Evaluation of the CO₂ Rebreathing Cardiac Output Method In Seriously Ill Patients

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SUMMARY The CO₂ rebreathing cardiac output method is a totally noninvasive Fick procedure needing validation in various disease states to become clinically applicable. Simultaneous measurements of cardiac output by CO₂ rebreathing and dye-dilution or direct Fick techniques were performed in 53 patients. In nine patients with pulmonary disease rebreathing cardiac output averaged 4.85 L/min compared to 5.18 L/min by dye-dilution or Fick (r = 0.16). In 14 instances of acute myocardial infarction cardiac output was 5.53 L/min by rebreathing and 5.87 L/min by dye-dilution (r = 0.95), while in nine shock cases it averaged 3.98 L/min by dye-dilution or Fick and 3.75 L/min by CO₂ rebreathing (r = 0.94). In five heart failure cases with mitral insufficiency, which may distort dye curves, correlation between standard and rebreathing methods was r = 0.09, but in 16 cases without mitral regurgitation, r = 0.89. Acute interventions in ten patients increased dye-dilution cardiac output by 0.92 L/min and rebreathing outputs by 0.60 L/min (r = 0.87). The data suggest that the CO₂ rebreathing cardiac output method may be useful in the CCU-MICU setting.

AVAILABILITY OF A RELIABLE, EASILY APPLIED, NONINVASIVE METHOD for measuring cardiac output would be of obvious benefit to both clinicians and investigators. Many approaches to noninvasive measurement of cardiac output have been attempted such as impedance cardiography, echocardiography, and ballistocardiography. Methods such as these have first had to establish the soundness of the principles involved in measuring cardiac output, and then to demonstrate that results obtained from the given technique are comparable to those of standard invasive methods.

The carbon dioxide rebreathing method for measuring cardiac output has been known for years but was limited by technical problems. The advent of rapidly responsive gas analyzers which permit breath-by-breath analysis of expired air has made the CO₂ rebreathing method more feasible. Cardiac output determination by the CO₂ rebreathing method is based on the well established Fick principle. The CO₂ rebreathing method merely estimates indirectly the arterial and mixed venous gas contents to be used in the Fick equation. Thus one need only demonstrate accuracy of the rebreathing method in comparison to the direct Fick or similar standard methods such as dye-dilution.

Since the CO₂ rebreathing method depends on normal pulmonary function, physiological or pathological changes affecting the lungs could alter results obtained by the CO₂ method. Despite a multitude of theoretical problems with this method, several investigators have demonstrated the validity of the CO₂ rebreathing method compared to standard invasive methods in normals at supine rest, as well as during exercise. We have recently reported close correlation between the CO₂ rebreathing and dye-dilution methods for measuring cardiac output in patients with uncomplicated hypertension and in a few patients with congestive heart failure. We found the method to be highly reproducible and to accurately reflect changes in cardiac output.

In recent years hemodynamic monitoring of seriously ill patients has become more commonplace. The techniques of hemodynamic monitoring are usually invasive and therefore may be technically difficult as well as uncomfortable and risky for the patient. The CO₂ rebreathing method for measuring cardiac output is quickly and easily applied, virtually without risk, and totally noninvasive. The present study was therefore carried out to compare the CO₂ rebreathing method to standard invasive cardiac output techniques in critically ill patients to see if the noninvasive method might be of value in obtaining information useful for the management of such patients.

Methods

Cardiac output by the CO₂ rebreathing method is calculated from the Fick equation,

\[
Q = \frac{\dot{V}_{CO_2}}{C_{VO_2} - C_{CO_2}}
\]

where \(Q\) = cardiac output (L/min), \(\dot{V}_{CO_2}\) = CO₂ production (ml/min), \(C_{VO_2}\) = CO₂ content of mixed venous blood.

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(ml/L), and \( C_{CO_2} \) = arterial CO2 content (ml/L). Production of CO2 is easily obtained by collecting expired air and measuring its volume and CO2 concentration. Since the \( P_{CO_2} \) of alveolar air and pulmonary capillary blood are virtually identical at the end of a normal expiration, rapid single breath gas analysis is used to measure the CO2 concentration at this point in the respiratory cycle.18, 19 A rebreathing procedure is employed to obtain mixed venous \( P_{CO_2} \). It is assumed that during the rebreathing of a bag mixture of CO2 and O2 the concentration of CO2 in the bag, alveoli, and pulmonary capillaries will achieve an equilibrium at which time no net CO2 exchange occurs across the alveolarcapillary membrane. The concentration of CO2 at this point will be equal to that of mixed venous blood. This equilibrium will persist until recirculation occurs and returns venous blood of higher CO2 content to the lungs.19, 20

If the initial bag mixture contains a high concentration of CO2, as alveolar gas enters the bag during rebreathing the CO2 concentration will fall until equilibrium is achieved. A recording of breath-by-breath CO2 concentration will show a "plateau" at equilibrium20 (fig. 1).

To complete the calculations, \( P_{CO_2} \) is obtained by multiplying CO2 percentage concentration by the barometric pressure - 47 mm Hg. Since the rebreathing bag mixture contains a high O2 concentration (91%), a standard CO2 dissociation curve for oxygenated blood may be used to convert \( P_{CO_2} \) to CO2 content.21, 22 Normal hemoglobin concentration and blood pH are assumed.

Studies were performed in 53 patients, 21 with clinical class II or III congestive heart failure (New York Heart Association classification), 14 with acute myocardial infarction in Kimball-Killip class I or II,23 nine with shock states, and nine with primary pulmonary disease. Congestive heart failure was diagnosed on the basis of clinical (dyspnea, \( S_3 \) gallop, post-tussive rales, jugular venous distention) and radiological evidence. Acute myocardial infarction was documented by serial electrocardiographic and serum enzyme changes, shock states were diagnosed on the basis of signs of underperfusion (cool skin, diaphoresis, mental obtundation, hypotension, and oliguria), and primary pulmonary disease was confirmed by blood gas analysis, chest X-ray, and pulmonary function studies.

Studies were performed after obtaining written informed consent. Patients either volunteered for this study or were undergoing diagnostic cardiac catheterization. All studies were performed with the patients at supine rest and were carried out at the patients' bedside in the coronary care unit (CCU) or intensive care unit (ICU), or in a special procedure room adjacent to the CCU-ICU areas. The apparatus necessary is contained on a portable cart (fig. 2). A brachial artery was cannulated with a short teflon catheter inserted percutaneously over an 18 gauge needle. A Swan-Ganz catheter was inserted percutaneously via an antecubital or femoral vein and positioned in the right atrium or pulmonary artery.27 Right heart pressures were recorded using a P23D Statham pressure transducer connected to a Hewlett-Packard direct writing multichannel recorder. In 49 patients cardiac output was determined in

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** CO2 rebreathing determination of cardiac output. \( A \) = average CO2 concentration; \( B \) = single breath analysis of CO2 concentration during slightly forced expiration used to estimate arterial CO2 content; top of each cycle equals end-expiration, bottom is end-inspiration. \( C \) = "plateau" of CO2 concentration during actual rebreathing of 9% CO2 and 91% O2 used to estimate mixed venous CO2 content. Actual rebreathing period lasts only 12-15 seconds or 5-6 breaths before satisfactory plateau is obtained. Note that tracing represents only that portion of the procedure during which CO2 concentrations are measured. Expired air volume measurement to obtain CO2 production began several minutes earlier.
duplicate by the dye-dilution method injecting 4 mg of indocyanine-green into the right atrium or pulmonary artery and sampling from the brachial artery through a Gilford densitometer connected to the Hewett-Packard recorder. Direct Fick method cardiac outputs were measured in six patients, two of whom also had dye-dilution curves done.

Duplicate cardiac outputs were measured by the CO₂ rebreathing method simultaneous with the dye curves or direct Fick determinations. Expired air was collected for 5-7 min and passed through a Parkinson Cowan dry gas meter and a Beckman LB-2 CO₂ analyzer whose outputs of expired air volume and average CO₂ concentration were displayed on a Beckman RR-2 recorder. At the end of this 5-7 min volume collection and after appropriate positioning of stopcocks to permit direct sampling from the mouthpiece, arterial CO₂ was obtained by having the patient perform a slightly forced expiration at the end of a normal tidal inspiration while the CO₂ analyzer performed breath-by-breath analysis. Mixed venous CO₂ was obtained by connecting a rebreathing bag to the mouthpiece and a small tube running from the mouthpiece of this system directly to the CO₂ analyzer allowed single breath analysis during rebreathing. Mixed venous CO₂ was measured by the Collier method, using a mixture of 9% CO₂ and 91% O₂. The rebreathing bag contained approximately 1.5 tidal volumes. Patients were instructed to breathe as normally as possible whenever the mouthpiece was in place; other than this, no other instruction or practice runs were made. At least 1 min was allowed to pass and the rebreathing bag was thoroughly flushed between rebreathing periods. Total time elapsed for completion of the indirect Fick procedure was approximately 10-12 min. Dye dilution curves or direct Fick determinations were done during the last 5 min of this period.

A “plateau” for the Collier method was considered acceptable if it occurred within 15 sec of the start of rebreathing, but not before the second breath, and if the CO₂ concentration of two successive expirations differed by less than 0.10%. Before each study the CO₂ analyzer was calibrated with previously analyzed test gases.

In ten patients cardiac output measurements by CO₂ rebreathing and standard methods were repeated after therapeutic interventions to see if the CO₂ rebreathing method reliably reflected acute changes in cardiac output.

In order to assess the effects of the CO₂ rebreathing procedure itself on hemodynamics, heart rate, pulmonary arterial pressure, and systemic arterial pressure were recorded without the mouthpiece in place, with the mouthpiece in position, and during the actual CO₂ rebreathing period in eight patients. In 13 patients cardiac output was measured by dye-dilution with and without the mouthpiece in place.

Correlation coefficients and percentage differences between CO₂ rebreathing and standard methods were calculated. Paired Student’s t-tests were used to analyze the hemodynamic effects of the CO₂ rebreathing procedure.

**Results**

No complications, side effects, or serious patient discomfort were observed in these 53 patients. One patient with an acute myocardial infarct experienced nausea and vomiting during the rebreathing procedure, but these symptoms were present before the procedure was started. Periodic respirations were present in two patients, who were nevertheless able to perform the rebreathing procedure satisfactorily. All patients were alert or easily arousable so as to be able to perform the rebreathing procedure.

Cardiac output in nine patients with primary lung disease averaged 4.85 ± 2.08 (1SD) L/min by CO₂ rebreathing and 5.18 ± 2.34 L/min by dye-dilution or Fick methods. The average difference between individual values for the CO₂ and the other methods was 108.3% and was extremely variable (standard deviation: 176.8%) and there was no correlation between them (r = 0.16).

Four of these patients had chronic obstructive lung disease, three had severe pulmonary fibrosis, one massive pleural effusion, and one extensive lobar pneumonia. Only three patients had arterial PCO₂ over 40 mm Hg, and the average arterial PCO₂ for the group was 40.6 mm Hg. None of these patients had evidence of other cardiovascular disease, and their pulmonary arterial wedge pressures averaged 6.5 mm Hg (range 5-10 mm Hg).

In nine patients with shock syndromes cardiac output averaged 3.75 ± 1.25 L/min by CO₂ rebreathing and 3.98 ± 1.65 L/min by dye-dilution or Fick techniques; the coefficient of correlation between the two is high (fig. 3). The average difference between the noninvasive and invasive methods was 10.4 ± 10.5%. Shock was cardiogenic in origin in five patients, due to sepsis in three, and hemorrhagic in one. Mean systemic arterial pressure averaged 73.4 mm Hg in this group; some patients were receiving pressor or inotropic agents at the time of study.

A very high correlation between the CO₂ rebreathing and standard dye-dilution or Fick methods was also observed in the 14 patients with acute myocardial infarction (fig. 4). Cardiac output averaged 5.53 ± 1.73 L/min by rebreathing and 5.87 ± 1.57 L/min by dye-dilution or Fick methods in these patients, and the difference between the rebreathing and standard invasive methods averaged only 8.5 ± 7.1%.
Pulmonary arterial wedge pressures were measured in 12 of these patients and averaged 11.3 mm Hg (14.8 mm Hg in five class II patients and 8.7 mm Hg in seven class I patients). No new arrhythmias or chest pain occurred during the CO₂ rebreathing procedure in these patients.

For all 21 patients with congestive heart failure cardiac outputs by the two methods were related: 3.50 ± 1.09 L/min by CO₂ rebreathing and 4.23 ± 1.17 L/min by the standard dye-dilution or Fick methods (r = 0.52). In five patients with mitral regurgitation (diagnosed by typical apical holosystolic murmur, S₂ gallop, and elevated “V” wave on pulmonary arterial wedge pressure tracings) cardiac outputs were not similar: 4.77 ± 0.91 L/min by CO₂ rebreathing and 2.56 ± 0.74 L/min by the standard methods (r = 0.09). The average differences in individual patients between methods was 101.2 ± 68.8%. In the 16 heart failure patients without mitral regurgitation there was a strong correlation between CO₂ rebreathing and dye-dilution or Fick methods (r = 0.89). In this subgroup cardiac output averaged 4.06 ± 1.21 L/min by CO₂ rebreathing compared to 3.80 ± 1.03 L/min by standard methods, with an average difference of only 9.1 ± 11.4%.

The standard method used for patients with mitral regurgitation was dye-dilution, and the CO₂ method consistently produced higher values for cardiac output. In two such patients direct Fick outputs were also measured. In one case CO₂ rebreathing gave an output of 4.18 L/min, direct Fick 4.08 L/min, and dye-dilution 1.48 L/min. In the other case the values were 5.14 L/min by CO₂ rebreathing, 5.72 L/min by direct Fick, and 2.31 L/min by dye-dilution. Thus, apparently the direct Fick and dye-dilution methods correlate poorly when the incompetent valve lies between the dye injection and sampling sites.

The effect of pulmonary arterial wedge pressure on cardiac output determination by the CO₂ rebreathing method was analyzed in 30 patients without primary lung disease or mitral regurgitation. Pulmonary arterial wedge pressure ranged from 8–32 mm Hg (mean 16.9 ± 6.7 mm Hg) and the average difference between CO₂ rebreathing and standard cardiac output methods in these patients was 10.4 ± 10.1% (range 0–41%). There was no correlation between pulmonary arterial wedge pressure and the percentage difference between invasive and noninvasive output methods (r = 0.02).

Accuracy of the CO₂ rebreathing method at extremes of cardiac output was also examined in patients without primary lung disease or mitral regurgitation. In 23 patients with low cardiac output (below 4.5 L/min by dye-dilution or Fick method) there was a strong correlation between CO₂ rebreathing and standard methods (r = 0.88). Similarly in six patients with high cardiac outputs (over 6.5 L/min by dye-dilution or Fick methods) the correlation coefficient was strong (r = 0.93) (fig. 5).

Therapeutic interventions including administration of pressors, inotropic agents, or vasodilators in ten patients raised cardiac output an average of 0.92 ± 1.15 L/min by dye-dilution and an average of 0.60 ± 1.07 L/min by CO₂ rebreathing. There was a high correlation between the
changes in cardiac output as measured by the invasive and
noninvasive methods ($r = 0.87$), and the increase in cardiac
output was significant by either method ($P < 0.05$ for each).
The CO₂ rebreathing procedure itself had no significant
hemodynamic effects. A representative case is shown in
figure 6 and the results are summarized in table 1. Dye
dilution cardiac outputs with and without the mouthpiece in
place correlated highly ($r = 0.96$), and the average
difference between them was 6.8%, which is the same as our
previously reported difference between successive duplicate
dye-dilution cardiac outputs.¹⁴

**Discussion**

The CO₂ rebreathing method for measuring cardiac output
has been extensively evaluated in recent years. This
technique has been considered more reliable during exer-
cise.¹⁵,¹⁶,²⁴ Muiesan et al. reported a correlation of 0.94
between CO₂ rebreathing and direct Fick methods in nor-
ma尔斯 at supine rest.¹⁰ Previous studies in adults with cardiac
or pulmonary disease showed poor correlation between the
CO₂ method and standard methods at rest, especially in
patients with primary lung disease.¹¹ We have recently
reported a high correlation ($r = 0.93$) between the CO₂
rebreathing and dye-dilution methods in patients with
hypertension or mild congestive heart failure studied at
supine rest.¹⁴ In addition, the CO₂ method was shown to be
highly reproducible in successive tests, and to accurately
reflect changes in cardiac output during exercise or after
beta-adrenergic blockade.

The present study, which was carried out to extend our
observations to seriously ill patients, tends to confirm the
earlier experience in that we found the CO₂ method to be un-
reliable in patients with primary lung disease, even without
hypercapnia, and we again found close correlation between
CO₂ and standard methods in patients with mild to severe
congestive heart failure.

The results in heart failure patients were not affected by
elevation of pulmonary arterial wedge pressure. This finding
is not altogether surprising since acute left ventricular
failure, while markedly affecting oxygen exchange across the
alveolar capillary membrane, rarely causes CO₂ retention.²⁵
Since increased pulmonary arterial wedge pressures had no
effect on the CO₂ rebreathing cardiac output determination,
this is not a likely mechanism to explain the poor correlation
between CO₂ and dye-dilution methods in patients with
mitral regurgitation.

The dye-dilution method performed in patients with an
incompetent valve may produce curves grossly distorted in
contour and from which extrapolation of the exponential of
the downslope is very difficult.²⁶⁻²⁸ It is likely that in some of
our patients with mitral regurgitation the dye-dilution
method was inaccurate since all our dye injections traversed
the incompetent mitral valve. The fact that direct Fick car-
diac outputs agreed closely with the CO₂ method but not the

**Table 1. Hemodynamic Effects of the CO₂ Rebreathing Method Itself**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mouthpiece Inserted</th>
<th>Rebreathing Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>82.3 ± 10.1</td>
<td>84.1 ± 12.6</td>
<td>85.0 ± 13.1</td>
</tr>
<tr>
<td>PAPs (mm Hg)</td>
<td>48.8 ± 21.7</td>
<td>48.9 ± 20.3</td>
<td>49.9 ± 20.7</td>
</tr>
<tr>
<td>PAPd (mm Hg)</td>
<td>23.4 ± 12.2</td>
<td>24.3 ± 10.8</td>
<td>23.6 ± 10.3</td>
</tr>
<tr>
<td>SAPs (mm Hg)</td>
<td>123.6 ± 28.7</td>
<td>124.6 ± 28.4</td>
<td>125.0 ± 29.9</td>
</tr>
<tr>
<td>SAPd (mm Hg)</td>
<td>66.4 ± 15.0</td>
<td>67.5 ± 19.1</td>
<td>68.5 ± 18.8</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.74 ± 1.21</td>
<td>3.68 ± 1.11</td>
<td>——</td>
</tr>
</tbody>
</table>
dye-dilution technique in two such patients supports this explanation. All our patients with marked discrepancies between the CO2 and dye-dilution methods had severe mitral regurgitation characterized by a loud holosystolic murmur and prominent S2. Milder degrees of mitral regurgitation, as judged by the duration and intensity of the murmur and prominence of S2, did not result in significant differences between methods.

To our knowledge this is the first demonstration that the CO2 rebreathing method can be used reliably and safely in patients with acute myocardial infarction or shock states to measure cardiac output. Since changes in cardiac output induced by therapeutic interventions were accurately reflected by the noninvasive technique, and since changes in pulmonary arterial wedge pressure had no effect on the CO2 rebreathing method, this technique might be useful in diagnosing and monitoring the hemodynamic status of such critically ill patients.

Despite its obvious advantages and acceptable accuracy, the CO2 rebreathing method has not been widely used to measure cardiac output. Both technical and theoretical factors may affect its accuracy. Recirculation may falsely elevate the "plateau" during rebreathing resulting in a false high veno-arterial CO2 difference and a low cardiac output measurement. The use of strict criteria to determine the acceptability of any given "plateau" largely minimizes the effects of recirculation.28 Proper rebreathing bag volume is important in obtaining a satisfactory plateau and this can usually be arrived at quickly by simple trial and error.

While these technical problems can be readily overcome with sufficient experience, many physiological considerations can be raised which can affect the validity of the CO2 method. Posture, physiological dead space, rebreathing time, and ventilation/perfusion distribution are all known to have definite but small effects on CO2 exchange.29-33 However, the effects of these physiological and technical problems on the CO2 rebreathing method are either small or canceled out by other offsetting factors. The final result of the CO2 method is a fairly accurate determination of cardiac output. This is further supported by our previously reported close agreement between directly measured and indirectly estimated values for arterial and mixed venous PCO2.14 We reported an average 1 mm Hg variation between direct and indirect veno-arterial PCO2 differences, which is virtually negligible when converted to CO2 content.

The CO2 rebreathing method is limited by other conditions. Significant pulmonary disease, especially if associated with hypercapnia or airway obstruction, invalidates the CO2 method. Other lung diseases with extensive involvement also appear to invalidate the method, but we do not as yet have established criteria for selecting out these diseases. In general, in patients who are very symptomatic from lung disease, especially if very tachypneic, the CO2 method cannot usually be reliably performed. In addition to requiring reasonably normal pulmonary function, the patient must be breathing spontaneously and be alert or arousable enough to perform the procedure. Almost all patients can perform the technique without prior training or experience. Thus, this method is currently not applicable to unconscious patients or those on assisted respiration. With technological modifications it may be possible to use the method during endotracheal intubation, but this application needs further evaluation.

A final consideration is the effect of the CO2 rebreathing procedure itself on cardiac output. In the present study the CO2 method itself had no effect on pulmonary and systemic pressures, heart rate, or cardiac output. The period of actual CO2 rebreathing lasts for only a few breaths or about 15 sec, and 91% O2 is also being administered at the same time. During most of the procedure the patient is breathing room air and expired air is collected, just as in the direct Fick technique. The hemodynamic effects of the brief exposure to CO2 are presumed to be minimal.

In conclusion, the CO2 rebreathing method for measuring cardiac output appears to be safe and reliable in critically ill patients. It cannot be used in patients with significant pulmonary dysfunction, but is useful in patients with congestive heart failure, acute myocardial infarction, or shock states. Because it is totally noninvasive, easily performed, and allows cardiac output to be measured repeatedly over long intervals, this method may be useful for monitoring cardiac output in conscious spontaneously-breathing patients in intensive care areas.

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The Effect of "Ischemic" Blood on Transmembrane Potentials of Normal Porcine Ventricular Myocardium

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SUMMARY "Ischemic" blood was obtained in pigs from a local coronary vein on release of coronary artery occlusion. The effects of this blood on transmembrane potentials of muscle strips taken from the same heart were compared with control blood. Whereas action potentials remained stable in control blood, ischemic blood collected after more than 15 minutes of coronary occlusion produced shortening of action potential duration, reduction of resting potential, upstroke velocity and amplitude, then postpolarization refractoriness and finally unresponsiveness. Ischemic blood collected after shorter periods of coronary occlusion produced only mild effects (shortening of action potential and postpolarization refractoriness).

These effects of ischemic blood could not be attributed to increased potassium concentration even in combination with acidosis, hypoxia and hypoglycemia. It appears that during ischemia unidentified factors are released which have potent depressant effects on the excitability of even normal myocardium.

THERE HAVE BEEN MANY REPORTS on the nature of biochemical changes in coronary venous blood which occur in response to myocardial ischemia.2–8 Changes in coronary venous potassium levels and their possible relationship to ventricular arrhythmias have attracted particular attention9–13 since Harris first implicated potassium as a major excitant of ventricular arrhythmias in myocardial ischemia.14 Despite such interest, both the mode of onset of early ventricular arrhythmias and their relationship to altered biochemical parameters remain matters for conjecture. This situation exists in part because there is no satisfactory model which enables study of ischemic changes in the intracellular electrophysiology of ventricular myocardium.

In an attempt to gain insight into the possible nature of such intracellular changes and their relationship to some of the altered biochemical parameters produced by ischemia, we examined the effects of coronary venous blood draining an ischemic region on action potentials recorded from an isolated strip of normal ventricular myocardium.

Methods

Thirty-two pigs weighing 20 to 25 kg were anesthetized by intravenous injection of sodium pentobarbital (20 mg/kg). Under artificial respiration the chest was opened by a midsternal incision and a pericardial cradle was constructed. A full-thickness piece of right ventricular wall from the outflow tract region was removed and the defect closed by a purse-string suture. The preparation was trimmed to about 0.5 cm² in area and 3 mm thickness. It was mounted endocardial side up in a 2 ml tissue bath superfused with running oxygenated modified Tyrode solution at a rate of 2 ml/min. The composition of the solution, in mEq/L, was: Na+ 156.5, K+ 4.7, Ca++ 1.5, Mg++ 0.7, H2PO4 0.5, HCO3 28.0, Cl- 137.0, and glucose 20 mM/L. Temperature was maintained constant at 37°C ± 0.5°C. The preparation was stimulated via a bipolar silver electrode, insulated except at the tips, at a basic cycle length of 700 msec, using rectangular current pulses with a duration of 2 msec and an intensity of

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