.9±9.9 ml · kg⁻¹ (at a Pmcf of 6 mm Hg) resulted in a small translocation of blood from the peripheral to the central circulation, which increased from 8.6±0.5 to 9.5±0.9 ml · kg⁻¹. However, the increase in CBV as a proportion of TBV was significant (Figure 7). Effective pulmonary (central) vascular compliance was also altered during failure as Ppcw increased more than expected as compared to the baseline relationship of Ppcw and CBV.

Total vascular capacitance is largely composed of venous capacitance as arterial capacity is such a small portion of the total (6.1±0.8 versus 97.4 ml · kg⁻¹ at baseline). Total vascular compliance also largely reflects venous compliance as the latter is considerably greater than arterial compliance (2.58±0.28 versus 0.066±0.008 ml · mm Hg⁻¹ · kg⁻¹). Although total vascular compliance was not significantly reduced with the development of failure, systemic arterial and pulmonary vascular compliance were both reduced. The reduction in systemic arterial compliance resulted in a reduction in arterial capacity and a net transfer of blood volume from arteries to veins. The reduction in pulmonary vascular compliance resulted in a higher pulmonary capillary wedge pressure for any given CBV than observed at baseline studies or in sham dogs.

These dogs underwent rapid recovery in the 2-week postpacing period. Only minimal reductions in CO and the CO response to volume loading remained along with
a nonsignificant reduction in TBV and unstressed volume, plus an increase in total vascular compliance causing a lower Pmcf.

The mechanism causing the marked reduction in total vascular capacitance due to a reduction in unstressed volume cannot be determined from these experiments. Active contraction of vascular beds without altering vascular compliance must have occurred as Pmcf was increased without altering the Pmcf–TBV relation. Some passive recoil of vascular beds as TBV diminished is also possible, but because Pmcf was increased, active contraction must have occurred. We speculate that the neuroendocrine response to RRVP and the development of heart failure is responsible for both the reduction in total vascular capacitance and the reduction in TBV.

The neuroendocrine response to RRVP and the development of heart failure is striking.\(^3\)\(^{-8},\)\(^23\)\(^{-30}\) There is a profound rise in both plasma atrial natriuretic factor (ANF) and norepinephrine (NE) with the onset of RRVP. Other investigators have demonstrated that 30 minutes of RRVP increased plasma ANF fivefold to 10-fold and NE twofold, with ANF peaking at about 1 week and NE peaking with the development of severe failure (average, 3–6 weeks).\(^23\)\(^{-28}\) Renin, angiotensin, vasopressin, and endothelin concentrations also rise with chronic RRVP.\(^23,\)\(^25,\)\(^29,\)\(^30\) All of these substances have considerable effects on the vasculature.

Vasopressin, angiotensin, and endothelin may be implicated in the reduction of vascular capacitance. Selective inhibition of vasopressin in rats with chronic heart failure secondary to myocardial infarction increased total vascular compliance.\(^31\) This suggests that vasopressin has a vasoconstrictor effect that alters compliance in animals with heart failure. Angiotensin infusion to dogs increased Pmcf and CBV and decreased CO and total vascular compliance without changing unstressed vascular volume.\(^32\) Large concentrations of endothelin are apparently required to raise Pmcf in ganglion-blocked rats.\(^33\) Thus, although vasopressin, angiotensin, or endothelin may be involved, they are not

**FIGURE 6.** Unstressed and stressed blood volume (upper graph), total blood and plasma volume (lower graph), at baseline, after 23.1±8.1 and 38.3±8.4 days of rapid right ventricular pacing at 250 bpm, and 1 and 2 weeks of recovery after pacing. With the development of failure, unstressed volume and total blood volume were reduced, while stressed volume was increased.

**FIGURE 7.** Central blood volume (CBV) as a percentage of total blood volume (TBV) at baseline, with the development of failure during rapid right ventricular pacing at 250 bpm and after 1 and 2 weeks of recovery after pacing.

**FIGURE 8.** Pulmonary capillary wedge pressure (Ppcw) plotted against central blood volume (CBV) at baseline (—) and during chronic rapid right ventricular pacing (○). The solid line is the regression of Ppcw against CBV at baseline with the dashed lines indicating 95% confidence limits of the line.
strong contenders for a primary role in reducing vascular capacitance without changing compliance. Both ANF and NE are more likely implicated in the reduction of total vascular capacitance without altering compliance. Trippodo et al.\cite{34} have demonstrated that ANF infusions reduced total vascular capacitance of areflexic rats by reducing unstressed volume without altering compliance. The concomitant infusion of NE with ANF further reduced capacitance in these animals. Drees and Rothe\cite{36} demonstrated that NE reduced the total vascular capacitance of ganglion-blocked dogs without altering compliance. Greenway et al.\cite{37} reported that NE reduced hepatic vascular capacitance but not compliance of the cat. α-Adrenoceptors, particularly α2-adrenoceptors, appear to be involved in the control of vascular capacitance in the cat and dog.\cite{40} Forster et al.\cite{13,14,15} have demonstrated enhanced responsiveness to α-adrenoceptor agonists of saphenous vein rings isolated from dogs in heart failure during chronic RRVP. Thus, the combined effect of elevated plasma ANF and NE during chronic RRVP would be a reduction in total vascular capacitance without a change in compliance. However, acute heart failure induced by aortic constriction reduces effective vascular compliance while increasing plasma NE.\cite{41} On the other hand, we have evidence that even brief periods of RRVP (15–40 minutes) will reduce vascular capacitance of anesthetized dogs and cause acute heart failure when a saline volume load is given.\cite{42} Chronic RRVP as shown in the present study apparently continues to have profound effects on total vascular capacitance over several weeks, causing profound changes in cardiac loading conditions. There have been no previous studies of vascular capacitance and compliance using the chronic RRVP model. Engler et al.\cite{43} reported a high Pmcf in anesthetized dogs with chronic failure due to tricuspid insufficiency and pulmonic stenosis. Gay et al.\cite{44,45} studied conscious rats with heart failure 3 weeks after coronary ligation. In this model, vascular capacitance was reduced due to a reduction in compliance as unstressed volume was unaltered. Larger infarcts were associated with an increased total blood and plasma volume and an increased unstressed volume along with further reductions in vascular compliance.\cite{45} These results contrast with the reduction in unstressed volume and TBV with unaltered vascular compliance observed in our dogs during chronic RRVP. Clearly, the mechanisms responsible for the reduction in total vascular capacitance observed in these two species and models of heart failure must be different, yet the result on cardiac function is identical. In the rat model, ganglion blockade with hexamethonium failed to modify the reduced vascular compliance, whereas captopril increased compliance and reduced the blood volume of rats with heart failure.\cite{44,45} It will be of interest to observe the effects of angiotensin converting enzyme therapy on vascular capacitance in animals with chronic heart failure due to RRVP. Other investigators have shown that captopril treatment resulted in lower values of Ps, Ppa, and higher CO during 7 days of RRVP than in untreated dogs along with less sodium and water retention.\cite{25,26} Modification of cardiac loading conditions by altering total vascular capacitance is a rational approach to the treatment of cardiac failure.

Acknowledgment

We gratefully acknowledge the supply of pacemaker generators and leads by Medtronic Canada.

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Effect of chronic rapid ventricular pacing on total vascular capacitance.
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Circulation. 1992;85:1524-1530
doi: 10.1161/01.CIR.85.4.1524
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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